IntechOpen

Diagnostics and Rehabilitation of Parkinson's Disease

Edited by Juliana Dushanova

DIAGNOSTICS AND REHABILITATION OF PARKINSON'S DISEASE

Edited by **Juliana Dushanova**

Diagnostics and Rehabilitation of Parkinson's Disease
http://dx.doi.org/10.5772/2709
Edited by Juliana Dushanova

Contributors

Silvia Marino, Pietro Lanzafame, Silvia Guerrera, Rosella Ciurleo, Placido Bramanti, Mario Pansera, Laura Pastor Sanz, Kevin Mulhall, Adrian J Cassar Gheiti, Joseph Baker, Yangho Kim, Youichi Saitoh, TANI Naoki, Po-Lei Lee, Jen-Chuen Hsieh, Yoshiyuki Takahashi, Osamu Nitta, Takashi Komeda, Jesús Seco, Ines Gago, Iris Reuter, Martin Engelhardt, Sabine Mehnert, Matthias Oechsner, Lilian Gobbi, Fabio Barbieri, Rodrigo Vitório, Marcelo Pereira, Claudia Teixeira-Arroyo, Elena Lukhanina, Irina Karaban, Natalia Berezetskaya, Lilian Beijer, Toni Rietveld, Saburo Sakoda, Takuyuki Endo, Masaru Yokoe, Harutoshi Fujimura, Katrien Colman, Roelien Bastiaanse, Zhiming M. Zhang, Xiaomine Wang, Jorge Quintero, Shin Kwak, Weidong Pan, Yoshiharu Yamamoto, Ryoichi Hayashi, Takeshi Hayashi, Junpei Aizawa, Hiroaki Nagase, Shinji Ohara, Sun Ha Paek, Juliana Dushanova, Hoe C Lee, Torbjorn Falkmer, Jessica Davies, Margherita Speziali, Michela Di Casa, Josep Valls-Sole, Joao Costa, Francesc Valldeoriola, Orgeret Gilles, Mamadou Moustapha Sarr, Alain Ghio, Robert Espesser, Moustapha Dramé, Bernard Teston, François Viallet

Notice

First published in Croatia, 2011 by INTECH d.o.o.
eBook (PDF) Published by IN TECH d.o.o.
Place and year of publication of eBook (PDF): Rijeka, 2019.
IntechOpen is the global imprint of IN TECH d.o.o.
Printed in Croatia

Legal deposit, Croatia: National and University Library in Zagreb

Additional hard and PDF copies can be obtained from orders@intechopen.com

Diagnostics and Rehabilitation of Parkinson's Disease
Edited by Juliana Dushanova

p. cm.

ISBN 978-953-307-791-8

eBook (PDF) ISBN 978-953-51-6598-9

Meet the editor

Dr. Dushanova's research interests are in motor neurophysiology, pathophysiology of Parkinson's disease and in the development of approaches for diagnostics. Her works span human and non-human primate research, computational modeling and simulations. She received her MS degree from Sofia University, Bulgaria, Predoctoral fellow by Prof. Pfurtscheller at Department of Medical Informatics, Ludwig Boltzmann Institute for Medical Informatics and Neuroinformatics, Technical University Graz, Austria, PhD from Institute of Neurobiology, Bulgarian Academy of Sciences and studied neurophysiology under Prof. J.P. Donoghue in the Neuroscience Department of Brown University, RI USA. Assoc. Prof. J. Dushanova's research is in the field of movement disorders and she has been involved in electroencephalography research and practice since 1994.

Contents

Preface

We have based this book on the philosophy that one has control on how Parkinson's disease affects the life of a person if the disease is battled with the belief that through support and maximization of personal strengths, life will continue to have meaning and richness. The battle begins with the partnership between the physicians and the patient. By understanding as much as possible about Parkinson's disease, medications, and non-drug therapies, a patient can actively participate in the health-care decisions that have an unique effect on the self. If a person has Parkinson's disease (PD), it does not necessarily mean that one will experience all possible symptoms. We have organized this book in sections, each one dealing with a different aspect of PD.

The idea was to edit a book that will reflect a professional wisdom, extended to the experiences of scientists from different fields. We hope that a positive attitude of the colleagues who have contributed to the expertise of this book will serve as a powerful instrument against this disease and that this handbook will also be useful for clinicians who take health care of people with PD and their families.

Parkinson's disease is a progressive neurologic disorder affecting 1 in 100 people over the age of 50. Typically the diagnosis is made in the sixth or seventh decade of life, with approximately 7% of people diagnosed before the age of 40. It has been well documented that PD is also characterized by a long preclinical phase from the onset of dopamine neuron loss to the onset of motor symptoms. In the recent years more light was thrown on non-motor symptoms such as autonomic dysfunction, pain and cognitive decline. Approximately 10% of subjects older than 60 years are in the prediagnostic phase of PD and exhibit the pathological hallmarks of PD, like Lewy bodies and neuronal loss at the substantia nigra (SN), without showing the motor signs during life time that allow the diagnosis of PD. There is enough evidence to show that cognitive deficits affect the quality of life. Thus, there is an urgent need to develop imaging modality to screen individuals who may be in the preclinical phase of PD for earlier diagnosis and treatment to slow down or even stop progression of the disease. Parkinsonian symptoms such as tremor, rigidity, akinesia, postural instability and facial expression are perceived subjectively, and therefore understanding the degree of the symptoms varies depending on the neurologist.

The neuroimaging examination could help to evaluate PD subjects in the preclinical stage. Conventional MR imaging, as well as different advanced MRI techniques,

including magnetic resonance spectroscopy, diffusion-weighted and diffusion tensor imaging are helpful to distinguish PD from atypical or secondary PD. The secondary symptoms of Parkinson's disease may affect some but not all people. These include changes in speech and swallowing, bowel and bladder function, fatigue, mood and memory, sexual function, and sleep. Speech of patients with Parkinson's disease (PD) is characterized as hypokinetic dysarthria, manifesting itself by low volume, diminished voice quality, flattened prosody and deteriorated articulation. Patients with mild cognitive deficits have a higher risk for developing dementia. The interventions in early stages of cognitive decline might slow down the progress of cognitive deficits or even prevent the development of dementia. Brain event-related oscillations are one of the promising candidates explaining the neural mechanisms at central nervous system in Parkinson's patients and give a useful tool for detecting subtle abnormalities of the cognitive processes.The sustained yield of a multidisciplinary training programme on cognitive function of PD patients with mild cognitive deficits is to support patients to manage their daily life better and to become more self-confident. When symptoms first appear, they are very mild and sometimes intermittent. As the disease progresses the symptoms become more pronounced and more persistent. The primary symptoms of Parkinson's disease are tremor, rigidity, bradykinesia (slowness), and impaired balance but not all symptoms need to be present to make the diagnosis. Tremor is most prominent when a person is sitting quietly, and improves or disappears when the person is using their arms or legs. That is why Parkinson tremor is described as a resting tremor. Rigidity is stiffness of muscles. As the disease progresses, the stiffness is perceived as a cramp or tired, aching muscles. This rigidity is associated with the flexion posture characteristic of Parkinson's disease. Rigidity responds well to a combination of medications and a vigorous stretching program. Bradykinesia means slowness of movement. Fine movements, such as writing, becomes more clumsy. Another manifestation of bradykinesia is loss of associated movements. These are movements outside of one's awareness: blinking the eyes, facial expression, swallowing, swinging the arms, and changes of posture. The overall appearance is one of unusual stillness when a person is sitting quietly. Bradykinesia also affects voluntary movement. Medication can be very helpful in improving bradykinesia. Impaired balance occurs because of a change in postural reflexes. These are the reflexes that facilitate rapid changes in the center of balance when walking or standing. A person will notice a feeling of unsteadiness and in later stages of disease may have a tendency to list to one side or the other and may even fall backwards or forwards. Medication is less helpful for balance problems than for rigidity or bradykinesia. Physical therapy can be very helpful in teaching safety maneuvers, balance exercises, and providing consultation regarding ambulation aids.

Parkinsonism is the loss of dopamine-producing cells in an area of the brain stem called the substantia nigra. These nerve cells project fibers to areas deep in the brain called the basal ganglia. The function of the neurochemical, dopamine, is to allow nerve impulses to run smoothly along these fibers and transmit messages to muscles of the body producing normal movement. When the supply of dopamine is decreased

by approximately 80% the symptoms of Parkinson's disease emerge. Over time the loss of dopamine-producing cells continues and symptoms become more severe. The current debate is whether nerve cell loss is something that has a genetic link occurring slowly over time or happens suddenly after being exposed to a toxic substance. It may be a combination of these two theories. It has been suggested that some people are genetically predisposed to developing Parkinson's disease and therefore more susceptible to the potential damage of a toxic exposure.

Parkinson's disease progresses slowly. The rate of progression varies, making it difficult to give patients and families definitive information that can provide them the comfort of knowing what to expect and how to prepare for their future. The studies that have attempted to describe the prognosis of Parkinson's disease have been hard to interpret because drug therapy treats the symptoms. Drug treatment, specifically levodopa therapy, slows the onset of disability. Disability will eventually occur and increase while on therapy but this is usually because of the emergence of new symptoms that do not respond to levodopa.

People should consider how Parkinson's symptoms might alter performance and think of ways to modify their work environment or their type of work. It is also important to remember that current research offers tangible possibilities that could change the course of Parkinson's disease. Gene therapy, surgical therapies, rehabilitation, and drugs that delay progression hold great hope for changing the disability of Parkinson's disease. The training tasks were allocated to different categories: concentration, strategy, improvement of orientation, planning, use of mnemonic devices. Impulse control, decision processes, listening training and memory, and also a special programme with the aim to learn motor sequences, dual tasking, orientation in a room. The motor training helped patients to deal with their cognitive problems; many patients are afraid of the cognitive deficits and rather try to hide than to approach the problems. Physical activity improves cognitive functions especially executive functions which are important for daily living. Sport is as well an activity to get the partners involved. Social aspects are important for the continuation of the training and as well important to prevent depression. Depression and social isolation are closely associated with cognitive decline. The new ICT systems are able to evaluate the variation of symptoms along whole the time the patient is wearing the sensors and provide useful information to physicians in order to allow them make decisions more accurate, more efficient and quicker. Long-term multimodal exercise programs can improve both motor and cognitive impairments in people with PD, which could have a broader impact on quality of life than specific exercise interventions.

Predating the diagnosis of PD and identifying subjects at risk will be one important goal for future research aimed to postpone the onset of the disease by neuroprotective therapy.

Part I of the book first gives an introduction to "prediagnostic" phase of PD or early markers for the diagnosis of Parkinson's disease as non-motor symptoms such as

mood disorders, olfactory, vegetative, sensory or neuropsychological signs may be noticed by the patients or physicians in advance of motor signs reflecting the dysfunction of dopaminergic or non-dopaminergic neurons. Several procedures in *chapter 1* have been proposed to identify subjects in early stages of PD as the saccadic eye movements to investigate and quantify motor impairments in PD, and a new vision-based nonintrusive eye tracker as a possible tool for supporting the diagnosis of PD in association with levodopa test. A more complex relationship between brain iron changes and disease state in PD has revealed different metabolic patterns and a reduced capacity of the macromolecules in brain tissue to exchange magnetization with the surrounding water molecules was found in the substantia nigra pars compacta, substantia nigra pars reticulate, red nucleus in PD. Diffusion Weighted Imaging and a statistical parametric mapping localized significant increases of diffusivity in the region of both olfactory tracts in patients with PD compared to healthy controls. This observation is in line with the well-established clinical finding of hyposmia in early PD. Olfactory dysfunction may be considered a reliable marker of PD. Objective olfaction tests are olfactory-evoked potentials or functional magnetic resonance imaging (fMRI). These techniques have been used to assess the severity of olfactory dysfunction and its correlation with cerebral changes in studies carried out in early PD patients. Effective differential diagnosis of Parkinson's disease needs in informative indexes that objectively reflect the functional state of the extrapyramidal system. Such informative diagnostic indexes in PD are surface electromyograms (EMGs) and brain evoked potentials (*Chap. 2*). The fractal analysis of EMG is sensitive to neuromuscular status. The contingent negative variation is a sensitive indicator for the objective evaluation of the severity of PD and to quantify the efficacy of the therapy. Deviations of the auditorily elicited brain oscillatory responses at specific frequencies in association with sensorimotor and cognitive processes for the Parkinson's patients compared to healthy controls are a evidence for disturbances in the temporal and regional integration of these frequency components and the relationships between cortical and the basal ganglia circuits in parkinsonism (*Chap. 3*). A method based on independent component analysis (ICA) and the use of a template-based correlation approach to extract Rolandic beta rhythm from magnetoencephalographic measurements of right finger lifting are presented in *chapter 4.* The objectives of the *chapter 5* are the use of neuroimaging such as magnetic resonance imaging, positron emission tomography or single-photon emission computed tomography in manganese-induced Parkinsonism and the assessment of the neural correlates of manganese-induced memory impairment in response to a subclinical dysfunction of working memory network in welders with chronic manganese exposure. *Chapter 6* has been trying to introduce in developing of MRI-based imaging biomarkers for early detection of PD. The imaging method as pharmacological MRI can detect functional deficiency of the nigrostriatal system. The purpose of the *chapter 7* is to give a systematic and exhaustive depiction of element levels (Cu, Fe, Zn, Cr, Be, Cd, Cr, Hg, Se, Si, V, Mn, Cu, Co, Pb , Ni) in the cerebrospinal fluid of PD patients and paired controls and to verify the influence on the results of number, age, gender of the subjects and health conditions with regard to clinical variables as duration and

severity of the disease and pharmacological therapies. The *chapter 8* considers the underlying mechanisms of the subtle language impairments in non-demented PD patients. Recently functional imaging in PD patients has begun to add information to the underlying nature of the language impairments in PD, both comprehension and production deficits at the word, sentence and discourse level.

Part II concentrates on the novel methods to evaluate symptoms in Parkinson's disease. This contribution in the book deals with the sensing systems identifying rigidity or spasticity and the nature of abnormal finger tapping in Parkinson' s disease, and show Parkinsonian symptoms as a system error in software of repetitive movement (*Chap. 9*). Among Parkinsonian signs, speech impairment represent an important disabling symptom able to lead towards a significant reduction of oral communication. The principal methods for PD speech evaluation will be reviewed briefly in the *chapter 10* prior to the presentation of the use and relevance of aerodynamic parameters for Parkinsonin dysarthria evaluation. The analytical method based on power-law temporal auto-correlation of physical activity collected by an actigraph device enables evaluation of the severity of Parkinsonism with sufficient sensitivity and reliability, and is useful for the evaluation of efficacy of therapy for Parkinsonism (*Chap. 11*). Postural control while sitting with or without arm raising and its association with risk of falls in patients with Parkinson disease was discussed in *chapter 12*.

Part III focuses on multidisciplinary cognitive rehabilitation in Parkinson`s disease. A study on cognitive training in Parkinson`s disease and compared different types of cognitive training is discussed in *chapter 13*. The studies assess the effect and sustained yield of a multidisciplinary training programme on cognitive function of PD patients with mild cognitive deficits. *Chapter 14* proposes modules known as systems for support the decision-making which allow doctors and clinicians be more agile in the decision-making process improving the time that they need and the quality of information that they have. The researches explore the impact of impaired decision making ability upon the driving performance of people with PD (*Chap. 15*). The effectiveness of a long-term multimodal exercise program based on the improvement of the functional capacity components in improving clinical parameters, functional mobility and cognitive function in people with PD was demonstrated in *chapter 16*. The research areas with respect to the development, implementation and evaluation of telehealth applications for speech therapy in dysarthric speakers with Parkinson's disease are addressed in *chapter 17*. The relevant and the long-term efficiency of a physiotherapy program in PD are demonstrated in *chapter 18*. Normotensive therapy is a specific rehabilitation to control of postures and it uses of a supporting elastic expander while exercising and a traumatic normalization of the tissues, and allow mobility to be restored without any pain (*Chap. 19*). A sit-to-stand assistance system is developed, and used to assist individuals with Parkinson's disease who could or could not stand up without help (*Chap. 20*).

Part IV deals with practical issues that are critical for the invasive methods examined in patients with Parkinson's disease. A review of the use of deep brain stimulation

(DPS) electrodes for externally controlled recording or stimulation at the level of basal ganglia nuclei discussed the physiological observations underlying the engagement of structures affected by the electrical field around the electrode in motor and sensory functions (*Chap. 21*). Based on the information from the fused images of preoperative MRI-postoperative computer tomography, it was emphasized that the documentation of the electrode position by using mutual information technique after unilateral or bilateral STN stimulation provides useful information for the prediction of the surgical outcome (*Chap. 22*). Fusion-image-based programming and reprogramming of the stimulator parameters using the visual information of the location of the electrode contacts propose to find the best sites and the best stimulation parameters for the advanced PD patients treated with deep brain stimulation of subthalamic nucleus (STN-DBS). The electrical motor cortex stimulation can improve axial symptom of PD, which is difficult even with STN-DBS, and is less surgical invasiveness than deep brain stimulation can make the surgery safer for the patients with advanced age or sever brain atrophy *(Chap. 23*). The last contribution in the book deals with the rational arthroplasty surgery and multidisciplinary approaches for the patients with Parkinson's disease (*Chap. 24*).

We would like to thank all the people who supported the preparation of this book, who contributed to the book, and in particular also to all who made the book possible due to their positive evaluations of the proposals for this book.

Dr. Juliana Dushanova
Institute of Neurobiology,
Bulgarian Academy of Sciences,
Sofia,
Bulgaria

Part 1

Biomarkers for Preclinical Diagnosis of PD

1

Early Marker for the Diagnosis of Parkinson's Disease

Silvia Marino, Pietro Lanzafame, Silvia Guerrera,
Rosella Ciurleo and Placido Bramanti
IRCCS Centro Neurolesi "Bonino-Pulejo"
Messina
Italy

1. Introduction

Parkinson's disease (PD) is a progressive disorder with a relentless neuronal cell loss in several brain areas and nuclei notably in the substantia nigra (SN). The course of this neuronal loss is still unclear and may be highly variable in different PD patients and at different phases of the disease.
At present, no treatment has proven to influence this progressive course of the disease by protecting neurons or by postponing cell death.
One potential reason for the lack of neuroprotective effects of various agents, which have been highly effective in animal experiments, is the fact that the neurodegenerative process has already substantially proceeded when the diagnosis is established on the basis of widely accepted diagnostic criteria for PD: when the patients fulfill the clinical criteria of PD, 60–70% of neurons of the SN are degenerated and the striatal dopamine content is reduced by 80%, suggesting that the remaining neurons of the SN are also altered.
The "preclinical" phase may give the incorrect impression of patients exhibiting no clinical signs or symptoms of the incipient disease. Conversely, it is known that motor signs develop insidiously and minor signs of asymmetric hypokinesia may be detected years before the diagnosis of PD can be established. In addition, non-motor symptoms such as mood disorders, olfactorial, vegetative, sensory or neuropsychological signs may be noticed by the patients or physicians in advance of motor signs reflecting the dysfunction of dopaminergic or non-dopaminergic neurons.
Therefore, the term "early" or "prediagnostic" phase of PD would more appropriately characterize this stage of the disease. The clinical impression of autonomic, olfactorial and affective symptoms preceding motor signs of PD are in line with the findings demonstrating that neuronal alteration, with regard to Lewy body formation, occurs first in the dorsal vagal nucleus, the olfactory bulb, the raphe and coeruleus nuclei before entering the SN.
According to neuropathological findings, it is suggested that approximately 10% of subjects older than 60 years are in the "prediagnostic" phase of PD. These subjects exhibit the pathological hallmarks of PD, like Lewy bodies and neuronal loss at the SN, without showing the motor signs during life time that allow the diagnosis of PD. In only 10% of this group with so-called "incidental Lewy body disease", neuronal loss will proceed reaching the degree where motor symptoms are distinct enough to allow the diagnosis of PD.

It would be of great interest with respect to research and treatment to identify those subjects at risk i) to initiate neuroprotective treatment earlier, giving them a better base to act and ii) to define the causes of more rapid neuronal loss and disease progression in those patients with "incidental Lewy body disease" who will cross the threshold of critical neuronal loss at the SN and develop PD.
The duration of the early or prediagnostic period remains unknown. The duration of this phase of PD was estimated to last from a few years up to several decades before the first symptoms are noticed by the patients.
Several procedures have been proposed to identify subjects in early ("prediagnostic") stages of PD. In the following we present some instrumental approaches to identify patients in the early stages of PD.
One set of simple behavioural tasks that may provide insight into the neural control of response suppression uses saccadic eye movements to investigate and quantify motor impairments in PD. The study of ocular movements has been increasingly used to detect subtle pathological modifications, caused by a wide variety of neurological diseases.
A recent method, a new vision-based, nonintrusive, eye tracker, previously described in de novo PD patients (Marino et al., 2007), was proposed as a possible tool for supporting the diagnosis of PD in association with levodopa test, as an add-on to the Unified Parkinson Disease Rating Scale (UPDRS) score (Marino et al., 2010).
In addition, conventional MR Imaging (cMRI), as well as different advanced MRI techniques, including magnetic resonance spectroscopy (MRS), magnetization transfer imaging (MTI), diffusion-weighted and diffusion tensor imaging (DWI/DTI) are helpful to distinguish PD from atypical or secondary PD, especially in early stage of disease where a differentiation of these conditions is not easy.
Objective olfaction tests, such as olfactory-evocated potentials or functional magnetic resonance imaging, can be used to assess the severity of olfactory dysfunction, an early clinical feature of PD, its correlation with cerebral changes, and then the risk of developing PD in asymptomatic subjects.

2. Analysis of pursuit ocular movements in Parkinson's disease by using a video-based eye tracking system

Patients with PD characteristically have difficulty initiating movements (akinesia). When movements are initiated, they are of low velocity (bradykinesia) and reduced amplitude (hypokinesia). In addition, patients with PD are unable to sustain repetitive motor action. When they attempt to open or close the hand rapidly or tap the foot on the ground, the movement rapidly decreases in amplitude and slows in speed until it ceases. This disability is easily appreciated in the progressive micrographia of the handwriting of PD patients.
Research in the past 30 years has established that PD impairs control of eye movements. Voluntary saccades, such as self-paced, predictive and remembered saccades, are hypometric, multistep, of reduced velocity and of increased duration. Visually guided saccades are normal. Advanced PD is known to be associated with reduced ocular smooth pursuit gain (Bares et al., 2003; Lekwuwa et al., 1999). This has been explained in terms of advanced PD affecting other structures outside the basal ganglia.
A recent study (Marino et al., 2007) described a new eye movement measurement and analysis system which was developed for generating a set of visual stimuli paradigms and which is able to measure, analyze and record the resulting horizontal eye movements.

Oculomotor movements are controlled by many brain areas including the cerebral cortex, basal ganglia, brain stem and cerebellum. PD is a condition of degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in progressive basal ganglia dysfunction. Because important eye movement pathways travel through the basal ganglia, aspects of oculomotor movement control should be impaired by the disease progression. This study showed that deficit in Pursuit Ocular Movements (POM) also occurs in patients with non-advanced PD and is closely correlated with clinical stage and motor scores.
The authors used a vision-based non-intrusive eye tracker. The developed interface provides the patients a visual stimulation. This system was able to measure, analyze and record the resulting horizontal eye movements.
The subjects were seated at 60 cm from the scene monitor, in front of the camera, on a chair which could be raised or lowered so that the subject's eyes were at the same height as the PC monitor, when the visual stimulus was administered on. The subjects were asked to perform the test three times.

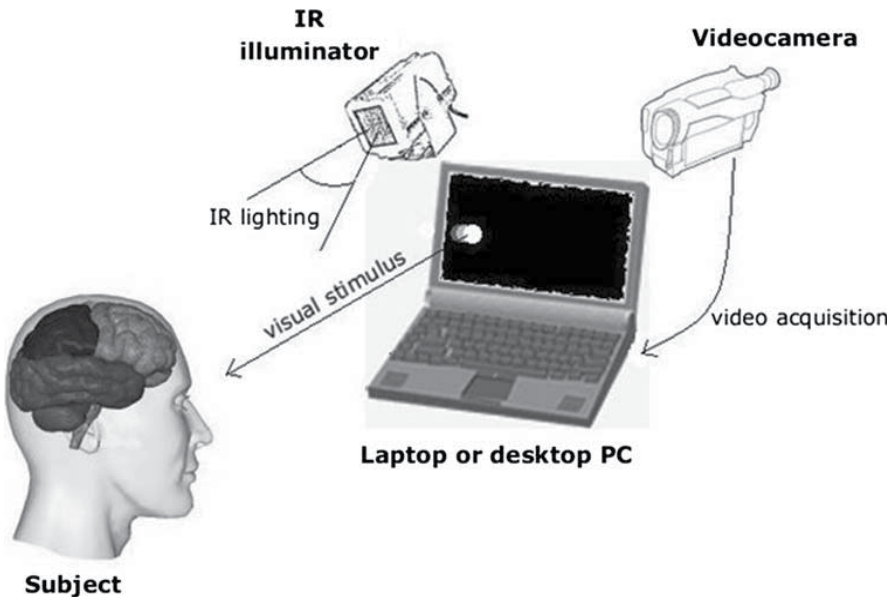


Fig. 1. Video-based eye-tracking functional scheme: subject looks at the screen (laptop or desktop PC) and all mechanical and electronic supports help to perform a real-time acquisition of eye movements.

The results of the study confirm that POM are clearly impaired in patients with de novo PD.
The same authors (Marino el al., 2010) studied the POM by using the same vision-based non-intrusive eye tracker, in patients with suspected PD, before and after L-Dopa administration.
All patients had a positive test demonstrated by the improvement of UPDRS motor subscore, after L-Dopa administration, and as a new finding, by the improvement of POM.
A plausible explanation is that the improvement of horizontal eye displacement gain was induced by the dopaminergic action of L-Dopa. Some newly diagnosed PD patients have been shown to improve POM after L-Dopa treatment and this suggested the possibility of dopaminergic control of ocular movements, particularly smooth pursuit and saccades.

The POM methodology could be considered as a not invasive, objective and repetitive method (and these conditions could be an advantage with respect to only UPDRS examination) to support the clinical evaluation.
This method could be considered as a possible tool for supporting the diagnosis of PD in association with levodopa test, as an add-on to the UPDRS score. These results showed that this vision-based eye tracker can be used as reliable indices of disease severity in early and suspected PD patients.

3. Diagnosis of Parkinson's disease by using MR techniques

PD in its early stages can easily be mistaken for any number of disorders. Indeed PD is most likely to be confused with various Atypical Parkinsonian Disorders (APDs) such as Progressive Supranuclear Palsy (PSP), Multiple-System Atrophy (MSA), especially the Parkinson variant of MSA (MSA-P), and Corticobasal Degeneration (CBD).
A differentiation of these clinical entities, each characterized by completely different natural histories, may be challenging, particularly in the early stages of the disease, where overlapping clinical signs lead to a high rate of misclassification. However, a differentiation between APDs and PD, that may make easier early diagnosis, is crucial for determining the prognosis and choosing a treatment strategy.
Magnetic Resonance Imaging (MRI) plays an important role in the differential diagnosis in PD. Conventional MRI (cMRI) and advanced MRI techniques, including proton magnetic resonance spectroscopy, diffusion-weighted and diffusion tensor imaging and magnetization transfer imaging, are helpful to distinguish PD from atypical or secondary PD.

3.1 Magnetic Resonance Spectroscopy

MRS is a non-invasive technique that can be used to measure the concentrations of different low-molecular weight chemicals. The technique is based on the same physical principles as MRI, i.e. the detection of energy exchanges between external magnetic fields and specific nuclei within atoms. MRS is the more modern version of Nuclear Magnetic Resonance which over the past five decades has evolved from a technique used in chemistry to determine the structure of molecules to a method with which to probe the metabolism of cells, tissues, intact animals and humans (Allen, 1990; Avison et al., 1986).
MRS has been demonstrated in vivo for different nuclei, including ^{1}H, ^{31}P, ^{13}C, ^{15}N, ^{19}F and ^{23}Na. While most of these nuclei are very difficult to detect, ^{1}H and ^{31}P are available in the human brain in significant concentration and have the appropriate physical configuration to be detected by MRS. For instance, ^{31}P-MRS has been the first to be applied to medicine in vivo, and can be used to evaluate brain energy metabolism by directly and non-invasively measuring of Adenosine Triphosphate (ATP), Phosphocreatine (PCr) or Inorganic Phosphate (Pi) concentrations. While ^{31}P-MRS was the first spectroscopic technique to be applied in vivo, the main nucleus studied today in neurospectroscopy is ^{1}H, which provides information on markers of neurons, myelin, energy metabolism and other metabolically active compounds.
^{1}H-MRS detects very small differences in the frequencies of proton resonances from comparatively large volumes (1 ml or more) of brain tissue. The frequency of the resonance is affected by its local chemical environment, while the amplitude reflects its concentration. As such, ^{1}H-MRS is able to provide a measurement of certain proton-containing chemical

markers. Proton spectroscopy presents the problem that metabolites at millimolar concentration must be detected in the presence of a background water signal that is present at about 100 molar. For this reason solvent-suppression techniques have been combined with localization schemes to produce spatially localized solvent-suppressed spectra. The two most commonly used localization methods are STEAM and PRESS. These methods can be implemented as single-voxel and multi-voxels methods. With the single voxel localization, the signal is acquired from a single brick-shaped volume of various sizes (minimum volume 2-3 cm^3). The multi-voxel or MR spectroscopic imaging (MRSI) or Chemical Shift Imaging (CSI) approach generates individual spectra from multiple voxels at the same time (minimum volume 0.5-1 cm^3). Single-voxel spectroscopy detects the signal from a single region during one measurement, whereas MRS imaging, using additional phase-encoding pulses, obtains the signal from multiple regions at the same time and provides the information of spatial distribution of major cerebral metabolites. The spatial information in MRI is done in 2-D for one or more slices and can generate low-resolution images for each metabolite by integration of the MR signals from each voxel (Ross & Bluml, 2001). The possibility to acquire the spectra from 2D multi-voxel allows to study the metabolite distribution of a large area of the brain with the advantage of identifying more anatomical and functional details. Most importantly, collecting data from many different adjacent regions simultaneously reduces the potential for systemic errors that can affect sequential measurements and thus results in more accurate repeated studies.

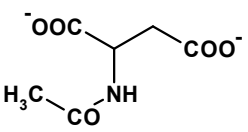
The metabolites detectable with ^{1}H-MRS include the prominent resonances of *N*-acetylaspartate (NAA), choline-containing compounds (Cho), creatine + phosphocreatine (Cr), myo-inositol (mI), lactate (Lac), and a variety of other resonances that might not be evident depending on type and quality of spectra as well as on the pathological condition (Figure 2) (Bonavita et al., 1999; Lin et al., 2005).

NAA, which resonates at 2.02 parts per million (ppm), represents the largest proton metabolic concentration in the human brain after water. Indeed the concentration of NAA reaches on the order of 10 µmol/g. NAA is widely interpreted as a neuronal marker and implicated in several neuronal processes, mitochondrial functioning and osmoregulation. NAA synthesis occurs in mitochondria and requires acetyl-CoA and L-aspartic acid as substrates. NAA has been proposed to serve as a mitochondrial shuttle of acetyl-CoA used for fatty acid synthesis. NAA undergoes dramatic increase during brain development and significant decrease during lesion progression in various neurodegenerative diseases, suggesting an important, unknown role in brain metabolism (Clark, 1998).

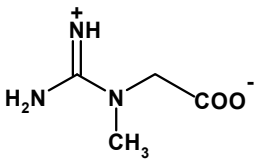
The Cho peak (3.2 ppm) represents a combination of several choline-containing compounds, including free Cho, phosphorylcholine and glycerophosphorylcholine, and to a small extent acetylcholine. Free Cho acts as a precursor to acetylcholine, while glycerophosphorylcholine is a product of breakdown of membrane phosphatidylcholine and acts as an osmoregulator.

The concentration of Cho is relatively low on the order of 0.5 to 1.5 µmol/g and can be altered in normal aging and many focal inflammatory diseases. The Cho peak is often viewed as a marker of membrane turnover or inflammation in ^{1}H MRS studies.

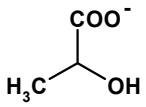
The concentration of total Cr is estimated on the order of 8 to 9 µmol/g and is approximately 20% higher in human gray matter than white matter. In ^{1}H-MRS, the resonance at 3.03 ppm represents total Cr and PCr supplies phosphate for conversion of ADP to ATP in creatine kinase reaction. Indeed these metabolites buffer the energy use and energy storage of cells. The level of total Cr mainly remains constant in many neuronal



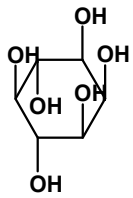
N-Acetylaspartate (NAA)



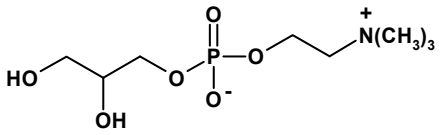
Creatine (Cre)

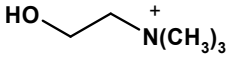


Lactate (Lac)



Myo-inositol (mI)





Choline - containing compounds (Cho)

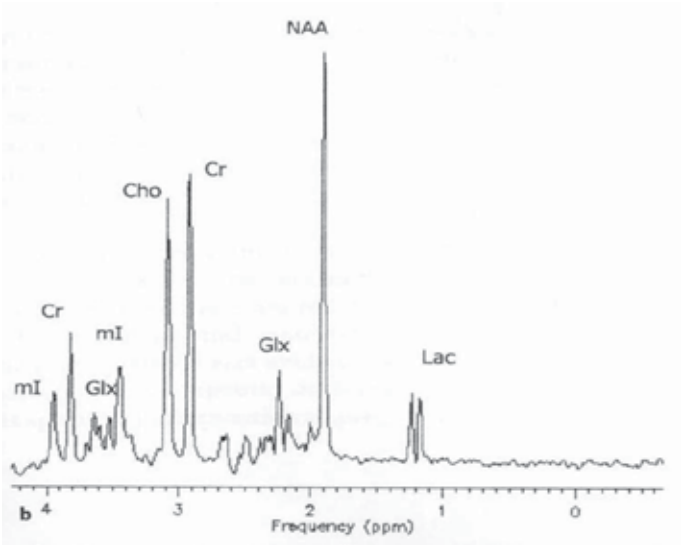


Fig. 2. Chemical structure of main cerebral metabolites detected by ^{1}H-MRS.

diseases. Thus, total Cr is often used as an internal reference (i.e., a denominator in metabolite signal ratio).

The mI (3.56 ppm) has been recognized as a cerebral osmolyte or an astrocyte marker due to its cellular specificity based on cell culture studies. mI is also been known as a breakdown product of myelin and precursor of inositol polyphosphate, an intracellular messenger. The concentration of mI is on the order of 5–10 µmol/g while one of its isomers, syllo-inositol, has substantially lower concentrations of on the order of less than 1 mol/g in the brain and remains relatively consistent in many diseases.

The Lac (1.3 ppm) is an end product of anaerobic glycolysis, thus increase in Lac concentrations often serves as an index of altered oxidative metabolism, i.e., in ischemia, hypoxia, and cancer. The concentration of Lac is on the order of about 1 µmol/g in normal

aerobic conditions. Increases of Lac in the brain are often accompanied by decreased intracellular pH and high-energy phosphates. The proposed role of Lac is a source of energy for neurons and the transport of Lac plays an essential role in the concept of metabolic coupling between neurons and glia.

The concentration changes of all metabolites detected by ^{1}H-MRS and ^{31}P-MRS could help to evaluate PD subjects in the "preclinical" stages, especially in early differential diagnosis.

^{1}H-MRS of striatal structures might differentiate PD from APDs by virtue of reduced NAA/Cr ratios in MSA but not PD. ^{1}H-MRS showed reduced NAA/Cr ratios in the lentiform nucleus in six of seven MSA-P cases, whereas normal levels of putaminal NAA were found in eight of nine PD subjects (Davie et al., 1995).

As compared to normal controls, in patients with PSP, CBD, and MSA, but not in those with PD, significant reduction of the NAA/Cr ratio in the frontal cortex was found (Abe et al., 2009). Patients with CBD showed significant reduction of the NAA/Cr ratio in the frontal cortex and putamen as compared to patients with PD and MSA. Patients with PSP showed a significant reduction of the NAA/Cr ratio in the putamen as compared with patients with PD and MSA. Patients with CBD showed clear asymmetry in the putamen as compared to controls and other patients (Abe et al., 2009). By application of ^{1}H-MRSI statistically significant difference in regional patterns of the NAA/Cr and NAA/Cho ratios between patients with PD and those with CBD and between patients with PD and those with PSP was found (Tedeschi et al., 1997).

Other ^{1}H-MRS examinations didn't show significant difference between the PD patients and the control subjects (Tedeschi et al., 1997), also in the striatum (Holshouser et al., 1995), in the putamen and globus pallidus (Federico et al., 1997), and in occipital lobe (Bowen et al., 1995). The NAA/Cho and NAA/Cr ratios were significantly reduced in the putamen and globus pallidus of MSA and the PSP patients, in which neuronal loss involves, compared with the control subjects (Federico et al., 1997). In another study Federico at al. showed that NAA/Cho peak ratio was significantly reduced in MSA and in PSP patients compared to PD patients and to control. Moreover the NAA/Cr peak ratio was significantly reduced in MSA, in PSP and in PD patients also compared to controls, but only in MSA compared to PD patients (Federico et al., 1999).

Normal ^{1}H-MRS data could suggest the clinical diagnosis of PD, whereas low striatal levels of NAA could suggest the diagnosis of MSA or PSP.

However, further MRS studies have shown reduced NAA/Cr and NAA/Cho ratios in the lentiform nucleus not only in APD, but also in PD (Clarke & Lowry, 2001; Firbank et al., 2002).

Technical factors such as MRS technique including different echo- time and relaxation-time, voxel sizes, field strength and pulse sequences used in the different studies, may be responsible for some of the variation of results seen in the published literature on ^{1}H-MRS for the differential diagnosis of neurodegenerative parkinsonism (Clarke & Lowry, 2001; Firbank et al., 2002). The development of ^{1}H-MRS at higher magnetic field strengths may lead ^{1}H-MRS to a more important role as imaging tool in the differential diagnosis of parkinsonian disorders.

^{1}H-MRS of the brain with high magnetic field at 3 Tesla has many advantages that, with respect to the well-established and technologically advanced 1.5 Tesla ^{1}H-MRS, include better signal to noise ratio (SNR) and increased spectral, spatial and temporal resolution,

allowing the acquisition of high quality, easily quantifiable spectra in acceptable imaging times (Di Costanzo et al., 2007).

The increase SNR associated with higher magnetic fields permits shorter imaging times for a given spatial resolution, higher resolution for a given imaging time or the combination of both.

The spectral resolution is linearly correlated with the field strength and is about twice at 3 Tesla as compared to 1.5 Tesla. Clinical 1.5 Tesla scanners equipped with ^{1}H-MRS packages allow the quantification of NAA, Cho, Cr and lactate at long echo-time, and further metabolites, such as mI and glutamate-glutamine (Gxl), at short echo-time. mI is a strongly coupled system and resonates at four chemical shift positions. At 1.5 Tesla, only the singlet component at 3.57 ppm is detected. However, at 3 Tesla this resonance is resolved into its components at 3.55 and 3.61 ppm. Therefore by increasing of spectral resolution and SNR, the quantification precision of mI is significantly better at 3 Tesla relative to 1.5 Tesla (Srinivasan et al., 2004).

Despite shorter T2 relaxation times and increased field inhomogeneity, the chemical shift doubling at 3 Tesla yields better spectral resolution. This is reflected by improved baseline separation of Cho and Cr, which are only 0.2 parts per million (ppm) apart, and by slightly better resolution of Glu/Gln region, between 2.05 and 2.5 ppm, at shorter TE.

Higher field strengths also lead to a flatter baseline that contributes to more reliable estimation of peak area and, hence, more precise quantification, in addition to a more accurate identification of each metabolite.

This has been shown by a recent study applying multiple regional single voxel ^{1}H-MRS including putamen, pontine basis and cerebral white matter at 3 Tesla in 24 patients with MSA compared to 11 PD patients and 18 controls. Significant NAA/Cr reductions have been shown in the pontine basis of both patients with MSA-C (cerebellar ataxia variant of MSA) and MSA-P, while putaminal NAA/Cr was only reduced in the patients with MSA-P. Eight of the 11 MSA-P patients compared to none of the PD and control group were classified correctly by combining individual NAA/Cr reductions in the pontine basis and in the putamen. These results suggest that combined assessment of NAA/Cr in the pontine basis and putamen may be effective in differentiating MSA-P from PD in terms of the high specificity of reduced NAA/Cr in the pontine basis or in the putamen in patients with MSA-P (Watanabe et al., 2004).

Moreover, in these studies, the metabolite concentrations were expressed in terms of semiquantitative ratios such as NAA/Cr, NAA/Cho, Cho/Cr and mI/Cr. In relative quantification, one of the metabolite peaks measured is used as the concentration standard and serves as the denominator of the peak ratios. As a result, the total number of quantifiable metabolites is decreased by one. Furthermore, alterations in the peak ratio do not necessarily reflect a change in the concentration of the numerator. The alteration may be caused by change in the concentration of the numerator, the denominator, or both or may be due to changes in relaxation behavior. The assumption that the concentration of certain reference metabolites (e.g. total creatine, choline) remains constant may be incorrect under normal conditions, as well as in many pathologic states. It is therefore advisable to obtain concentration expressed in standard units (such as millimoles per kilogram wet weight) by applying absolute quantification.

Combined ^{31}P- and ^{1}H-MRSI at 3 Tesla measuring absolute adenosine diphophosphate (ADP), ATP, Cr and PCr concentrations in two well-defined cohorts of patients with early and advanced PD has been performed to evaluate brain energy metabolism (Hattingen et

al., 2009). In the putamen and midbrain of both PD groups compared to control was found a bilateral reduction of high-energy phosphates such as ATP and PCr as final acceptors of energy from mitochondrial oxidative phosphorylation. In contrast, low-energy metabolites such as ADP and Pi were within normal ranges. Patients with early Parkinson's Disease, with clearly lateralized motor symptoms, exhibited a significant reduction of putamen high-energy phosphates in the less affected hemisphere with a less pronounced dopaminergic cell loss. Therefore, mitochondrial dysfunction is a rather early occurring and subsequently persistent event in the pathophysiology of dopaminergic degeneration in PD. These data strongly support the hypothesis that mitochondrial dysfunction is involved early in pathogenesis of PD and it may be used as early marker for this pathology.

In vivo MRS is increasingly utilized for the study of neurochemistry and cerebral energy metabolism in PD. Particularly, the recent technical advances of in vivo MRS including the availability of higher magnetic fields permitting improved spectral and spatial resolution, the development of a reliable method for absolute metabolite quantification, the development of various spectroscopic methods to enhance metabolite signal identification, and the application of combined ^{31}P- and ^{1}H-MRS can be use to examine the changes in neurochemical profile non–invasively and to achieve a differential diagnosis of PD versus other forms of parkinsonism, especially in early stages of disease when signs and symptoms of different forms of parkinsonism have greater overlap. However, several multicentre trials using a larger sample of patients, absolute quantification of tissue metabolite concentrations and a standardized technique are required to fully determine the place of MRS in early clinical differential diagnosis.

3.2 Conventional Magnetic Resonance

In the early disease stages the clinical separation of atypical parkinsonism disorders (APD)s from PD carries a high rate of misdiagnosis. An early differentiation between APD and PD, each characterized by completely different natural histories, is crucial for determining the prognosis and choosing a treatment strategy.

The principles of MR imaging are based on the ubiquitous presence of hydrogen in body tissues and the spin of the hydrogen atom proton, which induces a small magnetic field. In general, T2- weighted sequences are sensitive to changes in tissue properties, including tissue damage, due to changes of the transverse magnetization or T2 decay. Neurodegenerative processes characterized by cell loss, increased age-related deposition of iron or other paramagnetic substances, and by astroglial reaction and microglial proliferation may lead to signal changes in affected brain areas, like the basal ganglia or infratentorial structures, in neurodegenerative parkinsonism (Duguid et al., 1986; Gupta et al., 2008; Hirsch et al., 2007; Wilms et al., 2007).

Because cMRI is believed to be usually normal in patients with PD, while it frequently shows characteristic abnormalities in patients with APD, cMRI images takes a major part in excluding underlying pathologies such as vascular lesions, multiple sclerosis, brain tumors, normal pressure hydrocephalus, bilateral striopallidodentate calcinosis, and other potential, but rare, causes of symptomatic parkinsonism such as Wilson disease, manganese-induced parkinsonism, or different subtypes of neurodegeneration associated with brain iron accumulation.

At 1,5 T, patients with advanced PD, and sometimes those with APD, may show distinct abnormalities of the substantia nigra, including signal increase on T2-weighted MR images, smudging of the hypointensity in the substantia nigra towards the red nucleus or signal loss

when using inversion recovery MRI (Brooks, 2000; Rutledge et al., 1987; Savoiardo et al., 1994).
Biochemical studies have reported increased iron content in the substantia nigra pars compacta (SNc) in PD, with changes most marked in severe disease, suggesting that measurement of nigral iron content may provide an indication of the pathologic severity of the disease (Youdim et al.,1990). Iron accumulates in the brain as a function of age, primarily in the form of ferritin and particularly in oligodendrocytes, but also in neurons and microglia. The adult brain has a very high iron content, particularly in the basal ganglia. Brain iron concentration is highest in the globus pallidus, substantia nigra, red nucleus, caudate, and putamen. Abnormally elevated iron levels are evident in various neurodegenerative disorders, including PD where there is evidence of increased iron in the substantia nigra (Dexter et al.,1989; Sofic et al.,1988). Signal changes on T2-weighted images in the basal ganglia as well as in infratentorial structures have been reported for all APDs at 1.5 T, where they have been used as a differentiating criterion from PD. Furthermore, estimation of transverse relaxation in patients with PD, using a 1.5 Tesla whole body imaging system, showed shortened T2 values in substantia nigra, caudate and putamen in PD patients as compared to healthy controls (Antinoni et al., 1993). These data do suggest a potential utility of these measurements as a biomarker of disease progression.

3.3 Magnetization Transfer Imaging

Standard MR imaging detects signal only from hydrogen nuclei (protons) that are ''mobile'' (contained within a liquid); if a hydrogen atom is part of a molecule that is large and cannot move about freely, the signal from that hydrogen atom decays too quickly to be seen using a clinical MR imaging scanner. Such protons are found in large molecules (macromolecules), such as those of cell membranes and myelin. The mobile protons are in constant motion, however, and come into regular and intimate contact with the macromolecular protons, and the spin state (the proton magnetization state, which is measured with MR imaging) of the mobile protons can exchange with that of the macromolecular protons. This exchange of magnetization forms the basis of magnetization transfer imaging (Horsfield, 2005). Magnetization transfer is a physical phenomenon that results from interactions and exchanges between magnetized protons in water that are unrestricted in their molecular motion and those that are restricted because of their association with macromolecules. The latter have a much shorter T2 relaxation time and broader resonance, which makes it possible to selectively saturate their magnetization with an appropriate off-resonance pulse. The acquisition of two images, one obtained with the magnetization transfer saturation pulse turned on and the other with it turned off, can be used to generate a magnetization transfer ratio (MTR) image in which the signal intensity of each voxel is determined by the percent magnetization transfer in that voxel.
A MTR image is calculated from a pair of images acquired in an identical way, except that one has extra off-resonance RF pulses applied, which saturates the macromolecular magnetization pool. The MTR is calculated for every corresponding pair of pixels in the two images. If the intensity of the pixel in the image without saturation pulses is M0 and the corresponding intensity in the image with saturation pulses is Ms, the MTR is as follows:

$$MTR = [(M0 - Ms)/M0] * 100\%$$

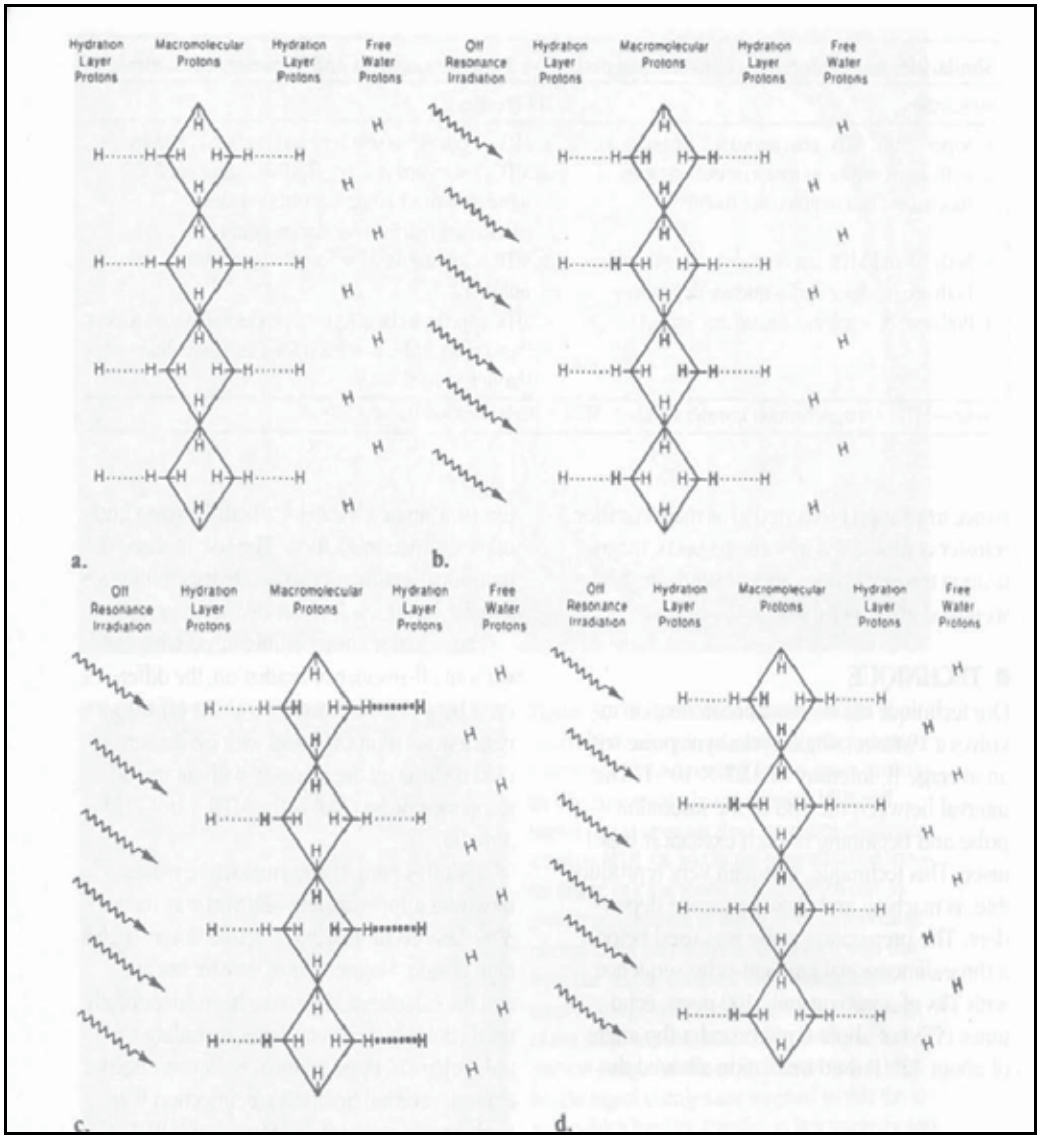


Fig. 3. Diagrams illustrate magnetization transfer, that is, the exchange of longitudinal magnetization between restricted protons associated with rigid macromolecules and free water protons. (a)Diagram shows macromolecular protons (H), including hydration layer protons and free water protons. (b) Off-resonance irradiation (arrows) saturates the immobile macromolecular protons (unsatured protons are designated H, while satured are designated H). (c) Saturation is transferred to hydration layer protons (…H). (d) Satured protons diffuse into the free water proton pool and decrease the signal from this pool.

Misregistration can occur if the subject moves between the two scans, but the M0 and Ms images must be in register; otherwise, artifacts appear at the edges of features in the calculated MTR image, with false MTR values. It is best to acquire the two images in an interleaved way (Barker et al., 1996; Inglese at al., 2001) although it is possible to register

them after acquisition. Two forms of data analysis have been used extensively for MTR images: region of interest (ROI) and histogram analysis. ROI analysis may be useful for elucidating the degree of tissue damage within individual lesions seen on T2-weighted scans or within anatomic regions associated with particular symptoms. ROI analysis, however, can be subject to operator bias, because the placement of regions is normally done manually. This could be overcome by first registering scans to an anatomic template and using ROIs defined on the template image. With MTR histogram analysis, a histogram of pixel MTR values is formed from the whole of the brain parenchyma; thus, focal damage and more widespread diffuse tissue damage are reflected in changes to the shape of the histogram, with a general shift toward lower MTR values as the density of macromolecules is reduced with demyelination or axonal loss. Extraction of the brain parenchyma, using the same procedures that are used in atrophy measurements, is a necessary preprocessing step. After normalization (to remove any effect of the absolute brain size), the MTR histogram can be characterized by several simple statistics, such as the histogram peak position, the peak height, and the average MTR. The employment of off-resonance irradiation was first proposed by Wolff and Balaban (Wolff & Balaban, 1989), who found that use of an off-resonance radio-frequency preparation pulse could generate excellent tissue contrast in images of rabbit kidney, and they referred to the technique as "magnetization transfer contrast." The initial magnetization transfer occurs between the macro-molecular protons and the transiently hound hydration layer protons. The efficiency of this interaction is directly related to the number of irradiation sites (hydrogen bonds) and their mobility. The utilization of magnetization transfer was extended to clinical imaging, including its use with gradient-echo imaging and MR angiography (Wolff et al.,1991; Pike et al., 1992). A decrease in the MTR, which reflects a reduction in the exchange of magnetization of protons that are tumbling freely and those that are bound to macromolecules, is evidence of demyelination in cerebral white matter. MTR imaging is sensitive to both microscopic and macroscopic pathology and provides quantitative data on the extent of myelin loss in MS.

By using MTI, abnormalities of the basal ganglia and SN have been reported in patients with PD, MSA and PSP. One study (Eckert et al., 2004) investigated the potential of MT imaging in the differential diagnosis of neurodegenerative parkinsonism, including 37 patients with different parkinsonian syndromes and 20 age-matched controls. The main finding in this study was a change in the MTR in the globus pallidus, putamen, caudate nucleus, SN, and white matter in PD, MSA, and PSP patients, matching the pathologic features of the underlying disorder. MTR were significantly reduced in the putamen in MSA patients compared with PD patients and healthy controls, as well as in the SN in patients with PSP, MSA, and PD. Another study (Yonca et al., 2007) determinated the role of MTR in the early period of 33 patients with PD, comparing the findings with those in 30 normal healthy volunteers. Signal intensity measurements were obtained from 15 anatomic regions: SNc, substantia nigra pars reticulate (SNPR), red nucleus, dentate nucleus, cerebellum, pons, globus pallidus, putamen, caudate nucleus, thalamus, internal capsule posterior horn, forceps major, forceps minor, genu, and splenium of corpus callosum. Results showed a significant decrease of MTR in the SNc, SNPR, red nucleus, and pons compared with normal healthy volunteers. No significant decrease in MTR were found at supratentorial paraventricular white matter and cerebellum, which may be attributed the duration of the disease.

Perhaps in the initial stages of PD, supratentorial paraventricular white matter is not influenced by the disease. The decrease of MTR at SNc, SNPR, red nucleus, and pons in PD patients can be attributed to neurodegeneration (Tambasco et al., 2003)).

These studies show that MTR analysis may be a useful technique for PD diagnosis and decrease in MTR probably begins previously than the clinical onset of the disease.

3.4 Diffusion-Weighted Imaging

DWI imaging visualizes the random movement of water molecules in the tissue by applying diffusion-sensitizing gradients to assess changes in diffusion magnitude and orientation of water molecules in tissue. Quantification of the diffusivity is achieved by applying diffusion-sensitizing gradients of different degrees in 3 orthogonal directions and calculating the apparent diffusion coefficient (ADC) for each direction. The ADC is very dependent on the direction of diffusion encoding.

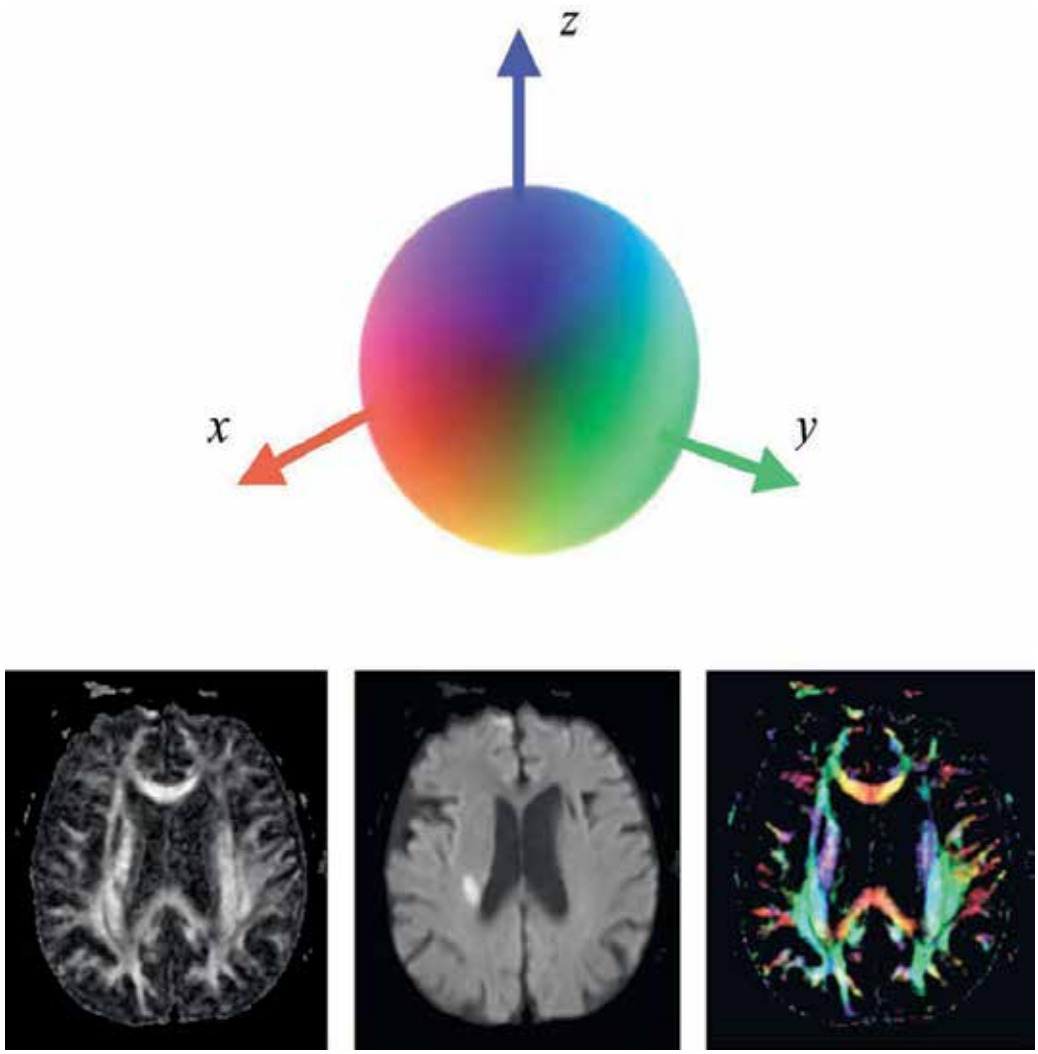


Fig. 4. Image-based visualization of diffusion tensor data. Top: Sphere representing directional color encoding. Second row: 2D images of image based visualization (from left: FA image, mean diffusivity image, and color-encoded image).

The random translational motion (diffusion) of water molecules in tissue is restricted by the highly organized architecture of fiber tracts in the central nervous system. Neuronal loss and gliosis disrupt this architecture, resulting in an increase of diffusivity and ADC. The complex neuronal architecture with its organization in fiber bundles that are surrounded by dense myelin sheaths leads also to a distinct anisotropy of water diffusion, which is facilitated along the direction of fiber tracts and restricted perpendicular to the fibers.
The degree of anisotropy can be quantified by applying diffusion-sensitizing gradients in at least 6 directions, which permits calculation of fractional anisotropy (FA). Decreased FA values represent tissue degeneration due to normal aging or due to pathologic reasons such as neurodegeneration. Both diffusivity and FA can be combined to form the so-called diffusion tensor, which indicates direction and extent of diffusivity with the help of a vector (Hagmann et al., 2006; Le Bihan, 2003; Schocke et al., 2004). The central nervous system (CNS) is highly organized in numerous tracts of myelinated fibre bundles, whereby the movement of the water molecules is restricted perpendicular to these fibre bundles. The resulting anisotropic diffusion is quantified by the FA, which is determined by diffusion-sensitised gradients in at least six directions. Both the diffusivity and the FA form the diffusion tensor (Le Bihan, 2003).
Widespread cerebral changes are observed in advanced stages of PD, suggesting that PD is a multisystem disorder.
Recently, several studies pointed out the capability of the histogram analysis of the apparent diffusion coefficient computed from diffusion-weighted images and of the mean diffusivity and FA computed from DTI to reveal brain-tissue damage in early clinical stages of neurodegenerative diseases. A recent study including 27 patients with de novo drug-naïve PD hypothesized that global measurements of brain volume and structure, such those possible with SIENAX software (part of FSL 4.0 http://www.fmrib.ox.ac.uk/fsl/) and histogram analysis of DTI could reveal subtle tissue changes in the early clinical phase of PD (Tessa et al., 2008). Accordingly, a group of patients with drug-naive de novo PD and a group of 16 healthy controls, were investigated with SIENAX and DTI. Results showed no significant differences for total brain, GM, and WM volumes and histogram-derived mean diffusivity metrics between controls and the whole group of patients with PD or any subgroup of patients with PD. As compared with controls, patients with PD as a whole and patients with the akinetic-rigid type showed an increase of the twenty-fifth percentile of the FA histogram. In patients with the akinetic-rigid type, there also was a trend toward an increase of the mean and fiftieth and seventy-fifth percentiles, and a reduction of the skewness of the FA histogram. This finding is consistent with the hypothesis that subtle GM loss is present in patients with PD since the early clinical phases and that this feature is more pronounced in patients with akinetic-rigid type. Another recent study including only patients with newly diagnosed PD used high-resolution DTI at 3 Tesla to evaluate rostral, middle, and caudal ROIs within the SN on a single slice of the midbrain and this study found that PD patients could be completely separated from the control group based on reduced FA values in the caudal ROI of the SN, such that further confirmatory studies seem to warrant. By using statistical parametric mapping analysis of DT imaging, changes in FA were found in the frontal lobes, including the supplementary motor area, the presupplementary motor area, and the cingulum in non demented PD patients relative to controls, whereas VBM analysis in the same patients revealed no volume loss (Karagulle

Kendi et al., 2008). These results confirm that the neurodegenerative process extends beyond the basal ganglia in PD (Tessa et al., 2008).
Olfactory impairment, which is common in PD and often predates clinical diagnosis, may be a useful biomarker for early PD. One study (Rolheiser et al., 2011) compared newly diagnosed PD patients with a matched control group using both olfactory testing and diffusion tensor imaging of the substantia nigra and anterior olfactory structures. Fourteen PD patients with stage 1-2 of Hoehn & Yahr were matched to a control group by age and sex. All subjects completed the University of Pennsylvania Smell Identification Test, as well as a series of MRI scans designed to examine diffusion characteristics of the olfactory tract and the substantia nigra. Olfactory testing revealed significant impairment in the patient group. Diffusion tensor imaging revealed significant group differences in both the substantia nigra and anterior olfactory region, with fractional anisotropy of the olfactory region clearly distinguishing the Parkinson's subjects from controls. This study has suggested that there may be value in combining behavioral (olfaction) and MRI testing to identify early Parkinson's disease (Rolheiser et al., 2011; Fulton & Barret, 2008).
Concluding DWI/DTI imaging especially bears several advantages. DWI/DTI imaging may detect diffusion abnormalities in the basal ganglia and infratentorial structures in patients with PD at an early stage of disease. Furthermore, DWI/DTI imaging sequences are widely available on whole body MR scanners and can be acquired within a few minutes.

3.5 Functional Magnetic Resonance Imaging

fMRI is based on the increase in blood flow to the local vasculature that accompanies neural activity in the brain. This results in a corresponding local reduction in deoxyhemoglobin because the increase in blood flow occurs without an increase of similar magnitude in oxygen extraction (Roy & Sherrington, 1890; Fox & Raichle, 1985). Since deoxyhemoglobin is paramagnetic, it alters the T2 weighted magnetic resonance image signal (Ogawa et al, 1990). Thus, deoxyhemoglobin is sometimes referred to as an endogenous contrast enhancing agent, and serves as the source of the signal for fMRI. Using an appropriate imaging sequence, human cortical functions can be observed without the use of exogenous contrast enhancing agents on a clinical strength (1.5 T) scanner (Bandettini et al., 1992, 1993; Kwong, et al, 1992; and Turner, et al, 1993; Schneider et al, 1993). Functional activity of the brain determined from the magnetic resonance signal has confirmed known anatomically distinct processing areas in the visual cortex (Belliveau, et al, 1991; Ogawa, et al, 1992; Schneider, et al, 1993), the motor cortex, and Broca's area of speech and language-related activities (Hinke et al., 1993; Kim et al., 1995). Further, a rapidly emerging body of literature documents corresponding findings between fMRI and conventional electrophysiological techniques to localize specific functions of the human brain (Atlas et al., 1996; Puce, et al, 1995; Burgess, 1995; Detre, et al, 1995; George, et al, 1995; Ives, et al, 1993). Consequently, the number of medical and research centers with fMRI capabilities and investigational programs continues to escalate.
The main advantages to fMRI as a technique to image brain activity related to a specific task or sensory process include:

- the signal does not require injections of radioactive isotopes
- the total scan time required can be very short
- the in-plane resolution of the functional image is generally about 1.5 x 1.5 mm although resolutions less than 1 mm are possible.

The function or dysfunction of the several cortical regions involved in many disease, like PD, can be investigated in vivo by means of functional imaging techniques such as fMRI.

4. Olfactory dysfunction as a early diagnostic marker for Parkinson's Disease

Olfactory dysfunction is a frequent non-motor symptom in PD and may be considered as an early clinical feature of the disease preceding motor symptoms by years (Ansari & Johnson, 1975). More than 96% of patients with PD present with olfactory dysfunction, compared with an established olfactory loss of at least 25% in the normal population over 52 years of age (Haehner et al., 2009). The majority of PD patients are functionally anosmic or severely hyposmic. Several studies have demonstrated an absence of correlation between olfactory loss and both duration of disease (Doty et al., 1988; Hawkes et al., 1997) and the clinical severity of PD (Ramaker et al., 2002), while other studies have found a correlation between the severity of PD and certain measures of olfactory function, such as latencies of olfactory event-related potentials (OERPs) (Hummel, 1999) and results from an odor discrimination task (Tissingh et al., 2001).

The cause of hyposmia in PD is not yet fully understood. It has been proposed that the develop of inclusion bodies, starting from the medulla oblongata and the anterior olfactory nucleus before the involvement of other central nervous structures, constitutes the reason of olfactory impairment before the motor symptoms appearance (Braak et al., 2003).

Moreover olfactory loss in PD is not a primary consequence of damage to the olfactory epithelium but rather result from distinct CNS abnormalities (Hummel et al., 2010). Studies based on biopsies from the olfactory epithelium did not reveal specific changes in the nasal mucosa of PD patients compared to patients who were hyposmic for other reasons (rhinitis, smoking or toxic agents). With regard to volumetrics of the olfactory bulb (OB) results indicated that there is little or no difference between PD patients with anosmia/hyposmia and healthy normosmic controls in terms of OB volume (Huisman et al., 2004; Hummel et al., 2010; Müller et al., 2005). Support for these results has come from a study that found an increase of (inhibitory) dopaminergic neurons in the OB in PD patients (Huisman et al., 2004). These findings have been interpreted within the context of a possible compensatory mechanism in response to the loss of dopaminergic neurons in the basal ganglia.

While cardinal motor symptoms in PD are closely related to a severe loss of dopaminergic cells in the nigro-striatal pathway, early clinical features such as olfactory impairment are more likely to be associated with extranigral pathology. Indeed atrophy in olfactory regions of the limbic and paralimbic cortex in early PD patients was found (Wattendorf et al., 2009). Moreover fMRI in PD patients indicated altered neuronal activity in the amygdaloid complex and hippocampal formation during olfactory stimulation (Takeda et al., 2010; Welge-Lüssen et al., 2009; Westermann et al., 2008). In addition, neuronal activity in components of cortico-striatal loops appears to be up-regulated indicating compensatory processes involving the dopaminergic system (Westermann et al., 2008).

Changes in olfactory function can also be observed using electrophysiological techniques such as recording OERPs (Kobal & Pattig, 1978). OERPs are the result of the sequential activation of numerous brain areas, starting with amygdala and regions of medial temporal lobe followed by the mid-orbito-frontal cortex and insular cortex, along with regions of the temporal lobe (Kettenmann et al., 1997). In PD patients OERPs are typically strongly delayed or even absent (Hawkes et al., 1999).

In a study combining fMRI and OERPs analysis in patients with PD, non-detectable OERPs patients exhibited reduced activity in the anterior cingulate gyrus and portions of the left striatum, while detectable ERP patients exhibited higher activation, especially in the amygdala, parahippocampal cortex, inferior frontal gyrus, insula, cingulate gyrus, striatum, and inferior temporal gyrus. The relationship between the expression of olfactory ERPs and cortical activation patterns seen during olfactory stimulation in fMRI in PD patients supports the idea that OERPs are a sensitive marker of neurodegeneration in olfactory regions, independent of the typically observed nigro-striatal degeneration in PD (Welge-Lüssen et al., 2009).

Olfactory dysfunction is more common in PD compared to atypical parkinsonian syndromes like PSP or MSA (Doty, 1991, 1993; Wenning et al., 1995). In a study including 37 patients with PD (Hoehn and Yahr I to IV) and 13 patients with MSA, CBD or PSP, 86 % of PD patients showed diminished sense of smell, or severe hyposmia, and 14 % were found to have moderate hyposmia, whereas 70 % of the patients with atypical parkinsonian syndromes exhibited moderate to mild hyposmia and 30 % normosmia (Muller et al., 2002).

Olfactory testing may be an additive, helpful and inexpensive diagnostic instrument to support the discrimination of PD from healthy subjects and atypical parkinsonian syndromes, before onset of motor symptoms.

For the clinical assessment of olfactory function, several validated psychophysical tests exist. The best-validated olfactory tests include the University of Pennsylvania Smell Identification Test, the Connecticut Chemosensory Clinical Research Center Test and the Sniffin' Sticks Test (Cain et al., 1988; Doty et al., 1984; Hummel, 1997, 2007; Kobal et al., 2000). The Sniffin' Sticks is based on pen-like odor dispensing devices. It consists of three tests namely for odor threshold, discrimination and identification, the sum of which is defined as "TDI score". This score can give an indication of patient's olfactory performance (normosmia: TDI≥30.5, hyposmia: TDI≤30.5, functional anosmia: TDI≤16.5).

A useful help for the clinical diagnosis of olfactory deficits is represented by system using human electro-physiological methods such as OERPs that requests an adequate methods to produce a selective and controlled stimulation of the olfactory system.

Based on the principles of air-dilution olfactometry, Kobal and Platting introduced a chemosensory stimulation with stimuli having a rectangular shape with rapid onset, precisely controlled in terms of timing, duration, intensity, not simultaneously activating other sensory systems (Kobal & Platting, 1978). This can be achieved by the olfactometer which is a complex instrument for creation of well defined, reproducible smell or pain stimuli in the nose without tactile or thermal stimulation.

In conclusion the detection of early olfactory dysfunction, less frequent in other form of parkinsonism, can be used to assess risk for developing PD in asymptomatic subjects.

5. Conclusions

The defining features of PD are characterized by their insidious onset and inexorable but variable progression. Reliable and well validated early markers for PD to identify individuals "at risk" before motor and non motor symptoms, accurately diagnose individuals at the threshold of clinical PD, and monitor PD progression throughout its course would dramatically improve patient care and accelerate research into both PD cause and therapeutics. During the past two decades, much progress has been made in identifying and assessing PD markers, but as yet, no fully validated marker for PD is available.

Nonetheless, there is increasing evidence that POM evaluation and advanced in vivo brain imaging will provide critical clues to assist in the early diagnosis and medical management of PD patients.
These methods are broadly defined as characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.
The lack of success of recent disease-modifying therapeutic trials coupled with the huge expense of other methods, such as the nuclear medicine, has highlighted the need for such an ambitious approach to identify and validate early markers of PD progression for future clinical studies of disease-modifying drugs.

6. References

Abe, K.; Terakawa, H.; Takanashi, M.; Watanable, Y.; Tanaka, H. et al. Proton magnetic resonance spectroscopy of patients with parkinsonism. *Brain Research Bulletin,* Vol.52, No.6, (August 2000), pp. 589-595, ISSN 0361-9230

Allen, P.S. In vivo nuclear-magnetic-resonance spectroscopy applied to medicine. *Canadian Association of Radiologists Journal,* Vol.41, No.1, (February 1990), pp. 39-44, ISSN 0008-2902

Ansari, K.A. & Johnson, A. Olfactory function in patients with Parkinson's disease. *Journal of Chronic Diseases,* Vol.28, No.9, (October 1975), pp. 493-497, ISSN 0021-9681

Atlas, S.W.; Howard, II R.S.; Maldijian, J.; Alsop, D.; Detre, J.A. et al. Functional magnetic resonance imaging of regional brain activity in patients with intracerebral gliomas: findings and implications for clinical management. *Neurosurgery*, Vol.38, No2, (February 1996), pp. 329-338, ISSN 0148-396X

Avison, M.J.; Hetherington, H.P. & Shulman R.G. Application of NMR to studies of tissue metabolism. *Annual Review of Biophysics and Biophysical Chemistry*, Vol.15, (June 1986), pp. 377-402, ISSN 0883-9182

Bandettini, P.A.; Jesmanowicz, A.; Wong, E.C. & Hyde, J.S. Processing strategies for time-course data sets in functional MRI of the human brain. *Magnetic Resonance in Medicine*, Vol.30, No2, (August 1993), pp. 161-173, ISSN 07403194

Bares, M.; Bràzdil, M.; Kanovsky, P.; Jurak, P.; Daniel, P.; et al. The effect of apomorphine administration on smooth pursit ocular movements in early Parkinsonian patients. *Parkinsonism & Related Disorders*, Vol. 9, No.3, (January 2003), pp. 139–144, ISSN 1353-8020

Barker, G.J.; Tofts, P.S. & Gass, A. An interleaved sequence for accurate and reproducible clinical measurement of magnetization transfer ratio. *Magnetic Resonance Imaging,* Vol.14, No.4, (1996), pp. 403-411, ISSN 0730-725X

Bonavita, S.; Di Salle, F. & Tedeschi, G. Proton MRS in neurological disorders. *European Journal of Radiology,* Vol.30, No.2, (May 1999), pp. 125-131, ISSN 0720-048X

Bowen, B.C.; Block, R.E.; Sanchez-Ramos, J.; Pattany, P.M.; Lampman, D.A. et al. Proton MR Spectroscopy of the Brain in 14 Patients with Parkinson Disease. *American Journal of Neuroradiology*, Vol.16, No.1, (January 1995), pp. 61-68, ISSN 0195-6108

Braak, H.; Del Tredici, K.; Rüb, U.; De Vos, R.A.I.; Jansen Steur, E.N.H. et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging,* Vol.24, No.2, (April 2003), pp. 197-211, ISSN 0197-4580

Brooks, D.J. Morphological and functional imaging studies on the diagnosis and progression of Parkinson's disease. *Journal of Neurololy,* Vol. 247, No2, (April 2000), pp. 11-18, ISSN 0340-5354

Cain, W.S.; Gent, J.F.; Goodspeed, R.B. & Leonard, G. Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center (CCCRC). *Laryngoscope*, Vol.98, No.1, (January 1988), pp. 83-88, ISSN 1531-4995

Clark, J.B. N-acetylaspartate: a marker for neuronal loss or mitochondrial dysfunction. *Developmental Neuroscience,* Vol.20, No.4-5, (July-October 1998), pp. 271-276, ISSN 0378-5866

Clarke, C.E. & Lowry, M. Systematic review of proton magnetic resonance spectroscopy of the striatum in parkinsonian syndromes. *European Journal of Neurology,* Vol.8, No.6, (November 2001), pp. 573-577, ISSN 1351-5101

Davie, C.A.; Wenning, G.K.; Barker, G.J.; Tofts, P.S.; Kendall, B.E. et al. Differentiation of multiple system atrophy from idiopathic Parkinson's disease using proton magnetic resonance spectroscopy. *Annals of Neurology,* Vol.37, No.2, (February 1995), pp. 204-210, ISSN 0364-5134

Dexter. D.T.; Wells, F.R.; Lees, A.J.; Agid, F.; Agid, Y. et al. Increased nigral iron content and alterations in other metal ions occurring in brain in Parkinson's disease. *Journal of Neurochemistry,* Vol.52, No6, (June 1989), pp. 1830-6, ISSN 0022-3042

Di Costanzo, A.; Trojsi, F.; Tosetti, M.; Schirmer, T.; Lechner, S.M. et al. Proton MR spectroscopy of the brain at 3T: an update. *European Radiology*, Vol.17, No.7, (July 2007), pp. 1651-1662, ISSN 0938-7994

Doty, R.L.; Deems, D. & Steller, S. Olfactory dysfunction in Parkinson's disease: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology,* Vol.38, No.8, (August 1988), pp. 1237-1244, ISSN 0028-3878

Doty, R.L.; Golbe, L.I.; McKeown, D.A.; Stern, M.B.; Lehrach, C.M. et al. Olfactory testing differentiates between progressive supranuclear palsy and idiopathic Parkinson's disease. *Neurology*, Vol.43, No.5, (May 1993), pp. 962-965, ISSN 0028-3878

Doty, R.L.; Perl, D.P.; Steele, J.C.; Chen; K.M.; Pierce, J.D. Jr. et al. Olfactory dysfunction in three neurodegenerative diseases. *Geriatrics,* Vol.46, No.1, (August 1991), pp. 47-51, ISSN 0016-867X

Doty, R.L.; Shaman, P.; Kimmelmann, C.P. & Dann, M.S. University of Pennsylvania Smell identification test: a rapid quantitative olfactory function test for the clinic. *Laryngoscope*, Vol.94, No.2, (February 1984), pp. 176-178, ISSN 1531-4995

Duguid, JR.; De La, P.R. & DeGroot, J. Magnetic resonance imaging of the midbrain in Parkinson's disease. *Annals of Neurology,* Vol.20, No.6, (December 1986), pp. 744-747, ISSN 0364-5134

Eckert, T.; Sailer, M.; Kaufmann, J.; Schrader, C.; Peschel, T. et al. Differentiation of idiopathic Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, and healthy controls using magnetization transfer imaging. *Neuroimage*, Vol.21, No.1, (January 2004), pp. 229-235, ISSN 1053-8119

Edelman, R.R.; Ahn, S.S.; Chien, D.; Li, W.; Goldmann, A. et al. Improved time-of-flight MR angiography of the brain with magnetization transfer contrast. *Radiology*, Vol.184, No.2, (August 1992), pp. 395-399, ISSN 0033-8419

Federico, F.; Simone, I.L.; Lucivero, V.; Iliceto, G.; De Mari, M. et al. Proton magnetic resonance spectroscopy in Parkinson's disease and atypical parkinsonian disorders. *Movement Disorders*, Vol.12, No.6, (November 1997), pp. 903-909, ISSN 0885-3185

Federico, F.; Simone, I.L.; Lucivero, V.; Mezzapesa, D.M.; De Mari, M. et al. Usefulness of proton magnetic resonance spectroscopy in differentiating parkinsonian syndromes. *Italian Journal of Neurological Sciences*, Vol.20, No.4, (August 1999), pp. 223-229, ISSN 0392-0461

Firbank, M.J.; Harrison, R.M. & O'Brien, J.T. A comprehensive review of proton magnetic resonance spectroscopy studies in dementia and Parkinson's disease. *Dementia And Geriatric Cognitive Disorders*, Vol.14, No.2, (July 2002), pp. 64-76, ISSN 1420-8008

Fox, P.T. & Raichle, M.E. Stimulus rate determines regional brain blood flow in striate cortex. *Annals of Neurology,* Vol.17, No3, (March 1985), pp.303-305, ISSN 0364-5134

Fulton, HG. & Barrett, SP. A demonstration of intravenous nicotine self-administration in humans? *Neuropsychopharmacology,* Vol.33, No8, (Jule 2008), pp. 2042-2043, ISSN 0893-133X

George, JS.; Aine, CJ.; Mosher, JC.; Schmidt, MD.; Ranken, DM. et al., Mapping function in the human brain with magneto encephalography, anatomical magnetic resonance imaging, and functional magnetic resonance imaging. *Journal of Clinical Neurophysiology,* Vol.12, No5, (September 1995), pp. 406-429 ISSN 1676-2649

Gupta, A.; Dawson, V.L. & Dawson, T.M. What causes cell death in Parkinson's disease? *Annals of Neurology,* Vol.64, No6, (December 2008), pp. S3-S15, ISSN 0364-5134

Haehner, A.; Boesveldt, S.; Berendse, H.W.; Mackay-Sim, A. Fleischmann, J. et al. Prevalence of smell loss in Parkinson's Disease - a multicenter study. *Parkinsonism & Related Disorders,* Vol.15, No.7, (August 2009), pp. 490-494, ISSN 1353-8020

Hagmann, P.; Jonasson, L.; Maeder, P.; Thiran, J.P.; Wedeen, V.J. et al. Understanding diffusion MR imaging techniques: from scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. *Radiographics*, Vol.26, Sp. Iss, (October 2006), pp. S205-U219, ISSN 0271-5333

Hattingen, E.; Magerkurth, J.; Pilatus, U.; Morez, A.; Seifried, C. et al. Phosphorus and proton magnetic resonance spectroscopy demonstrates mitochondrial dysfunction in early and advanced Parkinson's disease. *Brain,* Vol.132, No.12, (December 2009), pp. 3285-3297, ISSN 0006-8950

Hawkes, C.H.; Shephard, B.C. & Daniel, S.E. Olfactory disfunction in Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry,* Vol.62, No.5, (May 1997), pp. 436-446, ISSN 0022-3050

Hawkes, C.H.; Shephardm, B.C. & Daniel, S.E. Is Parkinson's disease a primary olfactory disorder? *Qjm-An International Journal of Medicine,* Vol.92, No.8, (August 1999), pp. 473-480, ISSN 1460-2725

Hinke, R.M.; Hu, X.; Stillman, A.E.; Kim, S.G.; Merkle, H. et al. Functional magnetic resonance imaging of Broca's area during internal speech. *NeuroReport*, Vol.4, No6, (June 1993) pp. 675-678 ISSN 0959-4965

Hirsch, E.C. & Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? *Lancet Neurology,* Vol.8, No.4, (April 2009), pp. 382-397, ISSN: 1474-4422

Holshouser, B.A.; Komu, M.; Moller, H.E.; Zijlmans, J.; Kolem, H. et al. Localized proton NMR spectroscopy in the striatum of patients with idiopathic Parkinson's disease: a

multicenter pilot study. *Magnetic Resonance in Medicine,* Vol.33, No.5, (May 1995), pp. 589-594, ISSN 0740-3194

Horsfield, M.A. Magnetization transfer imaging in multiple sclerosis. *Journal of Neuroimaging,* Vol.15, No.4, (2005), pp. 58-67, ISSN 1051-2284

Huisman, E.; Uylings, H.B. & Hoogland, P.V. A 100% increase of dopaminergic cells in the olfactory bulb may explain hyposmia in Parkinson's Disease. *Movement Disorders*, Vol.19, No.6, (June 2004), pp. 687-692, ISSN 0885-3185

Hummel, T. (1999). Olfactory evoked potentials as a tool to measure progression of Parkinson's disease. In: *Focus medicine – New development in the drug therapy of Parkinson's Disease,* T. Chase & P. Bedard, (Eds.), 47-53, ISBN 0-632-05174-4, Blackwell Science, Oxford, UK

Hummel, T.; Kobal, G.; Gudziol, H. & Mackay-Sim, A. Normative data for the "Sniffin'Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds:an upgrade based on a group of more than 3.000 subjects. *European Archives of Oto-Rhino-Laryngology,* Vol.264, No.3, (March 2007), pp. 237-243, ISSN 0937-4477

Hummel, T.; Sekinger, B.; Wolf, S.; Pauli, E. & Kobal G. "Sniffin' Sticks": olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chemical Senses,* Vol.22, No.1, (February 1997), pp. 39-52, ISSN 0379-864X

Hummel, T.; Witt, M.; Reichmann, H.; Welge-Luessen, A & Haehner A. Immunohistochemical, volumetric, and functional neuroimaging studies in patients with idiopathic Parkinson's disease. *Journal of the Neurological Sciences,* Vol.298, No.1-2, (February 2010), pp. 119-122, ISSN 0022-510X

Inglese, M.; Horsfield, M.A. & Filippi, M. Scan-rescan variation of measures derived from brain magnetization transfer ratio histograms obtained in healthy volunteers by use of a semi-interleaved magnetization transfer sequence. *American Journal of Neuroradiology,* Vol.22, No.4, (April 2001), pp. 681-684, ISSN 0195-6108

Karagulle Kendi, A.T.; Lehericy, S.; Luciana, M.; Ugurbil, K. & Tuite, P. Altered diffusion in the frontal lobe in Parkinson disease. *AJNR American Journal of Neuroradiology*, Vol.38, No3, (March 2008), pp. 501-5, ISSN 1936-959X

Kettenmann, B.; Hummel, C.; Stefan, H. & Kobal, G. Multiple olfactory activity in the human neocortex identified by magnetic source imaging. *Chemical Senses,* Vol.22, No.5, (October 1997), pp. 493-502, ISSN 0379-864X

Kim, K.; Hirsch, J.; DeLaPaz, R.L.; Relkin, N. & Lee, K.M. Comparison of cortical areas activated by primary and secondary languages in human brain using functional magnetic resonance imaging (fMRI). *Abstracts: Society of Neuroscience*, Vol.21, No3, (1993), pp.1763, ISSN 0270-6474

Kobal, G. & Plattig, K.H. Objective olfactometry: methodological annotations for recording olfactory EEG-responses from the awake human. *EEG EMG Z Elektroenzephalogr Elektromyogr Verwandte Geb.*, Vol.9, No.3, (September 1978), pp. 135-145, ISSN 0012-7590

Kobal, G.; Klimek, L.; Wolfensberger, M.; Gudziol, H.; Temmel, A. et al. Multicenter investigation of 1.036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and

olfactory thresholds. *European Archives of Oto-Rhino-Laryngology,* Vol.257, No.4, (April 2000), pp. 205-211, ISSN 0937-4477

Le Bihan, D. Looking into the functional architecture of the brain with diffusion MRI. *Nature Reviews Neuroscience*, Vol.4, No.6, (June 2003), pp. 469-480, ISSN 1471-0048

Lekwuwa, G.U.; Barnes, G.R.; Collins, C.J.S.; Limousin, P. Progressive bradykinesia and hypokinesia of ocular pursuit in Parkinson's disease. *Journal of Neurology Neurosurgery and Psychiatry,* Vol.66, No.6, (June 1999), pp. 746–753, ISSN 0022-3050

Lin, A.; Ross, B.D.; Harris, K. & Wong, W. Efficacy of proton magnetic resonance spectroscopy inneurological diagnosis and neurotherapic decision making. *NeuroRx: the journal of the American Society for Experimental NeuroTherapeutics,* Vol.2, No.2, (April 2005), pp. 197-214, ISSN 1545-5343

Marino, S.; Sessa, E.; Di Lorenzo, G.; Lanzafame, P.; Scullica, G.; et al. Quantitative analysis of pursuit ocular movements in Parkinson's disease by using a video-based eye tracking system. *European Neurology*, Vol. 58, No. 4, (September 2007), pp. 193-7, ISSN 0014-3022

Marino, S.; Lanzafame, P.; Sessa, E.; Bramanti, A.; Bramanti, P. The effect of L-Dopa administration on pursuit ocular movements in suspected Parkinson's disease. *Neurological Sciences*, Vol. 31,No. 3 (June 2010), pp. 381-385, ISSN 0022-510X

Muller, A.; Reichmann, H.; Livermore, A. & Hummel T. Olfactory function in idiopathic Parkinson's disease (IPD): results from cross-sectional studies in IPD patients and long-term follow-up of de-novo IPD patients. *Journal of Neural Transmission,* Vol.109, No.5-6, (May 2002), pp. 805-811, ISSN 0300-9564

Ogawa, S.; Lee, T.M.; Nayak, A. S.; & Glynn, P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magnetic Resonance in Medicine*, Vol.14, No1, (April 1990) pp.68-78, ISSN 07403194

Pike, G.B.; Hu, B.S.; Glover, G.H. & Enzmann, D.R. Magnetization transfer time-of-flight magnetic resonance angiography. *Magnetic Resonance in Medicine,* Vol.25, No.2, (June 1992), pp. 372-379, ISSN 0740-3194

Ramaker, C.; Marinus, J.; Stiggelbout, A.M. & Van Hilten, B.J. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. *Movement Disorders*, Vol.17, No.5, (September 2002), pp. 867-876, ISSN 0885-3185

Rolheiser, T.M.; Fulton, H.G.; Good, K.P.; Fisk, J.D.; McKelvey, J.R. et al. Diffusion tensor imaging and olfactory identification testing in early-stage Parkinson's disease. *Journal of Neurology,* (February 2011), ISSN 0340-5354

Ross, B. & Bluml, S. Magnetic resonace spectroscopy of the human brain. *The Anatomical Record,* Vol.265, No.2, (April 2001), pp. 54-84, ISSN 0003-276X

Roy, C. & Sherrington, C. On the regulation of the blood-supply of the brain. *The Journal of Physiology,* Vol.11, No1-2, (January 1890), pp.85-108, ISSN 1469-7793

Rutledge, J.N.; Hilal, S.K.; Silver, A.J.; Defendini, R. & Fahn S. Study of movement disorders and brain iron by MR. *AJR American Journal of Roentgenology,* Vol.149, No2, (August 1987), pp.365-379, ISSN 0361-803X

Savoiardo, M.; Girotti, F.; Strada, L. & Ciceri, E. Magnetic resonance imaging in progressive supranuclear palsy and other parkinsonian disorders. *Journal of Neural Transmission,* Vol.42, (1994), pp. 93-110, ISSN 0303-6995

Schneider, W.; Noll, D.C. & Cohen, J. D. Functional topographic mapping of the cortical ribbon in human vision with conventional MRI scanners. *Nature*, Vol365, No6442, (September 1993), pp. 150-152, ISSN 0028-0836

Schocke, M.F.; Seppi, K.; Esterhammer, R.; Kremser, C.; Mair, K.J. et al. Trace of diffusion tensor differentiates the Parkinson variant of multiple system atrophy and Parkinson's disease. *Neuroimage*, Vol.19, Suppl.9, (2004), pp. S53-S53, ISSN 08853185

Sofic, E.; Riederer, P.; Heinsen, H.; Beckmann, H.; Reynolds, G.P. et al. Increased iron (III) and total iron content in post mortem substantia nigra of parkinsonian brain. *Journal of Neural Transmission,* Vol.74, No3, (August 1988), pp.199-205, ISSN 0300-9564

Srinivasan, R.; Vigneron, D.; Sailasuta, N.; Hurd, R. & Nelson, S. A comparative study of myo-inositol quantification using LCmodel at 1.5 T and 3.0 T with 3D 1H proton spectroscopic imaging of the human brain. *Magnetic Resonance Imaging*, Vol.22, No.4, (May 2004), pp. 523-528, ISSN 0730-725X

Takeda, A.; Saito, N.; Baba, T.; Kikuchi, A.; Sugeno, N. et al. Functional imaging studies of hyposmia in Parkinson's disease. *Journal of the Neurological Sciences*, Vol.298, No.1-2, (February 2010), pp. 36-39, ISSN 0022-510X

Tambasco, N.; Pelliccioli, G.P.; Chiarini, P.; Montanari, G.E.; Leone, F. et al. Magnetization Transfer changes of gray and white matter in Parkinson 's disease. *Neuroradiology*, Vol.45, No.4, (April 2003), pp. 224-230, ISSN 0028-3940

Tedeschi, G.; Litvan, I.; Bonavita, S.; Bertolino, A.; Lundbom, N. et al. Proton magnetic resonance spectroscopic imaging in progressive supranuclear palsy, Parkinson's disease and corticobasal degeneration. *Brain,* Vol.120, No.9, (September 1997), pp. 1541-1552, ISSN 0006-8950

Tessa, C.; Giannelli, M.; Della Nave, R.; Lucetti, C.; Berti, C.A. et al. A whole-brain analysis in de novo Parkinson disease. *AJNR American Journal of Neuroradiology*, Vol.29, No4, (April 2008), pp. 674-680, ISSN 01956108

Tissingh, G.; Berendse, H.W.; Bergmans, P.; DeWaard, R.; Drukarch, B. et al. Loss of olfaction in de novo and treated Parkinson's disease: possible implications for early diagnosis. *Movement Disorders*, Vol.16, No.1, (January 2001), pp. 41-46, ISSN 0885-3185

Watanabe, H.; Fukatsu, H.; Katsuno, M.; Sugiura, M.; Hamada, K. et al. Multiple regional 1H-MR spectroscopy in multiple system atrophy: NAA/Cr reduction in pontine base as a valuable diagnostic marker. *Journal of Neurology, Neurosurgery, and Psychiatry,* Vol.75, No.1, (January 2004), pp. 103-109, ISSN 0022-3050

Wattendorf, E.; Welge-Lüssen, A.; Fiedler K.; Bilecen, D.; Wolfensberger, M. et al. Olfactory Impairment Predicts Brain Atrophy in Parkinson's Disease. *The Journal of Neuroscience*, Vol.29, No.49, (December 2009), pp. 15410-15413, ISSN 0270-6474

Welge-Lüssen, A.; Wattendorf, E.; Schwerdtfeger, U.; Fuhr, P.; Bilecen, D. et al. Olfactory induced brain activity in Parkinson's disease relates to the expression of event-related potentials—an fMRI study. *Neuroscience,* Vol.162, No.2, (August 2009), pp. 537-543, ISSN 0306-4522

Wenning, G.K.; Shephard, B.; Hawkes, C.; Petruckevitch, A.; Lees, A. et al. Olfactory function in atypical parkinsonian syndromes. *Acta Neurologica Scandinavica*, Vol.91, No.4, (April 1995), pp. 247-250, ISSN 0001-6314

Westermann, B.; Wattendorf, E.; Schwerdtfeger, U.; Husner, A.; Fuhr, P. et al. Functional imaging of the cerebral olfactory system in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry,* Vol.79, No.1, (January 2008), pp. 19-24, ISSN 0022-3050

Wilms, H.; Zecca, L.; Rosenstiel, P.; Sievers, J.; Deuschl, G. et al. Inflammation in Parkinson's diseases and other neurodegenerative diseases: cause and therapeutic implications. *Current Pharmaceutical Design,* Vol.13, No18, (June 2007), pp. 1925-1928, ISSN: 1381-6128

Wolff, S.D. & Balaban, R.S. Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. *Magnetic Resonance in Medicine,* Vol.10, No.1, (April 1989), pp. 135-144, ISSN 0740-3194

Wolff, S.D.; Eng, J. & Balaban, R.S. Magnetization transfer contrast: method for improving contrast in gradient-recalled-echo images. *Radiology*, Vol.179, No.1, (April 1991), pp. 133-137, ISSN 0033-8419

Yonca, A.; Pervin, I.; Ali, D.; Sezer, K. & Naighan, I. Magnetization Transfer Ratio in Early Period of Parkinson Disease. *Academic Radiology*, Vol.14, No.2, (February 2007), pp. 189-192, ISSN 1076-6332

Youdim, M.B.H.; Ben-Schachar, D.; Yehuda, S. & Riederer, P. The role of iron in the basal ganglia. *Advances in Neurology,* Vol.53, (1990) pp.155-162, ISSN: 0091-3952

2

Diagnosis of Parkinson's Disease by Electrophysiological Methods

Elena Lukhanina, Irina Karaban and Natalia Berezetskaya
Department of Brain Physiology, A.A. Bogomoletz Institute of Physiology,
Parkinson's Disease Treatment Centre, Institute of Gerontology,
Kiev,
Ukraine

1. Introduction

Effective differential diagnosis of Parkinson's disease (PD) needs in informative indices that objectively reflect the functional state of the extrapyramidal system. And also, when evaluating an efficacy of antiparkinsonian therapy, it is essential to have both, qualitative and quantitative characteristics, permitting to correct treatment and predict a disease course. One of informative diagnostic method in PD is surface (interference) electromyography. As know, a nigrostriatal dopamine deficit results in disturbances of the central supraspinal control over the muscle tonic activity and voluntary movements (Valls-Solé & Valldeoriola, 2002). Electromyographically, the extrapyradimal insufficiency shows itself by a high level of bioelectrical activity of muscles at rest, changes of motor unit conduction velocity and synchronization (Farina et al., 2004; Semmler & Nordstrom, 1999). The traditional methods to evaluate surface electromyograms (EMGs) are based on amplitude and spectral analysis. However, myoelectric signals are nonlinear by its nature (Nieminen & Takala, 1996). A surface EMG is formed by the summation of a number of single muscle fiber action potentials. Therefore different world clinics have been searching for new relevant methods based on nonlinear time-series analyses of EMG to quantify the motor features of the disorder in PD (Del Santo et al., 2007; Meigal et al., 2009). Some other novel EMG characteristics, such as dimensionality based on fractal analysis or higher order statistics of EMG distribution have also proved to be sensitive to neuromuscular status (Swie et al., 2005).

Although the cardinal symptoms of the disease are movement disorders the manifestations of PD also comprise a variety of diverse abnormalities including disturbance of sensory gating and cognitive decline (Lewis & Byblow, 2002). Several authors suggested that movement disorders in PD might be also developed because of dysregulation of sensory processing that affects sensorimotor integration (Abbruzzese & Berardelli, 2003). This is an important issue because one of the proposed key functions of basal ganglia is the gating of sensory input for motor control (Kaji, 2001). Numerous studies have demonstrated marked changes in the somatosensory (Rossini et al., 1998), acoustic (Teo et al., 1997;) and visual (Sadekov, 1997) evoked potentials in PD patients. Evaluation of brain evoked potentials may have potential in the assessment of the severity of PD. In contemporary neurophysiology,

studies of the central mechanisms underlying the organization of motor function and its impairments increasingly involve analysis of endogenous cortical event-related potentials, a set of potentials which includes contingent negative variation (CNV). The CNV extent depends on the level of attention, motivation, and volitional effort (Deecke, 2001). The magnitude of this potential is known to decrease in diseases accompanied by motor disorders, including PD (Aotsuka et al., 1996; Pulvenmuller et al., 1996). CNV has been shown to display significant increases after administration of levodopa in patients with Parkinson's disease, suggesting a role for the central dopaminergic system in its generation (Oishi et al., 1995).

Although electrophysiological methods objectively reflect motor and sensory dysfunctions, they are still used rather rarely in the clinical evaluation of PD. We carried out systematic and detailed research of surface EMG characteristics in PD patients in comparison with age-matched healthy subjects, paying the special attention on the correlation associations between EMG parameters and subitems of the Unified Parkinson's Disease Rating Scale (UPDRS). Amplitude and spectral features, statistics of distribution, fractal dynamics of the EMG signals were investigated. Separate research was dedicated to the study of EMG characteristics of clinically healthy kinsmen of the patients suffering from PD in order to detect latent symptoms of extrapyramidal insufficiency that can be considered genetic determinants of the risk of development of the above disease. Since the question of the relationship the early and late phases of CNV with the mechanisms controlling motor functions in PD has received inadequate study we conducted such research in patients with this disease. With the purpose of evaluation of the brain inhibitory processes in PD patients the study of cortical evoked potentials upon paired-click auditory stimulation was performed. The results of these investigations are presented below.

2. Surface electromyography

Surface EMG is a simple and noninvasive method that permits to estimate the severity of symptomatology in patients and also may help to exposure of the hidden manifestations of the disturbed muscles activity on the presymptomatic stage of the neurodegenerative process (Kryzhanovsky et al., 2002; Lukhanina et al., 2010). In PD patients the EMG characteristics of the tonic and phasic shoulder muscle activities at rest, during voluntary contraction and under tonic muscle strain were studied. In kinsmen of the patients, suffering from PD, EMGs in the resting state and under conditions of two functional tests (retention of load and retention of arms in the elevated and outstretched state) were recorded.

2.1 Amplitude and spectral analysis of EMGs in patients with Parkinson's disease

One of the informative EMG sign of extrapyramidal insufficiency appears to be the resting EMG amplitude values that reflect the muscle ability for relaxation. Spectral analysis of resting EMGs is used for assessing the burst muscle discharges with a frequency of 4-8 Hz reflecting parkinsonian tremor. Amplitude values of the EMGs recorded during the voluntary muscle contraction serve to calculate the phasic activation coefficient. This coefficient clearly reflects the competitive relationships between the tonic and phasic processes. Study of the reflex agonist/antagonist muscle involvement under tonic strain is valid for establishing coordinating muscle relationships.

2.1.1 Methods

Studies were performed in two groups: 48 patients with PD, 1.5-3.5 Hoehn-Yahr scale (23 men and 25 women, mean ± SE age 62.2 ± 1.6, range 49-75 years) and 42 age-matched healthy controls (20 men and 22 women, mean ± SE age 65.8 ± 1.43, range 58-74 years). All of them were right-handed persons. The study patients, who regularly underwent treatment at the Parkinson's Disease Centre of Institute of Gerontology, gave their written informed consent to participate in this investigation. They had 4-13-year history of an idiopathic PD and received an antiparkinsonian medication (an individual dose 0.250-12g of levodopa/carbidopa, daily). All patients were studied in the OFF state. For the quantitative evaluation of levodopa therapy 20 patients (in which the clinical "ON-OFF" phenomenon was verified) were studied also in the ON state, one hour after an intake of the single individual dose of levodopa/carbidopa. The motor activity of PD patients was evaluated in ON state, according to sections II-III of the UPDRS.

For each subject, we recorded the surface EMG from the flexors and extensors (mm. biceps and triceps brachii) of the right and left arms. The subject lay on his back, with the arms lying on the horizontal surface. The EMGs were recorded using four bipolar skin electrodes (0.5x1.0 cm) with an interelectrode distance constant of 1.5 cm. Bioelectrical potentials were amplified with a band pass of 10 Hz - 10 kHz. The amplified analogue signals were fed to a computer, which digitized them at a sampling rate of 1000 Hz and then stored the data for further measurements. The time of each recording was 10 sec. EMG recordings were made:

1. At a resting state, being cautious that the subject is relaxed.
2. During a voluntary m. biceps brachii contraction started after a command to bend the arm at the elbow, fingers touching the shoulder. The sound signal served as a command to initiate arm bending, and it was simultaneously registered on EMG. An electrical contact enclosure marked the start of arm lifting, being recorded simultaneously with the EMG on a free channel.
3. During a tonic m. biceps brachii strain under weight holding (2 kg) in the hand, with arm lifted upward and stretched forward, for 5 sec.

In resting EMG recordings, the average and maximal EMG amplitudes were calculated to evaluate the muscle ability for relaxation. An artefact-free section on the EMG record was selected by the experimenter. The single EMG wave amplitude was defined as the difference between the values of upper and lower peaks. The oscillations with no less than 2 μV amplitude were considered. The resting average EMG amplitude was calculated based on minimum 100 measurements. The maximum amplitude value was calculated on the same EMG section. The amplitude distribution histograms were constructed.

The resting EMG recordings were also used for assessing the burst muscle discharges For this purpose, the Fourier spectrum diagrams for the low frequency area were constructed. In doing this, part of the data with negative EMG amplitude meanings were discarded. Data with the positive EMG amplitude meanings underwent a Butterworth digital sinus low pass filtering with a band pass of 0-20 Hz As a result, the envelope of EMG amplitude was formed, which then served as the data array for fast Fourier transformation. The data for each lead were divided into several successive sections, each containing 512 points, which underwent the fast Fourier transformation. The obtained spectra were averaged, and the envelope of EMG amplitude frequency with a maximal power was determined (Fig 1). The statistical significance of the frequency peak was determined by means of constructing the 95% confidential intervals (M ± 2 S.D).

The EMG recordings made during the voluntary m. biceps brachii contraction served to calculate the phasic activation coefficient (PhAC), from a formula :

$$PhAC = (AVCa\text{-}ARa)/AVCa \quad (1)$$

where AVCa is the average EMG amplitude on a section with most marked changes in the muscle activity under voluntary contraction, and ARa is the average amplitude of resting EMG. In the conditions of low tonic muscle activity at rest the phasic muscle activation during voluntary movement is facilitated and the PhAC value is close to 1. On the contrary, when the resting tonic activity increases, the PhAC falls.

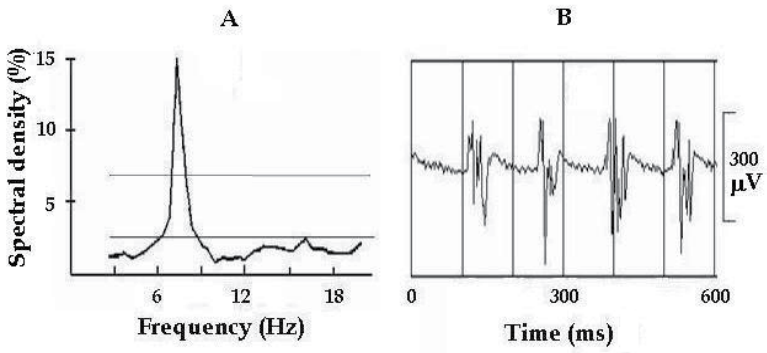


Fig. 1. The spectrogram of the power of EMG envelope frequency with 95% confidence intervals (A) and the corresponding resting EMG pattern of m. biceps brachii in a patient with Parkinson's disease (B). Peak deviation on the spectrogram reflects the frequency of the rhythmic burst muscle discharges.

The functional test with weight holding served for study of the reflex agonist and antagonist involvement during tonic muscle strain. We calculated the coefficients of reflex involvement of the muscles of the opposite arm, which characterized "distant" synergies. The coefficients of reflex involvement, respectively for the m. biceps brachii and m. triceps brachii of the opposite upper limb were obtained by calculation of the ratio of the mean amplitude recorded from the m. biceps (or triceps) on the resting side and mean amplitude recorded from the m. biceps on the side of retention of a load; the latter value was taken as 100%. In the norm, the value should not exceed 15%. An increase in this index is indicative of abnormal intensification of muscle coordinative interactions; if the coefficient of reflex involvement value exceeds 50%, such a disorder is qualified as gross.

Statistical analysis of the obtained data was performed using Statistic 8 software. Dispersion analysis ANOVA and a non-parametric two-tailed Mann-Whitney criterion were used in the course of comparison of the values observed in the different groups of the tested persons. Data obtained from the same patients before and after Levodopa treatment were compared using two-tailed paired t-test. The nonparametric Spearman test was used to evaluate possible correlation between above EMG parameters and subitems of UPDRS. Differences were considered to be significant at $P < 0.05$.

2.1.2 Results and discussion

In the group of age-matched healthy subjects, the EMG amplitude of the shoulder flexors and extensors during muscle relaxation showed low values (Fig 2, Controls 1, 2). The

average EMG amplitude values for mm. biceps and triceps brachii varied across the subjects within 3-12 μV and the maximal amplitude values within 4-34 μV. For the whole group of healthy subjects, mean ± SE average amplitude did not exceed 5.9 ± 0.2 μV and mean ± SE maximal amplitude was no more 12.8 ± 2.3 μV (Table 1).

	Healthy controls (n = 42)	PD patients (n = 48)
Average EMG amplitude (μV)		
m. biceps dexter	5.3±0.8	19.5±3.8 ***
m. biceps sinister	5.5±0.7	21.4±7.4 ***
m. triceps dexter	5.9±0.2	13.1±1.7 *
m. triceps sinister	5.4±0.8	12.5±3.1
Maximal EMG amplitude (μV)		
m. biceps dexter	12.5±2.1	74.0±17.9 ***
m. biceps sinister	12,8±2.3	73.8±15.6 ***
m. triceps dexter	11.9±1.3	60.1±7.4
m. triceps sinister	12.3±2.1	61.9±12.0

Table 1. Resting EMG amplitudes of shoulder muscles in healthy controls and patients with Parkinson's disease. Notes: values are Mean ± Standard Error; n - number of subjects in each group; *, *** significant difference compared to healthy controls according to Mann-Whitney test, $p< 0.05$ and $p< 0.001$, respectively.

There were no statistical differences in EMG amplitude values between men and women. A significant positive correlation ($p<0.05$) was found for the resting activities of the antagonist muscles of the upper extremities in the age-matched healthy subjects (Table 2). The use of the envelope EMG construction technique demonstrated the presence of rhythmic burst muscle discharges in those cases where they were badly visualized on the EMG. Low amplitude burst discharges were occasionally identified in healthy subjects with the help of this technique (Fig 2, Control 2). Of EMG recordings taken from flexors and extensors on both sides in 42 persons of the control group, 11 recordings (6.5%) made in eight subjects displayed the burst discharges, with a mean ± SE frequency of 6.1 ± 0.3 Hz. The maximal amplitude of burst discharges in control subjects did not exceed 11-18 μV (mean ± SE = 14.3 ± 1.1 μV).

Healthy controls		PD patients, OFF state		PD patients, ON state	
right side	left side	more impaired side	less impaired side	more impaired side	less impaired side
0.42**	0.40**	0.27	0.33*	- 0.26	0.32*

Table 2. Correlation coefficients between average EMG amplitudes of the antagonist shoulder muscles (mm. biceps and triceps brachii) at rest in healthy controls and PD patients. * significant correlation, $p< 0.05$; ** is . $p< 0.01$.

In the group of PD patients, we observed a significant increase in the resting EMG amplitudes, which was ascribed to muscle relaxation disturbances. The mean average amplitude values for various study muscles, estimated for a whole PD group, were 2-3 times

greater compared to control values, and the mean maximal amplitude values were approximately 5-6 times greater (Table 1). In some patients, average amplitude from a more impaired side reached 44-123 μV and maximal amplitude - 210-508 μV

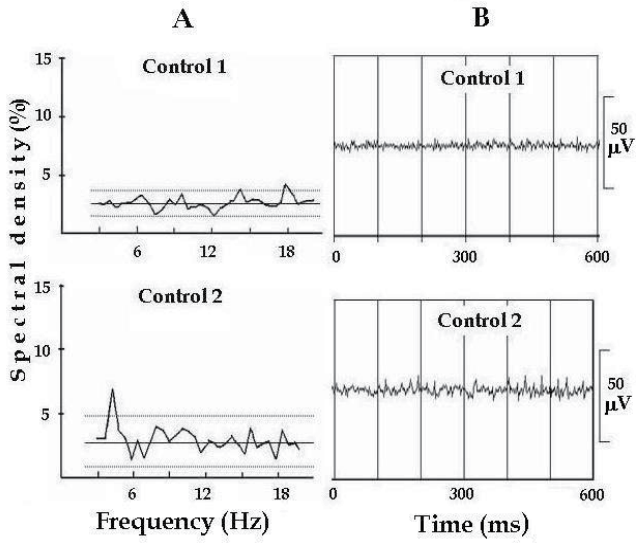


Fig. 2. The spectrograms of the power of EMG envelope frequency with 95% confidence intervals (A) and the corresponding resting EMG patterns of m. biceps brachii (B) in healthy controls (Control 1 and 2) Peak deviation on the spectrogram reflects the frequency of the rhythmic burst muscle discharges. Control 1: the absence of the burst muscle activity. Control 2: low amplitude burst muscle discharges with a frequency of 4 Hz in a healthy control subject.

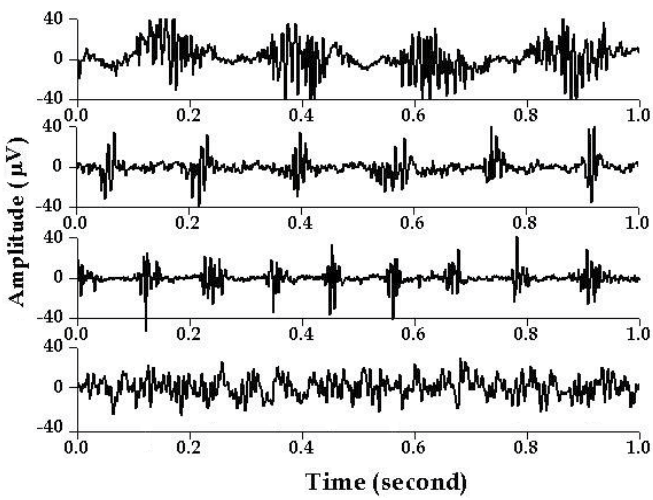


Fig. 3. Typical examples of EMGs registered in the resting state from three patients with the akinetic-rigid trembling form of Parkinson's disease (three upper records) and a patient with the akinetic-rigid form of this disease (low record).

Of interest is the fact that PD patients did not show a significant correlation between resting activities of the antagonist mm. biceps and triceps brachii on the dominant side, as has been true in the cases of the right and left sides in healthy subjects (Table 2). On the EMGs taken from PD patients with the akinetic-rigid-trembling form of the disease burst muscle discharges occurred as a rule with a frequency of 4-8 Hz. The mean ± SE frequency of the burst discharges was 5.2 ± 0.2 Hz. They had high amplitude (Fig.3). The maximal amplitude of burst discharges varied from 30 to 508 μV (mean ± SE = 89.8 ± 15.6 μV). Of special note, no significant correlation was found between resting EMG amplitude values and the occurrence of burst muscle discharges.

When comparing the data in OFF-state and ON-state, we observed a noticeable decrease in amplitude values. Mean ± SE average EMG amplitude of different muscles decreased to 8.2 ± 1.9 – 12.3 ± 5.1 μV and mean ± SE maximal amplitude decreased to 20.1± 5.3 – 32.1± 7.1 μV In this respect, the amplitude histograms made for the same patient during both states were very illustrative (Fig.4).

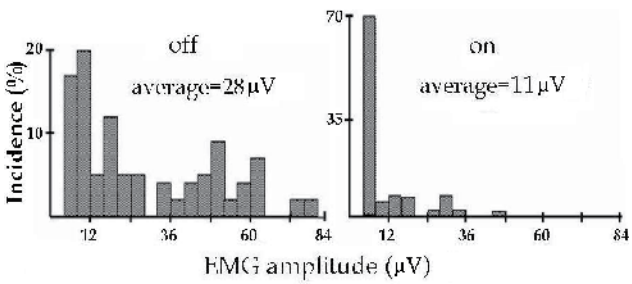


Fig. 4. The decrease of resting EMG amplitude values (calculated from peak to peak) of m. biceps brachii in a PD patient after intake of single dose of levodopa/carbidopa. OFF: the histograms of distribution of EMG amplitude values during the off-medication state; ON : one hour after drug intake. The bin of histograms is 4 μV.

But the treatment with levodopa did not result in the normalization of correlations between resting activities of the antagonist shoulder muscles (Table 2). Following a single dose of levodopa/carbidopa the number of cases displaying burst discharges with a frequency of 4-8 Hz decreased. In some patients the rhythmic discharges disappeared, as is shown in Figure 5, top records. In the other patients who displayed discharges after a dose of levodopa, an increase occurred in the discharges frequency (Fig. 5, lower records).

EMGs recorded during the performance of voluntary arm bending were found to differ considerably in healthy subjects and PD patients. In the healthy subjects, we clearly distinguished an onset of muscle phasic activation on the EMG (Fig. 6, Control). Means ± SE of average EMG amplitude of the mm. biceps brachii during their voluntary contraction was 49 ± 8 μV from the right and 44 ± 2 μV from the left, the maximal amplitude – 189 ± 31 μV and 137 ± 30 μV, respectively. In view of the low resting EMG amplitude value in healthy subjects, the coefficient of phasic activation in most cases was equal to 0.7-0.9; mean ± SE was 0.77 ± 0.04.

In contrast, in the PD patients it was often difficult to locate a site on the EMG at which the muscle phasic activation started because of increased resting tonic muscle activity and a very delayed rise in EMG amplitude after the delivery of a command to move (Fig. 6, PD). During peak voluntary flexor contraction, some patients showed a noticeable reduction of

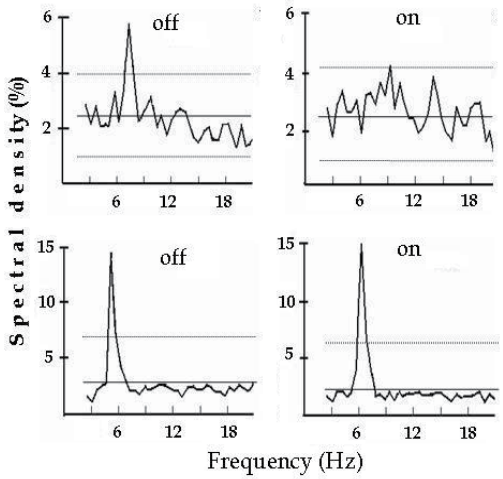


Fig. 5. Changes in the rhythmic (4-7 Hz) burst muscle discharges in patients with Parkinson's disease after the intake of an individual single dose of levodopa/carbidopa. The spectrograms of the power of EMG envelope frequency in two patients in an off-medication state (OFF) and one hour after drug intake (ON). After the drug intake, burst muscle discharges disappeared in one patient, while their frequency somewhat increased in another patient. For other notes see Fig. 1.

EMG amplitude, while other patients had the same meanings as healthy subjects. The coefficient of phasic activation of a voluntarily contracting mm biceps brachii in PD patients was generally decreased to 0.1-0.6 and, sometimes (when amplitude values at rest exceeded those that were observed during phasic activation), even had negative values; mean ± SE was 0.42 ± 0.08. The magnitude of the phasic activation decrease showed a distinct dependence on the side which was most affected. Reduction of the coefficient of phasic activation in the OFF patient group compared to healthy individuals was statistically significant ($p<0.01$).

Disturbance of coordinative muscle interactions was one more typical feature of the EMG recorded in Parkinson's patients. This was manifested in increased reflex involvement of the muscles of the opposite arm (distant synergy) at tonic tension of the m. biceps brachii at one of the sides within the period of retention of a load. In this group, the mean values of the coefficients of reflex involvement for the m. biceps brachii and m. triceps brachii of the opposite side exceeded 50%. As was already mentioned, these phenomena should be considered a gross disturbance of coordinative interactions. In control group the mean values of the coefficients of reflex involvement were 20-26%.

The dose of levodopa/carbidopa in PD patients produced a decrease in resting muscle activity parallel to an increase, more often, to normal values (0.8-0.9) of the coefficient of phasic activation during voluntary contraction of flexors. With regard to the reflex activation of the agonist and antagonist muscles during weight holding, a noticeable reduction of the coefficients of reflex involvement was only observed in some of the patients who took levodopa/carbidopa treatment. In seven patients, after medication even more marked enhancement developed in the agonist or antagonist muscles, and was registered during the performance of the functional test.

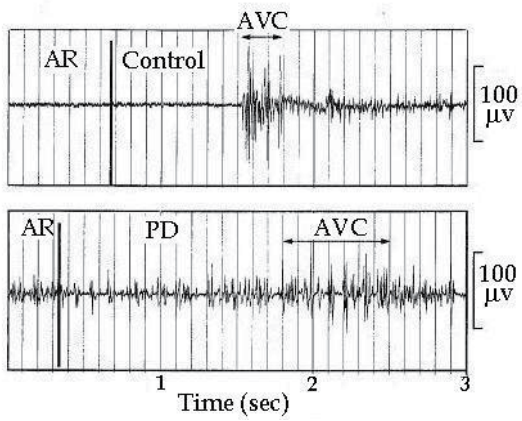


Fig. 6. The phasic activation of m. biceps brachii dexter during voluntary movement in healthy control and off-medication patient with Parkinson's disease. Two sections of native EMGs in a healthy 64-year old subject (Control) and in a 53-year old patient (PD). The vertical thick lines designate the moment of experimenter's command. The horizontal lines over EMGs designate the periods, at which the amplitude measurements of maximal muscular activity during voluntary contractions (AVC) were taken. The resting EMG amplitudes (AR) were measured during 5 s prior to command presentation.

The described quantitative EMG parameters added fundamentally to the clinical motor characteristics of PD patients and correlated selectively with definite UPDRS subitems. Thus, the most significant increases in the resting average and maximal EMG amplitude and decreases in the coefficient of phasic activation were observed in patients whose part III UPDRS scores exceeded 50. At the same time, the greatest involvement of the reciprocal muscles during the functional test was noted in patients with high part II UPDRS scores on the upper extremity daily activity. These patients also, had the greatest dyskinesia (disability) scores. We established the following statistically significant correlations (see Table 3). The resting muscle amplitudes from the more affected side correlated positively with the upper extremity rigidity and general motor scores. We found negative correlations between the phasic activation coefficient of m. biceps brachii from the more affected side and the upper extremity rigidity and general motor scores. The antagonist muscle involvement during the tonic strain holding a weight correlated positively with the handwriting, cutting food, dressing score and dyskinesia (disability) score. Levodopa intake did not influence essentially on the correlations between the reflex muscle involvement and UPDRS scores.

We found the present computer EMG analysis to be a sensitive tool for the objective evaluation of PD symptoms and to quantify the efficacy of levodopa therapy. One of the most useful EMG signs of extrapyramidal insufficiency appears to be the resting EMG amplitude value. In PD, the resting EMGs in the OFF state were characterized by the splashes of high muscle activity in contrast to the flat EMGs seen in age-matched healthy subjects. The average resting EMG amplitude was 2-3 times and the maximal amplitude was 5-6 times greater in PD patients than in the control group. Of interest are our data indicating the statistically significant correlation between levels of resting activity in the antagonist muscles (m. biceps and triceps brachii) in healthy subjects and the lack of such a correlation in PD patients on the most affected side. These findings appear to be an objective EMG

manifestation of the disorganisation of the brain's neuronal excitatory-inhibitory processes and the loss of functional balance between the structures which regulate muscle tone, all of which are due to a neostriatal dopamine deficit (DeLong, 1990).

EMG indices		Upper extremity rigidity score (point 22)	Motor score (points 18-31)	Handwriting, cutting food, dressing score (points 8-10)	Dyskinesia (disability) score (point 33)
Average amplitude of m. biceps at rest	ON	0.51 *	0.50 *	ns	ns
	OFF	ns	0.67 **	ns	ns
Phasic activation coefficient of m .biceps during voluntary contraction	ON	-0.49 *	-0.60 **	ns	ns
	OFF	ns	-0.64 **	ns	ns
M. biceps involvement under tonic strain of m. biceps of the opposite arm	ON	ns	ns	0.55 *	0.52*
	OFF	ns	ns	0.52 *	ns
M. triceps involvement under tonic strain of m. biceps of the opposite arm	ON	ns	ns	0.57 **	0.48*
	OFF	ns	ns	0.53 *	0.51*

Table 3. Significant correlations of EMG indices with the UPDRS scores studied in 20 PD patients in which the clinical "ON-OFF" phenomenon was verified. Data on the EMG indices and the upper extremity rigidity score for a more impaired side are presented. *- $p<0.05$; ** - $p<0.01$; "ns "- not statistically significant ($p\geq0.05$).

A distinguishing feature of the bioelectrical muscle activity at rest in PD patients was the presence of burst muscle discharges with a rhythm of 4-8 Hz. It should be noted that no significant correlation was found between resting EMG amplitude value and the occurrence of burst muscle discharges. This fact is consistent with the viewpoint that muscle rigidity and tremor at PD do not constitute symptoms which influence one another, and that different pathophysiological mechanisms underlie their origin (Furukawa et al., 1991; Otsuka et al., 1996).

The brain systems, regulating the tonic and phasic muscle activities, were shown to be antagonistically interrelated: the activation of the phasic processes is accompanied by an inhibition of the tonic impulses and, vice versa, the enhancement of tonic impulsation hampers the phasic activity (Houk, 1979). In PD, due to an increased tonic muscle activity at rest, increment in EMG amplitude during phasic activation was reduced relative to the

norm, and, in addition, a decrease in the active contraction amplitudes occurred in some of the patients. As a consequence, the phasic activation coefficient of the voluntarily contracting m. biceps brachii of the patients was generally reduced to 0.1-0.6 and even had negative values, while in healthy subjects the value of the phasic activation coefficient was in most cases 0.7-0.9. Our study data suggest that phasic activation coefficients represent a sufficiently informative index that may be used to quantify phasic muscle activity in PD.

Involvement of the agonist and antagonist muscles appeared to be useful for establishing coorditating muscle relationships. We demonstrated significantly ($p<0.05$) greater activation of the agonist and antagonist muscles during m. biceps brachii tonic strain in PD patients compared to age-matched healthy subjects. The present findings confirm the results of other investigators who consider this fact to be a consequence of increased excitation in the motor centers, caused by dopaminergic control failure (Kryzhanovsky et al, 2002).

When examining the action of an individual dose of levodopa/carbidopa in PD patients with ON-OFF phenomenon, we observed distinct positive drug effects in the following EMG parameters: average and maximal EMG amplitudes at rest; the number of cases with registered rhythmic burst muscle discharges of 4-8 Hz; value of the phasic activation coefficient during voluntary muscle contraction. However, levodopa therapy didn't appear to be effective in terms of the normalization of coordinating agonist - antagonist muscle relationships, either at rest and during holding a weight. In some of patients on levodopa/carbidopa, we even observed an enhancement of the activation of agonist and antagonist muscles during above functional test. We believe that such an increased coactivation of the agonist and antagonist muscles is an objective indicator of risk for developing levodopa-induced dyskinesia in PD patients. According to the literature data, the latter is the result of hypersensitivity of the dopamine receptors in the nigrostriatal system or of a disturbed balance between the degrees of activation of D1 and D2 dopamine receptors (Jenner, 1994).

2.2 Statistics of EMG distribution in patients with Parkinson's disease

The histograms of distribution of EMG amplitude values at rest are informative characteristic of muscle activity (Meigal, 2009). The histogram sharpness and statistical EMG parameters, such as range, variance and kurtosis reflect the magnitude of bioelectrical muscle signals and the level of motor unit synchronization.

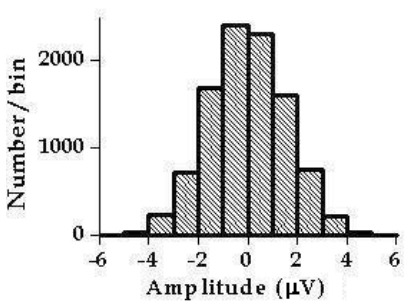


Fig. 7. Example of the histogram of resting EMG amplitudes distribution in healthy subject.

An artifact-free EMG recordings (no less than 10 seconds in duration) from the flexors and extensors (mm. biceps and triceps brachii), registered in 33 patients with PD and 24 age-

matched healthy subjects at rest, were analyzed by the computer programs "Origin 8" and "Statistic 8". EMG in healthy subjects was characterized by low amplitude, flat symmetric histogram (fig. 7) and small values of range, variance and kurtosis (table 4). Range did not exceed 20 μV, variance – 7 and kurtosis – 0.4. In patients with the akinetic-rigid form of the disease, the amplitude of EMG signals was considerably increased because of impossibility of entire muscle relaxation. The mean values of EMG statistical parameters, estimated for this PD group, were significantly ($p<0.001$) augmented as compared to control. In some patients range amounted to 66 μV, variance – 56 and kurtosis – 1.4 (table 4).

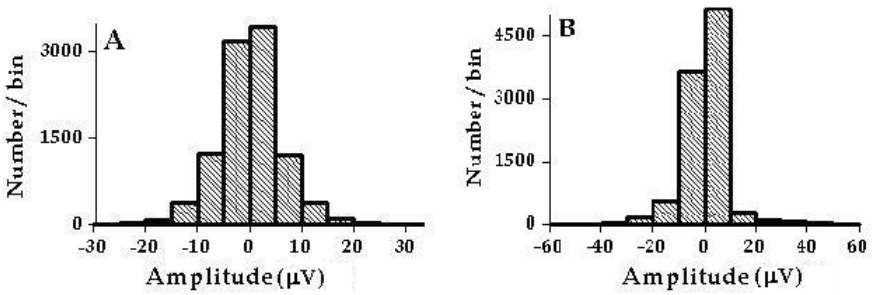


Fig. 8. Examples of the histograms of resting EMG amplitudes distribution in a patient with akinetic-rigid form of Parkinson's disease (A) and a patient with akinetic-rigid- trembling form of this disease (B).

Groups of the tested persons	Statistical parameters		
	Range (μV)	Variance	Kurtosis
Patients with akinetic-rigid-trembling form of the disease n=20	112.75 ± 16.80 *** (24.48 – 381.62)	147.20 ± 44.38 ** (6.91 – 950.63)	4.32 ± 0.51 *** (1.04 – 12.98)
Patients with akinetic-rigid form of the disease n=13	36.81 ± 3.96 *** (21.16 – 66.18)	20.26 ± 4.26 *** (7.89 – 56.16)	0.58 ± 0.14 *** (0.07 – 1.40)
Control group of age-matched healthy subjects n=24	11.18 ± 0.71 (7.08 – 16.46)	2.30 ± 0.31 (0.70 – 5.14)	-0.17 ± 0.03 (-0.10 to -0.30) n = 10 0.18 ± 0.04 (0.01 – 0.33) n = 14

Table 4. Statistical characteristics of EMG in patients with Parkinson's disease and age-matched healthy subjects. EMG characteristics in patients were taken at the side where morbid affection was more expressed; in healthy persons such characteristics were taken at the side where higher values were observed. ** $p<0.01$, *** $p<0.001$ compared to control group. n is number of subjects in each group. In brackets the range of indices in different tested persons is presented.

Patients with the akinetic-rigid-trembling form of PD had the highest values of the EMG statistical parameters. The histograms of EMG amplitude distribution had a sharp peak (fig. 8, B). In some patients of this PD group range reached 382 μV, variance – 951 and kurtosis – 13 (table 4). Correlation analyses revealed statistically significant connection of kurtosis with scores of the point 20 of UPDRS, estimating intensity of tremor of the hand, on which EMG was registered. A coefficient of nonparametric Spearman rank-order correlation between these indices was 0.46 ($p<0.01$). This fact is in accordance with the point of view (Meigal, 2009) that kurtosis well reflects synchronization of motor units responsible for the origin of burst muscle discharges.

2.3 Fractal dynamics of EMGs in patients with Parkinson's disease

Fractal analysis is a new method for biomedical signal processing. Nonlinear analysis techniques are necessary to understand the complexity of the EMG. Study of fractal dynamics of EMG data is based on detrended fluctuation analysis and calculation of Hurst exponent. The Hurst exponent is used as a measure of the long term memory of time series, i.e., the autocorrelation of the time series. (Talebinejad et al., 2010).

Fractal dynamics of EMG signals was studied in 33 patients with akinetic-rigid-trembling form of PD (mean ± SE age 62.1 ± 2.6, range 48-77 years), 30 age-matched healthy subjects (mean ± SE age 65.4 ± 1.9, range 57-78 years) and 20 persons of middle age (mean ± SE age 48.3 ± 1.49, range 45-58 years). EMGs were recorded from m. biceps brachii at the side, where morbid affection was more expressed, at rest no less than 10 seconds in duration.

The rescaled range was calculated for time series. The first step was calculation of the mean. Then mean-adjusted series were created and the cumulative deviate series were calculated from the formula:

$$y(k) = \sum_{i=1}^{k} (z_i - \overline{z}) \tag{2}$$

Where $\overline{z}$ is the mean and $\boldsymbol{z(i)}$ is the value from time series. Then the row of values $y(k)$, $k = 1,\ldots N$ was divided into the segments of length n, and within the limits of each segment the equalization of stright, approximating the sequence of $y(k)$, was defined by least squares method. It is considered that approximation of $y_n(k)$ is the local trend. Further a standard deviation was created from the formula:

$$F(n) = \sqrt{\frac{1}{N}[(y(k) - y_n(k)]^2} \tag{3}$$

Dependence $lg\ F(lg\ n)$ was further built, the angle of slope of approximating line was determined and the value of Hurst index was estimated (Stanley et al., 1999).

We identified three different patterns of surface EMG signals according to fractal dimension (Fig 9, 10): with one, two and three scaling regions, every of which is characteristic by own local exponent. In healthy subjects, the fractal dimension with two exponents was most frequently observed, in 60% among persons of middle age and in 50% among elderly individuals. One exponent was observed in 20% in both groups of healthy subjects and three exponents – in 20% and 30% in middle age and elderly, respectively. In patients with akinetic-rigid-trembling form of PD the fractal dimension of surface EMG signals with three exponents was most characteristic (64%). One exponent did not occur in PD patients (Fig. 11).

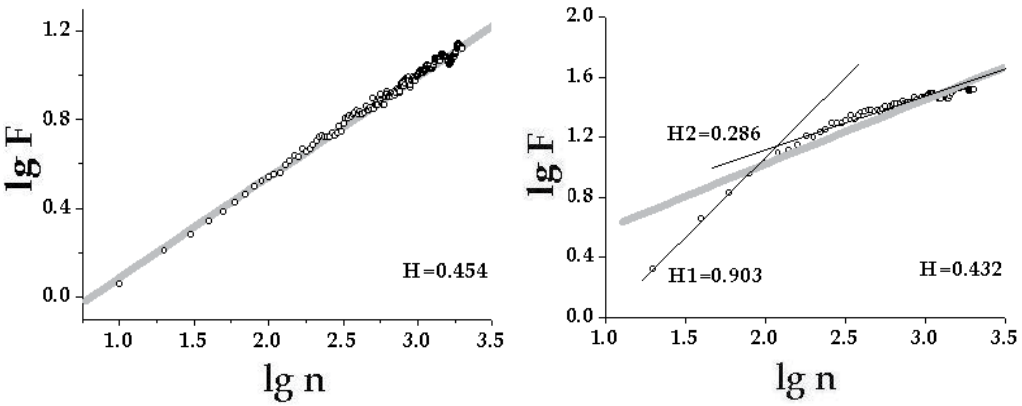


Fig. 9. Patterns of fractal dimension of the surface EMG signals with one and two exponents. Thick line is general exponent, thin lines are local exponents. H is general Hurst index; H1, H2, H3 are values of local Hurst indices.

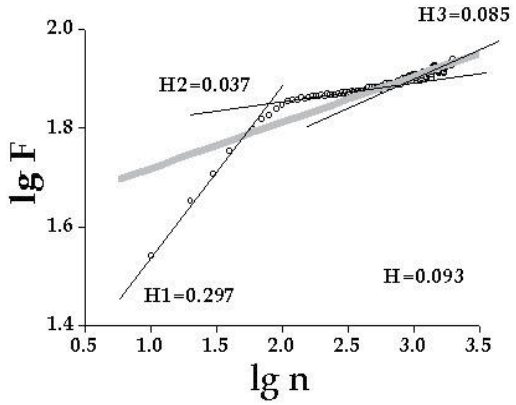


Fig. 10. Pattern of fractal dimension of the surface EMG signals with three exponents. Thick line is general exponent, thin lines are local exponents. H is general Hurst index; H1, H2, H3 are values of local Hurst indices.

Another difference concerned the value of general Hurst index (H). In persons of middle age mean value of H was 0.47 ± 0.02 (range 0.32 – 0.71) and in elderly – 0.44 ± 0.02 (range 0.33 – 0.57). In PD patients mean value of H was significantly ($p<0.01$) lower as compared to elderly subjects – 0.31 ± 0.03 (range 0.09 – 0.49). In PD patients, the value of Hurst index of the third scaling region (H3) in patterns with three exponents also significantly differed from H3 in healthy subjects. H3 was 0.30 ± 0.06 in middle-aged persons, 0.39 ± 0.05 in elderly and 0.14 ± 0.05 in patients with PD ($p<0.05$). It is of interest that the tendency to negative correlation between H and motor scores of part III UPDRS was observed in patients with PD ($r = -0.35$, $p = 0.05$).

Our data showed essential alterations in short and more long-range EMG correlation properties in patients with akinetic-rigid-trembling form of PD. The mean value of H1/H3 in patterns with three exponents in the group of PD patients came up to 27.2 ± 9.5 that

significantly ($p<0.001$) differed from same value in elderly subjects (2.7 ± 0.5). Negative correlation between H1 and H3 ($r = -0.67$, $p<0.01$) was revealed in PD patients.

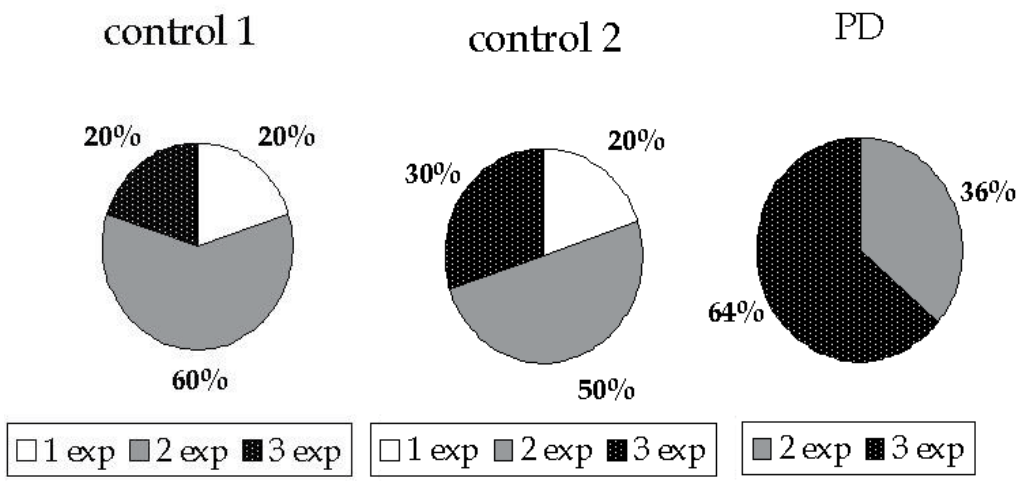


Fig. 11. Comparison of the incidence of different patterns of surface EMG signals fractal dimension (with one, two or three Hurst exponents) in persons of middle age (control 1), elderly subjects (control 2) and patients with Parkinson's disease (PD).

Overall, the present investigation has demonstrated the following distinctive features of surface EMG signals fractal dimension in patients with akinetic-rigid-trembling form of PD: 1) correlation behavior of the resting EMG time series in patients was more complex compared to healthy subjects and often suggested three scaling regions; 2) the value of Hurst exponent was significantly lower in patients, its value may descend to 0.1 - 0.2 that indicates a time series with negative autocorrelation (e.g. a decrease between values will probably be followed by an increase); 3) considerable degradation of short and longer range correlation properties, that, perhaps, is associated with the loss of integrated physiological responsiveness at this disease (Goldberger et al., 2002).

2.4 EMG characteristics of clinically healthy kinsmen of the patients with Parkinson's disease

According to modern concepts, the genetic factor plays a considerable role in the development of Parkinson's disease. Modifications in several genetic loci responsible for the development of this disease have been identified. The considerable role of the genetic factor for the propensity to Parkinson's disease has been confirmed by the data of epidemiological studies. The frequency of development of this disease in kinsmen of Parkinsonian patients is two to seven times higher than that in persons of the control groups (Elbaz et al., 1999). Symptoms of functional insufficiency of the extrapyramidal system can be identified very early, namely several decades prior to possible onset of the development of the clinical form of Parkinson's disease (Berg et al., 2002). Prevention or deceleration of the development of this disease can be provided by the detection of the early, presymptomatic stage of the neurodegenerative process and identification of informative "biomarkers" of PD (Illarioshkin, 2008). We studied surface EMG in clinically healthy kinsmen of the patients

suffering from PD in order to detect latent symptoms of extrapyramidal insufficiency that can be considered genetic determinants of the risk of development of the above disease. The task of our study included estimation of the frequency of occurrence of muscle activity disorders in kinsmen of the patients, characterization of correlations between the appearance symptoms of extrapyramidal insufficiency and age of the tested persons, and formulation of recommendations for individuals belonging, from the aspect of risk of development of PD, to a risk group.

We examined two groups of persons. The first group consisted of 37 clinically healthy kinsmen/kinswomen of patients suffering from PD (children, brothers, and sisters; 22 women and 15 men aged 30 to 56; mean age 45.6 ± 1.5 years). The second group (control) included 30 healthy young and middle-aged persons (19 women and 11 men; age nearly corresponding to that of persons of the first group , i.e., from 34 to 58 years, mean age 46.9 ± 2.2 years. All examined persons gave informed consent to be involved in the study. We recorded surface EMG at rest using superficial bipolar electrodes fixed on the flexor and extensor of the elbow joint (m. biceps brachii and m. triceps brachii, respectively); an electroneuromyograph NeuroMPF (Russia) was used. The detailed description of method is presented in section 2.1.1.

In 9 (24%) clinically healthy kinsmen of PD patients symptoms of functional insufficiency of the extrapyramidal system were evident. They demonstrated the mean amplitude value of 5.4-12.4 μV, maximal amplitude value of 25-93 μV, and the mean power of EMG oscillations reached 0.85- 1.8 mV/sec. In control group the mean amplitude value varied from 3.4 to 5.0 μV, maximal amplitude varied from 5.6 to 20.6 μV and the mean power of EMG oscillations did not exceed 0.02-0.71 mV/sec. Higher values of the intensity of electrical muscle activity in kinsmen of PD patients positively correlated with their age; it should be noted that, in this respect, age older than 45 years can be considered to be critical. The number of elder (older than 45 years) subjects with values of the mean power of EMG oscillations higher than the mean value of this parameter in persons of control group exceeded significantly the number of elder persons with low values of the mean power of EMG oscillations ($p < 0.05$, χ^2 criterion). The correlation coefficient between the age of the tested persons and the value of mean power of EMG oscillations was 0.40 ($p < 0.05$).

In 6 (16%) kinsmen of PD patients short burst-like discharges consisting of two to three oscillations generated with a frequency of 5-10 Hz were observed within the resting EMG (Fig. 12). As a rule, the amplitude of these potentials did not exceed 52 μV.

For more detailed investigation we used statistics of EMG distribution, namely such parameters as range, variance and kurtosis. Range and variance reflect the extent of bioelectrical muscle signals. Kurtosis characterizes motor unit synchronization. We supposed that statistical methods might appear effective for exposure of pathological signs of muscle activity. In control group of healthy middle-aged persons the extreme value of resting EMG amplitude range was 20 μV, variance – 7 and kurtosis – 0.4. The parameters of range, variance and kurtosis were considered going out outside a norm, if they exceeded the extreme values of these indices in the control group. We found 16 (43 %) kinsmen of patients with PD, who had high statistical parameters of EMG signals. In 14 kinsmen (38 %) range and variance were augmented compared to the extreme values of these indices in the control group. In 11 kinsmen (29 %) kurtosis had higher values than normal, presumably, reflecting enhanced synchronization in activity of motor units (Table 5).

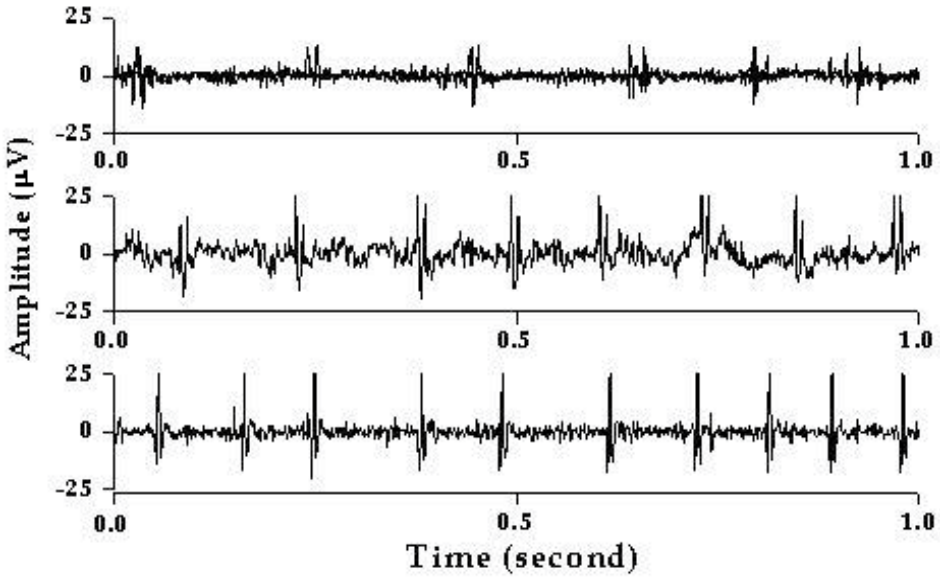


Fig. 12. Types of burst-like muscle discharges with frequency 6, 8 and 10 Hz recorded in three kinsmen of patients suffering from Parkinson's disease.

Statistical parameters	Number of tested persons
Range [22.46 – 113.61 μV] Variance [8.23 – 112.32] Kurtosis [0.43 – 16.30]	9 (24 %)
Range [24.22 – 28.33 μV] Variance [8.08 – 13.55]	5 (14 %)
Kurtosis [0.67; 0.70]	2 (5 %)
Total	16 (43 %)

Table 5. Incidence of resting EMG statistical parameters, going out outside a norm, in kinsmen of patients with Parkinson's disease. In square brackets the range of indices in different persons is presented.

The data obtained in our work agree with findings of other authors who emphasized that data obtained using EMG techniques are of a high informative value in the diagnostics of subclinical manifestations of weakening of the supraspinal control (Robichaud et al., 2009), and that the genetic factor responsible for the propensity for development of the extrapyramidal insufficiency is rather important (Elbaz et al., 1999; Illarioshkin, 2002).
A single common pathogenetic factor, namely conformational modifications of some cellular proteins at a post-translational stage of their synthesis, underlies most neurodegenerative diseases, including PD. Due to the existence of powerful compensatory and detoxication

systems in cells, such units are capable of successfully "overcoming" abnormal protein substrates for many years (Sherman & Goldberg, 2001). Delayed manifestation of clinical symptoms of the above disease is a feature of "conformational" pathologies of the brain. Latent pathological process can run course up to 30 years (Kryzhanovskii et al., 1995). The rate of pathological modifications in nerve cells within the presymptomatic period of PD is relatively low, but neuronal death is intensified significantly with transition to the stage of manifestation of this disease (Antonini et al., 1998). In relation to the above data, it is quite obvious that early diagnostics of the existence of latent extrapyramidal insufficiency is of exceptional importance. To prevent manifestations of PD in persons belonging to the risk group with respect to the development of parkinsonism, certain basic recommendations should be taken into account. They included a description of the rational daily routine, a recommended dietary intake with an increased content of vitamin B6 (pyridoxine, which is the main catalyzer in the synthesis of dopamine), and also a list of the drugs whose long-term administration should be avoided. Among the latter drugs are therapeutic agents whose administration leads either to depletion of the regulatory function of the dopaminergic system or to an increase in the functional activity of this system. Among such agents are haloperidol, the indole reserpine, fluoxetine (Prozac), metoclopramide (Cerucal), clozapine, and Cordarone, as well as derivatives of phenothiazine and butyrophenol, and also lithium preparations.

3. Investigation of contingent negative variation

Endogenous cortical movement-related reaction contingent negative variation (CNV) is a sensitive indicator for the objective evaluation of the severity of PD and quantifying the efficacy of antiparkinsonian therapy. Many authors identify two phases in CNV: an early phase, the Bereitschaftpotential, and a late phase, the negative slope (Filipovic et al., 1997). It has been suggested that these are generated by different brain structures: the cerebellar efferent system is more involved in generating the Bereitschaftpotential, while the basal ganglia are more involved in generating the negative slope (Ikeda et al., 1997). The question of the relationships between each of these phases and higher integrative processes and the mechanisms of direct motor control have received insufficient study. The aims of the present work were to study the extent to which the early and late phases of CNV depend on motor and mental functions and to determine what effect have neurotrophic agents on CNV. Tasks to be addressed were: 1) identification of the individual characteristics of the early and late phases of CNV in patients with PD as compared with subjects of similar age; 2) identification of correlation the measures of the two phases of CNV with clinical characteristics of the PD patients; 3) investigation the effect of the brain-derived peptide drug cerebrolysin on the amplitude characteristics of CNV in PD.

3.1 Methods

Studies were performed using 28 healthy subjects (13 male, 15 female, age 48–73 years, mean age 60.9 ± 1.2 years) and 56 patients with idiopathic PD (23 male, 33 female, age 45–74 years, mean age 61.3 ± 1.1 years). Patients were in stages 1.5–3.0 (2.2 ± 0.1) H-Y (international classification of Hoehn and Yaht, 1967). Patients received basic antiparkinsonism treatment with levodopa-containing agents (levodopa/carbidopa). Individual daily doses of levodopa were 250–750 mg. All subjects were right-handed.

Monopolar recordings were made of CNV from intermediate leads: frontal (Fz), central (Cz), and parietal (Pz). The indifferent electrode was located on the earlobe. The ground electrode was located on the left forearm. During studies, subjects were in a relaxed, calm state with the eyes closed. Bioelectrical signals were passed to an amplifier with a bandpass of 0.08–15 Hz and then to a computer hard disk. CNV was recorded using two sound stimuli of different intensities with a 1-sec interval: the ready signal was at 50 dB HL and the trigger signal was at 80 dB HL. The subject pressed a key in response to the trigger signal. Analysis was performed using computer programs. The sampling frequency was 200 Hz. The analysis time was 3.1 sec, the first 400 ms being a record of the baseline electroencephalogram. Mean initial activity was determined from an artefact-free part of the electroencephalogram trace. Averaging of 30 trials yielded: 1) the duration of CNV measured as the time interval between the start of the negative deviation from the baseline after the ready stimulus and the moment of presentation of the trigger stimulus (ms); 2) the areas of Bereitschaftpotential and negative slope, between the baseline and the negativity curve of the corresponding region $S = (\Sigma Ai) \times \Delta t$ (mV·ms), where Ai is the amplitude of the negative deviation from the initial level at a sampling frequency of 200 Hz and Δt is a time interval of duration 5 ms; 3) the mean amplitudes of Bereitschaftpotential and negative slope defined by $A = \Sigma Ai/n$ (μV). The program also allowed calculation of the simple sensorimotor reaction time (the mean latent period of pressing the key in response to the trigger signal).

Motor symptomatology was assessed quantitatively in patients with PD in points using the unified scale UPDRS. The total score was measured in each of three dimension scales: I (impairments in thought, mood), II (decreased daily activity, impairment of hygiene activities); and III (disturbances of motor function, including bradykinesia, rigidity, and tremor) using four-point subscales for each symptom. General cognitive status of the PD patients was characterized using the standard quantitative scale Mini Mental State Examination (MMSE). The overall assessment of mental functions in normal patients yielded 30 points. Decreases in the total score to less than 25 were regarded as a sign of early dementia.

The state of coordinatory muscle interactions was studied in 29 patients with PD (aged 47–72 years) by assessing the level of reciprocal involvement of the triceps brachii antagonist muscle (the extensor muscle of the shoulder) on functional loading of the biceps brachii muscle (the flexor of the shoulder) on the right side. EMGs were recorded using bipolar skin electrodes (0.5 × 1.0 cm^2) with a constant interelectrode distance of 1.5 cm. Bioelectrical signals were passed to the amplifiers of a Medikor MG440 (Budapest) electromyography with a bandpass of 10 Hz to 10 kHz. Functional loading on the biceps brachii muscle was applied by holding a load of 2 kg on the elevated and forward extended arm for 5 sec. With the patient in the calm, relaxed state and during holding of the load, at least 100 measurements were processed using the computer program to determine the mean EMG amplitude in the triceps brachii at rest (Ar) and loading (Al), the coefficient of reciprocal involvement of the antagonist muscle was calculated as $Al/(Ar + Al)$. This coefficient had a value of 0.5 when the amplitude on loading showed no change. If the amplitude decreased, then coefficient of reciprocal involvement had values of less than 0.5, while increases yielded coefficient of reciprocal involvement values of greater than 0.5.

The effects of cerebrolysin on measures of CNV were studied in 21 patients with PD that were taking antiparkinsonian therapy, which was not changed during one month before cerebrolysin treatment and under the whole cerebrolysin course (intravenously 10 ml, during 10 days). Before and after cerebrolysin treatment we studied clinical scores of UPDRS and CNV.

Data obtained in healthy subjects and patients with PD were compared using the non-parametric Mann–Whitney test. Data obtained in individual patients before and after administration of cerebrolysin were analyzed using the t- test for pairwise dependent variables. Correlations between the amplitudes of the two phases of CNV, the UPDRS and MMSE scales, and the levels of reciprocal involvement of antagonist muscles were identified by calculating the correlation coefficient by the non-parametric Spearman method (rS). Relationships were regarded as moderate at $0.3 \leq rS \leq 0.5$ and considerable at $rS > 0.5$. Differences were taken as significant at $p < 0.05$.

3.2 Results

3.2.1 Characteristics of the early and late phases of CNV in healthy subjects and patients with Parkinson's disease

Repeat studies in individual subjects showed that CNV had the most stable characteristics in the central medial lead (Cz), so data obtained from this lead were analyzed in detail. CNV in healthy subjects could usually be discriminated into two phases: an early phase (Bereitschaftpotential) 505–728 (596.3 ± 12.1) ms before the trigger signal and a late phase (negative slope) apparent as an additional negative deviation 170–365 (230.2 ± 15.4) ms before the trigger signal (Fig. 13). However, the second phase was not always clearly evident; in this situation CNV consisted of an initial drop-off followed by a uniform negative deviation from baseline lasting to the trigger signal. In these cases, the second half of CNV was analyzed as the second phase. In healthy subjects, the mean amplitudes of Bereitschaftpotential and negative slope were 9.0 ± 1.1 and 10.6 ± 1.0 μV respectively, with areas of 2.8 ± 0.4 and 3.2 ± 0.2 mV·ms (Table 6). Unlike healthy subjects, CNV in many patients was poorly evident, in some, no negativity at all developed between the ready and trigger signals (Fig. 14). Statistical analysis of the data revealed significant decreases in the mean amplitudes and areas of both phases of CNV in patients with PD as compared with healthy subjects (Table 6). In addition, patients showed an increase in the simple sensorimotor reaction time for pressing the key in response to the trigger signal, from 240.9 ± 13.7 ms in healthy subjects to 299.6 ± 17.3 ms ($p < 0.05$).

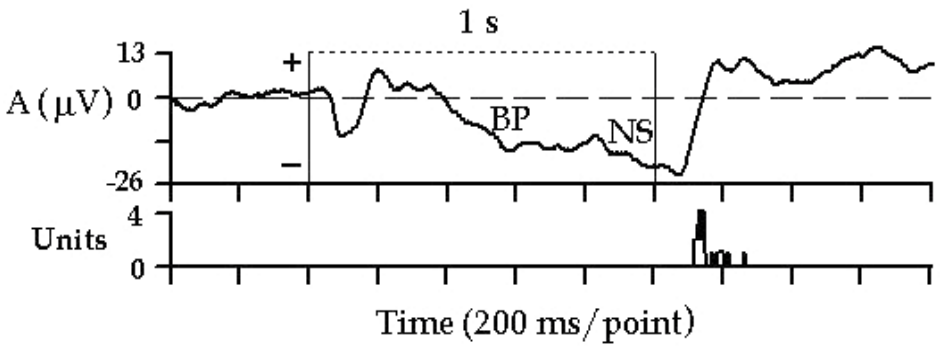


Fig. 13. Characteristic record of contingent negative variation (CNV) in healthy subject aged 64 years. A is the amplitude, μV. BP is the early phase and NS' is the late phase of CNV. Vertical lines show the moments of presentation of the warning and trigger signals, with an interval of 1 sec. Positivity is shown by upward deviations from the baseline and negativity by downward deviations. Low trace is simple sensorimotor reaction times for pressing the key after presentation of the trigger signal. Units show the number of keypresses.

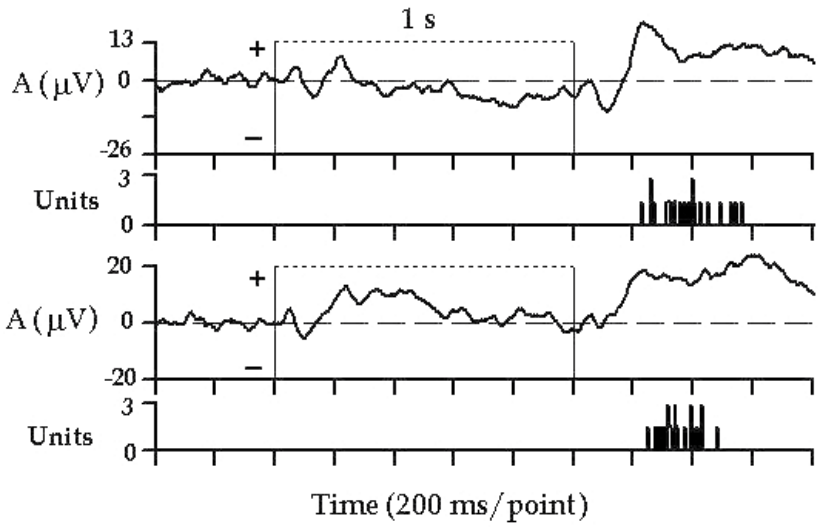


Fig. 14. Example traces of contingent negative variation (CNV) in two patients with Parkinson's disease aged 65 and 54, years. CNV in the first patient was poorly expressed, and the second patient showed no negative deviation. For further details see caption to Fig. 13.

Group	Area of early phase, mV·ms	Mean amplitude of early phase, μV	Area of late phase, mV·ms	Mean amplitude of late phase, μV
Healthy, n = 28	2,8 ± 0,4	9,0 ± 1,1	3,2 ± 0,2	10,6 ± 1,0
Patients, n = 53	1,8 ± 0,2 *	5,7 ± 0,4 *	1,7 ± 0,1 *	6,5 ± 0,5 *
p	< 0,01	< 0,01	< 0,001	< 0,01

Table 6. Differences in measures of the two phases of contingent negative variation in the median central lead (Cz) in healthy subjects and patients with Parkinson's disease. n is the number of subjects in the group.* is significant difference between patients with PD and healthy subjects (non-parametric Mann–Whitney test).

3.2.2 Correlation between the amplitudes of the early and late phases of CNV and characteristics of the patients with Parkinson's disease

Correlation analysis revealed moderately significant relationships between the amplitudes of the two phases of CNV and point scores for individual subscales on the UPDRS. Table 7 shows that the mean amplitudes of Bereitschaftpotential and negative slope were negatively related (rS = –0.31 and rS = –0.3 respectively, $p < 0.05$) to the total point score on UPDRS subscale II, which reflects decreases in the activities of daily living (impairments of hygiene habits, cutting and holding food, difficulty dressing and walking). It was interesting to note that there was a selective negative correlation (rS = –0.32, $p < 0.05$) between the magnitude of negative slope and symptoms on subscale II such as gait freezing, while Bereitschaftpotential showed no significant relationships of this type. There were no significant correlational relationships between measures of the two phases of CNV and the total score on UPDRS subscale III, reflecting intrinsic motor functions, or with clinical point scores for rigidity, tremor, or bradykinesia.

Clinical scale points	Mean amplitude of early phase	Mean amplitude of late phase
Total points on UPDRS subscale II; n=56	rS = -0,31 *	rS = -0,30 *
Points on UPDRS subscale II; item 14 (gait freezing); n=56	rS = -0,24	rS = -0,32 *
Coefficient of reciprocal involvement between antagonist muscles; n=29	rS = -0,58 **	rS = -0,51 **
Total score on MMSE (mental functions); n=28	rS = 0,47 *	rS = 0,47 *
Points on MMSE item 4 (memory); n=28	rS = 0,56 **	rS = 0,46 *

Table 7. Relationships between the amplitudes of the two phases of contingent negative variation in the median central lead (Cz) and clinical point scores in patients with Parkinson's disease. n is number of investigated persons. rS is the Spearman correlation coefficient.. * is $p<0.05$; ** is $p<0.01$.

The existence of a link between measures of the two phases of CNV and the state of coordinatory muscle interactions was addressed by studying the relationship between the amplitude characteristics of CNV and the extent of reciprocal impairments between antagonist muscles in patients with PD by calculating the coefficient of reciprocal involvement. Bereitschaftpotential and negative slope were completely absent in those patients in whom the coefficient of reciprocal involvement was high (0.67–0.8), which is evidence for an abnormal increase in the reciprocal involvement of the extensor muscles in the operation of the flexor muscles. Conversely, low coefficient of reciprocal involvement was associated with maximal amplitudes for both phases of CNV. The negative correlations between the extent of reciprocal muscle involvement and the amplitudes of Bereitschaftpotential and negative slope were significant (rS = –0.58 and rS = –0.51 respectively, $p < 0.01$). Comparison of the parameters of CNV and quantitative measures on the MMSE scale revealed an identical moderate positive relationship (rS = 0.47, $p < 0.05$) with the magnitudes of both phases and the state of mental functions in patients with PD (Table 7). The strongest relationship was between Bereitschaftpotential and point 4 of the MMSE scale, which reflects memory (rS = 0.56, $p < 0.01$).

3.2.3 Effects of cerebrolysin on measures of CNV in patients with Parkinson's disease

The results of the present study showed that the course of cerebrolysin treatment combined with levodopa has the positive therapeutic effect, such as: a significant decrease of the part I, II and III UPDRS scores. A decrease of the UPDRS part I scores (improvement in thought, mood) and part II scores (that is an increase of daily activity and ability of more full value selfattendance) was the most expressed. Significant increase of the CNV amplitude value and duration well reflected the enhancement of the brain activity (Table 8).

Time of investigation	Duration of CNV (ms)	Mean amplitude of CNV (μV)	UPDRS part I scores	UPDRS part II scores	UPDRS part III scores
Before CER	423.1 ± 43.3	3.1 ± 0.9	5.6 ± 0.7	14.2 ± 1.3	40.4 ± 3.4
After CER	600.6 ± 38.5*	6.8 ± 1.4***	3.5 ± 0.7***	11.3 ± 1.4***	32.9 ± 3.2*

Table 8. Change of contingent negative variation (CNV) and UPDRS scores in Parkinson's disease patients after cerebrolysin (CER) treatment. Footnotes: * - the significant change after cerebrolysin treatment, $p < 0.05$; *** - $p < 0.001$ (paired t-test).

3.3 Discussion

The results showed that patients with PD, as compared with healthy subjects, had significant decreases in the amplitudes and areas of both the early and late phases of CNV. We established that one significant factor decreasing both phases of CNV in patients with parkinsonism is impairment of coordinatory muscle interactions. Thus, the more significant the coordinatory impairment, apparent as an increase in the reciprocal involvement of the antagonist muscle during functional tests, the smaller the values of Bereitschaftpotential and negative slope in patients (rS = –0.58 and rS = –0.51 respectively; $p < 0.01$). As shown by the present data, a further significant factor affecting both phases of CNV was the state of mental functions. The positive correlation between Bereitschaftpotential amplitude and point 4 on the MMSE scale, characterizing memory (rS = 0.56, $p < 0.01$), was the most marked. This suggests that CNV can be regarded not only as a correlate of the initiation and preparation of motor structures for performing an action, but also as a neurophysiological component of mental functions. This point of view is in good agreement with published data showing sharp reductions in CNV in Alzheimer's-type dementia (Zappoli et al.,1991).

The suggestion (Ikeda et al., 1997), that the nigrostriatal dopaminergic system has a greater role in generating the late phase than the early phase of CNV is supported by our finding of the existence of a selective negative correlation ($p < 0.05$) between the magnitude of negative slope and the severity of symptoms such as gait freezing; there was no such correlation for Bereitschaftpotential. The symptom of "gait freezing" does not correlate with rigidity or bradykinesia (Bartels et al., 2003), is significantly decreased by levodopa (Schaarsma et al., 2003) and depends on the functional state of the globus pallidus: stimulation of its internal zone (the main source of the efferent output of the whole of the striopallidal complex) effectively eliminates the phenomenon of "gait freezing" (Katayama et al., 2000).

The results of the present study enlarge the perspectives in application of cerebrolysin and are in agreement with literature data on the efficacy of cerebrolysin in neurological practice. Thus, it was shown that cerebrolysin might be useful in patients with senile dementia of the Alzheimer type (Ruther, al., 2002). The positive therapeutic effect of the brain-derived peptide drug cerebrolysin can be connected with its ability to increase the expression of BBB-GLUT1 and MAP2 genes, that improves the transport of the glucose through blood-brain barrier and keeps the cytoskeleton wholeness accordingly (Boado, 2001). Cerebrolysin can also reduce the glutamate induced excitotoxicity (Hutter-Pair, al., 1998).

Obtained data proof that CNV appears to be a good tool for the evaluation of the medication efficiency. The parameters of CNV well reflected the improvement of the functional state of the patients after the course of cerebrolysin treatment.

4. Cortical evoked potentials upon paired-click auditory stimulation

It has been previously reported in clinical and experimental studies that movement disorders in PD largely occur due to the imbalance of inhibitory and excitatory processes in motor cortical and subcortical neuronal circuits following a nigrostriatal dopamine deficit (Ridding et al., 1995). A paired-pulse paradigm is usually used to study postexcitatory inhibition effect related to sensory gating mechanisms and synaptic processes in neurotransmitters release (Chu et al., 2009). There are two mechanisms that might explain paired-pulse inhibition phenomena. The first mechanism is the decrease in release probability of excitatory neurotransmitters from terminals of afferent axons (Szabo et al., 2000). Another possible mechanism of the decrement of the second response on paired stimulation is connected with synaptically released GABA from terminals of inhibitory interneurons (Chu & Hablitz, 2003). As the paired-pulse facilitation, paired-pulse inhibition is considered to be a form of a short-term synaptic plasticity. The investigation of cortical evoked potentials to paired-pulse sensory stimulation may provide additional information about mechanisms of neurological disturbances in PD.

The aim of this study was to investigate the postexcitatory inhibition of the N1/P2 complex of the cortical evoked potentials on auditory paired-click stimulation in patients with PD in comparison with age-matched healthy subjects. Our second goal was to evaluate the influence of neurotrophic drug cerebrolysin on postexcitatory cortical inhibition.

4.1 Methods

Studies were performed in two groups. The first group included 58 PD patients, with the severity of the disease corresponding to 1.5 - 3.0 of Hoehn M.M. and Yahr M.D. (1967) scale (28 men and 30 women, mean ± SE age 61.5 ± 1.1, range 45 - 74 years). The second group was control and consisted of 22 age-matched healthy subjects (10 men and 12 women, mean ± SE age 61.4 ± 1.1, range 48 - 73 years).

The study was approved in advance by the Ethical Committee of the Institute of Gerontology and was in accordance with the Declaration of Helsinki. The patients regularly underwent treatment at the Parkinson's Disease Centre of the Institute of Gerontology and gave written informed consent to participate in this study. The diagnosis of Parkinson's disease was determined according to the UK Bank Criteria (Hughes A. et al., 1992). The patients had from 2 to 22 year individual histories of idiopathic PD and were taking antiparkinsonian therapy at individual dose of 187.5 - 750 mg of levodopa / carbidopa daily. Besides levodopa / carbidopa, the patients were using other antiparkinsonian medication: selegiline, pramipexol, amantadine. The neurological status of PD patients was evaluated with Unified Parkinson's Disease Rating Scale (UPDRS; Fahn S. and R. Elton., 1987; Holloway R.G. et al., 2004) in the "ON" state 1 hour after levodopa / carbidopa intake. Mini Mental State Examination (MMSE) was used to study general cognitive status of the PD patients.

Auditory evoked potentials were recorded in the PD patients in their "OFF" state in the morning, after they were free from levodopa treatment and other antiparkinsonian medications for at least 12 hours. During registration of evoked potentials the subjects were sitting comfortably in a semi-reclined armchair in a quiet room with closed eyes. Cortical

auditory evoked potentials were recorded at the vertex (Cz) referenced to a linked-ear electrode. The ground electrode was placed at the left wrist. The impedance of the electrodes was less than 10 kΩ. The electrode signal was amplified using a bandpass filter (0.53 - 30 Hz), digitised with 200 Hz sampling rate and stored for further analysis.
The pattern for double stimulation consisted of paired auditory clicks with 500, 700, 800, 900, 1100 and 2000 ms interstimulus intervals. The identical parameters (duration of 0.15 ms and intensity of 80 dB HL - hearing level) were used for the preceding conditioning click and following test click. Pairs of clicks were delivered once every 7 s for each interstimulus interval. Previous studies have shown that stimulation at faster frequencies can lead to a decrement in the cortical evoked potentials. A 2000 - 3000 ms electroencephalography epoch was recorded for each trial, including a 300 ms pre-stimulus baseline. The recording time depended on interstimulus intervals. The epochs contaminated with blinks or other artefacts were excluded from the data and twenty acceptable artefact-free trials were averaged for each interstimulus interval and used for further analysis. In electroencephalography recordings upon paired stimulation, amplitudes of N1-P2 complex (peak to peak) in the first (A1) and the second (A2) responses were measured. The amplitudes of the components N1 and P2 were estimated in the 60 – 150 ms and 120 - 220 ms ranges of time, respectively. The percent of paired-pulse inhibition of the N1-P2 complex was calculated using the formula: (A1-A2)/A1×100.
The effects of cerebrolysin on the postexcitatory inhibition of the N1/P2 complex of the cortical evoked potentials on auditory paired-click stimulation were studied in 21 patients with PD that were taking antiparkinsonian therapy, which was not changed during one month before cerebrolysin treatment and under the whole cerebrolysin course (intravenously 10 ml, during 10 days).
The results were analyzed statistically. Comparisons between PD patients and control groups were made using a non-parametric two-tailed Mann-Whitney criterion. Data obtained from the same patients before and after cerebrolysin treatment were compared using two-tailed paired t-test.

4.2 Results

4.2.1 Investigation of the postexcitatory inhibition following paired stimulation

The postexcitatory cortical inhibition in response to auditory stimulation studied with a paired-pulse paradigm was significantly reduced in patients with PD compared to control subjects. Amplitudes of N1-P2 complexes following the second stimulus of a pair at interstimulus intervals of 500, 700 and 900 ms were greater in PD patients. The mean values of paired-pulse inhibition in the group of PD patients were decreased to 29.8 ± 4.8 % ($p<0.01$), 25.4 ± 3.2 % ($p<0.001$) and 15.1 ± 2.6 % ($p<0.001$) for intervals 500, 700 and 900 ms respectively as compared to these values (54.1 ± 4.2 %; 49.8 ± 2.3 % and 42.9 ± 2.7 %) in the group of age-matched controls (Table 9).
The mean amplitude of N1-P2 complex elicited by a single (first) auditory stimulus in the group of PD patients was 16.2 ± 0.8 μV which was less than in age-matched subjects (18.5 ± 1.6 μV) but this difference was not statistically significant ($p>0.05$).

4.2.2 The influence of cerebrolysin treatment on the postexcitatory inhibition

A distinct positive effect of the course of cerebrolysin treatment on the postexcitatory cortical inhibition at paired-click stimulation was observed in the group of 21 PD patients. A noticeable shift of the paired-pulse inhibition value for 700, 800 and 900 ms intervals towards the values of the healthy control was found (Table 10, Fig 15).

Investigated groups	Inhibition in % of the second N1-P2 complex at interstimulus intervals			Averaged
	500 ms	700 ms	900 ms	
Age-matched control	54.1 ± 4.2	49.8± 2.3	42.9 ± 2.7	48.0 ± 2,1
PD patients	* 29.8 ± 4.8	** 25.4 ± 3.2	** 15.1± 2.6	** 21,4 ±2,4

Table 9. Inhibition of the second N1-P2 complex of cortical auditory evoked potentials at paired-click stimulation in age-matched control group and patients with Parkinson's disease (Mean ± SE).
* - P<0.01; ** - P<0.001 compared to control subjects (nonparametric Mann-Whitney test).

Time of investigation	**Averaged value of paired-pulse inhibition** (%) **at interstimulus intervals (ms)**			
	700	**800**	900	**Averaged data**
Before cerebrolysin	29.9 ± 3.9	26.7 ± 3.4	17.1 ± 3.1	24.6 ± 2.3
After cerebrolysin	38.1 ± 3.2	37.1 ±3.3	27.5 ± 4.1	34.2 ± 2.9
P (paired t-test)	<0.01	<0.001	<0.05	<0.001

Table 10. The influence of the course of cerebrolysin treatment on the postexcitatory inhibition following paired-click auditory stimulation in patients with Parkinson's disease (Mean ± SE).

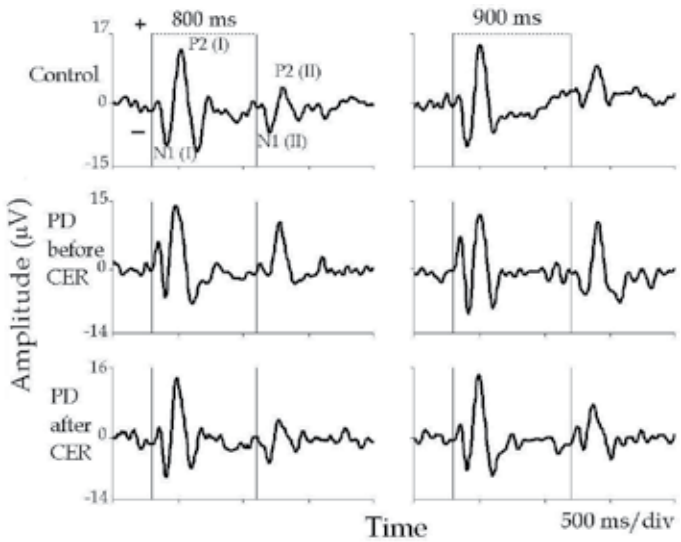


Fig. 15. Cortical auditory evoked potentials at paired auditory stimulation with interstimulus intervals of 800 and 900 ms in healthy control and patient with Parkinson's disease (PD) before and after the course of cerebrolysin (CER). N1(I), P2(I) – the components of cortical evoked potentials on the first conditional stimulus and N1(II), P2(II) – on the second test stimulus. Vertical solid bars on the records correspond to the onset of auditory signals.

4.3 Discussion

The main result of this study showed that PD patients had significantly reduced paired-pulse inhibition of the N1/P2 component of evoked potentials in the auditory cortex for interstimulus intervals of 500, 700 and 900 ms compared to the healthy age-matched subjects. Possible explanation of the reduced cortical inhibition in PD is the functional deficiency of inhibitory interneurons caused by depletion of dopaminergic innervation in the cerebral cortex (Gaspar et al., 1991). As already established (Krnjevic et al., 1966), afferent volleys after initial excitatory postsynaptic potentials (EPSPs) result in inhibitory postsynaptic potentials (IPSPs). A system of GABAergic interneurons, which can be activated by direct and indirect stimulation, may play the major role in the genesis of these IPSPs (Hanajima & Ugawa, 2000). The synaptic release of GABA is regulated by presynaptic GABA receptors of the B-type (Chu & Hablitz, 2003). There is also strong evidence that dopamine regulates inhibitory transmission at the synapses between pyramidal cells and interneurons by activating D1-like receptors located on the presynaptic terminals of GABAergic axons (Gonzalez-Islas & Hablitz, 2001). Dysfunction of cortical interneurons in PD also might be a result of noradrenergic denervation and monoamine terminal loss (Marie et al., 1995), as some investigations showed that cortical GABAergic interneurons can be excited via alpha-adrenoreceptors (Kawaguchi & Shindou, 1998).

Another possible explanation of the reduced inhibition in the auditory cortex in patients with PD may be the loss of dopaminergic transmission in the basal ganglia and the dysfunction of the caudal pallidum that sends its direct projections to the inferior colliculus, medial geniculate nucleus and temporal cerebral cortex (Shammah-Lagnado et al., 1996). The basal ganglia appear to "gate" sensory inputs at various levels and activation of basal ganglia outputs (entopeduncular nucleus and substantia nigra pars reticulate) is able to inhibit sensory responses (Boecker et al., 1999).

Our findings allow to suppose that drugs, which are able to activate cerebral inhibitory GABAergic system, can be useful in medication of PD. Phenibut (noofen) belongs to such drugs (Marshall & Foord, 2010). Application of noofen in complex therapy of PD appeared effective for the improvement of cognitive functions, enhancement of emotional state and increase of social adaptation of the PD patients (Karaban et al., 2006).

This study demonstrated that course of cerebrolysin treatment promotes normalization of the inhibitory brain processes. The positive effect of cerebrolysin indicates that neurotrophic drugs can also be useful in complex antiparkinsonian therapy for advance of the ability of the brain to provide normal inhibition.

5. Conclusion

The present investigation has shown that the surface EMG data add essential information to the clinical characteristics of PD patients. We found that separate EMG indices correlated, in a specific manner, with certain UPDRS sub-items, which could result in a better understanding of the pathogenesis of clinical PD symptoms. Motor disorders in PD (part III UPDRS scores) were found to be predominantly associated with disturbances in regulation of the tonic and phasic muscle activities. At the same time, disorders of the upper extremity daily activity (points 8-10 of UPDRS) and the dyskinesia (disability) (point 33 of UPDRS) are largely conditioned by the disturbance of reflex coordinating relationships between the muscles in PD. EMG analysis seems to be a useful tool for levodopa therapy adjustment and for predicting the course of disease.

In this study critical values of normal statistics of surface EMG distribution at rest were defined. Evaluation of statistical parameters of the EMG signals, to our opinion, appeared to be effective for the detection of signs of the disturbed muscle activity. Range and variance reflect the extent of bioelectrical muscle signals. Kurtosis characterizes motor unit synchronization. These EMG characteristics assist to detect latent symptoms of extrapyramidal insufficiency in clinically healthy kinsmen of the patients suffering from PD that can be considered genetic determinants of the risk of development of the above disease. Formulation of recommendations for individuals belonging to a risk group is of exceptional importance to prevent manifestations of PD.

Novel EMG characteristic is fractal dynamics of EMG data based on detrended fluctuation analysis and calculation of Hurst exponent. Fractal dimension studies the non-linear properties of EMG. The present investigation has demonstrated distinctive features of surface EMG signals fractal dimension at rest in patients with akinetic-rigid-trembling form of PD: 1) fractal dimension in PD patients is more complex compared to healthy subjects; 2) the value of Hurst exponent is significantly less in patients; 3) there is the considerable degradation of short and longer range correlation properties of EMG signals in PD. Fractal analysis has proved to be sensitive to neuromuscular status and may have potential in the assessment of the severity of PD

Evaluation of brain evoked potentials provides additional information about the mechanisms of neurological disturbances in PD. The results obtained in the present study produce evidence for significant relationships between both the early and late phases of movement-related potential CNV and the neurophysiological mechanisms supporting coordinatory muscle interactions and mental functions, including the simultaneous activity of numerous specific and non-specific brain structures (motor cortex, supplementary motor cortex, prefrontal cortex, cerebellar and thalamic projections). The existence of a selective negative correlation between the magnitude of the late CNV phase and the severity of symptoms such as "gait freezing" suggests a great role of efferent system of the basal ganglia in generating this phase of CNV. The investigation of cortical evoked potentials at paired-pulse sensory stimulation shows that inhibitory processes are deficient in PD patients. The findings may suggest that drugs, being the derivates of GABA, can be useful in treatment of PD. The parameters of CNV and the value of postexcitatory cortical inhibition at paired-click sensory stimulation well characterize the state of brain activity. Together with other neurophysiological parameters the brain evoked potentials might be a good tool for quantifying the efficacy of medication of PD patients.

6. References

Abbruzzese, G. & Berardelli, A. 2003. Sensorimotor integration in movement disorders. Mov. Disord., Vol. 18, pp. 231-240.

Antonini, A., Leenders, K. L. & Eidelberg, D. 1998. [11C]raclopride-PET studies of the Huntington's disease rate of progression: relevance of the trinucleotide repeat length. Ann. Neurol., Vol. 43, No. 2, pp. 253-255.

Aotsuka, A., Wheate, S. J., Dranke, M. E., Jr. & Paulson, G. W. 1996. Event-related potentials in Parkinson's disease. Electromyogr. Clin. Neurophysiol., Vol. 36, No. 4, pp. 215–220.

Bartels, A. L., Balash, Y., Gurevich, T., Schaafsma, J. D., Hausdorff, J. M. & Giladi N. 2003. Relationship between freezing of gait (FOG) and other features of Parkinson's:

FOG is not correlated with bradykinesia. J. Clin. Neurosci., Vol. 10, No. 5, pp. 584 - 588.

Berg, D., Roggendorf, W., Schroder, U. et al.. 2002. Echogenicity of the substantia nigra: association with increased iron content and marker for susceptibility to nigrostriatal injury. Arch. Neurol., Vol. 59, No. 6, pp. 999-1005.

Boado, R.J. 2001. Amplification of blood-brain barrier GLUTI glucose transporter gene expression by brain-derived peptides. Neurosci. Res, Vol. 40, No. 4, pp. 337-342.

Boecker, H., Ceballos-Baumann, A., Bartenstein, P., Weindl, A., Siebner, H.R., Fassbender, T., Munz, F., Schwaige,r M. & Conrad, B. 1999. Sensory processing in Parkinson's and Huntington's disease: investigations with 3D H(2) (15) O-PET. Brain, Vol. 122 (Pt 9), pp. 1651-1665.

Chu, Z., Hablitz, J.J. 2003. GABA (B) receptor-mediated heterosynaptic depression of excitatory synaptic transmission in rat frontal neocortex. Brain Res., Vol. 959, pp. 39-49.

Chu, J., Wagle-Shukla, A., Gunraj, C., Lang, A. E. & Chen R. 2009. Impaired presynaptic inhibition in the motor cortex in Parkinson disease. Neurology, vol. 72, No. 9, pp. 842–849.

Deecke, L. 2001. Clinical neurophysiology of Parkinson's disease. Bereitschaftpotential and contingent negative variation. Adv. Neurol., Vol. 86, pp. 257–271.

DeLong, M.R. 1990. Primate models of movement disorders of basal ganglia origin. Trends Neurosci., Vol. 13, pp. 281-286.

Del Santo, F, Gelli, F.,Mazzocchio, R. & Rossi, A. 2007. Recurrence quantification analysis of surface EMG detects changes in motor unit Synchronization induced by recurrent inhibition. Exp. Brain Res, Vol. 178, pp. 308-315.

Elbaz, A., Grigoletto, F., Baldereschi, M. et al. 1999. Familial aggregation of Parkinson's disease: a population-based case-control study in Europe. EUROPARKINSON Study Group. Neurology, Vol. 52, No. 9, pp. 1876-1882.

Fahn, S., Elton, R. & members of the UPDRS Development Committee. 1987.Unified Parkinson's disease rating scale. In: Recent developments in Parkinson's disease, Fahn, S., Marsden, C.D., Calne, D.B., & Goldstein, M., editors, Vol. 2, pp. 153-163, 293-304, NJ Macmillan Health Care Information, Florham Park.

Farina, D., Merletti, R. & Enoka, R.M. 2004. The extraction of neural strategies from the surface EMG. J. Appl. Physiol, Vol. 96, pp. 1486-1495.

Filipovic, S. R., Covickovic-Sternic, N., Radovic, V. M., Dragasevic, N., Stoyanovic-Svete, M. & Kostic, V. S.. 1997. Correlation between Bereitschaftspotential and reaction time measurements in patients with Parkinson's disease. Measuring the impaired supplementary motor area function? J. Neurol. Sci., Vol. 147, No. 2, pp. 177 - 183.

Furukawa, Y., Kondo, T., Nishi, K., Yokochi, F. & Narabayashi, H. 1991. Total biopterin levels in the ventricular CSF of patients with Parkinson's disease: a comparison between akineto-rigid and tremor types. J Neurol Sci,, Vol. 103, pp. 232-237

Gaspar, P., Duyckaerts, C., Alvarez, C., Javoy-Agid, F., & Berger B. 1991 Alterations of dopaminergic and noradrenergic innervations in motor cortex in Parkinson's disease. Ann. Neurol., Vol. 30, pp. 365-374.

Goldberger, A. L., Amaral, L.A.N., Hausdorff, J.V., Ivanov, P.Ch., Peng, C.-K. & Stanley, H.E. 2002. Fractal dynamics in physiology: alterations with disease and aging. Proc. Natl. Acad. Sci. USA, Vol. 99, Suppl. 1, pp. 2466-2472.

Gonzalez-Islas, C. & Hablitz, J.J. 2001. Dopamine inhibition of evoked IPSCs in rat prefrontal cortex. J. Neurophysiol., Vol. 86, pp. 2911-2918.

Hanajima, R. & Ugawa, Y. 2000. Intracortical inhibition of the motor cortex in movement disorders. Brain Dev., Vol. 22, Suppl. 1, pp. 132-135.

Holloway, R.G., Shoulson, I., Fahn, S. et al. 2004. Parkinson Study Group. Pramipexole *vs* levodopa as initial treatment for Parkinson's disease: a 4-year randomized controlled trial. Arch. Neurol., Vol. 61, pp. 1044-1053.

Houk, J.C. 1979. Regulation of stiffness by skeletomotor reflexes. Ann. Rev. Physio.l, Vol. 41, pp. 99-114.

Hughes, A.I., Ben-Shlomo, Y., Daniel, S.E. & Lees, A.I. 1992. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinico-pathologic study. Neurology, Vol. 42, pp. 1142-1146.

Hutter-Paier, B., Grygar, E., Fruhwirth, M., Temmel, I. & Windisch, M. 1998. Further evidence that Cerebrolysin protects cortical neurons from neurodegeneration in vitro. J. Neural. Transm., Vol. 53, pp. 363-372.

Ikeda, A., Shibasaki, H., Kaji, R., Terada, K., Nagamine, T., Honda, M. & Kimura, J. 1997. Dissociation between contingent negative variation (CNV) and Bereitschaftspotential (BP) in patients with parkinsonism. Electroencephalogr. Clin. Neurophysiol., Vol. 102, No. 2, pp. 142 - 151..

Illarioshkin, S. N. 2002. Conformational Disease of the Brain [in Russian], Yanus-K, Moscow.

Illarioshkin, S. N. 2008. Molecular basis of Parkinson's disease, in: Parkinson's Disease and Motor Disorders, pp. 8-17, Handbook for Physicians Based on Proceedings of I National Congress, Moscow.

Jenner, P. 1994. The contribution of dopamine receptor subtypes to the therapeutic actions and side-effects of anti-parkinsonian drugs. In: Beyond the Decade of the Brain, Stern, M.B., editor, pp. 131-156, Wells Medical Limited Chapel Place, Royal Tunbridge Wells, Kent.

Kaji, R., Urushihara, R., Murase, N., Shimazu, H. & Goto, S. 2005. Abnormal sensory gating in basal ganglia disorders. J. Neurol. 2005, Vol. 252, Suppl 4, 1V/13-1V/16.

Karaban, N., Lukhanina, E. P., Melnik, N. A. & Berezetskaya, N. M. 2006. Influence of course treatment with Noofen on motor activity, cognitive functions and emotional state in patients with Parkinson's disease. Ukrainskiy Vestnik Psihonevrologii, vol. 14, No. 46, pp. 26–30.

Katayama, Y., Kasai, M., Oshima, H., Fukaya, C. & Yamamoto T. 2000. Effects of anterodorsal pallidal stimulation on gait freezing (Kinesia paradoxa) in Parkinson's disease. Stereotact. Funct. Neurosurg., Vol. 74, No. 3-4, pp. 99-105.

Kawaguchi, Y. & Shindou, T. 1998. Noradrenergic excitation and inhibition of GABAergic cell types in rat frontal cortex. J. Neurosci., Vol. 18, pp. 6963-6976.

Krnjevic, K., Randic, M. & Straughan, D.W. 1966. Nature of a cortical inhibitory process. J. Physiol., Vol. 184, pp. 49-77.

Kryzhanovskii, G. N., Karaban', I. N., Magayeva, S. V. et al. 2002. Parkinson's Disease [in Russian], Meditsina, Moscow.

Lewis, G.N. & Byblow, W.D. 2002. Altered sensorimotor integration in Parkinson's disease. Brain, Vol. 125, pp. 2089-2099.

Lukhanina, E.P., Karaban', I.N., Chivliklii, M.A., Pil'kevich, N.A. & Berezetskaya, N.M. 2010. Electromyographic manifestations of hereditary signs of extrapiramidal insufficiency. Neurophysiology, Vol. 42, No 1, pp. 39-49.

Marie, R.M., Barre, L., Rioux, P., Allain, P., Lechevalier, B. & Baron J.C. 1995. PET imaging of neocortical monoaminergic terminals in Parkinson's disease. J. Neural. Transm. Park. Dis. Dement. Sect., Vol. 9, pp. 55-71.

Marshall, F. H. & Foord, S. M. 2010. Heterodimerization of the GABAB receptor-implications for GPCR signaling and drug discovery. Advances in Pharmacology, vol. 57, C, pp. 63– 91.

Meigal, A.I., Rissanen, S., Tarvainen, M.P., Karjalainen, P.A., Iudina-Vassel, I.A., Airaksinen, O. & Kankaanpää, M. 2009. Novel parameters of surface EMG in patients with Parkinson's disease and healthy young and old controls. J. Electromyogr. Kinesiol, Vol. 19, pp e206-e213.

Nieminen, H. & Takala E.P. 1996. Evidence of deterministic chaos in the myoelectric signal. Electromyogr. Clin. Neurophysiol, Vol. 36, pp. 49-58.

Oishi, M., Mochizuki, Y.C. Du. & Takasu T. 1995. Contingent negative variation and movement-related cortical potentials in parkinsonism. EEG Clin. Neurophysiol., Vol. 95, No. 5, pp. 346–349.

Otsuka, M., Ichiya, Y., Kuwabara, Y., Hosokawa, S., Sasaki, M., Yoshida, T., Fukumura, T., Masuda, K. & Kato, M. 1996. Differences in the reduced 18F-Dopa uptakes of the caudate and the putamen in Parkinson's disease: correlations with the three main symptoms. J. Neurol. Sci., Vol. 136, pp. 169-173.

Pulvermuller, F., Lutzenberger, W., Muller, V., Mohr, B., Dichgans, J. & Birbaumer, N. 1996. P3 and contingent negative variation in Parkinson's disease. EEG Clin. Neurophysiol., Vol. 98, No. 6, pp. 456–467.

Ridding, M.C., Inzelberg, R. & Rothwell, J.C. 1995. Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. Ann. Neurol., Vol. 37, pp. 181-188.

Robichaud, J. A., Pfann, K. D., Leurgans, S. et al. 2009. Variability of EMG patterns: a potential neurophysiological marker of Parkinson's disease? Clin. Neurophysiol., Vol. 120, No. 2, pp. 390-397.

Rossini, P.M., Filippi, M.M. & Vernieri, F. 1998. Neurophysiology of sensorimotor integration in Parkinson's disease. Clin. Neurosci., Vol. 5, pp. 121-130.

Ruether, E., Alvarez, X.A., Rainer, M. & Moessler, H. 2002. Sustained improvement of cognition and global function in patients with moderately severe Alzheimer's disease: a double-blind, placebo-controlled study with the neurotrophic agent Cerebrolysis. J. Neural. Transm., Suppl., Vol. 62, pp. 265-75.

Sadekov, R.A. 1997. Evoked potentials in parkinsonism. Zh. Nevropatol. Psikhiatr. Im. S. S. Korsakova, Vol. 97, pp. 64-65.

Schaafsma, J. D., Balash, Y., Gurevich, T., Bartels, A.. L., Hausdorff, J. M. & Giladi N. 2003. Characterization of freezing of gait subtypes and the response of each to levolopa in Parkinson's disease. Eur. J. Neurol., Vol. 10, No. 4, pp. 391 - 398.

Semmler, J.G. & Nordstrom, M.A. 1999. A comparison of cross-correlation and surface EMG techniques used to quantify motor unit Synchronization in humans. J. Neurosci. Methods, Vol. 90, pp. 47-55.

Shammah-Lagnado, S.J., Alheid, G.F. & Heimer, L. 1996. Efferent connections of the caudal part of the globus pallidus in the rat. J. Comp. Neurol., Vol. 376, pp. 489-507.

Sherman M. Y. & Goldberg A. L. 2001. Cellular defenses against unfolded proteins: a cell biologist thinks about neurodegenerative disease. Neuron, Vol 29, No. 1, pp. 15-32.

Stanley, H.E., Amaral, L.A.N., Goldberger, A.L., Havlin, S., Ivanov P.Ch. & Peng, C.-K. 1999. Statistical physics and physiology: monofractal and multifractal approaches. Physica, Vol. 270, p. 309.

Swie, Y. W., Sakamoto, K. & Ahimizu, Y. 2005. Chaotic analysis of electromyography signal at low back and lower limb muscles during forward bending posture. Electromyogr. Clin. Neurophysiol, Vol. 45, pp. 329-342.

Szabo, B., Wallmichrath, I., Mathonia, P. & Pfreundtner, C. 2000. Cannabinoids inhibit excitatory neurotransmission in the substantia nigra pars reticulate. Neuroscience, Vol. 97, No. 1, pp. 89–97.

Talebinejad, M., Chan, A.D. & Miri, A. 2010. Fatigue estimation using a novel multi-fractal detrended fluctuation analysis-based approach. J. Electromyogr. Kinesiol, Vol. 20, № 3, pp. 433-439.

Teo, Ch., Rasco, L., Al-Mefty, K., Skinner, R.D., Boop, F.A. & Garcia-Ril,l E. 1997. Decreased habituation of midlatency auditory evoked responses in Parkinson's disease. Mov. Disord., Vol. 12, pp. 655-664.

Valls-Solé, J. & Valldeoriola, F. 2002. Neurophysiological correlate of clinical signs in Parkinson' s disease. Clin. Neurophysiol., Vol. 113, pp. 792-805.

Zappoli, R., Versari, A., Arnetoli, G., Paganini, M., Muscas, G. C., Arneodo, M. G., Gangemi, P. F. & Bartelli M. 1991. Topographic CNV activity mapping, presenile mild primary cognitive decline and Alzheimer - type dementia. Neurophysiol. Clin., Vol. 21, No. 5-6, pp. 473-483.

3

Brain Event - Related Oscillations in Parkinsonian Patients During Discrimination Task Conditions

Juliana Dushanova
Institute of Neurobiology, Bulgarian Academy of Sciences
Bulgaria

1. Introduction

Parkinson's disease (PD) is caused by a disruption of dopaminergic neurotransmission in the basal ganglia, which serve as an integrative centre for the sensory and cognitive processing of information and as a mutual link between this processing and disturbed motor performance. The basal ganglia and the cerebellum transmit information via the thalamus to the cerebral cortex in order to regulate movement. The neurotransmitter changes affect the output of the striatum into the globus pallidus as well as into the thalamus and cerebral cortex beyond. The disease is a common and disabling disorder of movement characterized by poverty, slowness and impaired scaling of voluntary movements (akinesia and bradykinesia), muscle rigidity, and tremor of the limbs at rest. Alterations of the basal ganglia with proven neuronal degenerative disorders of dopaminergic neurons and a reduction in activity in frontostriatal neural circuitry have been suggested to play a role in the executive dysfunction of PD (Taylor et al., 1990; Innis et al., 1993; Lewis et al., 2003; Owen, 2004; Leblois et al., 2006; Anik et al., 2007). The slowed information processing, insufficient encoding strategies and planning, and attentional set-shifting are related to memory deficits and cognitive impairment in PD (Daum et al., 1995; Pillon et al., 1997; Knoke et al., 1998; Robertson & Empson, 1999; Sawamoto et al., 2002; Cools, 2006). Neuropsychological studies of PD patients report cognitive deficits even during the early stages of the disease (van Spaendonck et al., 2006). The primary working memory deficit in PD is associated with impaired free recall performances (Higginson et al., 2003).

Many electroencephalographic (EEG) studies on PD have used the event-related potential (ERP) method, where the early modal dependent and obligatory N1 and P2 components permit analysis of sensory events while the later N2 and P3 potentials reflect the cognitive processes involving the assessment of stimuli, decision making, strategy selection and recognition memory. ERP investigations have shown P3 predominantly with prolonged latencies and/or diminished amplitudes for Parkinsonian patients (PP) when compared to healthy subjects (HS) (Evarts et al., 1981; Tachibana et al., 1992; Philipova et al., 1997; Wascher et al., 1997; Minamoto et al., 2001; Antal et al., 2002; Wang et al., 2002). Such results have been interpreted as electrophysiological signs of cognitive slowing with respect to stimulus classification and attentional processing (Robertson & Empson, 1999).

One valuable means of assessing deviations from the normal state in PD is to study oscillatory brain processes. In the ERP method, however, the functional significance of the

responses in different frequency bands is lost. More clarification could be expected when attentional processes in PD during a representation of discrimination tasks (Vieregge et al., 1994) are examined using event-related desynchronization/synchronization (ERD/ERS) method. In the early stages, PD also affects cognitive functions (Cools, 2006). Cognitive processes require transient integration between different brain areas. Hence, dynamic links are formed, mediated by the ERS or ERD of neuronal assemblies. ERD is defined as a relative decrease in the power of a certain frequency band during stimulus processing, while ERS is a relative increase in the power of the same frequency (Pfurtscheller & Klimesch, 1991). The ERD/ERS method has been used to study auditory and visual working memory encoding and categorization processes in PP; studies indicate less theta-ERS and upper alpha-ERD reflected disturbance of both the basal ganglia activity as well as activity related to their thalamo-cortical neuronal nets at frontal electrode locations (Schmiedt et al., 2005; Ellfolk et al., 2006). The encoding of auditory stimuli elicits alpha- and theta-ERS, while memory retrieval during the presentation of a target stimulus elicits theta-ERS and alpha-ERD (Karrasch et al., 1998, 2004; Krause et al., 1996, 1999). Oscillations in the beta frequency band are associated with cognitive control of behaviour or "executive functions" (Pfurtscheller & Lopes da Silva, 1999; Engel et al., 2001). By means of an auditory stop-signal task, the differential participation of beta subbands in voluntary motor control can be revealed: ERD in the 20–30 Hz band is related to initiation of movement, while ERS in a low frequency beta band (12–16 Hz) is exclusively linked to the stopping of planned action (Pfurtscheller & Lopes da Silva, 1999; Engel et al., 2001). One proposed hypothesis for these observations is that lower-frequency beta subbands represent inhibitory components of cognitive control and are more generalized, while higher frequency beta subbands take part in response choice and activation and are more specialized in terms of both function and cortical distribution.

Some recent investigations (Basar, 2001; Ozgoren et al., 2005; Sutoh et al., 2000; Gurtubay et al., 2001) propose that beta and gamma cortical rhythms may serve cognitive processes such as linking perception to action or movement planning (Donoghue et al., 1998). Research both on animals and humans has suggested that gamma-frequency activity also plays an important role in attention as well as working and long-term memory (Herrmann et al., 2004). Current investigations using intracranial and high-density electro- and magnetoencephalographic recordings explore the involvement of gamma-band synchronization in various cognitive paradigms in humans (Engel et al., 2001; Basar et al., 2001; Herrmann et al., 2004; Pantev, 1995; Tallon-Baudry et al., 1996; Farmer, 1998; Fries et al., 2001). Other works associate the changes in EEG spectral power in the gamma frequency band to interactions between the cortex and basal ganglia (Gatev & Wichmann, 2008). Additionally, akinesia in PP has been related in some studies to abnormally increased beta (15–30 Hz) and decreased gamma (35–80 Hz) synchronous oscillatory activity in the basal ganglia (Weinberger et al., 2006). Other results suggest that resting tremor in PD is associated with an altered balance between beta and gamma oscillations in the motor circuits of the subthalamic nucleus (STN) and is exhibited as increased oscillatory activity in the low gamma frequency range (35–55 Hz) during periods with stronger tremor (Weinberger et al., 2008). Therapeutic doses of dopaminergic medication in PP attenuate the beta band power in the STN, giving rise to the hypothesis that the beta prominence is pathological in PD (Cassidy et al, 2002; Kühn et al., 2006; Levy et al., 2001; 2002; Priori et al., 2002). Treatment of PP with dopaminergic therapy leads to increased gamma band activity in the basal ganglia and thus to improvement in motor performance (Brown et al., 2001),

hence the suggestion that synchronization of the activity of populations of basal ganglia neurons in the gamma band may facilitate motor processing (Brown, 2003). Investigations based on local field potentials recorded from the STN in PP show increased power in the beta range (13–35 Hz) while the patient is at rest (Cassidy et al., 2002; Levy et al., 2002; Brown et al., 2001; Priori et al., 2004). This suggests that there is excessive synchrony in the basal ganglia networks in PD and some of the clinical signs of the disease, it is proposed, stem from this abnormal synchrony between basal ganglia and cortical circuits (Brown, 2003; Marsden et al., 2001).
The aim of the present study was to investigate the functional relationships between oscillatory EEG-dominant components with ERD/ERS method for PP and HS during auditory discrimination tasks within two poststimulus intervals of 0–250 and 250–600 ms. We first focused on time-frequency analysis of delta, theta and alpha rhythms, the appearance of which is well established in PD and is thought to reflect the degree of cortical activation during the information processing. We later shift our focus to the beta and gamma bands, where our aim is to assess the differences between PP and HS in these frequency bands and check an assumption that some PP clinical symptoms stem from excessive synchrony between the basal ganglia and cortical circuits. This investigation of the oscillatory processes and ERD/ERS in HS and PP could contribute to clarification of the disturbances of the neurophysiological mechanisms of this disease.

2. Methods

2.1 Experimental procedure

2.1.1 Subjects

We investigated eleven voluntary patients with a mean age of 61 ± 12.2 years (±s.d.; 7 males, 4 females) with a diagnosis of idiopathic Parkinson's disease for no longer than 2.8 years, assessed by a neurologist at the University Neurological Hospital, with score of I on the Hoehn–Yahr scale of motor function (Hoehn & Yahr, 1967). Patients receiving levodopa (L–dopa) drugs (Sinemet) were included in order to reduce the heterogeneity in the medication. During the experimental session, all patients were in off-phase of the medication. None of the patients had dementia, depression, a presence of atherosclerosis, attendant neurological complications or pronounced tremor. The same number of healthy volunteers was included as aged-matched healthy controls with a mean age of 59.5 ± 9.5 years. Screening confirmed that subjects were free of past or current psychiatric and neurological disorders. All participants were right handed and without deficits in hearing. Handedness was assessed by a questionnaire adapted from the Edinburgh Handedness Inventory (Oldfield, 1971). The study was performed with the approval of the local ethics committee. The subjects were introduced to the nature of the investigation and their informed written consent was obtained according to the declaration of Helsinki.

2.1.2 Stimuli and task

Each subject was comfortably seated in an ergonomically designed chair inside a Faraday cage, monitored by a Canon Video system. The experimental design included a binary sensory-motor reaction task. Each sensory-motor series consisted of 50 computer generated low frequency (LT – 800 Hz) and 50 high frequency (HT – 1000 Hz) acoustic stimuli with an intensity of 60 dB, duration of 50 ms, and an inter-stimulus interval of 2.5–3.5 s presented to the subject in a randomized order. PP and HS were asked to press a key with the index

finger of each hand and make rapid and accurate choice responses with the left hand to the high frequency (HT) or with the right hand to the low frequency (LT) tone. The movement performance from the stimulus presentation to the onset of voluntary force production (onset of reaction time) and from the stimulus presentation to the force peak (force peak latency) were measured by a force transducer. A surface electromyographic activity pattern of the first dorsal interosseus muscles was also registered.

2.1.3 EEG recording

An electroencephalogram (EEG) was recorded from Fz, Cz, Pz, C3′ and C4′ (10/20, system), using Ag/AgCl Nihon-Kohden electrodes with a reference to both processi mastoidei and a ground electrode, placed on the forehead. An oculogram (EOG) was recorded from m. orbicularis oculi dex. We placed two EOG electrodes next to the eyes to register eye movements. EEG and EOG data were recorded using a Nihon-Kohden EEG-4314F (cut-off frequencies of 0.3–70 Hz) and recorded together with markers of the movement performance as a force profile and a surface electromyographic activity pattern of the first dorsal interosseus muscles (bandpass filtered 0.03–500 Hz). The signals were digitized on-line (10 bit A/D converter, 256 samples/s). The data recordings for the sensorimotor task were synchronized to the marker of the stimulus onset (-0.2 s before and 0.8 s after the stimulus). Only recordings that were artifact-free with respect to event-related potentials were processed. We applied a Chebyshev Type II bandpass filter (1-70 Hz) and second-order notch filter at frequency 50 Hz (AC) component. We defined an independent reference interval in order to quantify the changes in the time-frequency energy density of the signal. We used stimulus-nonrelated subepochs within the resting condition series, distant enough (-1.4 s) from the stimulus onset, not including event-related properties, and exceeding the period of the lowest frequency studied in the signal (1.5 Hz, 0.67 s). We preselected trials by applying a bootstrap estimation within the reference period and a false discovery rate correction for multiple comparisons (0.05) to the available data across the indexes corresponding to time and number of the trial, eliminating the need for a strict assumption of ergodicity (Durka et al., 2004).

2.2 Analysis

The time-frequency analysis (TF) represented the power of a continuous EEG signal as a function of both time and frequency (Matlab®, Mathworks, Inc.). For time amplitude-frequency distributions, the filtered signal was analyzed with a sliding-window fast Fourier transform with length 200 ms and step 10 ms. The amplitude was computed for every time window t and frequency bin f by the real and imaginary Fourier coefficients. The amplitude modulations obtained for each frequency band for each subject in a group were added across trials in order to compare amplitude changes in the post-stimulus intervals with respect to pre-stimulus interval reference amplitudes, i.e. to derive ERD/ERS. This method characterizes the relative amplitude decrement/increment of the given frequency during the post-stimulus period in relation to pre-stimulus amplitude modulation of the same frequency (Pfurtscheller G, Klimesch, 1991). This resulted in ERD/ERS values which could then be presented as percentage changes with respect to the reference interval. Negative values indicate a relative power decrease (ERD), whereas positive values point to a relative power increase (ERS). Relatively, sensory processing takes place during the first post-stimulus interval (T1: 0–250 ms) and cognitive processing during the second post-stimulus

interval (T2: 250–600 ms), defined as beginning when a tone ends. The peak amplitude modulations, defined in 10 ms bins, were specified as dominating components. Afterwards, the high amplitudes in each frequency band, respectively, were added over trials and across subjects to compare their amplitude changes in the post-stimulus intervals with those in the reference interval. Thus, we calculated the ERD/ERS of delta (δ ~ 1.5–4 Hz), theta (θ ~ 4.1–7 Hz) and alpha (α ~ 7.1–13 Hz) waves as percentage power differences in each frequency band compared to the reference interval for both 0–250 ms and 250–600 ms post-stimulus intervals. We also defined the ERD/ERS of beta (β_1 ~ 13.1–20 Hz), (β_2 ~ 20.1–32 Hz) and gamma (γ ~ 32.1–50 Hz) frequency rhythms during the post-stimulus intervals T1 (0–250 ms) and T2 (250–600 ms).

We employed the detection of the temporally dynamic processes similar to the approach applied by Foffani et al. (Foffani et al., 2005) that describes the behaviour of β_1 -, β_2 -, γ - ERS rhythms in zones which vary both in amplitude and frequency. Each zone *i* is characterized by a value *ERSi* (*t*) and a frequency value *Fi* (*t*), both dependent on time, which separately describe event-related synchronization and corresponding frequency modulations for the beta1, beta2 and gamma rhythms in two post-stimulus time windows. The significance of the observed ERS values was tested for each frequency band and EEG channel using a permutation test, including corrections for multiple comparisons between time points for time course analysis (Mason & Newton, 1990). The latencies of ERS and corresponding frequency (relative to stimulus onset) were measured as the last zero-crossing before a significant modulation, after subtracting the baseline mean ERS value. Although the ERS clearly occurred, the relationship between the ERS peaks and the maximum of the average event-related synchronization (AERS) was not always evident. Since the AERSs of different channels were not identical, an exact coincidence between the peaks times was not observed. The probabilities for the amplitudes and latencies were not uniform and the activity distribution was clearly not Gaussian. We estimated the latency shift between the largest peaks for each pair of channels.

2.2.1 Statistics

We performed statistical analyses of the ERD/ERS for the two post-stimulus intervals and assessed the statistical difference between the groups (PP and HS) for each tone type and interval by means of a bootstrap nonparametric procedure (Mason & Newton, 1990). The characteristics were grouped by tone, interval, patients and healthy controls and analyzed by means of a permutation test for multiple comparisons (Mason & Newton, 1990). The computed random distribution for interval was analyzed with a nonparametric test (Kruskal-Wallis [KW] test, $p < 0.05$) for pairs comparison of the scalp leads between patient and control group. This procedure reduces the influence of random variations in experimental conditions between trials. The ERD/ERS analysis served to identify the most robust differences between groups and was generally done for the two time windows. The parameters of the movement performance (onset of reaction time, force peak latency and error of performance) were processed statistically by Mann–Whitney U test.

3. Experimental results

3.1 Response parameters

Parkinson's patients showed a longer reaction time onset, but the difference between the two groups was not significant: in response to a low tone—440.5 ± 135.8 ms in HS and 508.4

± 148.5 ms in PP (mean ± S.D., $p > 0.05$), in response to a high tone—455.7 ± 134.6 ms in HS and 500.4 ± 146.5 ms in PP ($p > 0.05$). Parkinson's patients had significantly longer force peak latency (FPL) in response to the two tone types. The FPLs were 672.8 ± 154.7 ms in HS and 919.96 ± 163.7 ms in PP in response to the low tone (mean ± s.d, $p < 0.02$). In response to the high tone, the FPLs were 690.7 ± 148.7 ms in HS and 934.9 ± 160.2 ms in PP ($p < 0.05$). The mean errors (false and missing responses) were 4.5 and 5.1 in PP, respectively, in response to the low and high tone. The mean errors were 3.5 and 4.4 in HS, respectively, in response to the low and high tone. The differences of errors between the two groups were not significant ($p > 0.05$).

3.2 Frequency components

The grand average ERD/ERS values as a function of time and frequency band at the frontal, central, parietal, left and right motor areas were used for assessment of group means with the standard errors (±SE) for the post-stimulus intervals T1 (0–250 ms) and T2 (250–600 ms). The statistical group comparison for pair channels are shown graphically to illustrate the delta-, theta-, alpha-, beta-, gamma- ERD/ERS following the low frequency tone type (Figs. 1A, 2A) and high frequency tone type (Figs. 1B, 2B) for the early (0–250 ms) and late (250–600 ms) post-stimulus intervals.

3.2.1 Delta

The patterns of δ-ERD/ERS were different between the groups for both intervals in response to both tone types (Dushanova et al., 2009). In the early post-stimulus interval, central δ-ERS amplitude responses were most pronounced in the HS after both tones (Cz, Fig. 1A, B, 1st row, left plots) and in the PP at the frontal side for the high tone (Fig. 1B, left) and parietal area for the low tone (Fig. 1A, left). The least pronounced δ-ERS were those appearing at the frontal side in the HS and in the left motor area in PP following both tones (Fig. 1A, B, left). The comparison by the bootstrap procedure of δ-ERS between the two groups after the low frequency tone determined that the control δ-ERS was significantly higher than that of the PP for all channels (Fz, Pz, $p < 0.05$; Cz, C3′, C4′, $p < 0.001$). Both groups displayed δ-ERS following the high frequency tone (Fig. 1B, left). This was significantly higher for the HS than the PP at centro-parietal, left and right motor areas (Cz, C3′, C4′ $p < 0.001$; Pz, $p < 0.05$). The PD patients' frontal δ-ERS, however, was greater than that of the HS ($p < 0.001$).

The HS maintained δ-ERS at all electrodes during the late post-stimulus interval T2 following the low frequency tone, while in the PP the early post-stimulus δ-ERS was reversed to become δ-ERD in the late post-stimulus interval (Fig. 1A, B, 1st row, right). The highest δ-ERS was located at parietal side for the HS, whereas the PP had a less enhanced parietal δ-ERD. The PP showed the most enhanced δ-ERD at the left motor area (Fig. 1B, right). Following the high frequency tone, δ-ERS was elicited at all electrodes in the HS (Fig. 1B, right). The PP group, in comparison with the HS, showed a less pronounced central δ-ERS (Cz, $p < 0.001$) and specific δ-ERD at parietal and left motor areas ($p < 0.001$).

3.2.2 Theta

In the first post-stimulus interval following both tone types, the θ-ERS responses were most prominent at parietal electrodes for both groups (Fig. 1, A, B, 2nd row, left). Following the low tone, the θ-ERS elicited was significantly higher for HS than for PP at frontal, left and

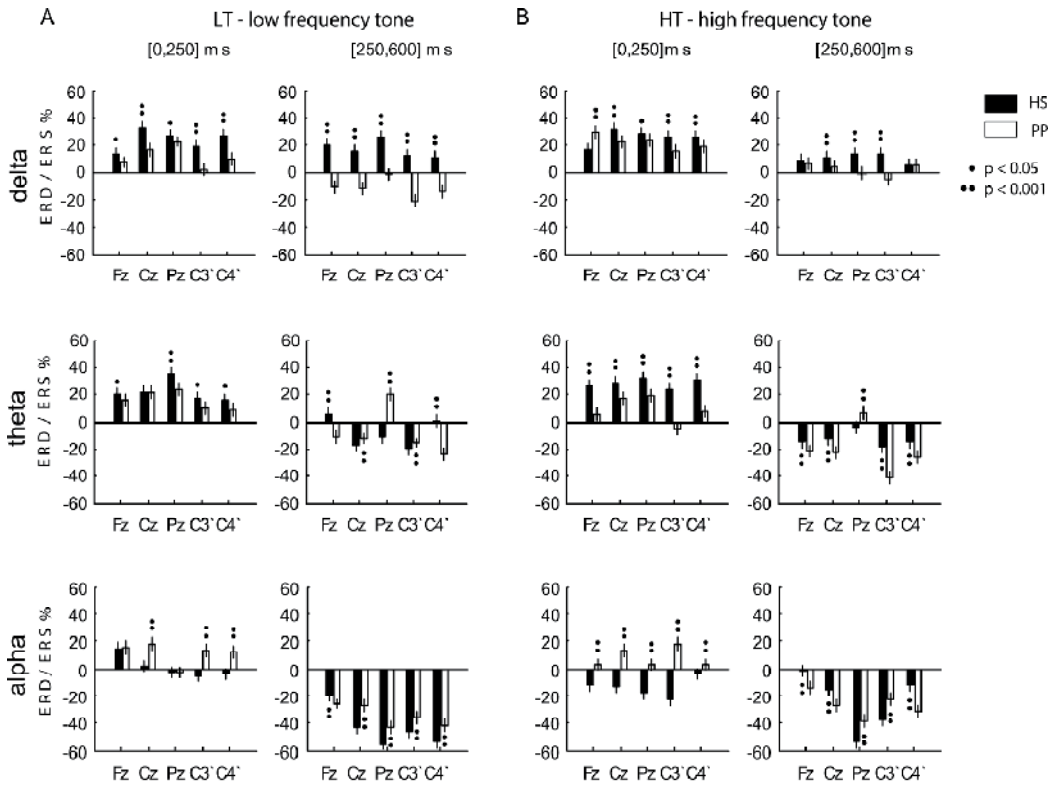


Fig. 1. Group means (±SE) and statistical results of δ-, θ-, α-ERD/ERS over all HS and PP trials after the low tone (A) and high tone type (B) for the early (left) and late time period (right) at all channels.

right motor areas ($p < 0.05$), parietal side ($p < 0.001$), and centrally was non-significantly different (Cz, $p > 0.05$; Fig. 1A, 2nd row, left). Following the high frequency tone, PP produced a significantly lower θ-ERS than the HS at right motor area, fronto-central and parietal sides ($p < 0.001$; Fig. 1B, left). The left motor area showed a pronounced θ-ERS for the HS and a weak θ-ERD in the PP following the high frequency tone.

The comparison of the groups during the late period following the low frequency tone showed θ-ERD in both groups at most electrodes with the following exceptions. PP recorded a large parietal θ-ERS while a less prominent θ-ERS appeared in HS at frontal and right motor areas (Fig. 1A, 2nd row, right). The most pronounced θ-ERDs for HS were at central and left motor areas ($p < 0.001$). The signal at the parietal area was characterized by a very prominent θ-ERS in the patients but by θ-ERD in the control group. In response to the high frequency tone, we found a significant θ-ERD for the PP as compared with the HS at fronto-central, left and right motor areas ($p < 0.001$; Fig. 1B, right). The signal at the parietal area was characterized in a similar manner to that elicited by a low tone, but with a less pronounced θ-ERS in the PP and smaller θ-ERD in the HS.

3.2.3 Alpha

The PP showed fronto-central, left and right motor α-ERS responses following the LT, while the HS had synchronization only at the fronto-central sides but α-ERD at the parietal side,

right and left motor areas (Fig. 1A, 3rd row, left). The alpha frequency band in the first interval after the LT showed an enhanced central α-ERS for the PP in comparison with the HS ($p < 0.001$; Fig. 1A, left). The right and left motor areas manifested different reversal alteration as α-ERS for the PP and weakly elicited α-ERD for the HS. Following the high tone, we detected significantly different processes, α-ERS in the PP contrasted with α-ERD in the HS at all electrodes, most prominently at the left motor side (Fig. 1B, left).
Alpha-ERD differences between the groups were observed after low as well as high frequency tones during the late period (Fig. 1A, B, right). After the low tone, the HS α-ERD means were significantly more pronounced than those of the PP at centro-parietal sides, left and right motor areas ($p < 0.001$; Fig. 1A, right). The PP displayed a higher frontal α-ERD than that in the HS ($p < 0.001$). Alpha-ERD differences were observed between the groups following the high tone (Fig. 1B, right). The α-ERD signals of HS at parietal and left motor areas were more pronounced than in the PP ($p < 0.001$). The PP fronto-central and right motor α-ERD signals had greater respective magnitudes than those in HS ($p < 0.001$).

3.2.4 Beta1

During the early post-stimulus interval T1, ERD/ERS β1 patterns appeared in the lower frequency portions of this band for each electrode and group (Dushanova et al., 2010). The maximum synchronized β1 bursts across the channels were localized over fronto-central sides for both groups after LT, but had significantly higher amplitude and shorter durations in PP than HS ($p < 0.001$, bootstrap, KW test; Table 1, **a**). Later β1 ERS bursts were found only in PP over the frontal side and left motor area (Table 1, LT (T1), **b**). Synchronized β1 bursts were centered on right motor side for PP and fronto-central sides for HS, following HT (Table 1, HT (T1)**, a**, **b**). In PP, the peaks were of a significantly lower amplitude and peaked later at centro-parietal sides than in HS (Table 1, HT (T1)**, a**). During the late post-stimulus interval T2, frontal synchronized β1 peaks at 20 Hz were extracted only in HS after HT and had a prolonged latency of 176 ± 11.5 ms (Table 1, HT (T2)**, f**).

3.2.5 Beta2

During T1, ERS β2 bursts were present only in PP after either tone (Table 2, LT(T1), HT(T1)). Their maximum amplitude across the scalp was localized over frontal side for either tone, right and left motor areas respectively for LT and HT (Table 2, **c**). They peaked earlier at the right than at the left motor area, fronto-central leads (Table 2, **c**), and parietal side (Table 2, **d**) for either tone, but in higher β2 frequency range after LT than after HT. During T2, the maximum value of β2 bursts across all recorded areas was centered on right motor area in PP (Table 2, **g**) but on parietal side in HS following LT (Table 2, LT(T2), **j**). More widely distributed, prolonged β2 ERS bursts were pronounced over all locations for PP following HT, but limited to frontal-central and right motor areas for HS (Table 2, HT(T2)). The maximum scalp β2 burst was localized at the right motor area in PP and frontal area in HS after HT (Table 2, **g - j**). At the right motor area, spectral peaks of low β2 exhibited significantly more exaggerated and prolonged bursts in PP than in HS ($p < 0.001$, Table 2, **g - j**). The frontal synchronized high frequency β2 bursts appeared in PP during two subintervals, the first one with a significantly shorter latency than the low frequency β2 bursts in HS ($p < 0.001$, Table 2, **g**). In PP, synchronized bursts of high β2 were generated on the left motor area (Table 2, **g**) earlier than larger synchronized bursts at low β2 (Table 2, **i**, **j**).

Channels	**Fz** **ERS(%)/ F/ t** (±SE) **D**	**Cz** **ERS(%)/ F/ t** (±SE) **D**	**Pz** **ERS(%)/ F/ t** (±SE) **D**	**C3′** **ERS(%)/ F/ t** (±SE) **D**	**C4′** **ERS(%)/F /t** (±SE) **D**
Subjects **Tone(period)**			**HS**		
LT (T1)	**64.1 (±1.2)/** 13 Hz 40 (±7.3) ms [8–72] ms (**a**)	50.1 (±5.8) /13 Hz 36 (±6.9) ms [8–64] ms (**a**)	18.8 (±0.5)/13 Hz 20 (±5.2) ms [8–32] ms (**a**)	41 (±3.3)* /13 Hz 36 (±28) ms [8–80] ms (**a**)	44.9(±5.2)*/13 Hz 32.0 (±6.5)** ms [8–72] ms (**a**)
HT (T1)	**68.6(±10.2)**/13.9(±0.3)Hz [13–15] Hz 36 (±6.9) ms [8–64] ms (**a**)	62.7(±8.5)*/13.7(±0.3)Hz [13–15] Hz 32 (±6.5)** ms [8–56] ms (**a**)	30.49(±3.3)*/13Hz 28(±6.1)** ms [8–48] ms (**a**)	54.7(±8.3)*/13.5(±0.3)Hz [13–15] Hz 32(±6.5) ms [8–56] ms (**a**)	50.4(±6.6)*/13 Hz 32(±6.5) ms [8–56] ms (**a**)
LT (T2)	–	–	–	–	–
HT (T2)	**51 (±3.2)**/20 Hz 516 (±11.5) ms [424–600] ms (**f**)	–	–	–	–
Subjects **Tone(period)**			**PP**		
LT (T1)	**69.4(±0.9)*/** 13 Hz 12 (±4)** ms [8–80] ms (**a**)	57.2(±3)*/13 Hz 16 (±4.6)** ms [8–64] ms (**a**)	–	36.8(±2.8)/13 Hz 12 (±4)** ms [8–16] ms (**a**)	33.9(±5)/13Hz 48 (±6.5) ms [24–72] ms (**a**)
	15.8(±0.2)/14(±0.6) Hz 124 (±5.2) ms [112–136] ms (**b**)	–	–	19.3(±1.3)/18 Hz 148 (±5.2) ms [136–160] ms (**b**)	–
HT (T1)	–	34.4(±3.8)/13.8(±0.3) Hz 53.6 (±11.2) ms [8–104] ms (**a**)	21.3(±0.8)/ 13 Hz 46 (±8.7) ms [8–88] ms (**a**)	35(±1.9)/ 13 Hz 20(±5.2)** ms [8–32] ms (**a**)	**40.2(±2.8)**/13 Hz 24 (±5.7) ** ms [8–40] ms (**a**)
	–	–	–	–	25(±1.1)/16 Hz 92 (±5.2) ms [80–112] ms (**b**)
LT (T2)	–	–	–	–	–
HT (T2)	–	–	–	–	–

Note: Bold-marked mean ERS β1 bursts (%) (±SE) are maximum across the channels for each condition and subject separately for LT(T1), HT(T1), LT(T2), HT(T2); **F** (Hz) – mean frequency peaks (±SE) of the maximum ERS β1 bursts across trials; **t** (ms) – mean times (±SE) of maximum ERS β1 bursts across trials during T1 (or T2) with respect to stimulus onset; **D** (ms) – time duration of these short–term zones with ERS β1 bursts; [1] * =a significant difference in ERS between the groups HS, PP for each channel and tone separately, marked the higher value ($p<0.001$, KW test); [2] ** =a significant difference in **t** between the groups for each channel and tone separately, marked the shorter value ($p<0.001$, KW test). Lower case letters in Table 1 marked consecutive sub-intervals with ERS β1 bursts: **a**, **b** during T1; **f** during T2.

Table 1. Mean ERS β1 bursts (%) across the trials with mean frequency peaks **F (**Hz) for HS and PP after LT and HT presented in short–term zones **D** (ms) during early T1 and late T2 period.

Channels	**Fz** **ERS(%)/ F/ t** (±SE) **D**	**Cz** **ERS(%)/F/ t** (±SE) **D**	**Pz** **ERS(%)/ F/ t** (±SE) **D**	**C3′** **ERS(%)/ F/ t** (±SE) **D**	**C4′** **ERS(%)/F /t** (±SE) **D**
Subjects tone(period)			**HS**		
LT (T1)	–	–	–	–	–
HT (T1)	–	–	–	–	–
LT (T2)	–	–	**25.8(±1.6)**/32Hz 584 (±6.5) ms [560–600] ms (**j**)	19.6(±1.3)/30.5(±0.2)Hz 588 (±6.1) ms [576–600] ms (**j**)	–
HT (T2)	**43.9(±3.1)**/23.1(±0.1)Hz 516 (±11.5) ms [424–600] ms (**g–j**)	18.1(±0.6)/21Hz 488(±5.7) ms [472–504] ms (**h**)	–	–	28.2(±2.3)/ 32 Hz 384 (±6.5)** ms [360–408] ms (**g**)
	-	–	–	–	40.6(±3.1)/23.4(±0.4)Hz 532 (±10.6) ms [456–600] ms (**h–j**)
Subjects tone(period)			**PP**		
LT (T1)	**61.1 (±1.1)**/ 32 Hz 40 (±5.7) ms [24–56] ms (**c**)	30.6(±4.7)/32Hz 48 (±5.7) ms [32–64] ms (**c**)	23.2(±1.7)/25.2(±1.6)Hz 64 (±9.2) ms [8–120] ms (**c**, **d**)	22.4(±3.7)/29.7(±0.3)Hz 32 (±4.6) ms [24–40] ms (**c**)	**60.3(±1.1)**/32Hz 12 (±4) ms [8–16] ms (**c**)
HT (T1)	41.2(±2)/24.3(±0.5)Hz 60 (±8.8) ms [32–88] ms (**c**)	29.8(±1.1)/23Hz 64 (±4.6) ms [56–72] ms (**c**)	28(±2.7)/24.2(±1.1)Hz 121.6 (±9.1) ms [64–160] ms (**d**)	**46(±2.8)**/23.9(±0.4) Hz 64 (±6.5) ms [40–88] ms (**c**)	38.1(±1.2)/22Hz 56 (±4.6) ms [48–72] ms (**c**)
	–	–	–	19.3(±0.8)/32 Hz 168 (±4.6) ms [160–176] ms (**e**)	–
LT (T2)	–	15.5(±0.1)/32Hz 392 (±4.6) ms [384–400] ms (**g**)	17.9(±1)/ 32 Hz 376 (±4.6) ms [368–384] ms (**g**)	–	**30.7(±2.1)**/32 Hz 368 (±8.6) ms [320–416] ms (**g**)
	–	–	24.7(±1.7)/30.9(±0.1)Hz 528 (±10.8) ms [448–600] ms (**h**)	26(±1.5)/29.3(±0.5)Hz 492 (±9.5) ms [432–552] ms (**h**)	–
HT (T2)	36.7(±2.9)/ 32Hz 388(±8.9)** ms [336–440] ms (**g**)	23.8(±1.3)*/32Hz 376 (±7.3)** ms [344–408] ms (**g**)	25.3(±0.7)/30(±0.03)Hz 452 (±14.8) ms [296–600] ms (**g-j**)	34.8(±2)/32Hz 352 (±11.8) ms [256–448] ms (**g**)	**60.6(±2)***/22.2(±0.1)Hz 444 (±15.1) ms [280–600] ms (**g–j**)
	26.1(±1.0)/ 32Hz 548 (±9.5) ms [488–600] ms (**i**)	–	–	44.8(±2.5)/25Hz 532 (±10.6) ms [456–600] ms (**i**, **j**)	–

Note: Lower case letters in Table 2 marked consecutive sub-intervals with ERS β2 bursts: **c**, **d**, **e** during T1 and **g**, **h**, **i**, **j** during T2.

Table 2. Mean ERS β2 bursts (%) across the trials with mean frequency peaks **F** (Hz) for HS and PP after LT and HT presented in short–term zones **D** (ms) during early T1 and late T2 period (same format as **Table 1).**

3.2.6 Gamma

The scalp γ burst topography was localized on frontal area for PP following either tone (Table 3, LT(T1), HT(T1), **a**) and for HS – on right motor area after LT and left motor area after HT during T1 (Table 3, **c**). The ERS γ bursts in PP peaked later than in HS at the fronto-central for either tone, and at right and left motor areas after LT (Table 3, **a, b, c**). They were of significantly greater amplitude and more prolonged duration in PP than in HS at the fronto-central and parietal sides after either tone ($p < 0.001$, Table 3). Later γ burst ERS was also found during T1 over right motor and parietal areas in PP after LT (Table 3, **b; c**), and over left motor area in PP, but parietal and right motor sides in HS, after HT (Table 3, **d**). During T2, synchronized frontal γ bursts were extracted from both groups after either tone (Table 3, **f**) and peaked later in PP. The scalp γ bursts were with significantly higher amplitudes in PP than the equivalent responses from HS ($p < 0.001$, Table 3).

In sum, despite the early short-term β1 synchrony during the two periods, both groups exhibited mean β1 ERD following either tone type and interval (Fig. 2A, B, 1st row), which was significantly greater for HS in comparison with PP in all channels ($p < 0.001$, bootstrap, KW test), except frontal mean β1 ERS for the control group following HT during T2 (Fig. 2B, 1st row; Pz, C3', C4', $p < 0.001$; Cz, $p < 0.05$). The prolonged β2 synchronized bursts for PP during T1 had an effect on the β2 band behavior during the entire early time period (T1, Fig. 2, 2nd row, left plot). The mean β2 ERS were prominent only in PP at frontal-parietal and right motor areas after LT and at parietal and left motor areas following HT during T1 (Fig. 2A, B). The comparison of the groups also showed mean β2 ERD in HS and β2 ERS in PP during T2 following either tone in all channels except for the frontal area, which showed mean β2 ERD in both groups after LT, significantly more prominently in HS (LT, $p < 0.05$; Fig. 2A, B). The results for γ closely resembled the β2-frequency band behaviour. The mean γ ERS were more prominent than those for β2 in PP. During the sensory processing (T1), PP showed mean γ ERS responses at fronto-parietal and right motor areas after LT, but not after HT (Fig. 2A, B, 3rd row, left). The γ ERD in HS and γ ERS in PP were observed in all channels after either tone during the cognitive processing (T2), except frontal γ ERS after HT, which was more pronounced in HS than in PP ($p < 0.001$, Fig. 2B, right plot).

Channels	**Fz** **ERS(%)/ F/ t** (±SE) **D**	**Cz** **ERS(%)/ F/ t** (±SE) **D**	**Pz** **ERS(%)/ F/ t** (±SE) **D**	**C3′** **ERS(%)/ F/ t** (±SE) **D**	**C4′** **ERS(%)/F /t** (±SE) **D**
Subjects tone(period)			**HS**		
LT (T1)	22.7(±2)/ 47 Hz (**c**) 20 (±5.2)** ms [8–32] ms	19.8(±2.8)/ 33 Hz (**a**) 12 (±4)** ms [8–16] ms	20.4(±1.1)/39.4(±1.3)Hz [35–48] Hz (**a, b, c**) 86.4 (±9.9) ms [24–144] ms	18.9(±1.4)/41(±5.2) Hz [32,50] Hz (**a, c**) 28 (±9.5)** ms [8–48] ms	**30.7(±1.9)**/47.6(±0.4)Hz [46–49] Hz (**c**) 40 (±7.3)** ms [8–72] ms
HT (T1)	18.4(±1)/42.2(±2.5)Hz [36,37,47,48] Hz (**a, b**) 28 (±6.1)** ms [8–48] ms –	19.4(±1.4)/36 Hz (**a**) 20 (±5.2)** ms [8–32] ms –	19.1(±0.5)/40.8(±0.2)Hz 72 (±8.6)** ms (**b**) [24–120] ms 32.2(±4)/ 42.6(±0.4) Hz 208 (±8.6) ms [160–250] ms (**d**)	**33.8(±2)/**43.8(±0.4) Hz 120 (±12.6) ms (**c**) [8–250] ms –	30.1(±2.3)*/39.9(±0.5)Hz 44 (±7.7) ms (**b**) [8–80] ms 32.8(±3.3)/41.5(±0.2) Hz 216(±8) ms [176–250] ms (**d**)

LT (T2)	16.9(±0.5)/ 38 Hz 260 (±4)** ms [250–264] ms (**f**)	21.8(±1.2)/40 (±0.5) Hz [38, 42] Hz 548 (±9.5) ms [488–600] ms (**i-j**)	**36.8(±1.6)**/38.8(±0.4)Hz [35–41] Hz 464 (±14.2) ms [320–600] ms (**g-j**)	24.3(±1.6)/34.1(±0.3)Hz [33–35] Hz 552.6 (±9.9) ms [496–600] ms (**i-j**)	16.6(±1.1)/39Hz 524(±5.2) ms [512-536] ms (**h**)
	24.6(±2)/ 35 Hz 568 (±6.5) ms [544–592] ms (**j**)	–	–	–	–
HT (T2)	36.3(±1.4)/43(±0.6)Hz [37,38,40,46,47] Hz 432 (±15.7) ms [250–600] ms (**f, g, j**)	25.6(±2.2)/45.9(±0.6) Hz [45, 49] Hz 312 (±7.3)** ms [280–344] ms (**f**)	53.7(±2)/ 43.2(±0.2) Hz 432(±15.7) ms [250–600] ms (**f, j**)	**55(±3)**/ 44.1(±0.3) Hz [39–45] Hz 432 (±15.7) ms [250–600] ms (**f, g, i, j**)	32.4(±1.9)/40.7(±0.4) Hz [39–44] Hz 376 (±13.1)** ms [250–496] ms (**f**)
	–	39(±3)/ 45 Hz 444 (±7.7) ms [408–488] ms (**g**)	–	–	46(±5.7)/39.3(±0.6) Hz 568 (±8) ms [528–600] ms (**j**)
	–	48(±7)/ 38.6 (±0.2) Hz 572 (±7.7) ms [536–600] ms (**j**)	–	–	–
Subjects tone(period)			**PP**		
LT (T1)	**49(±5.5)***/ 32 Hz (**a**) 44 (±7.7) ms [8–80] ms	36.4(±4)*/32.3(±0.7)Hz(**a**) 36 (±6.9) ms [8–64] ms	32.5(±2.1)*/45.5(±1.1)Hz [42–50] Hz (**c**) 56 (±8.6)** ms [8–104] ms	28.2(±3.4)*/37.5(±1.6)Hz [34,35,43] Hz (**a**) 36 (±6.9) ms [8–64] ms	32.4(±4.3)/43.2(±2.2) Hz [32,46,48,49,50]Hz (**a,d**) 56 (±8.6) ms [8–104] ms
	–	–	21.9(±0.8)/47.8(±1.4)Hz [33,49,50] Hz (**c**) 196 (±9.5) ms [136–250] ms	–	30.1(±2.7)/37.9(±0.1) Hz 192 (±8) ms (**b**) [152–232] ms
HT (T1)	**49.7(±3.5)***/34 Hz (**a**) 40 (±7.3) ms [8–72] ms	27.6(±2.4)*/34.9(±0.1)Hz 44 (±7) ms (**a**) [16–72] ms	34.3(±3)*/ 34.1 (±0.1) Hz 112 (±11.8) ms (**a**) [16–208] ms	29.5(±2.6)/34.4(±0.2) Hz 36 (±7)** ms (**a**) [8–64] ms	21.1(±2)/41(±3.5)Hz [34,36,47] Hz (**a**) 20 (±5.2)** ms [8–32] ms
	–	–	–	29.9(±1.5)/33.4(±0.1) Hz 188 (±10.1) ms (**d**) [120–250] ms	–
LT (T2)	39(±2.6)*/42.7(±0.9)Hz [34–42] Hz 468 (±14.0) ms [328–600] ms (**g-j**)	48.8(±4.2)*/44.3(±1.2)Hz [35–50] Hz 468 (±14) ms [328–600] ms (**g-j**)	68.9(±5.4) */ 45(±0.7) Hz [35–50] Hz 432 (±15.7) ms [250–600] ms (**g-j**)	**82.1(±5.2)** */47(±0.7) Hz [36–50] Hz 468 (±14.0) ms [328–600] ms (**g-j**)	54.3(±2.9)*/41.6(±0.7)Hz [38–50] Hz 452 (±14.8) ms [296–600] ms (**g-j**)
HT (T2)	**58(±3.5)***/40.3(±1.1)Hz [34,48,49] Hz 444 (±15.1)ms [280–600] ms (**f, g, j**)	43(±1.5)/44.9(±0.7)Hz, [47,50, 35,38,39] Hz 432 (±15.7) ms [250–600] ms (**f, g, i, j**)	52(±2.1)/ 37.8(±0.9) Hz [34,35, 41,45,49,50] Hz 436 (±15.5) ms [264–600] ms (**g, i, j**)	**55.5(±3.2)**/36.5(±0.9) Hz [33, 50] Hz 432 (±15.7) ms [250–600] ms (**f, g, i, j**)	41.6(±2.3)/42.4(±1.2)Hz [34–36, 49,50] Hz 448 (±15) ms [288–600] ms (**g, h, i, j**)

Note: Lower case letters in Table 3 marked consecutive sub-intervals with ERS γ bursts: **a**, **b**, **c** during T1 and **f**, **g**, **h**, **i**, **j** during T2.

Table 3. Mean ERS γ bursts (%) across the trials with mean spectral peaks **F** (Hz) for HS and PP after LT and HT presented in short–term zones **D** (ms) during early T1 and late T2 period (same format as **Table 1).**

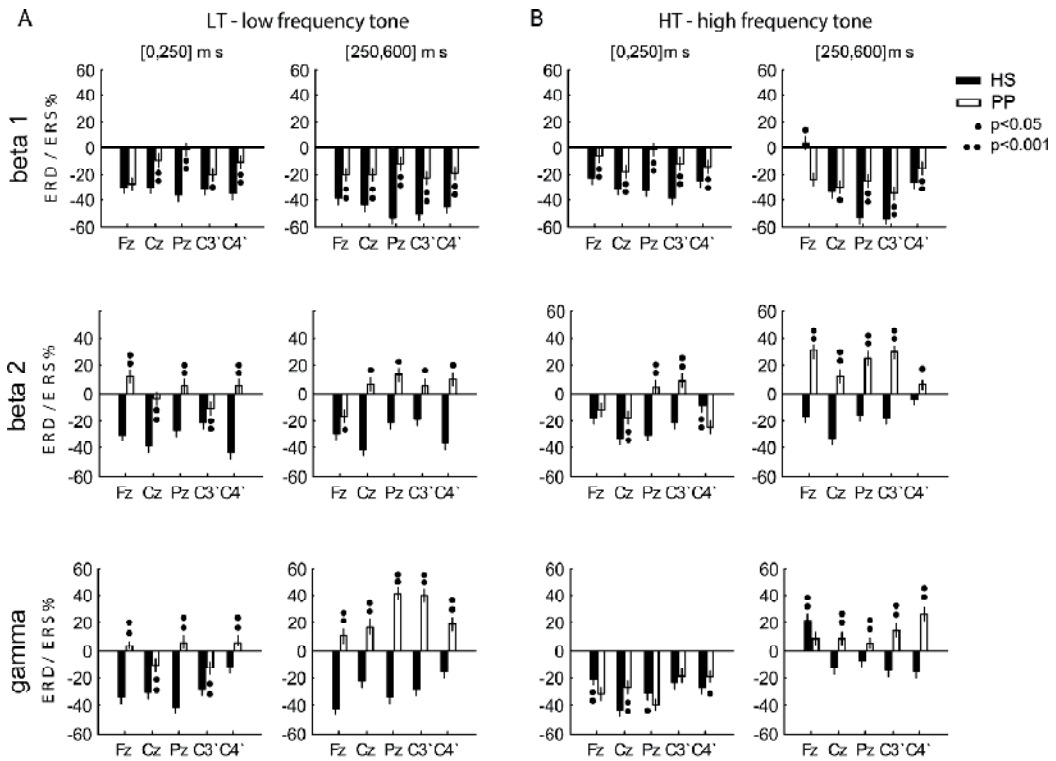


Fig. 2. Beta 1, Beta 2 and gamma band ERD/ERS over T1 and T2. Group means (±SE) are shown graphically to illustrate statistical results of β1-, β2-, γ-ERD/ERS following LT (A) and HT (B) for the early T1 (left) and late T2 (right) time periods. The significant difference in the ERD/ERS of HS and PP are presented for each pair of channels and marked by * (p <0.05) or ** (p <0.001, KW test).

4. Discussion

The data obtained confirmed that event-related oscillatory responses in different frequency bands vary with sensory and cognitive processes. We found functional differences between event-related oscillatory activity for cognitive and sensory-motor information processing, and a clear distinction between PP and HS in both the stimuli encoding (0–250 ms) and cognitive processing (250–600 ms) intervals. Attended stimuli produced theta response synchronizations in both groups, more markedly in HS, in the first period up to 250 ms after stimulation. Enhanced theta waves in the early period (up to 250 ms) of visual and auditory stimuli have also been described by Basar (1980), Schurmann and Basar-Eroglu (1994). Theta frequency rhythms are dominant oscillations within the hippocampal formation, which is of crucial importance for the encoding of new information (Klimesch, 1997; Klimesch et al., 2005). In the late post-stimulus period functionally related to cognitive processing, θ-ERD response was predominant, excluding the parietal θ-ERS in PP in response to both frequency tones and the frontal θ-ERS in HS in response to the low frequency tone.

Prominent differences in the α-ERD/ERS responses between the groups were observed during the first time period of 0–250 ms. A widely distributed fronto-central α-ERS

manifested in PP in response to both tone types during the first 250 ms after stimulus was absent in HS. In the second period after stimulus absence, α-ERD was found in both groups in response to both tone types. This was generally more prominent in HS, with the exception of frontal side in response to either a high or low frequency tone. Alpha-ERD was more prominent at central and right motor areas in response to the high frequency tone in PP.

Theta and alpha frequency ERD/ERS were significantly different between subject groups. It is known that the oscillatory alterations to θ-ERS are related to memory encoding (Klimesch et al., 2001; Jensen & Tesche, 2002).

Alpha-ERS most probably demonstrates active working memory or attentional processes (Klimesch, 1997; Jensen et al., 2002), whereas α-ERD is functionally related to mental activity (Basar, 1980) and reflects memory search processes (Klimesch, 1997; Klimesch et al., 2005; Pesonen et al., 2006). The recognition of auditory stimuli elicits widespread α-ERD responses (Krause et al., 1994). It is accepted that alpha oscillations are mainly generated by cortico-cortical and thalamo-cortical neuronal networks (Lopes da Silva et al., 1980; Schmiedt et al., 2005; Ellfolk et al., 2006). This fact, together with the changes in the metabolic patterns of thalamic, premotor and prefrontal cortex, parieto-occipital regions, etc., that occur in PP (Fukuda et al., 2001) could explain the abnormality of early time period α-ERS in the PP compared to the HS. Observed slight activity of the basal ganglia–thalamic and cerebellar–thalamic pathways might be implicated in the development of parkinsonian symptoms (Rolland et al., 2007).

Schmiedt et al. (2005) also found differences between PP and HS in the θ- and α-frequency ERD/ERS responses during working memory encoding but in a visual working memory paradigm. We cannot draw direct parallels between their results and ours in the present study because of the different stimulus modality. The early and late δ post-stimulus activities were enhanced in HS. The late period, related to cognitive information processing, exhibited δ-ERS in HS and δ-ERD in PP at most electrodes in response to a low frequency tone, and at parietal and left motor areas in response to the high frequency tone. Many authors agree that the main power of P300 is in the delta range (Demiralp et al., 1999; Karakas et al., 2000; Klimesch et al., 2000; Klimesch et al., 2006). The lower δ-ERS in PP in the late post-stimulus period, which becomes δ-ERD in some recordings, could explain the lower P3 amplitude observed in PP (Philipova et al., 1997). Our patients were medicated by L-dopa drugs and this medication may have had some effect on the present findings. One of the models (Leblois et al., 2006) supposed that high dopamine depletion could modify the network dynamic state from an imbalance between the feedbacks and lead to synchronous oscillations driven by a hyperdirect loop appearing in basal ganglia after inactivation of the striatum.

A reduction in this α-ERD/ERS abnormality and a consequent improvement in PP performance during working memory tasks have been found as the result of L-dopa (Lewis et al., 2003; Marini et al., 2003; Shohamy et al., 2005; Devos et al., 2004). Nevertheless, we found some differences between the two groups. The memory related and stimulus categorized ERD/ERS responses at all these frequencies reflected different underlying neuropathological and cognitive changes in this neurodegenerative disease. Theta activity is suggested to be mostly engaged in memory operations (Klimesch et al., 1996; Karakas et al., 2000; Jensen et al., 2002b) and this θ pathological synchronized enhancement in PD could explain the cognitive dysfunction commonly occurring even in the early stages of Parkinson's disease (Lewis et al., 2003). We found specific significant differences at left

motor area as θ-ERS in the HS and θ-ERD in the PP during sensory-motor processing (early period) following the high frequency tone. We also detected different processes of θ-ERS for the PP and ERD for the HS in the parietal lead during the cognitive information processing (late period) following both tones, which reflects different task-related activation of the associative posterior cortex.

These findings are probably due to the auditory cortex being located in the dorsal and lateral part of the superior temporal gyrus as well as in the inferior parietal lobule (Konig et al., 2005). The absence of α-ERD at the frontal electrode locations in the patients with PD indicated that the PP, compared with HS, used different cognitive strategies for stimulus response processing which are normally implemented by fronto-striatal circuits (Krause, 2006). The late higher fronto-central α-ERD in PP accompanied by a lower P3 component amplitude, especially in the fronto-central sides, reflects a disturbance in the frontal regulation of attentional processes as well a disturbance of the basal ganglia activity and their related thalamo-cortical neuronal nets (Stam et al., 1993; Piccirilli et al., 1989; Schmiedt et al., 2005).

In PP, we found hemispheric lateralization for sensory and cognitive processing concerning θ-ERD/ERS at left and right motor areas as well as a significantly higher α-ERS at left compared to right motor area. This finding corresponds with the results of Magnani et al., 1998, Defebvre et al., 1996. These authors suggested that other cortical areas may be activated both to compensate for a dysfunction of motor preparation and to increase the level of cortical activity necessary for the realization of the movement. Another possible explanation is that this hemispheric lateralization is connected with auditory attention and hemispheric differences in the processing of high and low frequencies (Ivry & Robertson, 1998).

Post-stimulus β1 ERD was elicited from both groups during sensory (T1) and cognitive information (T2) processing, though this was significantly more pronounced in HS in response to both tone types at all electrodes. The greater β1 ERD in HS can be explained by the increased excitability level of the neurons (Pfurtscheller & Lopes da Silva, 1999; Brown & Marsden, 1998). Late post-stimulus frontal β1 ERS (T2) was evident only in HS following HT. This HS ERS, comprising components in the band between 13 and 20 Hz, may represent an inhibited frontal cortical network, at least under certain circumstances (Pfurtscheller & Lopes da Silva, 199; Engel et al., 2001).

A frontal β2 ERD was maintained in both groups during the cognitive information processing (T2) following LT, though this was weaker in PP. β2 ERS was only observed in PP. These were weakly elicited during the sensory stimuli processing (T1) and appeared at fronto-parietal and left motor areas (LT: Fz, C3', Pz; HT: C3', Pz). β2 ERS in PP was more prominent during cognitive processing (T2) after either tone type, but particularly so following HT. The β2 change reversals compared to β1 which we observed for the PD patients support the hypothesis of Marceglia et al. (2009), that two distinct information channels in the cortico-basal ganglia–thalamo-cortical loop, involved in motor and non-motor information processing, are formed in the parkinsonian brain. The frontal β synchronization at 20–30 Hz arises both from communication with, and also from within, the STN (Williams et al., 2003). The β synchrony has been ascribed predominantly to a lack of dopaminergic activity in the striatum which, together with the STN, is the recipient of cortical input to the basal ganglia (Fogelson et al., 2006; Williams et al., 2002). Studies with unmedicated PD patients have revealed prominent oscillations in 'basal ganglia β frequency band' (Weinberger et al., 2006; Kühn et al., 2006; Priori et al., 2004; Fogelson et al., 2006). The

engagement of the basal ganglia in β band synchronization is found when there is acute or chronic dopaminergic hypoactivity, and while primarily associated with bradykinesia and rigidity, it has also been associated with impairments to complex movements and motor related cognitive behaviour because of the widespread basal ganglia connectivity with the cerebral cortex (Terman et al., 2002). Further, the pathological β synchrony in the cerebellum might lead to a purer breakdown of simple motor tasks because of more focal cerebellothalamic projections into the cerebral cortex that are concentrated on the primary motor cortex (Leblois et al., 2007). A relative functional division between activities in the β band might be supported by the evidence for different patterns of pharmacological sensitivity (Priori et al., 2004) and cortico-subthalamic coupling (Fogelson et al., 2006). The dopaminergic drug treatment suppressed mainly β1 synchrony, graded by the amount of drug-induced suppression in the STN (Kühn et al., 2006; Wang et al., 2005) and cerebral cortex, correlating with the level of improvement in bradykinesia and rigidity but not in parkinsonian rest tremor (Weinberger et al., 2006; Silberstein et al., 2005), the latter of which probably has an independent pathophysiological substrate (Rivlin-Etzion et al., 2006).

Our group of patients showed a significantly reduced γ–ERD compared with HS over central and left motor areas, and only PP showed γ–ERS over fronto-parietal and right motor areas following LT during the sensory stimuli processing (T1). A widespread γ–ERS appeared during later cognitive processing (T2), and then only in PP, following either tone type, with the exception of a more prominent frontal γ–ERS in HS following HT. In our study, we observed switches between cortical activity in the β2 and γ band oscillations. Hence we concluded that a reduction in β2-band synchronized activity allows higher frequency oscillatory activity in the γ range leading to its synchronization. The observed energy changes in the β2 and γ bands indicate that an increase in one is accompanied by a decrease in the other. These T2 changes in PP were more pronounced in the motor cortex than in the parietal and even frontal cortex data. In the parkinsonian state, there was a tendency towards increased synchronized higher frequency fluctuations, specifically in the motor cortex, where instances of peaks were found after both tone types. Except for the β2 band series of data during cognitive processing (T2) after HT, the difference between magnitude of the peaks in the frontal, parietal and contralateral motor areas did not reach significance. Recent data demonstrate that the disruptions of the beta and gamma range cortical rhythms are based on the disturbed temporal relationship between cortical oscillatory activity and basal ganglia activity in Parkinsonism (Gatev & Wichmann, 2008). This finding is also in agreement with studies of PP following dopaminergic medication, which promoted synchronized oscillatory activity at higher frequencies (γ) predominantly at the level of the frontal cortex and striatum (Levy et al., 2001; 2002; Brown et al., 2001; Williams et al., 2002; Leblois et al., 2007).

In recent MEG investigations of various cognitive and sensory tasks (Kaiser et al., 2003; Lutzenberger et al., 2002) the reported γ band activity over the higher sensory areas has not shown a sustained activation, but rather, a peaking activity. In our sensori-motor study, these transient responses were functionally dissociable between the two groups. We observed stimulus-specific γ band activity components over the fronto-parietal cortex, but this was differently manifest in each group and varied over the time course. The topography was compatible with the notion of an auditory dorsal space processing stream involving the posterior temporal, parietal and superior frontal cortex (Rauschecker, 1998; Arnott et al., 2004). If the cognitive processing (T2) γ band activity components represent similar

anticipatory activations both for LT and HT, one might assume that the same cortical networks should underlie the same stimulus representations. However, while all components were mainly localized over fronto-central areas, there was some variation between the conditions, showing significant effects on the parietal γ components for LT, but not for parietal γ activity for HT. This suggests that networks encoding the stimulus features are not fixed, and may vary with task demands.

The assessing EEG stimulus-specific oscillatory activity yielded insights into the temporal dynamics of sound processing in short-term memory. Contrasting oscillatory γ activity between the two stimuli, such as between LT ERS and HT ERD during the sensory processing (T1) in PP, as well as between LT ERD and HT ERS during the cognitive processing (T2) in HS, revealed stimulus-specific γ activity behavior in the 30–50 Hz range over the HS's frontal and PP's fronto-parietal cortex. This suggests that γ band activity reflects the general involvement of cortical networks in particular tasks but may index the specific content of short-term memory in each group.

The pronounced and well-synchronized γ burst in HS was present in the very short-term phases around 25–60 ms after the stimulus onset, with spectral peaks ranging from 30 to 45 Hz (Gurtubay et al., 2001). Despite this short-term high synchrony in HS, the common γ behavior during sensory stimuli processing (T1) was desynchronization. However, the PP processes were with higher short-term energy, which is a prerequisite for all maintenance-related processes, and thus defined a persistent synchronization during sensory stimuli processing, mainly at fronto-parietal and right motor areas following LT. It is clear that there is a difference between groups in the early and well-synchronized response that is basically a sensory phenomenon important to preparing the brain for the subsequent processing. This evidence suggests that γ oscillations may be modulated by attentional processes. Several cognitive paradigms for the auditory system have shown early spectral peak responses in the γ band between 30 and 40 Hz at around 25 ms after stimulus onset that last for about 100 ms (Pantev, 1995; Arnott et al., 2004).

Later peaking activity has been recorded in the 200–400 ms interval following an experimental task. The latency and scalp topography vary according to the type of stimulus, indicating task-dependent local network activation. The significantly varying magnitudes of differentiation demonstrated that the topography of stimulus-specific γ-band activity is also task-dependent within the groups (Tiitinen et al., 1993). We found restricted energy changes over all recorded areas in HS, but not in the frontal area after HT. The significant differences between groups in T2 recorded after both stimuli could be due to memory retrieval processes that are activated during the performance of the paradigms. The lower energy in HS during cognitive processing (T2) could be related to fewer attentional processes required to eventually perform a task. The relative strength of differentiation in the γ–band may suggest that performance depends on the different group's ability to retain a representation in memory of the relevant stimulus feature and thus to be able to neglect the irrelevant stimuli. The acquisition and retention of sound frequency information was accompanied by frontal gamma band activity components (Karakaş & Başar, 1998). The high-frequency stimuli were accompanied by more exaggerated, well–synchronized frontal γ band components in performing the tasks. Memory for low versus high frequency tones selectively enhanced oscillatory activity for the posterior versus the frontal components, thus directly demonstrating differentiation of the group's modulation of cortical activity by task demands.

A mechanism that underlies many of the immediately aforementioned cognitive functions is the match of sensory information with memory contents (Kaiser et al., 2009a; 2009b; Visscher et al., 2007). The 'early' γ-band activity occurring 150 ms after stimulus presentation reflects such a match with memory. The 'late' γ activity, which typically emerges with a latency of more than 150 ms, is a temporal signature of utilization processes such as response selection or context updating. We also found a later (250–400 ms) ERS γ response, following only HT in HS, over the frontal location, where this activity peaked in the 33–45 Hz range. In PP, the specific β2 and γ bursts (30–38 Hz) exhibited maximal scalp projection covering areas to the left and right of the motor areas**,** and with frontal, central or parietal participation that depended on the stimuli. This oscillatory burst reflects a later stimulus context process, although it has also been associated with the motor responses later in the task (Brown, 2003; Kaiser et al., 2009b). The β2/γ oscillation in the groups points to a direct relation to aspects of post-discrimination processes related to the P300 wave **(**Haig et al., 2000). This oscillatory burst (letters **g-j** for intervals from 320 to 550 ms) also showed a variable relationship to attention, as it was significantly different during the HT and LT task. The results also showed that EEG activity in the frontal, parietal and motor cortex is significantly different between groups, not only in temporal variations (always with a delay in PP) but also in frequency shifts (β2/γ ERD in HS compared to the ERS in PP). Although these shifts do not follow a simple pattern, they are significantly different from HS, raising the possibility that the interactions between basal ganglia activity and cortical rhythms are functionally relevant. Therefore, the normal higher frequency relationships between cortical and basal ganglia activity are strongly altered in the parkinsonian state (Gatev & Wichmann, 2008). The shifts of β/γ patterns occurring in the groups are probably associated with specific types of basal ganglia events related to transitions between cortical idling and more active states (Williams et al., 2003).

5. Conclusion

Our investigation further demonstrates the close relationship between physiological abnormalities in PD and disturbances in the EEG frequency characteristics. The results of this investigation in PD patients of both sensory and cognitive processing of auditory stimuli suggests that PD should be characterized by multiple impairments in oscillatory networks, which in turn indicates the presence of task-specific disturbances in the temporal and regional integration of all frequency components.

6. References

Anik, Y., Iseri, P., Demirci, A., Komsuoglu, S., Inan, N. (2007) Magnetization transfer ratio in early period of Parkinson disease. *Acad Radiol* 14(2), (2007 Feb), pp. 189–192, ISSN 1076-6332

Antal, A., Kéri, S., Dibó, G., Benedek, G., Janka, Z., Vécsei, L., Bodis-Wollner, I. (2002) Electrophysiological correlates of visual categorization, pp. evidence for cognitive dysfunctions in early Parkinson's disease. *Brain Res Cogn Brain Res* 13(2), (2002 Apr) ,pp. 153–158, ISSN 0926-6410

Arnott, S. R., Binns, M. A., Grady, C. L., Alain, C. (2004) Assessing the auditory dualpathway model in humans. *NeuroImage* 22(1), (2004 May), pp. 401-408, ISSN 1053-8119

Basar, E. (1980) EEG brain dynamics. Relations between EEG and brain evoked potentials. Elsevier, Amsterdam

Başar, E., Basar-Eroglu, C., Karakas, S., Schurmann, M. (2001) Gamma, alpha, delta, and theta oscillations govern cognitive processes. *Int J Psychophysiol* 39(2-3), (2001 Jan) pp. 241-248, ISSN 0167-8760

Brown, P. & Marsden, C. D. (1998) What do the basal ganglia do? Lancet 351(9118), (1998 Jun 13), pp. 1801-1804, ISSN 0140-6736

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P. & Di Lazzaro, V. (2001) Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J Neurosci* 21 (3), (2001 Feb 1) pp. 1033-1038, ISSN 0270-6474

Brown, P. (2003) Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov Disord* 18(4), (2003 Apr), pp. 357-363, ISSN 0885-3185

Cassidy, M., Mazzone, P., Oliviero, A., Insola, A., Tonali, P., Di Lazzaro, V., Brown, P. (2002) Movement-related changes in synchronization in the human basal ganglia. Brain 125(Pt 6), (2002 Jun), pp. 1235-1246, ISSN 0006-8950

Cools R (2006) Dopaminergic modulation of cognitive functionimplications for L-DOPA treatment in Parkinson's disease. *Neurosci Biobehav Rev* 30(1), (2005 Jun 1), pp. 1–23, ISSN 0149-7634

Gurtubay, I. G., Alegre, M., Labarga, A., Malanda, A., Iriarte, J., Artieda, J. (2001) Gamma band activity in an auditory oddball paradigm studied with the wavelet transform. *Clin Neurophysiol* 112(7), (2001 Jul), pp. 1219-1228, ISSN 1388-2457

Daum, I., Schugens, M. M., Spieker, S., Poser, U., Schönle, P. W., Birbaumer, N. (1995) Memory and skill acquisition in Parkinson's disease and frontal lobe dysfunction. *Cortex* 31(3), (1995 Sep), pp. 413–432, ISSN 0010-9452

Defebvre, L, Bouniez, JL, Destke, A, Guieu, JD (1996) Movement related ERD pattern preceding voluntary movement in untreated Parkinson's disease. *J Neurol Neurosurg Psychiatry* 60(3), (1996 Mar), pp. 307–312, ISSN 0022-3050

Demiralp, T., Ademoglu, A., Schürmann, M., Bas¸ar-Eroglu, C., Başar, E. (1999) Detection of P300 waves in single trials by the wavelet transform (WT). *Brain Lang* 66(1), (1999 Jan), pp. 108–128, ISSN 0093-934X

Devos, D., Labyt, E., Derambure, P., Bourriez, J. L., Cassim, F., Reyns, N., Blond, S., Guieu, J. D., Destée, A., Defebvre, L. (2004) Subthalamic nucleus stimulation modulates motor cortex oscillatory activity in Parkinson's disease. *Brain* 127(2), (2004 Feb), pp. 408–419, ISSN 0006-8950

Donoghue, J. P., Sanes, J. N., Hatsopoulos, N. G., Gaal, G. (1998) Neural discharge and local field potential oscillations in primate motor cortex during voluntary movements. *J Neurophysiol* 79(1), (1998 Jan), pp. 159-173, ISSN 0022-3077

Durka, P. J., Zygierewicz, J., Klekowicz, H., Ginter, J., Blinowska, K. J. (2004) On the statistical significance of event-related EEG desynchronization and synchronization in the time-frequency plane. *IEEE Trans Biomed Eng* 51(7), (2004 Jul), pp. 1167–1175, ISSN 0018-9294

Dushanova, J., Philipova, D., Nikolova., G. (2009) Event-related synchronization/ desynchronization during discrimination task conditions in patients with

Parkinson's disease. *Cell Mol Neurobiol* 29(6-7), (2009 Sep), pp. 971-980, ISSN 0272-4340

Dushanova, J., Philipova, D., Nikolova, G. (2010) Beta and gamma frequency-range abnormalities in parkinsonian patients under cognitive sensorimotor task. *Journal of the Neurological Sciences* 293(1-2), (2010 Jun 15), pp. 51–58, ISSN 0022-510X

Ellfolk, U., Karrasch, M., Laune, M., Pesonen, M., Krause, K. (2006) Event related desynchronisation/ERS during an auditory-verbal memory task in mild Parkinson's disease. *Clin Neurophysiol* 117(8), (2006 Aug), pp. 1737–1745, ISSN 1388-2457

Engel, A. K., Fries, P., & Singer, W. (2001) Dynamic predictions: oscillations and synchrony in top-down processing. *Nat Rev Neurosci* 2(10), (2001 Oct), pp. 704-716, ISSN 1471-003X

Evarts, E. V., Teräväinen, H., & Calne, D. B. (1981) Reaction time in Parkinson's disease. *Brain* 104(1), (1981 Mar), pp. 167–186, ISSN 0006-8950

Farmer, S. F. (1998) Rhythmicity, synchronization and binding in human and primate motor systems. *J Physiol* 509(1), (1998 May 15), pp. 3-14, ISSN 0022-3751

Fries, P., Reynolds, J. H., Rorie, A. E., Desimone, R. (2001) Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 291(5508), (2001 Feb 23), pp. 1560-1563, ISSN 0036-8075

Foffani, G., Bianchi ,A. M., Baselli, G., Priori, A. (2005) Movement-related frequency modulation of beta oscillatory activity in the human subthalamic nucleus, *J Physiol* 568(2), (2005 Oct 15), pp 699–711, ISSN 0022-3751

Fogelson, N., Williams, D., Tijssen, M., van Bruggen, G., Speelman, H., Brown, P. (2006) Different functional loops between cerebral cortex and the subthalmic area in Parkinson's disease. *Cereb Cortex* 16(1), (2006 Jan), pp. 64-75, ISSN 1047-3211

Fukuda, M., Edward, C., Eidelberg, D. (2001) Functional brain networks in Parkinson's disease. *Parkinsonism Relat Disord* 8(2), (2001 Oct), pp. 91–94, ISSN 1353-8020

Gatev, P., & Wichmann, T. (2008) Interactions between Cortical Rhythms and Spiking Activity of Single Basal Ganglia Neurons in the Normal and Parkinsonian State. *Cereb Cortex* 19(6), (2009 Jun), pp. 1330-44, ISSN 1047-3211

Haig, A. R., Gordon, E., Pascalis, V. D., Meares, R. A., Bahramali, H., Harris, A. (2000) Gamma activity in schizophrenia: evidence of impaired network binding? *Clin Neurophysiol* 111(8), (2000 Aug), pp. 1461–1468, ISSN 1388-2457

Herrmann, C. S., Munk, M. H. J., Engel, A. K. (2004) Cognitive functions of gamma-band activity: memory match and utilization. *Trends Cogn Sci* 8(8), (2004 Aug), pp. 347-355, ISSN 1364-6613

Higginson, C. I., King, D. S., Levine, D., Wheelock , V. L., Khamphay, N. O., Sigvardt, K. A. (2003) The relationship between executive function and verbal memory in Parkinson's disease. *Brain Cogn* 52(3), (2003 Aug), pp. 343–352, ISSN 0278-2626

Hoehn, M. M., Yahr, M. D. (1967) Parkinsonism: onset progression and mortality. *Neurology* 17(5), (1967 May), pp. 427-442, ISSN 0028-3878

Innis, R. B., Seibyl, J. P., Scanley, B. E., Laruelle, M., Abi-Dargham, A., Wallace, E., Baldwin, R. M., Zea-Ponce, Y., Zoghbi, S., Wang, S. (1993) Single photon emission computed tomographic imaging demonstrates loss of striatal dopamine transporters in

Parkinson disease. *Proc Natl Acad Sci USA* 90(24), (1993 Dec 15), pp. 11965–11969, ISSN 0027-8424

Ivry, R. B., Robertson, L. C. (1998) The two sides of perception. MIT Press, Cambridge, MA, ISBN 0-262-09034-1

Jensen, O., Tesche, C. D. (2002) Frontal theta activity in humans increases with memory load in a working memory task. *Eur J Neurosci* 15(8), (2002 Apr), pp. 1395–1399, ISSN 0953-816X

Jensen, O., Gelfand, J., Kounios, J., Lisman, J. E. (2002) Oscillations in the alpha band (9–12 Hz) increase with memory load during retention in a short-term memory task. *Cereb Cortex* 12(8), (2002 Aug), pp. 877– 882, ISSN 1047-3211

Kaiser, J., Ripper, B., Birbaumer, N., Lutzenberger, W. (2003) Dynamics of gamma-band activity in human magnetoencephalogram during auditory pattern working memory. *NeuroImage* 20(2), (2003 Oct), pp. 816-827, ISSN 1053-8119

Kaiser, J., Rahm, B., Lutzenberger, W. (2009a) Temporal dynamics of stimulus-specific gamma-band activity components during auditory short-term memory. *Neuroimage* 44(1), (2009 Jan 1), pp. 257-264, ISSN 1053-8119

Kaiser, J., Lutzenberge, W., Decker, C., Wibral, M., Rahm, B. (2009b) Task- and performance-related modulation of domain-specific auditory short-term memory representations in the gamma band. *Neuroimage* 46(4), (2009 Jul 15), pp. 1127-36, ISSN 1053-8119

Karakaş ,S., & Başar, E. (1998) Early gamma response is sensory in origin: a conclusion based on cross-comparison of results from multiple experimental paradigms. *Int J Psychophysiol* 31(1), (1998 Dec), pp. 13-31, ISSN 0167-8760

Karakas, S., Erzengin, O. U., & Başar, E. (2000) A new strategy involving multiple cognitive paradigms demonstrates that ERP components are determined by the superposition of oscillatory signals. *Clin Neurophysiol* 111(10), (2000 Oct), pp. 1719–1732, ISSN 1388-2457

Karrasch, M., Krause, C. M., Laine, M., Lang, H. A., Lehto, M. (1998) Eventrelated ERD and ERS during an auditory lexical matching task. *Electroencephalogr Clin Neurophysiol* 107(2), (1998 Aug), pp. 112–121, ISSN 0013-4694

Karrasch, M., Laine, M., Rapinoja, P., Krause, C. M. (2004) Effects of normal ageing on event-related ERD/ERS during a memory task in humans. *Neurosci Lett* 366(1), (2004 Aug 5), pp. 18–23, ISSN 0304-3940

Klimesch, W. (1997) EEG a-rhythms and memory processes. *Int J Psychophysiol* 26(1-3), (1997 Jun), pp. 319–340, ISSN 0167-8760

Klimesch, W., Doppelmay, M., Russegger, H., Pachinger, T. (1996) Theta band power in the human scalp EEG and the encoding of new information. *Neuroreport* 7(7), (1996 May 17), pp. 1235–1240, ISSN 0959-4965

Klimesch, W., Doppelmayr, M., Schwaiger, J., Winkler, T., Gruber W. (2000) Theta oscillations and the ERP old/new effect: independent phenomena? *Clin Neurophysiol* 111(5), (2000 May), pp. 781–793, ISSN 1388-2457

Klimesch, W., Doppelmayr, M., Stadler, W., Pollhuber, D., Sauseng, P., Rohm, D. (2001) Episodic retrieval is reflected by a process specific increase in human electroencephalographic h activity. *Neurosci Lett* 302(1), (2001 Apr 13), pp. 49–52, ISSN 0304-3940

Klimesch, W., Schnack, B., Sauseng, P. (2005) The functional significance of h and upper a-oscillations. *Exp Psychol* 52(2), pp. 99–108, ISSN 1618-3169

Klimesch, W., Hanslmayr, S., Sauseng, P., Gruber, W., Brozinsky, C. J., Kroll, N. E., Yonelinas, A. P., Doppelmayr, M. (2006) Oscillatory EEG correlates of episodic trace decay. *Cereb Cortex* 16(2), (2006 Feb), pp. 280–290, ISSN 1047-3211

Konig, R., Heil, P., Budinger, E., Scheich, H. (2005) The auditory cortex: a synthesis of human and animal research. Lawrence Erlbaum Associates, NJ. ISBN 0-8058-4938-6

Krause, C. M. (2006) Cognition- and memory-related ERD/ERS responses in the auditory stimulus modality. *Prog Brain Res* 159, pp. 197–207, ISSN 0079-6123

Krause, C. M., Lang, H. A., Laine, M., Helle, S. I., Kuusisto, M. J., Pörn, B. (1994) Event-related desynchronization evoked by auditory stimuli. *Brain Topogr* 7(2), (1994 Winter), pp. 107–112, ISSN 0896-0267

Krause, C. M., Lang, A. H., Laine, M., Kuusisto, M., Pörn, B. (1996) Eventrelated EEG desynchronization and synchronization during an auditory memory task. *Electroencephalogr Clin Neurophysiol* 98(4), (1996 Apr), pp. 319–326, ISSN 0013-4694

Krause, C. M., Aström, T., Karrasch, M., Laine, M., Sillanmäki, L. (1999) Cortical activation related to auditory semantic matching of concrete versus abstract words. *Clin Neurophysiol* 110(8), (1999 Aug), pp. 1371– 1377, ISSN 1388-2457

Knoke, D., Taylor, A. E., Saint-Cyr, J. A. (1998) The differential defects of ceing on recall in Parkinson's Disease and normal subjects. *Brain Cogn* 38(2), (1998 Nov), pp. 261–274, ISSN 0278-2626

Kühn, A. A., Kupsch, A., Schneider, G. H., Brown, P. (2006) Reduction in subthalamic 8–35 Hz oscillatory activity correlat with clinical improvement in PD. *Eur J Neurosci* 23(7), (2006 Apr), pp. 1956-1960, ISSN 0953-816X

Leblois, A., Boraud, T., Meissner, W., Bergman, H., Hansel, D. (2006) Competition between feedback loops underlies normal and pathological dynamics in the basal ganglia. *J Neurosci* 26(13), (2006 Mar 29), pp. 3567– 3583, ISSN 0270-6474

Leblois, A., Meissner, W., Bioulac, B., Gross, C. E., Hansel, D., Boraud, T. (2007) Late emergence of synchronized oscillatory activity in the pallidum during progressive parkinsonism. *Eur J Neurosci* 26(6), (2007 Sep), pp. 1701-1713, ISSN 0953-816X

Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., Owen, A. M. (2003) Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *J Neurosci* 23(15), (2003 Jul 16), pp. 6351–6356, ISSN 0270-6474

Levy, R., Dostrovsky, J. O., Lang, A. E., Sime, E., Hutchison, W. D., Lozano, A. M. (2001) Effects of apomorphine on subtalamic nucleus and globus pallidus internus neurons in patients with Parkinson's disease. *J Neurophysiology* 86(1), (2001 Jul), pp. 249-260, ISSN 0022-3077

Levy, R., Hutchison, W. D., Lozano, A. M., Dostrovsky, J. O. (2002) Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. *J Neuroscience* 22(7), (2002 Apr 1), pp. 2855-2861, ISSN 0270-6474

Lopes da Silva, F. H., Vos, J. E., Mooibroek, J., Van Rotterdam, A. (1980) Relative contributions of intracortical and thalamo-cortical processes in the generation of a-

rhythms, revealed by partial coherence analysis. *Electroencephalogr Clin Neurophysiol* 50(5-6), (1980 Dec), pp. 449–456, ISSN 0013-4694

Lutzenberger, W., Ripper, B., Busse, L., Birbaumer, N., Kaiser, J. (2002) Dynamics of gamma-band activity during an audiospatial working memory task in humans. J Neurosci 22(13), (2002 Jul 1), pp. 5630-5638, ISSN 0270-6474

Magnani, G., Cursi, M., Leocani, L., Volonté, M. A., Locatelli, T., Elia, A., Comi, G. (1998) Event-related ERD to contingent negative variation and self-paced movement paradigms in Parkinson's disease. *Mov Disord* 13(4), (1998 Jul), pp. 653–660, ISSN 0885-3185

Marsden, J. F., Limousin-Dowsey, P., Ashby, P., Pollak, P. & Brown, P. (2001) Subthalamic nucleus, sensorimotor cortex and muscle interrelationships on Parkinson's disease. *Brain* 124(2), (2001 Feb), pp. 378-388, ISSN 0006-8950

Mason, M., & Newton, M. (1990) A rank statistics approach to the consistency of the general bootstrap, *Ann. Statist* 20, pp. 1611–1624, ISSN 0090-5364

Marceglia, S., Fiorio, M., Foffani, G., Mrakic-Sposta, S., Tiriticco, M., Locatelli, M., Caputo, E., Tinazzi M., Priori, A. (2009) Modulation of beta oscillations in the subthalamic area during action observation in Parkinson's disease. *Neuroscience* 161(4), (2009 Jul 21), pp. 1027-1036, ISSN 0306-4522

Minamoto, H., Tachibana, H., Sugita, M., Okita, T. (2001) Recognition memory in normal ageing and Parkinson's disease: behavioural and electrophysiological measures. *Brain Res Cogn Brain Res* 11(1), (2001 Mar), pp. 23–32, ISSN 0926-6410

Oldfield, R. C. (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9(1), (1971 Mar), pp. 97-113, ISSN 0028-3932

Owen, A. M. (2004) Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. *Neuroscientist* 10(6), (2004 Dec), pp. 525–537, ISSN 1073-8584

Ozgoren, M., Basar-Eroglu, C., Basar, E. (2005) Beta oscillations in face recognition. *Int J Psychophysiol* 55(1), (2005 Jan), pp. 51-59, ISSN 0167-8760

Pantev, C. (1995) Evoked and induced gamma-band activity of the human cortex. *Brain Topogr* 7(4), (1995 Summer), pp. 321-330, ISSN 0896-0267

Pesonen, M., Björnberg, C. H., Hämäläinen, H., Krause, C. M. (2006) Brain oscillatory 1–30 Hz EEG ERD/ERS responses during the different stages of an auditory memory search task. *Neurosci Lett* 399(1–2), (2006 May 15), pp. 45–50, ISSN 0304-3940

Philipova, D., Gatchev, G., Vladova, T., Georgiev, D (1997) Event related potentials under auditory discrimination tasks. *Int J Psychophysiol* 27(1), (1997 Jul), pp. 69–78, ISSN 0167-8760

Piccirilli M., D'Alessandro P., Finali G., Piccinin G. L., Agostini L. (1989) Frontal lobe dysfunction in Parkinson's disease: prognostic value for dementia? *Eur Neurol* 29(2), pp. 71–76, ISSN 0014-3022

Pillon, B., Ertle, S., Deweer, B., Bonnet, A., Vidailhet, M., Dubois, B. (1997) Memory for spatial location in 'de novo' parkinsonian patients. *Neuropsychologia* 35(3), (1997 Mar), pp. 221–228, ISSN 0028-3932

Priori, A., Foffani, G., Pesenti, A., Bianchi, A., Chiesa, V., Baselli, G. (2002) Movement-related modulation of neural activity in human basal ganglia and its l-DOPA dependency: recordings from deep brain stimulation electrodes in patients with

Parkinson's disease. *Neurol Sci* 23(Suppl. 2), (2002 Sep), pp. S101-S102, ISSN 1590-1874

Priori ,A., Foffani, G., Pesenti, A., Tamma, F., Bianchi, A. M., Pellegrini, M., Locatelli, M., Moxon, K. A., Villani, R. M. (2004) Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp Neurol* 189(2), (2004 Oct), pp. 369-379, ISSN 0014-4886

Pfurtscheller, G., & Klimesch, W. (1991) Event-related ERD during motor behaviour and visual information processing. *Electroencephalogr Clin Neurophysiol Suppl* 42, pp. 58–65, ISSN 0424-8155

Pfurtscheller, G., & Lopes da Silva, F. H. (1999) Event-related desynchronization Handbook of Electroencephalography and Clinical Neurophysiulogy. Revised Series, Vol. 6, ISBN 0-444-82999-7

Rauschecker J. P. (1998) Cortical processing of complex sounds. *Curr Opin Neurobiol* 8(4), (1998 Aug), pp. 516-521, ISSN 0959-4388

Rivlin-Etzion, M., Marmor, O., Heimer, G., Raz, A., Nini, A., Bergman, H. (2006) Basal ganglia oscillations and pathophysiology of movement disorders. *Curr Opin Neurobiol* 16(6), (2006 Dec), pp. 629-637, ISSN 0959-4388

Robertson, C., Empson, J. (1999) Slowed cognitive processing and high workload in Parkinson's disease. *J Neurol Sci* 162(1), (1999 Jan 1), pp. 27–33, ISSN 0022-510X

Rolland, A.-S., Herrero, M.-T., Garcia-Martinez, V., Ruberg, M., Hirsch, E. C., Francois, C. (2007) Metabolic activity of cerebellar and basal ganglia-thalamic neurons is reduced in parkinsonism. *Brain* 130(1), (2007 Jan), pp. 265–275, ISSN 0006-8950

Sawamoto, N., Honda, M., Hanakawa, T., Fukuyama, H., Shibasaki, H. (2002) Cognitive slowing in Parkinson's disease: a behavioural evaluation independent of motor slowing. *J Neurosci* 22(12), (2002 Jun 15), pp. 5198–5203, ISSN 0270-6474

Schmiedt, C., Meistrowitz, A., Schwendemann, G., Herrmann, M., Basar-Eroglu, C. (2005) Theta and alpha oscillations reflect differences in memory strategy and visual discrimination performance in patients with Parkinson's disease. *Neurosci Lett* 388(3), (2005 Nov 18), pp. 138–143, ISSN 0304-3940

Schurmann, M., Basar-Eroglu, E. (1994) Topography of alpha and theta oscillatory responses upon auditory and visual stimuli in humans. *Biol Cybern* 72(2), pp. 161–174, ISSN 0340-1200

Shohamy, D., Myers, C. E., Grossman, S., Sage, J., Gluck, M. A. (2005) The role of dopamine in cognitive sequence learning: evidence from Parkinson's disease. *Behav Brain Res* 156(2), (2005 Jan 30), pp. 191–199, ISSN 0166-4328

Silberstein, P., Pogosyan, A., Kühn, A. A., Hotton, G., Tisch, S., Kupsch, A., Dowsey-Limousin, P., Hariz, M. I., Brown, P. (2005) Cortico-cortical coupling in Parkinson's disease and its modulation by therapy. *Brain* 128(6), (2005 Jun), pp. 1277-1291, ISSN 0006-8950

Stam, C. J., Visser, S. L., Op de Coul, A. A., De Sonneville, L. M., Schellens, R. L., Brunia, C. H., de Smet. J. S., Gielen, G. (1993) Disturbed frontal regulation of attention in Parkinson's disease. *Brain* 116(5), (1993 Oct), pp. 1139–1158, ISSN 0006-8950

Sutoh T., Yabe H., Sato Y., Hiruma T., Kaneko S. (2000) Event-related desynchronization during an auditory oddball task. *Clin Neurophysiol* 111(5), (2000 May), pp. 858-862, ISSN 1388-2457

Tachibana, H., Toda, K., Sugita, M. (1992) Actively and passively evoked P3 latency of event-related potentials in Parkinson's disease. *J Neurol Sci* 111(2), (1992 Sep), pp. 134–142, ISSN 0022-510X

Taylor, A. E., Saint-Cyr, J. A., Lang, A. E. (1990) Memory and learning in early Parkinson's disease: evidence for a ''frontal lobe syndrome''. *Brain Cogn* 13(2), (1990 Jul), pp. 211–232, ISSN 0278-2626

Tallon-Baudry, C., Bertrand, O., Delpuech, C., Pernier, J. (1996) Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. *J Neurosci* 16(13), (1996 Jul 1), pp. 4240-4249, ISSN 0270-6474

Terman, D., Rubin, J. E., Yew, A. C., Wilson, C. J. (2002) Activity patterns in a model for the subthalamopallidal network of the basal ganglia. *J Neurosci* 22(7), (2002 Apr 1), pp. 2963-2976, ISSN 0270-6474

Tiitinen, H., Sinkkonen, J., Reinikainen, K., Alho, K., Lavikainen, J., Näätänen, R. (1993) Selective attention enhances the auditory 40-Hz transient response in humans. *Nature* 364(6432), (1993 Jul 1), pp. 59-60, ISSN 0028-0836

van Spaendonck, K. P., Berger, H. J., Horstink, M. W., Cools, A. R. (1998) Cognitive deficits in Parkinson's disease. *Tijdschr Gerontol Geriatr* 29(4), (1998 Aug), pp. 189-195, ISSN 0167-9228

Vieregge, P., Verleger, R., Wascher, E., Stüven, F., Kömpf, D. (1994) Auditory selective attention is impaired in Parkinson's disease event-related evidence from EEG potentials. *Brain Res Cogn Brain Res* 2(2), (1994 Sep), pp. 117–129, ISSN 0926-6410

Visscher, K. M., Kaplan, E., Kahana, M. J., Sekuler, R. (2007) Auditory short-term memory behaves like visual short-term memory. *PLoS Biol* 5(3), (2007 Mar) e56, ISSN 1544-9173

Wang, H., Wang, Y., Wang, D., Cui L., Tian, S., Zhang, Y. (2002) Cognitive impairment in Parkinson's disease revealed by event-related potential N270. *J Neurol Sci* 194(1), (2002 Feb 15), pp. 49–53, ISSN 0022-510X

Wang, S. Y., Aziz, T. Z., Stein, J. F. & Liu, X. (2005) Time-frequency analysis of transient neuromuscular events: dynamic changes in activity of the subthalamic nucleus and forearm muscles related to the intermittent resting tremor. *J Neurosci Methods* 145(1-2), (2005 Jun 30), pp. 151-158, ISSN 0165-0270

Wascher, E., Verleger, R., Vieregge, P., Jaskowski ,P., Koch, S., Kömpf, D. (1997) Responses to cued signals in Parkinson's disease. Distinguishing between disorders of cognition and of activation. *Brain* 120(8), (1997 Aug), pp. 1355–1375, ISSN 0006-8950

Weinberger, M., Mahant, N., Hutchison, W. D., Lozano, A. M., Moro, E., Hodaie, M., Lang, A E., Dostrovsky, J. O. (2006) Beta oscillatory activity in the subthalamic nucleus and its relation to dopaminergic response in Parkinson's disease. *J Neurophysiol* 96(6), (2006 Dec), pp. 3248-3256, ISSN 0022-3077

Weinberger, M., Hutchison, W. D., Lozano, A. M., Hodaie, M., Dostrovsky, J. O. (2008) Increased gamma oscillatory activity in the subthalamic nucleus during tremor in Parkinson's disease patients. *J Neurophysiol* 101(2), (2009 Feb), pp. 789-802, ISSN 0022-3077

Williams, D., Kühn, A., Kupsch, A., Tijssen, M., van Bruggen, G., Speelman, H., Hotton, G., Yarrow, K. & Brown, P. (2003) Behavioural cues are associated with modulations of

synchronous oscillations in the human subthalamic nucleus. *Brain* 126(9), (2003 Sep), pp. 1975-1985, ISSN 0006-8950

Williams, D., Tijssen, M., van Bruggen, G., Bosch, A., Insola, A., Di Lazzaro, V., Mazzone, P., Oliviero, A., Quartarone, A., Speelman, H., & Brown, P (2002) Dopamine dependent changes in the functional connectivity between basal ganglia and cerebral cortex in the human. *Brain* 125(7), (2002 Jul), pp. 1558-1569, ISSN 0006-8950

4

Extraction of Single-Trial Post-Movement MEG Beta Synchronization in Normal and Parkinson's Patient Using ICA-Based Spatiotemporal Approach

Po-Lei Lee[1,2,3], Yu-Te Wu[2] and Jen-Chuen Hsieh[2]
[1]*Department of Electrical Engineering, National Central University,*
[2]*Institute of Brain Science, National Yang-Ming University,*
[3]*Center for Dynamical Biomarkers and Translational Medicine, National Central University, Taiwan*

1. Introduction

The human brain is a dynamic system that frequently changes functional mode (Lopes da Silva, 1991; Lopes da Silva, 1996). Spatiotemporal analysis of brain activities with regard to distinct spatial locations and frequency bands reveals task-specific brain activation which changes in a fraction of a second (Jensen & Vanni, 2002). At rest, Rolandic EEG and MEG rhythms are dominated by rhythmic activity around 10 (alpha band) and 20 (beta band) Hz. Electrocorticographic (Pfurtscheller et al., 1994) and neuromagnetic recordings have shown that the ~20-Hz rhythm mainly originates in the anterior bank of the central sulcus while the ~10-Hz rhythm is concentrated predominantly in the post-central cortex (Pfurtscheller & Lopes da Silva, 1999). These two frequency components appear to have different functional roles, with the ~20-Hz rhythm being more closely connected to movements and their termination and the ~10-Hz component behaving more like a classical "idling" rhythm (Salmelin et al., 1995). Voluntary movement is composed of three phases: planning, execution and recovery (Pfurtscheller et al., 1998a). It has been suggested that localized event-related alpha desynchronization (ERD) upon movement can be viewed as an EEG/MEG correlate of an activated cortical sensorimotor network, servicing planning and execution, while beta event-related synchronization (ERS) may reflect deactivation/inhibition during the recovery phase in the underlying cortical network (Pfurtscheller et al., 1996).

Movement-related ERD and ERS have been used as probes to study neurophysiology in normal brains and pathophysiology in the diseased (Tamas et al., 2003). It has been reported that the diagnostic features of patients with Parkinson's disease, in comparison with controls, are a slowing and suppression of the post-movement beta ERS independent of the amount of beta activity in the reference period (Pfurtscheller et al., 1998a). These findings imply that slowed and reduced recovery after the motor act impedes cortical preparation of the next movement (Pfurtscheller et al., 1996). Patients with Unverricht-Lundborg type myoclonic epilepsy demonstrate little rebound of beta activities contingent upon median nerve stimulation (Silen et al., 2000). The diminished beta ERS indicates that the myoclonic

patients have sustained motor cortex reactivity which can be attributed to impaired cortical inhibition (Pfurtscheller & Lopes da Silva, 1999).

ERD and ERS activities are time-locked, but not phase-locked, to external stimuli or tasks (Andrew & Pfurtscheller, 1995; Kalcher & Pfurtscheller, 1995; Pfurtscheller & Lopes da Silva, 1999). Existing methods for extraction of ERD/ERS signals essentially measure power or amplitude changes of corresponding frequency bands as derived from the average of dozens or hundreds of trials. The band power method squares and averages filtered brain signals within a selected frequency band (Pfurtscheller & Aranibar, 1977), and an inter-trial variance method to remove the phase-locked portion in the band power method was reported by Klimesch et al. (1998). Likewise, autoregressive and spectral decomposition methods have been used to extract significant frequency components in rhythmic signals (Florian & Pfurtscheller, 1995). Salmelin's temporal-spectral evolution method rectifies and averages filtered MEG signals (Salmelin et al., 1995). To increase the temporal resolution of the ERD/ERS technique, Clochon et al. (1996) proposed an amplitude modulation (AM) method based on the Hilbert transform to detect the envelope of filtered signals by squaring and summing their real and imaginary parts. All these approaches presume stereotypical frequency and temporal characteristics across trials and require an average of many trials for the ERD/ERS using a preset frequency filter and time window to preprocess every trial. However, non-phase-locked rhythmic signals can vary from trial-to-trial contingent upon variations in a subject's performance and state, which may be linked to fluctuations in expectation, attention, arousal, and task strategy (Bastiaansen et al., 2001; Bastiaansen et al., 1999; Earle, 1988; Haig et al., 1995; Hoffman et al., 1991; Yabe et al., 1993). Since trial-to-trial variability in amplitude, latencies, or scalp distribution might carry important information on cognitive and physiological states (Jung et al., 2001), a method that permits the extraction and analysis of the oscillatory signal on a single-trial base is crucial for the study of subtle brain dynamics. Furthermore, such a method should require fewer trials for analysis and hence shorter experiment time, which is beneficial for patients with impairment of motor and/or cognitive performance (Muller-Gerking et al., 1999).

Single-trial multi-channel EEG analysis has been developed for time-locked, phase-locked, evoked brain activities (Jung et al., 2001; Tang et al., 2002). However, approaches to single-trial movement-related oscillatory changes are less explored. Independent component analysis (ICA), a data-driven method for multivariate data analysis, has been used to reveal temporally-independent neuronal activities of EEG measurements (Jung et al., 2001; Makeig et al, 1997; McKeown et al., 1998), MEG measurements (Wu et al., 2002; Wu et al., 2003; Tang et al., 2002), fMRI (Duann et al., 2002; McKeown et al., 1998) and recently perfusion MRI (Kao et al., 2003). The present study proposes a new approach using ICA and the Hilbert transformation for the single-trial detection of movement-related beta rhythmic activity during a self-paced right finger lifting task. This study focuses on beta activity and beta ERS, centered around 20 Hz, because it has been demonstrated that the movement-related short bursts of beta oscillation have higher task and movement specificity than alpha ERD (Pfurtscheller & Aranibar, 1979b; Pfurtscheller et al., 1996).

Since brain oscillation may be expressed alone in a specific frequency band independent of artifacts (Ermer et al., 2000; Lins et al., 1993a; Lins et al., 1993b; Mosher et al., 1992), ICA is applied to transform brain signals across all channels (in a single trial) into mutually independent components by means of an unmixing matrix in which each column represents a spatial map tailoring the weights of the corresponding temporal component at each MEG sensor. The spatial maps and temporal waveforms of decomposed independent components

are categorized into task-related and task-unrelated groups respectively, based on temporal and spatial characteristics. This temporal template is the grand average of hundreds of vector-norm envelopes of the band-pass filtered, single-trial MEG measurements obtained from right index finger lifting. The spatial template can be derived from the spatial distribution at beta rebound activity either from the grand average of the generation group (for signal extraction) or from each individual (for verification). Correlations between the temporal template and component waveforms, as well as between the spatial template and spatial maps, are computed, and coupled component waveforms and spatial maps that conjointly survive with high correlation values are taken as task-related information and subjected to data reconstruction. In this way the phase and amplitude information of noise-free MEG beta activities can be preserved for profound studies of temporal and spectral variation across trials. Due to the high signal-to-noise ratio (SNR) in beta activities extracted through ICA, trial-specific reactive frequency ranges can be determined by means of the comparisons of two short time spectra between the reference and post-movement periods. Beta reactivity per single trial can be quantified using the amplitude modulation (AM) method (Clochon et al., 1996), and insignificant epochs can be determined using a nonparametric sign test (Brovelli et al., 2002). Source estimation and localization techniques can be successfully applied to single-trial epoch to estimate the source locations of beta modulation.
The current study presents: 1) a novel ICA-based spatiotemporal approach for single-trial analysis of event-related beta oscillatory modulations with a high extraction rate; 2) the prospect of trial-specific frequency bandpass filtering that takes into account subtle trial-by-trial brain dynamics; 3) the feasibility of using sophisticated source estimation/localization methods demanding high signal-to-noise ratio (SNR) on single trial data; and 4) a common template approach permitting an effective alternative in cases where lengthy procedures cannot be endured by participants or in clinical settings where patients have attention problems or are incapable of sustaining long experiments. The proposed ICA-based approach was applied to discover the mechanisms of beta ERS in one Parkinson's patient. It is helpful to investigate the reasoning of ERS vanishment due to suppression of post-movement beta rebound in each single-trial, rather than the cause of temporal jittering and/or loss of synchronization in Parkinson's disease.

2. Materials and methods

2.1 Subjects and task

The present study examined six healthy right-handed subjects (gender balanced), aged 24-30 years. Five of the healthy subjects were used in the model generation group, and MEG data from the last healthy subject were used for validation. Subjects performed self-paced lifting of the right index finger approximately once every 8 sec. Subjects were trained to perform the movement briskly for a duration of 200 to 300 ms, as monitored by surface electromyogram (EMG) on extensor digitorum communis, with a range of finger movement around 35~40°, while keeping their eyes open in order to suppress the occipital alpha rhythm. In addition, somatosensory evoked fields (SEFs) for right median nerve stimulation were measured to locate the primary sensorimotor area (SMI) in each subject as part of the procedure for the generation of a temporal template (see below). Informed written consent was obtained from all subjects. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital. In addition, one 56-year-old patient with idiopathic Parkinson's disease in Hoehn and Yahr stage 1 was also recruited as a demonstration in this study.

2.2 Data recording

Cortical magnetic signals were recorded with a 306-channel (102 sensor unit) whole-head neuromagnetometer (band-pass, 0.05-250 Hz; digitized at 1kHz; Vectorview; Neuromag Ltd., Helsinki, Finland) with subjects in sitting position. Each sensor unit was composed of a pair of planar gradiometers and a magnetometer. The magnetometer measured magnetic flux (B_z), normal to the sensor unit, while the gradiometers measured two tangential derivatives of B_z ($\partial B_z / \partial x$ and $\partial B_z / \partial y$, mutually orthogonal). Only magnetic signals measured by the gradiometers were used in this study. Bipolar horizontal and vertical electro-oculograms (EOG) were recorded using electrodes placed below and above the left eye and at the bilateral outer canthi to monitor eye movement and blinks. The exact position of the head with respect to the sensor array was determined by measuring magnetic signals from four head position indicator (HPI) coils placed on the scalp. Coil positions were identified with a three-dimensional digitizer with respect to three predetermined landmarks (naison and bilateral preauricular points) on the scalp, and this data used to superimpose MEG source signals on individual MRI images obtained with a 3.0 T Bruker MedSpec S300 system (Bruker, Kalsrube, Germany). The anatomical image was acquired using a high-resolution T1-weighted, 3D gradient-echo pulse sequence (MDEFT: Modified Driven Equilibrium Fourier Transform; TR/TE/TI= 88.1ms/4.12ms/650ms, 128*128*128 matrix, FOV=250mm).

Empty room measurements were recorded for 3 minutes. Approximately 100 EOG-free trials of right index finger lifting were acquired and analyzed off-line. Since the focus was on beta-activities, the signals were further band-pass-filtered between 6-50 Hz (zero-phase, tenth-order, IIR Butterworth filter) to remove dc drifts and 60 Hz noise. The initial finger movement (movement onset; zero time) was registered with an optical switch (Taniguchi et al., 2000). Electromyographic (EMG) activity from the extensor digitorum communis (digitized at 1 KHz) was continuously recorded to monitor performance (see above). Each epoch comprised data points from –4s to 3s relative to the movement onset (Salmelin et al., 1995; Salmelin and Hari, 1994a) and epochs were subjected to further single-trial ICA analysis.

For SEF measurement, the right median nerve was electrically stimulated every 2 sec with constant current pulses (0.3 msec in duration) exceeding the motor threshold. Approximately 100 EOG-free trials were acquired and digitized at 1 kHz for off-line analysis.

2.3 Data analysis

2.3.1 Independent Component Analysis of the single-trial MEG epoch

We take the advantages of sensitivity and localizing power of superficial sources by planar gradiometers (Rosell et al., 2001; Kajola et al., 1991). Each single-trial MEG epoch contains m channels (m = 204, 102 pairs of gradiometers) and n time points (usually m < n). The paired gradiometer signals ($\partial B_z / \partial x$ and $\partial B_z / \partial y$) are arranged into two $\frac{m}{2} \times n$ sub-matrices $\mathbf{B_1}$ and $\mathbf{B_2}$ and concatenated into an $m \times n$ matrix $\mathbf{B}$. The i^{th} rows ($i \leq 102$) of $\mathbf{B_1}$ and $\mathbf{B_2}$ contain the measured gradiometer signals from the i^{th} sensor location, and the j^{th} column in $\mathbf{B}$ contains the measured data at the j^{th} time point across all gradiometer channels.

Mathematically, we can consider each row of **B** as samples generated from one random variable b_i, i = 1, 2, …, m. In other words, matrix **B** is a realization of a random vector $b = [b_1\ b_2\ \cdots b_m]^T$.

The ICA techniques (Jung et al., 2001; Hyvarinen et al., 2001) seek to find a $p \times m$ ($p \le m$) matrix, **W**, which converts the random vector b into another vector variable, s, consisting of p mutually independent random variables, thus:

$$\underset{p\times 1}{\boldsymbol{s}} = \begin{bmatrix} s_1 \\ s_2 \\ . \\ . \\ . \\ s_p \end{bmatrix} = \underset{p\times m}{\mathbf{W}}\ \underset{m\times 1}{b} \tag{1}$$

The mutual independence of s_i, for i = 1,…, p, implies that if $P(s_i)$ represents the probability distribution of the i^{th} component, the joint probability distribution for all components can be factorized as:

$$P(s_1, s_2, ..., s_p) = P(s_1)P(s_2)...P(s_p) \tag{2}$$

The ICA techniques use this assumption of mutual independence to find the un-mixing matrix **W**.

All calculations in the present study were carried out using the FastICA algorithm which features high speed calculation (cubic convergence) and does not require selection of step size parameters or learning rate, unlike the gradient-based algorithm (Hyvarinen et al., 1997, 2001). The FastICA technique first removes means of row vectors in the **B** sample matrix such that each random variable bi has a zero mean, and then employs a whitening process using principal component analysis. After whitening, the covariance matrix of the whitened data becomes an identity matrix, and only the first p ($p \le m$) most significant principal components are preserved in the FastICA calculation.

The next step is to look for a matrix that transforms the whitened data into a set of components as mutually independent as possible. Mutual information, as a measure of the independence of random variables, is used as the criterion for finding such a transformation. Mutual information can be expressed in terms of negentropy, an important measure of non-Gaussianity (Hyvarinen et al., 1997, 2001). Therefore, the problem of finding the independent components (***s***) and the transform matrix (**W**) can be translated into a search for linear combinations of the whitened data that maximize the negentropy of the distributions of s_i, for i = 1,…, p.

After applying FastICA to the pre-processed single-trial MEG epochs, matrix **B** can be factored into a (mixing) matrix **U** and an (independent source) matrix **S** as follows:

$$\mathrm{B}_{\mathrm{mxn}} = \begin{bmatrix} \mathbf{B_1} \\ \mathbf{B_2} \end{bmatrix} = \mathrm{U}_{\mathrm{mxp}}\mathrm{S}_{\mathrm{pxn}}$$

$$= \begin{bmatrix} \begin{bmatrix} u_{1,1} & \cdots & u_{1,p} \\ \vdots & & \vdots \\ u_{\frac{m}{2},1} & \cdots & u_{\frac{m}{2},p} \end{bmatrix} \\ \begin{bmatrix} u_{\frac{m}{2}+1,1} & \cdots & u_{\frac{m}{2}+1,p} \\ \vdots & & \vdots \\ u_{m,1} & \cdots & u_{m,p} \end{bmatrix} \end{bmatrix}_{\mathrm{mxp}} \begin{bmatrix} \rightarrow \\ s_1 \\ \rightarrow \\ s_2 \\ \vdots \\ \rightarrow \\ s_p \end{bmatrix}_{\mathrm{pxn}} \tag{3}$$

in which each row $\vec{s_i}$ of matrix $\mathrm{S} \in \Re^{p \times n}$ represents samples of an independent component (IC) s_i, for i = 1,…, p and $\mathrm{U} \in \Re^{m \times p}$ is the pseudo-inverse of matrix **W** whose column vectors represent the weight distribution values of the corresponding ICs in ***S*** across all MEG gradiometer channels. In fact, matrix **U** is the "mixing matrix" that combines the p ICs to reconstruct signal **B**. These temporal ICs can be categorized into task-related ICs and task-unrelated ICs. Since the elicited brain activities or artifacts can be distributed over multiple ICs, no one-to-one correspondence between IC and source information is projected (Makeig et al., 1997). To facilitate the selection of task-related ICs, a temporal and spatial template pair was constructed prior to selection (see below). Spatial map $\bar{x}_j$ of the j^{th} IC was defined as the topographic display of all vector norms for weights of 102 gradiometer pairs in the j^{th} column vector of U,

$$\bar{x}_j = \left[\sqrt{{u_{1,j}}^2 + {u_{(\frac{m}{2}+1),j}}^2} \quad \sqrt{{u_{2,j}}^2 + {u_{(\frac{m}{2}+2),j}}^2} \quad \cdots \quad \sqrt{{u_{\frac{m}{2},j}}^2 + {u_{m,j}}^2} \right]^{\mathrm{T}} \tag{4}$$

in which $u_{i,j}$ is the entry in the i^{th} row and j^{th} column of **U** in Eq. (3). The spatial map is intended for component selection (see below).

2.3.2 Creation of a temporal template ($\mathrm{VAMW}_{\mathrm{template}}$) using amplitude modulation (envelope) of the MEG data

The recorded MEG signals at each gradiometer are filtered in the task-specific frequency band (Pfurtscheller & Lopes da Silva, 1999) and rectified by computing the AM waveform (envelope) using the amplitude modulation (AM) method (Clochon et al., 1996) as follows:

$$m(t) = \sqrt{M_{BP}(t)^2 + H(M_{BP}(t))^2} \tag{5}$$

in which $M_{BP}(t)$ is the band-passed MEG signal and $H(M_{BP}(t))$ is its Hilbert transform. The task-specific frequency band is determined by the contrast between two 1-s amplitude spectra calculated over about one hundred event-related EEG trials (Pfurtscheller and Lopes da Silva, 1999). One (serving as rest reference) is computed over the duration from 4s to 3s

preceding the onset of movement, and the other (serving as reactive target) from 0.8s to 1.8s after the onset of movement (see Fig. 1a, b). All beta-frequency components with significant modulation in terms of post-movement amplitude increase (above 95% confidence level, i.e. Z>3.09, P<0.01) in the differential amplitude spectrum (see Fig. 1c) are taken as the task-specific frequency band for subsequent processing (Pfurtscheller G. and Berghold A., 1989).

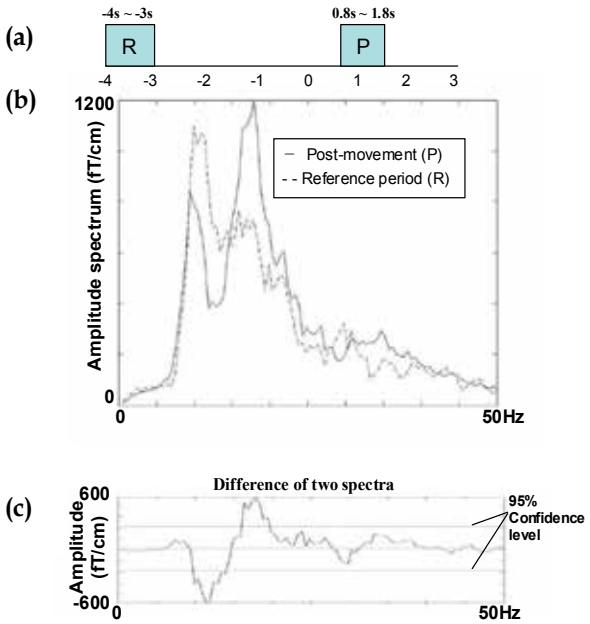


Fig. 1. Determination of task-specific frequency band using two 1-s amplitude spectra. (a) "R" represents the reference period from -4s to -3s preceding onset of movement and "P" represents the post-movement duration from 0.8s to 1.8s after onset of movement. (b) Two spectra computed over the reference (R) and post-movement periods (P), respectively. (c) The task-specific frequency band for beta-band VAMW is defined as the one where the difference between two spectra exceeds the 95% confidence level.

The vector norm of AM waveforms (VAMW) at each sensor site is computed using the square root of the AM waveforms of each gradiometer pair, i.e., $V(i,t)=\sqrt{m_x(i,t)^2+m_y(i,t)^2}$, in which $V(i,t)$ is the VAMW at the i^{th} sensor location, and $m_x(i,t)$ and $m_y(i,t)$ are the AM waveforms in $\frac{\partial B_z}{\partial x}$ and $\frac{\partial B_z}{\partial y}$ directions of the i^{th} sensor location. Event-related beta modulation is then computed as the difference in amplitude between the maximum amplitude of VAMW for each sensor site in the post-movement (0.8s to 1.8s) interval and mean activity between -2.5s and -2s (see Fig. 2a) (Leocani et al., 1997). Beta rebound (BR) is defined as the maximum amplitude of the computed event-related beta modulation from the subset of nine sensor sites in the vicinity of SMI (identified by SEF). The VAMWs of the BR calculation were averaged across the subjects (500 trials, 100 trials for each subject, 5 subjects pooled) to create the common temporal template, designated $VAMW_{template}$ (Fig. 2a).

2.3.3 Creation of a spatial template using topographical distribution of event-related beta modulation values

Individual spatial templates were first generated from the topographical distributions of event-related beta modulation values (see above). The five templates from the model generation group were then averaged to generate a common spatial template. In order to optimize conditions for spatial averaging, subjects' heads were carefully positioned before actual measurements to keep head positioning and orientation as similar as possible. Distances between head centers of the five subjects and the reference point (the origin of the MEG sensor array) in the horizontal plane were less than 4mm, and angles between the vertical axis of the helmet and that of the head (the normal vector of the plane constituted by the three landmark points, i.e., nasion, and both pre-auricular points) remained within 5.5° (maximum deviation 1.5°) between subjects.

Only the left half of the spatial map (unshaded in Fig. 2b) was used as the spatial template because this study focused on beta event-related activities in the hemisphere contralateral to the side of finger lifting; however, the other half can be generated analogously to extract activities in the ipsilateral hemisphere. Correlations among individual spatial templates ranged from 0.92 to 0.68. Respective correlations between the common spatial template and the individual spatial templates were 0.973, 0.811, 0.881, 0.904, and 0.915. These high correlation values support the use of the spatial template in component selection for each individual's magnetic signals.

2.3.4 Selection of pertinent independent components for the reconstruction of reactive beta activities

A spatial map (Eq. (4)) and corresponding VAMWs of each IC were generated for the selection of task-related ICs. Since the original signals may be decomposed into multiple ICs, the spectrum of each IC may vary from the one in the original signal due to the decomposition process. When settings for band-pass filtering for VAMW computation cannot be optimally determined using two-spectrum comparison for the generation of a $VAMW_{template}$ (Pfurtscheller & Lopes da Silva, 1999), three standard beta bands, 12-16, 16-20 and 20-24 Hz (Pfurtscheller G., 1981), enclosing the event-related beta activities in motor task, were used to band-pass filter (zero-phase, tenth-order, IIR Butterworth filter) for each single-trial IC such that the three frequency-laden resultant $VAMW_{IC}$s (the VAMWs band-pass filtered in three frequency bands of each IC) retained all task-related information. These $VAMW_{IC}$s were subsequently used in the selection of task-related ICs, which must fulfill the following dual criteria: 1) at least one of three corresponding $VAMW_{IC}$s has a correlation with the $VAMW_{template}$ higher than 95% ($Z>1.63$, $P<0.05$) among $VAMW_{IC}$s of all the ICs for that single epoch, and 2) correlation between the spatial map and spatial template is above 95% ($Z>1.63$, $P<0.05$) for the spatial maps of all ICs. Data processed via 3-standard band filtering are not used in subsequent data reconstruction, but rather are used in conjunction with the dual-criteria only in the procedure "selecting" the pertinent ICs. Unselected columns, i.e., task-unrelated components, of mixing matrix $\mathbf{U}$ (Eq. (3)) are zeroed to produce a matrix $\hat{\mathbf{U}}$ such that task-related rhythmic signals are reconstructed by multiplying $\hat{\mathbf{U}}$ and $\mathbf{S}$ (Fig. 3). The reconstructed data in each trial are then filtered within a trial-specific frequency band to extract reactive beta activities.

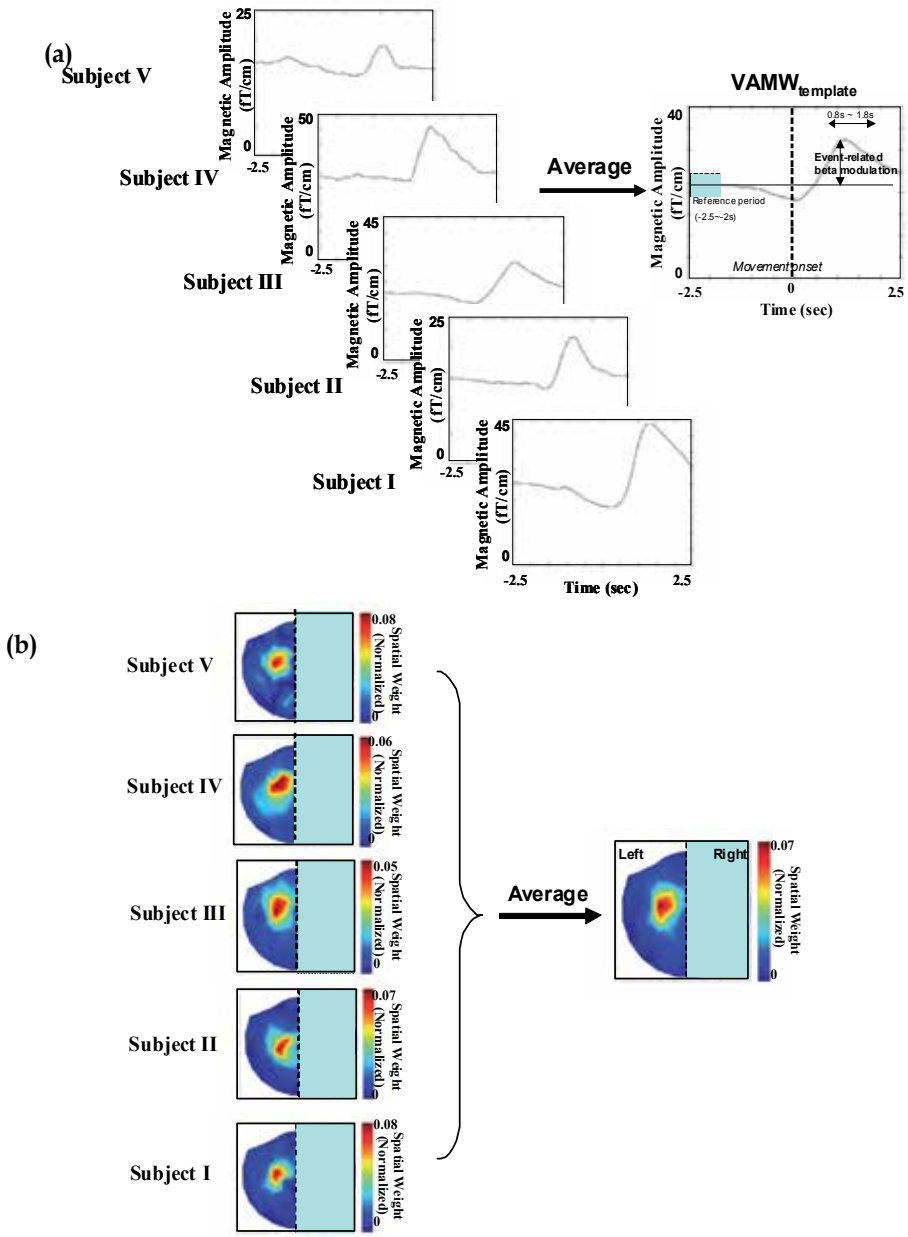


Fig. 2. Creation of common temporal and spatial templates. (a) The common temporal template, VAMW$_{template}$, is created by averaging VAMWs (500 trials, 100 trials for each subject, 5 subjects pooled). Event-related beta modulation is defined as the amplitude difference between the mean amplitude of baseline activity (-2.5 to -2 s) and maximum amplitude in the post-movement interval (0.8 to 1.8 s). (b) The common spatial template is the average of the topographical distributions of event-related beta modulations of five subjects from model generation group. Only the half the spatial map (unshaded) contralateral to the side of finger lifting is used as the spatial template.

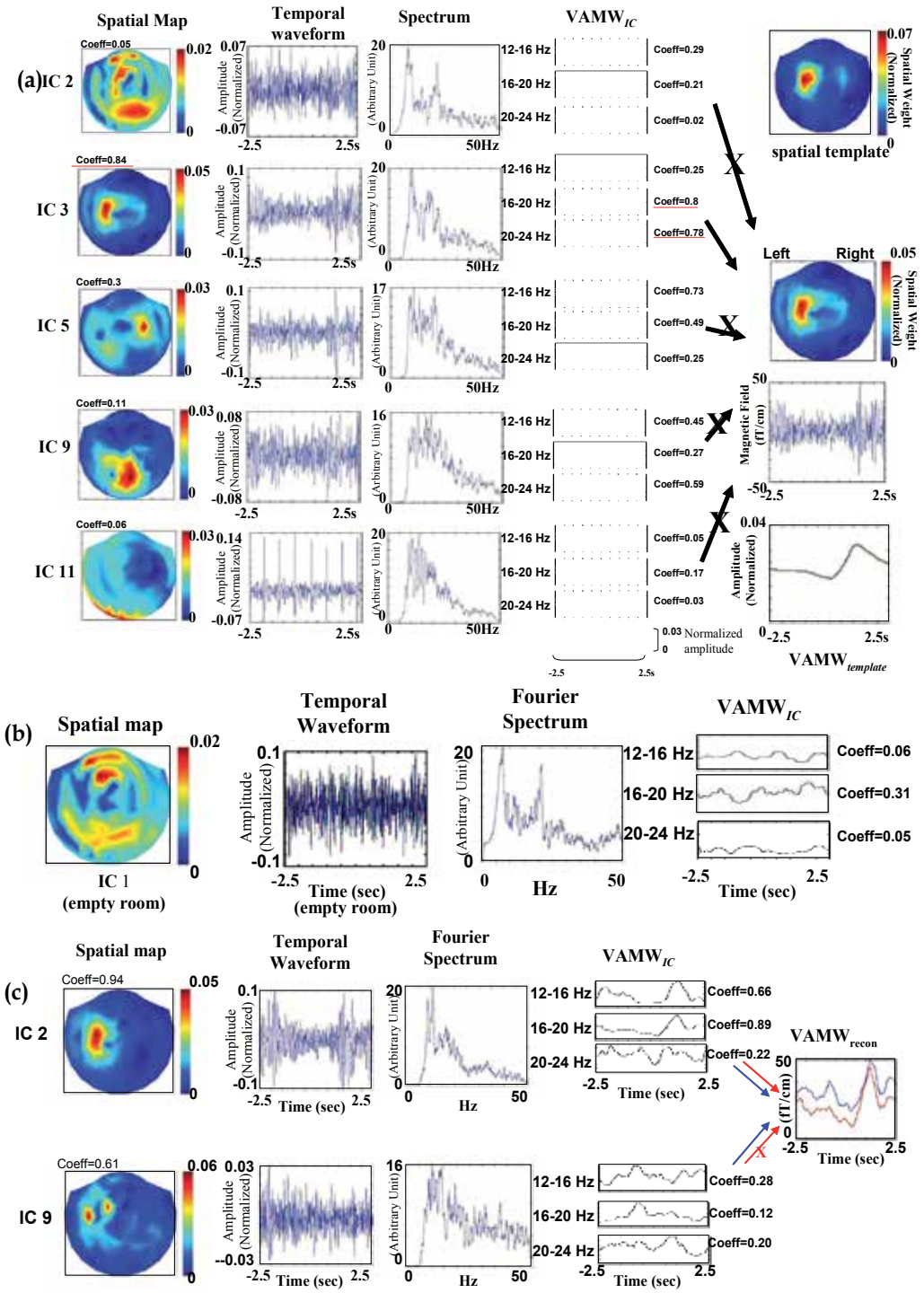


Fig. 3. Examples of IC-selection and signal reconstruction procedure. (a) Spatial maps, IC waveforms, Fourier spectra of IC waveforms and VAMW$_{IC}$s of five ICs obtained from one

single epoch by ICA. Only ICs fulfilling the dual criteria are selected for signal reconstruction. For example, IC 3 meets the dual criteria (underscored in red): i) correlation value between spatial map and spatial template is 0.84 (rank= 97%, Z= 1.89, P=0.03); ii) correlation value between16-20Hz $VAMW_{IC}$ and 20-24 Hz $VAMW_{IC}$ with $VAMW_{template}$ is 0.8 (rank= 99%, Z=3.08, P=0.01) and 0.78 (rank= 97.8%, Z= 2.85, P=0.022), respectively. (b) Noise identification and removal. The deselected IC 2 in Fig. 2a may emanate from background noise since it resembles the IC 1 extracted from empty room measurement. (c) The impact of including task-unrelated IC into signal reconstruction. This figure illustrates (a different trial from Fig. 3a) that inclusion of task-unrelated IC (IC 9) with a high spatial correlation (correlation value=0.61, rank= 95.2%, Z=1.67, P=0.048) but poor temporal correlation (correlation value=0.28, rank=13%, Z=0.34, P=0.87) causes deterioration in the beta BR from 28.9 fT/cm (arrows and trace in red; IC9 eliminated from reconstruction) to 18.6 fT/cm (arrows and trace in blue; IC9 included for reconstruction).

2.3.5 Detection of task-laden trial-specific frequency band and extraction of reactive beta activities

The trial-specific frequency band detected in each trial is used to confine the reconstructed data within the most reactive beta band for further BR computation and source estimation. This frequency band is defined by the reactive beta band of the sensor site showing highest event-related beta modulation value (see creation of temporal template) over the nine SMI vicinal sensor sites (identified by SEF) and is identified using the aforementioned two-spectrum procedure which has been suggested as the best approach for the determination of reactive frequencies (Pfurtscheller & Lopes da Silva, 1999). Following data filtering with a trial-specific frequency band (zero-phase, tenth-order, IIR Butterworth filter), reactive beta activities in each single epoch can be extracted. The extracted reactive beta activities are then subjected to source estimation and beta rebound (BR) computations.

2.3.6 Calculation of $VAMW_{recon}$ of reactive beta activities and single-trial epoch selection using a nonparametric sign test

Movement-related beta rebound (BR) can be quantified from single-epoch reactive beta activities and $VAMW_{recon}$ (VAMW of reconstructed data) for reactive beta activity at each sensor site computed. The $VAMW_{recon}$ of highest event-related beta modulation (see creation of temporal template) among the nine sensor sites vicinal to SMI is designated as $VAMW_{recon\_max}$ and is used in turn for single-trial epoch selection and BR computation, as the sensor site expressing $VAMW_{recon\_max}$ did not change throughout the experiment in our observations. A deterministic procedure, modified from Brovelli's et al. (2002) approach, is used to select the significant trial. A nonparametric sign test is applied to the $VAMW_{recon\_max}$ designated for BR calculation in each single trial by computing the Z-score at each time point as $Z(t) = (N^+(t) - \frac{1}{2}N) / (\frac{1}{2}\sqrt{N})$, in which $N^+(t)$ denotes the number of trials whose magnitudes are larger than the median value of their baseline activities at time point t, and N the total number of trials. Time points with Z values greater than 3.09 (P<0.01) are defined as the time interval-of-interest (IOI). After the determination of IOI for each subject, another sign test is then applied to find epochs showing significant increases in amplitude (Z>1.63, P<0.05) using $Z_{IOI}(i) = (N_{IOI}{}^+(i) - \frac{1}{2}N_{IOI}) / (\frac{1}{2}\sqrt{N_{IOI}})$, in which $Z_{IOI}(i)$ is the Z value of the

i^{th} trial, $N_{IOI}{}^{+}(i)$ is the number of data points in post-movement IOI with values larger than the median of baseline activities of the i^{th} trial, and N_{IOI} is the total number of time points in post-movement *IOI* (Brovelli et al., 2002). An example of single-trial epoch selection is given in Fig. 4 (Subject I). The first trial in Fig. 4 with a Z_{IOI} score equal to -4.53 is marked as an insignificant epoch and eliminated from further analysis.

2.3.7 Source estimation of the reactive beta activities

Source estimation of the MEG reactive beta activities was done using equivalent current dipole (ECD) analysis and minimum current estimation (MCE, Uutela et al., 1999; toolbox provided by Neuromag Ltd, Helsinki, Finland). A single dipole model was applied to explain the field every 1ms, and only dipoles showing goodness-of-fit (Jensen and Vanni, 2002) values higher than 80% were used for data explanation. In MCE, the lattice constant of the triangular grid was 10mm and locations closer than 30mm to the center of the conductor were excluded from current estimates. Both analyses used a realistic head model for each subject. Template generation and single-trial data processing procedure are schematized in Figs. 5a and 5b respectively. Epochs achieving significance in the increase of beta activities were chosen for subsequent BR calculation and dipole/source analysis.

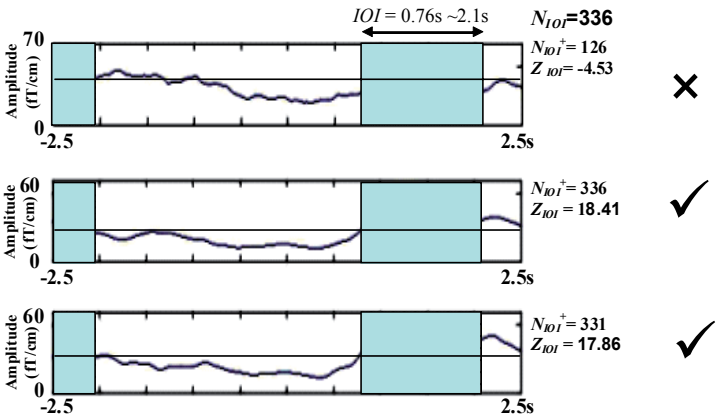


Fig. 4. Example of single-trial epoch selection based on a nonparametric sign test. Single-trial $VAMW_{recon_max}$s of reconstructed data are examined through a nonparametric sign test. $Z_{IOI}(i)$ is the Z value of the i^{th} trial, $N_{IOI}{}^{+}(i)$ is the number of data points in post-movement *IOI* with values larger than the median of baseline activities of the i^{th} trial, and N_{IOI} is the total number of time points in post-movement *IOI*. Only epochs showing significant increase of beta activities are chosen for further analysis. The first trial with a Z_{IOI} score equal to -4.53 is marked as an insignificant epoch and eliminated from further analysis.

2.3.8 Validation of coupled common spatial and temporal templates for single-trial analysis

Since there are inevitably differences in head size and variations in head positions inside the MEG scanner among subjects, BR amplitude differences were compared using both individual spatial templates and the common spatial template. The use of a pair of common

spatial and temporal templates for the extraction of individuals' neuromagnetic single-trial signals was further validated on one additional subject.

3. Results

Based on the known spatial location and temporal expression in terms of spatial and temporal templates, reactive beta activities were successfully extracted. Figure 3a shows that IC 3 meets the dual criteria: i) the correlation values between spatial map and spatial template is 0.84 (rank= 97%, Z= 1.89, P=0.03); ii) correlation values of 16-20Hz $VAMW_{IC}$ and 20-24 Hz $VAMW_{IC}$ vs. $VAMW_{template}$ are 0.8 (rank= 99%, Z=3.08, P=0.01) and 0.78 (rank= 97.8%, Z= 2.85, P=0.022), respectively. Fig. 3a illustrates that noise could also be identified and removed. IC2 in Fig. 3a correlates highly (=0.88) in spatial distribution with the IC1 extracted from empty room measurements (Fig. 3b), and is therefore rejected.

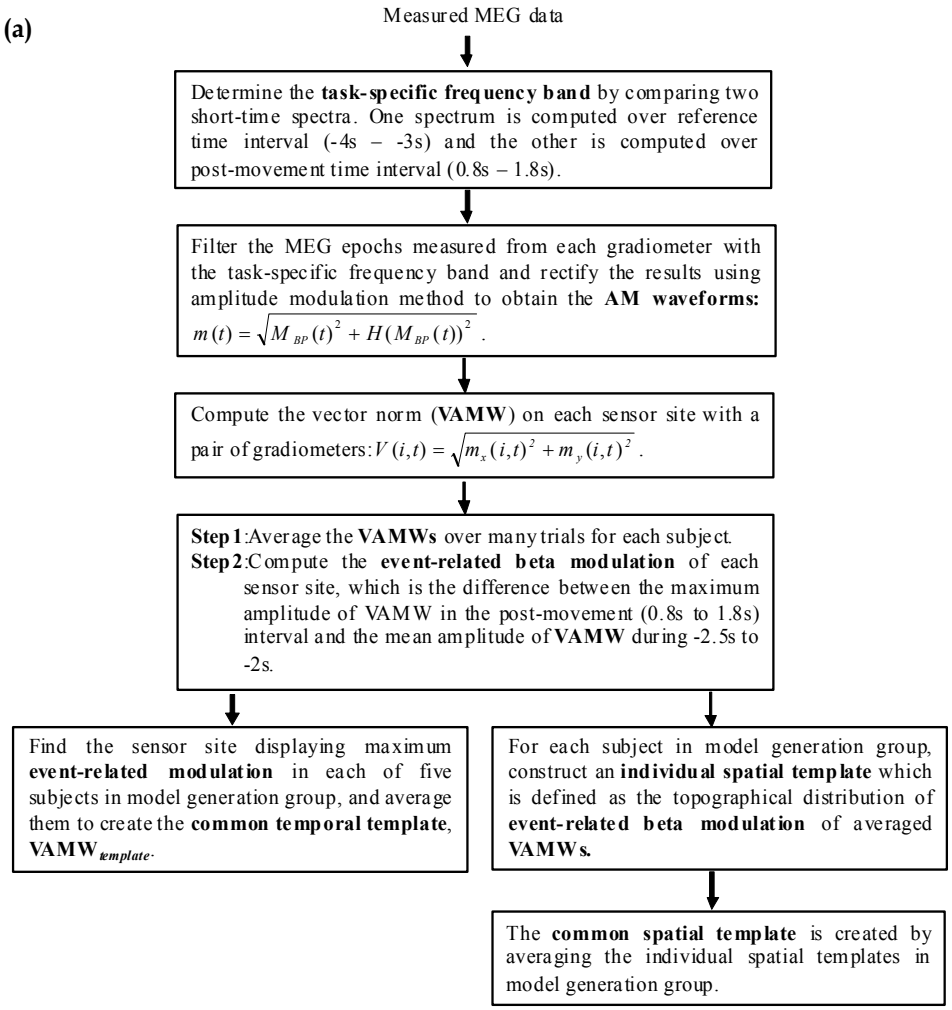


Fig. 5a. Flow chart for creation of common spatial and temporal templates.

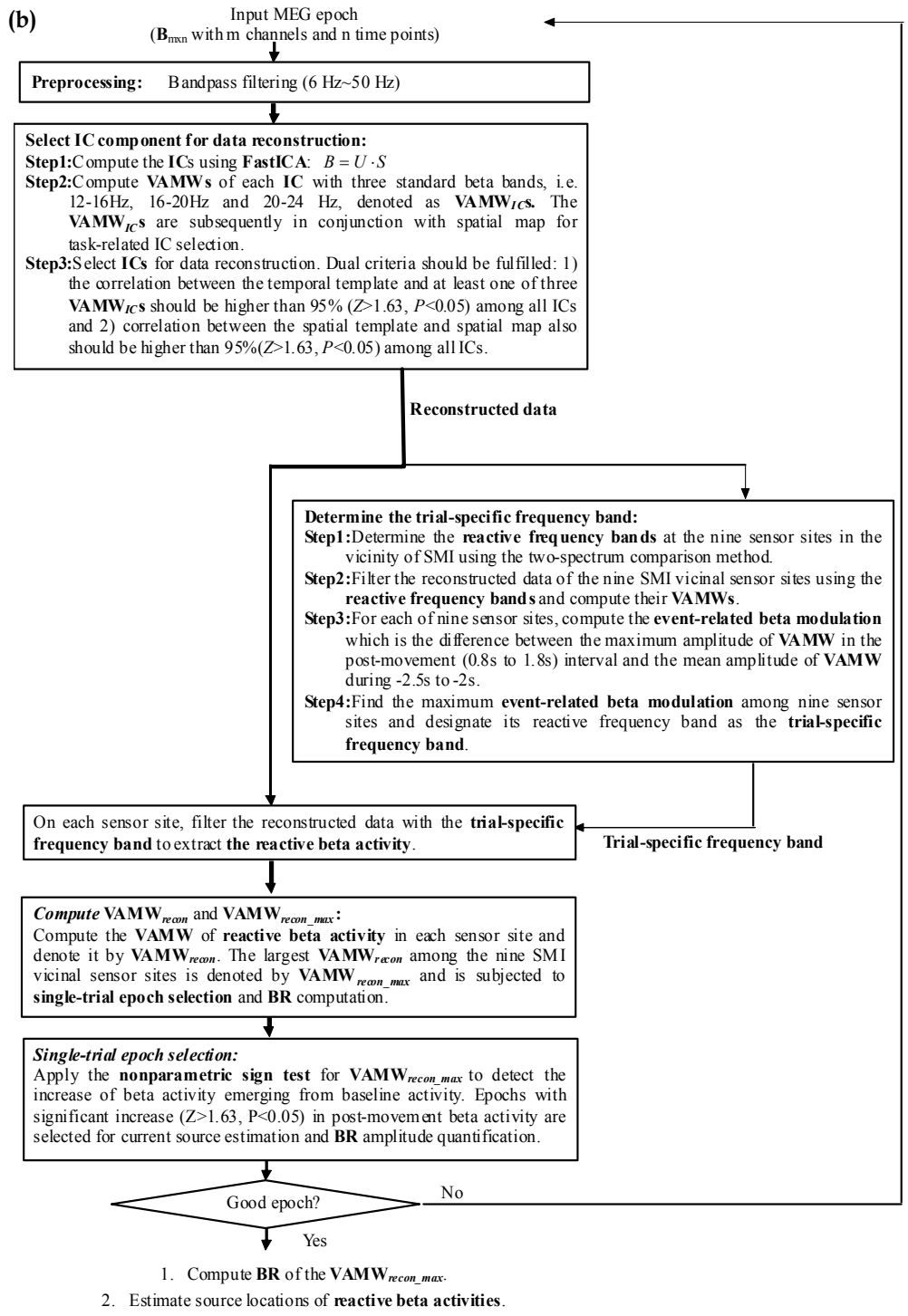
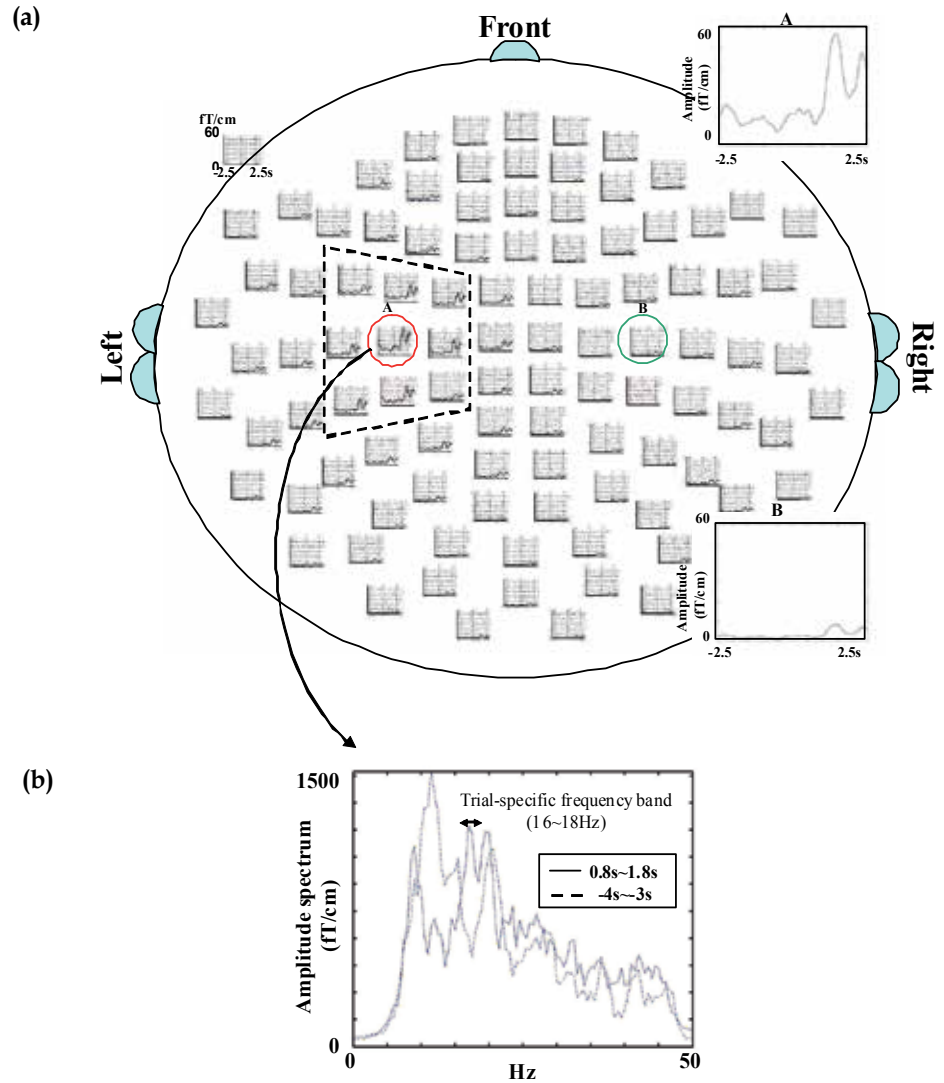


Fig. 5b. Flow chart for ICA-based single-trial analysis method.

Figure 6a depicts the single-trial VAMW$_{recon}$s of subject I filtered within the trial-specific frequency band (Fig. 6b). The conventional AM method on the average of 100 epochs reveals a bilateral post-movement rebound pattern with contralateral (left hemisphere) dominance, whereas the current ICA-based single-trial analysis (one hemisphere template) yields only activation (one trial) in the left hemisphere (Fig. 6a and 6c).

Epoch acceptance rates were 84% (65/78), 89% (83/91), 71% (60/85), 73% (68/93), and 87% (76/87), respectively for the model generation group and 81% (71/88) for the validation subject; the average for all six was 80.8%. The *IOI*s of significance were 0.76s - 2.1s, 0.66s - 1.5s, 0.8s - 1.75s, 0.46s - 1.49s, and 0.71s – 1.28s for the five subjects in the model generation group, and 0.88s – 1.67s for the validation subject. Averaged magnitude of BR was calculated from the reconstructed data on trials that survived the epoch-selection procedure.



(c)

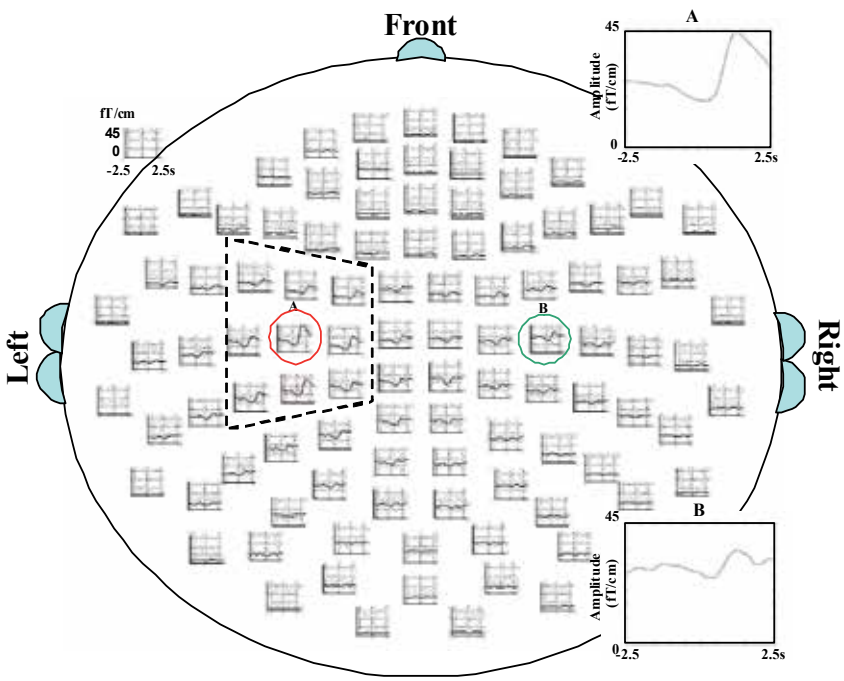


Fig. 6. Sensor-array display of VAMW$_{recon}$s and VAMWs. (a) One example of ICA single-trial VAMW$_{recon}$s of all sensor sites in subject I. The single-trial result shows only left sensorimotor area dominance of event-related activities, as the present study focuses on the area contralateral to movement side and only the left spatial template is used. The dashed trapezoid marks the nine SMI vicinal sensor sites and the VAMW$_{recon_max}$ is marked with the red circle. (b) Trial-specific frequency band used for VAMW$_{recon}$s calculation in Fig. 6a. (c) VAMWs obtained from the conventional averaging method over 100 trials in subject I. This figure shows a bilateral beta rebound pattern with contralateral (left hemisphere) dominance.

The BR amplitudes computed from individual spatial templates were 20.9±7.1 (mean±sd), 18.1±10.3, 16.2±6.2, 23.2±10.89, and 6.2±2.7 for the first 5 subjects, respectively, and 27.6±11.1 fT/cm for the 6th subject (Table 1). Using the common spatial template, BR amplitudes were 21.1±7.97, 19.02±9.7, 15.5±5.3, 19.75±8.75, 5.91±3.2, and 27.1±10.2 fT/cm, respectively (Table 1). There was no significant difference between the results obtained with two approaches (p=0.88; unpaired two-tailed t test). BR amplitudes obtained with the conventional method of averaging on 100 trials were 18.2, 7.254, 12.92, 16.4, 2.9, and 23.12 fT/cm, respectively. Means for single-trial ICA-derived BRs, using either individual or common spatial templates, were significantly higher than those obtained using the conventional method of averaging (p<0.005; Matched-pair Wilcoxon test; Table 1). The comparisons of BR amplitude and task-specific frequency band between ICA-based single-trial and conventional methods are given in Table 1.

The ICA-based single-trial approach shows remarkable latency jittering and inter-trial variability throughout the whole measurement process. Both factors can result in attenuation and smearing of averaged movement-related MEG responses. Figure 7a shows the raster plot of sixty-five normalized single-trial $VAMW_{recon_max}$s which survived the

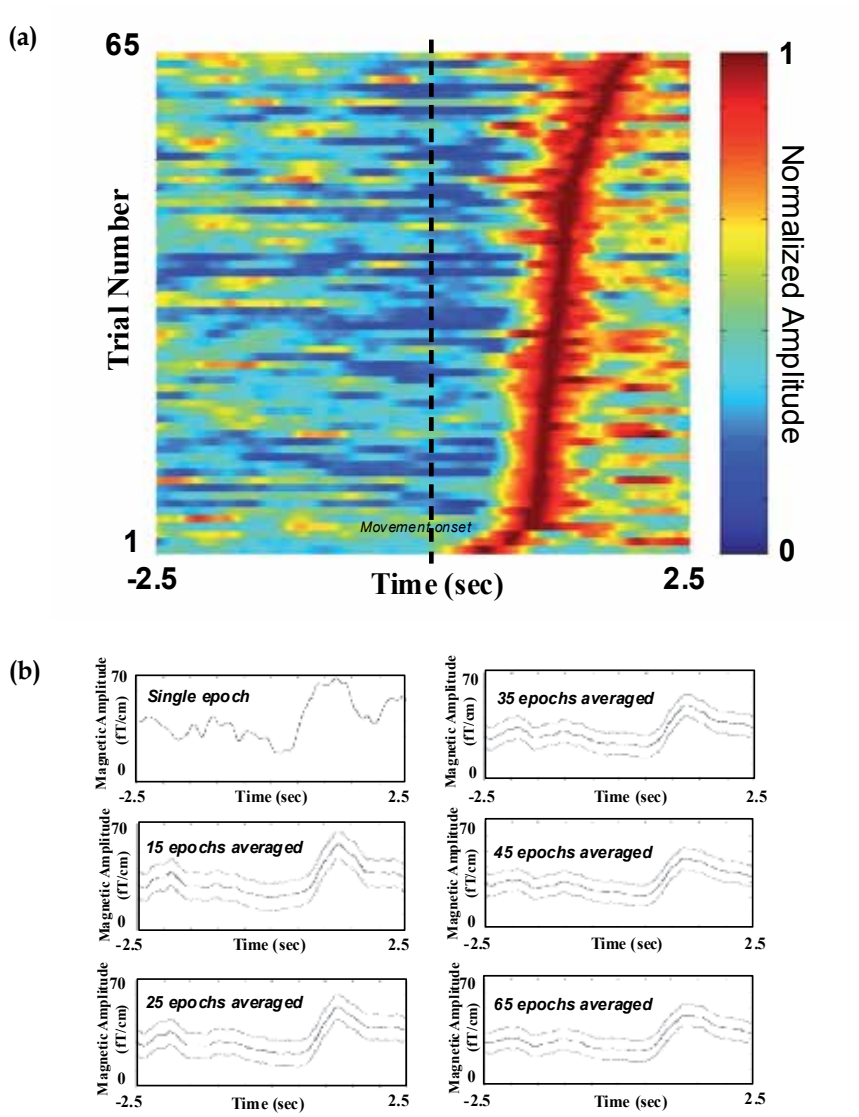


Fig. 7. Smearing of MEG profile and decrease of BR magnitude due to latency jittering. (a) Raster plot of normalized $VAMW_{recon_max}$s as sorted by the latency measured between the time of peak beta rebound and the movement onset. Black dashed line indicates movement onset time. (b) Latency jittering resulting in a smearing of the MEG profile and a decrease of BR magnitude when more $VAMW_{recon_max}$s are averaged, as is common in the conventional averaging method.

selection procedure for subject I, sorted by $VAMW_{recon\_max}$ peak latency as indexed to movement onset. The mean latency of peak beta rebound for the 65 trials was 1.41±0.43 s (mean±sd). With more epochs (random selection) averaged as with the conventional method of averaging, the averaged BR was attenuated (25.3, 24.6, 22.3, 21.5, 20.3 and 21.1 fT/cm for 1, 15, 25, 35, 45 and 65 trials averaged, respectively; values taken from the averaged $VAMW_{recon_max}$s using common spatial template) and the time-activity plots smeared (Fig. 7b).

	ICA based single-trial method				Conventional AM method	
	BR amplitude (fT/cm)		Trial-specific frequency band (Hz)		BR amplitude	Task-specific
Subject index	Individual spatial template	Common spatial template	Individual spatial template	Common spatial template	(fT/cm)	frequency band (Hz)
I	20.9±7.1	21.1±7.97	16.67±2.77 ~ 21.22±2.44	15.57±3.21~ 22.17±3.3	18.2	15~21
II	18.1±10.3	19.02±9.7	18.04±2.62 ~ 22.18±3.12	17.92±2.3~ 21.9±2.72	7.25	17~20
III	16.2±6.2	15.5±5.3	16.2±1.89 ~ 20.49±2.3	16.8±2.3~ 20.91±2.22	12.92	15~19
IV	23.2±10.89	19.75±8.75	16.1±2.37 ~ 20.7±3.08	15.5±3.3~ 19.2±2.77	16.4	14~17
V	6.2±2.7	5.91±3.2	17.31±3.23 ~ 20.77±3.67	16.8±3.1~ 21.2±2.9	2.9	17~20
VI (validation)	27.6±11.1	27.1±10.2	16.32±2.83 ~ 19.94±2.68	16.81±2.72~ 20.14±3.1	23.12	16~20

Table 1. The comparison of BR amplitude and specific frequency bands for ICA-based single-trial and conventional methods.

Source estimation using ECD and MCE both showed a cluster of current sources centered (mean coordinates) in the anterior bank of the central sulcus (see Fig. 8e and 8f) on data points around the rebound peak of extracted reactive beta activities (see Fig. 8d, time interval between 1202ms – 1302ms of one single epoch of subject I). The ECD-located dipoles oscillate and span a sector. Furthermore, the center of MCE-estimated current sources (yellow dots) lies less than 2mm from the center of ECD-estimated dipoles (red dots) (see Fig. 8f). These results cross-verify the validity of the ICA-based single-trial method.

Figure 10 depicts the time-frequency plot of a normal subject and a Parkinson's disease patient at an MEG channel in the vicinity of left sensorimotor area. Clear suppression of post-movement ERS (red circle) and an attenuated ERD (yellow circle) are observed in the Parkinson's disease patient. The VAMWs was significantly larger both in alpha band and beta band in the normal subject than in the Parkinson's patient. These imply the slowed and reduced recovery after motor act may impede cortical preparation of the next movement.

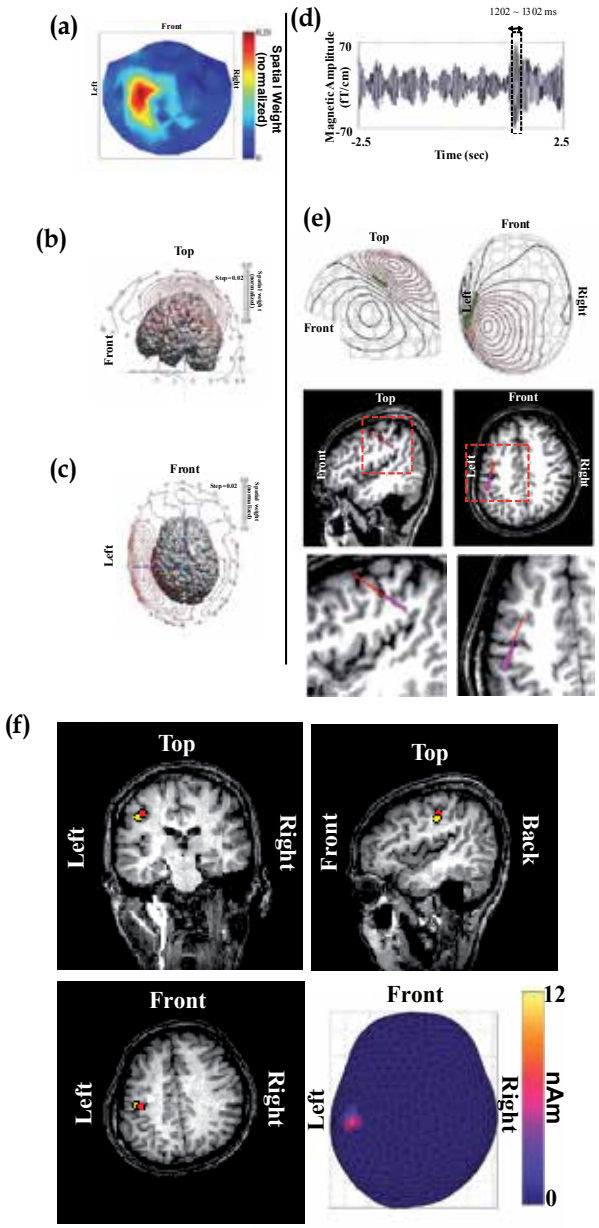


Fig. 8. Overlay of extracted reactive beta activities on MR image. (a) Spatial map reconstructed using $\bar{x}_{recon} = \sum_{j=1}^{k} \bar{x}_j$ (see Method Section). (b) and (c): Different views of superposition of the isocontour spatial map on the segmented MRI brain. (d) Representative trace of reconstructed reactive beta activities in the vicinity of SMI. (e) Upper panels are isocontour maps of reconstructed neuromagnetic signals at 1202 ms post movement. Lower panels show that all dipoles (from 1202 to 1302 ms after movement onset as box-framed in

(d)) are located in the primary motor area and oscillate accordingly. (f) The center of the MCE-estimated current sources (yellow dot) overlays the source location determined using the equivalent current dipole method (ECD) (red dot). Upper-left panel: coronal view. Upper-right panel: sagittal view. Lower-left panel: axial view. Lower-right panel: distribution of MCE estimated current sources.

Examining the single-trial variability using the proposed ICA-based method (Fig. 11), subtle dynamics of the beta rhythmic activities can be further studied. Figure 11 shows the ongoing trial-by-trial variabilities in amplitudes and latencies over 60 ICA de-noised post-movement ERS trials. With the utilization of ICA-based single-trial analysis, it is possible to investigate the reasoning of ERS vanishment is due to suppression of post-movement beta rebound in each single-trial, rather than the cause of temporal jittering and/or loss of synchronization. Even though the patient could perform lifting behavior well, his neuron activities show distinct sensorimotor patterns from normal subject, regardless of movement performance.

4. Discussion

The movement-related oscillatory modulations (ERD/ERS of alpha, beta and gamma) have been reported to be spatially extended (Babiloni et al., 1999; Crone et al., 1998a; Crone et al., 1998b; Leocani et al., 1997; Neuper and Pfurtscheller, 2001; Salmelin and Hari, 1994a; Taniguchi et al., 2000; van Burik et al., 1998). Source localizations using conventional filtering have also been reported to disperse among several regions (Salmelin & Hari, 1994a). However, our results strongly indicate that proper treatment when trial-by-trial dynamics can be accounted for yields clustered localizations congruent to neuroanatomical representations.

The present ICA-based spatiotemporal approach for single-trial analysis study is dedicated to the extraction of neuromagnetic measurements of event-related beta oscillatory activities. One distinct feature of the current ICA-based method as compared with other single-trial approaches (Guger et al., 2000; Ioannides et al., 1993; Jung et al., 2001) is the simultaneous use of a spatial template and a temporal template for component selection. The spatial template provides a priori spatial information for brain signals, while the temporal template contains temporal characteristics of event-related responses. Using the paired criteria for component selection, identification specificity of task-related components for signal reconstruction is significantly improved. As shown in Fig. 3c, the inclusion of IC 9 with high spatial correlation (correlation value=0.61, rank= 95.2%, Z=1.67, P=0.048) but devoid of temporal congruence (correlation value =0.28, rank=13%, Z=0.34, P=0.87) causes beta BR to deteriorate from 28.9 fT/cm (red curve) to 18.6 fT/cm (blue curve). The ICA-preprocessed dataset yields cleaner field maps (Fig. 9a), which result in circumscribed localizations (Figs. 9b-9c and 9e-9f., Salmelin and Hari, 1994a).

Significantly, the current method also makes possible the analysis of the reactive frequency band for every single trial once task-related rhythmic activities are extracted. The conventional method discounts this subtle but potentially important information. Notwithstanding, the idea of using a fixed window for signal filtering is neurophysiologically not optimal. We emphasize the precise identification of reactive trial-specific frequencies for BR calculation, since task-related frequency modulation might exist in one or multiple bands (Pfurtscheller & Lopes da Silva, 1999). The three-standard frequency band procedure is used for generation of $VAMW_{IC}$s to recover all possible task-related information and is followed by a two short-time spectra

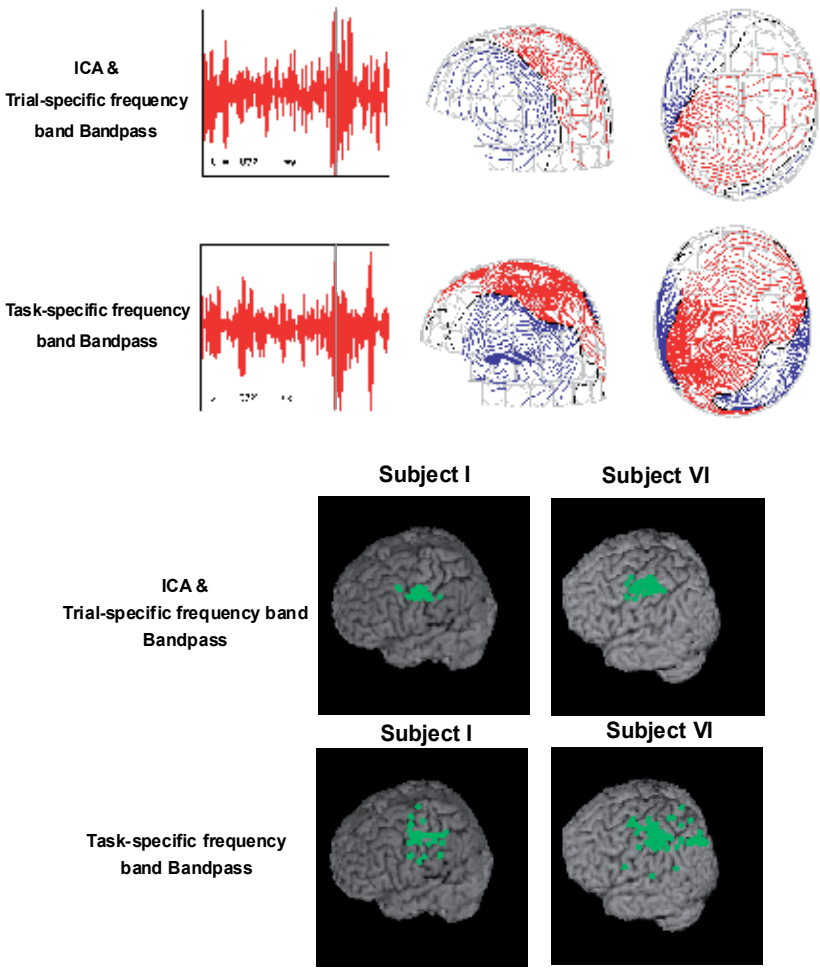


Fig. 9. Comparisons of magnetic fields and source locations preprocessed with ICA-bandpass trial specific (upper panel) and task-specific bandpass filtering (lower panel). (a) Neuromagnetic field maps. Data preprocessed with ICA-trial specific bandpass filter (15.57±3.21~22.17±3.3 Hz) gives a much less noisy neuromagnetic field pattern than that processed with the task-specific bandpass filtering method (15~21 Hz) (Pfurtscheller et al. 1999). Black vertical lines in the tracings of the left column denote time points of the corresponding field maps in the right column. (b) Source localizations by ECD model. Only dipoles in post-movement IOI (interval-of-interest) with goodness-of-fit higher than 80% are accepted. The one with highest goodness-of-fit value out of each trial is rendered onto the subjects' 3D MRI surfaces. The estimated source positions preprocessed by ICA-bandpass filtering (upper panel) are (x, y, z)= (-45±4.45, -3.9±6.33, 80.7±3.63mm; goodness-of-fit= 97.5±3.7%) in subject I (65 trials) and (x, y, z)=(-35.3±3.5, 5.7±6.02, 88.7±5.61mm; goodness-of-fit= 96.9±3.7%) in subject VI (71 trials), whereas task specific bandpass filtering (lower panel) yields (x, y, z)=(-46.3±11.6, -9.99±10.3, 84.51±6.7; goodness-of-fit=89.7±3.4%) in subject I (65 trials) and (x, y, z)=(-31.8±8.13, 0.5±14.01, 87.9±12.54mm; goodness-of-fit=87.2±4.5%) in subject VI (71 trials), respectively. The ICA-trial specific bandpass procedure yields better

results in terms of much focused source locations and higher goodness-of-fit. x, y, and z denote the dipole location in the head coordinate system as anchored by the HPI (head position indicator) coils. The x-axis passes through the preauricular points, pointing to the right; the positive y-axis traverses the nasion and is normal to the x-axis; the positive z-axis points upward and normal to the xy-plane.

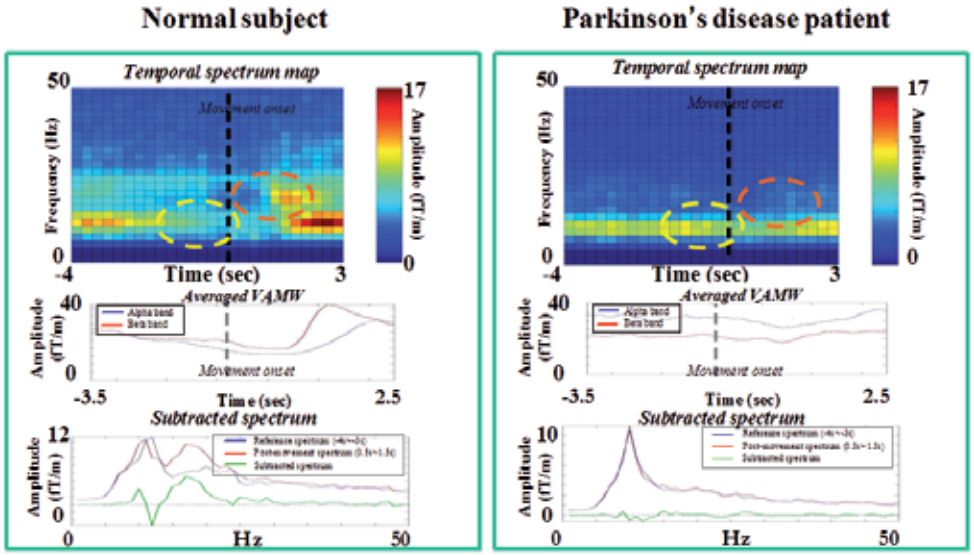


Fig. 10. The comparion of neural activity via time-frequency, VAMW and spectrum analysis obtained from one normal subject and a parkinson's disease patient. The ensemble averaging results reflect the ERD attenuation (yellow circle) and the ERS disappearance (red circle) in the pakinson's patient.

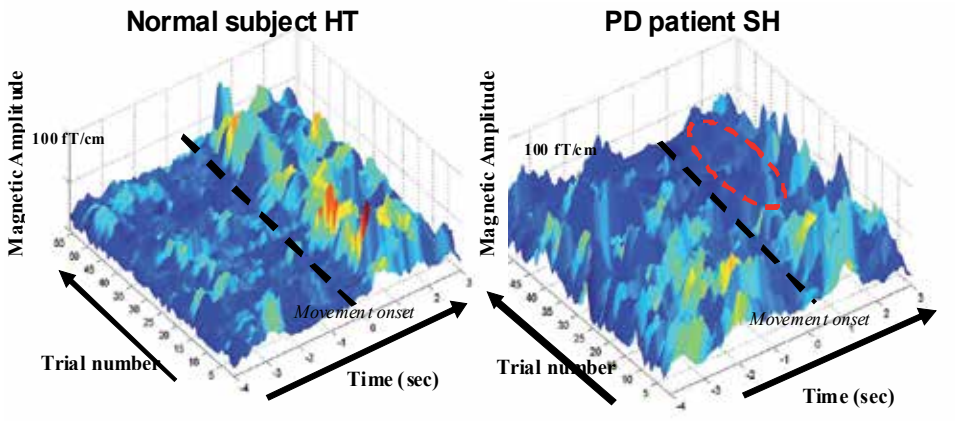


Fig. 11. Trial-by-trial comparison of VAMWs could be performed via the proposed ICA-based approach between the normal subject and the Parkinson's disease patient.

comparison procedure (Pfurtscheller & Lopes da Silva, 1999) for the identification of the optimal reactive trial-specific frequency band in the reconstructed epochs. The present approach not only extracts the specific reactive frequencies but also retains phase information on a trial-by-trial basis. The trial-specific frequency band of post-movement beta modulation anchors mainly (~85% of all trials) in the lower beta band (16Hz~20Hz) and less frequently (~15%) in the higher beta band (20~24Hz). Great variation of BR values is also seen, as reflected in large SD (Table 1). The revealed trial-by-trial dynamics provide a possibility for future profound study of subtle brain dynamics.

It is noteworthy that not all the data reconstructed from the selected ICs survives the statistical threshold. We have carefully monitored online and thoroughly checked offline the EMG measurements in terms of EMG onset (p=0.61, unpaired two-tailed t- test), termination (p=0.53, unpaired two-tailed t-test) and the EMG duration (p=0.573, unpaired two-tailed t-test) during finger lifting between significant and insignificant trials as indexed to the movement registration by the optic pad (Abbink et al., 1998). The data indicate an absence of prominent behavioral difference commensurate to the differential neuromagnetic responses. Some epochs with a fluctuating baseline, e.g., non-task-related spontaneous bursts of beta oscillatory activities, may manifest high baseline activity, which in turn results in a decrease in BR readout leading to exclusion after statistical manipulation (Fig 4). It has been suggested that baseline spontaneous activities may carry important information relevant to attention level, wakefulness, task difficulty, etc. (Buser & Rougeul-Buser, 1999; Sterman, 1999). The jittering of the neuromagnetic beta ERS is likewise interesting and may be also physiological. A zero-phase Butterworth filter was used to bandpass filter the raw data. The symmetric property of the zero-phase filter means that processed signals have precisely zero phase distortion and therefore no time shift of peak beta rebound was introduced. Hence, fluctuations of significance level and the jittering of central processing despite similar behavioral performance may be ascribed to the subject's variant cognitive states or the degree of training (Buser & Rougeul-Buser, 1999; Sterman, 1999; Flotzinger et al., 1992; Wolpaw et al., 1994; Bastiaansen et al., 2001; Bastiaansen et al., 1999; Earle, 1988; Haig et al., 1995; Hoffman et al., 1991; Yabe et al., 1993). The exploration of underlying mechanisms mandates more meticulous designs in the future. Using the conventional method of averaging, certain diseases, such as Parkinson's and Unverricht-Lundborg myoclonic epilepsy, have been observed to show either attenuated, prolonged or abolished ERS responses (Silen et al., 2000; Tamas et al., 2003). Such cases can be further examined using the current ICA-based single-trial method for the time course and trial-by-trial dynamics to disclose hitherto unexplored mechanisms underlying these phenomena.

A concern with any data driven method is that prominent artifacts or noise can be intermingled with task-specific information (Ermer et al., 2000; Lins et al., 1993a; Lins et al., 1993b). However, previous ICA reports (Makeig et al., 2002; Mckeown & Radtke, 2001) indicate that brain rhythmic signals generated from different sources usually have their own oscillatory frequencies with distinct phases and are located in specific brain regions with patterns that are distinct from artifacts or noise (see also Fig. 3). This endorses the feasibility of using ICA to separate targeted rhythmic signals from irrelevant ones. The high epoch-acceptance rate (~80%) can be attributed to an improved SNR as compared to other studies on single-trial approaches to sensorimotor oscillatory activities (Brovelli et al., 2002; Wolpaw and McFarland, 1994). For instance, the spatial map of IC2 in Fig. 2a correlates highly (0.88) with the spatial map of IC1 from empty room measurement as shown in Fig. 3b; this

suggests that the neuromagnetic signal IC2, deselected for subsequent processing, can be accounted for by background noise in the shielding room. IC11 in Fig. 3a has a stationary cycle around 1.2 Hz, and its spatial map has higher weights at the outer rim of the MEG sensor array, which suggests a plausible connection with cardiac cycles. It was also observed (Fig. 3) that rhythmic activities in left and right SMIs as well as the occipital areas could be extracted into separate ICs that can be reminiscent of various mechanisms and time courses of different brain oscillatory activities (Pfurtscheller & Lopes da Silva, 1999; Pfurtscheller et al., 1997; Pfurtscheller et al., 1998b; Stancak and Pfurtscheller, 1996a; Stancak & Pfurtscheller, 1996b; Andrew & Pfurtscheller, 1999).

Since most task irrelevant signals, e.g., internal and external noises, can be removed by proper de-selection of ICs, it is possible to reconstitute the representative spatial map of all contributing ICs using $\bar{x}_{recon} = \sum_{j=1}^{k} \bar{x}_j$, in which $\bar{x}_{recon}$ is the reconstructed spatial map, k is the number of selected ICs and $\bar{x}_i$ is the spatial map of the i^{th} selected IC in Fig. (4) (Fig. 8a). This spatial map of reconstructed signals, which is a topographical distribution of weighting factors on the sensor array, can be overlaid with the segmented MRI brain (Fig. 8b & 8c; ASA program, ANT Software, Dutch). The highest weight is shown to project over the SMI area, which demonstrates that the high SNR of the ICA-extracted rhythmic activities of each trial has made possible the use on single-trial data of source estimation methods that require high SNR on input data for processing, e.g., the equivalent current dipole technique (ECD), minimum current estimation (MCE), and minimum norm estimation (MNE) (Delorme et al., 2001; Delorme et al., 2002; Jung et al., 2001; Makeig et al., 1997; Mckeown et al., 2001). Conventionally, these estimation methods exploit averaged data out of a large amount of trials.

Another reason why the intricate phase-unlocked signal can be preserved is the fact that no averaging procedure is needed; such a procedure would otherwise inherently distort the embedded information. Accordingly, as shown in Fig. 8d, source modeling with a moving dipole on a msec by msec basis on the reconstructed oscillatory beta signals during the rebound period (Brovelli et al., 2002) of a single-trial epoch results in a focused clustering of dipole foci at the pre-central area, i.e., the primary motor cortex (Fig. 8e). Figure 8 shows the result of MCE modeling (Uutela et al, 1999), where the center of MCE-estimated current sources (yellow dot) is very close (< 2mm distance) to the dipole location as estimated using the ECD approach (red dot).

It can be argued that one can first localize the generator area and then build a spatial filter for extracting single-trial data so that the subsequent analysis can be conducted on the source level instead of the sensor level. One premise and justification of using a source-area-generated spatial filter is that the source area can be precisely localized for the generation of a spatial filter (Tesche et al., 1995). The very first step is to filter the signals to obtain a presupposed reactive frequency band. However, using conventional simple filtering techniques, ambient noise with ~20Hz components cannot be optimally removed, and this will cause localization uncertainty for the probed sources (Fig 9). However, ICA pre-processing decomposes the compound neuromagnetic signals into various independent task-related and task-unrelated/noise components so that ~20Hz activities not related to the a priori spatiotemporal profile will not confound the selected ones. Furthermore, our ICA-based method differs from other spatial filtering techniques, e.g., signal space projection (SSP) which is a fixed spatial filter for signal extraction (Tesche et al., 1995). The ICA-based

method blindly decomposes the MEG epochs (**B**) into a spatially distributed map (**U**) multiplied by temporal signals (**S**), i.e. $\mathbf{B}=\mathbf{U}\cdot\mathbf{S}$, on the basis of independency among sources (Vigario & Oja, 2000), whereas SSP mandates a pre-defined spatial filter ($\mathbf{U}_{\_sf}$) for recovering signals (**S**), i.e. $\mathbf{S}=\mathbf{U}_{\_sf}^{+}\cdot\mathbf{B}$, where + denotes pseudo inverse, based on orthogonal projection. When ambient noise and the spatial filter are not mutually orthogonal, the SSP has difficulty in resolving the two. Subsequent application of ICA following SSP does not ensure finer signal extraction or further noise removal since the data recovered from SSP are already linear mixtures of components out of a pre-defined spatial filter, which is a constraint drag on the optimal performance of ICA designed for blind decomposition.

Left and right sensorimotor rhythms can be decomposed into two distinct ICs (IC3 and IC5 in Fig. 3), implying possible independent modulatory mechanisms between the two hemispheres. This view is corroborated by an event-related coherence study (Andrew and Pfurtscheller, 1999) that reports a lack of interhemispheric coherence in human post-movement beta activities. Movement-related beta oscillatory activities of the right hemisphere can be extracted in the same way using spatial and temporal templates for right sensorimotor rhythm. The source locations for extracted right hemispheric beta activities were mainly in the right premotor area (data not shown), which agrees with previous studies (Brovelli et al., 2002; Ilmoniemi, R. J., 1991). Event-related beta activities in SMA and posterior parietal cortical areas (Brovelli et al., 2002; Joliot et al., 1999) are not observed in our data, possibly due to the fact that the contributing sources here are radial in orientation and thus could not be optimally detected by MEG (Salmelin and Hari, 1994b).

The agreement between the values of BR amplitude obtained with the common spatial/temporal templates and the individually generated ones (Table 1) promises a flexibility in both experimental design and analytical strategy. The proposed ICA-based spatiotemporal approach for single trial analysis can also be applied on fewer trials (Fig 7b), which is a great advantage over conventional methods. Given meticulous head positioning (see above the Method Section), common spatial and temporal templates can be used to extract pertinent movement-related neuromagnetic signals from subjects, which may shorten the overall time needed to run an experiment. We have no preference for the use of a grand averaged template over individual ones. On the contrary, the use of an individual template is suggested for any profound individual–based ERD/ERS study. However, the feasibility of using a grand averaged template provides an effective alternative in cases where lengthy procedures cannot be endured by the participants. This is particularly true for clinical settings where patients have attention problems or are incapable of sustaining long experiments so that individual templates cannot be optimally obtained. Nevertheless, caution should be exercised when applying the current ICA-based single-trial method for clinical studies. For patients whose heads cannot be properly positioned in the center of the MEG helmet, the use of a common spatial template may fail, making a customized individual spatial template mandatory for IC selection. For patients whose motor performance deviates significantly from normal, e.g., victims of motor stroke or severe movement disorders, the use of the common temporal template might not be justified since the time courses of event-related brain activities may be significantly altered due to primary deficit or secondary plasticity. Accordingly, in such situations, an individual spatial template can be applied without a temporal template as an aid to component selection. Our future investigations will combine the current dual-template approach with a source estimation method so that a spatial filter of better precision and higher dimensions can be

designed, which will make possible sophisticated analysis on the source level instead of the sensor level, eliminating the positioning problem.
Degeneration of the dopaminergic neurons in substania nigra pars compacta (SNc) in Parkinson's patients result in abnormal projection in thalamo-cortical pathway which causes an abnormal projection from thalamus to supplementary motor area (SMA). Pfurtscheller et al. (1998) also have demonstrated that Parkinson's patients have delayed ERD and abolished post-movement ERS and speculated there is dysfunction in subcortico-cortical connections in Parkinson's patients. In this study, we analyzed post-movement ERS in one Parkinson's patient. The present ICA-based approach may be helpful for disclosing the mechanism of movement-related brain rhythms which could be used as a clinical index for diagnosing Parkinson's patients.

5. Conclusions

The present novel ICA-based spatiotemporal approach for single trial analysis features a paired-template matching for stringent component selection. The spatial template provides a priori spatial information for targeted brain signals while the temporal template contains temporal characteristics of event-related responses. The method promises not only a high extraction rate of post-movement beta synchronization but also better localization of the corresponding sources. Various source modeling methods commanding high SNR can now be applied to single trial data as extracted using the ICA-spatiotemporal procedure. Our method takes into account subtle trial-by-trial dynamics. The reconstructed MEG brain signals per trial unravel the temporal information and inter-trial variations of reactive oscillatory activities, which in turn may shed light on the subtle dynamics of brain processing. The embodied common template approach permits an effective alternative in cases where lengthy procedures cannot be endured by the participants or in clinical settings where patients have attention problems or are incapable of sustaining long experiments.

6. Acknowledgment

This study was funded by the National Central University, Center for Dynamical Biomarkers and Translational Medicine (99-2911-1-008-100), National Science Council (99-2628- E-008-003, 99-2628- E-008-012, 100-2628-E-008-013, 100-2628-E-008-001, 100-2613-E-008-006-D), and Veterans General Hospital University System of Taiwan Joint Research Program (VGHUST96-P4-15, VGHUST97-P3-11, VGHUST98-98- P3-09).

7. References

Andrew, C. & Pfurtscheller G. (1995). Event-related coherence during finger movement: a pilot study, *Biomedizinische Technik*, Vol. 40, pp. 326-332.

Andrew, C. & Pfurtscheller, G. (1999). Lack of bilateral coherence of post-movement central beta oscillations in the human electroencephalography, *Neuroscience letters*, Vol. 273, pp. 82-89.

Bastiaansen, M. C. M.; Bocker, K. B. E.; Cluitmans, P. J. M. & Brunia, C. H. M. (1999). Event-related desynchronization related to the anticipation of a stimulus providing knowledge of results, *Clinical Neurophysiology*, Vol. 110, pp. 250-260.

Bastiaansen, M. C. M.; Bocker, K. B. E. & Brunia, C. H. M. (2001). Event-related desynchronization during anticipatory attention for an upcoming stimulus: a comparative EEG/MEG study, *Clinical Neurophysiology*, Vol. 112, pp. 393-403.

Brovelli, A.; Battaglini, P. P.; Naranjo, J. R. & Budai, R. (2002). Medium-range oscillatory network and the 20-Hz sensorimotor induced potential, *Neuroimage*, Vol. 16, pp. 130-141.

Buser, P. & Rougeul-Buser A. (1999). EEG synchronization in cat, monkey and human during attentive states: a brief survey, In: *Event-related desynchronization. Handbook of electroencephalography and clinical neurophysiology*, G. Pfurtscheller & F. H. Lopes da Silva, 13-32, Elsevier, Amsterdam.

Clochon, P.; Fontbonne, J. M. & Etevenon, P. (1996). A new method for quantifying EEG event-related desynchronization: amplitude envelope analysis, *Electroencephalography and Clinical Neurophysiology*, Vol. 98, pp. 126-129.

Delorme, A.; Makeig, S.; Fabre-Thorpe, M. & Sejnowske, T. 2001. From single-trial EEG to Brain Area dynamics, *Neurocomputing*, Vol. 44, pp. 1057-1064.

Delorme, A. & Makeig, S. (2003). EEG changes accompanying learned regulation of 12-Hz EEG activity, *IEEE transactions on rehabilitation engineering*, Vol. 11, pp. 133-137.

Earle, J. B. (1988). Task difficulty and EEG alpha asymmetry: an amplitude and frequency analysis, *Neuropsychobiology*, Vol. 20, pp. 95-112.

Ermer, J. J.; Mosher, J. C.; Huang, M. & Leahy, R. M. (2000). Paired MEG data set source localization using recursively applied and projected (RAP) MUSIC, *IEEE Transactions on Biomedical Engineering*, Vol. 47, pp. 1248-1260.

Florian, G. & Pfurtscheller, G. (1995). Dynamic spectral analysis of event-related EEG data, *Electroencephalography and Clinical Neurophysiology*, Vol. 95, pp. 393-396.

Flotzinger, D.; Kalcher, J. & Pfurtscheller, G. (1992). EEG classification by learning vector quantization, *Biomedizinische Technik*, Vol. 37, pp. 303-309.

Guger, C.; Ramoser, H. & Pfurtscheller, G. (2000). Real-time EEG analysis with subject-specific spatial patterns for a brain-computer interface (BCI). *IEEE Transactions on Rehabilitation Engineering*, Vol. 8, pp. 447-456.

Haig, A. R.; Gordon, E.; Rogers, G., & Anderson, J. (1995). Classification of single-trial ERP sub-types: application of globally optimal vector quantization using simulated annealing, *Electroencephalography and Clinical Neurophysiology*, Vol. 94, pp. 288-297.

Hoffman, R. E.; Buchsbaum, M. S.; Escobar, M. D.; Makuch, R. W.; Nuechterlein, K. H. & Guich, S. M. (1991). EEG coherence of prefrontal areas in normal and schizophrenic males during perceptual activation, *Journal of Neuropsychiatry and Clinical Neurosciences*, Vol. 3, pp. 169-175.

Hyvarinen, A.; Karhunen, J. & Oja, E. (2001). *Independent component analysis.* John Wiley and Sons, New York.

Hyvarinen, A & Oja, E. (1997). A fast fixed-point algorithm for independent component analysis, *Neural Computation*, Vol. 9, pp. 1483-1492.

Ilmoniemi, R. J. (1991). Estimates of neuronal current distributions, *Acta Otolaryngol*, Vol. 49(Suppl.), pp. 80–87.

Ioannides, A. A.; Singh, K. D.; Hasson, R.; Baumann, S. B.; Rogers, R. L.; Guinto, F. C. & Papanicolaou, A. C. (1993). Comparison of current dipole and magnetic field tomography analyses of the cortical response to auditory stimuli, *Brain Topography*, Vol. 6, pp. 27-34.

Jensen, O. & Vanni, S. (2002). A new method to identify multiple sources of oscillatory activity from magnetoencephalographic data, *Neuroimage*, Vol. 15, pp. 568-574.

Joliot, M.; Papathanassiou, D.; Mellet, E.; Quinton, O.; Mazoyer, N.; Courtheoux, P. & Mazoyer, B. (1999). FMRI and PET of self-paced finger movement: comparison of intersubject stereotaxic averaged data, *Neuroimage*, Vol. 10, pp. 430-447.

Jung, T. P.; Makeig, S.; Westerfield, M.; Townsend, J.; Courchesne,E. & Sejnowski, J. T. (2001). Analysis and Visualization of Single-Trial Event-Related Potentials, *Human Brain Mapping*, Vol. 14, pp. 166-185.

Kajola, M.; Ahonen, A.; Hamalainen, M. S.; Knuutila, J.; Lounasmaa, O. V.; Simola, J. & Vilkman, V. (1991). Development of multichannel neuromagnetic instrumentation in Finland, *Clinical Physics & Physiological Measurement*, Vol. 12, pp. 39-44.

Kao, Y. H.; Guo, W. Y.; Wu, Y. T.; Liu, K. C.; Chai, W. Y.; Lin,C. Y.; Hwang, Y. H.; Liou, A. J. K.; Cheng, H. C.; Yeh, T. C.; Hsieh, J. C. & Teng, M. M. H. (2003). Hemodynamic segmentation of MR brain perfusion images using independent component, thresholding and Bayesian estimation, *Magnetic Resonance in Medicine*, Vol. 49, pp. 885-894.

Kalcher, J. & Pfurtscheller, G. (1995). Discrimination between phase-locked and non-phase-locked event-related EEG activity, *Electroencephalography and Clinical Neurophysiology*, Vol. 94, pp. 381-384.

Klimesch, W.; Russegger, H.; Doppelmayr, M. & Pachinger, T. (1998). A method for the calculation of induced band power: implications for the significance of brain oscillation, *Electroencephalography and Clinical Neurophysiology*, Vol. 108, pp. 123-130.

Leocani, L.; Manganotti, C. T.; Zhuang, P. & Hallett, M. (1997). Event-related coherence and event-related desynchronization/synchronization in the 10 Hz and 20 Hz EEG during self-paced movements, *Electroencephalography and clinical neurophysiology*, Vol. 103, pp. 199-206.

Lins, O. G.; Picton, T. W.; Berg, P. & Scherg, M. (1993a). Ocular artifacts in EEG and event-reated potentials. I. Scalp topography, *Brain Topography*, Vol. 6, pp. 51-63.

Lins, O. G.; Picton, T. W.; Berg,P. & Scherg, M. (1993b). Ocular artifacts in recording EEGs and event-related potentials. II. Source dipoles and source components, *Brain Topography*, Vol. 6, pp. 65-78.

Lopes da Silva, F. H. (1991). Neural mechanisms underlying brain waves: from neural membranes to networks, *Electroencephalography and Clinical Neurophysiology*, Vol. 79, pp. 81-93.

Lopes da Silva, F. H. (1996). The generation of electric and magnetic signals of the brain by local networks, *Comprehensive human physiology*, Vol. 1, pp. 509-531.

Makeig, S.; Jung, T. P.; Bell, A. J.; Ghahremani, D. & Sejnowski, T. (1997). Blind separation of auditory event-related brain responses into independent components, Proceedings of the National Academy of Sciences of the United States of America, Vol. 94, pp. 10979-10984.

McKeown, M. J.; Makeig, S.; Brown. G. G.; Jung. T. P.; Kindermann. S. S.; Bell. A. J & Sejnowski, T. J. (1998). Analysis of fMRI data by blind separation into independent spatial components, *Human Brain Mapping*, Vol. 6, pp. 160-188.

Mckeown, M. & Radtke, R. (2001). Phasic and tonic coupling between EEG and EMG demonstrated with independent component analysis, *Journal of clinical neurophysiology*, Vol. 18, pp. 45-57.

Mosher, J. C.; Lewis, P. S. & Leahy, R. M. (1992). Multiple dipole modeling and localization from spatio-temporal MEG data, *IEEE Transactions on Biomedical Engineering*, Vol. 39, pp. 541-557.

Muller-Gerking, J.; Pfurtscheller, G. & Flyvbjerg, H. (1999). Designing optimal spatial filters for single-trial EEG classification in a movement task, *Clinical Neurophysiology*, Vol. 110, pp. 787-798.

Pfurtscheller, G. & Aranibar A. 1(977). Event-related cortical desynchronization detected by power measurements of scalp EEG, *Electroencephalography and Clinical Neurophysiology*, Vol. 42, pp. 817-826.

Pfurtscheller, G. & Aranibar A. (1979a). Evaluation of event-related desynchronization (ERD) preceding and following voluntary self-paced movement, *Electroencephalography and Clinical Neurophysiology*, Vol. 46, pp. 138-146.

Pfurtscheller, G. & Aranibar A. (1979b). Evaluation of event-related desynchronization (ERD) preceding and following voluntary self-paced movements, *Electroencephalography and Clinical Neurophysiology*, Vol. 46, pp. 138-146.

Pfurtscheller, G. (1981). Central beta rhythm during sensorimotor activities in man, *Electroencephalography and Clinical Neurophysiology*, Vol. 51, pp. 253-264.

Pfurtscheller, G. & Berghold, A. (1989). Patterns of cortical activation during planning of voluntary movement, *Electroencephalography and Clinical Neurophysiology*, Vol. 72, pp. 250-258.

Pfurtscheller, G.; Pregenzer M. & Neuper C. (1994). Visualization of sensorimotor areas involved in preparation for hand movement based on classification of alpha and central beta rhythms in single EEG trials in man, *Neuroscience Letters*, Vol. 181, pp. 43-46.

Pfurtscheller, G.; Stancak A., Jr. & Neuper C. (1996). Post-movement beta synchronization: a correlate of an idling motor area?, *Electroencephalography and Clinical Neurophysiology*, Vol. 98, pp. 281-293.

Pfurtscheller, G.; Neuper C.; Flotzinger D. & Pregenzer M. (1997). EEG-based discrimination between imagination of right and left hand movement, *Electroencephalography and Clinical Neurophysiology*, Vol. 103, pp. 642-651.

Pfurtscheller, G.; Pichler-Zalaudek K.; Ortmayr B.; Diez J. & Reisecker F. (1998a). Postmovement beta synchronization in patients with Parkinson's disease, *Journal of Clinical Neurophysiology*, Vol. 15, pp. 243-250.

Pfurtscheller, G.; Zalaudek K. & Neuper C. (1998b). Event-related beta synchronization after wrist, finger and thumb movement, *Electroencephalography and Clinical Neurophysiology*, Vol. 109, pp. 154-160.

Pfurtscheller, G. & Lopes da Silva F. H. (1999). Event-related EEG/MEG synchronization and desynchronization: basic principles, *Clinical Neurophysiology*, Vol. 110, pp. 1842-1857.

Rosell, J.; Casanas, R. & Scharfetter H. (2001). Sensitivity maps and system requirements for magnetic induction tomography using a plannar gradiometer, *Physiological Measurement,* Vol. 22, pp. 121-130.

Salmelin, R. & Hari, R. (1994a). Characterization of spontaneous MEG rhythms in healthy adults, *Electroencephalography and Clinical Neurophysiology*, Vol. 91, pp. 237-248.

Salmelin, R. & Hari, R. (1994b). Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement, *Neuroscience*, Vol. 60, pp. 537-550.

Salmelin, R.; Hamalainen, M.; Kajola, M. & Hari, R. (1995). Functional segregation of movement-related rhythmic activity in the human brain, *Neuroimage*, Vol. 2, pp. 237-243.

Silen T.; Forss, N.; Jensen, O. & Hari, R. (2000). Abnormal Reactivity of the ~20-Hz Motor Cortex Rhythm in Unverricht Lundborg Type Progressive Myoclonus Epilepsy, *Neuroimage*, Vol. 12, pp. 707-712.

Stancak, A. Jr. & Pfurtscheller G. (1996a). The effects of handedness and type of movement on the contralateral preponderance of mu-rhythm desynchronization, *Electroencephalography and Clinical Neurophysiology*, Vol. 99, pp. 174-182.

Stancak, A. Jr. & Pfurtscheller G. (1996b). Mu-rhythm changes in brisk and slow self-paced finger movements, *Neuroreport*, Vol. 7, pp. 1161-1164.

Sterman, M. B. (1999). Event-related EEG response correlates of task difficulty, sleep deprivation and sensory distraction, In: *Event-related desynchronization. Handbook of electroencephalography and clinical neurophysiology*. G. Pfurtscheller & F. H. Lopes da Silva, 233-242, Elsevier, Amsterdam.

Tamas, G.; Szirmai, I.; Palvolgyi, L.; Takats, A. & Kamondi, A. (2003). Impairment of post-movement beta synchronization in parkinson's disease is related to laterality of tremor, *Clinical Neurophysiology*, Vol. 114, pp. 614-623.

Tang, A. C.; Pearlmutter, B. A.; Malaszenko, N. A. & Phung, D. B. (2002). Independent components of magnetoencephalography: single-trial response onset times, *Neuroimage*, Vol. 17, pp. 1773-1789.

Taniguchi, M.; Kato, A.; Fujita, N.; Hirata, M.; Tanaka, H.; Kihara, T.; Ninomiya, H.; Hirabuki, N.; Nakamura, H.; Robinson, S. E.; Cheyne, D. & Yoshimine, T. (2000). Movement-related desynchronization of the cerebral cortex studied with spatially filtered magnetoencephalograpy, *Neuroimage*, Vol. 12, pp. 298-306.

Tesche, C. D.; Unsitalo M. A.; Ilmoniemi R. J.; Huotilainen M.; Kajola M. & Salonen O. (1995). Signal-space projections of MEG data characterize both distributed and well-localized neuroal sources, Electroencephalography and Clinical Neurophysiology, Vol. 95, pp. 189-200.

Uutela, K.; Hamalainen, M. & Somersalo, E. (1999). Visualization of magnetoencephalography data using minimum current estimates, *Neuroimage*, Vol. 10, pp. 173-180.

Wolpaw, J. R. & McFarland, D. J. (1994). Multichannel EEG-based brain-computer communication, *Electroencephalography and clinical Neurophysiology*, Vol. 90, pp. 444-449.

Wu, Y. T.; Lee, P. L.; Chen, L. F.; Yeh, T. C. & Hsieh, J. C. (2002). Single-trial quantification of imagery beta-band Mu rhythm in finger lifting task using independent component analysis (ICA). *Proceeding of BioMag 13th international conference on biomagnetism*, pp. 1045-1047.

Wu, Y. T.; Lee, P. L.; Chen, L. F.; Yeh, T. C. & Hsieh, J. C. (2003). Quantification of movement-related modulation on beta activity of single-trial magnetoencephalography measuring using independent component analysis (ICA). *Proceeding of the 1st international IEEE EMBS conference on neural engineering*, pp. 396-398.

Yabe, H.; Satio, F. & Fukushima, Y. (1993). Median method for detecting endogenous event-related brain potentials, *Electroencephalography and clinical Neurophysiology*, Vol. 87, pp. 403-407.

5

Developing an MRI-Based Biomarker for Early Diagnosis of Parkinson's Disease

Jorge E. Quintero[1], Xiaomin Wang[3] and Zhiming Zhang[1,2,*]
[1]*Department of Anatomy and Neurobiology, Morris K. Udall Parkinson's Disease Research Center of Excellence,*
[2]*Magnetic Resonance Imaging and Spectroscopy Center, University of Kentucky Chandler Medical Center, Lexington,*
[3]*Department of Physiology, Key Laboratory for Neurodegenerative Disorders of the Ministry Education, Capital Medical University, Beijing*
[1,2]*USA*
[3]*PR of China*

1. Introduction

Parkinson's disease (PD) is a relentlessly progressive disorder causing disability in most individuals and cannot be controlled with available medication. PD is currently considered a systemic disease with complex motor disorders and non-motor deficits which appear before or in parallel with motor deficits and then worsen with disease progression (Chaudhuri *et al*., 2006; Ferrer *et al*., 2010). In a recent survey, the projected number of individuals with PD will dramatically increase in 20 years especially in the most populated countries like China, India, Brazil and the United States (Dorsey *et al*., 2007). Current causative theories for PD include complex interactions between genetic susceptibility and environmental factors. These and possibly other mechanisms lead to a progressive and variable degree of dopamine (DA) neuron loss in the substantia nigra compacta (SNc) resulting in DA depletion in the striatum (Hornykiewicz & Kish, 1987; Marsden & Obeso, 1994) that then leads to the clinical manifestation of PD. Studies have demonstrated that PD is characterized by a presymptomatic phase, likely lasting years, or even decades, during which neuronal degeneration is occurring but before clinical symptoms appear (Hubble, 2000; DeKosky & Marek, 2003; Katzenschlager & Lees, 2004). In addition, studies have demonstrated that most patients when diagnosed with PD have already lost a significant amount of SNc DA neurons in the range of 50% cell loss. Based on detailed pathological studies, Fearnley and Lees (1991) have proposed the notion that the loss of nigral neurons would occur exponentially, with greater loss occurring within the first decade in the disease process, and then reaching over 90% loss at the time of death.

While our understanding of PD has grown over the course of the last two centuries and PD is one of the best understood neurodegenerative diseases, our ability to treat PD remains limited. Given the progressive nature of the disease, the question becomes is it possible to divert or change the rate of the progression? Inherent to this question is our ability to identify where an individual is along the path of this disease. Thus it would behoove us to

be able to establish indicators of the disease stage while intervention remains a possibility. Here we describe the development of using non-invasive functional imaging as a biomarker for the early diagnosis of PD.

1.1 Difficulty of early detection of PD

The diagnosis and treatment of PD is fraught with problems: 1) so far, no objective measures are available for the diagnosis of PD (Wu *et al.*, 2011); 2) it is unknown whether a linear relationship exists between a worsening in the Unified Parkinson's Disease Rating Scale (UPDRS), or other clinical scales, and the progressive degeneration of the nigrostriatal system; 3) no objective measures are available for testing responsiveness of therapy. Therefore, biomarkers of disease progression before the appearance of symptoms would be of onsiderable value; thus, neuroimaging techniques may be good candidates for meeting the challenges. In the past decade, radiotracer imaging of the nigrostriatal dopaminergic system has been extensively explored with positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging protocols and has become a prominent biomarker in PD although these techniques are still controversial in some aspects such as the interpretation of imaging data and disconnection with clinical outcomes (Brooks *et al.*, 2003; Ravina *et al.*, 2005). However, the spatial resolution of these techniques is relatively poor, thus reducing their utility in mapping subtle changes in neuroanatomy and neurochemistry with PD progression (Snow *et al.*, 2000). Furthermore, PET imaging is not widely available and is expensive (~US$3,000-$6,000) because of the need to generate and use radioactive nucleotides onsite. Clearly there is a need for imaging techniques that do not require radioactive isotopes but ones that would still be sensitive enough to usefully and longitudinally monitor the development, progression, and treatment of PD. The ideal technique would 1) permit high-resolution imaging of brain sites affected by PD processes, 2) provide valid assessment of the underlying neuroanatomical state, and 3) be safe to allow repeated tests. A hypothesis for PD is that the disease severity corresponds to the magnitude and pattern of histological and neuroimaging abnormalities (DeKosky & Marek, 2003; Eckert & Eidelberg, 2004; Seibyl *et al.*, 2005). Based on our own previous studies, and those of others in rodents, nonhuman primates, and humans, pharmacological MRI (phMRI; or functional MRI with specific pharmacological stimulation) would be a good candidate because of its high resolution, sensitivity, reproducibility, wide availability, and low cost (Nguyen *et al.*, 2000; Tracey, 2001; Honey & Bullmore, 2004; Jenkins *et al.*, 2004; Chin *et al.*, 2008; Thiel, 2009; Rasmussen Jr, 2010).

1.2 Why is a new imaging protocol needed for PD?

In the past decade, PET and SPECT have become the most widely used and accepted imaging methods for PD research (de la Fuente-Fernandez & Stoessl, 2002; Eckert & Eidelberg, 2004). Worsening motor disability along with ^{18}F-dopa uptake decreases in the putamen (Brooks *et al.*, 1990) correlate with the storage of DA within vesicles (Hoshi *et al.*, 1993) and with the number of functioning DA terminals in the striatum (Snow *et al.*, 1993). Currently, *in vivo* measurements can be conducted using SPECT with ligands for the DA transporter (DAT) such as [$^{(123)}$I]N-omega-fluoropropyl-2beta-carbomethoxy-3beta-{4-iodophenyl}nortropane (FP-CIT) that provide a measure of DA terminal integrity (DeKosky & Marek, 2003; Andringa *et al.*, 2005). Although the aforementioned studies have shown that these neuroimaging techniques are capable of mapping changes in dopaminergic function in

the basal ganglia, much controversy still exists. Recent problems have been encountered in clinical trials that have used radioligand imaging to quantify medication response. For example, there appears to be a discrepancy between current imaging protocols and clinical outcomes. In National Institutes of Health (NIH) sponsored randomized double-blind studies on PD patients receiving either fetal tissue transplants or sham surgery, a 40% increase in ^{18}F-dopa uptake in the putamen contrasted with a modest (non-significant) 18% improvement in the mean UPDRS in one study involving 40 patients (Freed *et al.*, 2001). In the second study involving 34 patients, a 20-30% increase of ^{18}F-dopa uptake was seen in the striatum, but clinical changes failed to reach statistical significance (Brooks, 2004). Most recently, a significant increase was found in ^{18}F-dopa uptake in the putamen of PD patients receiving trophic therapy, while clinical improvements did not differ significantly from the control group (Lang *et al.*, 2006).

1.3 What are imaging biomarkers for PD?

In general, biomarkers must be biologically and clinically relevant, analytically sound, operationally practical, timely, interpretable and cost effective. On the other hand, biomarkers must be objectively measured indicators of biological and pathobiological process or pharmacologic responses to treatment. The biomarkers should be used to substitute for a clinical endpoint (predict benefit or harm) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence (Biomarkers definition working group, 2001). Specifically for PD, the biomarkers must be indicators of biological processes that change with the progression of the nigrostriatal system. The biomarkers should 1) correlate to some extents with severity of PD assessed by behavior and with pathophysiological changes such as the number of surviving neurons in the SNc; 2) reflect true disease status or predict clinical outcomes; 3) be used to assess efficacy and/or responsiveness of treatment, and 4) be used as surrogate endpoints.

1.4 What is BOLD-phMRI?

Our preliminary studies have shown evidence that blood-oxygenation-level-dependent (BOLD)-phMRI can be used as a non-invasive imaging modality to detect functional changes of the dopamine system in parkinsonian monkeys. More importantly, the studies were conducted in a conventional clinical MRI scanner without the injection of contrast agents. Using this imaging method, a significant correlation was found between the amphetamine-evoked BOLD response and the number of surviving dopamine neurons in the substantia nigra, which was also significantly correlated with bradykinesia scores on the nonhuman primate parkinsonian rating scale (Ovadia *et al.*, 1995), suggesting that phMRI may be used as a biomarker to assess dopamine neuronal loss in PD. Recently, fMRI has become a popular tool for imaging of functionally active brain regions in healthy and diseased brains. The use of fMRI is promoting the emergence of a new area of research, one that is complementary to more invasive techniques for measuring neural activity in animal models while better understanding the function and dysfunction of the human brain. The most common method of fMRI is the BOLD imaging technique. fMRI takes advantage of the coupling between neural activity and hemodynamics (the local control of blood flow and oxygenation) in the brain to allow the non-invasive localization and measurement of brain activity (Fig. 1).

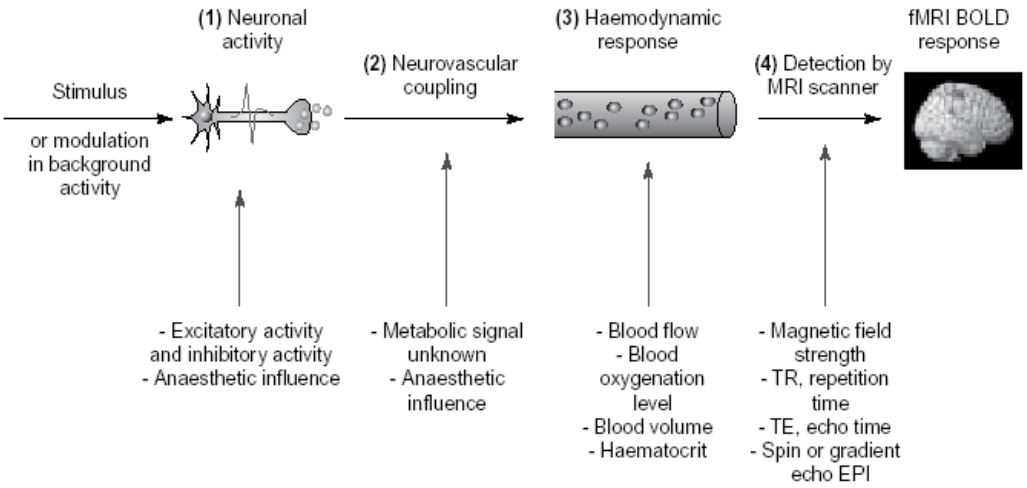


Fig. 1. fMRI provides an insight into neural activity. The BOLD signal has several constituents: (1) the neuronal response to a stimulus or background modulation; (2) the complex relationship between neuronal activity and triggering a haemodynamic response (termed neurovascular coupling); (3) the haemodynamic response itself; and (4) the detection of the response by an MRI scanner (from Arthurs & Boniface, 2002).

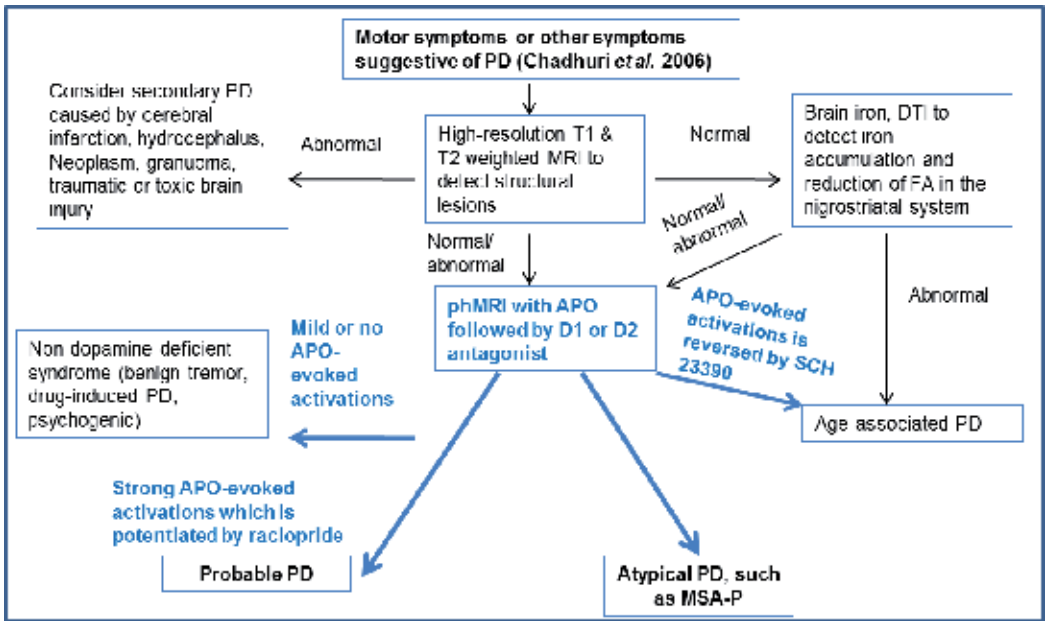


Fig. 2. Using phMRI for the early diagnosis of PD. As part of a multi-factor approach, phMRI provides a possible means of screening for the underlying neurological changes in parkinsonism or PD.

We hypothesize that the BOLD-fMRI response to a specific DA stimulation could serve as a potential biomarker for PD because of its unique features which are different from other neuroimaging technologies as follows: 1) High sensitivity and reproducibility, and relatively high specificity, 2) Minimal invasiveness or patient discomfort ("subject friendly"), 3) Low per-usage cost (this is especially important if widespread screening is contemplated), and 4) wide availability.

2. phMRI detects dopamine deficiency in parkinsonian monkeys

2.1 An animal model of dopamine deficiency in rhesus monkeys

A reliable and reproducible model of dopamine deficiency/a model simulating human PD is developed by unilateral administration of neurotoxin 1-methyl-4-phenyl-1,2,3,6-etrahydropyridine (MPTP) through the carotid artery. The specific neurotoxic actions of MPTP are produced when it is metabolized by monoamine oxidase B into 1-methyl-4-phenylpyridinium (MPP +), a complex I mitochondrial neurotoxin with relative specificity for dopamine neurons in the substantia nigra (Langston & Ballard, 1983; Nicklas *et al.*, 1987; Richardson *et al.*, 2007). Ding and colleagues (2008) described the key features modeled by MPTP toxicity including 1) all animals show parkinsonian features often seen in idiopathic PD such as bradykinesia, rigidity, postural, and balance instability, 2) these PD features can be partially normalized by levodopa treatment, which is the most efficacious drug to treat PD motor symptoms and is widely considered the "gold standard" treatment for the disease, 3) massive neuronal loss of dopaminergic neurons in the SNc and dopaminergic fibers in the striatum, and 4) remarkable declines in DA and DA metabolites.

2.2 phMRI procedures

1) Mapping of MPTP-induced functional changes with d-amphetamine stimulations (from a pre-synaptic perspective) and 2) Mapping of MPTP-induced functional changes with APO challenge (from a post-synaptic perspective). In early studies, the scans were conducted on a Siemens VISION 1.5 T MRI scanner using the body coil to transmit radio frequency and an 8 cm diameter surface coil placed above the monkey's head for RF signal reception. The anatomical structures of interest were visualized using a 3D FLASH sequence with 1 mm isotropic resolution (TR/TE=21/6 ms, flip angle = 30°, image matrix size = 128x128x90, field of view = 128 mm). The functional MR images from pharmacological challenges were acquired continuously using a FLASH 2D multiple gradient-recalled-echo (MGRE) navigator sequence (Chen *et al.*, 1996). The ROI dimensions were 3x3x3 mm, each representing a 27 mm^3 volume. ROIs were manually selected in both hemispheres of MPTP-lesioned and normal control animals based on the co-registered 3D anatomical images acquired from the FLASH sequence. Because of variability in the inherent noise level due to differences in positioning animals for each scan and the movements during scanning, the replicate scans were treated as independent observations in the analysis. For later studies, images were acquired on a Siemens 3T Trio clinical MRI system using a dedicated receive-only coil for reception, which was designed and developed by our group. The BOLD-effect weighted MR images used to measure the phMRI response were acquired in an anatomically coronal plane. The image planes of the acquisition were arranged to cover the motor cortex and the basal ganglia. A segmented gradient-echo EPI sequence with TE=28 ms and a turbo factor of 7 was used to reduce echo train length and minimize magnetic susceptibility-related artifacts. The EPI sequence acquisition parameters are FOV=112x98 mm and image matrix 64x56 for an in-plane resolution of 1.75 mm. A total of 15 contiguous

slices, each 2 mm-thick, were acquired at a rate of 15 s per EPI volume. The overall scan duration was 80 minutes with 128 volumes acquired prior to apomorphine (APO) administration as a baseline and 192 after APO to track the response. Images were motion corrected and spatially smoothed using a Gaussian kernel of width 3.5 mm. phMRI response was calculated as the fractional signal change in % of the average of the post-APO image data relative to the pre-APO baseline. A co-registered high-resolution (0.67×0.67×1 mm) T1-weighted anatomical MRI scan was acquired in each session for spatial localization of the activation response. Prior to the administration of d-amphetamine (2.0mg/kg) or APO (0.1 mg/kg), a total of 40 image frames were collected over 20 min to determine the baseline state. Following injection of d-amphetamine or APO, an additional 40 frames were collected to track the dynamic response (Zhang *et al.*, 2001; Andersen *et al.*, 2002). The change in R_2^*, i.e. ΔR_2^* which represents the phMRI activation response to drug, was determined as the difference between the mean R_2^* across 20 images post drug administration during the period of peak response (5-15 min) and the mean R_2^* within the 40 baseline images. A reduction ("negative" change) in R_2^* associated with a local decrease of paramagnetic deoxyhemoglobin is an indicator of BOLD-effect activation (Chen *et al.*, 1996).

2.3 phMRI-responses correlate with severity of PD

Six out of six animals responded positively to APO treatment represented by 44% improvements in parkinsonian symptoms. The same dose of APO also evoked phMRI responses by increasing the phMRI signal intensity. The typical phMRI (BOLD effect) responses to APO were gradually increased after APO administration only in the structure on the ipsilateral side receiving MPTP administration. Interestingly, but not surprising, APO-induced behavioral changes (PD features) were significantly correlated with APO-induced phMRI responses in the putamen, premotor cortex, and cingulate gyrus. When compared with standard but objective measures, there was a significant negative correlation between the phMRI responses in the putamen and distance travelled and movement speed. Similar relationships were also seen between phMRI responses in the motor cortex and daytime home-cage activity and between phMRI responses in the caudate nucleus and movement speed.

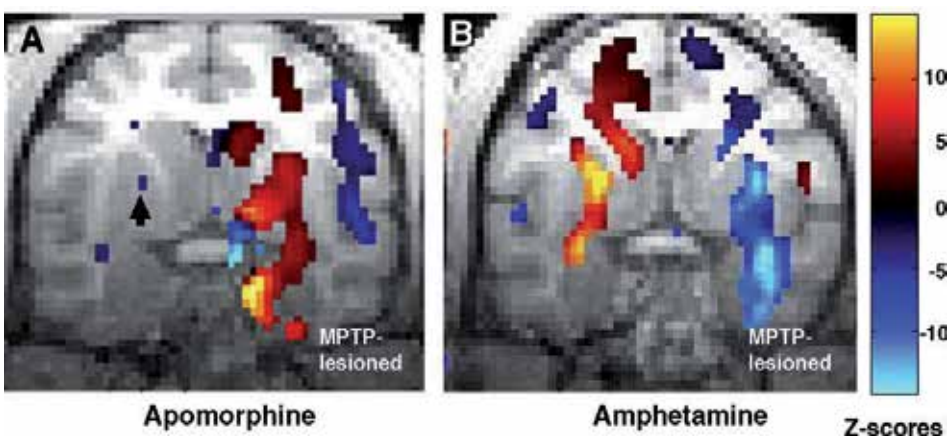


Fig. 3. phMRI reveals nigrostriatal system responsiveness to dopamine stimulation. Coronal MRI scans depicting areas of activation and deactivation (represented by the pseudocolor) in the brain after an APO or amphetamine challenge in unitalteral MPTP-lesioned nonhuman primates (from Zhang *et al.*, 2006).

2.4 phMRI-response and MPTP-induced dopamine deficiency

2.4.1 phMRI responses in MPTP-lesioned structures

Apomorphine administration strongly activated the MPTP-denervated putamen (Figs. 3A and 4C) and substantia nigra (Fig.4D). An opposite response (a positive ΔR_2* value) was evident in the contralateral putamen (Fig. 4G) and substantia nigra (Fig. 4H). The differences between the intact and lesioned substantia nigra and between the intact and lesioned putamen were highly significant, $P < 0.01$(*t*-test), in both cases. In contrast, ΔR_2* responses in the caudate nucleus and in the corpus callosum were not significant, nor were there significant hemispheric differences in activation or deactivation with the contralateral caudate or with a comparable region in the contralateral callosum (Figs. 4A and 4E).

The phMRI responses to amphetamine treatment in the putamen (Figs. 3B and 4G) and substantia nigra (Fig. 4H) were the inverse of those seen with apomorphine. Amphetamine-induced decreases (positive ΔR2* values) in the lesioned putamen and substantia nigra suggested diminished neuronal activity in both sites. In contrast, amphetamine induced the opposite ΔR2* response in the intact left side, tending to increase activation in the putamen and substantia nigra. The responses in the intact putamen and intact substantia nigra were significantly different from their lesioned counterparts. Again, the corpus callosum and the caudate nucleus displayed only small, insignificant changes in response to amphetamine stimulation (Figs. 4E and 4F).

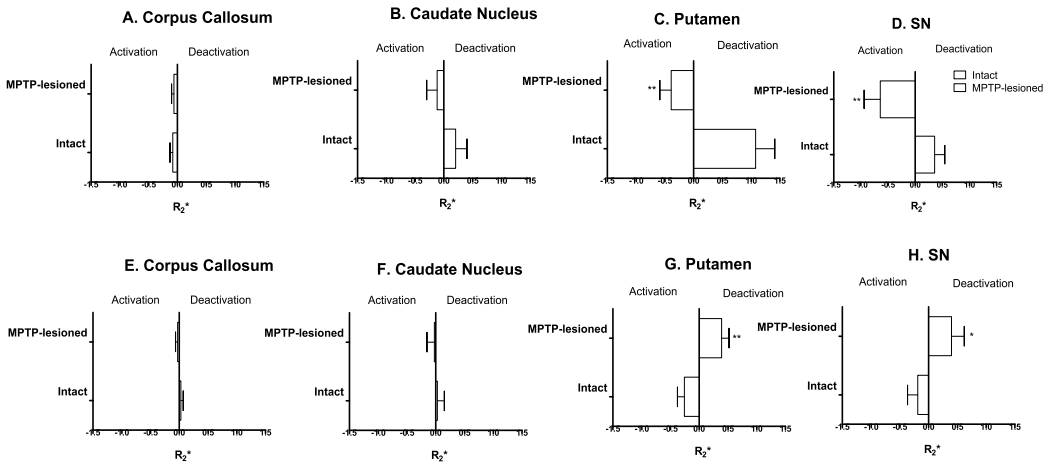


Fig. 4. phMRI responses in the nigrostriatal system. Depending on the means of stimulation, phMRI reveals a differential activations and deactivations in the nigrostriatal system. After APO stimulation (A-D) or *d*-amphetamine stimulation (E-H). ***P*<0.01; **P*<0.05; unpaired *t*-test (from Zhang *et al.*, 2006).

2.4.2 phMRI-responses and loss of DA neurons in the SN

In a later study, post-mortem histopathological evaluation revealed that the unilateral MPTP administration (received 5 years before the analysis) produced a massive (85%) loss of the rate-limiting enzyme for DA formation, tyrosine hydroxylase, (TH^+) cells in the midbrain on the ipsilateral side receiving the infusion of the neurotoxin. TH^+ cell numbers were significantly higher on the un-lesioned side compared to the MPTP-lesioned side. More importantly, the number of TH^+ cells was strongly correlated with the phMRI responses in

the caudate nucleus and in the cingulate gyrus. When comparing d-amphetamine-induced DA release in the putamen and DA neuron counts in the SNc, a significant correlation was also seen. In an earlier study (Zhang *et al*., 2006), amphetamine administration evoked a BOLD response in the SN that correlated with the number of TH^+ dopamine neurons in the same structure. These data support that there is a strong relationship between BOLD-responses to dopaminergic challenge and the number of dopaminergic neurons in the midbrain.

2.4.3 phMRI-responses and loss of DA fibers in the striatum

Similar to the effect on dopaminergic neurons, the MPTP administration also produced a remarkable reduction of TH^+ fibers on the ipsilateral side of the lesion. A comparison of the fiber density in the putamen on the MPTP-lesioned side with other elements of the cortico-basal ganglia-cortical circuit (Braak & Del Tredici, 2008) such as ipsilateral phMRI responses in the motor cortex (Fig. 5A) and caudate nucleus (Fig. 5B) showed strong correlations. In addition, the fiber density in the MPTP-lesioned caudate nucleus was strongly correlated with phMRI responses in the premotor cortex, caudate nucleus, and cingulate gyrus. Those changes in TH^+ fiber density were also correlated with behavior and DA levels in the striatum and with the number of DA neurons in the SNc.

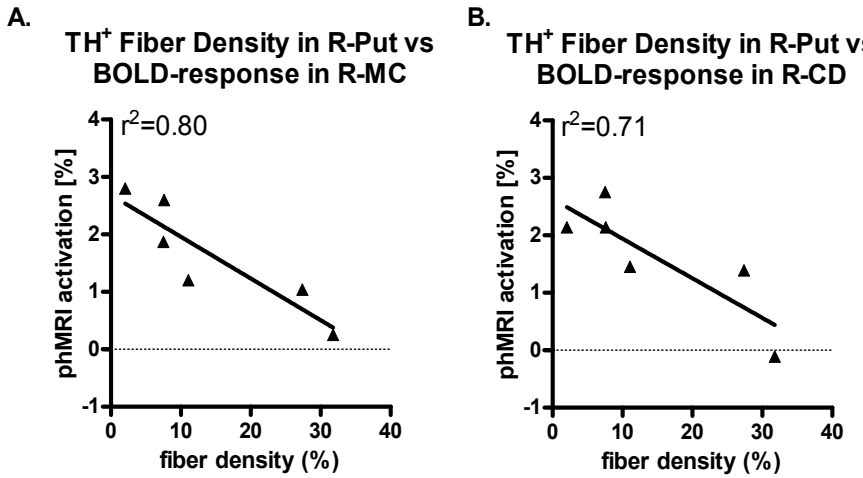


Fig. 5. Lower TH^+ fiber density in the ipsilesional putamen corresponds with higher phMRI activation. TH^+ fiber density in the right putamen (R-Put) is inversely correlated with phMRI activation in A) the right motor cortex (R-MC) and B) the right caudate nucleus (R-CD).

2.4.4 phMRI-responses correlate with dopamine overflow

The microdialysis experiments were conducted months after the parkinsonian symptoms had been fully developed and stabilized. First, the single administration of MPTP produced significant reduction in both potassium- and d-amphetamine-evoked overflow of DA in the putamen (Fig. 6A) and SNc (Fig.6B) on the ipsilateral side of the lesion. Second, there were several important correlations between DA levels in the putamen and SNc and the phMRI responses. For example, both potassium- and d-amphetamine-evoked overflow of DA in

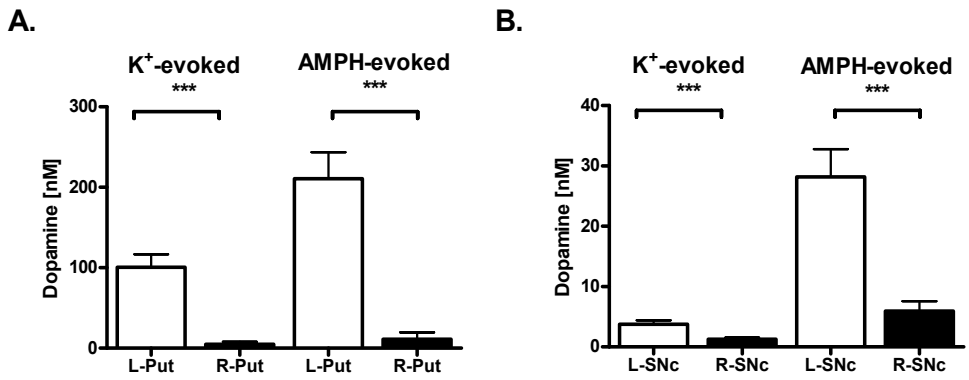


Fig. 6. Hemiparkinsonian nonhuman primates have markedly dimished dopaminergic function. K^+ (100 mM)- and amphetamine (250 μM)-evoked DA release was significantly attenuated in the ipsilesional A) putamen (Put) and B) SNc; ***: $P < 0.0001$ (paired *t*-test).

the putamen (each measured for a single time point, 30 minutes after stimulus administration) had significant correlations with phMRI responses in the putamen. DA levels in the putamen were also significantly correlated with phMRI responses in the premotor cortex and cingulate gyrus, as well as in the caudate nucleus. Finally, d-amphetamine-evoked DA release in the SNc was found to have a significant, but negatively correlated relationship with the motor cortex (Fig. 7).

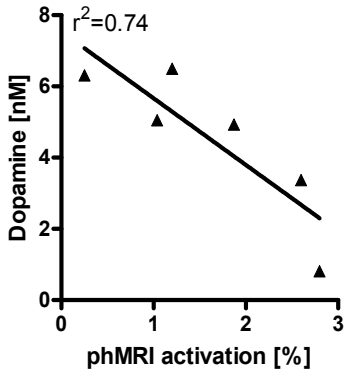


Fig. 7. DA levels in the right SNc correlate with the BOLD responses in the right motor cortex. In animals with lower DA levels in the right SNc, less activation was observed in the right motor cortex

3. Using phMRI to monitor therapeutic effects in parkinsonian monkeys

There is a great need for the development of noninvasive, highly sensitive, and widely available imaging methods which can potentially be used to longitudinally monitor treatment of PD. We reported the monitoring of glial-cell-line-derived neurotrophic factor (GDNF) induced functional changes of the basal ganglia in hemiparkinsonian monkeys via phMRI measuring the BOLD response to a direct dopamine agonist, APO, (Luan *et al.*, 2008). The effectiveness of GDNF to protect and restore the nigrostriatal dopaminergic system in rodent and nonhuman primate models of PD has been extensively documented (Beck *et al.*,

1995; Tomac *et al.*, 1995; Gash *et al.*, 1996; Kordower *et al.*, 2000; Grondin *et al.*, 2002). This trophic factor has also shown promise in Phase I clinical trials for the treatment of PD (Gill *et al.*, 2003; Slevin *et al.*, 2005). Ample evidence supports the idea that GDNF can protect and promote survival of pre-synaptic dopaminergic neurons in the SNc and axons in the striatum (Gash *et al.*, 1996). After testing BOLD responses to APO in their normal state, additional scans were taken with the same dose of APO stimulation after MPTP-induced hemiparkinsonism. Then, the animals were chronically treated with GDNF for 18 weeks by a programmable pump and catheter system. The catheter was surgically implanted into the right putamen and connected to the pump via flexible polyurethane tubing. phMRI scans were taken at both 6 and 18 weeks while they received 22.5μg of GDNF per day (Fig. 8). In addition, behavioral changes were monitored throughout the entire study. The primary finding of this study was that APO-evoked activations in the DA denervated putamen were attenuated by the chronic intraputamenal infusion of GDNF accompanied by improvements of parkinsonian features, movement speed and APO-induced rotation compared to data collected before the chronic GDNF treatment. The results suggest that phMRI methods in combination with administration of a selective DA agonist may be useful for monitoring neurorestorative therapies in PD patients in the future.

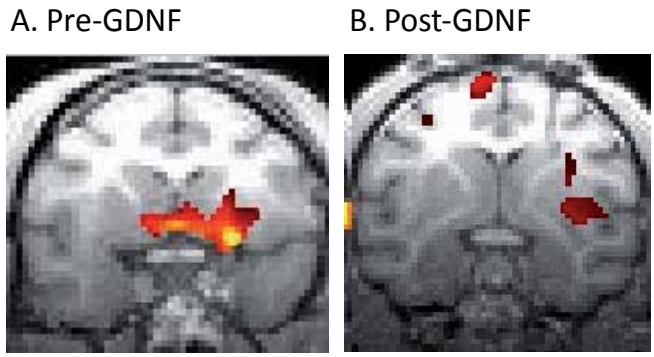


Fig. 8. phMRI (BOLD)-responses to APO can be used to monitor GDNF-induced neurorestorative therapeutic effects in rhesus monkeys with MPTP-induced hemiparkinsonisms. phMRI activation reveals differences in dopaminergic activity after GDNF treatment (from Luan *et al.*, 2008).

4. Brain iron and motor deficits in rhesus monkeys

Schuff (2009) notes in a recent review, perhaps the most consistently reported MRI findings in PD have been the detection of signal changes related to excessive iron, most likely related to ferritin, the main iron-storage protein within the brain. Under normal condition, iron is essential for normal metabolism and used in production of DA. Brain iron may also play an essential role in learning and memory (Fretham *et al.*, 2011). Several years ago, we reported a correlation of R_2 with total iron concentration in the brains of rhesus monkeys (Hardy *et al.*, 2005). The results show that the transverse relaxation rate $R_2 = 1/T_2$ is highly correlated to and varies linearly with iron content. In the study, Hardy and colleagues demonstrated that R_2 was highly correlated with the total iron concentration and that the relationship between R_2 and tissue iron concentration appeared to depend upon the iron concentration. In another multidiscipline study of brain iron in a large group of rhesus monkeys ranging in age from 4

to 32 years old, Cass and colleagues (2006) found significant decreases in motor performance, decreases in striatal DA release, and increases in striatal iron levels in rhesus monkeys as they aged from young adulthood. A comprehensive statistical analysis relating age, motor performance, DA release, and iron content indicated that the best predictor of decreases in motor ability, above and beyond levels of performance that could be explained by age alone, was iron accumulation in the striatum. Compared to the young animals, the relaxation rate $1/T_2^*$ used as an indicator of iron content was elevated by 38-43% in all three regions in the middle-aged monkeys (Fig. 9). In the aged animals, iron content was increased by 55%, 61%, and 79% in the caudate, putamen, and nigra, respectively, compared to the young animals (Fig. 9). Iron content in the nigra of the aged animals was also 30% higher than in the middle-aged animals. ROI data for $1/T_2$ measures are not shown but exhibited a similar dependence on age. Regression analysis extended the group statistics and further confirmed the strong age-associated increase of the MRI relaxation rate $1/T_2^*$ (equivalent to a T_2^*-shortening) in each of the three regions of interest ($n = 24$; $p<0.0001$). The intercept and rate of increase were 16.537+ 0.598 sec^{-1}/year, 15.728+0.734 sec^{-1}/year, and 19.047+0.791 sec^{-1}/year for the caudate, putamen, and substantia nigra, respectively. This suggests that striatal iron levels may be a biomarker of motor dysfunction in aging; and as such, can be monitored non-invasively by longitudinal brain MRI scans.

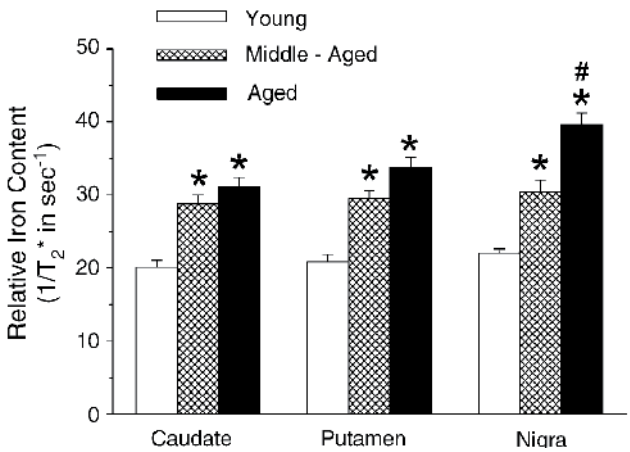


Fig. 9. Using MR imaging of iron content to identify alterations in the aging brain. The use of MR imaging to identify the relative iron content in particular brain structures illustrates the potential usefulness for a non-invasive means of assessing changes in the nigrostriatal system with aging. *: P <0.05; #: P <0.01 (one-way ANOVA). (from Cass *et al.*, 2006)

5. Diffusion Tensor Image (DTI) and dopamine deficiency in rhesus monkeys

Diffusion tensor imaging (DTI) has been increasingly used in PD related research (Schuff, 2009). DTI can be used to noninvasively investigate and identify white matter (WM) changes associated with PD. DTI is able to obtain quantitative information about fractional anisotropy (FA) and mean diffusivity (MD). A diminished FA is thought to reflect axonal loss and demyelination. A recent DTI study was conducted by our group in normal (n=9) and hemiparkinsonian (n=8) monkeys to explore the MPTP-effects on WM using the DTI parameters of FA and MD. Under general anesthesia, DTI data was obtained on a 3T Siemens

Trio MRI scanner with a custom-built, single channel, receive-only coil, built on a fiberglass frame and used to enhance the received signal. Imaging consisted of single shot (SS), double pulsed gradient spin echo (double-PGSE), diffusion weighted, echo planar imaging (EPI) with a spatial resolution of 1.23×1.23×2.0 mm^3. Images were processed and analyzed by using the publicly available image processing software FSL (http://www.fmrib.ox.ac.uk/fsl) (Smith *et al.*, 2004; Smith *et al.*, 2006). All of the processing tools referred to by their FSL acronyms are available for download at the website. First, we observed a WM tract in the vicinity of the basal ganglia (BG) with FA greater ($P<0.01$, *t*-test) in the aged-matched control animals than MPTP-treated animals in the same structure. Second, we observed multiple WM tracts in the sensory cortex, with FA greater ($P<0.05$, *t*-test) in the MPTP-treated than untreated side in the same animals. The result from the pilot study supports the idea that high resolution DTI has the potential to distinguish animals with a MPTP-lesioned nigrostriatal system from normal age-matched, healthy controls on an animal-by-animal basis.

6. Conclusion and perspectives

Since a diagnosis of PD still solely depends on the judgment of the clinician, there is an urgent demand for the development of reliable and applicable test systems or biomarkers to provide a level of certainty to the diagnosis. Objective biomarkers of PD are pivotal to tracking the disease progression and confirm the therapeutic effects. Non- or minimally-invasive imaging techniques provide a unique, real-time opportunity to assess the changes that occur with neurodegenerative diseases. In addition, with the rapidly expanding use of fMRI to provide a dramatically greater understanding of brain function, imaging techniques such as phMRI are only bound to benefit from this new wealth of knowledge.

The advantage of MRI is that MRIs are far more widely available than other imaging modalities and are most commonly used in clinical practice to differentiate idiopathic PD from secondary cause of parkinsonism (Pavese & Brooks, 2009). Recent advancement in high field MRI technology offers even better opportunities for noninvasively, longitudinally, and objectively assessing brain alterations in PD. For example functional and pharmacological MRI has been increasingly employed for preclinical and clinical research of the disease. Ample evidence supports that MRI signals have the potential to be developed as a noninvasive state biomarker in PD. For example, several MRI methodologies such as structural MRI, imaging of brain iron, DTI, functional MRI and pharmacological MRI have provided meaningful insight of brain alteration in PD. That said, we note that while we have gained greater understanding of the changes that occur in disorders of dopaminergic dysfunction with the use of phMRI in the rhesus model of PD, nevertheless the studies are works in progress and ones that still require cautious interpretation because conditions in patients with PD are more complex than in the animal model used in these studies.

In our hands, MRI studies conducted at the University of Kentucky have demonstrated that phMRI-responses to dopaminergic challenges in MPTP-treated monkeys are highly correlated with 1) the severity of parkinsonism, 2) the loss of dopamine neurons and terminals, 3) the decline of dopamine overflow and 4) the functional recovery from GDNF treatment. In addition, results from imaging brain iron suggest that striatal iron levels may constitute a biomarker for motor dysfunction in aged animals with parkinsonism. As shown in Fig. 10, combining various MRI methodologies may be used to screen populations at high risk, to differentiate idiopathic PD from second causes of parkinsonisms, and to monitor progression of the disease and the therapeutic effects.

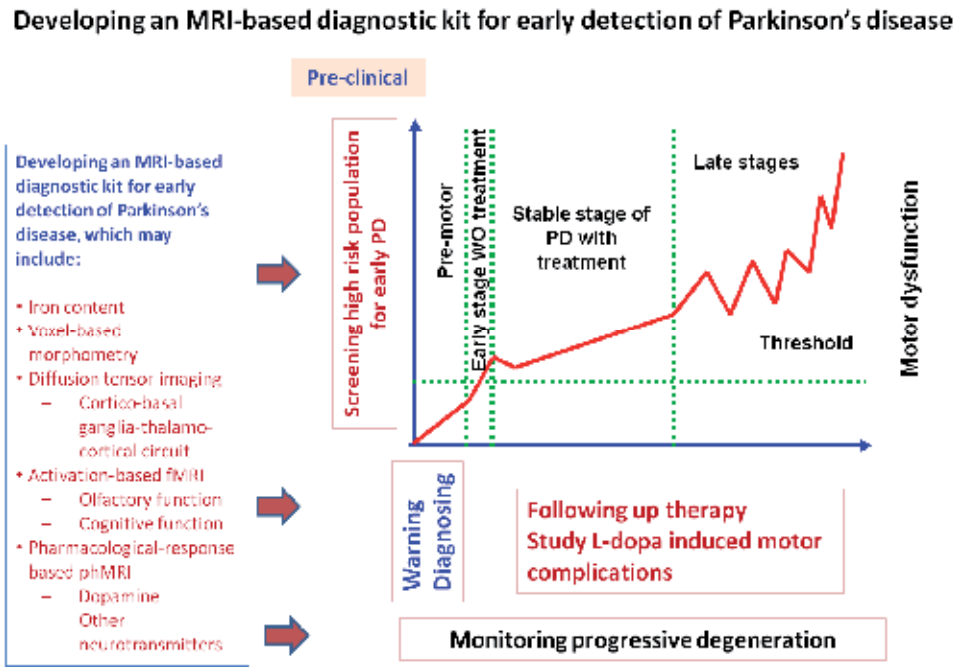


Fig. 10. Employing MRI methodologies in the clinic for PD.

7. Acknowledgment

We thank Drs. Anders Andersen, Peter Hardy, and Richard Grondin for their technical help in data analysis, behavioral evaluation, and discussions. Support provided by USPHS NIH grants NS50242, NS39787, and AG13494.

8. References

Andersen, A.H., Zhang, Z., Barber, T., Rayens, W.S., Zhang, J., Grondin, R., Hardy, P., Gerhardt, G.A. & Gash, D.M. (2002) Functional MRI studies in awake rhesus monkeys: methodological and analytical strategies. *J Neurosci Methods*, 118, 141-152.

Andringa, G., Drukarch, B., Bol, J.G., de Bruin, K., Sorman, K., Habraken, J.B. & Booij, J. (2005) Pinhole SPECT imaging of dopamine transporters correlates with dopamine transporter immunohistochemical analysis in the MPTP mouse model of Parkinson's disease. *Neuroimage*, 26, 1150-1158.

Arthurs, O.J. & Boniface, S. (2002) How well do we understand the neural origins of the fMRI BOLD signal? *Trends Neurosci*, 25, 27-31.

Beck, K.D., Valverde, J., Alexi, T., Poulsen, K., Moffat, B., Vandlen, R.A., Rosenthal, A. & Hefti, F. (1995) Mesencephalic dopaminergic neurons protected by GDNF from axotomy-induced degeneration in the adult brain. *Nature*, 373, 339-341.

Braak, H. & Del Tredici, K. (2008) Cortico-basal ganglia-cortical circuitry in Parkinson's disease reconsidered. *Exp Neurol*, 212, 226-229.

Brooks, D.J. (2004) Neuroimaging in Parkinson's disease. *NeuroRx*, 1, 243-254.

Brooks, D.J., Frey, K.A., Marek, K.L., Oakes, D., Paty, D., Prentice, R., Shults, C.W. & Stoessl, A.J. (2003) Assessment of neuroimaging techniques as

biomarkers of the progression of Parkinson's disease. *Exp Neurol*, 184 Suppl 1, S68-79.

Brooks, D.J., Ibanez, V., Sawle, G.V., Quinn, N., Lees, A.J., Mathias, C.J., Bannister, R., Marsden, C.D. & Frackowiak, R.S. (1990) Differing patterns of striatal 18F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Ann Neurol*, 28, 547-555.

Cass, W.A., Grondin, R., Andersen, A.H., Zhang, Z., Hardy, P.A., Hussey-Andersen, L.K., Rayens, W.S., Gerhardt, G.A. & Gash, D.M. (2006) Iron accumulation in the striatum predicts aging-related decline in motor function in rhesus monkeys. *Neurobiol.Aging*.

Chaudhuri, K.R., Healy, D.G. & Schapira, A.H.V. (2006) Non-motor symptoms of Parkinson's disease: diagnosis and management. *The Lancet Neurology*, 5, 235-245.

Chen, Q., Andersen, A.H., Zhang, Z., Ovadia, A., Gash, D.M. & Avison, M.J. (1996) Mapping drug-induced changes in cerebral R2* by Multiple Gradient Recalled Echo functional MRI. *Magn Reson Imaging*, 14, 469-476.

Chin, C.L., Tovcimak, A.E., Hradil, V.P., Seifert, T.R., Hollingsworth, P.R., Chandran, P., Zhu, C.Z., Gauvin, D., Pai, M., Wetter, J., Hsieh, G.C., Honore, P., Frost, J.M., Dart, M.J., Meyer, M.D., Yao, B.B., Cox, B.F. & Fox, G.B. (2008) Differential effects of cannabinoid receptor agonists on regional brain activity using pharmacological MRI. *British Journal of Pharmacology*, 153, 367-379.

de la Fuente-Fernandez, R. & Stoessl, A.J. (2002) Parkinson's disease: imaging update. *Curr Opin Neurol*, 15, 477-482.

DeKosky, S.T. & Marek, K. (2003) Looking backward to move forward: early detection of neurodegenerative disorders. *Science*, 302, 830-834.

Ding, F., Luan, L., Ai, Y., Walton, A., Gerhardt, G.A., Gash, D.M., Grondin, R. & Zhang, Z. (2008) Development of a stable, early stage unilateral model of Parkinson's disease in middle-aged rhesus monkeys. *Exp Neurol*, 212, 431-439.

Dorsey, E.R., Constantinescu, R., Thompson, J.P., Biglan, K.M., Holloway, R.G., Kieburtz, K., Marshall, F.J., Ravina, B.M., Schifitto, G., Siderowf, A. & Tanner, C.M. (2007) Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*, 68, 384-386.

Eckert, T. & Eidelberg, D. (2004) The role of functional neuroimaging in the differential diagnosis of idiopathic Parkinson's disease and multiple system atrophy. *Clin Auton Res*, 14, 84-91.

Fearnley, J.M. & Lees, A.J. (1991) Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain*, 114 (Pt 5), 2283-2301.

Ferrer, I., Martinez, A., Blanco, R., Dalfó, E. & Carmona, M. (2010) Neuropathology of sporadic Parkinson disease before the appearance of parkinsonism: preclinical Parkinson disease. *Journal of Neural Transmission*, 1-19.

Freed, C.R., Greene, P.E., Breeze, R.E., Tsai, W.Y., DuMouchel, W., Kao, R., Dillon, S., Winfield, H., Culver, S., Trojanowski, J.Q., Eidelberg, D. & Fahn, S. (2001) Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med*, 344, 710-719.

Fretham, S.J.B., Carlson, E.S. & Georgieff, M.K. (2011) The Role of Iron in Learning and Memory. *Advances in Nutrition: An International Review Journal*, 2, 112-121.

Gash, D.M., Zhang, Z., Ovadia, A., Cass, W.A., Yi, A., Simmerman, L., Russell, D., Martin, D., Lapchak, P.A., Collins, F., Hoffer, B.J. & Gerhardt, G.A. (1996) Functional recovery in parkinsonian monkeys treated with GDNF. *Nature*, 380, 252-255.

Gill, S.S., Patel, N.K., Hotton, G.R., O'Sullivan, K., McCarter, R., Bunnage, M., Brooks, D.J., Svendsen, C.N. & Heywood, P. (2003) Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. *Nat Med*, 9, 589-595.

Grondin, R., Zhang, Z., Yi, A., Cass, W.A., Maswood, N., Andersen, A.H., Elsberry, D.D., Klein, M.C., Gerhardt, G.A. & Gash, D.M. (2002) Chronic, controlled GDNF infusion promotes structural and functional recovery in advanced parkinsonian monkeys. *Brain*, 125, 2191-2201.

Group, B.D.W. (2001) Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework*. *Clin Pharmacol Ther*, 69, 89-95.

Hardy, P.A., Gash, D., Yokel, R., Andersen, A., Ai, Y. & Zhang, Z. (2005) Correlation of R2 with total iron concentration in the brains of rhesus monkeys. *J Magn Reson Imaging*, 21, 118-127.

Honey, G. & Bullmore, E. (2004) Human pharmacological MRI. *Trends Pharmacol Sci*, 25, 366-374.

Hornykiewicz, O. & Kish, S.J. (1987) Biochemical pathophysiology of Parkinson's disease. *Adv Neurol*, 45, 19-34.

Hoshi, H., Kuwabara, H., Leger, G., Cumming, P., Guttman, M. & Gjedde, A. (1993) 6-[18F]fluoro-L-dopa metabolism in living human brain: a comparison of six analytical methods. *J Cereb Blood Flow Metab*, 13, 57-69.

Hubble, J.P. (2000) Pre-clinical studies of pramipexole: clinical relevance. *Eur J Neurol*, 7 Suppl 1, 15-20.

Jenkins, B.G., Sanchez-Pernaute, R., Brownell, A.L., Chen, Y.C. & Isacson, O. (2004) Mapping dopamine function in primates using pharmacologic magnetic resonance imaging. *J Neurosci*, 24, 9553-9560.

Katzenschlager, R. & Lees, A.J. (2004) Olfaction and Parkinson's syndromes: its role in differential diagnosis. *Curr Opin Neurol*, 17, 417-423.

Kordower, J.H., Emborg, M.E., Bloch, J., Ma, S.Y., Chu, Y., Leventhal, L., McBride, J., Chen, E.Y., Palfi, S., Roitberg, B.Z., Brown, W.D., Holden, J.E., Pyzalski, R., Taylor, M.D., Carvey, P., Ling, Z., Trono, D., Hantraye, P., Deglon, N. & Aebischer, P. (2000) Neurodegeneration prevented by lentiviral vector delivery of GDNF in primate models of Parkinson's disease. *Science*, 290, 767-773.

Lang, A.E., Gill, S., Patel, N.K., Lozano, A., Nutt, J.G., Penn, R., Brooks, D.J., Hotton, G., Moro, E., Heywood, P., Brodsky, M.A., Burchiel, K., Kelly, P., Dalvi, A., Scott, B., Stacy, M., Turner, D., Wooten, V.G., Elias, W.J., Laws, E.R., Dhawan, V., Stoessl, A.J., Matcham, J., Coffey, R.J. & Traub, M. (2006) Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. *Ann Neurol*, 59, 459-466.

Langston, J.W. & Ballard, P.A., Jr. (1983) Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *N Engl J Med*, 309, 310.

Luan, L., Ding, F., Ai, Y., Andersen, A., Hardy, P., Forman, E., Gerhardt, G.A., Gash, D.M., Grondin, R. & Zhang, Z. (2008) Pharmacological MRI (phMRI) monitoring of treatment in hemiparkinsonian rhesus monkeys. *Cell Transplant*, 17, 417-425.

Marsden, C.D. & Obeso, J.A. (1994) The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain*, 117 (Pt 4), 877-897.

Nguyen, T.V., Brownell, A.L., Iris Chen, Y.C., Livni, E., Coyle, J.T., Rosen, B.R., Cavagna, F. & Jenkins, B.G. (2000) Detection of the effects of dopamine receptor supersensitivity using pharmacological MRI and correlations with PET. *Synapse*, 36, 57-65.

Nicklas, W.J., Youngster, S.K., Kindt, M.V. & Heikkila, R.E. (1987) MPTP, MPP+ and mitochondrial function. *Life Sci*, 40, 721-729.

Ovadia, A., Zhang, Z. & Gash, D.M. (1995) Increased susceptibility to MPTP toxicity in middle-aged rhesus monkeys. *Neurobiol Aging*, 16, 931-937.

Pavese, N. & Brooks, D.J. (2009) Imaging neurodegeneration in Parkinson's disease. *Biochim Biophys Acta*, 1792, 722-729.

Rasmussen Jr, I. (2010) Psychopharmacological MRI. *Acta Neuropsychiatrica*, 22, 38-39.

Ravina, B., Eidelberg, D., Ahlskog, J.E., Albin, R.L., Brooks, D.J., Carbon, M., Dhawan, V., Feigin, A., Fahn, S., Guttman, M., Gwinn-Hardy, K., McFarland, H., Innis, R., Katz, R.G., Kieburtz, K., Kish, S.J., Lange, N., Langston, J.W., Marek, K., Morin, L., Moy, C., Murphy, D., Oertel, W.H., Oliver, G., Palesch, Y., Powers, W., Seibyl, J., Sethi, K.D., Shults, C.W., Sheehy, P., Stoessl, A.J. & Holloway, R. (2005) The role of radiotracer imaging in Parkinson disease. *Neurology*, 64, 208-215.

Richardson, J.R., Caudle, W.M., Guillot, T.S., Watson, J.L., Nakamaru-Ogiso, E., Seo, B.B., Sherer, T.B., Greenamyre, J.T., Yagi, T., Matsuno-Yagi, A. & Miller, G.W. (2007) Obligatory role for complex I inhibition in the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Toxicol Sci*, 95, 196-204.

Schuff, N. (2009) Potential role of high-field MRI for studies in Parkinson's disease. *Mov Disord*, 24 Suppl 2, S684-690.

Seibyl, J., Jennings, D., Tabamo, R. & Marek, K. (2005) The role of neuroimaging in the early diagnosis and evaluation of Parkinson's disease. *Minerva Med*, 96, 353-364.

Slevin, J.T., Gerhardt, G.A., Smith, C.D., Gash, D.M., Kryscio, R. & Young, B. (2005) Improvement of bilateral motor functions in patients with Parkinson disease through the unilateral intraputaminal infusion of glial cell line-derived neurotrophic factor. *J Neurosurg.*, 102, 216-222.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M. & Behrens, T.E. (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*, 31, 1487-1505.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M. & Matthews, P.M. (2004) Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, 23 Suppl 1, S208-219.

Snow, B.J., Tooyama, I., McGeer, E.G., Yamada, T., Calne, D.B., Takahashi, H. & Kimura, H. (1993) Human positron emission tomographic [18F]fluorodopa studies correlate with dopamine cell counts and levels. *Ann Neurol*, 34, 324-330.

Snow, B.J., Vingerhoets, F.J., Langston, J.W., Tetrud, J.W., Sossi, V. & Calne, D.B. (2000) Pattern of dopaminergic loss in the striatum of humans with MPTP induced parkinsonism. *J Neurol Neurosurg Psychiatry*, 68, 313-316.

Thiel, C.M. (2009) Neuropharmacological fMRI. *Neuropharmakologisches fMRT*, 40, 233-238.

Tomac, A., Lindqvist, E., Lin, L.F., Ogren, S.O., Young, D., Hoffer, B.J. & Olson, L. (1995) Protection and repair of the nigrostriatal dopaminergic system by GDNF in vivo. *Nature*, 373, 335-339.

Tracey, I. (2001) Prospects for human pharmacological functional magnetic resonance imaging (phMRI). *J Clin Pharmacol*, Suppl, 21S-28S.

Wu, Y., Le, W. & Jankovic, J. (2011) Preclinical Biomarkers of Parkinson Disease. *Arch Neurol*, 68, 22-30.

Zhang, Z., Andersen, A., Grondin, R., Barber, T., Avison, R., Gerhardt, G. & Gash, D. (2001) Pharmacological MRI mapping of age-associated changes in basal ganglia circuitry of awake rhesus monkeys. *Neuroimage*, 14, 1159-1167.

Zhang, Z., Andersen, A.H., Ai, Y., Loveland, A., Hardy, P.A., Gerhardt, G.A. & Gash, D.M. (2006) Assessing nigrostriatal dysfunctions by pharmacological MRI in parkinsonian rhesus macaques. *Neuroimage*, 33, 636-643.

6

Neuroimaging in Manganese-Induced Parkinsonism

Yangho Kim
Department of Occupational and Environmental Medicine,
Ulsan University Hospital, University of Ulsan College of Medicine,
Ulsan,
Korea

1. Introduction

Over the last 20 years, the impact of imaging on the clinical sciences has been immense. Tremendous progress has been made in medical imaging of the human body since the invention of computed tomography (CT) and magnetic resonance imaging (MRI). Neuroimaging of patients with metal neurotoxicity can be divided into two types: morphological neuroimaging (anatomy-based imaging) including CT and MRI; and functional neuroimaging (physiology-based imaging) such as magnetic resonance spectroscopy (MRS), single-photon emission computed tomography (SPECT), positron emission tomography (PET), diffusion tensor imaging (DTI), and functional MRI (fMRI). Neuroimaging is undergoing a shift from morphological to functional imaging as new technologies are introduced and technical problems associated with the local production of radioisotopes are solved (Lang, 2000; Walker et al., 2004). MRI, PET, and SPECT have been used for 10 years or more to evaluate workers exposed to manganese (Mn), and to examine the neurological consequences of such exposure. Very recently, functional neuroimaging modalities such as fMRI, MRS, and DTI have been applied to this end.
The objectives of this chapter are (1) to review the use of neuroimaging in Mn-induced parkinsonism, and (2) to discuss recent developments in the functional neuroimaging in Mn-induced parkinsonism.

2. The pallidal MRI T1-signal reflects the target organ dose of Mn exposure

The Mn ion (Mn^{2+}) has five unpaired electrons in the 3d orbital, which results in a large magnetic moment, resulting in the shortening of proton T1-relaxation time and an increased signal intensity on T1-weighted MRI. Because of this paramagnetic quality of Mn^{2+}, a bilateral symmetrical increase in signal intensity, mainly confined to the globus pallidus and midbrain, can be observed on T1-weighted MRI, but with no concomitant alteration on the T2-weighted image (Kim et al., 1999a) (Fig. 1).
However, Mn-induced high signals on T1-weighted MRI do not correspond to any abnormal findings on brain CT (Park et al., 2003). The characteristic high signal caused by Mn can be differentiated from signals that increase in intensity for other reasons. Thus, high signals from fat, hemoglobin breakdown products, melanomas, neurofibromatosis, and

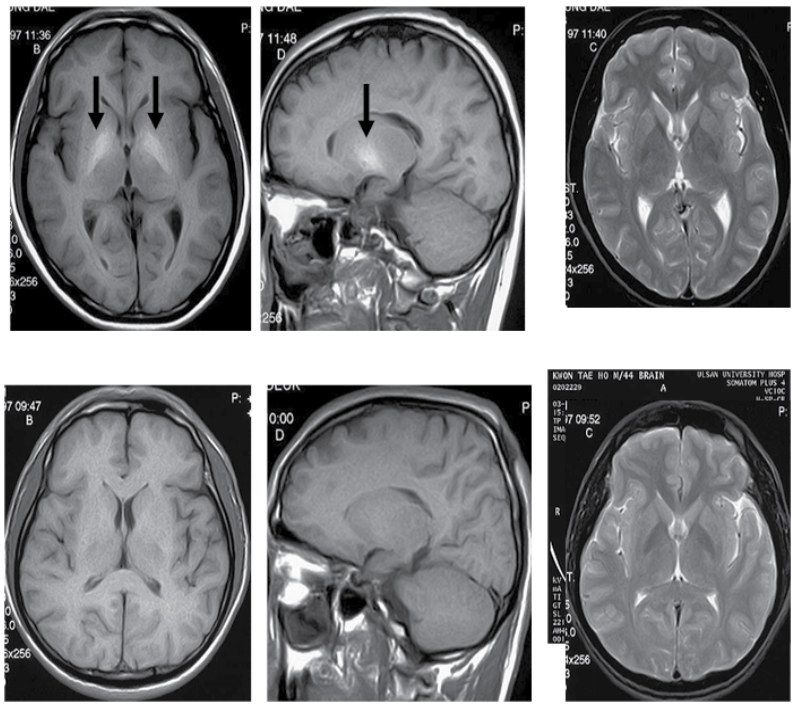


Fig. 1. T1-weighted MRI scans with or without increased signal intensities. Axial and sagittal sections show increase in signal intensities mainly confined to the globus pallidus, but with no concomitant alteration on T2-weighted image in workers exposed to manganese (Mn) in the upper row. In the lower row, worker without Mn exposure does not show increased signal intensities (Arrow indicates high signal. Left and middle column: T1-weighted image; right column: T2-weighted image.

calcification, can be seen on T1-weighted images. High signals from hemoglobin breakdown products, melanomas, and neurofibromatosis can be differentiated from Mn-induced high signals on the basis of signal site and symmetry. Iron deposits cause a greater shortening of the T2-relaxation time than the T1-relaxation time, resulting in low signal intensity upon T2-weighted imaging, distinct from that of an Mn deposit. Calcification can be easily identified by CT (Ahn et al., 2003). Krieger et al. (1995) coined the term ''pallidus index'' (PI) to quantify Mn accumulation in the globus pallidus, defined as the ratio of the signal intensity in the globus pallidus to that in the subcortical frontal white matter (WM) in axial T1-weighted MRI planes, multiplied by 100. An increase in signal upon T1-weighted imaging was observed during experimental Mn poisoning of non-human primates (Erikson et al., 1992; Newland et al., 1989). Nelson et al. (1993) were the first to report increased signal intensities in a patient with occupational Mn neurointoxication. A similar MRI pattern has also been observed in patients receiving total parenteral nutrition (TPN) by direct intravenous administration (Ejima et al., 1992; Mirowitz et al., 1991) and in patients with portal systemic shunts such as individuals with liver cirrhosis, leading to an inability to clear Mn via biliary excretion (Butterworth et al., 1995; Hauser et al., 1994, 1996; Krieger et al., 1995; Park et al., 2003; Spahr et al., 1996). A high pallidal signal is very frequently observed in patients with established liver cirrhosis, but who lack exposure to Mn (Park et

al., 2003). Mn-induced high signals can occasionally be observed in patients with severe iron-deficiency anemia (Kim et al., 2005). Kim et al. (1999a) showed, for the first time, that the characteristic high T1 signals were also frequently observed in asymptomatic workers exposed to Mn. The cited authors found a high prevalence (41.6%) of increased MRI signals in Mn-exposed workers, and, interestingly, 73.5% of welders showed increased signal intensities compared to none of the non-exposed clerical workers in the same factories. The cited authors found that the increased signal intensities resolved significantly approximately 1 year after Mn exposure ceased (Kim et al., 1999b). The disappearance of high signal abnormalities on MRI following withdrawal of the Mn source has been shown after the cessation of occupational exposure (Nelson et al., 1993), after discontinuation of TPN (Mirowitz et al., 1991), and after liver transplantation in patients with hepatic failure (Choi et al., 2005; Pujol et al., 1993). These findings suggest that increased signal intensities on a T1-weighted image reflect exposure to Mn, but do not necessarily indicate the presence of manganism. This is very important when the similarities and differences between idiopathic Parkinson's disease (IPD) and manganism are considered. Many reports have shown that blood Mn concentration is highly correlated with PI in liver cirrhotics (Hauser et al., 1996; Krieger et al., 1995; Spahr et al., 1996). In Mn-exposed workers, blood Mn concentration was also found to correlate with PI (Chang et al., 2009a; Dietz et al., 1999; Jiang et al., 2007; Kim et al., 1999a).

A recent study showed that PI was significantly associated with digit symbol test results, digit span backward ratings, scores on the Stroop Word and Stroop Error indices, and Grooved Pegboard (dominant hand) data (Chang et al., 2009a). This means that PI is a good predictor of neurobehavioral performance in welders without clinical manganism. In particular, PI was a better predictor of neurobehavioral performance than was blood Mn levels in such welders.

Taken together, the data suggest that PI on MRI may reflect a target organ dose of occupational Mn exposure (Kim, 2006). In addition, Mn in brain has a longer half-life than in blood (Lucchini and Kim, 2009). Thus, PI reflects the cumulative dose better than does blood Mn level. However, the level of signal intensity indicating progression to manganism from Mn exposure remains to be determined. The development of an animal model of manganism would assist in this regard, but the fact that the routes of exposure in humans differ, and that data on non-human species may not be transferable to human situations, are limiting factors. Hence, a prospective study correlating increases in T1 signal intensities with clinical and neuropsychological findings in Mn-exposed workers is needed.

3. PET/SPECT as an index of the integrity of the dopaminergic nigrostriatal pathway

The dopaminergic nigrostriatal pathway is the primary focus of neurodegeneration in IPD (Brooks et al., 1990; Morrish et al., 1995, 1996). In IPD, dopamine uptake is reduced in the striatum, particularly the posterior putamen. This finding is in accord with the 40-60% loss of dopaminergic cells seen in the nigrostriatal pathway of patients with IPD. In non-human primates and humans intoxicated with Mn, [^{18}F]-dopa (fluorodopa) PET scans are normal (Erikson et al., 1992; Kim et al., 1998; Shinotoh et al., 1995, 1997; Wolters et al., 1989). This supports the view that, in instances of Mn intoxication, the nigrostriatal pathway is relatively well preserved, consistent with many pathological observations showing that Mn-

induced damage occurs primarily in pathways postsynaptic to the nigrostriatal system. Dopamine transporter (DAT) imaging using (1r)-2b-carboxymethoxy-3b-(4-iodophenyl)tropane (β-CIT), employed as a SPECT ligand, reveals the density of DAT, and therefore explores the integrity of the nigrostriatal dopaminergic system. DAT is a protein located in the presynaptic nerve terminals of this system. β-CIT binds to DAT with high affinity and a low level of nonspecificity (Laruelle et al., 1993). In IPD, [^{123}I]-β-CIT SPECT reveals that specific striatal β-CIT uptake is reduced (Seibyl et al., 1995). Earlier data showed that this method can distinguish IPD patients from normal controls (Jeon et al., 1998a, 1998b). Further, striatal DAT uptake is nearly normal in patients with Mn-induced parkinsonism, but is markedly reduced in IPD patients (Huang et al., 2003). Various ligands that bind to DAT, such as [^{123}I]-β-CIT, [^{123}I]-fluoropropyl-CIT, and [^{99m}Tc]-TRODAT-1 have been used in SPECT studies (Huang et al., 2003; Kim et al., 2002). DAT SPECT is more easily accessible and less expensive than is fluorodopa PET. Fluorodopa and DAT uptake values are (nearly) normal in patients with manganism (Huang et al., 2003; Kim et al., 1998; Shinotoh et al., 1997; Wolters et al., 1989), whereas uptake is markedly reduced in IPD patients. However, Guilarte et al. (2008) reported that, in the non-human primate brain, chronic Mn exposure inhibited dopaminergic transmission, leading to motor deficits, in the absence of changes to presynaptic dopaminergic nerve terminals.

Racette et al. (2005) found relatively symmetrical and severely reduced fluorodopa uptake on PET in the posterior putamen of a patient with manganism secondary to liver failure, together with T1 hyperintensities in the basal ganglia on MRI. This is the only reported case of secondary manganism accompanied by abnormal fluorodopa PET findings. However, SPECT data from our secondary manganism patients (Kim et al., 2010) revealed two different patterns of clinical and neuroradiological features. Four of five patients showed atypical parkinsonism, with normal DAT density, which could be clearly differentiated from PD, whereas one patient showed levodopa-responsive parkinsonism with reduced DAT density (classical PD). These findings are remarkably different from those of Racette et al. (2005). PET/SPECT findings in patients with manganism caused by liver failure should be further studied, with respect to both clinical and pathological features. Further, the pathogenesis, clinical characteristics, and neuroimaging might differ between patients with primary and secondary manganism. Liver cirrhosis might confound the symptoms and accelerate the signs of parkinsonism. It is unclear whether secondary manganism caused by liver cirrhosis, for example, differs (from a neuroimaging standpoint) from manganism associated with occupational or environmental exposure to Mn.

Some welders showed clinical features and PET/SPECT findings typical of IPD, with concurrent Mn exposure (Kim et al., 1999b, 2002; Racette et al., 2001). Initially, Kim et al. (1999b) reported that one welder showed IPD with incidental exposure to Mn. However, they subsequently developed the hypothesis that Mn might have been a risk factor for development of IPD, although they could not exclude the possibility that the patient simply suffered from IPD, with coincidental exposure to Mn (Kim et al., 2002). Racette et al. (2001) suggested that welding might be a possible risk factor for development of early-onset IPD. However, it remains unclear whether Mn causes or accelerates IPD. The link between Mn exposure and an increased risk of IPD should be further examined in clinical, pathological, and epidemiological studies focusing on PET/SPECT findings.

Neuroimaging modalities such as MRI and PET/SPECT may be useful for the differential diagnosis of parkinsonism (Calne et al., 1994; Kim, 2006) (Fig. 2).

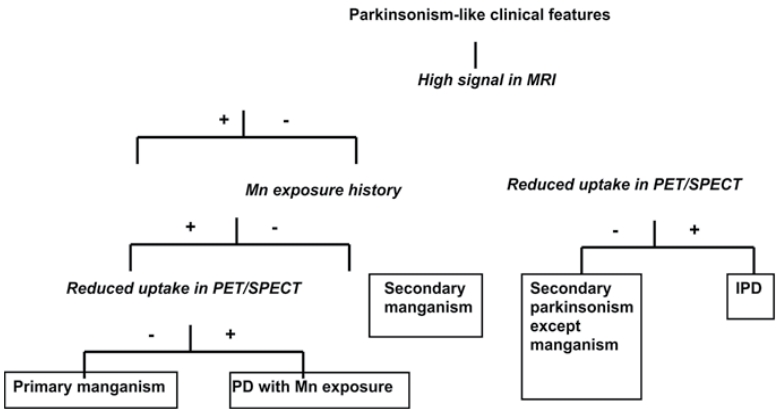


Fig. 2. Differential diagnosis of manganism from parkinson's disease (Kim, 2006)

When a patient exhibits parkinsonian features, MRI is recommended. Observation of bilateral symmetrical increases in signal intensities, mainly confined to the globus pallidus on T1-weighted MRI, in a patient confirms recent CNS exposure to Mn. It should be noted that a negative MRI signal can occur when worker exposure to Mn ceased more than 6–12 months prior to testing. When a patient with a high T1 signal and an Mn exposure history also shows normal uptake by PET/SPECT, primary manganism should be highly suspected. If a patient who has a high T1 signal and an Mn exposure history also shows reduced uptake upon PET/SPECT, the patient should be categorized as suffering from IPD with coincidental Mn exposure. When a patient yielding a high T1 signal upon MRI does not have an Mn exposure history, but shows normal uptake upon PET/SPECT, he/she may be diagnosed with secondary manganism attributable to liver cirrhosis or TPN. If a patient without a high T1 signal shows reduced uptake on PET/SPECT, he/she could possibly have IPD. When a patient without a high T1 signal on MRI shows normal uptake on PET/SPECT, he/she would be under suspicion of a form of secondary parkinsonism other than manganism (Kim 2006). However, neuroimaging should be combined with clinical evaluation for the differential diagnosis of parkinsonism (Ravina et al., 2005).

4. Recent developments in functional neuroimaging in Mn-induced parkinsonism

4.1 MRS

In vivo proton magnetic resonance spectroscopy ([^{1}H]-MRS) is an image-guided, noninvasive method for monitoring of neurochemical metabolites in the brain (Rosen and Lenkinski, 2007). Currently, [^{1}H]-MRS is the biomedical technique that is most commonly employed to obtain metabolic information to aid in the diagnosis of many neurological diseases, and also allows disease progression to be followed and response to treatment to be evaluated (Ross et al., 2006). Although MRS permits noninvasive, in vivo measurement of brain metabolites, only a few MRS investigations have been performed to date in efforts to assess the neurological effects of heavy metals in the environmental or occupational health. Recently, a few reports have analyzed the impact of lead exposure on brain metabolism in vivo in adults and children (Meng et al., 2005; Trope et al., 2001; Weisskopf, 2007; Weisskopf et al., 2007). However, little is known about the effects of chronic Mn exposure on brain metabolites in vivo. Two reports employed MRS to investigate the potential neurotoxic effects of chronic Mn exposure on the

brain (Guilarte et al., 2006; Kim et al., 2007). Guilarte et al. (2006) assessed the toxic effects of chronic Mn exposure on the levels of brain metabolites in non-human primates. This [^{1}H]-MRS study found a decrease in the N-acetylaspartate/creatine (NAA/Cr) ratio in the parietal cortex and frontal WM at the end of the period of exposure to Mn, relative to baseline, indicating ongoing neuronal degeneration or dysfunction. NAA is known to serve as a neuronal marker (Birken and Oldendorf, 1989). A reduction in NAA levels in the brain can be interpreted as indicating neuronal dysfunction or even neuronal loss (Vion-Dury et al., 1994). Kim et al. (2007) investigated the potential neurotoxic effects of chronic Mn exposure in welders. Using point-resolved spectroscopy (PRESS) at 1.5 T, the cited authors measured the NAA/Cr, choline/creatine (Cho/Cr), and NAA/Cho ratios in the basal ganglia, and found no significant differences between welders and control subjects.

In a recent study, Chang et al., (2009b) sought to determine whether metabolic differences existed between 35 welders chronically exposed to Mn and 20 healthy age-matched control individuals, by measuring brain metabolites using [^{1}H]-MRS. MRI and in vivo single-voxel MRS were performed using the GE 3T MRI system (Signa Excite HD, General Electric Medical Systems, Milwaukee, WI) equipped with an eight-channel RF head coil. The MRS spectra of individual metabolites were analyzed using a Linear Combination Model (Provencher, 1993) running a Linux system. Five brain metabolites—NAA; the Glx complex, including both glutamine (Gln) and glutamate (Glu); total creatine (tCr); total choline (tCho); and myoinositol (mI)—were measured in the anterior cingulate cortex (ACC) and parietal WM. Further, the cited authors investigated correlations between neurochemical changes in the ACC of the brain and neurobehavioral alterations, to assess possible associations between chronic Mn exposure and cognitive deficits (Chang et al., 2009b). The means and standard deviations of blood Mn concentration in welders and controls were found to be 1.53 ± 0.42 and 1.06 ± 0.29 μg/dL, respectively. The mean value of workplace Mn air concentrations was 0.15 mg/m^3. The welders had worked for 21.3 ± 7.2 (mean ± SD) years. All welders were shown to be devoid of clinical manganism, by neurological examination. This study on welders using proton-MRS showed that the NAA/tCr, Glx/tCr, and tCho/tCr ratios in both the ACC and parietal WM did not differ significantly between welders and controls. However, the mI levels in the ACC, but not in the parietal WM, were significantly lower in welders compared with control individuals. Further, in the frontal lobe of the brain, the mI/tCr ratio was significantly correlated with verbal memory scores as well as blood Mn concentrations. Kim et al. (2007) found no statistically significant differences in the levels of brain metabolites (NAA and Cho only were measured) between welders and controls. However, although the cited authors used a PRESS sequence with a short echo time, mI levels was not analyzed, unlike in the study of Chang et al. cited above. The results of the latter work agree with those of a previous study (Kim et al., 2007), but a direct comparison of mI levels is not possible. Guilarte et al. (2006) reported a decrease in NAA level in the parietal cortex and frontal WM of the brains of Mn-exposed monkeys. However, when the spectroscopic findings of the work of Chang (2009b) and that of Guilarte et al. (2006) are compared, it is important to consider methodological differences between a human and animal study. MI is known to serve as a cerebral osmoregulator (Strange et al., 1994), and hence may play a role as an intracellular osmolyte. Thus, ml depletion may reflect glial cell swelling associated with long-term exposure to Mn. Previous [^{1}H]-MRS studies on the brains of cirrhotic patients with overt hepatic encephalopathy (HE) often found a large increase in Glx concentration, and depletion of mI, but no change in

NAA level, in the ACC and basal ganglia; these changes are considered to be typical metabolic abnormalities associated with HE (Geissler et al., 1997; Laubenberger et al., 1997; Weissenborn & Kolbe, 1998). In the early stages of HE, spectral alterations in mI and/or choline levels have been observed, but without corresponding increases in the Glx concentration (Kreis et al., 1992; Laubenberger et al., 1997; Miese et al., 2006; Naegele et al., 2000; Spahr et al., 2000). Compared with HE patients, welders did not show any abnormal change in Glx metabolism in a study by Chang et al. (2009b). The MRS results in welders are compatible with findings in patients in the early stages of HE. The cited study suggested that the depletion of mI in welders may reflect a possible glial cell effect rather than a neuronal effect, associated with long-term exposure to Mn. More recently, Dydak et al. (2011) used MRS to investigate brain metabolites in the globus pallidus, putamen, thalamus, and frontal cortex of 10 Mn-exposed smelters and 10 age- and gender-matched controls. Additionally, they used the MEGA-PRESS sequence to determine GABA levels in the thalamus. In addition to a significant decrease in the NAA/Cr ratio in the frontal cortex of exposed subjects, a significant increase in GABA level was observed in the thalamus, attributable to Mn exposure. The authors recommended that a combination of PI assessment and measurement of GABA level may provide a powerful, non-invasive biomarker of both Mn exposure and pre-symptomatic Mn neurotoxicity. Further studies using MRS are needed to identify brain metabolites in Mn-exposed workers.

4.2 fMRI

The use of fMRI to study neurological diseases has become much more common over the last decade. However, employing fMRI to assess neurotoxicity in humans is a rather novel approach. Chang et al. (2010a) performed the first-ever fMRI experiment, using sequential finger-tapping, to investigate the behavioral significance of additionally recruited brain regions in welders who had experienced chronic Mn exposure. The study population consisted of 42 males, aged 40 years or older, who were current full-time welders, with more than 5 years of welding experience in a factory (Chang et al., 2010a). The control population consisted of 26 age- and gender-matched non-welding production workers from the same factory, who were not exposed to other hazardous materials such as paint. MRI examinations were performed using a 3.0 T whole-body scanner (Signa Excite HD), and blood oxygenation level-dependent (BOLD) contrast data were collected for each participant. T2*-weighted echo planar imaging was used in fMRI acquisition. In the finger-tapping test, each participant was asked to place the thumb on the tip of the index finger, middle finger, ring finger, little finger, ring finger, middle finger, index finger and another finger, in that order, as quickly and precisely as possible. In the cited study, the mean and standard deviation of blood Mn concentrations in welders and control individuals were 1.55 ± 0.45 and 1.15 ± 0.31 μg/dL, respectively. The mean workplace air Mn concentration was 0.14 mg/m^3. The welders had an average welding experience of 20.5 years. All welders were shown to be devoid of clinical manganism by neurological examination. Performance on the Grooved Pegboard and finger-tapping tests (right and left hand) were significantly lower among welders than controls. Maximum frequencies, as determined by evaluation of hand pronation/supination, and finger-tapping test results using CAT SYS 2000 (Danish Product Development), were significantly lower among welders than controls. No difference in the results of other rhythmic tests (slow/fast), again using CAT SYS 2000, was evident between the groups.

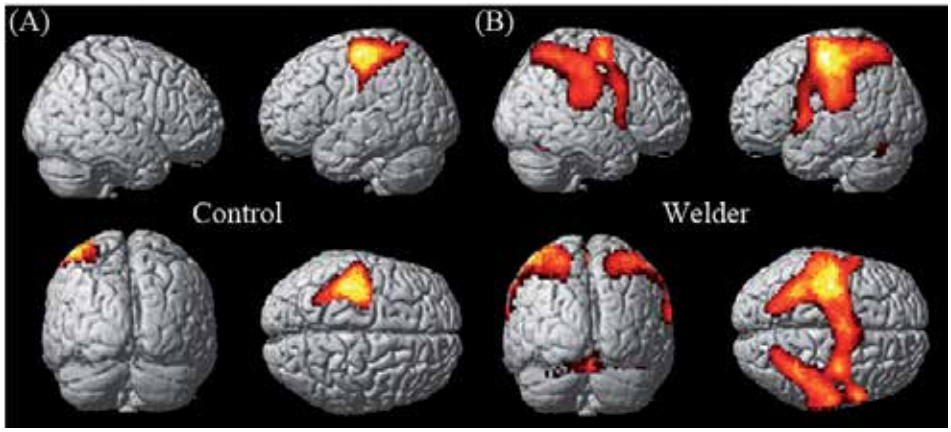


Fig. 3. Statistical parametric maps (SPM) of sequential finger tapping movement with right hand for control (A) and welder group (B) displayed on 3D SPM template brain. All activation voxels are significant at P<0.00001 FDR corrected for multiple comparison across whole brain. Chang et al. (2010a)

During finger-tapping tasks conducted on welders who were chronically exposed to Mn, significant activation foci were noted in the bilateral primary sensorimotor cortex (SM1), the bilateral supplementary motor area (SMA), the bilateral dorsolateral premotor cortex (dPMC), the bilateral superior parietal cortex, and the bilateral dentate nucleus, when data from movement and rest periods were compared. In contrast, control participants exhibited significant activation of the contralateral (left) SM1 (Fig. 3). Activation of the bilateral SM1, bilateral SMA, bilateral dPMC, bilateral superior parietal cortex, and ipsilateral dentate nucleus was higher in the welding group than in the control group. No region showed significantly more activation in controls compared to welders. PI correlated with activation observed in the contralateral SM1, in terms of finger-tapping test data from the left hand. The fMRI variables correlated with motor behavior. Grooved Pegboard performance (right hand) correlated with activation, as seen also in ipsilateral and contralateral SMA data obtained during finger-tapping with the right hand. Left-hand finger-tapping data collected during the first 10 sec of the task significantly correlated with activation of the ipsilateral and contralateral SMA when finger-tapping was evaluated on the left side. Bilateral SM1 hyperactivity may reflect motor re-organization in the brains of Mn-exposed welders, which might compensate for existing subclinical motor deficits. It seems likely that the mechanisms regulating sensorimotor control (i.e., systems operative from the basal ganglial output to the cortical sensorimotor regions, via the thalamus) may compensate for abnormalities in the basal ganglia and thereby prevent the appearance of symptoms in presymptomatic welders. In addition, hyperactivity of the SMA suggests that it is more difficult for welders (compared to controls) to perform a simple sequential finger-tapping task; thus, more SMA activity is recruited via the basal ganglial-thalamo-cortical loop, which allows for successful performance of the sequential finger-tapping task. However, these findings do not agree with those reported for patients with IPD. Functional neuroimaging of participants performing tasks requiring motor selection and initiation showed that the SMA was hypoactivated in patients with IPD, compared to normal participants (Sabatini et al., 2000).
In summary, the collective findings suggest that, when relatively simple tasks are set, fMRI may uncover evidence of compromised brain functioning in patients with subclinical

manganism. The finding of excessive recruitment of the cortical motor network in chronically Mn-exposed group is in line with the emerging concept of use of adaptive neural mechanisms to compensate for latent dysfunction in the basal ganglia (Buhmann et al., 2005).

Chang et al. (2010b) also performed fMRI, combined with two-back memory tests, to assess the neural correlates of Mn-induced memory impairment in response to subclinical dysfunction in the working memory networks of welders exposed to Mn for extended periods of time. The study population consisted of 23 males, aged 40 years or older, who were current full-time welders with more than 5 years of welding experience in a factory. The control population consisted of 21 age- and gender-matched non-welding production workers from the same factory, who were not exposed to other hazardous materials such as paint. The MRI equipment and the fMRI protocol were identical to those used in the report on fMRI data obtained using the finger-tapping task (this work is summarized above). The working memory paradigm consisted of a two-back memory task combined with a "rest" control task. Stimuli were projected onto a viewing screen, attached within the bore of the scanner, and viewed at a distance of approximately 20 cm from the eyes of the participant, after reflection from two mirrors positioned on top of the head coil. In the cited study, Mn exposure status was similar to that of subjects recruited for the fMRI study that employed the finger-tapping task. All welders were shown to be devoid of clinical manganism, by neurological examination. Welders showed significantly lower performance on cognitive neurobehavioral tests, including the Korean Auditory Verbal Learning Test (K-AVLT) (i.e., delayed recall and recognition), the Korean Complex Figure Test (K-CFT) (i.e., copy,

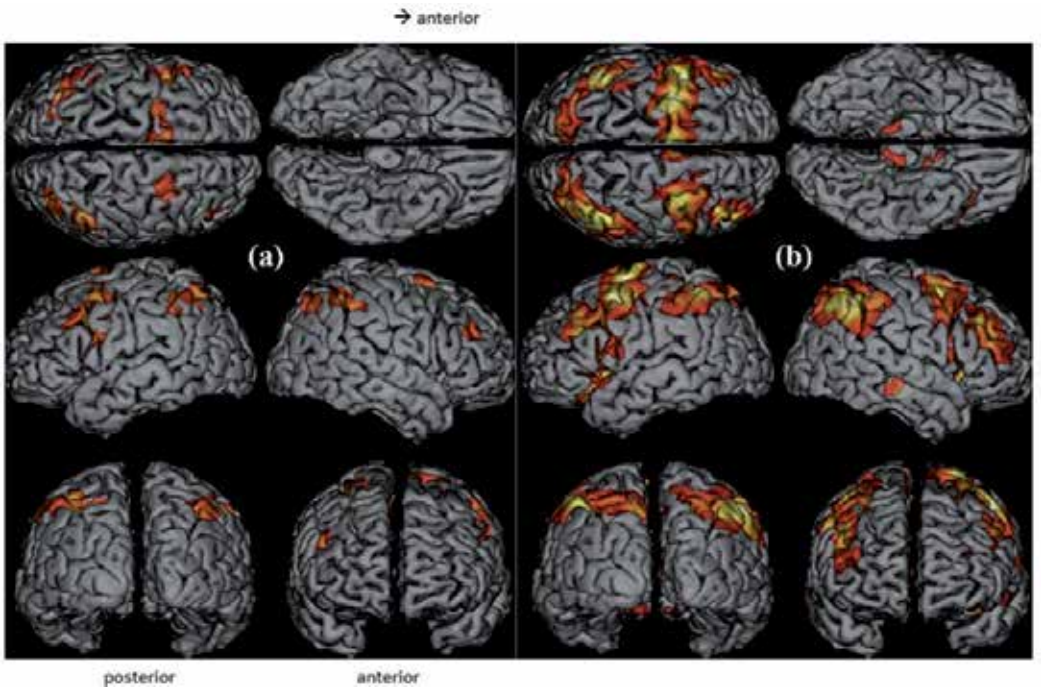


Fig. 4. The activations in fMRI with two-back memory tests from within group analysis in (a) controls and (b) welders ($p < 0.05$, FDR corrected for multiple comparison). Chang et al. (2010b)

immediate recall, and delayed recall), digit span tests (both forward and backward), and the Stroop tests, compared to controls. Chronic Mn exposure caused increased brain activity in working memory networks during the two-back verbal working memory task.

The cited authors observed activation of the inferior frontal cortex, the basal ganglia (including the putamen), and the bilateral cerebellum, as well as activation of the common memory-related network of frontal and parietal cortical areas including the premotor cortex, the middle frontal cortex, the inferior and superior frontal cortex, the inferior and superior parietal cortex, the precuneus, and the cuneus, in welders exposed to Mn (Fig. 4). Between-group analysis revealed increased brain activity in the left (contralateral) SM1, the right inferior parietal cortex, the anterior and posterior cingulated cortex, the bilateral inferior frontal cortex, and the basal ganglia of welders, compared to controls, during the memory task. No region was significantly more activated in controls compared to welders. After controlling for age and educational level, the percentage change in activation of the parietal cortex was associated with K-AVLT (i.e., delayed recall and recognition). The percentage change in activation of the inferior frontal cortex was significantly associated with scores on the Stroop color and error indices. The percentage change in activation of the ACC was significantly associated with K-AVLT (i.e., recognition) and digit span (i.e., forward) test results.

The basal ganglial-thalamo-cortical circuitry was originally viewed as almost exclusively involved in control of movement. However, these structures are now considered to be essential for non-motor function (DeLong & Wichmann, 2009). Considering that the basal ganglia are the brain regions that receive most Mn deposits, a speculative explanation of the higher basal ganglial activity in welders is that, if performance is to be matched to that of normal subjects, an increased recruitment of basal ganglial cells is required in welders to compensate for a diminished working memory capacity. Together, the fMRI findings indicate that welders might need to recruit more neural resources to the working memory network, to compensate for subtle working memory deficits and alterations in working memory processes, if they are to perform tasks at the same level as is possible by healthy control individuals.

4.3 DTI

DTI is a unique method used to characterize WM micro-integrity, and relies on the principle that water diffusion is highly anisotropic in brain WM structures (Beaulieu, 2002). Thus, DTI reveals the orientation of WM tracts in vivo, and yields indices of microstructural integrity by quantification of the directionality of water diffusion (Le Bihanetal, 2001; Moseley et al., 1990). Although a few previous studies have explored the neurotoxicity associated with exposure to heavy metals such as Hg (Kinoshita et al., 1999) and Mn (McKinney et al., 2004) using diffusion-weighted image (DWI), no report on DTI-detected alteration of microscopic integrity within the WM of subjects experiencing chronic Mn exposure has appeared. Kim et al. (2011) used DTI to investigate whether welders exposed to Mn exhibited differences in WM integrity, compared to control subjects. MRI examinations were performed using a 3.0 T whole body scanner (Signa Excite HD). Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were measured on a voxel-wise basis in 30 male welders exposed to Mn and in 19 age- and gender-matched control subjects (Kim et al., 2011). In the cited study, the means and standard deviations of blood Mn concentration in welders and control individuals were 1.52 ± 0.47 μg/dL and 1.17 ± 0.33 μg/dL, respectively.

The mean workplace Mn air concentration was 0.15 mg/m^3. The welders had an average welding experience of 20.6 years. All welders were shown to be devoid of clinical manganism by neurological examination. Welders showed significantly lower performances in all of the digit symbol, digit span, Stroop, Grooved Pegboard, and finger-tapping tests, compared to controls. Further, the results of the digit symbol, digit span, and Stroop tests were significantly associated with PI and blood Mn level after controlling for age, educational level, smoking status, and alcohol consumption. In addition, relationships between dependent measures and PI were stronger than those seen when blood Mn was used as an independent variable. Direct comparisons between welders and controls using investigator-independent Statistical Parametric Mapping (SPM) voxel-wise analysis of DTI metrics revealed a reduction in FA in the genu, body, and splenium of the corpus callosum (CC), and the frontal WM, in Mn-exposed welders. PI showed a statistically significant correlation with FA in the genu (left), body, and splenium of the CC. Blood Mn levels showed statistically significant correlations with FA in the genu (left) and body of the CC, and in the frontal WM. Further, marked increases in RD, but negligible changes in AD, were evident in the genu, body, and splenium of the CC, and the frontal WM. PI was significantly correlated with RD in the body of the CC. However, the blood Mn level did not show a statistically significant correlation with RD. All of these findings suggested that microstructural changes in the CC and the frontal WM result from a compromised radial directionality of fibers in such areas, primarily caused by demyelination. As the digit span (forward) test is more likely to measure attention and immediate recall, and the digit span (backward) test more specifically explores working memory, the statistically significant positive correlation between FA and digit span performance score (forward) suggests that the reduced FA in the frontal WM is in part responsible for the impaired attention of welders. The Stroop word and color/word tests are often used to measure executive function. Therefore, correlations between FA in the frontal WM, and the Stroop word and color/word test scores, suggest that poor performance on executive functioning, as measured using the Stroop word test (information processing) and the color/word test (executive function), are closely associated with lower FA values in the frontal WM.

In summary, correlation of DTI matrices with motor and cognitive neurobehavioral performance indices suggested that the observed microstructural abnormalities were associated with subtle motor and cognitive differences between welders and controls. This was the first study to use DTI to examine Mn-exposed workers (Kim et al., 2011). However, the functional significance of reduced frontal WM integrity evident in welders with chronic Mn exposure needs to be established in further work.

5. Conclusion

Neuroimaging is undergoing a shift from morphological to functional approaches as new technologies are gradually introduced. For morphological neuroimaging reflecting Mn exposure, PI on T1-weighted MRI data exploring target organ dosages of Mn reflects the cumulative Mn dose better than does assessment of blood Mn. For use in functional neuroimaging exploring Mn exposure, fluorodopa-PET/DAT SPECT serves as an index of the integrity of the dopaminergic nigrostriatal pathway, and is useful to differentiate between manganism and IPD. Recently, proton MRS has been used to identify brain metabolites in Mn-exposed workers. Chang et al. (1999b) suggested that subclinical neurologic effects attributable to long-term Mn exposure are associated with possible glial

cell effect rather than neuronal deficits. The use of fMRI, combined with motor tasks, has suggested that cortical hyperactivity may reflect motor re-organization in the brains of Mn-exposed welders, to compensate for subclinical motor deficits. When cognitive tasks are set, fMRI findings indicate that welders might need to recruit more neural resources to the working memory network to compensate for subtle subclinical working memory deficits. Therefore, fMRI is useful to detect subclinical cortical deficits in subjects who have experienced chronic exposure to Mn. DTI revealed microstructural deficits in WM integrity in welders exposed to Mn. Thus, functional neuroimaging can evaluate both subclinical WM integrity and cortical function in those exposed to Mn. Such neuroimaging combined with neurobehavioral performance evaluation shows promise in the elucidation of the pathophysiology of Mn neurotoxicity.

6. References

Ahn, J., Yoo, C-I., Lee, C.R., Lee, J.H., Lee, H., Park, J.K., Sakai, T., Yoon, C.S. & Kim, Y. (2003). Calcification mimicking manganese-induced increased signal intensities in T1-weighted MR images in a patient taking herbal medicine: case report. *Neurotoxicology* Vol.24, No.6, (December 2003), pp. 835-838, ISSN 0161-813X

Beaulieu, C. (2002). The basis of anisotropic diffusion imaging in the nervous system. *NMR Biomed* Vol.15, No.7-8, (November-December 2002), pp. 435–455. ISSN 0952-3480

Birken, D.L., & Oldendorf, W.H. (1989). N-Acetyl-L-aspartic acid: a literature review of a compound prominent in 1H-NMR spectroscopic studies of brain. *Neurosci Biobehav Rev* Vol.13, No.1, (Spring 1989), pp. 23–31, ISSN 0149-7634

Brooks, D.J., Salmon, E.P., Mathias, C.J., Quinn, N., Leenders, K.L., Bannister. R., Marsden, C.D. & Frackowiakm R.S. (1990). The relationship between locomotor disability, autonomic dysfunction, and the integrity of the striatal dopaminergic system in patients with multiple system atrophy, pure autonomic failure and Parkinson's disease, studied with PET. *Brain* Vol.113, No.5, (October 1990), pp. 1539–1552, ISSN 0006-8950

Buhmann, C., Binkofski, F., Klein, C., Büchel, C., van Eimeren, T., Erdmann, C., Hedrich, K., Kasten, M., Hagenah, J., Deuschl, G., Pramstaller, P.P. & Siebner, H.R. (2005) Motor reorganization in asymptomatic carriers of a single mutant Parkin allele: a human model for presymptomatic parkinsonism. *Brain* Vol.128, No.10, (October 2005), pp. 2281-2290, ISSN 0006-8950

Butterworth, R.F., Spahr, L., Fontaine, S. & Layrargues, G.P. (1995) Manganese toxicity, dopaminergic dysfunction and hepatic encephalopathy. *Metab Brain Dis* Vol.10, No.4, (December 1995), pp. 259–267, ISSN 0885-7490

Calne, D.B., Chu, N.S., Huang, C.C., Lu, C.S. & Olanow W. (1994) Manganism and idiopathic parkinsonism: similarities and differences. *Neurology* Vol.44, No.9 (September 1994), pp. 1583–1586, ISSN 0028-3878

Chang, Y., Kim, Y., Woo, S-T., Song, H-J., Kim, S.H., Lee, H., Kwon, Y.J., Ahn, J.H., Park, S-J., Chung, I-S. & Jeong, K.S. (2009) High signal intensity on magnetic resonance imaging is a better predictor of neurobehavioral performances than blood manganese in asymptomatic welders. *Neurotoxicology* Vol.30, No.4 (July 2009), pp. 555-563, ISSN 0161-813X

Chang, Y., Woo, S-T., Lee, J-J., Song, H-J., Lee, H.J., Yoo, D-S., Kim, S.H., Lee, H., Kwon, Y.J., Ahn, H.J., Ahn, J.H., Park, S-J., Weon, Y.C., Chung, I-S., Jeong, K.S. & Kim, Y. (2009)

Neurochemical changes in welders revealed by proton magnetic resonance spectroscopy. *Neurotoxicology* Vol.30, No.6, (November 2009), pp. 950-957, ISSN 0161-813X

Chang, Y., Song, H-J., Lee, J-J., Seo, J.H., Kim, J-H., Lee, H.J., Kim, H.J., Ahn, J-H., Park, S-J., Kwon, J.H., Jeong, K.S., Jung, D-K. & Kim, Y. (2010a) Neuroplastic changes within the brains of manganese-exposed welders: Recruiting additional neural resources for successful motor performance. *Occup Environ Med* Vol.67, No.12, (December 2010), pp. 809-815, ISSN 1351-0711

Chang, Y., Lee, J.J., Seo, J.H., Song, H.J., Kim, J.H., Bae, S.J., Ahn, J.H., Park, S.J., Jeong, K.S., Kwon. Y.J., Kim, S.H. & Kim, Y. (2010b) Altered working memory process in the manganese-exposed brain. *Neuroimage* Vol.53, No.4, (December 2010), pp. 1279-1285, ISSN 1053-8119

Choi, Y., Park, J.K., Park, N.H., Shin, J.W., Yoo, C-I., Lee, C.R., Lee, H., Kim, H.K., Kim, S-R., Jung, T-H., Park, J., Yoon, C.S. & Kim, Y. (2005) Whole blood and red blood cell manganese reflected signal intensities of T1-weighted MRI better than plasma manganese in liver cirrhotics. *J Occup Health* Vol.47, No.1, (January 2005), pp. 68–73, ISSN 1341-9145

DeLong, M. & Wichmann, T. (2009) Update on models of basal ganglia function and dysfunction. *Parkinsonism Relat Disord* Suppliment 3., pp. 237–240, ISSN 1353-8020

Dietz, M.C., Ihrig, A., Bader, M., Wradzillo, W. & Triebig, G. (1999) Effects on the nervous system of manganese exposed workers in a dry cell battery factory. In: Proceedings of the seventh international symposium on neurobehavioral methods and effects in occupational and environmental health.

Dydak, U., Jiang, Y.M., Long, L.L., Zhu, H.,Chen, J., Li, W.M., Edden, R.A., Hu, S., Fu, X., Long, Z., Mo, X.A., Meier, D., Harezlak, J., Aschner, M., Murdoch, J.B. & Zheng, W. (2011) In vivo measurement of brain GABA concentrations by magnetic resonance spectroscopy in smelters occupationally exposed to manganese. *Environ Health Perspect* Vol.119, No.2, (February 2011), pp. 219–224,, ISSN 0091-6765

Ejima, A., Imamur, T., Nakamura, S., Saito, H., Matsumoto, K. & Momono, S. (1992) Manganese intoxication during total parental nutrition. *Lancet* Vol.339, No.8790, (February 1992), pp. 426, ISSN 0140-6736

Erikson, H., Tedroff, J., Thuomas, K.A., Aquilonius, S.M., Hartvig, P., Fasth, K.J., Bjurling, P., Långström, B., Hedström, K.G. & Heilbronn, E. (1992) Manganese induced brain lesions in Macaca fasciculularis as revealed by positron emission tomography and magnetic resonance imaging. *Arch Toxicol* Vol.66, No.6. (June 1992), pp. 403–407, ISSN 0340-5761

Geissler, A., Lock, G., Frund, R., Held, P., Hollerbach, S., Andus, T., Schölmerich, J., Feuerbach, S. & Holstege, A. (1997) Cerebral abnormalities in patients with cirrhosis detected by proton magnetic resonance spectroscopy and magnetic resonance imaging. *Hepatology* Vol.25, No.1, (January 1997), pp. 48–54, ISSN 0270-9139

Guilarte, T.R., McGlothan, J.L., Degaonkar, M., Chen, M.K., Barker, P.B., Syversen, T. & Schneider, J,S. (2006) Evidence for cortical dysfunction and widespread manganese accumulation in the nonhuman primate brain following chronic manganese exposure: a 1H-MRS and MRI study. *Toxicol Sci* Vol.94, No.2 (December 2006):351–358, ISSN 1096-6080

Guilarte, T.R., Burton, N.C., McGlothan, J.L., Vernia, T., Zhou, Y., Alexander, M., Pham, L., Griswold, M., Wong, D.F., Syversen, T. & Schneider, J.S. (2008) Impairment of nigrostriatal dopamine neurotransmission by manganese is mediated by presynaptic mechanism(s): implications to manganese-induced parkinsonism. *J Neurochem* Vol.107, No.5, (December 2008), pp. 1236–1247, ISSN 0022-3042

Hauser, R.A., Zesiewicz, T.A., Rosemurgy, A.S., Martinez, C. & Olanow, C.W. (1994) Manganese intoxication and chronic liver failure. *Ann Neurol* Vol.36, No.6 (December 1994), pp. 871–875, ISSN 0364-5134

Hauser, R.A., Zesiewicz, T.A., Martinez, C., Rosemurgy, A.S. & Olanow, C.W. (1996) Blood manganese correlates with brain magnetic resonance imaging changes in patients with liver disease. *Can J Neurol Sci* Vol.23, No.2, (May 1996), pp. 95–98, ISSN 0317-1671

Huang, C.C., Weng, Y.H., Lu, C.S., Chu, N.S. & Yen, T.C. (2003) Dopamine transporter binding in chronic manganese intoxication. *J Neurol* Vol.250, No.11. (November 2003), pp. 1335–1339, ISSN 0340-5354

Jeon, B., Jeong, J.M., Park, S.S., Kim, J.M., Chang, Y.S., Song, H.C., Kim, K.M., Yoon, K.Y., Lee, M.C. & Lee, S.B. (1998a) Dopamine transporter density measured by [123I]beta-CIT single-photon emission computed tomography is normal in dopa-responsive dystonia. *Ann Neurol* Vol.43, No.6, (June 1998), pp. 792–800, ISSN 0364-5134

Jeon, B., Kim, J.M., Jeong, J.M., Kim, K.M., Chang, Y.S., Lee, D.S. & Lee. M.C. (1998b) Dopamine transporter imaging with [123I]beta-CIT demonstrates presynaptic nigrostriatal dopaminergic damage in Wilson's disease. *J Neurol Neurosurg Psychiatry* Vol.65, No.1, (July 1998), pp. 60–64, ISSN 0022-3050

Jiang, Y.M., Zheng, W., Long, L.L, Zhao, W.J., Li, X.R., Mo, X.A., Lu, J., Fu, X., Li, W., Liu, S., Long, Q., Huang. J. & Pira, E. (2007) Brain magnetic resonance imaging and manganese concentrations in red blood cells of smelting workers: search for biomarkers of manganese exposure. *Neurotoxicology* Vol.28, No.1, (January 2007). pp. 126–135, ISSN 0161-813X

Kim, E.A., Cheong, H.K., Choi, D.S., Sakong, J., Ryoo, J.W., Park, I. & Kang. D.M. (2007) Effect of occupational manganese exposure on the central nervous system of welders: 1H magnetic resonance spectroscopy and MRI findings. *Neurotoxicology* Vol.28, No.2, (March 2007), pp. 276–283, ISSN 0161-813X

Kim, Y. (2006) Neuroimaging in manganism. *Neurotoxicology* Vol.27, No.3, (May 2006), pp. 369–372, ISSN 0161-813X

Kim, J.M., Kim, J.S., Jeong, S.H., Kim, Y.K., Kim, S.E., Kim, S.H. & Kim, Y. (2010) Dopaminergic neuronal integrity in parkinsonism associated with liver cirrhosis. *Neurotoxicology*. Vol.31, No.4, (August 2010), pp. 351-355, ISSN 0161-813X

Kim, J.W., Kim, Y., Cheong, H.K. & Ito, K. (1998) Manganese induced parkinsonism: a case report. *J Korean Med Sci* Vol.13, No.4, (August 1998), pp. 437–439, ISSN 1011-8934

Kim, Y., Kim, K.S., Yang, J.S., Park, I.J., Kim, E., Jin, Y., Kwon, K.R., Chang, K.H., Kim, J.W., Park, S,H,, Lim,. H.S., Cheong, H.K., Shin, Y.C., Park, J. & Moon, Y. (1999a) Increase in signal intensities on T1-weighted magnetic resonance images in asymptomatic manganese-exposed workers. *Neurotoxicology* Vol.20, No.6, (December 1999), pp. 901–907, ISSN 0161-813X

Kim, Y., Kim, J., Ito, K., Lim, H-S., Cheong, H-K., Kim, J.Y., Shin, Y.C., Kim, K.S. & Moon, Y (1999b) Idiopathic parkinsonism with superimposed manganese exposure: utility of positron emission tomography. *Neurotoxicology* Vol.20, No.2-3, (April 1999), pp. 249–252, ISSN 0161-813X

Kim, Y., Kim, J.M., Kim, J., Yoo, C., Lee, C.R., Lee, J.H., Kim, H.K., Yang, S.O., Park, J., Chung, H.K., Lee, D.S. & Jeon, B. (2002) Dopamine transporter density is decreased in parkinsonian patients with a history of manganese exposure; what does it mean? *Mov Disord* Vol.17, No.3, (May 2002) pp. 568–575, ISSN 0885-3185

Kim, Y., Park, J.K., Choi, Y., Yoo, C-I., Lee, C.R., Lee, H., Lee, J-H., Kim, S-R., Jung, T-H., Yoon, C.S. & Park J-H. (2005) Blood manganese concentration is elevated in iron deficiency anemia patients, whereas globus pallidus signal intensity is minimally affected. *Neurotoxicology* Vol.26, No.1, (January 2005), pp. 107-111, ISSN 0161-813X

Kim, Y., Jeong, K.S., Song, H-J., Lee, J-J., Seo, J-H., Kim, G-C., Lee, H.J., Kim, H.J., Ahn, J-H., Park, S-J., Kim, S.H., Kwon, Y.J. & Chang, Y. (2011) Altered white matter microstructural integrity revealed by voxel-wise analysis of diffusion tensor imaging in welders with manganese exposure. *Neurotoxicology* Vol.32, No.1, (January 2011), pp. 100-109, ISSN 0161-813X

Kinoshita, Y., Ohnishi, A., Kohshi, K. & Yokota, A. (1999) Apparent diffusion coefficient on rat brain and nerves intoxicated with methylmercury. *Environ Res* Vol.80, No.4, (May 1999) pp. 348–354, ISSN 0013-9351

Kreis, R., Ross, B.D., Farrow, N.A. & Ackerman, Z. (1992) Metabolic disorders of the brain in chronic hepatic encephalopathy detected with H-1 MR spectroscopy. *Radiology* Vol.182, No.1, (January 1992), pp. 19–27, ISSN 0033-8419

Krieger, D., Krieger, S., Jansen, O., Gass, P., Theilmann, L. & Lichtnecker, H. (1995) Manganese and chronic hepatic encephalopathy. *Lancet* Vol.346, No.8970, (July 1995) pp. 270–274, ISSN 0140-6736

Lang, C.J. (2000) The use of neuroimaging techniques for clinical detection of neurotoxicity: a review. *Neurotoxicology* Vol.21, No.5, (October 2000), pp. 847-855, ISSN 0161-813X

Laubenberger, J., Haussinger, D., Bayer, S., Gufler, H., Hennig, J. & Langer, M. (1997) Proton magnetic resonance spectroscopy of the brain in symptomatic and asymptomatic patients with liver cirrhosis. *Gastroenterology* Vol.112, No.5, (May 1997), pp. 1610–1616 ISSN 0016-5085

Laruelle, M., Baldwin, R.M., Malison, R.T., Zea-Ponce, Y., Zoghbi, S.S., al-Tikriti, M., Sybirska, E.H., Zimmermann, R.C., Wisniewski, G. & Neumeyer, J.L. (1993) SPECT imaging of dopamine and serotonin transporters with [123I]beta-CIT SPECT: pharmacological characterization of brain uptake in nonhuman primates. *Synapse* Vol.13, No.4, (April 1993), pp. 295–309, ISSN 0887-4476

Le Bihan, D., Mangin, J.F., Poupon, C., Clark, C.A., Pappata, S., Molko, N. & Chabriat, H. (2001) Diffusion tensor imaging: concepts and applications. J Magn Reson Vol.13, No.4, (April 2001), pp. 534–546, ISSN 1090-7807

Lucchini, R. & Kim, Y. (2009) Manganese, Health Effects. In Vojtisek, M and Prakash, R Eds. Metals and Neurotoxicity. Society for Science and Environment. 81-92, India.

McKinney, A.M., Filice, R.W., Teksam, M., Casey, S., Truwit, C., Clark, H.B., Woon, C. & Liu, H.Y. (2004) Diffusion abnormalities of the globi pallidi in manganese neurotoxicity. *Neuroradiology* Vol.46, No.4 (April 2004), pp. 291–295, ISSN 0028-3940

Meng, X.M., Zhu, D.M., Ruan, D.Y., She, J.Q. & Luo, L. (2005) Effects of chronic lead exposure on 1H MRS of hippocampus and frontal lobes in children. *Neurology* Vol.64, No.9, (May 2005), pp. 1644–1647, ISSN 0028-3878

Miese, F., Kircheis, G., Wittsack, H.J., Wenserski, F., Hemker, J., Mödder, U., Häussinger, D. & Cohnen, M. (2006) 1H-MR spectroscopy, magnetization transfer, and diffusion-weighted imaging in alcoholic and nonalcoholic patients with cirrhosis with hepatic encephalopathy. *AJNR Am J Neuroradiol* Vol.27, No.5, (May 2006):1019–1026, ISSN 0195-6108

Mirowitz, S.A., Westrich, T.J. & Hirsch, J.D. (1991) Hyperintense basal ganglia on T1-weighted MR images in patients receiving parenteral nutrition. *Radiology* Vol.181, No.1, (October, 1991), pp. 117–120, ISSN 0033-8419

Morrish, P.K., Sawle, G.V. & Brooks, D.J. (1995) Clinical and [18F]dopa PET findings in early Parkinson's disease. *J Neurol Neurosurg Psychiatry* Vol.59, No.6, (December 1995), pp. 597–600, ISSN 0364-5134

Morrish, P.K., Sawle, G.V. & Brooks, D.J. (1996) An [18F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. *Brain* Vol.119, No.2 (April 1996), pp. 585–591, ISSN 0006-8950

Moseley, M.E., Cohen, Y. & Kucharczyk, J. (1990) Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology* Vol.176, No.2, (August 1990), pp.439–446, ISSN 0033-8419

Naegele, T., Grodd, W., Viebahn, R., Seeger, U., Klose, U., Seitz, D., Kaiser, S., Mader, I., Mayer, J., Lauchart, W., Gregor, M. & Voigt, K. (2000) MR imaging and (1)H spectroscopy of brain metabolites in hepatic encephalopathy: time-course of renormalization after liver transplantation. *Radiology* Vol.216, No.3, (September 2000), pp. 683–691, ISSN 0033-8419

Nelson, K., Golnick, J., Korn, T. & Angle, C. (1993) Manganese encephalopathy: utility of early magnetic resonance imaging. *Br J Ind Med* Vol.50, No.6, (June 1993), pp. 510–513, ISSN 0007-1072

Newland, M.C., Ceckler, T.L., Kordower, J.H. & Weiss, B. (1989) Visualizing manganese in the primate basal ganglia with magnetic resonance imaging. *Exp Neurol* Vol.106, No.3, (December 1989), pp. 251–258, ISSN 0014-4886

Park, N.H., Park, J.K., Choi, Y., Yoo, C-I., Lee, C.R., Lee, H., Kim, H.K., Kim, S-R., Jung, T.H., Park, J., Yoon, C.S. & Kim, Y (2003) Whole blood manganese correlates with high signal intensities on T1-weighted MRI in patients with liver cirrhosis. *Neurotoxicology* Vol.24, No.6, (December 2003), pp. 909–915, ISSN 0161-813X

Pujol, A., Pujol, J., Graus, F., Rimola, A., Peri, J., Mercader, J.M., García-Pagan, J.C., Bosch, J., Rodés, J. & Tolosa, E. (1993) Hyperintense globus pallidus on T1-weighted MRI in cirrhotic patients is associated with severity of liver failure. *Neurology* Vol.43, No.1, (January 1993), pp. 65–69, ISSN 0028-3878

Racette, B.A., McGee-Minnich, L., Moerlein, S.M., Mink, J.W., Videen, T.O. & Perlmutter, J.S. (2001) Welding-related parkinsonism: clinical features, treatment, and pathophysiology. *Neurology* Vol.56, No.1, (January 2001), pp. 8–13, ISSN 0028-3878

Racette, B.A., Antenor, J.A., McGee-Minnich, L., Moerlein, S.M., Videen, T.O., Kotagal, V. & Perlmutter, J.S. (2005) [18F]FDOPA PET and clinical features in parkinsonism due to manganism. *Mov Disord* Vol.20, No.4, (April 2005), pp. 492–496, ISSN 0885-3185

Ravina, B., Eidelberg, D., Ahlskog, J.E., Albin, R.L., Brooks, D.J., Carbon, M., Dhawan, V., Feigin, A., Fahn, S., Guttman, M., Gwinn-Hardy, K., McFarland, H., Innis, R., Katz, R.G., Kieburtz, K., Kish, S.J., Lange, N., Langston, J.W., Marek, K., Morin, L., Moy, C., Murphy, D., Oertel, W.H., Oliver, G, Palesch, Y., Powers, W., Seibyl, J., Sethi, K.D., Shults, C.W., Sheehy, P., Stoessl, A.J. & Holloway, R. (2005) The role of radiotracer imaging in Parkinson's disease. *Neurology* Vol.64, No.2, (January 2005), pp. 208–215, ISSN 0028-3878

Rosen, Y, & Lenkinski, R.E. (2007) Recent advances in magnetic resonance neurospectroscopy. *Neurotherapeutics* Vol.4, No.3, (July 2007), pp. 330–345, ISSN 1933-7213

Ross, A.J., Sachdev, P.S., Wen, W., Brodaty, H., Joscelyne, A. & Lorentz, L.M. (2006) Prediction of cognitive decline after stroke using proton magnetic resonance spectroscopy. *J Neurol Sci* Vol.251, No.1–2, (December 2006), pp. 62–69, ISSN 0022-510X

Sabatini, U., Boulanouar, K., Fabre, N., Martin, F., Carel, C., Colonnese, C., Bozzao, L., Berry, I., Montastruc, J.L., Chollet, F. & Rascol, O. (2000) Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. *Brain* Vol.123, No.2, (February 2000), pp. 394-403, ISSN 0006-8950

Seibyl, J.P., Marek, K.L., Quinlan, D., Sheff, K., Zoghbi, S., Zea-Ponce, Y., Baldwin, R.M., Fussell, B., Smith, E.O., Charney, D.S. & van Dyck, C. (1995) Decreased single-photon emission computed tomographic [123I]beta-CIT striatal uptake correlates with symptom severity in Parkinson's disease. *Ann Neurol* Vol.38, No.4, (October 1995), pp. 589–598, ISSN 0364-5134

Shinotoh, H., Snow, B.J., Hewitt, K.A., Pate, B.D., Doudet, D., Nugent, R., Perl, D.P., Olanow, W. & Calne, D.B. (1995) MRI and PET studies of manganese-intoxicated monkeys. *Neurology* Vol.45, No.6, (June 1995), pp. 1199–1204, ISSN 0028-3878

Shinotoh, H., Snow, B.J., Chu, N.S., Huang, C.C., Lu, C.S., Lee, C., Takahashi, H. & Calne, DB. (1997) Presynaptic and postsynaptic striatal dopaminergic function in patients with manganese intoxication: a position emission tomography study. *Neurology* Vol.48, No.4, (April 1997), pp. 1053–1056, ISSN 0028-3878

Spahr, L., Butterworth, R.F., Fontaine, S., Bui, L., Therrien, G., Milette, P.C., Lebrun, L.H., Zayed, J., Leblanc, A. & Pomier-Layrargues, G. (1996) Increased blood manganese in cirrhotic patients: relationship to pallidal magnetic resonance signal hyperintensity and neurological symptoms. *Hepatology* Vol.24, No.5, (November 1996), pp. 1116–1120, ISSN 0270-9139

Spahr, L., Vingerhoets, F., Lazeyras, F., Delavelle, J., DuPasquier, R., Giostra, E., Mentha, G., Terrier, F. & Hadengue, A. (2000) Magnetic resonance imaging and proton spectroscopic alterations correlate with parkinsonian signs in patients with cirrhosis. *Gastroenterology* Vol.119, No.3, (September 2000), pp. 774–781, ISSN 0016-5085

Strange, K., Emma, F., Paredes, A. & Morrison R. (1994) Osmoregulatory changes in myo-inositol content and Na+/myo-inositol cotransport in rat cortical astrocytes. *Glia* Vol.12, No.1, (September 1994), pp. 35–43, ISSN 0894-1491

Trope, I., Lopez-Villegas, D., Cecil, K.M. & Lenkinski, R.E. (2001) Exposure to lead appears to selectively alter metabolism of cortical gray matter. *Pediatrics* Vol.107, No.6, (June 2001), pp.1437–1442, ISSN 0031-4005

Vion-Dury, J., Meyerhoff, D.J., Cozzone, P.J. & Weiner MW. (1994) What might be the impact on neurology of the analysis of brain metabolism by in vivo magnetic resonance spectroscopy? *J Neurol* Vol.241, No.6, (May 1994), pp. 354–371, ISSN 0340-5354

Walker, R..C, Purnell, G.L., Jones-Jackson, L.B., Thomas, K.L., Brito, J.A. & Ferris EJ. (2004) Introduction to PET imaging with emphasis on biomedical research. *Neurotoxicology* Vol.25, No.4, (June 2004), pp. 533-542, ISSN 0161-813X

Weissenborn, K. & Kolbe, H. (1998) The basal ganglia and portal-systemic encephalopathy. *Metab Brain Dis* Vol.13, No.4, (December 1998), pp. 261–272, ISSN 0885-7490

Weisskopf, M.G. Magnetic resonance spectroscopy and environmental toxicant exposure. (2007) *Ann N Y Acad Sci* Vol.1097, (February 2007), pp. 179–182, ISSN 0077-8923

Weisskopf, M.G., Hu, H., Sparrow, D., Lenkinski, R.E. & Wright, R.O. (2007) Proton magnetic resonance spectroscopic evidence of glial effects of cumulative lead exposure in the adult human hippocampus. *Environ Health Perspect* Vol.115, No.4, (April 2007), pp. 519–523, ISSN 0091-6765

Wolters, E.C., Huang, C.C., Clark, C., Peppard, R.F., Okada, J., Chu, N.S., Adam, M.J., Ruth, T.J., Li, D. & Calne, D.B. (1989) Positron emission tomography in manganese intoxication. *Ann Neurol* Vol.26, No.5, (November 1989), pp. 647–651, ISSN 0364-5134

7

Minor and Trace Elements in Cerebrospinal Fluid of Parkinson's Patients – Suggestions After a Critical Review of the Analytical Data

Margherita Speziali[1] and Michela Di Casa[2]
[1]*CNR-IENI (Institute for Energetics and Interphases), Department of Pavia, University of Pavia, Pavia,*
[2] *Department of Chemistry, University of Pavia, Pavia, Italy*

1. Introduction

Patients suffering from neurodegenerative diseases are known to present, in comparison to controls, variations on the contents of minor and trace elements in body tissues and fluids. For individuals affected by Parkinson's disease (PD), some findings, regarding brain and serum, are cited hereafter. BRAIN. Various brain areas were characterized for trace element levels and some alterations were observed in patients. Higher concentrations of aluminum were determined by Yasui et al. (1992) in different sites; increased levels of copper were detected by Riederer et al. (1989) in raphe plus reticular formation, whereas diminished amounts were found in substantia nigra by Rajput et al. (1985) and Dexter et al. (1989). Dexter et al. (1991) and Griffits et al. (1999) observed an iron enrichment in substantia nigra; regarding to zinc, Dexter et al. (1989) found more elevated amounts in a few areas, while Riederer et al. (1989) noticed lower contents in raphe formation. Variations of aluminum, copper, iron and zinc levels in definite brain sites of PD patients were reviewed by Speziali & Orvini (2003). SERUM. For PD patients, trace element changes were observed also in serum. Several studies were carried out at the Italian Istituto Superiore di Sanità (ISS) by Bocca et al. (2004, 2006), Forte et al. (2004, 2005), Alimonti et al. (2007a). A decreasing trend for aluminum was observed by Bocca et al. (2004) and Forte et al. (2004), as well as by Hedge et al. (2004) and Pande et al. (2005). Copper resulted elevated in these last two works and in a paper by Mindadse & Tschikowani (1967); in other investigations, by Bocca et al. (2006), Forte et al. (2004) and Tan et al. (2007), copper resulted diminished. Hedge et al. (2004), Pande et al. (2005), Forte et al. (2005), Alimonti et al. (2007a) detected lower iron concentrations, whereas Tan et al. (2007) reported a higher amount. In the case of zinc, a slight increase was noticed by Tan et al. (2007), whereas Hedge et al. (2004), Pande et al. (2005), Forte et al. (2005), Alimonti et al. (2007a) observed a significant decrease. A lower mercury content was found by Gellein et al. (2008).

From this survey, it emerges that disagreeing findings for the same element are quite frequent. In the case of brain, we can suppose that the discrepancies among the various trials are related to the different areas examined. The less expected controversial findings for serum stimulated us to examine the up to date knowledge about the CSF of PD subjects. We have already published a short review on this topic (Speziali & Di Casa, 2009). In this

Chapter we present in a series of tables, for the first time, all the original values retrieved, along with several parameters that can influence the results. Here we discuss more extensively the role of all the factors affecting the results, which are the parameters reported in the tables along with the criteria for the enrollment of subjects, the analytical procedures and the statistical tests used. Finally, we propose with wider completeness several suggestions useful for possible future studies.

C = Controls	Et-AAS = Electrothermal Atomic Absorption Spectrometry
PD = Parkinson's disease patients	ICP-AES = Inductively Coupled Plasma - Atomic Emission Spectometry
PD (On) = PD with positive response to the therapy	DCP-AES = Direct Current Plasma -AES
PD (On/Off) = PD without positive response to the therapy	SF-ICP-MS = Sector Field – Inductively Coupled Plasma – Mass Spectrometry
PDCN = PD cognitively normal patients	S = significant or highly significant difference
PDD = PD demented patients	NS = non-significant difference
SD = Standard Deviation	
M = male	
F = female	

Table 1. Captions for the tables

2. Aim

We performed an investigation on the minor and trace element amounts, available in the literature, regarding the CSF of PD patients and paired controls. Our purpose was to obtain a comprehensive picture of the element concentrations and to verify possible imbalances in the CSF of the diseased individuals.

3. Data presentation

We considered only studies where: a) both patients and controls were examined in the same investigation; b) the concentration values determined were reported as numbers; c) statistical tests were employed to verify the significance of potential changes of element amounts in the CSF of patients. The scientific publications were retrieved through the data bank Medline along with the Personal Alert Service of Thomson Reuters, Philadelphia, PA. From the bibliographies of the recruited papers further references were derived. The concentration data we recruited in the literature were published from 1987 to 2008. Values of Al, Ba, Be, Bi, Ca, Cd, Co, Cr, Cu, Fe, Hg, Li, Mg, Mn, Mo, Ni, Pb, Sb, Se, Si, Sn, Sr, Tl, V, W, Zn and Zr were found. In Tab. 1 we set out the captions useful for all our tables. In Tab. 2 - 11 we report the mean concentration values, along with the standard deviations; we also show several parameters affecting the results: number, gender and age of the subjects enrolled, analytical technique employed, significance of possible differences between concentration values for patients and controls. The simultaneous availability of all these factors allows scientists to evaluate immediately the reliability of each trial findings. From the tables, indications can be also deducted on the possibility (or not) to compare directly the results of different trials; increasing or decreasing element trends in patients are evident right away. Finally, in Tab. 12 we sum up some indications recorded in other publications of interest.

Element	Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Significance	References
Ca	C	24.696	1.997	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES	NS	Forte et al., 2004
	PD	27.911	4.964	26 (24 M + 2 F)	64.9 ± 10.8			
	C	26.956 {median: 25.579}	5.515	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES	NS	Alimonti et al., 2007b
	PD	27.312 {median: 27.301}	3.385	42 (36 M + 6 F)	64.5 ± 10.7			
Mg	C	21.229	3.160	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES	NS	Forte et al., 2004
	PD	20.913	2.024	26 (24 M + 2 F)	64.9 ± 10.8			
	C	21.868 {median: 22.665}	3.509	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES	NS	Alimonti et al., 2007b
	PD	23.693 {median: 22.365}	4.263	42 (36 M + 6 F)	64.5 ± 10.7			

Table 2. Calcium and magnesium in Controls and Patients (mg/L)

Subjects	Mean	SD	N. of subjects (Gender)	Age, *y* (Range)	Technique	Significance	References
C	75.9	153.6	22 (20 M + 2 F)	age-matched	Et-AAS		Gazzaniga et al., 1992
PD tot	181	75.1	11 (10 M + 1 F)	64.9 (49-78)		NS	
PD untreated	28.3 *	141.5*	6	63.1 (49-78)		NS	
PD treated	266.4	183.6	5	67 (59-77)		NS	
C	210	150	37 (16 M + 21 F)	62.4 ± 17.8	Et-AAS		Jiménez-Jiménez et al., 1998
PD	170	170	37 (14 M + 23 F)	65.7 ± 8.8		NS	
C	73.3	72.7	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES		Forte et al., 2004
PD	33.0	29.4	26 (24 M + 2 F)	64.9 ± 10.8		NS	
C	237	37	21 (13 M + 8 F)	62 ± 11	Et-AAS		Qureshi et al., 2005 and 2006
PD (On)	345	47	17 (10 M + 7 F)	70 ± 15		S >	
PD (On/Off)	397	50	19 (13 M + 6 F)	72 ± 17		S >	
C	45.0	30.2	18 (10 M + 8 F)	63.8 ± 13.8	ICP-AES		Bocca et al., 2006
PD	28.2	14.6	91 (64 M + 27 F)	65.5 ± 9.7		S <	
C	35.5 {median: 36.8}	5.03	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES		Alimonti et al., 2007b
PD	28.2 {median: 24.4}	14.6	42 (36 M + 6 F)	64.5 ± 10.7		S <	

* these two values are incoherent

Table 3. Iron in Controls and Patients (μg/L)

4. Considerations on factors influencing the results

As already pointed out in the **Introduction**, many factors affect the results, conditioning then the comparability among the findings of the various studies. We describe now in details the influence of each factor as it emerged in the examined publications.

4.1 Criteria for subject enrollment

4.1.1 Health conditions

In the subject enrollment, the criteria for inclusion/exclusion are fundamental and should absolutely include health conditions along with age and gender. Ideally, exposures due to environmental pollution or occupational activities and diet should also be considered.
In the reviewed papers, only a few teams give full details of the selection criteria used. The researchers of the Italian Istituto Superiore di Sanità (ISS), Bocca, Forte, Alimonti and coworkers, along with the Spanish scientists (Jiménez-Jiménez et al. 1998 and Aguilar et al. 1998) are among the few authors who describe extensively the criteria employed. The diseases affecting the individuals recruited as patients or controls are often not precisely described, mainly in the less recent works. In some publications, incongruities appear within the text or among the text and the data presented in the tables. It is not always clear whether the patients were affected by comorbidities. Due to the fact that severe illnesses of heart, liver, kidney and also tumors are known to affect the levels of trace elements in human fluids and tissues, an exhaustive health report is also necessary in the case of controls. For these subjects, very heterogeneous situations have been observed. In Bourrier-Guerin et al. (1985) - see Tab. 12 - controls were not enrolled at all. Mindadse & Tschikowani (1967) - see Tab. 12 - employed blood donors. In Qureshi et al. (2005, 2006) control individuals, simply defined "healthy", were affected by tension headache, ischemic cerebrovascular disease or polyneuropathy. The Spanish group selected "healthy" subjects with suspected subarachnoid hemorrhage or pseudotumor cerebri, oculomotor palsies, etc. The scientists of the ISS enrolled individuals not suffering from any central neurological disease. Kjellin (1967a and 1967b - see Tab. 12) assumed psychoneurotic outpatients as representative of the "normal" condition. It is evident that, in the diverse investigations, were enrolled as controls subjects in really different health conditions. It is worth considering that, differently from blood, the samples of CSF are not easily available; therefore, the control specimens are mostly withdrawn from subjects undergoing lumbar puncture for clinical analyses. In the case of patients, the differences among the groups enrolled in the diverse studies are amplified by some clinical variables, as duration and severity of the disease along with medical treatments and possible comorbidities. Regarding duration and severity of the disease, in the trial by Aguilar et al. (1998) Se and Cr levels showed no correlation with age at onset and duration of the illness. On the other hand, Alimonti et al. (2007b) detected in patients a negative association of Cr amount and severity and duration of the illness; in the same study, Pb appeared to be negatively related to the severity of the disorder, while Sn resulted to be negatively associated with the duration of the disease. The authors also found that age at onset did not affect the concentration of Fe and of the other elements that resulted significantly different between controls and patients (Co, Cr, Pb, Si, Sn). Bocca et al. (2006) observed that duration and severity of the disease appeared not to be correlated with Al, Ca, Cu, Fe, Mn, Si and Zn amounts; on the other hand, Mg level decreased with the duration and severity of the illness. Concerning medical treatments, the therapies followed by patients are described by

Subjects	Mean	SD	N. of subjects (Gender)	Age, *y* (Range)	Technique	Signif-icance	References
C	19.2 (range: 10 – 33)	5.8	21		DCP-AES	NS	Belliveau et al., 1990
PD	18.7 (range: 7 – 30)	6.3	16				
C	64.9	14.4	22 (20 M + 2 F)	age-matched	Et-AAS	NS	Gazzaniga et al., 1992
PD tot	67.7	19.9	11 (10 M + 1 F)	64.9 (49 – 78)		NS	
PD untreated	63.2	11.5	6	63.1 (49 – 78)		NS	
PD treated	67.0	18.5	5	67 (59 – 77)			
C	109.1	88.2	37 (16 M + 21 F)	62.4 ± 17.8	Et-AAS	NS	Jiménez-Jiménez et al., 1998
PD	104.9	86.3	37 (14 M + 23 F)	65.7 ± 8.8			
C	22.5	4.76	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES	NS	Forte et al., 2004
PD	23.7	10.5	26 (24 M + 2 F)	64.9 ± 10.8			
C	132	17	21 (13 M + 8 F)	62 ± 11	Et-AAS	NS	Qureshi et al., 2005 and 2006
PD (On)	119	18	17 (10 M + 7 F)	70 ± 15		NS	
PD (On/Off)	109	19	19 (13 M + 6 F)	72 ± 17			
C	21.9 {median: 2.2}	4.77	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES	NS	Alimonti et al., 2007b
PD	19.4 {median: 17.0}	7.97	42 (36 M + 6 F)	64.5 ± 10.7			
C	19.6	1.3	32	85.2 ± 1.0		NS	Sparks et al., 2008
PDCN	17.4	4.3	12	85.3 ± 1.4		NS	
PDD	10.0	1.1	5	78.6 ± 2.2			

Table 4. Copper in Controls and Patients (µg/L)

many authors, as Gazzaniga et al. (1992), Qureshi et al. (2005, 2006), Aguilar et al. (1998), Jimenez-Jimenez et al. (1998), Bocca et al. (2004, 2006), Forte et al. (2004), Alimonti et al. (2007b) along with Campanella et al. (1973) and Takahashi et al. (1994). Aguilar et al. (1998) carried out studies about the influence of antiparkinsonian treatment with various drugs on Se and Cr levels; in the entire group of PD patients, Se showed a non significant increase compared to controls, but the elevation attained the significance when only patients not treated with levodopa were considered. This interesting observation is just recorded in the article text. Jimenez-Jimenez et al. (1998) studied the effects of the same drugs on the concentrations of Fe, Cu, Zn and Mn; they did not observe any significant influence. Gazzaniga et al. (1992), confronting long-term levodopa treated and untreated patients, did not find any significant differences in the amounts of Cu, Fe and Mn. Qureshi et al. (2005, 2006) determined the amounts of Cu, Fe, Se and Zn in patients treated with levodopa, who were divided into two groups (PD On and PD On/Off), depending on the positive or negative response to the therapy. Fe and Se were found to be markedly higher than in controls in both kinds of patients; Zn resulted instead significantly reduced in both groups. Bocca et al. (2006) evaluated that the type of therapy did not influence the concentrations of all the elements studied (Al, Ca, Cu, Fe, Mg, Mn, Si, Zn). Alimonti et al. (2007b) observed that diverse drugs did not affect the concentration of Fe; on the contrary, they influenced the amounts of the elements which resulted significantly different between controls and patients (Co, Cr, Pb, Si, Sn). Takahashi et al. (1994 - see Tab. 12) found that the Mg concentration in both untreated and treated (with levodopa) patients was lower than in controls.

4.1.2 Age

The subject age is known to influence the amounts of some elements in tissues and fluids. In serum, it has been documented for Cu by Ghayour-Mobarhan et al. (2005) and Kouremenou-Dona et al. (2006); for Se by Lopes et al. (2004). In brain, Markesbery et al. (1984), Ongkana et al. (2010) and Tohno et al. (2010) found age-related changes for several

Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Signif-icance	References
C	170	140	37 (16 M + 21 F)	62.4 ± 17.8	Et-AAS	S <	Jiménez-Jiménez et al., 1998
PD	100	60	37 (14 M + 23 F)	65.7 ± 8.8			
C	32.9	8.85	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES	NS	Forte et al., 2004
PD	27.3	10.5	26 (24 M + 2 F)	64.9 ± 10.8			
C	161	31	21 (13 M + 8 F)	62 ± 11	Et-AAS	S <	Qureshi et al., 2005 and 2006
PD (On)	117	19	17 (10 M + 7 F)	70 ± 15		S <	
PD (On/Off)	96	11	19 (13 M + 6 F)	72 ± 17			
C	32.3 {median: 33.5}	11.4	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES	NS	Alimonti et al., 2007b
PD	27.7 {median: 27.8}	9.01	42 (36 M + 6 F)	64.5 ± 10.7			

Table 5. Zinc in Controls and Patients (µg/L)

Subjects	Mean	SD	N. of subjects (Gender)	Age, *y* (Range)	Technique	Signif-icance	References
C	0.97 ♥	0.34 ♥	29		Et-AAS	NS	Pall et al., 1987
PD	0.96 ♥	0.36 ♥	9				
C	5.7	1.8	22 (20 M + 2 F)	age-matched	Et-AAS	NS	Gazzaniga et al., 1992
PD tot	5.4	3.9	11 (10 M + 1 F)	64.9 (49 - 78)		NS	
PD untreated	6.0	1.3	6	63.1 (49 - 78)		NS	
PD treated	5.4	2.4	5	67 (59 - 77)			
C	0.88	0.76	37 (16 M + 21 F)	62.4 ± 17.8	Et-AAS	NS	Jiménez-Jiménez et al., 1998
PD	1.20	0.98	37 (14 M + 23 F)	65.7 ± 8.8			
C	0.85 {median: 0.91}	0.36	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	NS	Bocca et al., 2004 and Forte et al., 2004
PD	0.63 {median: 0.54}	0.43	26 (24 M + 2 F)	64.9 ± 10.8			
C	0.95	0.39	18 (10 M + 8 F)	63.8 ± 13.8	SF-ICP-MS	NS	Bocca et al., 2006
PD	0.69	0.42	91 (64 M + 27 F)	65.5 ± 9.7			
C	0.95 {median: 1.02}	0.39	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
PD	0.69 {median: 0.58}	0.42	42 (36 M + 6 F)	64.5 ± 10.7			

♥ data converted from nmol/L

Table 6. Manganese in Controls and Patients (µg/L)

elements. All authors who studied CSF and published element concentration values also for patients reported the mean age of each subject group; Gazzaniga et al. (1992) specified also the age range. Regarding element changes with age, Aguilar et al. (1998) found that Se and Cr levels were not correlated with the age of PD patients. Bocca et al. (2006) found no Zn changes in patients (no data given); in controls, they observed a significant Zn increment in subjects elder than 70 years in comparison with younger individuals, but these differences disappeared in patients.

4.1.3 Gender

This parameter also influences trace element levels. For changes of Se, Cu and Zn in serum, see Lopes et al. (2004) and Ghayour-Mobarhan et al. (2005). For Zn variations in brain, see Ongkana et al. (2010). Regarding CSF, Bocca et al. (2006) noticed lesser Fe amounts in PD males than in females, whereas the opposite was found in controls. They also report that Si concentration resulted significantly lower in patients than in controls and that in PD females it was two-times lower than in males. This remarkable observation could come out because the authors calculated distinct values, not published, for the two genders.

Element	Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Significance	References
Cr	C	14.6	6.3	43 (19 M + 24 F)	65.2 ± 13.0	Et-AAS	NS	Aguilar et al., 1998
	PD	14.5	7.4	28 (11 M + 17 F)	65.5 ± 9.1			
	C	1.39 {median: 1.47}	0.64	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.60 {median: 0.54}	0.47	26 (24 M + 2 F)	64.9 ± 10.8			
	C	1.28 {median: 1.39}	0.59	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	S <	Alimonti et al., 2007b
	PD	0.65 {median: 0.55}	0.46	42 (36 M + 6 F)	64.5 ± 10.7			
Se	C	13.5	8.2	43 (19 M + 24 F)	65.2 ± 13.0	Et-AAS	NS	Aguilar et al., 1998
	PD	17.9	12.3	28 (11 M + 17 F)	65.5 ± 9.1			
	C	14.2	1.8	21 (13 M + 8 F)	62 ± 11	Et-AAS	S >	Qureshi et al., 2006
	PD (On)	19.7	1.9	17 (10 M + 7 F)	70 ± 15		S >	
	PD (On/Off)	22.7	2.1	19 (13 M + 6 F)	72 ± 17			

Table 7. Chromium and selenium in Controls and Patients (μg/L)

Element	Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Significance	References
Pb	C	1.06 {median: 1.0}	0.34	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.42 {median: 0.30}	0.38	26 (24 M + 2 F)	64.9 ± 10.8			
	C	0.91 {median: 0.84}	0.36	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	S <	Alimonti et al., 2007b
	PD	0.46 {median: 0.43}	0.24	42 (36 M + 6 F)	64.5 ± 10.7			
Si	C	105	39.3	13 (6 M + 7 F)	63.8 ± 13.7	ICP-AES	S <	Forte et al., 2004
	PD	66.9	49.7	26 (24 M + 2 F)	64.9 ± 10.8			
	C	95.0	38.0	18 (10 M + 8 F)	63.8 ± 13.8	ICP-AES		Bocca et al., 2006
	"	92.5	44.3	1 F				
	PD	58.4 •	44.8	91 (64 M + 27 F)	65.5 ± 9.7		S <	
	"	63.9	46.5	1 M			S <	
	"	28.9	13.7	1 F			S <	
	C	95.0 {median: 96.3}	38.3	20 (17 M + 3 F)	66.2 ± 14.7	ICP-AES	S <	Alimonti et al., 2007b
	PD	58.4 {median: 52.3}	44.8	42 (36 M + 6 F)	64.5 ± 10.7			

• For gender difference, see text (section 4.1.3 Gender)

Table 8. Lead and silicon in Controls and Patients (μg/L)

4.1.4 Number of subjects examined

In the reviewed papers, the authors usually publish the total number of controls and patients, and even the numbers of males and females; however, they frequently do not report the information actually needed, that is the number of individuals really tested for each element. In our review, we observed that Be, Cd, Hg, and V were determined in two investigations by the team of ISS (Bocca et al. 2004 and Alimonti et al. 2007b). In the previous one, where a lower number of individuals was considered, the element decrements in patients were evaluated as significant; in the second trial, where more subjects were enrolled, the variations came out to be not significant. Fe resulted decreased in patients at the limits of significance ($p = 0.052$) in a trial carried out by Forte et al. (2004); in two successive investigations by the same team (Bocca et al. 2006 and Alimonti et al. 2007b), with a higher number of individuals, Fe was found to be significantly reduced. The control and patient groups of successive trials by the same authors probably included the corresponding groups already examined in the previous ones; the disagreeing findings could be due to the

Element	Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Significance	References
Co	C	0.15 {median: 0.16}	0.04	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.04 {median: 0.03}	0.04	26 (24 M + 2 F)	64.9 ± 10.8			
	C	0.13 {median: 0.13}	0.05	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	S <	Alimonti et al., 2007b
	PD	0.09 {median: 0.06}	0.09	42 (36 M + 6 F)	64.5 ± 10.7			
Ni	C	8.01 {median: 7.54}	1.39	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	NS	Bocca et al., 2004
	PD	4.37 {median: 1.07}	5.61	26 (24 M + 2 F)	64.9 ± 10.8			
	C	5.40 {median: 6.44}	3.33	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
	PD	3.34 {median: 1.53}	3.61	42 (36 M + 6 F)	64.5 ± 10.7			

Table 9. Cobalt and nickel in Controls and Patients (μg/L)

Element	Subjects	Mean	SD	N. of subjects (Gender)	Age, *y*	Technique	Significance	References
Be	C	0.87 {median: 0.85}	0.33	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.44 {median: 0.44}	0.13	26 (24 M + 2 F)	64.9 ± 10.8			
	C	0.70 {median: 0.55}	0.37	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
	PD	0.56 {median: 0.54}	0.21	42 (36 M + 6 F)	64.5 ± 10.7			
Cd	C	0.06 {median: 0.06}	0.02	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.03 {median: 0.03}	0.01	26 (24 M + 2 F)	64.9 ± 10.8			
	C	0.05 {median: 0.05}	0.03	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
	PD	0.04 {median: 0.4}	0.02	42 (36 M + 6 F)	64.5 ± 10.7			
Hg	C	1.20 {median: 1.19}	0.50	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.67 {median: 0.74}	0.32	26 (24 M + 2 F)	64.9 ± 10.8			
	C	1.05 {median: 0.85}	0.46	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
	PD	0.73 {median: 0.81}	0.32	42 (36 M + 6 F)	64.5 ± 10.7			
V	C	0.12 {median: 0.11}	0.06	13 (6 M + 7 F)	63.8 ± 13.7	SF-ICP-MS	S <	Bocca et al., 2004
	PD	0.07 {median: 0.08}	0.03	26 (24 M + 2 F)	64.9 ± 10.8			
	C	0.09 {median: 0.10}	0.03	20 (17 M + 3 F)	66.2 ± 14.7	SF-ICP-MS	NS	Alimonti et al., 2007b
	PD	0.07 {median: 0.07}	0.03	42 (36 M + 6 F)	64.5 ± 10.7			

Table 10. Berillium, cadmium, mercury and vanadium in Controls and Patients (μg/L)

different number of the considered subjects. In the case of Co, Cr, Pb and Si, the outcomes for significance are always the same when the number of subjects, in both control and patient groups, is either lower or higher. We wonder whether the changes in patients of these elements are so marked that result noticeable in every case. As a general consideration, it is obvious that the higher is the number of the subjects examined, the higher is the representativeness of the results obtained.

4.2 Analytical procedures

When determining elements at trace levels, the entire analytical process is critical. Sampling and storage should be carried out in an appropriate way to minimize contamination and losses, following the recognized requirements in the field. The chemical treatments needed by each method should be as standardized as possible. The analytical technique employed must assure high sensitivity and good reproducibility.

In the reviewed studies, the preanalytical steps were described with more or less details; the techniques employed were cited by all authors, except Sparks et al. (2008). A careful description of the method is generally available in the most recent papers, that sometimes refer

to previous publications. The techniques used for the most studied elements were principally electrothermal atomic absorption spectrometry (Et-AAS) and inductively coupled plasma atomic emission spectrometry (ICP-AES). For some elements, sector field inductively coupled plasma mass spectrometry (SF-ICP-MS) was also employed by the team of ISS. All these analytical techniques are widely used for trace element determination in human samples.

Element	Subjects	Mean	SD	Median	Significance
Al	C	2.64	0.51	2.72	NS
	PD	2.15	1.03	2.05	
Ba	C	0.35	0.15	0.31	NS
	PD	0.26	0.13	0.24	
Bi	C	0.10	0.07	0.09	NS
	PD	0.08	0.05	0.06	
Li	C	0.52	0.13	0.52	NS
	PD	0.82	0.53	0.65	
Mo	C	0.45	0.27	0.43	NS
	PD	0.33	0.17	0.27	
Sb	C	0.08	0.02	0.09	NS
	PD	0.06	0.04	0.07	
Sn	C	0.32	0.07	0.31	S <
	PD	0.26	0.11	0.24	
Sr	C	30.0	8.69	27.7	NS
	PD	24.6	8.66	22.6	
Tl	C	0.01	0.01	0.01	NS
	PD	0.01	0.007	0.01	
W	C	0.04	0.02	0.04	NS
	PD	0.03	0.02	0.03	
Zr	C	0.06	0.05	0.06	NS
	PD	0.04	0.03	0.04	
N. of subjects (Gender)				Age, *y*	
C 20 (17 M + 3 F)				66.2 ± 14.7	
PD 42 (36 M + 6 F)				64.5 ± 10.7	
Technique: SF-ICP-MS					

Table 11. Other trace elements in Controls and Patients (µg/L); (modified from Alimonti et al., 2007b)

4.3 Statistical tests

In this kind of studies, statistical tests of various types are required for diverse appraisals. Within each study and for each element considered, tests are applied at first to evaluate whether the concentrations found for controls and patients are significantly different or not. In the same trial, other tests can reveal non negligible dissimilarities among the control and patient groups, regarding one or more factors affecting the results. When a significant

discrepancy is disclosed, the comparison between the mean concentration values for controls and those for patients results rather inappropriate.
A crucial point, worth of a close investigation by the scientists of the field, is to assess at what extent the outcomes for significance of the various tests applied are the same. When comparing the results of different investigations, the diversity of the statistical tests applied in each one causes an amplification of the general inhomogeneity.
In the reviewed papers, the statistical tests used to verify the difference between the results for controls and patients are generally indicated. Some authors checked also possible differences, for one or more variability factors, among the various subject groups; their information is therefore more accurate.

5. Summary of the retrieved data

The retrieved data are non numerous, being the withdrawal of the fluid unpleasant; the control samples are taken from individuals undergoing lumbar puncture for neurological exams. Some values have been found for Cu, Fe, Mn and Zn, whereas only few results have been retrieved for Cr and Si. As far as other elements are concerned, the data are absolutely scarce or determined only once, mainly by the scientists of ISS.
Examining the collected values, regarding **copper** - see Tab. 4 - no significant variations for patients as compared to controls were found in trials performed by diverse teams; nevertheless, in other papers (not showing analytical data for Cu), Pall et al. (1987) and Pan et al. (1997) - see Tab. 12 - assess to have observed a remarkable elevation. In the case of **manganese** too – see Tab. 6 - no changes were observed in the different investigations; of note, the levels determined by Gazzaniga et al. (1992) are higher than those found by the other author groups. Concerning **calcium** and **magnesium** - see Tab. 2 - no significant alterations are reported; however, Takahashi et al. (1994) - see Tab. 12 - assess to have found a lesser Mg level in patients. As for **zinc** - see Tab. 5 - Forte et al. (2004) and Alimonti et al. (2007b) observed in PD a slight diminution, which in the trials by Jiménez- Jiménez et al. (1998) and Qureshi et al. (2005 and 2006) attained the significance. Aguilar et al (1998) found for PD subjects a non significant **selenium** increment - see Tab. 7; a significant elevation resulted instead in all the patients, with both positive and negative response to the therapy, enrolled by Qureshi et al. (2006). **Lead** - see Tab. 8 - was found to be significantly reduced in patients by the team of ISS (Bocca et al. 2004 and Alimonti et al. 2007b), that obtained the same finding also for **silicon** (Forte et al. 2004, Bocca et al. 2006, Alimonti et al. 2007b) - see Table 8. In the case of **iron** - see Tab. 3 - the most interesting element for PD, discordant results were unfortunately recruited. A significant depletion was found by Bocca et al. 2006 and Alimonti et al. 2007b; for a detailed description, see the paragraph 4.1.4. An elevation, also significant, was seen by Qureshi et al. (2005 and 2006); other scientists as Gazzaniga et al. (1992) and Jiménez- Jiménez et al. (1998) did not observe noticeable variations. The values determined by the ISS team appear to be remarkably lower than those published by the other groups. Dealing with **chromium** - see Tab. 7 - Aguilar et al. (1998) found similar amounts in the CSF of patients and controls; differently, Bocca et al. (2004) and Alimonti et al. (2007b) obtained much lower values and noticed a significant decrement in patients. **Al**, **Ba**, **Be, Bi**, **Co**, **Li**, **Mo**, **Ni**, **Sb**, **Sn, Sr**, **Tl**, **V, W** and **Zr** were determined only by the scientists of ISS - see Tab. 9, 10, 11. No variations were observed, except significant decreases of Co and Sn. Regarding the results for Be and V, see the paragraph 4.1.4, where are described also the findings for **Cd** and **Hg**; the values for these last four elements are shown in Tab. 10.

Bourrier-Guerin et al. 1985 report values for 13 elements in 70 patients (34 M and 36 F) affected by different neurodegenerative diseases; patients were grouped all together. Si and Zn resulted to be significantly higher in men than in women.

Campanella et al. 1973 enrolled 18 individuals (5 controls; 7 untreated patients; 6 patients treated with dopaminergic drugs), age > 39 y, no gender given. They published the Cu mean amount found for each subject. For both patients groups, the range of the mean values was wider than for controls.

Kjellin 1967a and 1967b reported Cu and Fe amounts in the CSF of a female patient (69 y) suffering from parkinsonism.
Cu and Fe resulted respectively higher and lesser in comparison to a unique control, who was probably in both cases a male of 65 y.

Mindadse & Tschikowani 1967 found that Au amount in PD patients was 66 μg/g, about the double than in controls. The Au concentration in controls (blood donors) is however not reported.

Pall et al. 1987 found in patients (24) with untreated, idiopathic PD, a higher Cu concentration than in controls (34) with various other neurological diseases. For Fe, they did not observe a difference between patients (26) and controls (33).

Pan et al. 1997 observed that Cu increased significantly in PD patients; on the other hand, the amounts of Cd, Fe, Mn and Zn did not change.

Takahashi et al. 1994 evaluated Br, Cu, Fe, Se, Zn and Mg levels in 25 controls and 20 PD patients (13 untreated and 7 treated with L-dopa). The mean Mg concentration in both treated and untreated parkinsonians was found to be lower than in controls.

Woodbury et al. 1968 determined in one PD patient a Mg amount overlapping the mean value found for controls (11). Always in one patient, these authors determined a higher zinc concentration than in controls (2).

Table 12. Additional information

6. Conclusion

Regarding the matrix CSF, the first remark we make is that the element concentration values available in the literature are non numerous, probably due to the rareness of the

samples. Among the recruited papers, the range of values was recorded only in that by Belliveau et al. (1990). Knowing the ranges for controls and patients would allow to establish a range of normalcy for each element and, as a consequence, to individuate in patients a possible shift towards elevation or diminution. Examining the retrieved data, it is evident that for some elements the results obtained by the various research groups are of different levels. For Cu, the values published by the different teams vary from less than two decades to more than a hundred of μg/L. For Fe and Zn, the scientists of ISS determined concentrations much lesser than the other teams. For Cr, Aguilar et al. (1998) found values an order of magnitude higher than those reported by the team of ISS. The discrepancies regarding the element levels are difficult to explain. The mean values retrieved have often very large standard deviations. In the case of Be, Cd, Cr Hg, Se, Si, V, the SDs are sometimes as high as the half of the mean. A similar situation resulted for Mn and Cu in the study by Jiménez-Jiménez et al. (1998). Dealing with Fe, Jiménez-Jiménez et al. (1998) and Forte et al. (2004) detected SD values very close to the mean. SDs close to the mean were also found for Co and Pb by the researchers of ISS; they report, for Ni, SDs even higher. The large SDs can be due to the individual variability and/or to the low number of the subjects enrolled; they are not surprising also when the element concentration level is very low (a few μg/L or less). In the case of Cr and Se, and mostly in that of Fe and Si, high SDs are less expected. Obviously, they make it really difficult to evaluate the significance of the difference among the results.

In this review, we have verified the influence, on the results, of number, age, gender of the subjects enrolled; health conditions (with regard also to clinical variables as duration and severity of the disease and pharmacological therapies) were demonstrated to be other influencing factors. The importance of adequate analytical procedures and statistical tests has been previously described (see the respective paragraphs).

At this point, we can suggest that, in a trial, attention should be paid to match, as far as possible, age and health conditions of the subjects belonging to the same group; this is more difficult to obtain in the case of patients. Concerning gender, separate male and female groups could reveal possible unexpected information. A similar number of individuals in the various groups should be enrolled; anyway, we are aware that, in the clinical practice, the scarceness of the CSF control samples and the prevalent number of male PD patients (Alimonti et al. 2007b) make these requirements not always achievable. In addition, all the previously mentioned factors should be not too different when confronting the results of the various studies, to allow a proper comparison. It is evident that this is a truly unattainable task.

In our opinion, a real upgrading in this field could actually be achieved if many specific indications were recorded in the single studies. Regarding every subject enrolled, information as age, gender, health condition, lifestyle and environmental exposure should be clearly reported; for each individual, also the results obtained for every element should be published. A detailed description of the various steps of sampling and analytical procedures should also be given; the single steps should be performed according to the indications most recently standardized.

Following all these suggestions, a database useful for diverse kind of investigations would be obtained; retrospective studies as meta-analyses, based on single factors affecting the results, could be derived; even findings not detectable at the moment could arise.

7. References

Aguilar, M.V.; Jimenez-Jimenez, F.J.; Molina, J.A.; Meseguer, I.; Mateos-Vega, C.J.; Gonzalez-Munoz, M.J.; de Bustos, F.; Gomez-Escalonilla, C.; Ortí-Pareja, M.; Zurdo, M. & Martinez-Para, M.C. (1998). Cerebrospinal fluid selenium and chromium levels in patients with Parkinson's disease. *J. Neural Transm*., Vol.105, pp. 1245-1251

Alimonti, A.; Ristori, G.; Giubilei F.; Stazi, M.A.; Pino, A.; Visconti, A.; Brescianini, S.; Sepe Monti, M.; Forte, G.; Stanzione, P.; Bocca, B.; Bomboi, G.; D'Ippolito, C.; Annibali, V.; Salvetti, M. & Sancesario, G. (2007a). Serum chemical elements and oxidative status in Alzheimer's disease, Parkinson disease and multiple sclerosis. *Neurotoxicol.,* Vol.28, pp. 450-456

Alimonti, A.; Bocca, B.; Pino, A.; Ruggieri, F.; Forte, G. & Sancesario, G. (2007b). Elemental profile of cerebrospinal fluid in patients with Parkinson's disease. *J. Trace Elem. Med. Biol*., Vol.21, pp. 234-241

Belliveau, J.F.; Friedman, J.H.; O'Leary, G.P. Jr. & Guarrera, D. (1990). Evaluation of increased copper levels in the cerebrospinal-fluid of Parkinson's patients, In: *Metal Ions in Biology and Medicine,* P. Collery, L.A. Poirier, M. Manfait & J.C. Etienne, (Eds.) 89-91, John Libbey Eurotext, London-Paris

Bocca, B.; Alimonti, A.; Petrucci, F.; Violante, N.; Sancesario, G.; Forte, G. & Senofonte, O. (2004). Quantification of trace elements by sector field inductively coupled plasma mass spectrometry in urine, serum, blood and cerebrospinal fluid of patients with Parkinson's disease. *Spectrochim. Acta Part B*, Vol.59, pp. 559-566

Bocca, B.; Alimonti, A.; Senofonte, O.; Pino, A.; Violante, N.; Petrucci, F.; Sancesario, G. & Forte, G. (2006). Metal changes in CSF and peripheral compartments of PD patients. *J. Neurol. Sci*., Vol.248, pp. 23-30

Bourrier-Guerin, L.; Mauras, Y.; Truelle, J.L. & Allain, P. (1985). CSF and plasma concentrations of 13 elements in various neurological disorders. *Trace Elem. Med*., Vol.2, pp. 88-91

Campanella, G.; Carrieri, P.; Romito, D. & Pasqual-Marsettin, E. (1973). Ferro, transferrina, rame e ceruloplasmina del siero e del liquor nelle malattie extrapiramidali e nelle miopatie primitive. [Iron, transferrin, copper and ceruloplasmin of the serum and cerebrospinal fluid in extrapyramidal diseases and primary myopathies]. *Acta Neurol*. (Napoli), Vol.28, pp. 1-34

Dexter, D.T.; Wells, F.R.; Lees, A.J.; Agid, F.; Agid, Y.; Jenner, P. & Marsde, C.D. (1989). Increased nigral iron content and alterations in other metal ions occurring in brain in Parkinson's disease. *J. Neurochem*., Vol.52, pp. 1830-1836

Dexter, D.T.; Carayon, A.; Javoy-Agid, F.; Agid, Y.; Wells, F.R.; Daniel, S.E.; Lees, A.J.; Jenner, P. & Marsden, C.D. (1991). Alterations in the levels of iron, ferritin and other trace metals in Parkinson's disease and other neurodegenerative diseases affecting the basal ganglia. *Brain,* Vol.114, pp. 1953-1975

Forte, G.; Bocca, B.; Senofonte, O.; Petrucci, F.; Brusa, L.; Stanzione, P.; Zannino, S.; Violante, N.; Alimonti, A. & Sancesario, G. (2004). Trace and major elements in whole blood, serum, CSF and urine of patients with PD. *J. Neural Trans*., Vol.111, pp. 1031-1040

Forte, G.; Alimonti, A.; Pino, A.; Stanzione, P.; Brescianini, S.; Brusa, L.; Sancesario, G.; Violante, N. & Bocca, B. (2005). Metals and oxidative stress in patients with Parkinson's disease. *Ann. Ist. Super. Sanità*, Vol.41, pp. 189-195

Gazzaniga, G.C.; Ferraro, B.; Camerlingo, M.; Casto, L.; Viscardi, M. & Mamoli, A. (1992). A case control study of CSF copper, iron and manganese in Parkinson disease. *Ital. J. Neurol. Sci*., Vol.13, pp. 239-243

Gellein, K.; Syversen, T.; Steinnes, E.; Nilsen, T.I.; Dahl, O.P.; Mitrovic, S.; Duraj, D. & Flaten, T.P. (2008). Trace elements in serum from patients with Parkinson's disease - A prospective case-control study - The Nord-Trøndelag Health Study (HUNT). *Brain Res*., Vol.1219, pp. 111-115

Ghayour-Mobarhan, M.; Taylor, A.; New, S.A.; Lamb, D.J. & Ferns, G.A. (2005). Determinants of serum copper, zinc and selenium in healthy subjects. *Ann. Clin. Biochem*., Vol.42, pp. 364-375

Griffiths, P.D.; Dobson, B.R.; Jones, G.R. & Clarke, D.T. (1999). Iron in the basal ganglia in Parkinson's disease. An in vitro study using extended X-ray absorption fine structure and cryo-electron microscopy. *Brain*, Vol.122, pp. 667-673

Hegde, M.L.; Shanmugavelu, P.; Vengamma, B.; Rao, T.S.; Menon, R.B.; Rao, R.V. & Rao, K.S. (2004). Serum trace element levels and the complexity of inter-element relations in patients with Parkinson's disease. *J. Trace Elem. Med. Biol*., Vol.18, pp. 163-171

Jimenez-Jimenez, F.J.; Molina, J.A.; Aguilar, M.V.; Meseguer, I.; Mateos-Vega, C.J.; Gonzalez-Munoz, M.J.; de Bustos, F.; Martínez-Salio, A.; Ortí-Pareja, M.; Zurdo, M. & Martinez-Para, M.C. (1998). Cerebrospinal fluid levels of transition metals in patients with Parkinson's disease. *J. Neural Transm*., Vol.105, pp. 497-505

Kjellin, K.G. (1967). Trace elements in the cerebrospinal fluid, In: *Nuclear Activation Techniques in The Life Sciences*, A. Ericson, (Ed.), 517-532, IAEA Proc. Series SM-91/3

Kjellin, K.G. (1967). The CSF iron in patients with neurological diseases. *Acta Neurol. Scand*., Vol.43, pp. 299-313

Kouremenou-Dona, E.; Dona, A.; Papoutsis, J. & Spiliopoulou, C. (2006). Copper and zinc concentrations in serum of healthy Greek adults. *Sci. Total Environ*., Vol.359, pp. 76-81

Lopes, P.A.; Santos, M.C.; Vicente, L.; Rodrigues, M.O.; Pavão, M.L.; Nève, J. & Viegas-Crespo, A.M. (2004). Trace element status (Se, Cu, Zn) in healthy Portuguese subjects of Lisbon population: a reference study. *Biol. Trace Elem. Res*., Vol.101, pp. 1-17

Markesbery, W.R.; Ehmann, W.D.; Alauddin, M. & Hossain, T.I. (1984). Brain trace element concentrations in aging. *Neurobiol. Aging*, Vol.5, pp. 19-28

Mindadse, A.A. & Tschikowani, T.I. (1967). Über die Verteilung von Spurenelementen (Mangan, Kupfer, Zink und Gold) im Serum und Liquor bei Epilepsie und Parkinsonsyndrom [On the distribution of trace elements (manganese, copper, zinc, and gold) in serum and cerebro-spinal fluid in epilepsy and parkinsonism]. *Dtsch Gesundheitsw*., Vol.22, pp. 1746-1748

Ongkana, N.; Tohno, S.; Tohno, Y.; Suwannahoy, P.; Mahakkanukrauh, P.; Azuma, C. & Minami, T.(2010). Age-related changes of elements in the anterior commissures and the relationships among their elements. *Biol. Trace Elem. Res.,* Vol.135, pp.86-97

Pall, H.S.; Williams, A.; Blake, D.R.; Lunec, J.; Gutteridge, J.M.; Hall, M. & Taylor, A. (1987). Raised cerebrospinal-fluid copper concentration in Parkinson's disease. *Lancet*, Vol.2, pp. 238-241

Pan, B.Y.; Cheng, Q.L.; He, Z.X. & Su, C.C. (1997). Transition metals in serum and CSF of patients with Parkinson's disease. *Mov. Disord.*, Vol.12 (Suppl.), p. 33

Pande, M.B.; Nagabhushan, P.; Hegde, M.L.; Rao, T.S. & Rao, K.S. (2005). An algorithmic approach to understand trace elemental homeostasis in serum samples of Parkinson disease. *Comput. Biol. Med.*, Vol.35, pp. 475-493

Qureshi, G.A.; Qureshi, A.A.; Memon, S.A.; Sarwar, M. & Parvez, S.H. (2005). The role of iron, copper and zinc and their effects in on/off Parkinson's patients on L-dopa therapy. *Biogenic Amines*, Vol.19, pp. 257-267

Qureshi, G.A.; Qureshi, A.A.; Memon, S.A. & Parvez, S.H. (2006). Impact of selenium, iron, copper and zinc in on/off Parkinson's patients on L-dopa therapy. *J. Neural Transm.*, Vol.71, (Suppl.), pp. 229-236

Rajput, A.H.; Uitti, R.J.; Rozdilsky, B. & Yuen, W.K. (1985). Distribution of metals in Parkinson's disease and control brains. *Neurol.*, Volo.35 (Suppl. 1), p. 224.

Riederer, P.; Sofic, E.; Rausch, W.D.; Schmidt, B.; Reynolds, G.P.; Jellinger, K. & Youdim, M.B. (1989). Transition metals, ferritin, glutathione and ascorbic acid in parkinsonian brains. *J. Neurochem.*, Vol.52, pp. 515-520

Sparks, D.L.; Ziolkowski, C.; Connor, D.; Beach, T.; Adler, C. & Sabbagh, M. (2008). Copper and cognition in Alzheimer's disease and Parkinson's disease. *Cell Biol. Toxicol.*, Vol.24, pp. 426-430

Speziali, M. & Orvini, E. (2003). Metals distribution and regionalization in the brain, In: *Metal Ions and Neurodegenerative Disorders*, P. Zatta (Ed.) 15-65,World Scientific Publishing Co., Singapore-New Jersey

Speziali, M. & Di Casa, M. (2009) Copper, iron, zinc and other element concentrations in cerebrospinal fluid of Parkinson's disease patients – considerations on literature data. *Trace Elem. Electrol.*, Vol.26, pp. 171-176

Takahashi, S.; Takahashi, J.; Osawa, N.; Abe, T.; Yonezawa, H.; Sera, K. & Tohgi, H. (1994). Trace elements analysis of serum and cerebrospinal fluid with PIXE - Effect of age and changes in parkinsonian patients. *Nippon Ronen Igakkai Zasshi*, Vol.31, pp. 865-871

Tan, X.; Luo, Y.; Pan, J.; Huang, B. & Wang P.Q. (2007). Serum Cu, Fe, Mn, and Zn levels and Parkinson's disease. *Parkinsonism Rel. Dis.* Vol.13 (Suppl.), p. S134

Tohno, Y.; Tohno, S.; Ongkana, N.; Suwannahoy, P.; Azuma, C.; Minami, T. & Mahakkanukrauh, P. (2010). Age-related changes of elements and relationships among elements in human hippocampus, dentate gyrus, and fornix. *Biol. Trace Elem. Res.* ,Vol.138, pp. 42-52.

Woodbury, J.; Lyons, K.; Carretta, R.; Hahn, A. & Sullivan, J.F. (1968). Cerebrospinal fluid and serum levels of magnesium, zinc, and calcium in man. *Neurol.*, Vol.18, pp. 700-705

Yasui, M.; Kihira, T. & Ota, K. (1992). Calcium, magnesium and aluminum concentrations in Parkinson's disease. *Neurotoxicol*., Vol.13, pp. 593-600.

8

Language Processing in Parkinson's Disease Patients Without Dementia

Katrien Colman and Roelien Bastiaanse
University of Groningen
The Netherlands

1. Introduction

One of the major pathophysiological features in Parkinson's disease, from now on referred to as PD, is the loss of dopaminergic neurons in the substantia nigra, which in turn results in dysfunction of the cortico-striato-cortical circuits (Bartels & Leenders, 2009). In PD the components of the cortico-striato-cortical circuits are not in an optimal interaction, leading to insufficient engagement of for example the frontal and prefrontal lobes. Motor symptoms of tremor, bradykinesia, and rigidity are the clinical hallmark of PD (Wolters & Bosboom, 2007), however, non-motor symptoms are often present (Dubois & Pillon, 1995, 1997). In particular cognitive impairments in the domain of executive functioning have frequently been observed, both in late and also in very early stages of PD (Muslimovic et al., 2005). The term 'executive functioning' is used as a blanket term referring to a set of abilities that allow individuals to achieve goal-oriented behavior. These aspects of behavior can be regarded as top-down processes, in contrast to bottom-up processes that only represent stimulus-driven processing. Strauss et al. (2006) defined executive functioning as a collection of processes that are responsible for guiding, directing, and managing cognitive, emotional and behavioral functions, particularly during active, novel problem solving. As PD progresses, more severe cognitive impairments or dementia can occur (Aarsland et al., 2003). The dementia in PD exhibits normal or only slightly decreased performance in gnosis and praxis functions, and is typically characterized by a progressive dysexecutive syndrome with disturbed memory functions and attention (Dubois & Pillon, 1997).
In addition, it has repeatedly been shown that language functions in PD patients with dementia are affected. Demented PD patients show reduced verbal fluency, poor confrontation naming abilities, decreased word list generation, and difficulties in word-finding (Dubois & Pillon, 1997; Pahwa et al., 1998). However, prior to dementia, PD patients also evidence subtle language impairments. The question whether the language system itself is impaired, as for example in aphasia, or whether language performance is disrupted because of non-linguistic executive function disorders in PD is still unanswered. We assume that, intact executive functioning is a prerequisite for normal language functioning. Therefore, language processing deficits in PD will always be associated with executive function deficits. Under this view, the language faculty is not considered to be totally modular in nature, but thought to depend on other cognitive functions, since, for example, comprehending a sentence demands that a listener flexibly guides his/her attention to relevant linguistic information, maintains information in working memory during the

incremental development of the sentence interpretation and inhibits prepotent or incorrect parsing. This raises the question which aspect(s) of executive functioning are most important for language comprehension.

The studies described in this review reported on PD patients' production and comprehension in several languages (English, French, German, Greek and Dutch). From the literature it is clear that PD disrupts the processes involved in both language production and language comprehension.

In the present chapter, we will use Levelt's framework for sentence processing (1983, 1989) to clarify production and comprehension of spoken language. This includes implementation of the distinction between controlled and automatic cognitive processing. Figure 1 depicts Levelt's "Blueprint for the speaker" and shows the complex architecture of the various processes involved in speech production and comprehension.

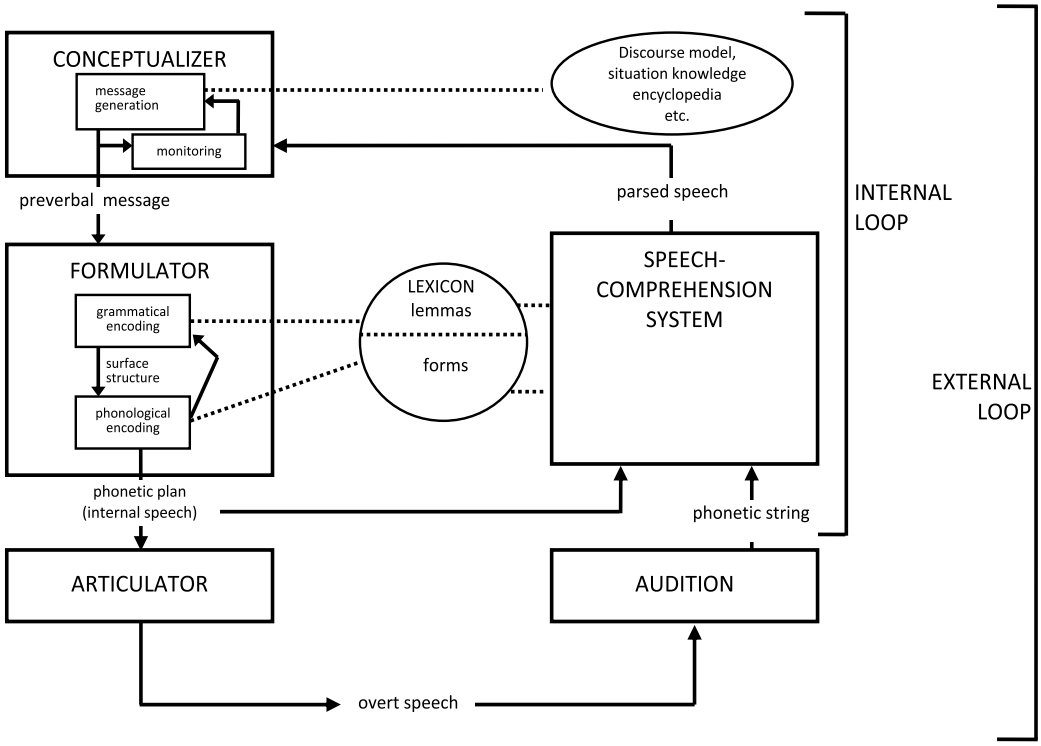


Fig. 1. Blueprint for the speaker (Adapted from Levelt, 1989)

In this figure, the boxes represent processing components and the circle as well as the ellipse represent knowledge stores. The framework consists of two subsystems, one for production and one for comprehension. The Production System is further divided into a Conceptualizer, a Formulator and an Articulator. When a speaker produces speech, he starts with an idea that he intends to communicate in the Conceptualizer. Conceptualizing demands working memory (Levelt, 1989), since during this stage an intention needs to be conceived and relevant information needs to be retrieved from long-term memory and ordered while keeping track of the discourse. In short, the Conceptualizer provides an interface between thought and language and produces a pre-verbal message. Then, using

two steps, the Formulator translates this pre-verbal message into a linguistic structure. In a first step, the Grammatical Encoder must access lemma information[1] from the mental lexicon (i.e., declarative knowledge) and activate syntactic building procedures stored in the Grammatical Encoder (i.e., procedural knowledge). Based on the properties of the message, the Grammatical Encoder will assign grammatical functions to the words and build a phrasal representation (e.g., verb phrases or noun phrases), specifying the hierarchical relation between syntactic constituents and their linear order. In a second step, the Phonological Encoder fills in the word forms in the structure that was generated by the Grammatical Encoder. It then constructs a phonetic plan, which is transformed into a spoken utterance by the Articulator. Formulation is "a largely automatic process" (Levelt, 1989, p. 21), implying that lexical retrieval and syntactic planning during production do not rely much on executive functions. However, declarative and procedural memory are both not disconnected from executive functions. For example, during the course of syntactic structure building the selected lemmas from declarative memory need to be maintained and updated by executive functions until the process is terminated.

On the right-hand side in Fig. 1, the Speech Comprehension System is depicted. During comprehension, a spoken utterance is mapped to a phonetic string by the Audition component, from which the Speech Comprehension System computes parsed speech, a representation of the input in terms of phonological, morphological, syntactic, and semantic composition. This representation is further processed by the Conceptualizer. Sentence parsing during comprehension is constrained by working memory capacity (Caplan & Waters, 1999; Just & Carpenter, 1992; Just et al., 1996; Waters & Caplan, 1996).

Speakers inspect their overt and covert speech for errors, thereby allowing themselves to inhibit and repair erroneous utterances. As Levelt (1989, p. 13) says, "a speaker is his own listener". Levelt localizes the central Monitor in the Conceptualizer (see Fig. 1). Very much simplified, Levelt's framework proposes that during language production the speaker monitors production through the Comprehension module. This proposal is known as the 'perceptual loop theory of speech monitoring', and claims that a speaker's phonetic plan is processed by the Speech Comprehension System during speech production, which allows the speaker to compare the comprehension of what he is about to say ('the internal loop') to what he originally intended to express. Speakers are also hypothesized to listen to their own overt speech, giving them another chance to detect errors ('the external loop'). In that case, they use the Audition component to analyze their own speech. Both feedback loops will reach the Monitor located in the Conceptualizer, which checks whether the parsed speech matches the intended speech. Upon error detection, the Monitor signals the speech production system to interrupt speech and to plan a repair process. The Monitor in Levelt's framework has been described as being a central, conscious process that oversees end products of speech production (Postma, 2000). Analogously to the monitoring system in speech production, Van Herten (2006), Van Herten et al. (2006), Vissers (2008), and Van de Meerendonk et al. (2009) proposed a monitoring process during comprehension inspired by the conflict monitoring theory of Botvinick et al. (2001). In the same line, Kuperberg (2007) suggested a monitoring process embedded in her non-syntactocentric, dynamic model of language processing.

[1] The lemma of a word contains the semantic and syntactic information, necessary for the construction of the syntactic structure of the sentence. A lemma is still very abstract and distinct from the word forms, that are stored at a different level in the Lexicon

This chapter presents an overview of the extensive and still growing literature examining the underlying mechanisms of the subtle language impairments in non-demented PD patients. The connectivity of the basal ganglia with especially the frontal cortical regions explains why language processing is a vulnerable cognitive function in the course of PD. We start with reviewing what is known about language production deficits in non-demented patients with PD, followed by a summary of the receptive language deficits in PD. This review will not be limited to deficits at the sentence level, but will also consider deficits at the word and discourse level. Over the years, a variety of methodologies have been used, and recently functional imaging in PD patients has begun to add information to the neural instantiation of the patients' language impairments. Studying language processing in PD allows researchers to analyze the effects of poorly functioning, yet still engaged cortico-striato-cortical circuitry during language performance. Some of the studies reviewed in this chapter aimed at examining language processing in PD, to ultimately define the role of the basal ganglia in language processing (e.g., Ullman et al., 1997; Friederici et al., 2003; Grossman et al., 2003; Kotz et al., 2003). In the final section of this chapter, advice for communication guidelines that would guarantee a better quality of life for patients suffering from PD is given. The chapter will be concluded with suggestions for future research on language processing in PD.

2. Language production in PD

2.1 Spontaneous speech

Spontaneous speech in PD patients is often characterized by hypokinetic dysarthria and hypophonia, joined in the term 'dysarthrophonia' (Ackermann & Ziegler, 1989). Some PD patients in the advanced disease stage produce repetitions of speech, which are also labeled as stuttering, speech iterations, or palilalia (Benke et al., 2000). The major complaints reported by PD patients are not as much related to the acoustic, perceptual and physiological changes to their speech, but are related to the effect of these changes on communication overall, their view of themselves and the detrimental effects of the effort required to overcome physical and mental limitations (Miller et al., 2006). Also, PD patients' prosody, facial expression and gestures are abnormal, probably because these are influenced by the cardinal motor impairment.

One of the focuses of this review on language processing is grammatical effects in the spontaneous speech of PD patients, which were first reported by Illes et al. (1988). The sentences produced by the moderately impaired PD patients were syntactically simple. The pattern may reflect an adaptive, compensatory mechanism to reduce speech-motor difficulty, or may actually be evidence of a language impairment intrinsic to the disease process. Illes and colleagues (Illes, 1989; Illes et al., 1988) favored the adaptation hypothesis, stating that as the severity of the disease and, hence, the dysarthria increases, PD patients adapt to or compensate for their motor speech difficulties. Using a verbal picture description task, Murray (2000) observed compromised grammar and informativeness of spoken language in PD patients. Furthermore, a relationship between syntactic changes in production and concomitant cognitive changes was found. While analyzing conversational speech, Murray and Lenz (2001) found that patients with greater cognitive deficits and dysarthria performed more poorly on syntactic measures than patients with either more intact cognitive abilities or more intelligible speech. They suggested that PD patients show syntax limitations in production, but only under certain task requirements or related to

other cognitive deficits. This conversational speech analysis showed that changes in language production in PD reflect concomitant cognitive and motor speech impairments, rather than being a pure language deficit. Ellis et al. (2006, see also Ellis, 2006 and Ellis & Rosenbek, 2007) analyzed narrative discourse in individuals with PD and in healthy control speakers. According to Ellis et al. (2006) the analysis of narrative discourse is as a method to differentially characterize expressive language form versus use[2]. They concluded that patients with mild to moderate PD demonstrate deficits in language use while maintaining spared language form.

Earlier, McNamara et al. (1992) suggested that mildly to moderately impaired PD patients have a reduced capacity to simultaneously speak and monitor one's own speech resulting in self-monitoring impairments during narrative discourse. To test overt speech monitoring in narrative discourse of patients with PD, they used the procedures of the Cookie Theft picture description task of the Boston Diagnostic Aphasia Examination (BDAE, Goodglass & Kaplan, 1972). The number and the distribution of uncorrected errors and two repair types were tallied. The results showed that PD patients made three times more errors than the age-matched control speakers and used both repair strategies, but relatively less often than the control speakers. According to the authors, this significant unawareness of speech errors is related to attentional dysfunctioning in PD. They furthermore suggested that PD patients display reduced sensitivity to context, which may complicate their language comprehension. In order to explicitly evaluate PD patients' pragmatic skills[3], McNamara and Durso (2003) used a formal pragmatic communication skills protocol (Prutting & Kirchner, 1987). The pragmatic communication skills were also rated on the basis of the assessment of (self-)awareness of the problem by individual PD patients and their spouses. It was concluded that PD patients were significantly impaired on measures of pragmatic communication abilities and were less aware of their communication problems. In line with Levelt's framework (1989, see Fig. 1) it is concluded that PD patients have a problem in their monitoring system and, thus, are not aware of their errors or, in other words, do not detect the mismatch when comparing their intentions and the actual speech output.

2.2 Verb production in sentence context

In 1997, Ullman and colleagues obtained evidence for a role of the basal ganglia in morphosyntactic production. Ullman et al. (1997) reported the results of a sentence completion task, which required the participants to read aloud randomly ordered sentence pairs and to fill in a past tensed verb. The authors found a correlation between right-side hypokinesia and the impaired production of rule-generated (regular) past tense forms in PD. The authors concluded that PD leads to the suppression of both motor activity and grammatical rule application. In essence, Ullman et al. (1997) and Ullman (2001) proposed that the frontal basal ganglia system, which is damaged in PD, constitutes the procedural memory system that regulates grammar (Grammatical Encoder in Fig. 1) and that the

[2] In defining 'what is language', Bloom and Lahey (1978) divided language into three different, but overlapping aspects: content, form and use. In brief, language content includes factors such as semantics, including word knowledge and world knowledge, and vocabulary. Language form refers to the grammar of the language, while language use is akin to the area of pragmatics.

[3] Pragmatic skills involve the ability to use and interpret verbal and nonverbal language appropriately within the social context in which communication occurs, requiring a degree of inference and interpretation (Perkins, 2005).

mental lexicon depends on declarative memory (see Fig. 1), embedded in the temporal lobe, which is largely intact in PD. Set in Levelt's framework (Fig. 1), it is proposed that PD patients have a deficit in grammatical encoding. As a result, PD patients are not able to produce the past tense form of regular verbs.

In the following years, the vast majority of studies on verbal morphosyntactic production in PD focused on testing the Declarative-Procedural hypothesis of Ullman et al. (1997), but the PD data of the Ullman study could not be replicated (Almor et al., 2002; Longworth et al., 2003; Longworth et al., 2005; Penke et al., 2005; Terzi et al., 2005). Longworth et al. (2005) found a tendency in English-speaking PD patients (among other patients with striatal damage) to perseverate on the cue (i.e., verb stem) rather than to produce past tense verbs as requested. Longworth et al. (2005) argued against an isolated grammatical deficit in PD and suggested that the striatum plays a general (i.e., not specific to language), inhibitory role in the later, controlled stages of language comprehension and production. The deficits in PD may reflect impairment of inhibition of competing alternatives during the later controlled processes involved in both comprehension and production (Longworth et al., 2005). Related is our evidence for executive dysfunctions being correlated to deficits in verb production in sentence context (Colman et al., 2009). Contrary to the findings of Ullman et al. (1997), but consistent with the findings of Longworth et al. (2005), no influence of regularity on verb production in sentence context was detected in the Dutch-speaking PD patients. In a study on verb production in sentence context, we showed that a deficit with regular inflection is not a characteristic for Dutch-speaking PD patients (Colman et al., 2009). We furthermore suggested that because of failing automaticity, PD patients relied more on the cortically represented executive functions. Unfortunately, due to the disturbed intimate relation between the basal ganglia and the frontal cortex, these executive functions are also dysfunctional. We manipulated the grammatical features of the test sentences, in order to simultaneously test verb retrieval and sentence integration processes in a group of PD patients compared to a control group consisting of age and education matched healthy participants. All subjects were assessed on both verb production in sentence context as well as on cognitive functions relevant for sentence processing. The verb production performances of the PD patients were correlated to their scores on executive function tasks. Analyses of PD patients' performance revealed that they have set-switching deficits and decreased sustained visual attention. The performance on verb production of PD patients was associated with the set-switching deficits, suggesting that PD patients who show poor set-switching have more difficulties with verb production. Many verb tense errors were made in sentences targeting the present tense. In our verb production task participants were instructed to inflect the verb in the past tense only in the presence of a temporal adverb referring to the past (e.g., 'yesterday') and in the present tense if the adverbial time phrase was absent. It is therefore suggested that the test materials and associated instructions provoked the tense errors. Due to the absence of a temporal adverb, PD patients were unable to switch to the present tense and showed 'stuck-in-set perseverations' which were evoked by the previous sentences. Evidence for self-monitoring deficits has earlier been reported by McNamara et al. (1992). While monitoring their performance, PD patients seemed to forget the instruction, especially in the longer subordinate sentences where working memory was challenged more than in the short main clauses. Hence, in Colman et al. (2009) set-switching impairments played a major role in performing the task assessing verb production in sentence context. These set-switching impairments reduce PD patients' performance seriously. Although the PD patients in our study did not show a decreased

working memory capacity compared to healthy speakers, verb production was associated with working memory in PD patients. In healthy speakers, the production of verbs is a rather automatic language processing task, which is confirmed by the fact that no association was found between verb production and working memory in healthy controls. Automatic behavior is thought to be mediated by the basal ganglia (Saling & Phillips, 2007). Since PD is characterized by a dopaminergic dysfunction of the basal ganglia, we assume that PD patients cannot produce verbs in a rather automatic way as well as healthy speakers and, therefore, they need to rely more on their working memory, which we consider to be a compensatory mechanism.

2.3 Single word production tasks

The tests of word fluency that were employed in the studies that will be discussed in the next paragraphs all test, apart from semantic memory, aspects of executive functioning. In a standard word fluency task the subjects are asked to name as many words as possible within a given semantic category (known as semantic or category fluency) or starting with a certain letter (known as phonemic or letter fluency) during a restricted time period. During an alternating fluency task, subjects have to generate words alternately using two fluency probes, which could either be from the same domain (i.e., letter-letter or category-category) or from different domains (i.e., category-letter). In a standard fluency task, planning abilities are evaluated, while in an alternative fluency task, set shifting abilities are evaluated.

Impairments in non-demented PD patients have been reported in both semantic and phonemic fluency, but the most consistent finding is impaired performance in semantic fluency (e.g., Flowers et al., 1995; Grossman, Carvell et al., 1992, Grossman et al., 1993; Gurd & Ward, 1989; Van Spaendonck et al., 1996).

Henry and Crawford (2004) did a meta-analysis of 68 studies published between 1983 and 2002 which included more than 4600 PD participants. One of the aims was to find out if the word fluency deficit associated with PD predominantly reflects executive dysfunction, or problems with semantic memory, which is related to declarative memory. The outcome of the analysis was that, although PD was associated with deficits upon tests of phonemic and semantic fluency for studies that assessed both measures, the semantic fluency deficit was significantly larger than the phonemic fluency deficit. Moreover, since the confrontation naming deficit for the Boston Naming Test (BNT; Kaplan et al., 1983), a measure that imposes only minimal demands upon cognitive speed and effortful retrieval, was equivalent in magnitude to the deficits of these two types of fluency, Henry and Crawford concluded that PD is associated with a particular deficit in semantic memory. However, tests of alternating fluency were associated with slightly larger deficits than standard measures of fluency, which supports evidence for a specific deficit in cognitive set-shifting (Henry & Crawford, 2004). Some PD patients evidenced impairments in semantic knowledge, which correlate with their executive dysfunctions (Portin et al. 2000). The exact underlying nature of the semantic deficits has yet to be determined.

Interestingly, Auriacombe et al. (1993) examined the traditional semantic and phonemic fluency tasks, but also examined fluency performance in the non-verbal modality (i.e., design fluency and category drawing task). They found that PD patients' performance on the non-verbal fluency task was comparable to healthy speakers, and confirmed the discrepancy between relatively intact phonemic fluency and impaired semantic fluency. It is not necessary to retrieve a word form during category drawing, since knowledge of the concept underlying a target superordinate (i.e., vegetable) and the exemplars that contribute

to a superordinate is sufficient. To check the hypothesis that PD patients are impaired in the retrieval of semantic information, Auriacombe et al. (1993) also administered a supraspan verbal learning task. A large proportion of the PD patients showed difficulties with free recall, but these patients were accurate at recognition, which is consistent with a retrieval deficit, and not an impairment of semantic memory itself. PD patients thus have difficulties retrieving the phonological form that is the label of an exemplar (Levelt et al., 1991).

In addition, in PD, action naming is often found to be more impaired than object naming (Bertella et al., 2002; Cotelli et al., 2007), a phenomenon also observed in agrammatic/Broca's aphasic patients. Related to this, Signorini and Volpato (2006) found that PD patients were impaired on an action fluency task but not on semantic and phonemic fluency tasks. However, analysis of spontaneous speech production of PD patients did not show the expected discrepancy between nouns and verbs, which supports the hypothesis that it is not the representation of verbs, but rather the utilization of the verb emerging under specific task demands that is troublesome (Pignatti et al., 2006). Moreover, verb fluency scores also discriminate between demented PD patients and non-demented PD patients and healthy elderly control participants, whereas tests of letter or category verbal fluency do not (Piatt et al., 1999a and 1999b). Piatt et al. (1999a, 1999b) concluded that verb fluency was particularly sensitive to the fronto-striatal pathophysiology of PD patients with dementia. According to these authors, verb fluency reflects the underlying integrity of frontal lobe circuitry, and problems on verbal fluency tasks could therefore indicate deficits in executive functioning.

Péran et al. (2003) developed a French word generation task that requires a semantic and grammar driven selection of single words over a limited time period. Compared to healthy control participants, non-demented PD patients made more grammatical errors in the noun-verb-generation task than in the verb-noun-generation task. Péran et al. (2003) suggested that this discrepancy was due to the combined effect of impaired set switching and a specific grammatical impairment in verb production. The authors assume that in the verb-noun task, the impact of impaired switching is compensated by the easier noun production, whereas in the noun-verb task both the switching and production of the verb were dysfunctional.

However, the argument that PD specifically affects verb processing was contradicted in a recent word generation study in PD conducted by Crescentini et al. (2008). Behavioral tasks already showed before that the Reaction Times (RTs) and accuracy of word generation both depend on the number of possible responses (response selection) and on the strength of association between cues and responses (associative strength) (Cheng & Martin, 2005; Martin & Cheng, 2006; Thompson-Schill & Botvinick, 2006). Based on these findings, Crescentini et al. (2008) controlled the response selection demands and association strength of the verb and the noun stimuli during a word generation task. The critical condition for PD patients was the one with a weak association between the stimulus and the response as opposed to the grammatical class. Crescentini et al. (2008) suggested that the verb generation problem in PD is caused by the fact that nouns are typically more associated with other nouns than with verbs in the semantic network. During the noun-verb condition, PD patients seem to have problems with both switching to task-relevant representations (i.e., verbs) and with inhibiting the task-irrelevant and more strongly activated options (i.e., nouns). Based on these findings, the authors proposed a non-language-specific involvement of the basal ganglia in the controlled rather than the routine semantic processes required during lexical retrieval.

One explanation for the discrepancy between verb and noun retrieval is that verb retrieval is more demanding than noun retrieval in terms of executive functioning (e.g., Péran et al., 2003; Piatt et al., 1999a and 1999b). The idea is that retrieving the name of an object elicits a more automatic lexical retrieval response than retrieval of the action name, which demands a more controlled retrieval. In other words, impaired action naming is seen as a result of executive function impairment. According to Levelt's framework (see Fig. 1), the lemmas contain information about word meaning, and word class. The lemmas of verbs additionally contain information on thematic roles, argument structure, and subcategorisation frame. Comparable to what was found for individuals with Broca's aphasia (Bastiaanse & Van Zonneveld, 2004), we suggest that for PD patients verbs are more difficult to produce than nouns, because verb lemmas contain simply more grammatical information than noun lemmas.

An alternative hypothesis for the discrepancy between verb and noun retrieval is that the link between representation of action words and representation of motor acts per se in the human motor and premotor cortex is damaged, leading to verb retrieval problems. The existence of a similar verb-naming deficit in other motor disorders, such as corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) (Cotelli et al., 2006), has provided a major argument for the idea that semantic mechanisms concerning the verb are grounded in the motor system of the brain. To test whether the motor system comes into play during the processing of verbs, Boulenger et al. (2008) compared lexical decision latencies for action verbs and concrete nouns of non-demented PD patients (off and on dopaminergic medication) using a masked priming paradigm. Priming effects for action verbs, but not for concrete nouns, were nearly absent in PD patients off treatment, confirming that processing lexico-semantic information of action words depends on the integrity of the motor system. As a follow up to their earlier French verb generation task, Péran et al. (2009) explored the relationship between the motor deficit in PD patients and brain activation in noun and verb generation tasks conducting a functional neuroimaging study. Although they did not find differences between the brain activity during the production of object-related action words and of object names, they did observe a clear relationship between brain activity and the severity of the motor deficit (as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS), Fahn et al., 1987) in PD. This relation was particularly found during generation of action verbs in response to manipulable biological objects, in the pre- and post-central gyri bilaterally, left frontal operculum, left supplementary motor area and right superior temporal cortex. The impairment in the motor cortico-striato-cortical circuits in PD may result in the recruitment of a wider cortical network designed to alleviate the disturbed motor representations during the demanding generation of action verbs in response to manipulable objects.

3. Receptive language functions in PD

In the following section, receptive language functions in PD, with a particular focus on sentence comprehension of non-canonical sentences, will be discussed.

3.1 Comprehension of non-canonical sentences

From the early nineties of the last century, off-line tasks such as sentence-to-picture matching and grammaticality judgment have revealed that comprehension of complex syntactic structures (i.e., non-canonical structures such as passives) is vulnerable in

individuals with PD (see Grossman, 1999 and Murray, 2008 for an extensive review). Sentences are defined as syntactically complex when the thematic roles are not in base (or canonical) word order and therefore require extra grammatical operations. The following examples are given of an active (a) and a passive (b) sentence in Dutch. Important to note is that base word order in Dutch is Subject-Object-Verb (SOV).

a. De kinderen plukken de appels
   'The children pick the apples'
b. De appels$_i$ worden door de kinderen t_i geplukt
   'The apples are by the children picked'

In passive constructions, the *grammatical roles* are in base order. In sentence (b) the subject ('the apples') precedes the finite verb ('are') which precedes the prepositional phrase ('by the children'). However, the *thematic (semantic) roles* are not in their base position. The theme ('apples'), precedes the finite verb, whereas the agent ('children') follows the finite verb.

Lieberman et al. (1990) were among the first to find a comprehension deficit that could not be attributed to compensatory motor strategies, which had been claimed to be responsible for the sentence production deficits in PD till then (Illes et al., 1988; Illes, 1989). Lieberman et al. (1990) attributed the sentence comprehension errors in PD to "some deterioration of the patient's ability to make use of the syntactic 'rules' involved in English" (1990, p. 364). Similarly, researchers have attributed the sentence comprehension deficit to an impairment of some aspects of grammatical processing as such (Cohen et al., 1994; Natsopoulos et al., 1991, 1993). However, according to Lieberman et al. (1990), the cognitive impairments and syntactic comprehension deficits in PD have a common physiological basis; they are both caused by disruption of the cortico-striato-cortical circuits. Lieberman et al. (1990, 1992) do not regard grammatical processing and executive functions as separate mechanisms. They take the position that syntax comprehension is achieved by the operations of non-domain-specific executive functions over language-specific knowledge. Consistent with this view, some researchers claim that it is not syntax itself, but rather the interaction with executive dysfunction that might reflect the sentence comprehension deficits in PD (see for example Colman, 2011; Colman et al., 2006; Geyer & Grossman, 1994; Grossman, Carvell et al., 1992; Hochstadt et al., 2006, 2009; Kemmerer, 1999; Lieberman et al., 1990, 1992). In addition, some researchers reported deficits in lexical-semantic processing during sentence comprehension. For example, Angwin et al. (2005) reported a general semantic processing deficit, but also reported that PD patients with comprehension deficits for non-canonical sentences showed a delayed time course of semantic activation. This finding added evidence to the proposal that slowed information processing is one of the causes of the sentence processing deficits in patients with PD (Grossman, Zurif et al., 2002; Lee et al., 2003).

Grossman, Lee et al. (2002) administered both a traditional off-line sentence processing task and an on-line word detection task to the same PD patients. Subjects were instructed to press a button as soon as they heard the target word in an auditorily presented sentence. Half of the sentences contained a grammatical agreement violation (e.g., subject-verb agreement violation) prior to the target word. In healthy persons, responses to the target word were slowed down when they immediately followed a morphosyntactic error. The off-line measure of sentence comprehension required subjects to answer a simple question about a semantically unconstrained sentence. In addition to the language tasks, a battery of executive function tests was also run. Off-line, PD patients were significantly impaired on non-canonical sentences and their comprehension was correlated with the executive measures. However, PD patients and healthy control participants were equally sensitive to

violations of grammatical agreements during on-line word detection. The comprehension impairment on the traditional measure in PD was argued to be related to impairments in inhibition and planning, emphasizing the important influence of task requirements on sentence comprehension in PD.

In the same year another study by Grossman and colleagues was published, using a different on-line methodology, that is, a list priming task (Grossman, Zurif et al., 2002). Those PD patients who had problems comprehending sentences with a non-canonical structure when measured off-line (e.g., "The boy that the girl chased was friendly") showed delayed lexical retrieval during the priming task. This was reported earlier for Broca's aphasic patients (Swinney et al., 1996; Zurif et al., 1993).

The Grossman group gained additional information on the connection between slowed lexical activation and sentence comprehension deficits in PD by applying the same word detection methodology as before, but by using a different violation type. Based on previous observation of PD patients' difficulty detecting phonetic errors in grammatical morphemes (Grossman, Carvell et al., 1992), the researchers tested phonetic errors in free grammatical morphemes and words as violation type (Lee et al., 2003). PD patients were insensitive to phonetic errors in free grammatical morphemes and showed a slowed sensitivity to words located in the non-canonical sentences. This delayed sensitivity was correlated with the measure of planning, which was seen as evidence for the fundamental contribution of executive functions to sentence comprehension. Lee et al. (2003) concluded that sentence comprehension impairments are due to limitations in specific executive resources such as attention to grammatical morphemes and delayed lexical retrieval of words, rather than being a pure linguistic deficit.

Hochstadt et al. (2006) conducted the first off-line study that also tested the inter-relationship between the distinct executive functions. The authors concluded that limits on sequencing and/or verbal working memory (i.e., executive component and articulatory rehearsal) are responsible for the sentence comprehension deficits in PD. Later, Hochstadt (2009) used eye-tracking to minimize the extraneous executive demands during off-line sentence-picture matching. Some of the PD patients in this study showed difficulties comprehending passive sentences and they looked toward a distractor picture before giving a response. One of the proposed explanations by Hochstadt (2009) for the errors in passive sentences is the exaggerated agent-first bias pointing to a reliance on heuristics to compensate for impaired syntax processing. However, this explanation did not hold for passives in general, since there was no evidence that the bias differed between patients with high and low error rates in final passive trials as compared to center passive trials.

To further explore the hypothesis that executive dysfunctions are involved in the comprehension deficits of passive sentences in PD (Lieberman et al., 1992), we recently tested Dutch-speaking PD patients on the comprehension of sentences that were varied for phrase structure complexity and sentence length (Colman, 2011) to see whether there was a relation between the processing of the sentences and relevant executive function deficits. In general, the PD patients showed slightly poorer sentence comprehension compared to healthy control participants. However, the difficulties encountered by PD patients were not limited to one specific grammatical aspect. Decreased set-switching, inhibition, and working memory abilities were all associated with comprehending non-canonical passive sentences, rather than one specific executive function being primarily associated with the comprehension difficulties. Deficits in sustained visual attention appear to underlie PD patients' overall comprehension performance, possibly due to the demands of the picture-

sentence matching task. Generally, our study confirms that the language faculty is not independent from executive functioning.

Several studies using Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) have investigated the pattern of brain activation during sentence processing in non-brain-damaged individuals. However, only a few imaging studies have investigated the underlying neural activity during sentence processing in PD patients. In an fMRI study, Grossman et al. (2003) found striatal activation in exclusively the brains of healthy senior volunteers for long sentences, relative to short sentences. Moreover, PD patients engaged significantly more brain regions associated with working memory than healthy participants to achieve the same level of comprehension accuracy as the control subjects. According to Grossman et al. (2003) the striatum contributes to cognitive resources such as working memory and information-processing speed. PD patients' sentence comprehension difficulties have been ascribed to their limited striatal recruitment, which causes an interruption of a large scale network important for cognitive resources that can interfere with sentence processing (Grossman et al., 2003).

Using Event Related Potential (ERP) studies, Friederici and colleagues have demonstrated that degeneration of the basal ganglia due to PD influences language-related ERP components dramatically and correlates with different aspects of language processing during comprehension (for an overview see Kutas & Van Petten, 1994; Osterhout & Holcomb, 1995) . In a study by Kotz et al. (2002) and by Friederici et al. (2003), the PD patients included showed an intact ELAN (reflecting highly automatic first-pass parsing processes), but a strongly reduced P600. The P600 is an ERP component that is controlled by attention and is explained as indicating secondary syntactic processes such as reanalysis and repair (Friederici & Mecklinger, 1996), or as reflecting syntactic integration processes in general (Kaan et al., 2000). According to Friederici et al. (2003), the alteration in the P600 reflected distortions of the late controlled syntactic integration processes in PD. This reduction in amplitude points to a failure in the activation of the generators of this ERP component in PD patients. The reduction in PD patients' P600 amplitude points to a lack of integrity of the cortico-striato-cortical circuits responsible for the P600 generation. The patient studies by Friederici and colleagues suggest that the frontal cortex and the basal ganglia are differently involved in sentence processing or are active during different stages of auditory sentence processing. The left frontal cortex and the left anterior temporal cortex both contribute to the early automatic processing underlying the (E)LAN, whereas the left basal ganglia contribute to the late controlled syntactic integration processes underlying the P600. The difficulties with syntactic integration processes as described by Friederici et al. suggest that the language system itself is disrupted in PD patients.

In a recent fMRI study, we evaluated the patterns of activation during the comprehension of sentences in which canonicity and grammaticality were manipulated in fifteen patients with PD compared to fifteen healthy older adults (Colman, 2011). Here we focus on the activation patterns related to the processing of the passives by the PD patients and healthy control participants. Our intergroup analysis contradicted the expectation of compensatory cortical activation (Grossman et al., 2003). However, PD patients showed significant increased activation for passive versus active sentences in the left medial/superior frontal gyrus compared to healthy control participants. Three possible explanations for the activation in this frontal area during the processing of passive sentences are suggested. PD patients may rely on working memory, lexical semantics or higher-level semantic processes involved in evaluation of plausibility to compensate for the lack of activation seen in the healthy control

participants when dealing with non-canonical passive sentences. First, Carpenter et al. (1994) hypothesized that working memory load is directly related to sentence complexity. As mentioned before, higher sentence complexity is related to the non-canonical order of roles (such as in passives). All in all, non-canonical sentences impose a higher demand on working memory than canonical sentences (King & Just, 1991). The PD patients possibly relied more on their intact working memory allocated in the prefrontal cortex to compensate for their difficulties to process the non-canonical passive sentences (for a review see Wager & Smith, 2003). Secondly, examining ambiguity resolution, Stowe et al. (2004) reported a similar left medial prefrontal area as in our study, which they linked to supporting higher-level semantic processes involved in evaluation of plausibility. Finally, it is suggested that the exclusive activation of the prefrontal cortex in PD patients for passive sentences reflects a lexical-semantic strategy for dealing with word order information, which was probably not always a guarantee for successful comprehension.

3.2 Lexical and semantic processing

Semantic priming tasks are a straightforward measure for the evaluation of lexical and semantic processes in patients with PD. In healthy participants, RTs to the target word are faster if the prime and the target are semantically related (doctor-NURSE) as compared to when the prime and target are not related (doctor-FLOWER) (see Neely, 1991 for extensive review on priming tasks). Copland (2003) found that PD patients are unable to suppress the infrequent meaning of homophones (bank-RIVER) and proposes therefore that the selective attentional engagement of the semantic network is impaired. Thus, PD compromises the controlled aspects of semantic processing rather than the automatic processes. During sentence comprehension tasks, lexical-semantic processing has been found to be abnormal in PD patients as well (Angwin et al., 2005). Angwin et al. (2004, 2006) also found that semantic processing deficits in PD are related to striatal dopamine deficiency since automatic semantic activation was compromised in PD patients when off medication .

Spicer et al. (1994) were the first to evidence a unique increased semantic priming effect in PD patients as compared to the normal control subjects, which they called 'hyperpriming'. This hyperpriming was suggested to be caused by slowness in the unrelated prime-target conditions. Spicer et al. (1994) suggested two possible levels of the deficit, either the pre-lexical level or the post-lexical level. Somewhat later, the same research group (McDonald et al., 1996) revised their theory and concluded that PD patients show poor performance whenever the task requires switching between response sets or different semantic categories. However, rather than hyperpriming reflecting a switching problem between semantically unrelated words, Mari-Beffa et al. (2005) suggested that a lack of lexical-semantic inhibitory control in participants with PD is responsible for it. This idea was confirmed by Castner er al. (2007), who furthermore concluded that subthalamic nucleus stimulation restored these inhibitory processes. Consequently, it is concluded that the basal ganglia are involved in both the automatic and controlled aspects of semantic priming and thus support both the involved facilitation and inhibition processes.

3.3 Verb processing

Using receptive tasks, the existence of a specific verb processing deficit in PD was found. Grossman et al. (1994) reported impaired verb learning. They taught PD patients and healthy age-matched controls the grammatical and semantic information of a new verb ('to wamble'). The semantic and grammatical information of the new verb was probed by sentence judgment

and picture classification. Significant impairment in recalling some aspects of the new verb was seen in 55% of the PD patients. These patients demonstrated a language-sensitive deficit in "appreciating grammatical information represented in the new verb" (Grossman et al., 1994, p. 413). However, a small number of PD patients responded randomly to probes of all information about the new verb, which suggests a memory impairment in these patients. More recently, Whiting et al. (2005) evaluated verb and context processing in PD by using a self-paced stop making sense task. The participants had to pace themselves through a sentence that was preceded by a context, which made the thematic role of the verb plausible or implausible. They found that PD patients were impaired in thematic role mapping, which was consistent with previous findings of Geyer and Grossman from 1994. Whiting et al. (2005) proposed that PD participants in their study processed sentences "on a more superficial level" than control subjects and concluded that the PD patients' performance was caused by both global discourse comprehension difficulties and impaired working memory.

3.4 Perceptive pragmatic language abilities

In daily life, healthy individuals interpret the intended meaning of language appropriate to the social context. Another line of research in receptive language functions has been focusing on the pragmatic language skills of PD patients. Pragmatic language use entails the ability to interpret nonliteral elements of language such as metaphors, proverbs, idioms, etc. Berg et al. (2003) conducted a survey of pragmatic language abilities and reported that PD patients exhibit impairments in making inferences,, comprehending metaphors and lexical ambiguities. The study by Whiting et al. (2005) showed that PD patients were less accurate than the control participants in using previously encountered discourse antecedents when deciding that a sentence stopped making sense. This is in line with the finding of Grossman, Crino et al. (1992) in which PD participants displayed an impaired ability to answer questions about previously encountered discourse elements compared to control participants. In addition, patients with PD have these problems also when resolving lexical ambiguities (Copland et al., 2001).

Monetta and Pell (2007) investigated how PD patients process metaphors using a timed property verification task (by Gernsbacher et al., 2001) compared to healthy control participants. The impact of PD on metaphor comprehension varied as a function of working memory ability, meaning that PD patients with a reduced working memory capacity were impaired in the comprehension of metaphors, whereas PD participants at a similar stage of disease but without working memory difficulties performed as good as the healthy control participants (Monetta & Pell, 2007). In a follow-up, similar resutls were found for inference generation (Monetta et al., 2008) and irony comprehension (Monetta et al., 2009). McKinlay et al. (2009) related pragmatic language skills to cognitive functions and suggested that processing speed was a stronger determiner of pragmatic language performance than working memory.

Research relating the pragmatic language problems of PD to their executive function deficits might be influenced by the research investigating morphosyntactic processes during sentence comprehension in PD patients.

4. Impact of language processing deficits on the daily life of PD patients

The subtle deficits in language comprehension and production in PD will lead to communication problems that may result in decreased socialization and participation in

society. Miller et al. (2006) investigated the impact of particularly 'speech and voice' deficits on the life of the individual with PD and their family. To this purpose, a group of PD patients was interviewed to explore the onset of speech changes, their impact and patients' strategies to manage these changes. In general, the changes in PD patients' speech and voice had an effect on the overall communication, roles and relationships of those confronted with the disease. It was shown that alterations in speech do not need to be severe to have a significant impact. However, in addition to the speech and voice problems some of the interviewees reported difficulties with word retrieval, sentence formulation and comprehension. This suggests the necessity to refer all newly diagnosed PD patients to speech and language therapy. According to us, this preventive therapy will not only serve articulation and intelligibility abilities, but should also focus on the assessment and remediation of language problems. From our review it is clear that some PD patients suffer from unawareness of the extent of their communicative problems. During social conversations, deficit in the monitoring system influenced turn taking abilities and topic maintenance (McNamara et al., 2003). This unawareness or self-monitoring deficit can prevent the development of adaptive coping strategies, provokes feelings of frustration and might lead to complete withdrawal from communication. PD patients can profit from insights in their language disorders, for example it can help them to use effective compensation strategies or to simply inform the other speech partner of the impact of their disease on communication. From our clinical experience it is clear that patients and their caregivers are often surprised to hear that not only motor symptoms, but also language processing can be affected in the course of the disease. This review on language problems in PD may help in bringing the topic under the attention of those confronted with the disease, meaning that professionals need more up-to-date information. Up-to-date knowledge on the language problems on the part of the patients' environment will facilitate successful communication and, thus, support good family relations. Hence, including routine screening for cognitive decline and language problems early in the disease, in addition to supplying information on PD patients' language problems to caregivers and professionals could keep the PD patients from becoming socially isolated. Examples of communication advice for caregivers could be to simplify and avoid redundancy of information. Speech and language therapy must provide information in tune with the patient's individual limitations and whishes towards language and speech, which in turn can facilitate patients and their environment to implement coping strategies when communicative contexts are arising. In addition, we expect that intensive training of cognitive functions and strategies in PD patients will positively influence processing in the language domain. In the near future a therapy effectiveness study will be developed, which will remediate language problems in combination with executive function deficits in PD.

5. Suggestions for future research

Medication with levodopa is well known to improve the motor symptoms. However, the effects on cognitive functions are more complex: both positive as well as negative effects have been observed. According to Cools (2006), these contrasting effects of levodopa are due to the spatio-temporal progression of dopamine (DA) depletion in PD. PD starts in the dorsal striatum (tail of the Caudate nucleus) and progresses to the ventral striatum (head of the Caudate nucleus). Levodopa in early stages of the disease may improve cognitive functions of the dorsal striatum while simultaneously 'over-dosing' functions of the ventral

striatum. This effect of over-dosing is related to the base level of DA in underlying cortico-striato-cortical circuitry and the task instructions. Therefore, in future research, to control for the influence of dopaminergic medication on cognitive processing, we suggest conducting experiments in the practically defined 'off state'. This is typically following an overnight fast from the patient's anti-Parkinson medications. More positive results are expected in this 'off state', but we also expect more influence of other factors such as frustrations with task performance and tremors and rigidity making testing in the MRI scanner impossible. Ultimately, conducting experiments in drug naïve 'de novo' patients is preferred, but clinically these patients are not always willing to participate in research. Apart from the important effects of medication on language processing, the variables of disease duration and age of onset of PD should be taken in consideration in future research.

Future studies on the influence of set-shifting and working memory on sentence processing in PD can benefit from the use of better-controlled and better-understood methods than the clinical accepted neuropsychological tests which were used in the studies reported above. For example, reading span tasks have been used as tests of working memory because they require active manipulation of information and concurrent item retention (Just & Carpenter, 1992). However, reading span tasks rely on many of the same processes as reading comprehension tasks (Engle et al., 1992), which makes it difficult to draw any strong conclusions in terms of the mediating value of working memory for exactly that language process.

In the near future, the nature of the connectivity between the inferior frontal gyrus and the basal ganglia can be further explored. A functional connectivity analysis can provide functional evidence for a basal ganglia-frontal cortical network during the comprehension of sentences in which the variables of canonicity and grammaticality are crossed. However, it is generally known that in fMRI, temporal resolution is inferior and that it cannot index neural activity that is specifically time-locked to the critical word itself. The temporal coarseness of the fMRI method probably blurred the linguistic processes. Simultaneous ERP/fMRI may allow improved localization of neural generators as well as enhanced temporal resolution of BOLD activation foci. Functional connectivity analysis can be used to examine the degree of collaboration between language-specific cortical areas and the basal ganglia, when processing violated compared to non-violated sentences. In on-line behavioral tasks, the impact of executive functions necessary for syntactic processes per se and the executive functions necessary for the task can potentially be disentangled. Therefore, a valuable technique for obtaining on-line data from sentence-picture matching is the eye-tracking method as suggested by Hochstadt (2009).

Finally, as evidenced by this review, there exists an extensive amount of literature on language processing in PD, but language processing in other motor syndromes has received little attention. The existence of a similar verb naming deficit in other movement disorders, such as CBD and PSP (Cotelli et al., 2006) has provided a major argument for the theory that semantic characteristics of the verb are grounded in the motor system of the brain. It will be interesting to test verb production related to cognitive functions in the following movement disorders:

Multiple system atrophy (MSA) is an adult-onset, sporadic, progressive neurodegenerative disease characterized by varying severity of Parkinsonian features, cerebellar ataxia, autonomic failure, urogenital dysfunction, and corticospinal disorders (Gilman et al., 2008). MSA is also accompanied by cognitive impairments associated with dysfunctional cortico-striato-cortical circuits (Herting et al., 2007).

PSP is a neurodegenerative disease characterized by defects in the vertical ocular gaze, bulbar dysfunction, increased frequency of falling, and akinetic-rigid features. In addition, cognitive impairments, in particular executive dysfunctions associated with alterations within the frontostriatal circuitry, occur (Millar et al., 2006).
CBD is characterized by slowly progressing, unilateral Parkinsonism with dystonia or myoclonus, unresponsiveness to Levodopa, and limb apraxia. Patients with CBD often demonstrate impairments in visuospatial processing and visuoconstruction (Tang-Wai et al., 2003) in combination with acalculia, dysexecutive symptoms and aphasia (McMonagle et al., 2006).
Thus far, only a few studies have investigated language processing in patients with atypical Parkinson syndromes, such as MSA (Apostolova et al., 2006), PSP and CBD (Josephs & Duffy, 2008; McMonagle et al., 2006).

6. Conclusion

This review highlights that the progressive degeneration of the cortico-striato-cortical circuits due to PD disturbs executive functioning and, thus contributes to deficits in language production and comprehension. One of the major conclusions based on this review is the importance of evaluating both the executive functions and modalities of language processing (i.e., comprehension and production) in patients with PD. This is not only crucial for our understanding of PD and for the relationship between languages and executive functions, but it is also particularly useful for efficiently identifying the needs for direct intervention
More research still needs to be done to illuminate further the impact of PD on language processing. Future research needs focus on the clinical implementation of evidence-based communication guidelines in order to guarantee a better quality of life for patients suffering from PD.

7. Acknowledgements

This chapter was written on the basis of Katrien Colman's PhD dissertation. Roelien Bastiaanse was the principal supervisor of the PhD project. This research project was funded by the Stichting Internationaal Parkinson Fonds (Hoofddorp, the Netherlands).

8. References

Aarsland, D., Andersen, K., Larsen, J. P., & Lolk, A. (2003). Prevalence and characteristics of dementia in parkinson disease: An 8-year prospective study. *Archives of Neurology, 60* (3), 387-392, ISSN-L 0003-9942.

Ackermann, H., & Ziegler, W. (1989). [Dysarthrophonia of parkinson syndrome]. *Fortschritte Der Neurologie-Psychiatrie, 57*(4), 149-160, ISSN 0720-4299.

Almor, A., Kempler, D., Andersen, E. S., Macdonald, M. C., Hayes, U. L., & Hintiryan, H. (2002). The production of regularly and irregularly inflected nouns and verbs in alzheimer and parkinson patients. *Brain and Language, 83*(1), 149-151, ISSN-L 0093-934X.

Angwin, A. J., Chenery, H. J., Copland, D. A., Murdoch, B. E., & Silburn, P. A. (2004). The time course of semantic activation in parkinson's disease. *Brain and Language, 91*(1), 145-146, ISSN-L 0093-934X.

Angwin, A. J., Chenery, H. J., Copland, D. A., Murdoch, B. E., & Silburn, P. A. (2005). Summation of semantic priming and complex sentence comprehension in parkinson's disease. *Cognitive Brain Research, 25*(1), 78-89, ISSN-L 0926-6410.

Angwin, A. J., Copland, D. A., Chenery, H. J., Murdoch, B. E., & Silburn, P. A. (2006). The influence of dopamine on semantic activation in parkinson's disease: Evidence from a multipriming task. *Neuropsychology, 20*(3), 299-306, ISSN-L 0894-4105.

Apostolova, L. G., Klement, I., Bronstein, Y., Vinters, H. V., & Cummings, J. L. (2006). Multiple system atrophy presenting with language impairment. *Neurology, 67*(4), 726-727, ISSN-L 0028-3878.

Auriacombe, S., Grossman, M., Carvell, S., Gollomp, S., Stern, M. B., & Hurtig, H. I. (1993). Verbal fluency deficits in parkinson's disease. *Neuropsychology, 7*(2), 182-192, ISSN-L 0894-4105.

Bartels, A. L., & Leenders, K. L. (2009). Parkinson's disease: The syndrome, the pathogenesis and pathophysiology. *Cortex, 45*(8), 915-921, ISSN-L 0010-9452.

Bastiaanse, R., & van Zonneveld, R. (2004). Broca's aphasia, verbs and the mental lexicon. *Brain and Language, 90*(1-3), 198-202, ISSN-L 0093-934X.

Benke, T., Hohenstein, C., Poewe, W., & Butterworth, B. (2000). Repetitive speech phenomena in parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 69*(3), 319-324, ISSN-L 0022-3050.

Berg, E., Bjornram, C., Hartelius, L., Laakso, K., & Johnels, B. (2003). High-level language difficulties in parkinson's disease. *Clinical Linguistics and Phonetics, 17*(1), 63-80, ISSN-L 0269-9206.

Bertella, L., Albani, G., Greco, E., Priano, L., Mauro, A., Marchi, S., . . . Semenza, C. (2002). Noun verb dissociation in parkinson's disease. *Brain and Cognition, 48*(2-3), 277-280, ISSN-L 0278-2626.

Bloom, L., & Lahey, M. (1978). *Language development and language disorders*. New York: John Wiley & Sons, ISBN 0-471-04438-5.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108*(3), 624-652, ISSN-L 0033-295X.

Boulenger, V., Mechtouff, L., Thobois, S., Broussolle, E., Jeannerod, M., & Nazir, T. A. (2008). Word processing in parkinson's disease is impaired for action verbs but not for concrete nouns. *Neuropsychologia, 46*(2), 743-756, ISSN-L 0028-3932.

Caplan, D., & Waters, G. S. (1999). Verbal working memory and sentence comprehension. *The Behavioral and Brain Sciences, 22*(1), 77-94, ISSN-L 0140-525X.

Castner, J. E., Copland, D. A., Silburn, P. A., Coyne, T. J., Sinclair, F., & Chenery, H. J. (2007). Lexical-semantic inhibitory mechanisms in parkinson's disease as a function of subthalamic stimulation. *Neuropsychologia, 45*(14), 3167-3177, ISSN-L 0028-3932.

Cheng, Y., & Martin, R. (2005). Selection demands vs. association strength in the verb generation task. *Brain and Language, 95*(1), 193-194, ISSN-L 0093-934X.

Cohen, H., Bouchard, S., Scherzer, P., & Whitaker, H. (1994). Language and verbal reasoning in parkinson's disease. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology, 7* (3), 166-175, ISSN-L 0894-878X.

Colman, K., Koerts, J., van Beilen, M., Leenders, K. L., & Bastiaanse, R. (2006). The role of cognitive mechanisms in sentence comprehension in dutch speaking parkinson's disease patients: Preliminary data. *Brain and Language, 99*(1-2), 109-110, ISSN-L 0093-934X.

Colman, K. S. F. (2011). *Behavioral and neuroimaging studies on language processing in Dutch speakers with parkinson's disease.* (Unpublished PhD thesis). University of Groningen, Groningen, The Netherlands, ISBN (digital version) 9789036747530.

Colman, K. S. F., Koerts, J., van Beilen, M., Leenders, K. L., Post, W. J., & Bastiaanse, R. (2009). The impact of executive functions on verb production in patients with parkinson's disease. *Cortex, 45*(8), 930-942, ISSN-L 0010-9452.

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in parkinson's disease. *Neuroscience and Biobehavioral Reviews, 30*(1), 1-23, ISSN-L 0149-7634.

Copland, D. A., Chenery, H. J., & Murdoch, B. E. (2001). Discourse priming of homophones in individuals with dominant nonthalamic subcortical lesions, cortical lesions and parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 23*(4), 538-556, ISSN-L 1380-3395.

Copland, D. A. (2003). The basal ganglia and semantic engagement: Potential insights from semantic priming in individuals with subcortical vascular lesions, parkinson's disease, and cortical lesions. *Journal of the International Neuropsychological Society, 9*(7), 1041-1052, ISSN-L 1355-6177.

Cotelli, M., Borroni, B., Manenti, R., Alberici, A., Calabria, M., Agosti, C., . . . Cappa, S. F. (2006). Action and object naming in frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration. *Neuropsychology, 20*(5), 558-565, ISSN-L 0894-4105.

Cotelli, M., Borroni, B., Manenti, R., Zanetti, M., Arévalo, A., Cappa, S. F., & Padovani, A. (2007). Action and object naming in parkinson's disease without dementia. *European Journal of Neurology, 14*(6), 632-637, ISSN-L 1351-5101.

Crescentini, C., Mondolo, F., Biasutti, E., & Shallice, T. (2008). Supervisory and routine processes in noun and verb generation in nondemented patients with parkinson's disease. *Neuropsychologia, 46*(2), 434-447, ISSN-L 0028-3932.

Dubois, B., & Pillon, B. (1995). Do cognitive changes of parkinson's disease result from dopamine depletion? *Journal of Neural Transmission. Supplementum, 45,* 27-34, ISSN-L 0303-6995.

Dubois, B., & Pillon, B. (1997). Cognitive deficits in parkinson's disease. *Journal of Neurology, 244*(1), 2-8, ISSN-L 0340-5354.

Ellis, C. (2006). *The contribution of the basal ganglia to expressive language performance.* (Unpublished PhD thesis), University of Florida, Gainesville, ISBN 9780542351716.

Ellis, C., okun, M. S., Gonzalez-Rothi, I. J., Crosson, B., Rogalski, Y., & Rosenbek, J. C. (2006). Expressive language after PD: Deficits in use but not form. *Movement Disorders, 21*, 897-898, ISSN-L 0885-3185.

Ellis, C., & Rosenbek, J. C. (2007). The basal ganglia and expressive language. A review and directions for research. *Communicative Disorders Review, 1*(1), 1-15, ISSN-L 1933-2831.

Engle, R. W., Cantor, J., & Carullo, J. J. (1992). Individual differences in working memory and comprehension: A test of four hypotheses. *Journal of Experimental Psychology. Learning, Memory, and Cognition, 18*(5), 972-992, ISSN-L 0278-7393.

Fahn, S., & Elton, R. (1987). Unified parkinson's disease rating scale. In: Fahn, S., Marsden, C. D., Calne, D. B., Goldstein, M. (Eds.), *Recent Developments in Parkinson's Disease, Volume 2*, (153-163), Florham Park, NJ. Macmillan Health Care Information.

Flowers, K. A., Robertson, C., & Sheridan, M. R. (1995). Some characteristics of word fluency in parkinson's disease. *Journal of Neurolinguistics, 9*(1), 33-46, ISSN-L 0911-6044.

Friederici, A. D., Kotz, S. A., Werheid, K., Hein, G., & von Cramon, D. Y. (2003). Syntactic comprehension in parkinson'd disease: Investigating early automatic and late integrational processes using event-related potentials. *Neuropsychology, 17*(1), 133-142, ISSN-L 0894-4105.

Friederici, A. D., & Mecklinger, A. (1996). Syntactic parsing as revealed by brain responses: First-pass and second-pass parsing processes. *Journal of Psycholinguistic Research, 25*(1), 157-176, ISSN-L 0090-6905.

Gernsbacher, M. A., Keysar, B., Robertson, R. R. W., & Werner, N. K. (2001). The role of suppression and enhancement in understanding metaphors. *Journal of Memory and Language, 45*(3), 433-450, ISSN-L 0749-596X.

Geyer, H. L., & Grossman, M. (1994). Investigating the basis for the sentence comprehension deficit in parkinson's disease. *Journal of Neurolinguistics, 8*(3), 191-205, ISSN-L 0911-6044.

Gilman, S., Wenning, G. K., Low, P. A., Brooks, D. J., Mathias, C. J., Trojanowski, J. Q., . . . Vidailhet, M. (2008). Second consensus statement on the diagnosis of multiple system atrophy. *Neurology, 71*(9), 670-676, ISSN-L 0028-3878.

Goodglass, H., & Kaplan, E. (1972). *The assessment of aphasia and related disorders*. Philadelphia: Lea & Febiger, ISBN 0812103572.

Grossman, M. (1999). Sentence processing in parkinson's disease. *Brain and Cognition, 40*(2), 387-413, ISSN-L 0278-2626.

Grossman, M., Carvell, S., Gollomp, S., Stern, M. B., Reivich, M., Morrison, D., . Hurtig, H. I. (1993). Cognitive and physiological substrates of impaired sentence processing in parkinson's disease. *Journal of Cognitive Neuroscience, 5*(4), 480-498, 1530-8898, ISSN 1530-8898.

Grossman, M., Carvell, S., Stern, M. B., Gollomp, S., & Hurtig, H. I. (1992). Sentence comprehension in parkinson's disease: The role of attention and memory. *Brain and Language, 42*(4), 347-384, ISSN-L 0093-934X.

Grossman, M., Cooke, A., DeVita, C., Lee, C., Alsop, D., Detre, J., . Hurtig, H. I. (2003). Grammatical and resource components of sentence processing in parkinson's disease: An fMRI study. *Neurology, 60*(5), 775-781, ISSN-L 0028-3878.

Grossman, M., Lee, C., Morris, J., Stern, M. B., & Hurtig, H. I. (2002). Assessing resource demands during sentence processing in parkinson's disease. *Brain and Language, 80*(3), 603-616, ISSN-L 0093-934X.

Grossman, M., Stern, M. B., Gollomp, S., Vernon, G., & Hurtig, H. I. (1994). Verb learning in parkinson's disease. *Neuropsychology, 8*(3), 413-423, ISSN-L 0894-4105.

Grossman, M., Zurif, E., Lee, C., Prather, P., Kalmanson, J., Stern, M. B., & Hurtig, H. I. (2002). Information processing speed and sentence comprehension in parkinson's disease. *Neuropsychology, 16*(2), 174-181, ISSN-L 0894-4105.

Gurd, J. M., & Ward, C. D. (1989). Retrieval from semantic and letter-initial categories in patients with parkinson's disease. *Neuropsychologia, 27*(5), 743-746, ISSN-L 0028-3932.

Henry, J. D., & Crawford, J. R. (2004). Verbal fluency deficits in parkinson's disease: A meta-analysis. *Journal of the International Neuropsychological Society, 10*(4), 608-622, ISSN-L 1355-6177.

Herting, B., Beuthien-Baumann, B., Pöttrich, K., Donix, M., Triemer, A., Lampe, J. B., . . . Holthoff, V. A. (2007). Prefrontal cortex dysfunction and depression in atypical parkinsonian syndromes. *Movement Disorders, 22*(4), 490-497, ISSN-L 0885-3185.

Hochstadt, J., Nakano, H., Lieberman, P., & Friedman, J. (2006). The roles of sequencing and verbal working memory in sentence comprehension deficits in parkinson's disease. *Brain and Language, 97*(3), 243-257, ISSN-L 0093-934X.

Hochstadt, J. (2009). Set-shifting and the on-line processing of relative clauses in parkinson's disease: Results from a novel eye-tracking method. *Cortex, 45*(8), 991-1011, ISSN-L 0010-9452.

Illes, J. (1989). Neurolinguistic features of spontaneous language production dissociate three forms of neurodegenerative disease: Alzheimer's, huntington's, and parkinson's. *Brain and Language, 37*(4), 628-642, ISSN-L 0093-934X.

Illes, J., Metter, E. J., Hanson, W. R., & Iritani, S. (1988). Language production in parkinson's disease: Acoustic and linguistic considerations. *Brain and Language, 33*(1), 146-160, ISSN-L 0093-934X.

Josephs, K. A., & Duffy, J. R. (2008). Apraxia of speech and nonfluent aphasia: A new clinical marker for corticobasal degeneration and progressive supranuclear palsy. *Current Opinion in Neurology, 21*(6), 688-692, ISSN-L 1080-8248.

Just, M. A., & Carpenter, P. A. (1992). A capacity theory of comprehension: Individual differences in working memory. *Psychological Review, 99*(1), 122-149, ISSN-L 0033-295X.

Just, M. A., Carpenter, P. A., & Keller, T. A. (1996). The capacity theory of comprehension: New frontiers of evidence and arguments. *Psychological Review, 103*(4), 773-780, ISSN-L 0033-295X.

Kaan, E., Harris, A., Gibson, E., & Holcomb, P. (2000). The P600 as an index of syntactic integration difficulty. *Language and Cognitive Processes, 15*(2), 159-201, ISSN-L 0169-0965.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston naming test*. Philadelphia: Lea & Febiger, ISBN 9780812101003.

Kemmerer, D. (1999). Impaired comprehension of raising-to-subject constructions in parkinson's disease, *Brain and Language, 66*(3), 311-328, ISSN-L 0093-934X.

Kotz, S. A., Frisch, S., von Cramon, D. Y., & Friederici, A. D. (2003). Syntactic language processing: ERP lesion data on the role of the basal ganglia. *Journal of the International Neuropsychological Society, 9*(7), 1053-1060, ISSN-L 1355-6177.

Kotz, S. A., Frisch, S., Werheid, K., Hein, G., von Cramon, D. Y., & Friederici, A. D. (2002). The role of the basal ganglia in syntactic language processing: Event-related potential evidence from different patient populations and syntactic paradigms. *Brain and Language, 83*(1), 69-70, ISSN-L 0093-934X.

Kuperberg, G. R. (2007). Neural mechanisms of language comprehension: Challenges to syntax. *Brain Research, 1146*, 23-49, ISSN-L 0006-8993.

Kutas, M., & Van Petten, C. K. (1994). Psycholinguistics electrified: Event-related brain potential investigations. In M. A. Gernsbacher (Ed.), *Handbook of psycholinguistics* (83-143). San Diego: Academic Press, ISBN 0122808908.

Lee, C., Grossman, M., Morris, J., Stern, M. B., & Hurtig, H. I. (2003). Attentional resource and processing speed limitations during sentence processing in parkinson's disease. *Brain and Language, 85*(3), 347-356, ISSN-L 0093-934X.

Levelt, W. J. M. (1983). Monitoring and self-repair in speech. *Cognition, 14*(1), 41-104, ISSN-L 0010-0277.

Levelt, W. J. M. (1989). *Speaking: From intention to articulation*. Cambridge, MA: MIT Press, ISBN 0262121379.

Levelt, W. J. M., Schriefers, H., Vorberg, D., Meyer, A. S., Pechmann, T., & Havinga, J. (1991). The time course of lexical access in speech production: A study of picture naming. *Psychological Review, 98*(1), 122-142, ISSN-L 0033-295X.

Lieberman, P., Friedman, J., & Feldman, L. S. (1990). Syntax comprehension deficits in parkinson's disease. *The Journal of Nervous and Mental Disease, 178*(6), 360-365, ISSN-L 0022-3018.

Lieberman, P., Kako, E., Friedman, J., Tajchman, G., Feldman, L. S., & Jiminez, E. B. (1992). Speech production, syntax comprehension, and cognitive deficits in parkinson's disease. *Brain and Language, 43*(2), 169-189, ISSN-L 0093-934X.

Longworth, C. E., Keenan, S. E., Barker, R. A., Marslen-Wilson, W. D., & Tyler, L. K. (2005). The basal ganglia and rule-governed language use: Evidence from vascular and degenerative conditions. *Brain, 128*(3), 584-596, Online ISSN 1460-2156.

Longworth, C. E., Tyler, L. K., & Marslen-Wilson, W. D. (2003). Language deficits and basal ganglia lesions: The past tense. *Brain and Language, 87*(1), 7-8, ISSN-L 0093-934X.

Mari-Beffa, P., Hayes, A. E., Machado, L., & Hindle, J. V. (2005). Lack of inhibition in parkinson's disease: Evidence from a lexical decision task. *Neuropsychologia, 43*(4), 638-646, ISSN-L 0028-3932.

Martin, R. C., & Cheng, Y. (2006). Selection demands versus association strength in the verb generation task. *Psychonomic Bulletin and Review, 13*(3), 396-401, ISSN-L 1069-9384.

McDonald, C., Brown, G. G., & Gorell, J. M. (1996). Impaired set-shifting in parkinson's disease: New evidence from a lexical decision task. *Journal of Clinical and Experimental Neuropsychology, 18*(6), 793-809, ISSN-L 1380-3395.

McKinlay, A., Dalrymple-Alford, J. C., Grace, R. C., & Roger, D. (2009). The effect of attentional set-shifting, working memory, and processing speed on pragmatic language functioning in parkinson's disease. *European Journal of Cognitive Psychology, 21*(2), 330-346, ISSN-L 0954-1446.

McMonagle, P., Blair, M., & Kertesz, A. (2006). Corticobasal degeneration and progressive aphasia. *Neurology, 67*(8), 1444-1451, ISSN-L 0028-3878.

McNamara, P., & Durso, R. (2003). Pragmatic communication skills in patients with parkinson's disease. *Brain and Language, 84*(3), 414-423, ISSN-L 0093-934X.

McNamara, P., Obler, L. K., Au, R., Durso, R., & Albert, M. L. (1992). Speech monitoring skills in alzheimer's disease, parkinson's disease, and normal aging. *Brain and Language, 42*(1), 38-51, ISSN-L 0093-934X.

Millar, D., Griffiths, P., Zermansky, A. J., & Burn, D. J. (2006). Characterizing behavioral and cognitive dysexecutive changes in progressive supranuclear palsy. *Movement Disorders, 21*(2), 199-207, ISSN-L 0885-3185.

Miller, N., Noble, E., Jones, D., & Burn, D. J. (2006). Life with communication changes in parkinson's disease. *Age and Ageing, 35*(3), 235-239, ISSN-L 0002-0729.

Monetta, L., Grindrod, C. M., & Pell, M. D. (2008). Effects of working memory capacity on inference generation during story comprehension in adults with parkinson's disease. *Journal of Neurolinguistics, 21*(5), 400-417, ISSN-L 0911-6044.

Monetta, L., Grindrod, C. M., & Pell, M. D. (2009). Irony comprehension and theory of mind deficits in patients with parkinson's disease. *Cortex, 45*(8), 972-981, ISSN-L 0010-9452.

Monetta, L., & Pell, M. D. (2007). Effects of verbal working memory deficits on metaphor comprehension in patients with parkinson's disease. *Brain and Language, 101*(1), 80-89, ISSN-L 0093-934X.

Murray, L. L. (2000). Spoken language production in huntington's and parkinson's diseases. *Journal of Speech, Language, and Hearing Research, 43*(6), 1350-1366, ISSN-L 1092-4388.

Murray, L. L. (2008). Language and parkinson's disease. *Annual Review of Applied Linguistics, 28*(-1), 113-127, ISSN-L 0267-1905.

Murray, L. L., & Lenz, L. P. (2001). Productive syntax abilities in huntington's and parkinson's diseases. *Brain and Cognition, 46*(1-2), 213-219, ISSN-L 0278-2626.

Muslimović, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed parkinson disease. *Neurology, 65*(8), 1239-1245, ISSN-L 0028-3878.

Natsopoulos, D., Grouios, G., Bostantzopoulou, S., Mentenopoulos, G., Katsarou, Z., & Logothetis, J. (1993). Algorithmic and heuristic strategies in comprehension of complement clauses by patients with parkinson's disease. *Neuropsychologia, 31*(9), 951-964, ISSN-L 0028-3932.

Natsopoulos, D., Katsarou, Z., Bostantzopoulou, S., Grouios, G., Mentenopoulos, G., & Logothetis, J. (1991). Strategies in comprehension of relative clauses by parkinsonian patients. *Cortex, 27*(2), 255-268, ISSN-L 0010-9452.

Osterhout, L., & Holcomb, P. (1995). Event related potentials and language comprehension. In M. D. Rugg, & M. G. H. Coles (Eds.), *Electrophysiology of mind: Event-related brain potentials and cognition* (171-215). New York: Oxford University Press, ISBN 0198521359.

Pahwa, R., Paolo, A., Troster, A., & Koller, W. (1998). Cognitive impairment in parkinson's disease. *European Journal of Neurology, 5*(5), 431-441, ISSN-L 1351-5101.

Péran, P., Rascol, O., Demonet, J. F., Celsis, P., Nespoulous, J. L., Dubois, B., & Cardebat, D. (2003). Deficit of verb generation in nondemented patients with parkinson's disease. *Movement Disorders, 18*(2), 150-156, ISSN-L 0885-3185.

Péran, P., Cardebat, D., Cherubini, A., Piras, F., Luccichenti, G., Peppe, A., . . . Sabatini, U. (2009). Object naming and action-verb generation in parkinson's disease: A fMRI study. *Cortex, 45*(8), 960-971, ISSN-L 0010-9452.

Perkins, M. R. (2005). Pragmatic ability and disability as emergent phenomena. *Clinical Linguistics and Phonetics, 19*(5), 367-377, ISSN-L 0269-9206.

Piatt, A. L., Fields, J. A., Paolo, A. M., Koller, W. C., & Tröster, A. I. (1999a). Lexical, semantic, and action verbal fluency in parkinson's disease with and without dementia. *Journal of Clinical and Experimental Neuropsychology, 21*(4), 435-443, ISSN-L 1380-3395.

Piatt, A. L., Fields, J. A., Paolo, A. M., & Tröster, A. I. (1999b). Action (verb naming) fluency as an executive function measure: Convergent and divergent evidence of validity. *Neuropsychologia, 37*(13), 1499-1503, ISSN-L 0028-3932.

Pignatti, R., Ceriani, F., Bertella, L., Mori, I., & Semenza, C. (2006). Naming abilities in spontaneous speech in Parkinson's and Alzheimer's disease. *Brain and Language, 99*(1-2), 113-114, ISSN-L 0093-934X.

Portin, R., Laatu, S., Revonsuo, A., & Rinne, U. K. (2000). Impairment of semantic knowledge in parkinson disease. *Archives of Neurology, 57*(9), 1338-1343, ISSN-L 0003-9942.

Postma, A. (2000). Detection of errors during speech production: A review of speech monitoring models. *Cognition, 77*(2), 97-132, ISSN-L 0010-0277.

Prutting, C. A., & Kirchner, D. M. (1987). A clinical appraisal of the pragmatic aspects of language. *The Journal of Speech and Hearing Disorders, 52*(2), 105-119, ISSN-L 0022-4677.

Saling, L. L., & Phillips, J. G. (2007). Automatic behaviour: Efficient not mindless. *Brain Research Bulletin, 73*(1-3), 1-20, ISSN-L 0361-9230.

Signorini, M., & Volpato, C. (2006). Action fluency in parkinson's disease: A follow-up study. *Movement Disorders, 21*(4), 467-472, ISSN-L 0885-3185.

Spicer, K. B., Brown, G. G., & Gorell, J. M. (1994). Lexical decision in parkinson disease: Lack of evidence for generalized bradyphrenia. *Journal of Clinical and Experimental Neuropsychology, 16*(3), 457-471, ISSN-L 1380-3395.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms and commentary*. New York: Oxford University Press, ISBN 9780195159578.

Swinney, D., Zurif, E. B., Prather, P., & Love, T. (1996). Neurological distribution of processing resources underlying language comprehension. *Journal of Cognitive Neuroscience, 8*, 174-184, ISSN 1530-8898.

Tang-Wai, D. F., Josephs, K. A., Boeve, B. F., Dickson, D. W., Parisi, J. E., & Petersen, R. C. (2003). Pathologically confirmed corticobasal degeneration presenting with visuospatial dysfunction. *Neurology, 61*(8), 1134-1135, ISSN-L 0028-3878.

Thompson-Schill, S. L., & Botvinick, M. M. (2006). Resolving conflict: A response to martin and cheng (2006). *Psychonomic Bulletin and Review, 13*(3), 402-408, ISSN-L 1069-9384.

Ullman, M. T. (2001). A neurocognitive perspective on language: The declarative/procedural model. *Nature Reviews Neuroscience, 2*(10), 717-726, ISSN-L 1471-003X.

Ullman, M. T., Corkin, S., Coppola, M., Hickok, G., Growdon, J. H., Koroshetz, W. J., & Pinker, S. (1997). A neural dissociation within language: Evidence that the mental dictionary is part of declarative memory, and that grammatical rules are processed by the procedural system. *Journal of Cognitive Neuroscience, 9*(2), 266-276, ISSN 1530-8898.

van de Meerendonk, N., Kolk, H. H. J., Chwilla, D. J., & Vissers, C. T. W. M. (2009). Monitoring in language perception *Language and Linguistics Compass, 3*(5), 1211-1224, ISSN-L 1749-818X.

van Spaendonck, K. P. M., Berger, H. J. C., Horstink, M. W. I. M., Buytenhuijs, E. L., & Cools, A. R. (1996). Executive functions and disease characteristics in parkinson's disease. *Neuropsychologia, 34*(7), 617-626, ISSN-L 0028-3932.

van, Herten M. (2006). *Executive control of sentence perception: An electrophysiological investigation.* (Unpublished PhD thesis). Radbout Universiteit Nijmegen, the Netherlands, ISBN 9090208984.

van, Herten M., Chwilla, D. J., & Kolk, H. H. (2006). When heuristics clash with parsing routines: ERP evidence for conflict monitoring in sentence perception. *Journal of Cognitive Neuroscience, 18*(7), 1181-1197, ISSN 1530-8898.

Vissers, C. T. W. M. (2008). *Monitoring in language perception: An electrophysiological investigation.* (Unpublished PhD thesis). Radbout Universiteit Nijmegen, the Netherlands, ISBN 9789090230061.

Waters, G. S., & Caplan, D. (1996). The measurement of verbal working memory capacity and its relation to reading comprehension. *The Quarterly Journal of Experimental Psychology. A, 49*(1), 51-75, ISSN-L 0272-4987.

Whiting, E., Copland, D., & Angwin, A. (2005). Verb and context processing in parkinson's disease. *Journal of Neurolinguistics, 18*(3), 259-276, ISSN-L 0911-6044.

Wolters, E. C., & Bosboom, J. L. W. (2007). Parkinson's disease. In E. C. Wolters, T. van Laar & H. W. Berendse (Eds.), *Parkinsonism and related disorders*. Amsterdam: VU University Press, ISBN 9789086591503.

Zurif, E., Swinney, D., Prather, P., Solomon, J., & Bushell, C. (1993). An on-line analysis of syntactic processing in broca's and wernicke's aphasia. *Brain and Language, 45*(3), 448-464, ISSN-L 0093-934X.

Part 2

Novel Methods to Evaluate the Symptoms in Parkinson's Disease

9

Novel Methods to Evaluate Symptoms in Parkinson's Disease – Rigidity and Finger Tapping

Takuyuki Endo[1]*, Masaru Yokoe[2*], Harutoshi Fujimura[1] and Saburo Sakoda[1†]
[1]*Toneyama National Hospital,*
[2]*Osaka University Graduate School of Medicine,*
Japan

1. Introduction

Parkinsonian symptoms such as tremor, rigidity, akinesia, and postural instability are perceived subjectively, and therefore understanding the degree of the symptoms varies depending on the neurologist. Sensing technologies and computer science have advanced and can now detect neurological symptoms and the detected data can be analyzed by software and described in a similar manner to how neurologists perceive those symptoms. This chapter discusses two popular neurological examinations in Parkinson's disease (PD); one is rigidity, which is representative of passive movement, and the other is finger tapping, which is representative of active movement.

Rigidity, a well known symptom of PD, is defined as increased muscle tone that is elicited when an examiner moves the patient's limbs, neck, or trunk, and this increased resistance to passive movement is equal in all directions (Fahn & Przedborski 2005). Many researchers have analyzed rigidity by applying biomedical engineering principles and electrophysiological techniques (Fung et al. 2000, Prochazka et al. 1997, Teravainen et al. 1989). However, we do not know exactly what we feel in muscle tone in PD.

Finger tapping, one of The Unified Parkinson's Disease Rating Scale (UPDRS) items, is commonly used in daily neurological examinations. Its evaluation includes velocity, amplitude, and rhythm. However, observation of these is subjective.

To evaluate rigidity and finger tapping, it is necessary to sense muscle tone and finger movement. We have previously developed novel methods to evaluate rigidity and finger tapping (Endo et al. 2009, Kandori et al., 2004). In this chapter, we showed the usefulness of these systems as objective markers of treatment.

2. Evaluating the effects of deep brain stimulation on rigidity and finger tapping

We evaluated the effects of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on rigidity and finger tapping using our measuring materials. The preceded study of the

*equally contributed authors
†corresponding author

effects of STN-DBS revealed that rigidity responded immediately upon tuning DBS, while improvement of finger tapping needed longer time to manifest after tuning DBS. Thus, we analyzed Parkinsonian rigidity by comparing the DBS on state to the DBS off state and finger tapping by comparing pre-operation DBS to post-operation DBS in this study.

2.1 Subjects

Five patients in whom PD was diagnosed according to British Brain Bank clinical criteria (Gibb & Lees 1988) and who received STN-DBS were included in this study. Clinical details of patients with PD who participated in rigidity analysis are shown in Table 1, and those in finger tapping are shown in Table 2. Prior to measurement, patients with PD were assessed using the UPDRS Part III. In this examination, rigidity was scored using a five-point scale (0 = no rigidity, 1 = slight or detectable only when activated, 2 = mild to moderate, 3 = marked, and 4 = severe), and finger-tapping was also scored using the five-point scale (0 = normal; 1 = mild slowing and/or reduction in amplitude; 2 = moderately impaired, definite and early fatiguing, may have occasional arrests in movement; 3 = severely impaired, frequent hesitation in initiating movements or arrests in ongoing movement; and 4 = can barely perform the task). This study was approved by the Institutional Review Board of Osaka University Hospital and written informed consent was obtained from all subjects.

	Age (y)	Sex	Disease duration (y)	Duration after DBS	UPDRS score		
					Part III (*on)	Rigidity (Right)	Rigidity (Left)
pd1	73	M	5	One month	28	1/1(*on/off)	1/1(*on/off)
pd2	70	F	13	One month	8	1/2	1/1
pd3	60	F	11	One year	59	2/3	2/2
pd4	63	F	18	6 years	40	1/2	1/1
pd5	72	F	29	5 years	29	1/1	1/1

Table 1. Clinical details of patients who participated in rigidity analysis. * on/off; DBS-on/off

	Age (y)	**Sex**	**Handed**	**Initially affected site**	**Evaluation interval between pre and post (month)**	**UPDRS PartIII**		**UPDRS PartⅢ Finger-tapping score**	
						Pre	**Post**	**Pre (L/R)**	**Post (L/R)**
PD1	67	M	Right	Left	3	49	29	3/2	2/1
PD2	69	F	Right	Right	1	26	8	1/2	1/1
PD3	69	M	Right	Right	2	24	17	1/2	1/1
PD4	62	F	Right	Right	1	40	20	2/2	1/1
PD5	73	F	Right	Left	1	34	29	2/1	1/1

Table 2. Clinical details of patients who participated in finger tapping analysis

2.2 Sensing methods

2.2.1 Muscle tonus measurement device

Figure 1 shows a schematic diagram of the muscle tonus measurement system. Details of the device were described in a previous report (Endo et al. 2009). Briefly, elbow joint torque was estimated using the force along the Z-axis and the longitudinal length of the forearm. The elbow joint angle was calculated from the signal generated by the gyroscope. The EMG activity was recorded from surface electrodes attached to the *biceps brachii* and *triceps brachii*.

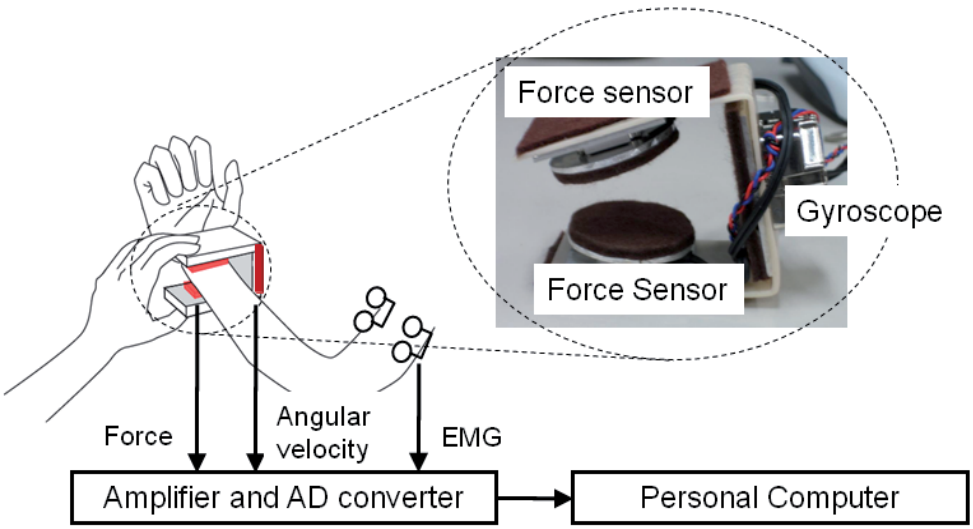


Fig. 1. Schematic diagram of the muscle tonus measurement system

2.2.2 Finger tapping measurement system

The basic method for sensing finger tap movement has been described previously (Kandori et al. 2003, Shima et al. 2008). The finger-tapping measurement system used in this study is shown in Figure 2. A magnetic sensor consisting of two coils is used to measure finger-tapping movement. The coil voltage depending on the distance between the two coils enables estimation of the distance between two fingertips. We calculated the rhythm, amplitude, and velocity of the finger-tapping movement.

2.3 Protocols

2.3.1 Protocols for measuring rigidity

Each subject with DBS-on state or DBS-off state was instructed to relax in a sitting position; the examiner applied the measuring device to the wrist joint of the subject and practiced passive flexion and extension movements at the elbow joint. The measurement of DBS-off state started at 1 min after DBS was turned off. The measurement was made by repeating the four phases of movement as described in a previous report (Endo et al. 2009): (1) holding the elbow at maximum extension for at least 3 s (Fig. 3A), (2) passive flexion for 2 s, (3) holding the elbow at maximum flexion for at least 3 s (Fig. 3B), and (4) passive extension for 2 s (ramp-and-hold). This measurement was repeated twice for each of the left and right upper limbs and the resulting values were averaged on each side independently. Two measurements each for left and right upper limbs were obtained per subject.

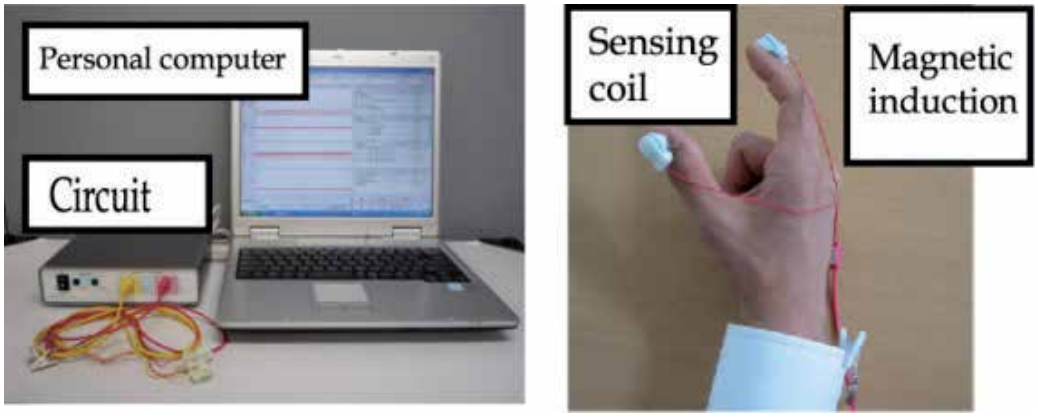


Fig. 2. Finger-tapping measurement system

Figure 4A and Figure 5A shows the typical longitudinal data extracted from the right upper limb of patient pd3 in Table 1 with a UPDRS rigidity score of 2/3 (DBS-on/off). Figure 4A represents the DBS-off state and Figure 5A represents the DBS-on state. Torque-angle characteristics in passive flexion and passive extension are also shown in Figure 4B (DBS-off state) and Figure 5B (DBS-on state).

2.3.2 Protocols for measuring finger tapping

Five patients with PD were evaluated 1 week before and 3 to 5 months after surgery. The magnetic sensors were worn on the subject's index finger and thumb. The subject practiced the finger tapping movement for about 10 s. The subject was asked to execute the finger tapping movements as quickly and widely as possible for 15 s. The finger-tapping wave of patient PD1 before and after intervention is shown in Figure 6.

2.4 Data analysis

2.4.1 Data analysis for rigidity

The resulting data were analyzed by extracting features from elbow joint torque-angle characteristics during passive flexion and extension as shown in Figure 7. The features used here were elastic coefficients in extension and flexion and the sum of the differences of averaged torque values. These were calculated as follows: for the elastic coefficients, the slopes of the regression lines for both flexion and extension were estimated based on the torque-angle data. The data from the start point to the last maximal extension phase were used to calculate the elastic coefficient, which included four to five cycles. At this time, torque values were adjusted for gravity using the mass of the forearms and hands as estimated from the subject's body weight (de Leva 1996). For the sum of the differences of averaged torque values, first we averaged the flexion torque values across four trials at a certain joint angle and also averaged the extension torque values similarly. Then, the differences of the averaged torque values at 30°, 60°, and 90° were calculated and the resulting values were summed.

These three features, that is, the elastic coefficients in extension and flexion and the sum of the differences of averaged torque values, were normalized using the mass of the subject's body weight, because these are dependent on the subject's muscle mass.

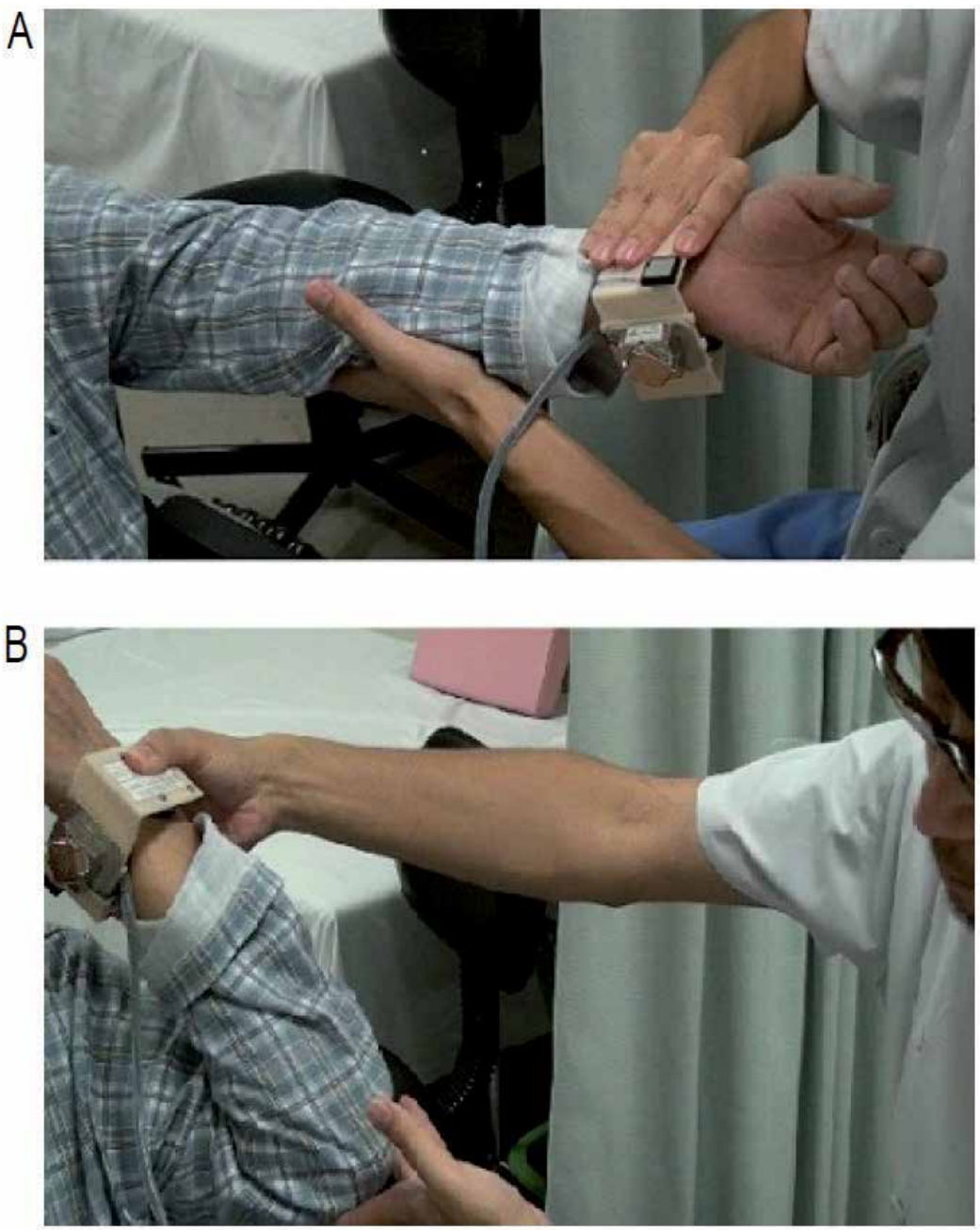


Fig. 3. Measuring protocol. A: holding the elbow at maximum extension. B: holding the elbow at maximum flexion

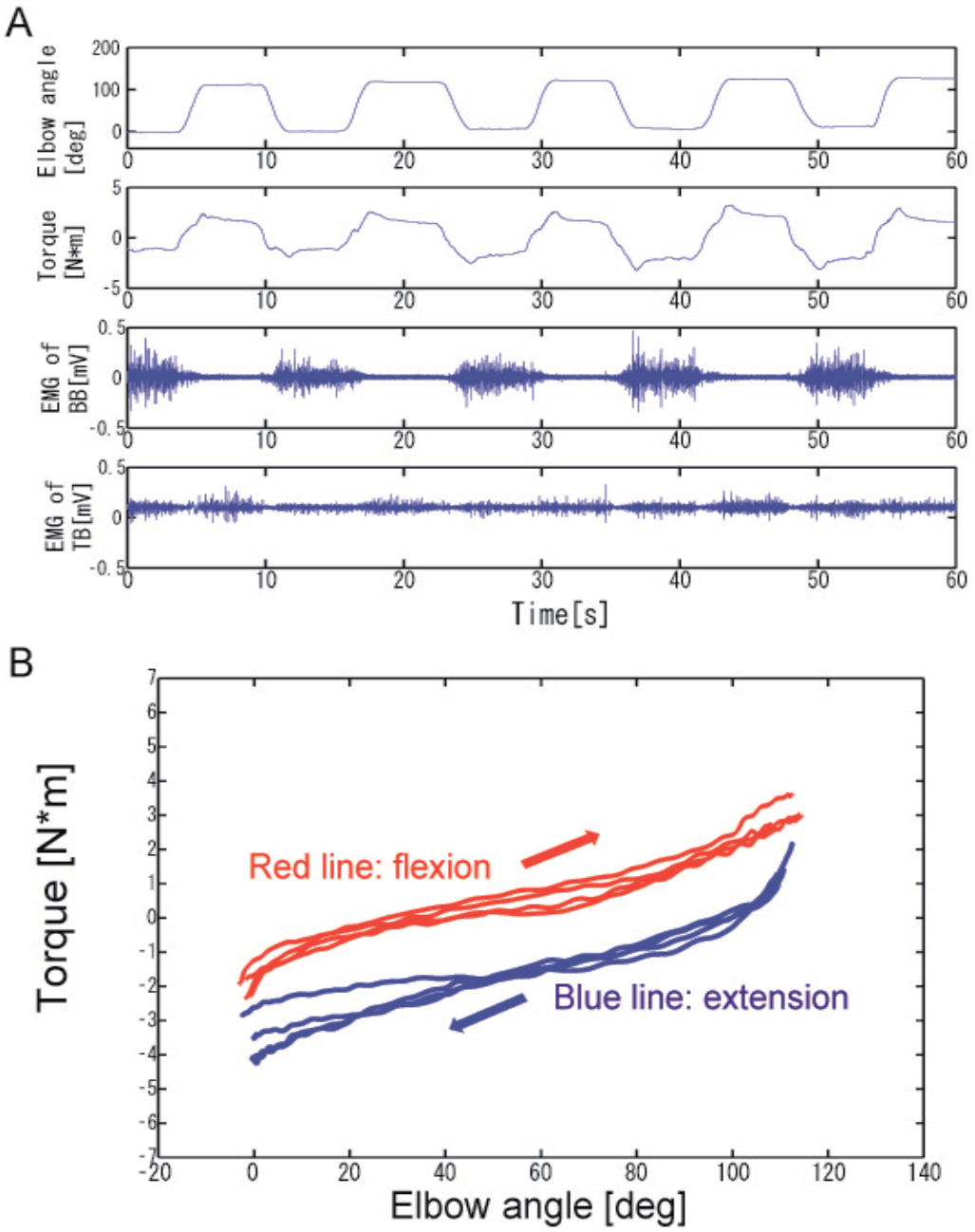


Fig. 4. Typical longitudinal data (A) and torque-angle characteristics (B) in passive flexion and passive extension (DBS-off state) obtained from the right upper limb of patient pd3 with UPDRS rigidity score 3.

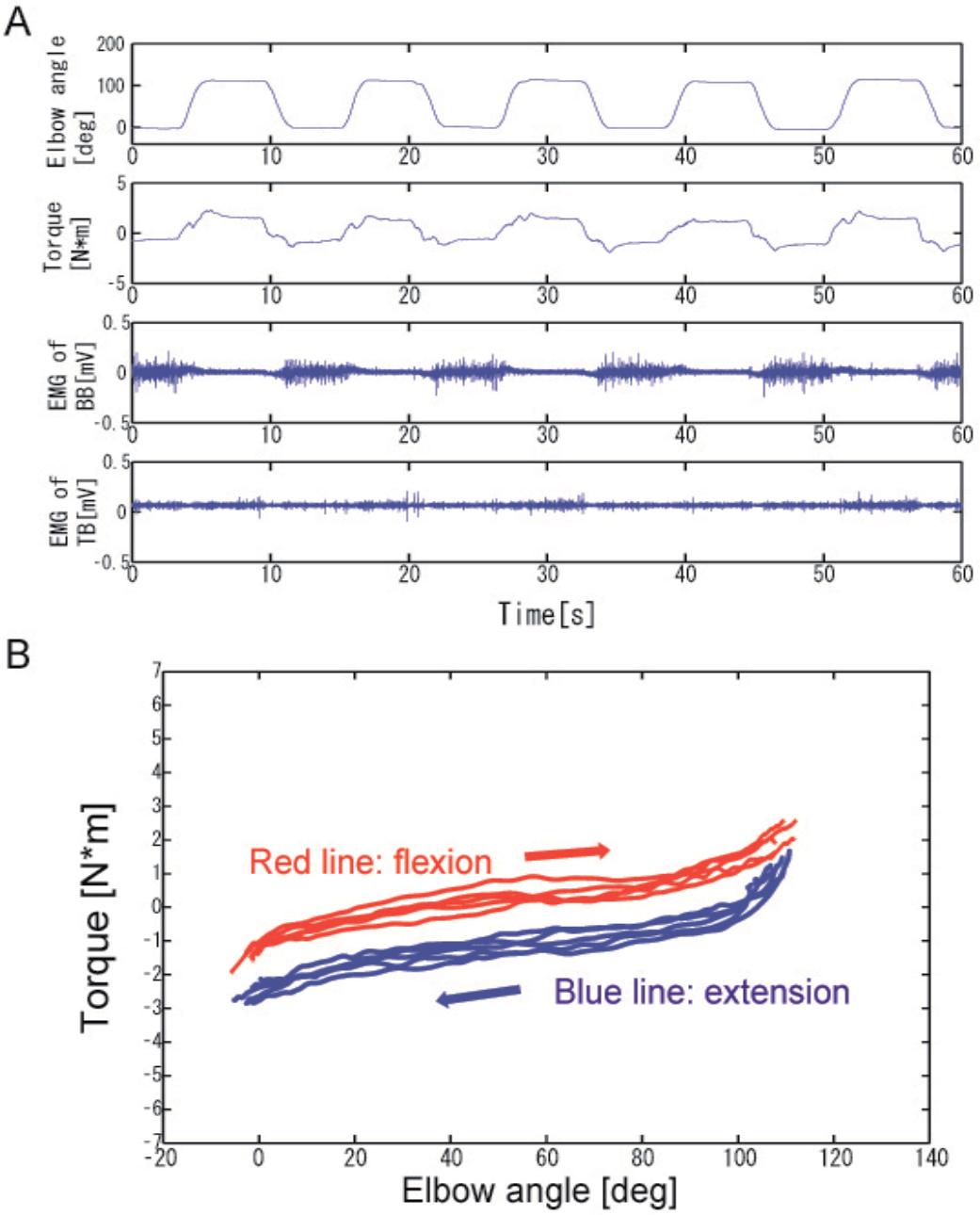


Fig. 5. Typical longitudinal data (A) and torque-angle characteristics (B) in passive flexion and passive extension (DBS-on state) obtained from the right upper limb of patient pd3 with UPDRS rigidity score 2.

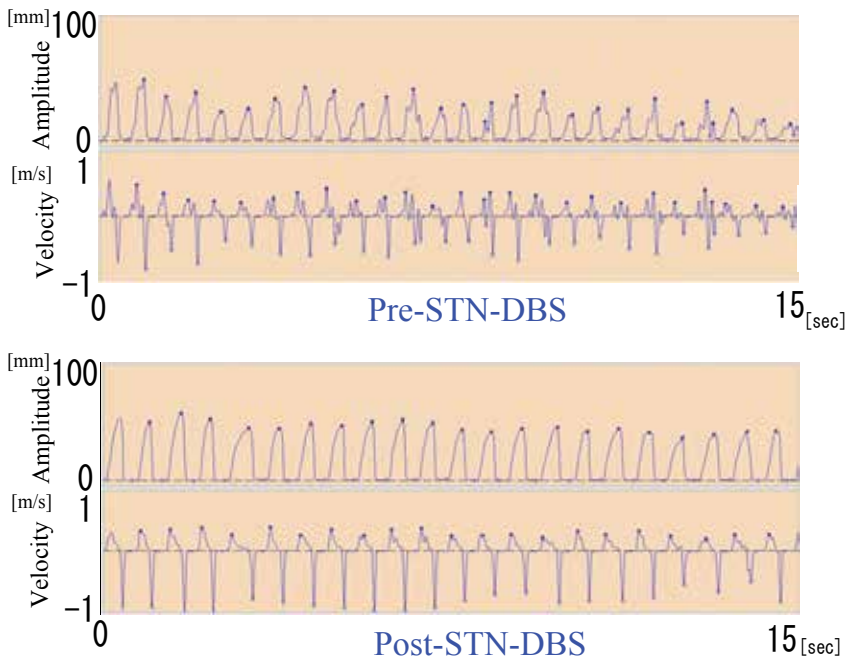


Fig. 6. The finger-tapping wave of patient PD1 before and after intervention

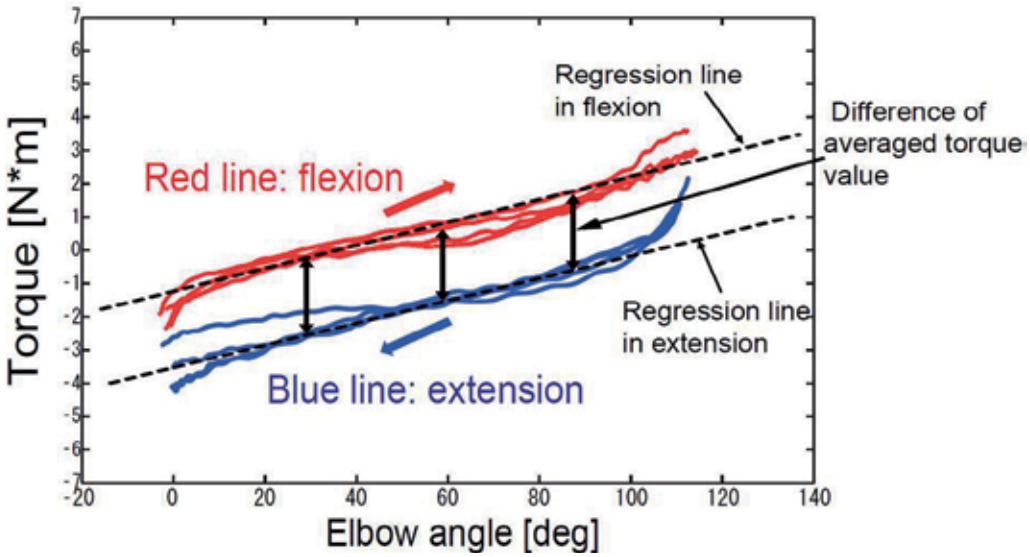


Fig. 7. Extracting features from torque-angle characteristics. Elastic coefficients in flexion and extension were calculated by estimating the slopes of the regression lines for both phases. Differences in the averaged torque values were calculated at 30°, 60°, and 90°.

2.4.2 Data analysis for finger tapping

We statistically analyzed five parameters of repetitive index finger-to-thumb oppositions for 15 seconds (Fig. 8). A single finger-tapping interval (FTI) was defined as the interval between the onset of a finger tap and the onset of the next finger tap. We measured the following: the maximum opening velocity (MoV) in a single finger-tapping movement; the maximum closing velocity (McV) in a single finger-tapping movement; the maximum amplitude (MA) during a single finger-tapping movement; and the standard deviation (SD) of FTI, the index of rhythm as the variation of finger-tapping coordination. The mean MA, MoV, and McV for 15 s were calculated. The frequency was the number of finger taps in 15 s (NFT).

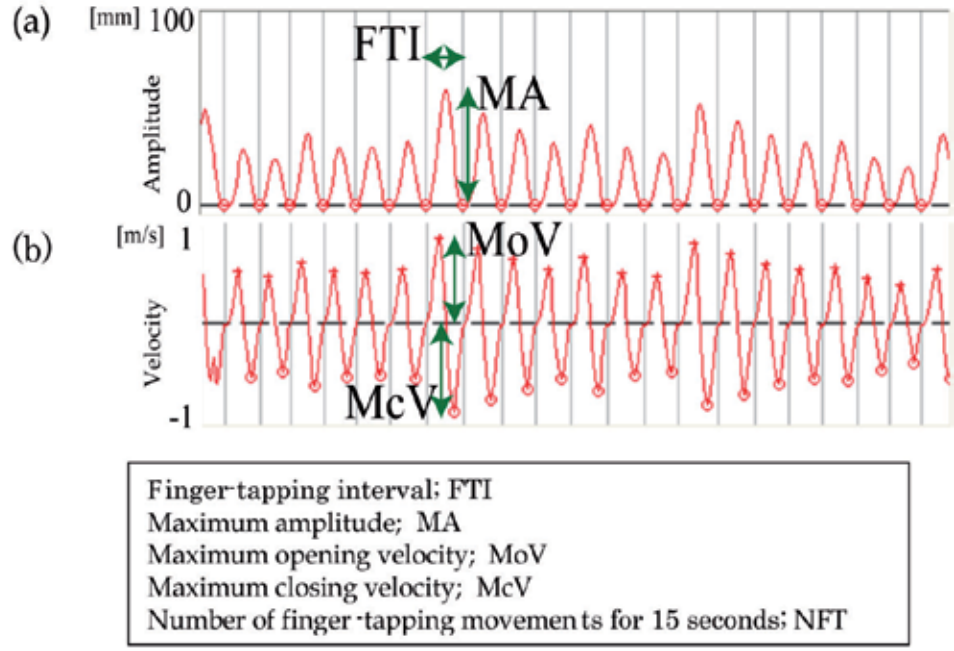


Fig. 8. Measured amplitude and calculated velocity in finger-tapping movement. (a) Measured amplitude, (b) Calculated velocity.

2.5 Results

Rigidity

Using the data obtained from both left and right upper limbs of five patients with PD, 10 data sets on muscle tonus were available for final analysis. The effects of STN-DBS on three parameters are shown in Figures 9, 10, and 11. Age-matched normal values of elastic coefficients in extension and flexion and the sum of the differences of averaged torque values from 20 control subjects were 1.0[N*m/rad*kg], 1.0[N*m/rad*kg], and 1.0[N*m/kg], respectively.

In the arms with a UPDRS rigidity score 2 or 3 in the DBS-off state, DBS-on improved their scores. Figures of elastic coefficients in extension and flexion and the sum of the differences of averaged torque values in this muscle tonus system supported UPDRS rigidity score improvement. In addition, these three parameters also showed improvement even in arms where the UPDRS rigidity scores did not improve in the DBS-on state. This result indicates

that this muscle tonus measuring system is sensitive, objective, and precise. On the other hand, in arms with a UPDRS rigidity score of 1, which is a subtle change in muscle tonus, apparent improvement was not detected using this system. The difference of averaged torque values is the most sensitive among the three parameters.

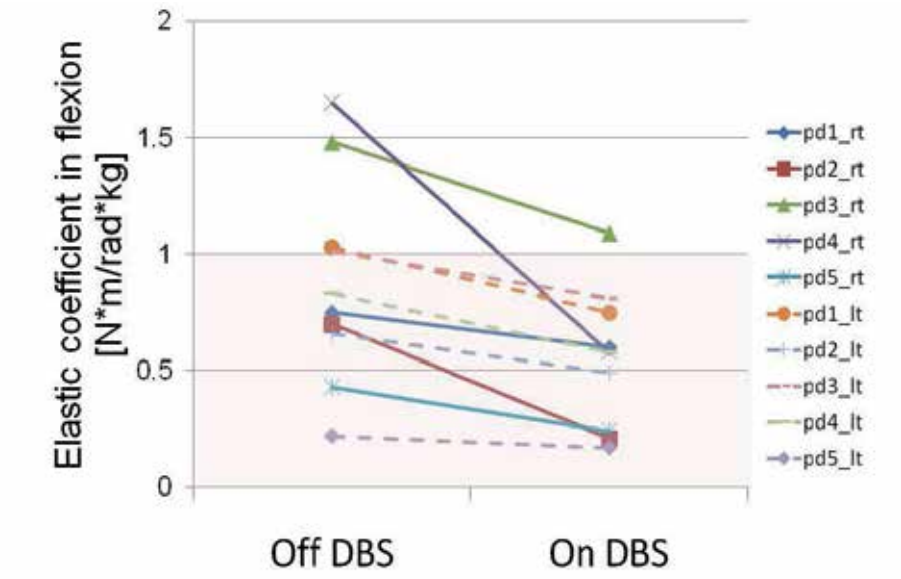


Fig. 9. Effects of deep brain stimulation on the elastic coefficient in flexion. The filled area (less than 1.0[N*m/rad*kg]) represents the normal region.

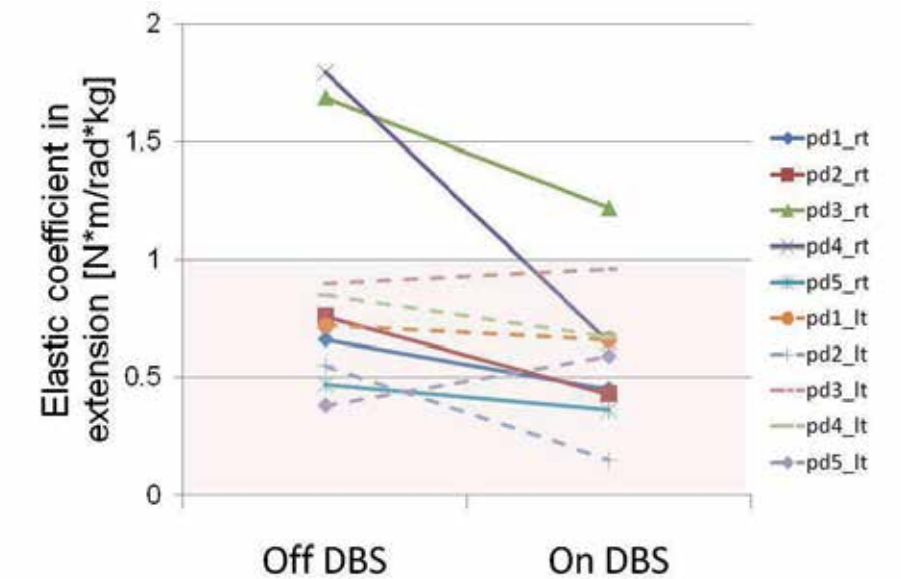


Fig. 10. Effects of deep brain stimulation on the elastic coefficient in extension. The filled area (less than 1.0[N*m/rad*kg]) represents the normal region.

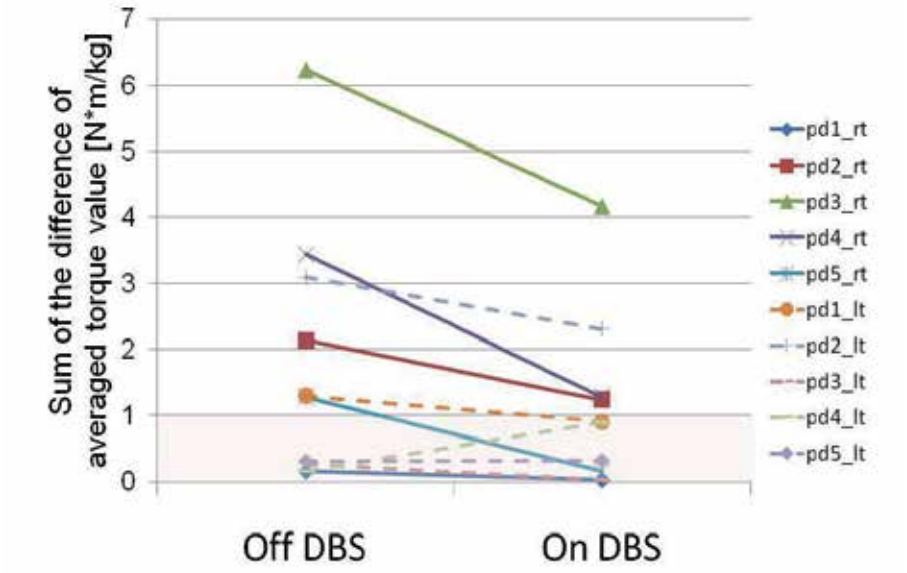


Fig. 11. Effects of deep brain stimulation on the sum of the differences of averaged torque values. The filled area (less than 1.0[N*m/kg]) represents the normal region.

Finger tapping

As shown in Table 2, improvement in UPDRS finger-tapping score after DBS was observed in PD1, PD2, and PD4. The finger-tapping wave of PD1 before and after intervention is shown in Figure 6. Irregular and disordered finger tapping changed to a smooth and correct performance after DBS. This system allows examiners to understand improvement at first sight. In the parameter analysis of finger-tapping movement, all patients with PD showed significant improvement after DBS in three parameters: mean of MoV, mean of McV, and mean of MA. However, it was not necessarily the case that STN-DBS improved the SD of FTI (Fig. 12). In summary, MoV, McV, and MA in PD1, PD2, and PD4 apparently improved, suggesting these are possible treatment markers.

3. Conclusion

We succeeded in showing the effects of DBS on rigidity and finger-tapping movement quantitatively using these instruments. The severity of symptoms obtained by these systems would not show much difference among examiners. Because neurologists could grasp subtle changes after not only DBS but also an increase in drug dose such as dopamine receptor agonists, these instruments would indicate treatment efficacy to neurologists before patients realized the improvement in their symptoms.

In the present analysis, rigidity was quantified by "work", in which the average work was done by the torque motor over one cycle (Shapiro et al. 2007). However, the concept of "work" views the flexion and extension movements as a single system, and strictly speaking, it is different from the sum of the differences of averaged torque values that we extracted. If one repeats sinusoidal flexion and extension movements as a measurement protocol, most features could not be properly evaluated at each phase because the stretch reflex has greater impact when the flexion phase is switched to the extension phase.

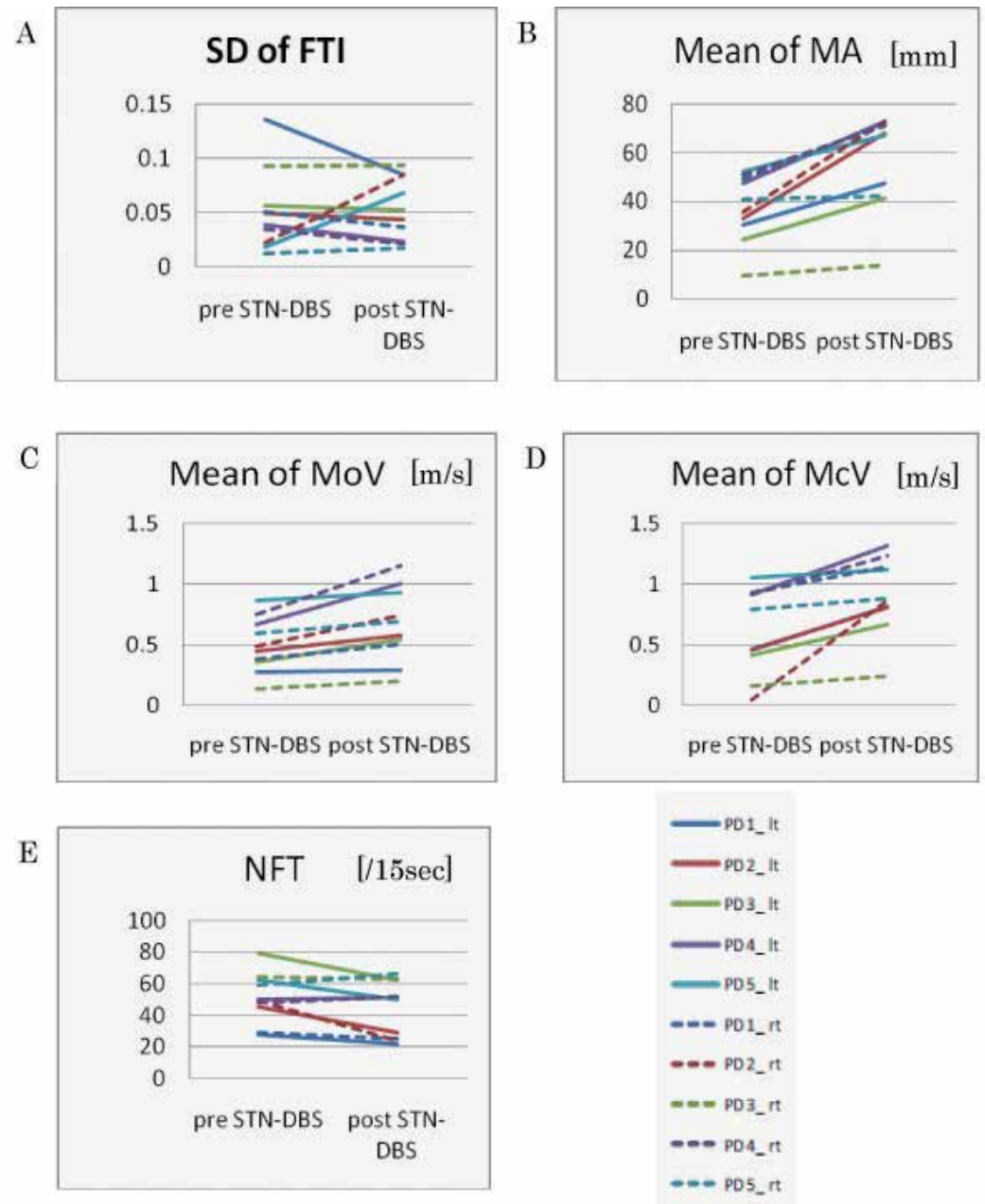


Fig. 12. Differences in five finger tapping parameters between before and after STN-DBS (A)SD of FTI (B)Mean of MA (C)Mean of MoV (D)Mean of McV (E)NFT

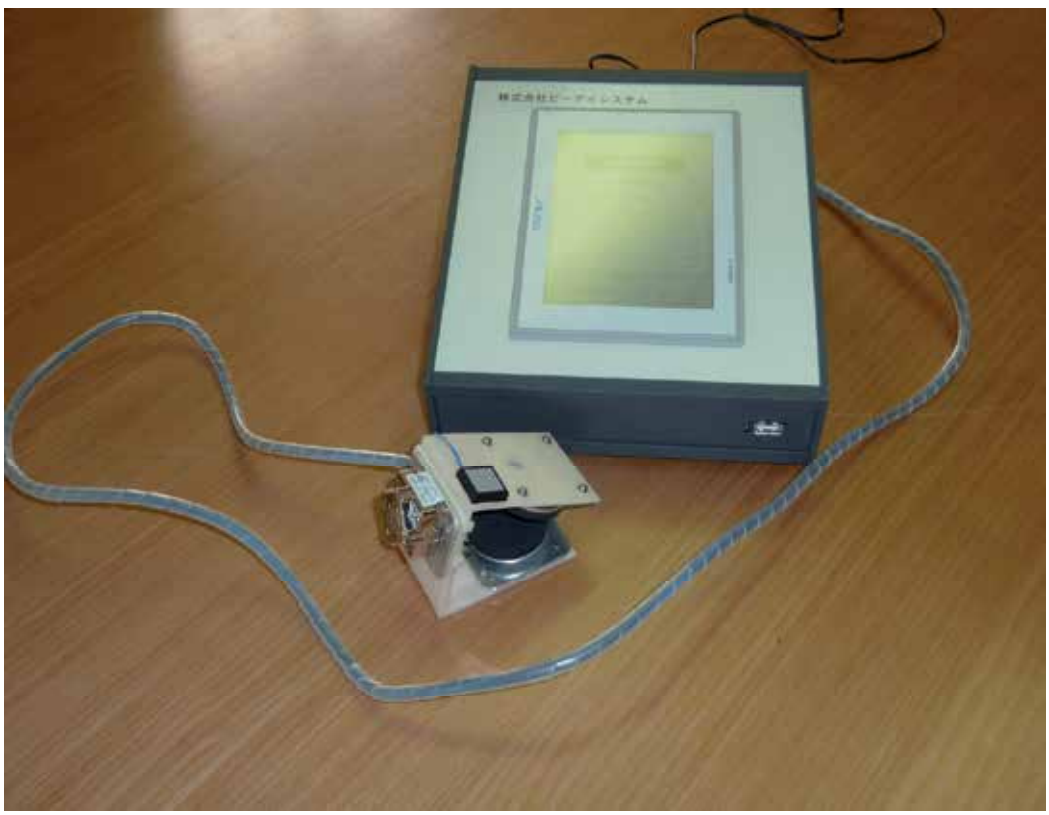


Fig. 13. Prototype of compact muscle tonus measurement system

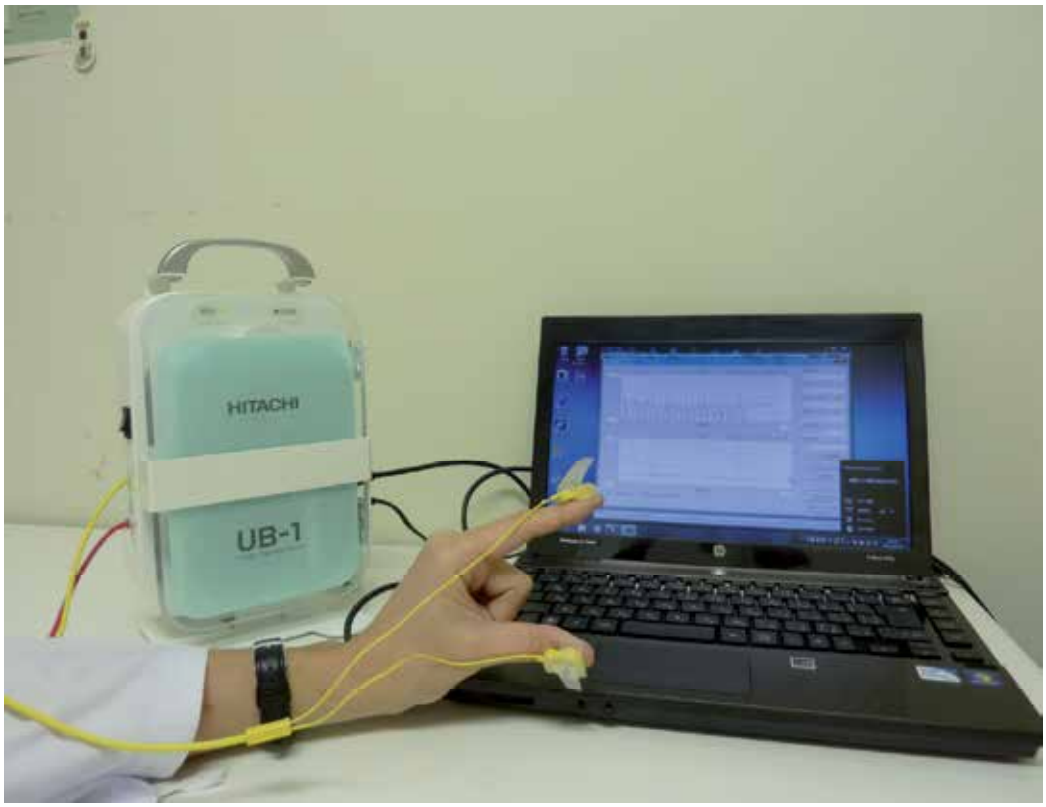


Fig. 14. New finger tapping analysis system by Hitachi Co. Ltd. (Hitachi Computer Peripherals Co. Ltd., Tokyo branch, 1-11-1, Ohmorikita, Ohta-ku, Tokyo, Zip.143-0016, JAPAN, TEL: +81-3-5753-6870, FAX: +81-3-5753-6872)

We previously reported that the muscle activity index in the static phase (EMG index) obtained for *biceps brachii* muscles, elastic coefficients, and sum of the differences of averaged torque values correlated well with the UPDRS score. Recently, we found that the EMG index is a good marker to distinguish a UPDRS rigidity score of 1 from the normal control (unpublished data). Because the elastic coefficients and the sum of the differences of averaged torque values seemed to be simple and better indicators of drug efficacy than the EMG index (unpublished data), we decided to use elastic coefficients and the sum of the differences of averaged torque values in this study. Rigidity is a clinical sign that gets worse immediately after DBS and therefore, this system is suitable for the tuning of DBS.

In finger tapping, we previously reported fourteen parameters of finger-tapping movement and a radar chart showed obvious differences in most of these parameters between normal controls and patients with PD (Yokoe et al. 2009). Principal component analysis showed that these parameters could be classified into three components: (1) mean of both amplitude and velocity, (2) number of finger tappings and mean FTI, and (3) SD of FTI. The first (velocity- and amplitude-related parameters) and third (rhythm-related parameters) components contributed to the discrimination of PD from normal controls. Regarding which component reflects treatment efficacy, parameters in the first component, including mean of MoV, mean of McV, and mean of MA, are good markers. The second component, including the number of finger tappings, does not reflect treatment efficacy. The third component, including the SD of FTI, depends on the patient. The left hand of PD1 showed improvement, although the right hand of PD2 worsened. However, both fingers moved faster and larger after DBS (Fig. 12). These results indicate that DBS works on the first component parameters rather than those of the third component.

These novel systems for testing muscle tonus and finger-tapping, which are compact, simple, and efficient, are very useful for daily neurological examinations. The muscle tonus measurement system was recently established, as shown in Figure 13 (product of PI System Co. Ltd, http://www.pis.co.jp), and the finger-tapping measurement system recently came on the market in Japan from Hitachi Co. Ltd. as shown in Figure 14.

These sensing systems identify rigidity or spasticity and the nature of abnormal finger tapping in PD and show Parkinsonian symptoms as a system error in software of repetitive movement.

4. Acknowledgment

We thank Dr. Kenzo Akazawa (Osaka Institute of Technology, Department of Biomedical Engineering), Dr. Ryuhei Okuno (Setsunan University, Department of Electrical and Electronic Engineering), Dr. Toshio Tsuji (Hiroshima University, Faculty of Engineering), Dr. Akihiko Kandori (Hitachi Co. Ltd., Advanced Research Laboratory) and Dr. Kei Fukada (Osaka General Medical Center) for their assistance during the design of this study. This study was supported by the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO).

5. References

de Leva, P. (1996). Adjustments to Zatsiorsky-Seluyanov's segment inertia parameters. *Journal of Biomechanics* Vol.29, No.9, (September1996), pp.1223-1230, ISSN 0022-0949

Endo, T.; Okuno, R.; Yokoe, M.; Akazawa, K. & Sakoda, S. (2009). A Novel Method for Systematic Analysis of Rigidity in Parkinson's Disease. *Movement Disorders,* Vol.24, No.15, (November 2009), pp. 2218-2224, ISSN 0885-3185

Fahn, S.M.C.; Calne, D. & Goldstein, M. (1987). UPDRS Development Comittee. Unified Parkinson's disease rating scale, In: *Recent Developments in Parkinson's Disease,* Macmillan Healthcare Innformation, ISBN: 0-8816-7132-0, USA

Fahn, S. & Przedborski S. (2005). Parkinsonism, In: *Merritt's Neurology, eleventh edition,* Lewis P. Rawland, pp. 828-846, Lippincott Williams & Wilkins, ISBN 0-7817-5311-2, USA

Fung, V.S.; Burne, J.A. & Morris, J.G.(2000). Objective quantification of resting and activated parkinsonian rigidity: a comparison of angular impulse and work scores. *Movement Disorders,* Vol.15, No.1, (January 2000), pp.48-55, ISSN 0885-3185

Gibb, W.R. & Lees, A.J. (1988). The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease.*Journal of Neurology, Neurosurgery and Psychiatry,* Vol.51, No6, (June 1988), pp745-752, ISSN 0022-3050

Kandori, A.; Yokoe, M.; Sakoda, S.; Abe, K.; Miyashita, T.; Oe, H.; Naritomi, H.; Ogata, K. & Tsukada, K. (2004). Quantitative magnetic detection of finger movements in patients with Parkinson's disease, *Neuroscience Research*, Vol.49, No.2 (June 2004), pp.253-260, ISSN 0306-4552

Prochazka, A.; Bennett, D.J.; Stephens, M.J.; Patric, S.K.; Sears-Duru, R.; Roberts, T. & Jhamandas, J.H. (1997). Measurement of rigidity in Parkinson's disease. *Movement Disorders,* Vol.12, No.1, (January 1997), pp.24-32, ISSN 0885-3185

Shapiro, M. B.; Vaillancourt, D. E.; Sturman, M. M.; Metman, L. V.; Bakay, R. A. E.; & Corcos, D. M.(2007). Effects of STN DBS on Rigidity in Parkinson's Disease. *IEEE TRANSACTIONS ON NEURAL SYSTEMS AND REHABILITATION ENGINEERING,* Vol.15, No.2, (June 2007), pp. 173-181, ISSN 1534-4320

Shima, K.; Tsui, T.; Kan, E.; Kandori, A.; Yokoe, M. & Sakoda, S. (2008). Measurement and evaluation of finger tapping movements using magnetic sensors. *Conference Proceedings of IEEE Engineering in Medicine and Biology Society,* (August 2008), pp.5628-5631, ISBN 978-1-4244-1814-5

Teravainen, H.; Tsui, J.K.; Mak, E. & Calne, D.B. (1989). Optimal indices for testing parkinsonian rigidity. *Canadian Journal of Neurological Scieince,* Vol.16, No.2, (May1989), pp.180-183, ISSN:0317-1671

Yokoe, M.; Okuno, R.; Hamasaki, T.; Kurachi, Y.; Akazawa, K. & Sakoda, S. (2009). Opening velocity, a novel parameter, for finger tapping test in patients with Parkinson's disease, *Parkinsonism & Related Disorders*, Vol.15, No.6, (July 2009), pp.440-444, ISSN 1353-8020

10

Relevance of Aerodynamic Evaluation in Parkinsonian Dysarthria

Sarr Mamadou Moustapha[1], Ghio Alain[2], Espesser Robert[2], Teston Bernard[2], Dramé Moustapha[3] and Viallet François[2,4]
[1]*UFR Santé- Université deThiès*
[2]*Laboratoire Parole et Langage-Aix-en-Provence*
[3]*Université de Reims*
[4]*Service de Neurologie du Centre Hospitalier du Pays d'Aix- Aix-en-Provence*
[1]*Sénégal*
[2,3,4]*France*

1. Introduction

Parkinsonian dysarthria is generally known under the name of hypokinetic dysarthria. Dysarthria, according to Darley et al (1969), is characterized by all speech disorders related to disturbances of muscular control of the speech organs, whose origin is a central or peripheral nervous system injury. So we must understand by dysarthria all failures related to either different levels of speech production (respiratory, phonatory, articulatory and even prosodic). Parkinsonian dysarthria, meanwhile, is mainly based on rigidity and hypokinesia. That's why it is considered as « hypokinetic » (Darley et al., 1975; Gentil et al., 1995). This term refers not only to reduction of articulatory movements but also to decreasing of speech prosody modulation described as monotonic (Viallet & Teston, 2007). Parkinsonian dysarthria arises, like other signs of Parkinson's disease, the depletion of dopamine in charge of phonatory incompetence by muscular hypokinesia. It is a major handicap factor that may compromise in long-term oral communication of the patient, as worsening over the course of the disease, responding less well to treatment and thereby posing additional difficulties in support. So we thought to better assess this dysarthria in order to gain a better understanding and improve management. This assessment can be done by perceptual analysis. She could also be done by various instrumental methods (acoustic and physiological) focusing on one of the speech production levels mentioned above. Such studies are numerous in literature and we will report some examples in this chapter. What is more rare in literature is assessment of parkinsonian dysarthria in study combined several levels as might allow, for example, the dual approach appealing to physiology of speech production with firstly an aerodynamic component related to pneumophonic coordination (respiratory and phonatory levels) and, secondly, an acoustic component in relation to phonoarticulatory coordination (phonatory and articulatory levels). Through this chapter we want show that it is possible to assess appropriately parkinsonian dysarthria by using aerodynamic parameters that combine respiratory and phonatory levels, so such an experiment that we report in this chapter after having reviewed main methods of evaluation.

2. Perceptual analysis

Perceptual analysis is subject to a large degree of subjectivity and inter or intra individual differences. However it can capture all functions involved in speech production system and is main foundation of parkinsonian dysarthria evaluation. On perceptual side, major disorder of parkinsonian speech is dysprosody. Prosody is defined as using of three vocal parameters (pitch, intensity and duration) which variations contribute to emotional and linguistic information. Parkinsonian voice is often described as low, monotonous, altered in timbre, too slow with hoarse character and difficult starting (Hartelius & Svensson, 1994). In addition articulations'problems were reported including a certain loss of identity of phonemes, the most suitable example being realization of plosives (/ t /, / d /) as fricatives (/ s /, / z /) due to insufficient closure of vocal tract (Robert & Spezza, 2005). These disorders can occur very early during disease's course, perhaps as early as the clinical onset of it even at the presymptomatic stage (Harel et al., 2004). Dysphonia is first manifestation that appears early. It is secondarily complemented by articulatory disorders and airflow dysfunctions (Ho et al. 1998; Logeman et al., 1978). However articulatory disorders and airflow dysfunctions alter intelligibility more than dysphonia. Chronological order of disorders appearing suggests abnormalities progression down to up of the vocal tract during disease's course. Disorders begin at laryngeal level and end with bilabial constriction via lingual and palate constriction also. In all cases, perceptual marks of parkinsonian dysarthria were well reported by Selby (1968). Points of emphasis disappear, voice volume decreases, while consonants pronunciation is deteriorating and sentence ends in a whisper. At clinical onset of parkinsonian dysarthria, voice is low, monotonous (no variation in height). After, progressive worsening of dysarthria leads to inaudible and unintelligible diction. In some cases general slowness of movement is also reflected in speech rate. In others cases patients talk quickly, tangle words and sometimes carry words acceleration until sentence ending, imitating feast walking. Perceptual disturbances of Parkinsonian speech could also be summarized by identifying two clusters. On the one hand, a main cluster of prosodic insufficiency that combines monotony of pitch and intensity, accent reduction, quick acceleration, variable flow and consonants imprecision. On the other hand, an accessory cluster of phonatory incompetence that is related to voice disturbances.
Despite large amount of information it provides, perceptual analysis must be supplemented by more objective methods of assessment.

3. Acoustic analysis

Instrumental methods are generally limited in their analysis field. Despite this limitation, they allow, from quantified data, complex functions evaluation and objective comparisons between patients and normal subjects.
On acoustic side, perceptual impressions physical basis of Parkinsonian dysarthria have been studied by measuring several parameters.

3.1 Fundamental frequency

Measurements of voice fundamental frequency (F0) reported mixed results. However, most studies concluded that a F0 average increase in PD patients during sustained vowel, text reading or spontaneous speech (Flint et al. 1992; Hertrich & Ackermann, 1993; Robert & Spezza, 2005). For example, Ludlow and Bassich (1984) found a F0 average of 165.8 Hz for

PD patients while F0 average value for control subject apparied in age and sex was 143.2 Hz. As well Canter (1963) found F0 average values of 129 Hz for patients and 106 Hz for normal subjects. F0 increased with disease severity (Metter & Hanson, 1986). Nevertheless, other studies have clearly demonstrated a F0 average reduction (Jankowski et al., 2004; Sanabria et al. 2001; Viallet et al., 2002,). It is therefore logical to agree on a certain diversity of trends in F0 that can be either lowered or increased or unchanged. F0 trends diversity could be due to biases related to patient age, gender, disease duration, variability of performance inter- and intra-individual as well as heterogeneity of measurement or evaluation methods. Regarding F0 variability in sentences production, it is reported much lower values in PD patients than normal subjects. Thus Canter (1963) noted frequency variations between 0.15 and 0.59 octaves for PD patients against 0.60 and 1.64 octaves for normal subjects. This limited variability observed in PD may be related to laryngeal rigidity that induces insufficient contraction including lack of crico-thyroid muscle which is mainly responsible for F0 increase. In sustained vowel task, there is disclosed an increase in F0 variability from cycle to cycle (Jitter) in patients, indicating an alteration of pneumophonic control stability (Jankowski et al, 2004).

3.2 Intensity

Regarding the vocal intensity, the results of perceptual analysis and acoustic measurements are not always consistent. For example, Fox and Ramig (1997) reported that the sonorous volume of PD patients was significantly lower than control subjects, around 2 to 4 decibels during speech production or other speech tasks such as sustained vowel. This result demonstrates clearly the hypophonic caracter of parkinsonian dysarthria. The results of other acoustic studies showed no significant differences between PD patients and normal subjects (Canter, 1963; Metter & Hanson, 1986). The alteration or no of the sonorous volume rather depend on the degree of severity of illness (Ludlow & Bassich, 1984). Despite these mixed results, however, there would be leaning towards a small reduction of mean intensity which falls within the phonatory incompetence associated with the subglottic pressure decreasing. The shimmer is for intensity what the jitter is for frequency, and it reflects intensity variability of sound vibration from cycle to cycle. A shimmer increasing in the task of sustained vowel has been reported in Parkinson's disease (PD) patients compared with control subjects, indicating an alteration of laryngeal stability control (Jimenez et al., 1997). These findings suggest that a reflex part of speech production control appears to be intact, contrary to the dysfunction of voluntary control directly induced by the disease.

3.3 Abnormalities of vocal timbre

Acoustic measurements during sustained vowel confirmed the perceptual abnormalities of timbre (blown, frayed or tremulous character) in addition to showing F0 and intensity increasing variability from cycle to cycle, changes longer term due mainly to the tremor, with a reduction of signal/noise ratio (Viallet & Teston, 2007).

3.4 Speed of speech

The speed of speech of PD patients is highly variable from one subject to another (Darley et al, 1975). Some studies showed no significant difference between parkinsonian and normal subjects (Ackermann & Ziegler, 1991; Ludlow et al. 1987). Other studies have reported a

faster speech rate in PD patients (Weismes, 1984). Finally, the speech speed can also be slower (Volkmann et al., 1992). These differences reflect not only the variability between subjects, but also the possible variation of results depending on the task (Ho et al., 1998). In all cases, Parkinsonian speech is marked by abnormalities which are described a long time and may impact on speed: festination, palilalia and pseudo-stuttering with dysfluences (Monfrais-Pfauwadel, 2005). What is more, the fine analysis of the acoustic signal from read speech extracts with attentive listening has led to a better study of the Parkinsonian speech temporal organization: the speed of speech tends to be slower. This slowness seems correlated with a longer pause time, duration of breaks was found significantly higher in PD patients compared with control subjects (Duez, 2005). In addition breaks inside of words have been observed in PD patients and not in controls subjects. Finally many dysfluences, such as omissions, repetitions and false starts, were found almost exclusively in PD patients. Numerous breaks and dysfluences not only slow the speed of speech, but also deconstruct the language units, disrupt perceptive waiting of listeners and finally degrade intelligibility.

3.5 Imprecise consonants

The most typical perceptual error articulatory in Parkinsonian dysarthria, namely the realization of consonants as fricatives was also confirmed by the acoustic analysis. In effect during these tests, it is found, instead of a silence due to normally carried out occlusion, a signal corresponding to a low intensity friction noise due to air passage and defined as the spirantisation phenomenon. Similarly, the lack of acoustic contrasts reflecting a lack of articulation is a common feature of parkinsonian speech spectrograms (Kent & Rosenbek, 1982).

3.6 Other anomalies

Finally, other deviations were reported always in acoustic studies: the reduced duration of formant transitions (Connor et al. 1989; Forrest et al., 1989), the voicing of voiceless consonants assigned to the rigidity of the larynx, a control loss of voice onset time (VOT), that is to say, the time between the release of the consonant and the beginning of voicing, resulting in a lack of coordination between the larynx and articulatory organs (Forrest et al., 1989; Lieberman et al., 1992).

4. Physiological analysis

It essentially uses electromyographic methods, vidéocinematographic, kinematic and aerodynamic. It provides quantitative data on respiratory plans, phonatory and articulatory (Teston, 2007).

4.1. Respiratory system

Kinematic studies have measured the thoracic and abdominal movements. The spirometric measurements allowed to assess the volumes of mobilized air during inspiration and expiration. At rest PD patients respiration is characterized by a shortening of respiratory cycle at the expense of expiration and, moreover, a relative decline of thoracic participation in respiratory movement. During speech production, it was noted in PD patients an inspiratory volume reduction of the thoracic cage, and an increase in inspiratory abdominal volume, which suggests an alteration of expiratory airflow necessary to set the appropriate contribution of laryngeal vibrator (Solomon & Hixon, 1993).

4.2 Phonatory system

The rigidity of the laryngeal musculature is a major determinant of hypophonia associated with parkinsonian dysarthria. It has been demonstrated by studies in laryngoscopy which provided direct light on the anomalies of the larynx. Larynx anomalies include glottal gap by chord adherence default, sometimes hypertonia of ventricular bands and tremor which can be localized at chordal level or above glottal part of vocal tract (Jiang et al., 1999; Yuceturk et al., 2002). Laryngeal rigidity induces a particularly curved form of vocal cords responsible for the unusually large and constant aperture of the vocal tract (Smith et al., 1995).

4.3 Articulatory system

On physiological side it is mainly explored by electromyographic and kinematic methods. In fact electromyographic and kinematic methods permit to analyze strenght and movement of articulatory organs in order to better understand the motor speech disorders

4.3.1 Articulatory organs movement

The mobility of articulatory organs of speech, like other movements, is disturbed by two major symptoms of Parkinson's disease: rigidity and hypokinesia.

The rigidity incrimination has been strengthened on the basis of certain works. For example Hunker et al. (1982) were able to evaluate a coefficient of rigidity by applying known forces on labial muscles and observing the resulting displacement. The lower lip of PD patients showed a significantly higher rigidity than control subjects, whereas for the upper lip, there was no significant difference between the two groups. Moreover a correlation between the degree of rigidity and the movements' reduction was observed by recording the lips movement with a strain- gauge system in connection with the muscular activities of inferior orbicularis and mentalis, (Barlow et al., 1983). However, this rigidity is not expressed identically on all articulatory organs, affecting preferentially muscles which are poor in neuro-muscular spindles and without stretch reflex such as the tongue comparatively to other muscles which are richer in neuro-muscular spindles and with monosynaptic reflex activity such as the jaw elevators (Abbs et al., 1987).

The hypokinetic character of some articulatory movements during parkinsonian speech is reported in particular by Ackermann et al. (1993). In this study recording the lips and tongue movements with an electromagnetic system during the repetition of syllables [pa] and [ta], there was an increased frequency and decreased amplitude of articulatory movements during the repetition of the syllable [ta] and no anomaly was found during the repetition of the syllable [pa]. This result suggests that there may be different mechanical properties between the tongue and lips. Kinematic studies also showed that hypokinesia of muscles, thus the nature of motor performance, may depend on factors such as familiarity of the task, the existence of visual guidance (Connor and Abbs, 1991) or even speed of speech (Caligiuri, 1989). Finally the kinematic studies have also confirmed, in PD patients, lack of coordination between different muscles involved in the complex activity that is speech production. Indeed the kinematic analysis of jaw, upper and lower lip showed a different motor behavior of these three structures. The lower lip was working normally when the upper lip and jaw had velocity peaks and/or reduced amplitude of movement (Connor et al., 1989).

4.3.2 The articulatory organs forces

It is usually assessed by using force transducers (Barlow et al., 1983). Muscle abnormalities are also detectable by using electromyographic explorations (Leanderson et al., 1971). The latter, despite their relative inaccessibility to non-medical researchers and the difficulties attached to their technical realization and interpretation, can provide a wealth of information on the chronology of muscular events and agonist-antagonists relation (Teston, 2007). It has been noted in parkinsonian dysarthria abnormal electromyographic signal during the study of orbicularis upper lip activity in repetition of the syllable [pa]. Indeed, in PD patients comparatively with control subjects and during repetition, the short bursts of muscle activity associated with each syllable had duration of shorter and shorter with an associated reduction in their amplitude (Netsel et al., 1975).

These physiological analysis concerning only one level of peripheral production of speech should be more and more replaced by the combined study of at least two levels; example of such a combined analysis is provided by the study of pneumophonic coordination.

4.4 The pneumophonic coordination

It reflects the synergy of action that must exist during speech production between respiratory and laryngeal levels. The measurement of subglottic pressure (SGP) is a good indicator of this pneumophonic coordination. Indeed, the SGP is evaluable indirectly via the intraoral pressure (IOP) during the production of plosives and depends on both the expiratory airflow and laryngeal resistance. In other words, SGP results from a dynamic conflict between air thrust forces and laryngeal resistance, so the evaluation of its trend in a group of breath can give a powerful index of the speaker pneumophonic coordination (Teston, 2007). So such a parameter, related to the aerodynamic side of speech production with in addition its non-invasive character, can be relevant in the assessment of parkinsonian dysarthria.

5. Relevance of the evaluation of aerodynamic parameters

Our research team has experience of using aerodynamic parameters in the assessment of parkinsonian dysarthria. The measurement of such parameters has been performed in PD patients and control subjects by using the voice evaluation system Eva 2 of SQ LAB society in Aix-En-Provence.

5.1 Used parameters

We worked primarily on three parameters: the intra-oral pressure (IOP), the mean oral airflow (MOAF) and laryngeal resistance (LR).

IOP is an indirect reflection of subglottic pressure which is itself nothing other than the pressure exerted by the expiratory air column on the vocal cords. Subglottic pressure is an important aerodynamic parameter and could allow a better understanding of some dysfunctions in speech production system (Baken & Orlikoff, 2000).

The MOAF is another important aerodynamic parameter associated with the laryngeal function and speech production. MOAF and subglottic pressure allow together a better description of the aerodynamic component of speech production.

Finally, the LR is the ratio of IOP on the MOAF and should be able to give an idea about the functioning level of laryngeal stage.

5.2 Equipement and measurement technique

5.2.1 Equipement

We used in this study the vocal evaluation system EVA 2 developed by the Laboratory of Speech and Language and sold by SQ-Lab society. EVA 2 operates as a workstation PC in the Windows environment (**See Figures 1 and 2**) with different software applications dedicated to acoustic and aerodynamic analysis of speech production.

The recording device includes an acoustic channel and two aerodynamic channels: one for measurement of mean oral airflow (MOAF), the other for the IOP measurement. It is thus possible to measure IOP during holding of a voiceless plosive. As a reminder, IOP is the estimated subglottic pressure.

Fig. 1. General Feature of Eva 2 (workstation PC in the Windows environment)

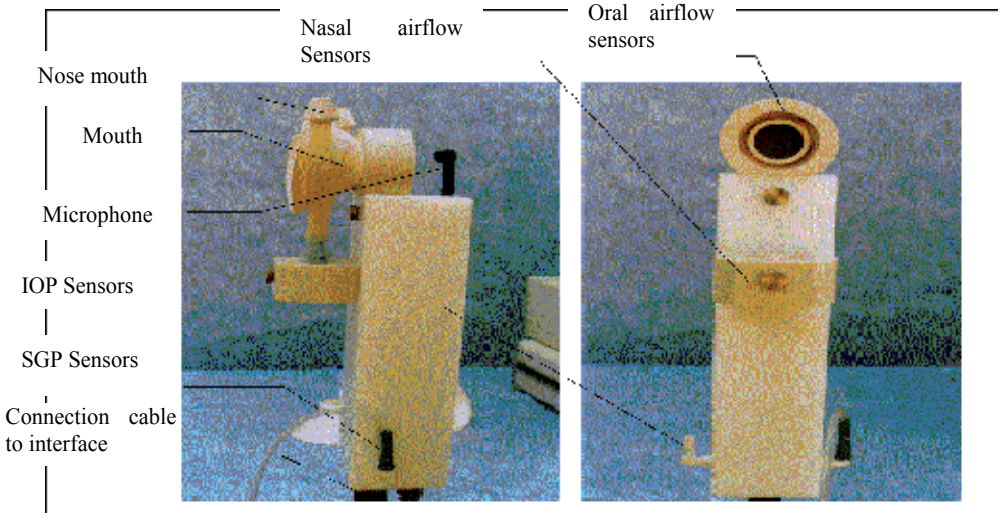


Fig. 2. EVA 2 hand piece with accessories (microphone, mouth, sensors etc.)

5.2.2 Technique

The measurement technique derives from the general theory of fluids dynamic applied to the airway. According to this theory it is possible by adjustments of valves to estimate pressure-flow upstream from the direct measurement of pressure-flow downstream of the target site. The adjustments of valves in question occur naturally during the pronunciation of certain sounds. For example, during production of the consonant / p / the lips are closed while the glottis is open. In contrary during pronunciation of the vowel / a / the lips are open while the glottis is closed. The different conformation of these examples of valves located on the airway (glottis and lips) has a physical impact on the pressure and flow dynamics prevailing inside airway. So during the realization of a voiceless plosive (/ p /), there is a momentary equilibration of intra-oral and subglottic pressures. This equilibration allows indirect assessment of SGP (upstream) via the direct measurement of IOP (downstream). The momentary equilibration of subglottic and intra-oral pressures occurs when holding the voiceless plosive because at this moment there is no phonation, the lips are closed and the glottis is open. Thus the peak pressure generated by holding a voiceless plosive may be considered as a "snapshot" of the subglottic pressure immediately preceding phonation. Similarly during the realization of the vowel (/ a /) following a voiceless plosive (lips are open and glottis is closed), it is possible to consider the oral airflow as a snapshot of translaryngeal airflow because of continuity of flow through the upper airway when the mouth is open. Once we got the two parameters, it suffices to calculate the ratio of intra-oral pressure on the oral airflow to determine the laryngeal resistance (Smitheran & Hixon, 1981; Demolin et al, 1997) (**See Figure 3**).

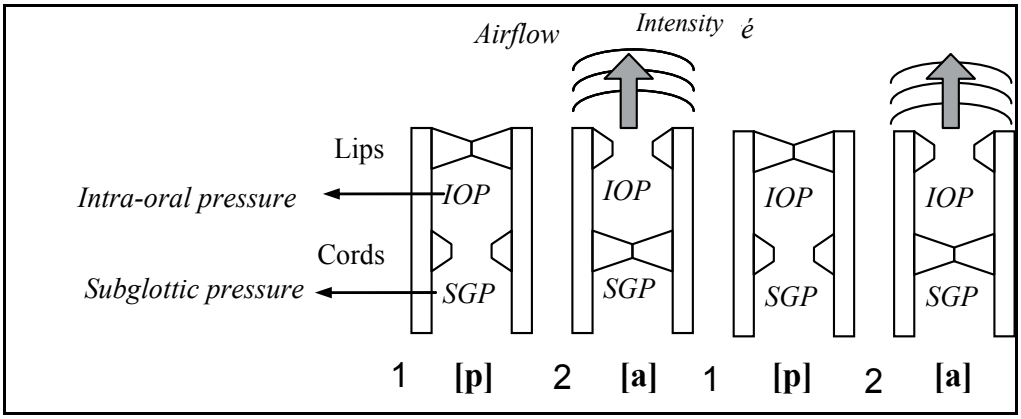


Fig. 3. Evaluation of the subglottic pressure.

Intraoral pressure (IOP) is equivalent to the subglottic pressure (PSG) during the labial occlusion of phoneme "p". Subglottic pressure is estimated indirectly by "Interrupted Airway Method" (Smitheran & Hixon, 1981), method validated notably by Demolin et al. (1997).

Measurements were performed while the subject produced at a constant rate the sentence “Papa ne m’a pas parlé de beau-papa” (Daddy did not speak to me about daddy-in-law). During this production, oral mouth was firmly against the underside of the face to minimize air leakage (**see Figure 4**). Taking IOP is performed using a disposable suction catheter approximately 4 mm (**See Figure 5**). The probe was placed between the incisors and should not be crushed between the teeth or be obstructed by saliva.

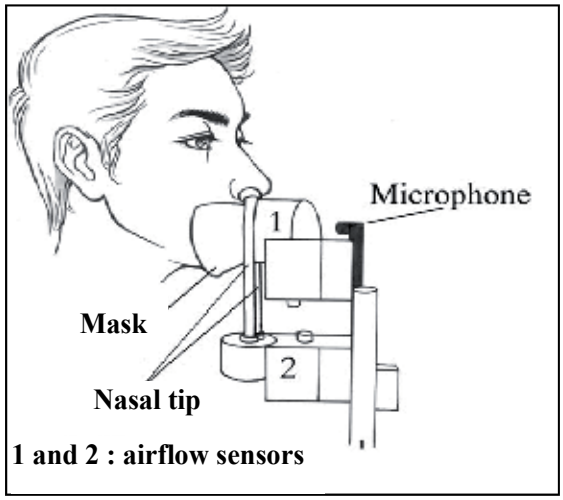


Fig. 4. Oral mouth firmly against the underside of the face

Fig. 5. Note the suction probe for taking IOP (indicated by red arrow)

5.3 Patients and control subjects

The study included 24 subjects with PD who had an average age of 59 years (SD = 5.65) with a mean duration of disease about 9, 9 years (SD = 3.27). Patients were recorded after withdrawal of L-dopa for at least 12 h (condition called OFF DOPA).

50 healthy subjects served as controls. They had an average age of 61 years (SD = 10, 5).

5.4 Statistical analysis

Statistical comparisons between groups (CTRL vs. OFF DOPA) were conducted on the basis of a linear mixed model (software "R" version 2.6.2, http://www.r-project.org). This model emerged as best suited to the analysis of grouped data. Indeed, the repeated measurements, longitudinal studies are data that are presenting a group structure. And in our case, a single individual is undergoing multiple measures, and structured data in this way no longer meet one of the fundamental prerequisites for the validity of a classical linear model, namely the independence of measures. We set our statistical comparisons as follows: measurements of aerodynamic parameters (IOP, MOAF and LR) accounted for the numerical factor of the model, the group (CTRL, OFF DOPA), the position of the consonant / p / in the sentence produced (P1, P2, P3, P4, P5, P6) and the subject (patients, controls) were the three factors model variability.

A p-value less than 0.05 was accepted as statistical significance.

5.5 Results

In a study that involved 20 male patients registered in terms ON / OFF STIM and 11 control subjects, measurement of IOP showed a statistically significant fall of this parameter in OFF STIM patients compared to controls. The stimulation of Subthalamic nucleus (STN) improved partially IOP with a statistically significant difference at the first two measurement points whereas there was an effect of convergence on the third point (Sarr et al., 2009).

In another study that focused on 24 patients registered in OFF DOPA condition and compared with 50 control subjects, three parameters (IOP, MOAF and LR) were measured on six / P / (P1 to P6) of the sentence « Papa ne m'a pas parlé de beau papa » that subjects pronounced at a constant rate.

Here too, there was, as regards the IOP, a statistically significant decrease in patients compared to controls (p = 0.0001) (**See Table 1 and Figure 6**).

	P1	**P2**	**P3**	**P4**	**P5**	**P6**
OFF DOPA	3,84 (1,9)	6,22 (2,2)	4,46 (1,8)	4,7 (1,9)	4,49 (1,9)	4,26 (1,7)
CTRL	5,23 (2,00)	6,97 (2,15)	5,73 (1,90)	5,9 (1,93)	6,06 (1,98)	5,67 (2,00)

Table 1. Average of intraoral pressure (IOP) in control subjects (CTRL) and OFF DOPA patients at six measurement points. Standard deviations are in parentheses.

Concerning mean oral airflow (MOAF) the curve of mean values at six points of measurement in control subjects (CTRL) and OFF DOPA patients showed an convergent aspect at extremities so that P1 and P6 while at the other measurement points (P2 to P5), the two curves were clearly separated: that of control subjects remain above that of OFF DOPA patients (**see Table 2 and Figure 7**). The comparison between the two groups was statistically significant (p = 0.001).

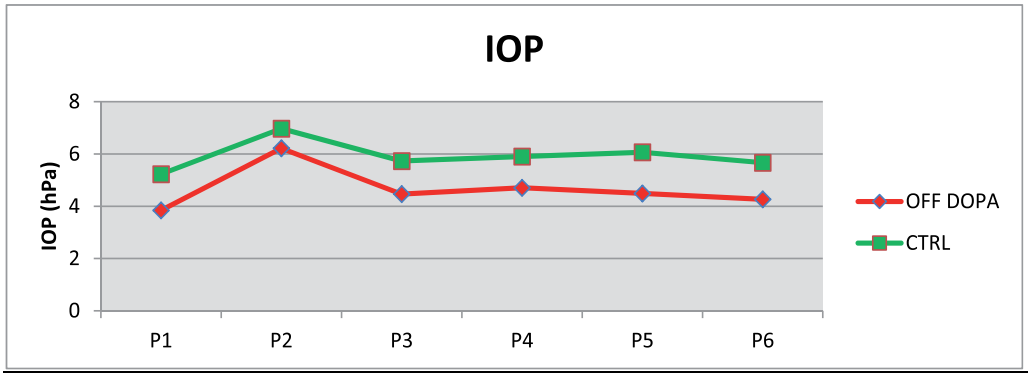


Fig. 6. Curve of the intra-oral pressure (IOP) in control subjects (CTRL) and OFF DOPA patients at six measurement points.

	DAOM 1	DAOM 2	DAOM 3	DAOM 4	DAOM 5	DAOM 6
OFF DOPA	0,2 (0,09)	0,16 (0,08)	0,17 (0,08)	0,17 (0,08)	0,19 (0,07)	0,2 (0,08)
CTRL	0,2 (0,08)	0,21 (0,07)	0,21 (0,07)	0,20 (0,08)	0,21 (0,06)	0,2 (0,06)

Table 2. Average of mean oral airflow (MOAF) in control subjects (CTRL) and OFF DOPA patients at six measurement points. Standard deviations are in parentheses.

NB: DAOM is the french abbreviation of mean oral air flow (MOAF)

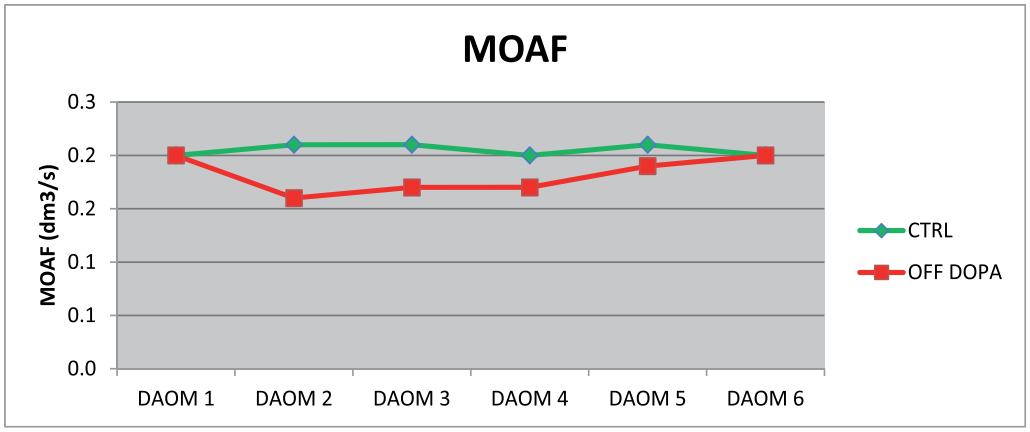


Fig. 7. Curve of mean oral airflow (MOAF) in control subjects (CTRL) and OFF DOPA patients at six measurement points.

Finally for the LR, the graphical representation of mean values at six points of measurement in control subjects (CTRL) and OFF DOPA patients showed on one hand a more linear overall appearance of the control-subjects 'curve, on the other hand, a curve of OFF Dopa patients above that of control subjects from P1 to P4 and then, below, beyond P4. In addition standard deviations were significantly larger in OFF DOPA patients than in control subjects (**See Table 3 and Figure 8**). The comparison between the two groups was statistically significant ($p < 0.05$).

	RL 1	RL 2	RL 3	RL 4	RL 5	RL 6
OFF DOPA	28,05 (20,50)	51,22 (40,14)	33,77 (23,1)	33,99 (21,97)	27,09 (16,27)	29,21 (26,74)
CTRL	25,75 (16,92)	35,38 (13,54)	30,81 (11,83)	33,40 (14,09)	30,84 (11,64)	33,64 (13,51)

Table 3. Mean of laryngeal resistance in control subjects (CTRL) and OFF DOPA patients at six measurement points. Standard deviations are in parentheses.

NB: RL is the french abbreviation of laryngeal resistance (LR)

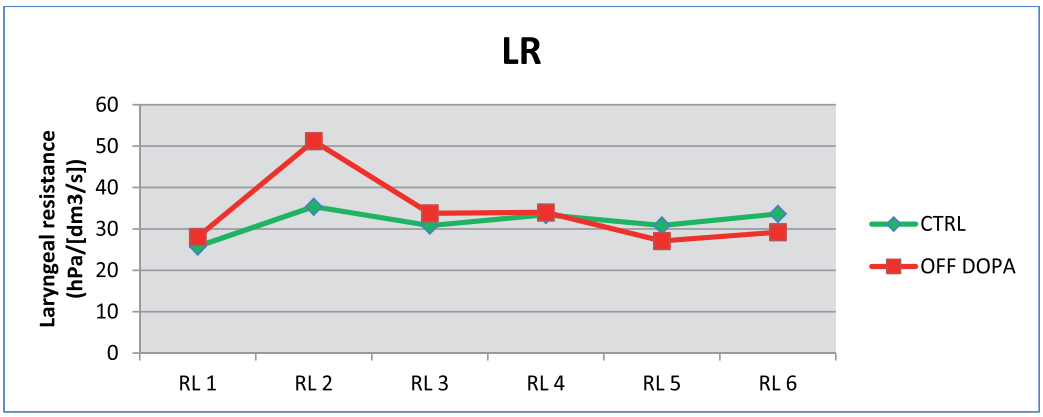


Fig. 8. Curve of mean values of laryngeal resistance (LR) in control subjects (CTRL) and OFF DOPA patients at six measurement points.

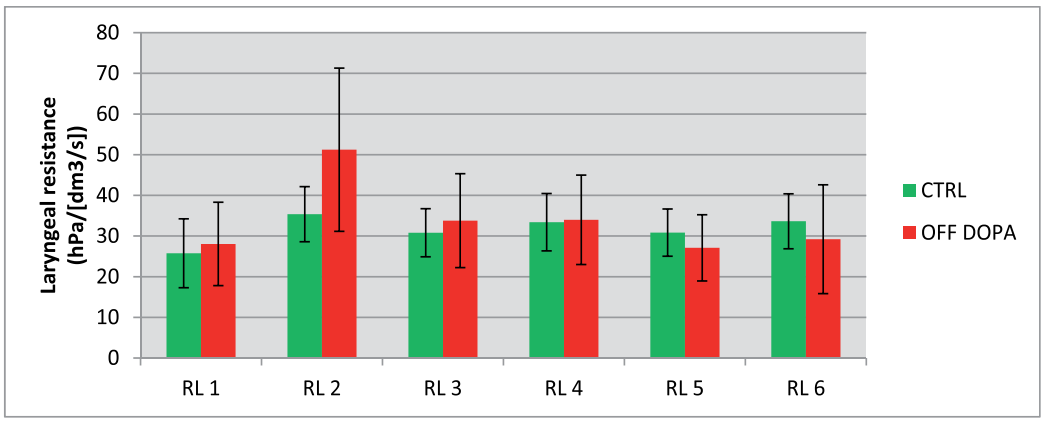


Fig. 9. Histogram of mean values of laryngeal resistance (LR) in control subjects (CTRL) and patients OFF DOPA at six measurement points, with standard deviations. The histogram allows to better see the standard deviations significantly larger in patients.

5.6 Discussions

This new study that examined 24 patients and 50 control subjects confirms the decrease of IOP on all six measurement points of the sentence when comparing patients with control

subjects. The decrease of IOP, found in a previous study (Sarr et al., 2009), seems to confirm definitively the alteration of this parameter in parkinsonian dysarthria. The decrease of IOP in patients is due to dopamine deficiency inherent in PD. Dopamine deficiency induces a dysfunction of the respiratory muscles that is partly responsible for the dysarthria (Murdoch et al., 1989). Indeed there are, within overall poor control of expiratory airflow, an alteration of the air quantity needed for the vibration of vocal cords (Jiang et al., 1999a ; Solomon & Hixon, 1993). However, the SGP is the result of a surge in air column by the pressure of lung with laryngeal resistance (Crevier-Buchman, 2007; Solomon, 2007). In the particular context of this study, when measuring IOP via the GSP, the glottis is open, at that time so it's a pressure gradient which is measured and not a static value. This gradient is the result of coordinated action between the respiratory muscles and laryngeal floor, so it indicates pneumophonic coordination quality. In PD, the fall in pulmonary pressure associated with hypokinetic movements of laryngeal muscles induced an alteration of the SGP. So we have shown in this study that it is possible to consider the GSP, or IOP, as a strong indicator of Parkinsonian dysarthria in general and its pneumophonic side particularly. We confirm in same time the results already published in a preliminary study (Sarr et al., 2009). Therefore, the measurement of IOP may allow together, comparing OFF DOPA patients and control subjects, assessment of the disease impact on speech disorders and contribution to evaluation of somes therapies such as L-dopa and subthalamic nucleus stimulation on parkinsonian dysarthria. As a reminder in our study (Sarr et al., 2009), STN stimulation improves IOP significantly in the initial part of the expiratory phase.

Regarding the mean oral airflow (MOAF), no difference was found between patients in OFF DOPA and control subjects at the first and last measurement point (P1 and P6). That means patients and control subjects would develop the same speed to start and finish the sentence « Papa ne m'a pas parlé de beau-papa ». Difference between the two groups was only noted during the course of sentence production. Indeed at other measurement points (P2 to P5), the curve of control subjects is well above that of patients in OFF DOPA, the difference between the two groups was significant ($p = 0.001$). It is also found that the curve of control subjects had a more stable pace with its roughly more linear shape **(See figure 7).** This could reflect a greater mastery of oral airflow by control subjects. In other words, the relatively greater irregularity of the curve of average values of MOAF in patients could reinforce the idea of a less good control of the MOAF. The reported decrease of MOAF could merely be a consequence of the fall in IOP. For example, assuming that laryngeal resistance is constant, the drop in IOP is necessarily associated with diminution in MOAF. However it seems exist in this study a large variability in laryngeal resistance in patients, as an overview was provided us in the morphological analysis of their value curves. This suggests a relatively fluctuating fall in MOAF which may also be related to tissue properties, configuration of the glottis and impedance of the vocal apparatus (Jiang & Tao, 2007). It is reported more generally in extrapyramidal syndromes glottic and supraglottic disorders such as movement disorders. These disorders can obstruct completely or partially the upper airway to induce sometimes severe airflow decrease (Vincken et al., 1984). The MOAF decline during speech production of PD patients could also be explained by similar mechanisms, among others.

Finally for the laryngeal resistance (LR), Parkinson's disease could induce a greater variability of this parameter in patients compared to control subjects, as evidenced by the general morphology of control subjects and OFF DOPA patients' curves. In other words, control subjects would have more stable values of LR, which would mean that Parkinson's disease induces instability of laryngeal resistance. The values of standard deviations

significantly larger in OFF DOPA patients than control subjects, again reflecting greater variability in the values of LR at all measurement points, seem to confirm this trend (**See Figure 9**). The study of LR values distribution histogram in the two groups seems to be in the same direction. Indeed, the histogram shows a fairly symmetrical distribution for control subjects where OFF DOPA patients have more skewed distributions, with thus a tendency to give most often higher LR values compared to control subjects (**See Figure 10**).

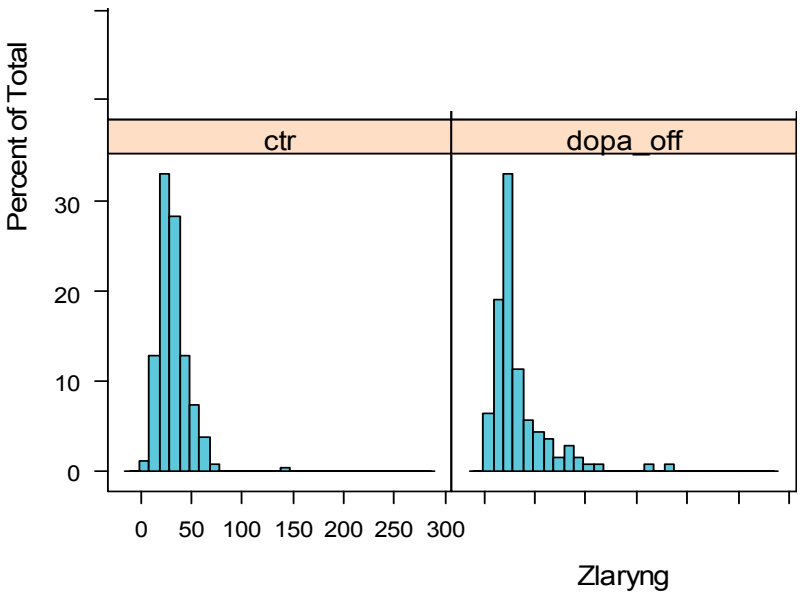


Fig. 10. Histogram of the distribution of values of laryngeal resistance (Zlaryng).
There is a fairly symmetrical distribution for control subjects, while values distributions are more skewed in OFF DOPA patients.

Laryngeal resistance is equal to the ratio of IOP on MOAF; its greater constancy among control subjects may indicate a more perfect mastery of these two parameters. Besides this relative constancy of laryngeal resistance in control subjects was found in the measures performed by Smitheran and Hixon (1981). Smitheran and Hixon measurements were performed to compare laryngeal resistance values in non-invasive technique of measurement with those of invasive procedures. The mean laryngeal resistance in their patients was 35.7 + / - 3.3 cm H20/LPS (all measurements are between 30 and 43, 1). Blosser et al. (1992) reported similar values with a mean of 38.4 + / - 7.43 cm H20/LPS. In addition laryngeal resistance may reflect the larynx subject behavior. This has been demonstrated in a canine animal model which is able of maintaining, like humans, a constant subglottic pressure during phonation. In this model it was found a significant rise in laryngeal resistance when increasing the recurrent laryngeal nerve stimulation while the same nerve paralysis induced a significant drop of laryngeal resistance (Nasri et al., 1994). This significant rise in LR was also found in other disease involving larynx impairment with patients 'average to 65 + / - 8.15 cm H20/LPS (Blosser et al., 1992). We can therefore assume that the instability of laryngeal resistance in OFF DOPA patients reflects a more variable behavior of their larynx, but also a greater fluctuation in IOP and MOAF. We know, as seen previously, that patients have IOP lower than those of control subjects at all measurement

points. So the important rise of patients' laryngeal resistance in the first half of the sentence, beyond the intrinsic behavior of larynx, may result from a larger drop of their airflow as we had also seen. Therefore the decline in patients' IOP in the second half of the sentence would induce the consequent decline of their laryngeal resistance. That's why the global evolutionary pace of patients' curve shows increased laryngeal resistance in the first half of the sentence and significant drop in the second half. These high laryngeal resistances in the beginning of the sentence could be related to a lack of pneumophonic coordination, that is to say a kind of phase shift between the air expiratory thrust and resistance state of the larynx. Everything would go as if, when the expiratory air exerts its thrust, the larynx is still at resistance level higher than normal. The larynx would amount only to a resistance normal level later, which would explain the decrease of laryngeal resistance in the second half of the sentence. In short, this phenomenon simply imitate, but this time at the pneumophonic floor, the mechanism of control loss of voice onset time (VOT) which reflects a lack of coordination between the larynx and articulatory organs (Forrest et al. 1989; Lieberman et al., 1992).

It thus appears that there is in Parkinson's disease pneumophonic coordination impairments which are evidenced by the fall in IOP and that of MOAF in patients compared with control subjects. And it follows from the alteration of these two parameters a greater instability of laryngeal resistance which is none other than ratio of two above mentioned parameters. For didactic sake, we attempted to separately discuss the different parameters (IOP, MOAF and LR). However it should be borne in mind that these parameters are closely related functionally, and that any change in one inevitably has repercussions on the other two. Indeed, the SGP (reflected here by the IOP) depends on the air expiratory column thrust and laryngeal resistance (LR) while translaryngeal airflow (reflected here by the MOAF) is merely the result of the conflict between expiratory thrust forces (SGP) and laryngeal resistance (LR) forces (Crevier-Buchman, 2007; Solomon, 2007). Reported disturbances in the three parameters pose the problem of events' real chronology because of parameters' correlation. Is it the increase in LR at the beginning of the sentence which induces a fall in MOAF or, conversely, would it fall in MOAF resulting of expiratory thrust poor dynamic that would cause the increase in LR? It could probably be a simultaneous mechanism combining both alteration of expiratory dynamic (leading to fall in IOP and MOAF) and elevated laryngeal resistance notably at sentence beginning (reinforcing the fall in MOAF). Such a mechanism would both explain decrease in IOP and initial elevation of laryngeal resistance which both lead to a decline in MOAF that patients would be tempted to correct by vocal abuse. Finally, such a mechanism would fit perfectly to a lack of pneumophonic coordination imitating, as we noted above, the lack of coordination in phono-articulatory stage which induces the voice onset time (VOT).

6. Conclusion

Parkinson's disease, given the study of these three parameters, likely induces an alteration of pneumophonic coordination involving a decrease in IOP, a decrease in MOAF and instability of the LR. So the measurements of these three aerodynamics parameters, by reflecting the dysfunction induced by disease, may well be relevant factors in parkinsonian dysarthria evaluation. These parameters can also be valuable in evaluation of several therapies used in Parkinson's disease treatment in general and dysarthria in particular. A limit of the present work is the lack of acoustic parameters assessment. In fact we thought

that the sentence "Papa ne m'a pas parlé de beau-papa" is less appropriate than other tasks such as sustained vowel for evaluation of acoustic parameters. In any case, increasingly, methods for assessing parkinsonian dysarthria should be larger, including both central and peripheral levels of speech production. Future research to better understand and assess parkinsonian dysarthria would benefit from taking more account of a more global study of dysarthria contours.

7. References

Abbs JH, Hartman DE, Vishwanat B. *Orofacial motor control impairment in Parkinson's disease*. Neurology 1987, 37: 394-398.

Ackermann H, Grone BF, Hoch G, Schonle PW. *Speech freezing in Parkinson's disease: a kinematic analysis of orofacial movement by means of electromyographic articulography*. Folia phoniat 1993, 45: 84-89.

Ackermann H, Ziegler W. *Articulatory deficits in parkinsonian dysarthria: an acoustic analysis*. Journal of Neurology, Neurosurgery, and Psychiatry 1991, 54: 1093-1098.

Baken RJ and Orlikoff RF (2000). *Clinical Measurement of Speech and Voice*, 2nd ed. (Singular, Thomson Learning, San Diego).

Barlow SM, Abbs JH. *Force transducers for the evaluation of labial, lingual, and mandibular motor impairments*. Journal of Speech and Hearing Research 1983, 26: 616-621.

Blosser S, Wigley FM, Wise RA. *Increase in translaryngeal resistance during phonation in rheumatoid arthritis*. Chest 1992, 102(2):387-90.

Caligiuri M. *The influence of speaking rate on articulatory hypokinesia in parkinsonian dysarthria*. Brain lang 1989, 36: 493-502.

Canter GJ. *Speech characteristics of patients with Parkinson's disease: I Intensity, pitch and duration*. J Speech Hearing Dis 1963, 28: 221-229.

Connor NP, Abbs JH. *Task-dependent variations in parkinsonian motor impairment*. Brain 1991, 114: 321-332.

Connor NP, Abbs JH, Cole KJ, Gracco VL. *Parkinsonian deficits in serial multiarticulate movements for speech*. Brain 1989, 112: 997-1009.

Crevier-Buchman L. *Modélisation du fonctionnement laryngé*. In Auzou P, Monnoury-Rolland V, Pinto S, Özsancak C (eds),Les dysarthries. Solal. Marseille. 2007 pp 91-100.

Darley FL, Aronson AE, Brown JR. *Differential diagnostic patterns of dysarthria*. Journal of Speech and Hearing Research 1969, 12: 246-269.

Darley FL, Aronson AE, Brown JR. (1975). *Motor speech disorders*, pp. 171-197. Saunders WB, Philadelphia.

Demolin D, Giovanni A, Hassid S, Heim C, Lecuit V, Socquet A (1997). "*Direct and indirect measurements of subglottic pressure*", Proc. Larynx 97, Marseille, p.69-72.

Duez D. *Organisation temporelle de la parole et dysarthrie parkinsonienne*. In Özsancak C, Auzou P (ed). Les troubles de la parole et de la déglutition dans la maladie de Parkinson. Solal. Marseille. 2005, pp 195-211.

Flint AJ, Black SE, Campbell-Taylor I, Gailey GF, Levinton C. *Acoustic analysis in the differentiation of Parkinson's disease and major depression*. Journal of Psycholinguistic Research 1992, 21: 383-389.

Forrest K, Weismer G, Turner GS. *Kinematic, acoustic and perceptual analyses of connected speech produced by parkinsonian and normal geriatric adults*. J Acoust Soc Am 1989, 85: 2608-2622.

Fox C, Ramig LO. *Vocal sound pressure level and self-perception of speech and voice in men and women with idiopathic Parkinson disease*. American Journal of Speech-Language Pathology 1997, 6: 85-94.

Gentil M, Pollak P, Perret J. *La dysarthrie parkinsonienne*. Rev. Neurol. (Paris) 1995, 151, 2, 105-112.

Harel B, Cannizzaro M, Snyder PJ. *Variability in fundamental frequency during speech in prodromal and incipient Parkinson's disease: a longitudinal case study*. Brain Cognition 2004, 56: 24-29.

Hartelius L, Svensson P. *Speech and swallowing symptoms associated with Parkinson's disease and Multiple sclerosis : A survey*. Folia Phoniatr Logop 1994, 46: 9-17.

Hertrich I, Ackermann H. *Acoustic analysis of speech prosody in Huntington's and Parkinson's disease: a preliminary report*. Clin Ling Phonetics 1993, 7:285-297.

Ho AK, Iansek R, Bradshaw JL. *Regulation of parkinsonian speech volume: the effect of interlocutor distance*. J Neurol Neurosurg Psychiatry 1999, 67 :199-202.

Ho AK, Iansek R, Marigliani C, Bradshaw JL, Gates S. *Speech impairment in a large sample of patients with Parkinson's disease*. Behav Neurol 1998, 11: 131-137.

Hunker CJ, Abbs JH, Barlow SM. *The relationship between parkinsonian rigidity and hypokinesia in the oro-facial system: a quantitative analysis*. Neurology 1982, 32: 749-754.

Jankowski L, Purson A, Teston B, Viallet F. *Effets de la L-Dopa sur la dysprosodie et le fonctionnement laryngien de patients parkinsoniens*. Actes des XXVèmes journées d'études sur la parole, Fès, Maroc, 19-22 avril 2004.

Jiang J, Tao C. *The minimum glottal airflow to initiate vocal fold oscillation*. J Acoust Soc Am 2007, 121(5):2873-81.

Jiang J, Lin E, Wang J, Hanson DG. *Glottographic measures before and after Levodopa treament in Parkinson's disease*. Laryngoscope 1999, 109: 1287-1294.

Jiang J, O'Mara T, Chen HJ, Stern JI, Vlagos D, Hanson D. *Aerodynamic measurements of patients with Parkinson's desease*. J Voice 1999a, 13:583-591.

Jimenez-Jimenez FJ, Gamboa J, Nieto A, Guerrero J, Orti-Pareja M, Molina JA, Garcia-Albea E, Cobeta I. *Acoustic voice analysis in untreated patients with Parkinson's disease*. Parkinsonism & Related Disorders 1997, 3: 111-116.

Kent RD, Rosenbek JC. *Prosodic disturbance and neurologic lesions*. Brain Lang 1982, 15: 259-291.

Leanderson R, Persson A, Ohman S. *Electromyographic studies of facial muscle activity in speech*. Acta Oto-laryngologica 1971, 72: 361-369.

Lieberman P, Kako E, Friedman J, Tajchman G, Feldman LS, Jiminez EB. *Speech production, syntax comprehension and cognitive deficits in Parkinson's disease*. Brain Lang 1992, 43: 169-189.

Logemann JA, Fisher HB, Boshes B, Blonsky ER. *Frequency and cooccurrence of vocal tract dysfunctions in the speech of a large sample of Parkinson patients*. J Speech Hear Dis 1978, 43: 47-57.

Ludlow CL, Connor NP, Bassich CJ. *Speech timing in Parkinson's and Huntington's disease*. Brain and Language 1987, 32: 195-214.

Ludlow CL, Bassich CJ. (1984). *Relationship between perceptual ratings and acoustic measures of hypokinetic speech.* In: McNeil M, Rosenbek JC, Aronson AE (eds), The dysarthrias : Physiology, acoustic, perception, management, pp. 163-196. College Hill Press, San Diego.

Metter EJ, Hanson WR. *Clinical and acoustical variability in hypokinetic dysarthria*. J Comm Disorders 1986, 19: 347-366.

Monfrais-Pfauwadel MC. *Palilalies et pseudobégaiements*. In Özsancak C, Auzou P (eds). Les troubles de la parole et de la déglutition dans la maladie de Parkinson. Solal. Marseille. 2005, pp 213-222.

Murdoch BE, Chenery HJ, Bowler S, Ingram JC. *Respiratory function in parkinson's subjects exhibiting a perceptible speech deficit: a kinematic and spirometric analysis*. J Speech Hear Dis 1989, 54:610-626.

Nasri S, Namazie A, Kreiman J, Sercarz JA, Gerrat BR, Berke GS. *A pressure-regulated model of normal and pathologic phonation*. Otolaryngol Head Neck Surg. 1994, 111 (6):807-15.

Netsell R, Daniel B, Celesia GG. *Acceleration and weakness in parkinsonian dysarthria*. J Speech Hearing Dis 1975, 40: 170-178.

Robert D, Spezza C. *La dysphonie parkinsonienne et les troubles articulatoires dans la dysarthrie parkinsonienne*. In Özsancak C, Auzou P (eds). Les troubles de la parole et de la déglutition dans la maladie de Parkinson. Solal. Marseille. 2005, pp 131-159.

Sanabria J, Garcia Ruiz P, Guttierez R. *The effect of Levodopa on vocal function in Parkinson's disease*. Clin Neuropharmacol 2001, 24: 99-102.

Sarr MM, Pinto S, Jankowski L, Teston B, Purson A, Ghio A, Régis J, Peragut JC, Viallet F. *Contribution de la mesure de la pression intra-orale pour la compréhension des troubles de la coordination pneumophonique dans la dysarthrie parkinsonienne*. Rev Neurol 2009, 165: 1055 – 1061.

Selby G. (1968). *Parkinson's disease*. In: PJ Winken & GW Bruyn, Handbook of clinical neurology, pp. 173-211. North Holland Publishing Company, Amsterdam.

Smith ME, Ramig LO, Dromey C, Perez KS, Samandari R. *Intensive voice treatment in Parkinson disease: laryngostroboscopic finding*. Journal of Voice 1995, 9: 453-459.

Smitheran J., Hixon T. *A Clinical method for estimating laryngeal airway resistance during vowel production*. J Speech Hear Dis 1981, 46:138-146.

Solomon NP. *La fonction respiratoire dans la production de parole*. In Auzou P, Monnoury-Rolland V, Pinto S, Özsancak C (eds),Les dysarthries. Solal. Marseille. 2007 pp 44-55.

Solomon NP, Hixton TJ. *Speech breathing in Parkinson's disease*. Journal of Speech and Hearing Research 1993, 36: 294-310.

Teston B. *L'étude instrumentale des gestes dans la production de la parole : Importance de l'aérophonométrie*. In Auzou P, Monnoury-Rolland V, Pinto S, Özsancak C (eds),Les dysarthries. Solal. Marseille. 2007 pp 248-258.

Viallet F, Teston B. *La dysarthrie dans la maladie de Parkinson*. In Auzou P, Monnoury-Rolland V, Pinto S, Özsancak C (eds),Les dysarthries. Solal. Marseille. 2007 pp 375-382.

Viallet F, Teston B, Jankowski L, Purson A, Peragut J, Régis J, Witgas T. *Effects of pharmacological versus electrophysical treatements on parkinsonian dysprosody*. In : Speech prosody, pp 679-682. Aix-en-Provence (2002)

Vincken WG, Gauthier SG, Dollfuss RE, Hanson RE, Darauay CM, Cosio MG. *Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation*. N Engl J Med. 1984, 311(7):438-42.

Volkmann J, Hefter H, Lange HW, Freund HJ. *Impairment of temporal organization of speech in basal ganglion diseases*. Brain Lang 1992, 43: 386-399.

Weismer G. (1984) *Articulatory characteristics of parkinsonian dysarthria*. In: The dysarthrias: Physiology, acoustics, perception, management (McNeil M, Rosenbek J, Aronson AE, eds), pp 101-130. San Diego: College Hill Press.

Yuceturk AV, Yilmaz H, Egrilmez M, Karaca S. *Voice analysis and videolaryngostroboscopy in patients with Parkinson's disease*. Eur Arch Otorhinolaryngol 2002, 259: 290-293.

11

Objective Evaluation of the Severity of Parkinsonism Using Power-Law Temporal Auto-Correlation of Activity

Weidong Pan[1,3], Yoshiharu Yamamoto[2] and Shin Kwak[1]
[1]Department of Neurology, Graduate School of Medicine, The University of Tokyo,
[2]Educational Physiology Laboratory, Graduate School of Education, The University of Tokyo,
[3]Department of Neurology, Shuguang Hospital Affiliated to Shanghai University of TCM,
[1,2]Japan,
[3]China

1. Introduction

Parkinson disease (PD) is a neurodegenerative disorder not only with motor symptoms, including resting tremor, rigidity, bradykinesia and postural instability, but also with non-motor symptoms, including autonomic disturbance, sleep disturbance and depression. Due to the lack of objective biomarkers like the blood glucose level for diabetes mellitus, severity of parkinsonism has been evaluated by using the symptom-based Unified Parkinson Disease Rating Scale (UPDRS) (Martinez-Martin et al., 1994) that covers the various aspects of symptoms in patients with PD. Although the UPDRS is the standard method for the assessment of parkinsonism and the evaluation of drug effects, the scoring is not free from inter-rater variance or the fluctuation of the symptoms.

Wearable accelerometers enable long-term recording of patient's movement during activities of daily living, and hence might be a suitable device for quantitative assessment of the disease severity and progression. Alterations in locomotor-activity levels and disturbances in rest-activity rhythms have long been recognized as integral signs of major psychiatric and neurological disorders (Teicher, 1995; Witting et al., 1990). Improvement of ambulatory activity monitors (actigraph) has enabled precise calibration and storage of thousands of activity measurements acquired at predetermined times, hence enabled long-term recording of patient's movement during ordinary daily living (Katayama, 2001; Korte et al., 2004; Mormont et al., 2000; Okawa et al., 1995; Teicher, 1995; Tuisku et al., 2003; van Someren et al., 1996). It has been demonstrated that use of these devices is useful for the quantitative estimation of human behavior properties in normal subjects and patients with a variety of diseases, including depression, pain syndrome, and PD (Jean-Louis et al., 2000; Korszun et al., 2002; Nakamura et al., 2007; Ohashi et al., 2003; Pan et al., 2007; van Someren et al., 1993; 1998; 2006). However, because the pattern of daily activity greatly influences the recording with accelerometers, recorded activity levels may not adequately reflect the disease severity (Fig 1). Therefore, reliable analytical methods of the body acceleration signal free from the level of activity are required to describe the characteristics of body activity during daily living. Recently, fractal analysis was shown to be a robust tool to

disclose hidden auto-correlation patterns in biological data, such as heartbeat and limb movement (Ohashi et al., 2003; Pan et al., 2007; Peng et al., 1995; Sekine et al., 2004; Struzik et al., 2006). Power-law auto-correlation exponents for local maxima and minima of fluctuations of locomotor activity would be the most useful for our purpose, as they represent the level of persistency of movement patterns (Ohashi et al., 2003; Pan et al., 2007).

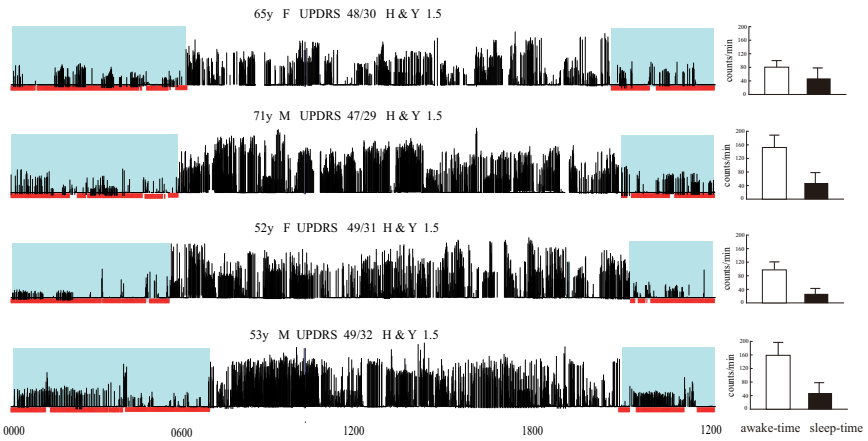


Fig. 1. Examples of 24 h actigraph recording. (left) Each vertical bar indicates activity counts per min. Sleep time is indicated in blue. Patients with approximately the same severity show different activity patterns and the activity counts (right: mean ± S.D.). UPDRS total/Part III.

In this review, we show how we can extract hidden autocorrelation patterns reflecting the severity of parkinsonism from the actigraph recording of patients' activity, and demonstrate that the analysis using power-law exponents is useful for the evaluation of effects of therapy on motor and non-motor symptoms of parkinsonism.

2. Analytical method of the motionlogger recordings for power-law auto-correlation exponents

We analyzed patients' physical activity records collected by an actigraph device using power-law exponents probing temporal auto-correlation of the activity counts. The power-law exponent for local maxima most sensitively and reliably reflects disability without being influenced by the presence of tremor or the patterns of daily living (Pan et al., 2007).

To examine temporal auto-correlation of the physical activity time series (i.e., *dynamic* aspects of physical activity), we used an extended, random-walk analysis, the detrended fluctuation analysis (DFA) (Peng et al., 1995), with a modification (Ohashi et al., 2003) for various "real-world" signals including activity time series. Briefly, a daytime physical activity time series was integrated, as in DFA, and wavelets with different time scales (S) were slid along the time series and correlated with the data to obtain the wavelet coefficients ($W(S)$) at each point. The third derivative of the Gaussian function was used as the so-called "mother wavelet":

$$\Psi(t) = t(3-t^2)e^{-0.5t^2}$$

where t is time. This is equivalent to using the Gaussian second derivative (so-called "Mexican hat") wavelet to examine the raw signals (Fig. 2), though the integration approach automatically removes the local mean and the local linear trend, as in DFA. By changing the scale of the wavelet, this "hat-shaped" template dilates or contracts in time, probing transient increases or decreases in activity records in different time scales. The transient increases (low-high-low activity patterns) yield local maxima of the wavelet coefficients at their time points, while the decreases (high-low-high activity patterns) yield local minima of the wavelet coefficients (see Fig. 2). Next, the squared wavelet coefficients at the local maxima or minima were averaged for all the available days. As the coefficient gives the magnitude of local fluctuations matching the shape of $\psi(t)$ with different time scales, the squared $W(S)$ was used, again as in DFA. Finally, the power-law exponent (α) was obtained separately for local maxima and minima as the slope of a straight line fit in the double-logarithmic plot of S vs. $W(S)^2$. This method yields the same α–values as does DFA (Ohashi et al., 2003), but separately for periods with higher and lower activity levels. The power-law (scaling) exponent, α, reflects the probability of a simultaneous increase or decrease in the variability at two distant points in time in the time series, applied to all distances up to *long-range* time scales, thereby probing the nature of "switching" patterns between high and low values in a statistical sense. Larger power-law exponents indicate positive temporal auto-correlation or *persistency* in the increase or decrease, and lower values correspond to negative auto-correlation or *anti-persistency* (Ohashi et al., 2003).

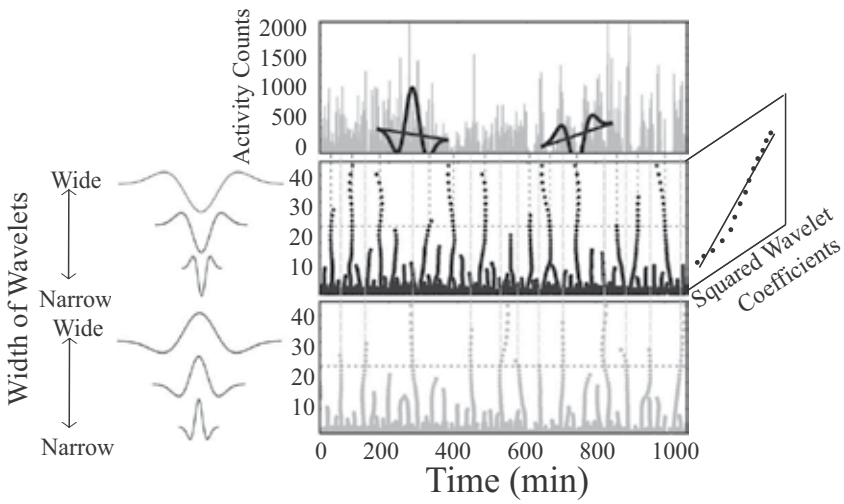


Fig. 2. Conceptual explanation of the method to obtain power-law exponents for local maxima and minima. (*top*) Various widths of hat-shaped wavelets are slid along the data to detect local minima (*middle*) and local maxima (*bottom*) of the wavelet coefficients. Note that the local minima and maxima appear at the transient decreases and increases of the activity, respectively. The power-law exponents are calculated from the slope of the log-log plot of squared wavelet coefficients vs. the scale for local minima and maxima. In the actual analysis, we used an integrated, rather than raw, time series and $\psi(t)$, i.e., the derivative of the "hat-shaped" wavelet. This yields the same power-law exponents as those obtained by the DFA method for the same local maxima and minima as obtained in this figure. Reprinted with permission from (Pan et al., 2007).

This method enables to evaluate relationships between time scales and magnitudes of fluctuation within each time scale, eliminating *non-stationarity* in the input data (i.e., changes in the baseline and trends within the data windows at different scales) that could affect calculation of the magnitudes of fluctuation. Therefore, this approach is suitable for the analysis of the long-term data collected in ambulatory settings (Pan et al., 2007).

3. Quantitative analysis of parkinsonism using power-law auto-correlation exponents

The data acquired during awake-time and sleep-time were separated with Action-W, Version 2 (Ambulatory Monitors Inc., Ardsley, NY) (Fig. 1) and the data during awake-time were used for analyses. Average wavelet coefficients for local maxima and minima of the severe and mild groups provided straight lines in the range of 8-35 min (Fig. 3A), indicative of very robust α-values. When the mean α-values for local maxima and minima were compared, they found a significantly lower α-value for local maxima in the mild group than in the severe group (Fig. 3B). All the patients (13 male and 9 female patients with Parkinson disease) in both the severe (Hoeh-Yahl score > 3.0; n=9)) and mild groups (H-Y score ≦ 3.0; n=10)) showed significantly lower α-values for local maxima on good-condition (GC) days than on bad-condition (BC) days that were classified according to diary scores, whereas there was no significant difference in the mean α-values for local minima (Fig. 3C).

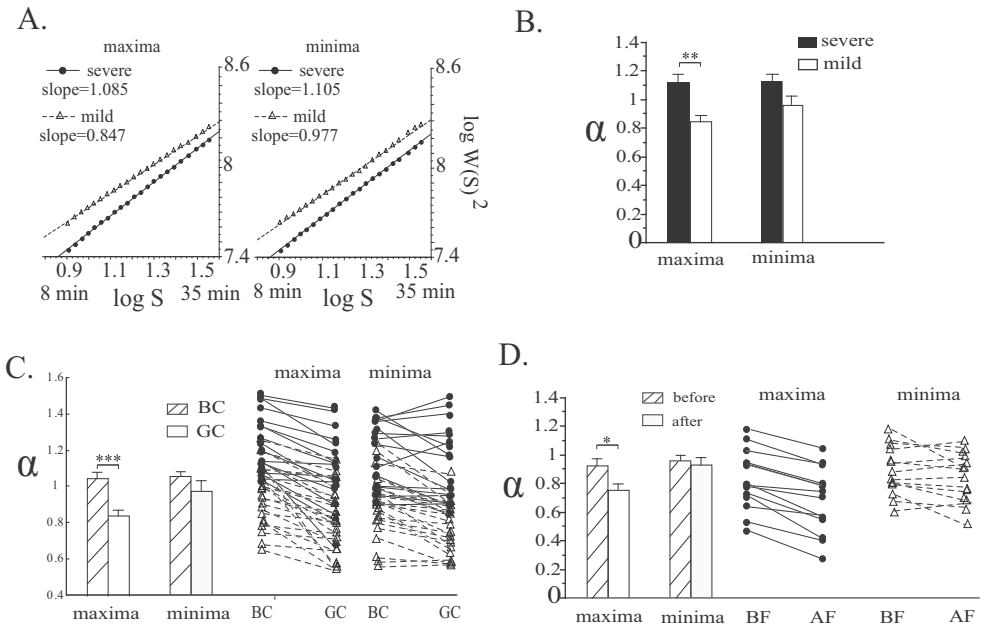


Fig. 3. Local maxima and minima of fluctuation of physical activity. (A) Average wavelet coefficients, as a function of the wavelet scale, for local maxima and minima. The slopes are power-law exponents, α. (B) Comparisons of the mean for the severe and the mild groups, (C) for BC and GC days and for individual patients, and (D) for days before and after antiparkinsonism medication and for each patient. *: $P < 0.05$, **: $P < 0.01$, and ***: $P < 0.001$. Reprinted with permission from (Pan et al., 2007).

When the effects of medication were examined, we found that all the patients who did not take any medication at the time of enrolement (n=6) showed lower α-values for local maxima on days more than three weeks after they received clinically effective anti-parkinsonism medication than on those before (Fig. 3D). Although presence of tremor significantly increased the activity counts in the arms with tremor as compared with those without tremor (Fig. 4A), power-law scaling of the records from arms with tremor showed a linear correlation between log S and log $W(S)^2$ in the range of 8 to 35 min (Fig. 4B) and α-values for local maxima were the same between the arms with tremor and those without tremor (Fig. 4B) with significantly higher α-values in patient arms than in control arms (Fig. 4C)

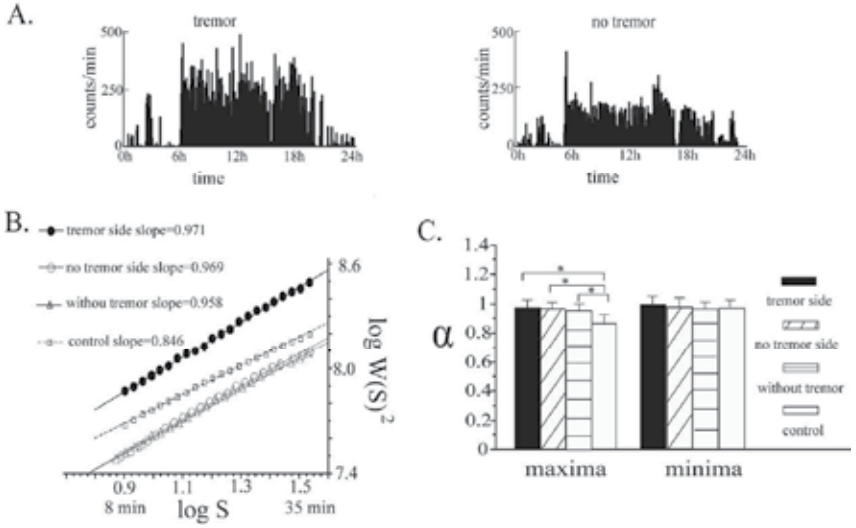


Fig. 4. Effects of tremor on actigraph counts and the power-law exponents. (A) Daily profiles of physical activity for the arm affected with tremor and that without tremor of a patient with unilaterally predominant parkinsonism with continuous tremor on one side. (B) Average wavelet coefficients for local maxima among arms with tremor (tremor) and without tremor (no tremor) of 6 patients with tremor, 26 arms of 13 patients without tremor (without tremor) and 20 arms of 10 control subjects (control). (C) The power-law exponents for local maxima and minima. *: $P < 0.05$. Reprinted with permission from (Pan et al., 2007).

Larger power-law exponents (α) indicate positive temporal auto-correlation, or *persistency*, in the increase or decrease in the variability of activity at two distant points in time in the time series, and lower values correspond to negative auto-correlation or *anti-persistency* (Ohashi et al., 2003). In other words, a lower α for local maxima or minima of activity records reflects more frequent switching behavior from low to high or high to low physical activity, respectively, and the switching behavior from lower to higher activity levels is considered to be related to akinesia in patients with parkinsonism. We found lower α-values for local maxima during GC days than during BC days, in the mild group than in the severe group, and before medication than after medication. Thus, these results demonstrate that the power-law analyses accurately describe the well known phenomenon that under these conditions patients switch their physical activity from lower to higher levels more easily, in

other words they exhibit milder akinesia, when the parkinsonism is mild than when it is severe. It is worthy to note that lower α-values for local maxima were obtained for all the patients after medication than before, and when in good condition than in bad condition (Fig. 3C, D), thereby providing a temporal profile of parkinsonism in each individual patient.

These results thus suggest that analysis of power-law temporal auto-correlation of physical activity time series using the bi-directional extension (Ohashi et al., 2003) is applicable to patients with parkinsonism for the evaluation of motor dysfunction irrespective of the presence of tremor and may provide useful objective data necessary for the control of drug dosage in the out-patient clinic and also for the evaluation of new drugs for parkinsonism (Pan et al., 2007).

4. Evaluation of effects of traditional Chinese medicine on parkinsonian symptoms

Conventional antiparkinsonism drugs effectively ameliorate the symptoms of patients with PD during the initial several years of onset, but become increasingly less effective and induce motor fluctuations including wearing-off, on-off, dopa-induced dyskinesia, and agonist-induced sleep attack (Arnulf et al., 2002; Comella, 2002; Hobson et al., 2002; Ondo et al., 2001; Pahwa et al., 2006). PD patients not infrequently suffer from non-motor symptoms, such as neuropsychiatric symptoms, autonomic symptoms, gastrointestinal symptoms, sensory symptoms, non-motor fluctuations (autonomic symptoms, cognitive or psychiatric symptoms, sensory symptoms including pain), fatigue, and sleep disturbance (Chaudhuri& Schapira, 2009; Miyasaki et al., 2006; Park& Stacy, 2009), and these non-motor symptoms may be intrinsic to the disease pathology or may be the result of treatment with dopaminergic agents. Several studies have established that the non-motor symptoms of PD are common, occur across all stages of PD, and are a key determinant of quality of life (Chaudhuri& Schapira, 2009).

Herbal remedies have a long history of use (particularly in East Asian countries) for alleviating various symptoms and have been increasingly used as alternative medicines worldwide, including the United States (De Smet, 2002). Traditional Chinese medicines (TCM) ameliorate various symptoms, particularly the ageing-related symptoms, and hence are likely to be beneficial for chronic diseases such as PD (Iwasaki et al., 2004; 2005a; 2005b). Good compliance for long-term use with few side effects may be another merit of TCM suitable for patients with PD (Lian& Luo, 2007; Zhao et al., 2007).

In order to evaluate the effects of TCM on symptoms of parkinsonism, we evaluated the effects of Zeng-xiao An-shen Zhi-chan 2 (ZAZ2) on patients with PD using this method together with conventional scales for parkinsonism (Pan et al., 2011a). ZAZ2 granule is made up of 14 kinds of herbs*; Uncaria rhynchophylla* 10 g, *Rehmanniae radix* 10 g, *Cornus officinalis* 8 g, *Asnaragus cochinchinensic* 10 g, *Paeonia lactiflora* 10 g, *Desertliving cistanche* 10 g, *Puerariae radix* 10 g, *Arisaema consanguineum Schott* 10 g, *Salviae Miltiorrhizae radix* 10 g, *Acorus tatarinowii* 10 g, *Curcuma longa Linn* 12 g, *Morindae officinalis radix* 10 g, *Rhizoma gastrodiae* 10 g, and*Rhizoma chuanxiong* 10 g. One hundred and fifteen patients with idiopathic PD took 8 g of either ZAZ2 granule or placebo granule that was not distinguished by appearance or taste for 13 weeks. Patients were randomly assigned to the ZAZ2 group (n=59) or placebo group (n=56). There was no difference in the mean age, gender ratio or disease duration between the ZAZ2 and placebo groups, and the post hoc test revealed no

significant baseline (week 0) differences in UPDRS scores, Hoehn & Yahr stages, mean counts, power-law temporal exponent α values, or in the dosage of antiparkinonian drugs between the two groups. All the patients were evaluated at week 0, week 1, and week 13 for the actigraph recording, UPDRS and Secondary Symptom Score, which is conventionally used in China to evaluate the effects of antiparkinsonism drugs and consists of 8 parts, including the assessments of non-fluent speech, vertigo, insomnia/nightmares, headache, sweating or night sweats, tiredness, sense of cold, and dysuria (Long, 1992). The awake-time and sleep-time actigraph data were used separately for the power-law temporal analyses.

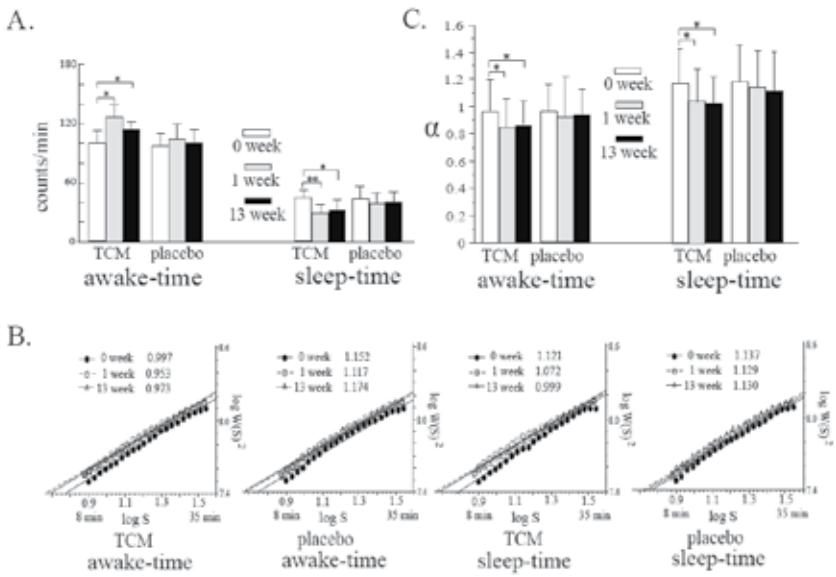


Fig. 5. Effects of TCM and placebo granules on actigraph recondings. (A) Counts of physical activity (mean ± S.D.). (B) Average wavelet coefficients, as a function of the wavelet scale for awake-time and sleep-time. The slopes are power-law exponents α. (C) Power-law exponents α (mean ± S.D.). *: $P < 0.05$, **: $P < 0.01$. (Pan et al., 2011a)

The local power-law exponent α values during both awake-time and sleep-time were significantly decreased after taking ZAZ2 granule, but not after taking placebo granule (Table 1, Fig 5). The average wavelet coefficients exhibited linear relationships in the range of scales from 8 min to 35 min both for the ZAZ2 and placebo groups (Fig. 5B). The local power-law exponent α values during both awake-time and sleep-time were significantly decreased both week 1 and 13 in the ZAZ2 group, but not in the placebo group (Table 1 and Fig 5C, $P<0.01$; Bonferroni test). The beneficial effects of ZAZ2 were shown with UPDRS scores, as well; significant and persistent improvements were found in the scores of Part II, Part II + Part III, and Part IV (Table 1). These scores at week 13 were significantly different between the ZAZ2 group and the placebo group. As the exploratory outcome of this study, most of the secondary symptoms were improved after taking ZAZ2 granule, whereas only a few symptoms were transiently improved in the placebo group (Table 2).

We evaluated the beneficial effects of TCM specifically on sleep disturbance of patients with parkinsonism. We used placebo-controlled, randomized study design, in which 48 patients

	Placebo（n = 54）			TCM（n = 56）		
	Week 0	Week 1	Week 13	Week 0	Week 1	Week 13
UPDRS total score	46.6 ± 16.3	44.7 ± 15.3	45.9 ± 18.1	46.3 ± 17.1	37.1 ± 11.2*##	40.7 ± 15.1*#
UPDRS I	2.5 ± 0.7	2.3 ± 1.1	2.4 ± 1.2	2.6 ± 0.8	2.1 ± 0.7*	2.3 ± 0.9
UPDRS II	15.7 ± 9.3	14.8 ± 11.2	15.3 ± 11.6	15.9 ± 11.3	12.5 ± 4.6*#	13.4 ± 9.8*#
UPDRS III	25.5 ± 12.9	23.8 ± 10.6*	24.9 ± 12.7	25.4 ± 10.1	19.3 ± 9.8*#	21.6 ± 10.4*
UPDRS IV	3.1 ± 1.1	2.9 ± 1.6	3.0 ± 1.4	3.2 ± 1.4	2.6 ± 0.8*#	2.7±1.3*#
Awake-time (counts/min)	98.5 ± 14.1	102.6 ± 18.9	100.7 ± 16.9	99.8 ± 17.8	126.7 ± 13.4*##	118.4 ± 11.8*##
Sleep-time (counts/min)	42.9 ± 17.1	38.8 ± 15.6*	40.1 ± 14.8	43.2 ± 11.6	35.6 ± 13.6*#	32.8 ± 13.6*#
α(awake-time)	0.97 ± 0.21	0.95 ± 0.28	0.96 ± 0.18	0.97 ± 0.24	0.88 ± 0.21*#	0.86 ± 0.19*##
α(sleep-time)	1.19 ± 0.28	1.16 ± 0.27	1.15 ± 0.29	1.18 ± 0.26	1.04 ± 0.22*#	1.02 ± 0.18*##

Data presented are mean ± SD.*:P < 0.05; **:P < 0.01 compared to week 0 (Repeated-measure ANOVAs).
#:P < 0.05; ##:P < 0.01 compared to placebo (Bonferroni test). UPDRS: Unified Parkinson's Disease Rating Scale.
α: power-law exponent.

Table 1. Measurements before and after taking test granules. (Pan et al., 2011a)

Group	Time	Non-fluent speech	Vertigo	Insomnia/ nightmare	Headache	Sweating or night sweats	Tiredness	Sense of cold	Dysuria
TCM	week 0	1.08 ± 0.74	1.33 ± 0.83	2.77 ± 0.98	0.92 ± 0.56	2.11 ± 0.68	1.66 ± 0.57	1.90 ± 0.67	2.23 ± 0.69
	week 1	0.56 ± 0.28*	0.84 ± 0.26*#	2.03 ± 0.78*	0.64 ± 0.28*##	1.38 ± 0.69*#	1.21 ± 0.46*	1.48 ± 0.57*	1.43 ± 0.31*#
	week 13	0.65 ± 0.33*##	0.95 ± 0.37*	1.73 ± 0.38*#	0.63 ±0.19*#	1.48 ± 0.28*##	1.27 ± 0.51*#	1.58 ± 0.61	1.46 ± 0.36*##
Placebo	week 0	1.12 ± 0.59	1.31 ± 0.97	2.67 ± 0.87	1.03 ± 0.75	2.13 ± 1.32	1.70 ± 0.97	1.78 ± 0.39	2.29 ± 1.02
	week 1	0.69 ± 0.32*	1.12 ± 0.69	2.40 ± 0.69*	0.96 ± 0.36*	1.87 ± 0.58	1.35 ± 0.69*	1.39 ± 0.81	1.69 ± 0.92*
	week 13	1.02 ± 0.36	1.28 ± 0.53	2.45 ± 0.38	0.99 ± 0.65	2.18 ± 0.56	1.58 ± 0.66	1.64 ± 0.58	2.18 ± 1.30

Data presented are mean ± SD.*: P < 0.05, **: P < 0.01 compared with 0 weeks (Repeated-measure ANOVAs).
#:P < 0.05, ##:P < 0.01 compared to placebo (Bonferroni test).

Table 2. Secondary symptom scores before and after taking test granules. (Pan et al., 2011a)

with idiopathic PD who had at least three awakenings per night occurring at least 3 nights per week participated. Patients wore the actigraph on the wrist of their non-dominant hand for seven consecutive days twice at week 0 (before) and week 6 of taking either one of the granule. For control, age-matched 25 patients with non-neurological diseases who had neither sleep disturbance nor parkinsonism wore the actigraph for seven consecutive days. Daily profiles of activity counts clearly demonstrated an improvement of the biological rhythm after the additional treatment in the TCM group but not in the placebo group (Fig. 6A). After treatment, sleep latency, median sleep efficiency and the median 5 least active hour, all of which were the parameters specifically reflected sleep disturbance (Pan et al., 2011b), shifted towards the values of the control group in the TCM group, but not in the placebo group (Fig 6B).

Scores in UPDRS Part II reflects the long-term outcome of the patients (Harrison et al., 2009). That both α-values for local maxima and the scores in UPDRS Part II, Part II + Part III and Part IV improved after TCM suggested that α-values for local maxima reflected patients' overall ADL, including motor symptoms and non-motor symptoms. Therefore, it is likely that analysis of the α-values is useful for the evaluation of drug effects on the long-term outcome of patient with PD (Pan et al., 2011a; 2011b).

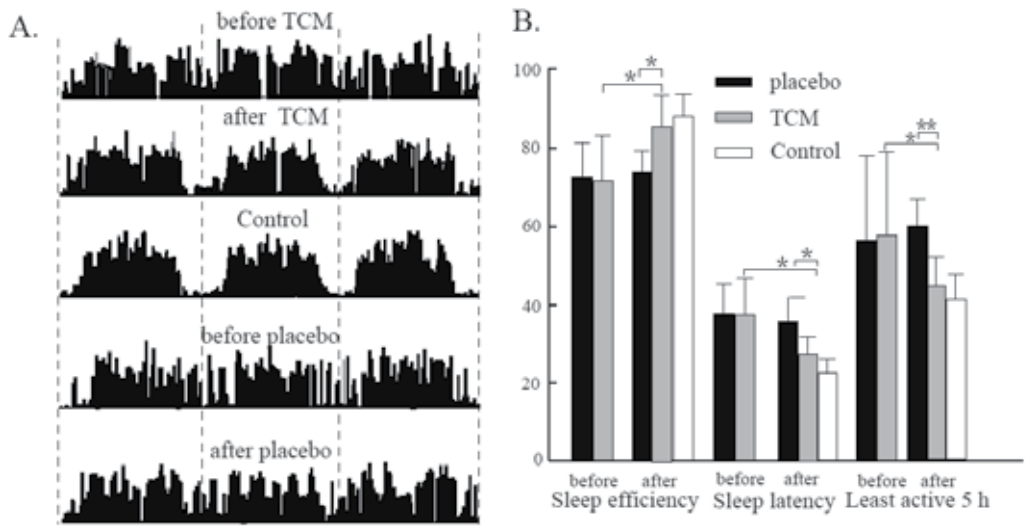


Fig. 6. Effects of cerebral granule (TCM). (A) Daily profiles of actigraph count for three consecutive days before and after taking TCM. Dashed line: midnight. (B) Changes from baseline in actigraph counts. Columns and bars (mean ± S.D.) indicate sleep efficiency (%), sleep latency (min) and the 5 least active hours (counts/min). *: $p < 0.05$; **: $p < 0.01$. Reprinted with permission from (Pan et al., 2011b).

5. Assessment for effects of GVS for ameliorating parkinsonism

Enhancing neuronal transmission is a possible non-pharmacological therapeutic strategy for neurological diseases. The cranial nerves send direct inputs to the brain, and their stimulation may lead to alterations in various central functions. Such stimulation may potentially be a therapeutic strategy for brain disorders due to the low invasiveness as compared to deep brain stimulation. Considering its central connections, the vestibular nerve can influence limbic-to-motor functions, and we applied non-invasive and non-nociceptive noisy galvanic vestibular stimulation (GVS) to the patients with parkinsonism. We successfully improved parkinsonian symptoms by using noisy GVS at a low-frequency range targeting the vestibular nerves of patients with levodopa responsive PD and levodopa unresponsive parkinsonism (Yamamoto et al., 2005). This effect is presumably through the demonstrated vestibule-cerebellar connections, and input noise played the beneficial role in sensitizing neural systems, possibly through a mechanism known as stochastic resonance, a basic physical mechanism underlying noise-enhanced responses of nonlinear systems to weak signals. It is hypothesized that a central circuit signaling the onset of movement of which the threshold is relatively increased due to the diseases may benefit from noisy emulation of the afferent firing rates. We analyzed whether the beneficial effects of GVS on parkinsonism was reflected in a decrease of the α-value for local maxima.

As previously described (Yamamoto et al., 2005), a portable GVS device was used to deliver currents using a bilateral unipolar configuration, in which electrodes were placed over the patient's bilateral mastoid processes with the reference electrodes placed on the forehead. The waveform, a zero-mean, linearly detrended noisy current with a 1/f-type power

spectrum (Struzik et al., 2006) within a range of 0.01-2.0 Hz or a constant zero current for control, with a duration of 300 sec was continuously repeated during the tests. The magnitude of noisy GVS was set to 60% of each subject's nociceptive threshold (0.29 ± 0.20 mA). Then either the noisy GVS or the control zero current was continuously applied for the first 24 hours, and then switched to the counter-part and applied for another 24 hours, while the patients' wrist activity was monitored continuously for 48 hours. The order of noisy GVS and the control zero current was determined for each patient by random selection.

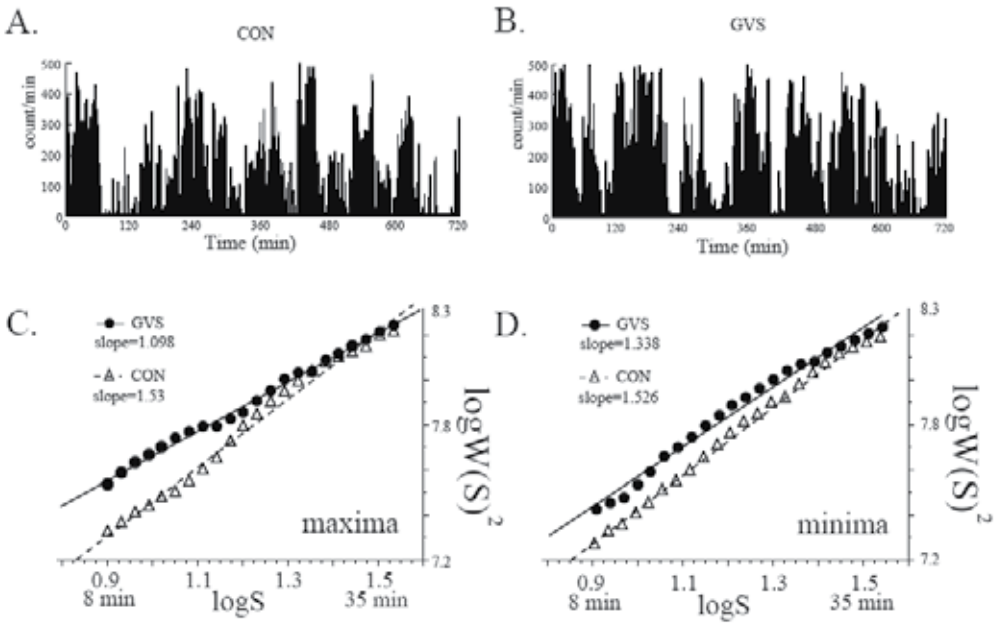


Fig. 7. Illustrative examples of wrist activity data of a PD patient during the control (CON) period (A) and during GVS application (B). The wavelet coefficients ($W(S)$) of these data, as a function of the wavelet scale (S) are shown for local maxima (C) and minima (D). The slopes are power-law exponents α. Reprinted with permission from (Pan et al., 2008).

The representative wrist activity data of a PD patient during the control period and during the application of GVS were shown in Fig. 7A, B. Compared to control, GVS was associated with more frequent switching between higher and lower levels of activity. This resulted in a higher wavelet power ($W(S)^2$) with GVS (Fig. 7C, D), particularly at smaller scales (S), or higher frequencies, for local maxima (Fig.7C). The power-law exponent α, given by the slope of the log S vs. Log $W(S)^2$ relationship and characterizing the nature of switching patterns between high and low values in a statistical sense, was smaller with GVS than with control stimulation, especially for the local maxima (Fig. 7C,D).

The group average wavelet coefficients exhibited linear relationships in the range of scales (S) from 8 min to 35 min both for local maxima and minima and for GVS and control conditions (Fig. 8A, B). The slope for local maxima with noisy GVS was substantially less than that with control stimulation. For local maxima, the mean power-law exponent was significantly smaller for GVS than for the control (Fig. 8C). The difference in the mean α for local minima was much less than that for the local maxima. When the mean α-values for the

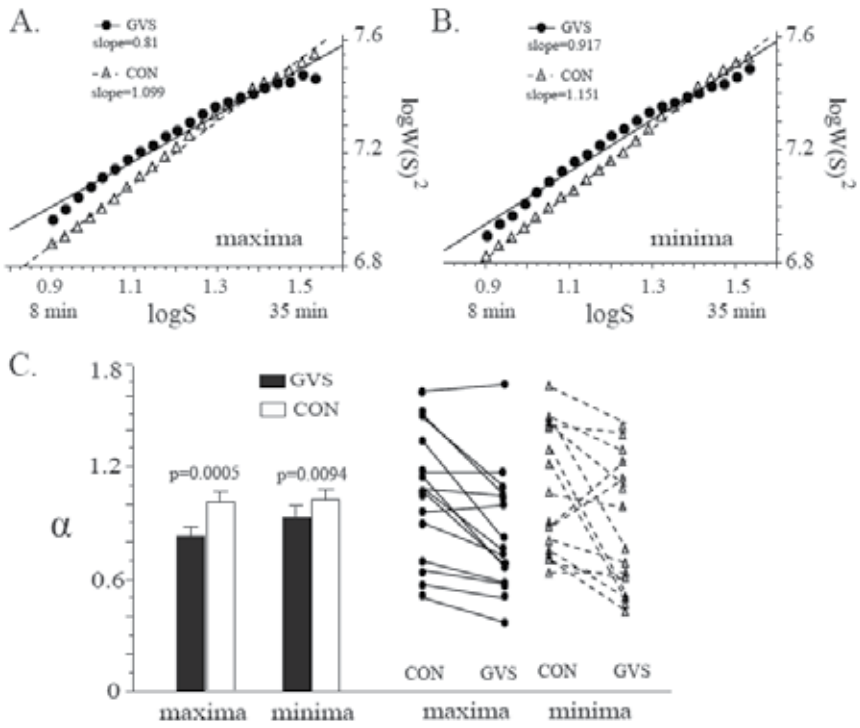


Fig. 8. The group average wavelet coefficients for local maxima (A) and minima (B) for GVS and control (CON) conditions. (C) Comparisons of the mean α for GVS and CON (left) and the within-individual differences (right). The error bars represent SEM. Reprinted with permission from (Pan et al., 2008).

first and the second days were compared, significant differences were not observed either for local maxima or minima, suggesting that the above differences were due to the GVS application itself, not to an order effect.
We confirmed that measurement of the mean α for local maxima detected the improvement of parkinsonism during GVS with sufficient sensitivity (Pan et al., 2008).

6. Conclusion

Analysis of patients' physical activity records collected by an actigraph device using power-law exponents probing temporal autocorrelation of the activity counts provides methods for the evaluation of disability resulting from motor and non-motor parkinsonism without being influenced by the presence of tremor or different patterns of daily living (Pan et al., 2007). Sufficient sensitivity and reliability of this method warrants the objectivity in the evaluation of symptom severity (Pan et al., 2008; Pan et al., 2011a) , hence this method may be useful for the evaluation of disease progression and efficacy of new drug.

7. Acknowledgement

This study was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Health, Labor, and Welfare of Japan to S.K.

8. References

Arnulf, I., Konofal, E., Merino-Andreu, M., Houeto, J.L., Mesnage, V., Welter, M.L., Lacomblez, L., Golmard, J.L., Derenne, J.P. & Agid, Y. (2002). Parkinson's disease and sleepiness: an integral part of PD. *Neurology,* Vol. 58, No. 7, (Apr 2002), pp. 1019-1024, ISSN 0028-3878

Chaudhuri, K.R. & Schapira, A.H. (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol,* Vol. 8, No. 5, (May 2009), pp. 464-474, ISSN 1474-4422

Comella, C.L. (2002). Daytime sleepiness, agonist therapy, and driving in Parkinson disease. *JAMA,* Vol. 287, No. 4, (Jan 2002), pp. 509-511, ISSN 0098-7484

Comella, C.L., Morrissey, M. & Janko, K. (2005). Nocturnal activity with nighttime pergolide in Parkinson disease: a controlled study using actigraphy. *Neurology,* Vol. 64, No. 8, (Apr 2005), pp. 1450-1451, ISSN 1526-632X

De Smet, P.A. (2002). Herbal remedies. *N Engl J Med,* Vol. 347, No. 25, (Dec 2002), pp. 2046-2056, ISSN 1533-4406

Harrison, M.B., Wylie, S.A., Frysinger, R.C., Patrie, J.T., Huss, D.S., Currie, L.J. & Wooten, G.F. (2009). UPDRS activity of daily living score as a marker of Parkinson's disease progression. *Mov Disord,* Vol. 24, No. 2, (Jan 2009), pp. 224-230, ISSN 1531-8257

Hobson, D.E., Lang, A.E., Martin, W.R., Razmy, A., Rivest, J. & Fleming, J. (2002). Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA,* Vol. 287, No. 4, (Jan 2002), pp. 455-463, ISSN 0098-7484

Iwasaki, K., Kobayashi, S., Chimura, Y., Taguchi, M., Inoue, K., Cho, S., Akiba, T., Arai, H., Cyong, J.C. & Sasaki, H. (2004). A randomized, double-blind, placebo-controlled clinical trial of the Chinese herbal medicine "ba wei di huang wan" in the treatment of dementia. *J Am Geriatr Soc,* Vol. 52, No. 9, (Sep 2004), pp. 1518-1521, ISSN 0002-8614

Iwasaki, K., Maruyama, M., Tomita, N., Furukawa, K., Nemoto, M., Fujiwara, H., Seki, T., Fujii, M., Kodama, M. & Arai, H. (2005a). Effects of the traditional Chinese herbal medicine Yi-Gan San for cholinesterase inhibitor-resistant visual hallucinations and neuropsychiatric symptoms in patients with dementia with Lewy bodies. *J Clin Psychiatry,* Vol. 66, No. 12, (Dec 2005), pp. 1612-1613, ISSN 0160-6689

Iwasaki, K., Satoh-Nakagawa, T., Maruyama, M., Monma, Y., Nemoto, M., Tomita, N., Tanji, H., Fujiwara, H., Seki, T., Fujii, M., Arai, H. & Sasaki, H. (2005b). A randomized, observer-blind, controlled trial of the traditional Chinese medicine Yi-Gan San for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. *J Clin Psychiatry,* Vol. 66, No. 2, (Feb 2005), pp. 248-252, ISSN 0160-6689

Jean-Louis, G., Mendlowicz, M.V., Gillin, J.C., Rapaport, M.H., Kelsoe, J.R., Zizi, F., Landolt, H. & von Gizycki, H. (2000). Sleep estimation from wrist activity in patients with major depression. *Physiol Behav,* Vol. 70, No. 1-2, (Jul 2000), pp. 49-53, ISSN 0031-9384

Katayama, S. (2001). Actigraph analysis of diurnal motor fluctuations during dopamine agonist therapy. *Eur Neurol,* Vol. 46, No. Suppl 1, (2001), pp. 11-17, ISSN 0014-3022

Korszun, A., Young, E.A., Engleberg, N.C., Brucksch, C.B., Greden, J.F. & Crofford, L.A. (2002). Use of actigraphy for monitoring sleep and activity levels in patients with fibromyalgia and depression. *J Psychosom Res,* Vol. 52, No. 6, (Jun 2002), pp. 439-443, ISSN 0022-3999

Korte, J., Hoehn, T. & Siegmund, R. (2004). Actigraphic recordings of activity-rest rhythms of neonates born by different delivery modes. *Chronobiol Int,* Vol. 21, No. 1, (Jan 2004), pp. 95-106, ISSN 0742-0528

Lian, X.F. & Luo, X.D. (2007). [Effect of TCM treatment according to syndrome differentiation in enhancing curative effect and reducing side-effect of madopa]. *Zhongguo Zhong Xi Yi Jie He Za Zhi,* Vol. 27, No. 9, (Sep 2007), pp. 796-799, ISSN 1003-5370

Long, C. (1992). Definition and evaluation of parkinsonism in TCM. *Journal of Beijing University of Traditional Chinese Medicine* Vol. 4, No. 15, (1992), pp. 39.

Martinez-Martin, P., Gil-Nagel, A., Gracia, L.M., Gomez, J.B., Martinez-Sarries, J. & Bermejo, F. (1994). Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. *Mov Disord,* Vol. 9, No. 1, (Jan 1994), pp. 76-83, ISSN 0885-3185

Miyasaki, J.M., Shannon, K., Voon, V., Ravina, B., Kleiner-Fisman, G., Anderson, K., Shulman, L.M., Gronseth, G. & Weiner, W.J. (2006). Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology,* Vol. 66, No. 7, (Apr 2006), pp. 996-1002, ISSN 1526-632X

Mormont, M.C., Waterhouse, J., Bleuzen, P., Giacchetti, S., Jami, A., Bogdan, A., Lellouch, J., Misset, J.L., Touitou, Y. & Levi, F. (2000). Marked 24-h rest/activity rhythms are associated with better quality of life, better response, and longer survival in patients with metastatic colorectal cancer and good performance status. *Clin Cancer Res,* Vol. 6, No. 8, (Aug 2000), pp. 3038-3045, ISSN 1078-0432

Nakamura, T., Kiyono, K., Yoshiuchi, K., Nakahara, R., Struzik, Z.R. & Yamamoto, Y. (2007). Universal scaling law in human behavioral organization. *Phys Rev Lett,* Vol. 99, No. 13, (Sep 2007), pp. 138103, ISSN 0031-9007

Ohashi, K., Nunes Amaral, L.A., Natelson, B.H. & Yamamoto, Y. (2003). Asymmetrical singularities in real-world signals. *Phys Rev E Stat Nonlin Soft Matter Phys,* Vol. 68, No. 6 Pt 2, (Dec 2003), pp. 065204, ISSN 1539-3755

Okawa, M., Mishima, K., Hishikawa, Y. & Hozumi, S. (1995). [Rest-activity and body-temperature rhythm disorders in elderly patients with dementia--senile dementia of Alzheimer's type and multi-infarct dementia]. *Rinsho Shinkeigaku,* Vol. 35, No. 1, (Jan 1995), pp. 18-23, ISSN 0009-918X

Ondo, W.G., Dat Vuong, K., Khan, H., Atassi, F., Kwak, C. & Jankovic, J. (2001). Daytime sleepiness and other sleep disorders in Parkinson's disease. *Neurology,* Vol. 57, No. 8, (Oct 2001), pp. 1392-1396, ISSN 0028-3878

Pahwa, R., Factor, S.A., Lyons, K.E., Ondo, W.G., Gronseth, G., Bronte-Stewart, H., Hallett, M., Miyasaki, J., Stevens, J. & Weiner, W.J. (2006). Practice Parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology,* Vol. 66, No. 7, (Apr 2006), pp. 983-995, ISSN 1526-632X

Pan, W., Kwak, S., Liu, Y., Sun, Y., Fang, Z., Qin, B. & Yamamoto, Y. (2011a). Traditional Chinese medicine improves nocturnal activity in Parkinson's disease. *Parkinson's disease,* in press. doi:10.4061/2011/789506,ISSN 2042-0080

Pan, W., Liu, Y., Fang, Z., Zhu, X., Kwak, S. & Yamamoto, Y. (2011b). A compound belonging to traditional Chinese medicine improves nocturnal activity in Parkinson's disease. *Sleep Med,* Vol. 12, No. 3, (Mar 2011), pp. 307-308, ISSN 1878-5506

Pan, W., Ohashi, K., Yamamoto, Y. & Kwak, S. (2007). Power-law temporal autocorrelation of activity reflects severity of parkinsonism. *Mov Disord,* Vol. 22, No. 9, (Jul 2007), pp.1308-1313, ISSN 1531-8257

Pan, W., Soma, R., Kwak, S. & Yamamoto, Y. (2008). Improvement of motor functions by noisy vestibular stimulation in central neurodegenerative disorders. *J Neurol,* Vol. 255, No. 11, (Nov 2008), pp. 1657-1661, ISSN 0340-5354

Park, A. & Stacy, M. (2009). Non-motor symptoms in Parkinson's disease. *J Neurol,* Vol. 256, No. Suppl 3, (Aug 2009), pp. 293-298, ISSN 1432-1459

Peng, C.K., Havlin, S., Stanley, H.E. & Goldberger, A.L. (1995). Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos,* Vol. 5, No. 1, (1995), pp. 82-87, ISSN 1054-1500

Sekine, M., Akay, M., Tamura, T., Higashi, Y. & Fujimoto, T. (2004). Fractal dynamics of body motion in patients with Parkinson's disease. *J Neural Eng,* Vol. 1, No. 1, (Mar 2004), pp. 8-15, ISSN 1741-2560

Struzik, Z.R., Hayano, J., Sakata, S., Kwak, S. & Yamamoto, Y. (2004). 1/f scaling in heart rate requires antagonistic autonomic control. *Phys Rev E Stat Nonlin Soft Matter Phys,* Vol. 70, No. 5, (Nov 2004), pp. 050901, ISSN 1539-3755

Struzik, Z.R., Hayano, J., Soma, R., Kwak, S. & Yamamoto, Y. (2006). Aging of complex heart rate dynamics. *IEEE Trans Biomed Eng,* Vol. 53, No. 1, (Jan 2006), pp. 89-94, ISSN 0018-9294

Teicher, M.H. (1995). Actigraphy and motion analysis: new tools for psychiatry. *Harv Rev Psychiatry,* Vol. 3, No. 1, (May-Jun 1995), pp. 18-35, ISSN 1067-3229)

Tuisku, K., Holi, M.M., Wahlbeck, K., Ahlgren, A.J. & Lauerma, H. (2003). Quantitative rest activity in ambulatory monitoring as a physiological marker of restless legs syndrome: a controlled study. *Mov Disord,* Vol. 18, No. 4, (Apr 2003), pp. 442-448, ISSN 0885-3185

van Someren, E.J., Hagebeuk, E.E., Lijzenga, C., Scheltens, P., de Rooij, S.E., Jonker, C., Pot, A.M., Mirmiran, M. & Swaab, D.F. (1996). Circadian rest-activity rhythm disturbances in Alzheimer's disease. *Biol Psychiatry,* Vol. 40, No. 4, (Aug 1996), pp. 259-270, ISSN 0006-3223

van Someren, E.J., Pticek, M.D., Speelman, J.D., Schuurman, P.R., Esselink, R. & Swaab, D.F. (2006). New actigraph for long-term tremor recording. *Mov Disord,* Vol. 21, No. 8, (Aug 2006), pp. 1136-1143, ISSN 0885-3185

van Someren, E.J., van Gool, W.A., Vonk, B.F., Mirmiran, M., Speelman, J.D., Bosch, D.A. & Swaab, D.F. (1993). Ambulatory monitoring of tremor and other movements before and after thalamotomy: a new quantitative technique. *J Neurol Sci,* Vol. 117, No. 1-2, (Jul 1993), pp. 16-23, ISSN 0022-510X

van Someren, E.J., Vonk, B.F., Thijssen, W.A., Speelman, J.D., Schuurman, P.R., Mirmiran, M. & Swaab, D.F. (1998). A new actigraph for long-term registration of the duration and intensity of tremor and movement. *IEEE Trans Biomed Eng,* Vol. 45, No. 3, (Mar 1998), pp. 386-395, ISSN 0018-9294

Witting, W., Kwa, I.H., Eikelenboom, P., Mirmiran, M. & Swaab, D.F. (1990). Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. *Biol Psychiatry,* Vol. 27, No. 6, (Mar 1990), pp. 563-572, ISSN 0006-3223

Yamamoto, Y., Struzik, Z.R., Soma, R., Ohashi, K. & Kwak, S. (2005). Noisy vestibular stimulation improves autonomic and motor responsiveness in central neurodegenerative disorders. *Ann Neurol,* Vol. 58, No. 2, (Aug 2005), pp. 175-181, ISSN 0364-5134

Zhao, H., Li, W.W. & Gao, J.P. (2007). [Clinical trial on treatment of Parkinson's disease of Gan-Shen yin deficiency type by recipe for nourishing Gan-Shen]. *Zhongguo Zhong Xi Yi Jie He Za Zhi,* Vol. 27, No. 9, (Sep 2007), pp. 780-784, ISSN 1003-5370

12

Postural Control While Sitting and Its Association with Risk of Falls in Patients with Parkinson's Disease

Ryoichi Hayashi[1], Takeshi Hayashi[2], Junpei Aizawa[3], Hiroaki Nagase[4] and Shinji Ohara[5]
[1]*Department of Neurology, Okaya City Hospital,*
[2]*Department of Computer Science and Systems Engineering, Graduate School of Engineering Kobe University*
[3]*Department of Material Technology, Nagano Prefecture General Industrial Technology Center,*
[4]*Department of Information Technology, Nagano Prefecture General Industrial Technology Center*
[5]*Department of Neurology, Matsumoto Medical Center*
Japan

1. Introduction

Abnormal postures and falls in patients with Parkinson's disease (PD) have been well recognized from the time of its earliest clinical description (Parkinson, 1817). Abnormal postures in PD are observed in the entire body, including flexion to the anterior, lateral, or anterolateral direction of the trunk, neck flexion, flexion of the extremities, and abnormal postures of the hands, fingers, and toes. A lateral deviation of the spine and a corresponding tendency to lean to one side was reported (Duvoisin and Marsden 1975; Hayashi et al., 2010). These postural abnormalities cause postural instability and falls. In a recent study, approximately 50% of the PD patients had fallen, compared to about 15% of healthy elderly subjects, and approximately 75% of falls in PD patients occurred during activities associated with daily living, such as turning around, standing up, and bending forward (Bloem et al., 2001). Postural instability is caused by an inability to adjust the center of gravity quickly enough to account for perturbations in the environment (Shivitz et al., 2006). Maki and colleagues (1994) have suggested that increased lateral sway is associated with increased risk of falling in elderly persons. Several studies have quantified postural stability during quiet stance in patients with PD and revealed that PD patients have more difficulty in controlling lateral postural sway than anteroposterior sway (Mitchell et al., 1995; Rocchi et al., 2002).

In the standing position, postural adjustments can be accomplished with responses at the ankle, knee, hip, and trunk joints, independently or combined (Hodges et al., 2002; Krishnamoorthy et al., 2005) and these complex structures consisting of multiple linked segments must be maintained in a stable position on a relatively narrow support base

formed by the feet. Lee and coworkers (1995) studied preparatory postural adjustments associated with a lateral leg-raising task in parkinsonian patients with postural instability. In the sitting position, the influence of hip joints and lower extremities can be minimized to study the postural control of the trunk. Van der Burg and coworkers (2006) studied the postural control of the trunk during unstable sitting in PD patients and revealed that PD patients showed difficulty in truncal control. They suggested that these changes may be related to postural instability and fall risk.

In this study, the body movement in PD patients during sitting was investigated by measuring center of pressure (COP) excursions and trunk deviations under two conditions: 1) sitting at rest for two minutes, 2) raising his/her arm laterally to 90 degrees. An additional aim was to study differences in trunk control between patients who had a history of falling (fallers) and patients who did not have a history of falling (non-fallers). The aim of this study is also to test the hypothesis that postural abnormality in a lateral direction may, or would be a high risk factor for falling during the daily activities of PD patients and further attempts to formulate the pattern of muscle tone abnormalities that may underline this disturbance.

2. Patients and methods

2.1 Patients

17 consecutive idiopathic PD patients and 8 age-matched normal controls were studied. These 17 patients received regular outpatient treatment every month over the course of a one-year follow-up period. All patients satisfied the following inclusion criteria: Hoehn and Yahr stage II or higher while off medication (II=1, III=11, IV=5), a clear history of significant responsiveness to levodopa and an absence of other neurologic diseases including significant dementia or autonomic dysfunction. The patients' clinical data are given in Table 1. All patients (mean age ± sd: 72±6 years) did not have any neurological or other diseases that might affect their postural stability or ability to perform the experimental tasks.

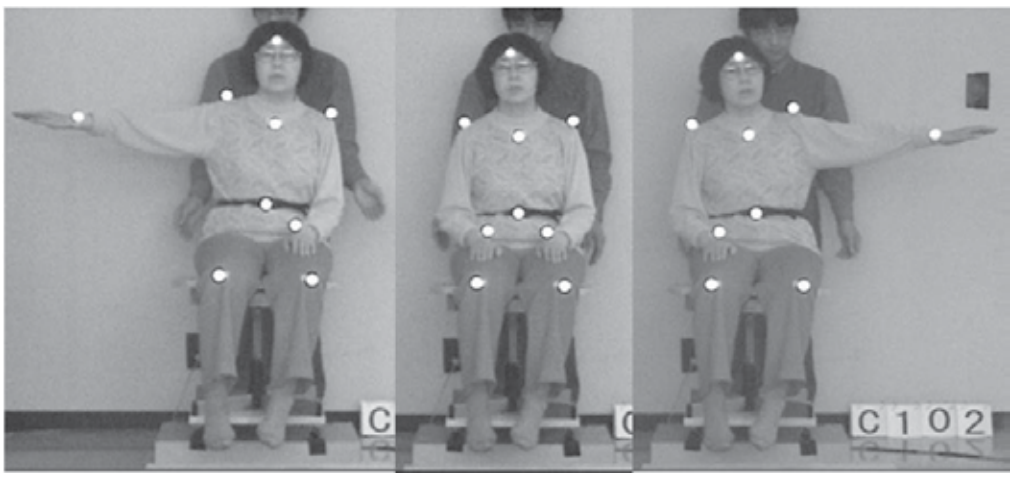
Patient	Sex	Age (years)	Hoehn & Yahr	Duration (years)	Number of falls (per year)
1	F	70	3	12	more than 5
2	F	65	3	12	under 5
3	M	65	4	8	under 5
4	F	77	3	7	more than 5
5	F	64	3	11	0
6	M	75	3	6	under 5
7	F	67	3	11	0
8	M	78	3	13	under 5
9	F	75	2	4	0
10	F	75	4	11	under 5
11	M	71	3	6	0
12	M	75	4	8	under 5
13	F	81	3	6	0
14	F	79	4	11	more than 5
15	F	62	3	25	0
16	M	78	4	6	more than 5
17	F	69	3	11	more than 5

Table 1. Clinical characteristics of PD patient

This study was approved by the Okaya City Hospital Committee for Research on Human Subjects, and informed consent was obtained from all test subjects.

2.2 Experimental setup and procedure

A stable stool was placed on a force platform (Kistler platform type 9281CA, Winterthur, Switzerland). The stool was high enough so that each subject's legs could hang down without touching the platform (Fig. 1). Subjects sat on the stool at ease. At that time, if subjects presented a tilt of the trunk away from the vertical position, they were not asked to correct their trunk to the vertical position. Subjects were asked to maintain a sitting posture on the stool for 1) 2 minutes at rest, and 2) 30 seconds with a lateral arm raised alternatively up to 90 degrees with their legs hanging down and their hand placed on each thigh except for a raising arm. Subjects were also asked to keep their eyes open and to focus on the target point in front of them.



Raising right arm At rest Raising left arm

Fig. 1. Example of postural changes both during sitting on a stool at resting posture and during the raising of each arm.

Using the forced plate with a sampling frequency of 500Hz, the excursion of the centre of pressure (COP) was measured. The position of the body segments was also measured using a video image processing system, with the images being developed in our laboratory. Nine reflective markers (1 cm in diameter) were placed on the forehead, the upper part of the sternum, shoulders, wrists, knees, and the level of the umbilicus, and reflections from the markers were recorded with a sampling rate of 30 Hz.

2.3 Evaluation of truncal inclination at rest

Both COP excursions and the body-marker displacement were recorded simultaneously for 2 minutes. Values for the initial 10 seconds and the last 10 seconds were averaged, and the difference was calculated for each trial. The values obtained by the two trials for each subject were averaged.

2.4 Evaluation of truncal inclination while raising arm

After evaluation of truncal inclination at rest, the patient was studied when each of their arms were raised laterally up to 90 degrees two times in the following sequence: at rest for

30 seconds, raising the right arm for 30 seconds, at rest for 30 seconds, then raising the left arm for 30 seconds.

2.5 Statistical analysis

For each posturographic parameter and clinical measurement, Student's t-test or an analysis of variance (ANOVA) was used to compare group means between normal controls and PD patients. Correlation between the degree of COP displacement and the degree of body displacement was evaluated with Spearman's rank correlation coefficient.

3. Results

3.1 Clinical features

On examination, in all 17 patients, the side of initial symptoms was also the side of dominant clinical signs. Over the one-year follow-up period, 6 of 17 patients (35%) experienced no falls. The remaining 11 patients (65%) fell at least two times. Five of patients experienced more than 5 falls during the one-year follow-up, and these patients were described as "frequent fallers" in this paper. Patients who experienced less than 5 falls were described as a "less frequent fallers." This study found a strong correlation between disease severity and frequency of falls. The mean value with standard deviation of the Hoehn and Yahr stage in non-fallers and "less frequent fallers" was 2.8±0.4, and that of the "frequent fallers" was 3.5±0.5 ($p<0.02$). There was no significant difference between "frequent fallers" and "non-fallers" and "less frequent fallers" in age or duration of illness (73.3±5.2 years versus 70.0±7.0 years, $p=0.3$ in age; 9.5±2.6 years versus 10.5±7.7 years, $p=0.7$ in duration).

3.2 Body inclination during sitting

A consistency in lateral displacement was observed in all 17 patients. Table 2 shows the values of two parameters of body inclination in each group. There was a tendency toward increased values of both lateral COP displacement and trunk displacement in a group of PD patients compared with controls. However, there was no significant difference in these parameters between that of the control group and the PD-patient group. When each parameter obtained by "frequent fallers" is compared with controls, there was a significant difference in each parameter (lateral COP displacement $p=0.01$, trunk displacement $p=0.01$).

	Control	PD		
		all	non-fallers & fallers (under 5)	Fallers (more than 5)
	n=8	n=17	n=12	n=5
Lateral COP displacement	2.0 ± 1.7	6.2 ± 7.0 (p=0.11)	3.5 ± 2.5 (p=0.16)	12.9 ± 12.9 (p=0.01)
Trunk displacement	7.1 ± 4.8	17.3 ± 18.2 (p=0.14)	10.1 ± 7.7 (p=0.35)	34.5 ± 34.5 (p=0.01)

unit: mm

Table 2. This data represents the mean value with one standard deviation of each parameter of body inclination in control subjects and in PD patients at rest for 2 minutes. Each mean value was calculated using an absolute value of each parameter obtained from each subject.

Fig. 2 shows the relationship between changes of lateral COP displacement and trunk displacement obtained from all 17 patients. The amount of lateral COP displacement was correlated significantly with that of trunk displacement ($r=0.94$, $p<0.0001$).

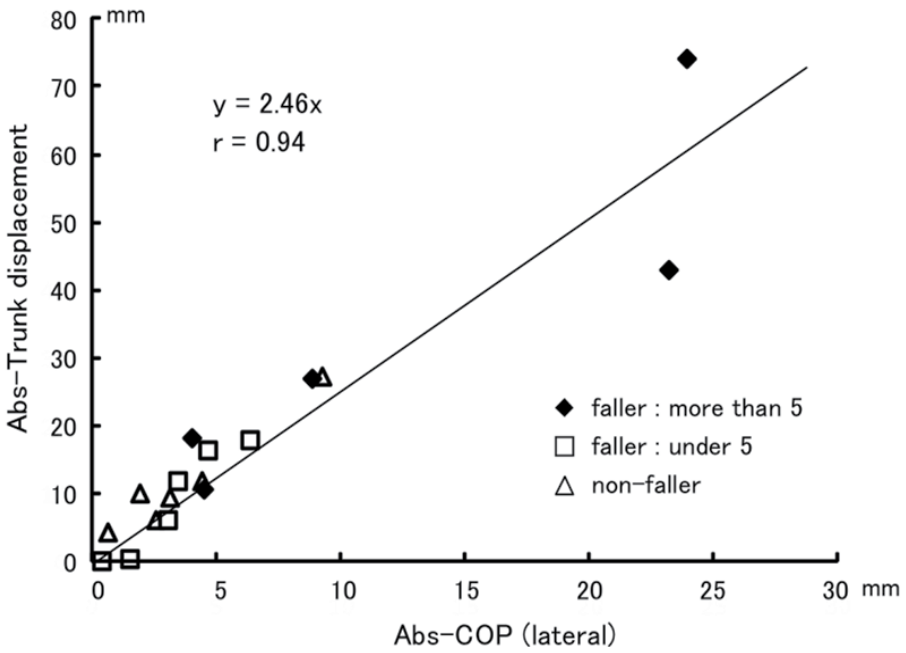


Fig. 2. The relationship between the absolute value of lateral COP displacement (Abs-COP) and the absolute value of trunk displacement (Abs- trunk displacement) obtained from 17 patients at rest.

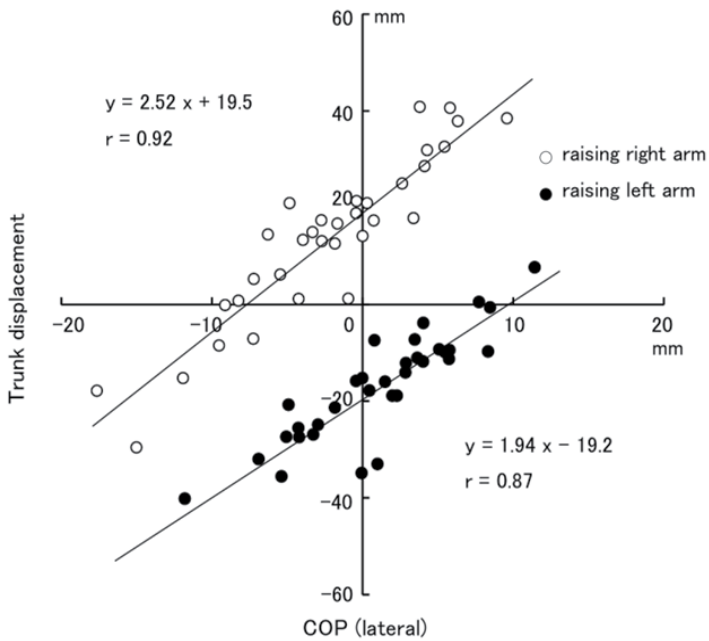


Fig. 3. The relationship between the value of lateral COP displacement (COP) and the value of trunk displacement obtained from 17 patients during arm-raising examination.

3.3 Postural change during arm raising

Two patients, who were "frequent fallers" and showed a large lateral inclination, had difficulty in keeping their sitting posture for more than 10 seconds and had to be supported by experimenters to prevent them from falling during arm-raising test. Therefore, the following was analyzed: 1) the relationship between the lateral COP displacement and the trunk displacement using the value observed at 1 second after raising the arm to 90 degrees for all 17 patients, and 2) changes of the body axis during the arm-raising for 15 patients.
A postural change observed from one patient during the arm-raising test is shown in Figure 1. When the patient raised her arm laterally up to 90 degrees, the trunk marker shifted to the opposite side. In Figure 3, the relationship between the lateral COP displacement and the trunk displacement obtained from all 17 patients is shown.

	Control	PD		
		all	non-fallers & fallers (under 5)	Fallers (more than 5)
	n=8	n=17	n=12	n=3
Raising right arm	4.4 ± 1.6	4.5 ± 2.1 (p=0.5)	4.3 ± 2.0 (p=0.9)	5.1 ± 2.8 (p=0.6)
Raising leftt arm	3.7 ± 0.9	5.3 ± 2.7 (p=0.2)	4.4 ± 2.3 (p=0.4)	5.3 ± 1.5 (p=0.3)

unit: degree

Table 3. The absolute mean value with one standard deviation of each change of body inclination in control subjects and in PD patients when each subject raised each arm 90 degrees.

A positive relationship with a high correlation coefficient was observed, which was the same as the relationship observed during maintaining sitting posture at rest, only the shift of the initial position of the trunk marker. Table 3 shows the change of body axis associated with the arm-raising in each group. There was no significant difference between both the control group and the PD patient group, or between the control group and the "frequent faller" PD patient group.
In this test, R was defined as the following equation under a hypothesis that the relationship between the lateral COP displacement (∆G) and the trunk displacement (∆L) obtained during the sitting condition also applied to the lateral arm raising condition. In the sitting test, the relationship between ∆L and ∆G is expressed as following equation; ∆L=2.46*∆G (cf. Figure 2).

$$R=\Delta L - 2.46*\Delta G$$

Figure 4 shows each parameter obtained from one subject during the arm raising test and the calculated results applied using the equation above. The calculated data showed a square change during the arm-raising phase (Figure 4B). The square change associated with the arm raising was observed in all patients except two patients who had fallen.

3.4 Estimation of trunk muscle tone

In this paper, we proposed a simulation model (cf. Figure 7) and an estimation of trunk muscle tone was made using patient's data under following conditions: 1) to mimic a sitting posture at rest and 2) to mimic a sitting posture with an arm raising. A detail of the model and a calculation procedure are described in the Appendix of this paper. Each body segment

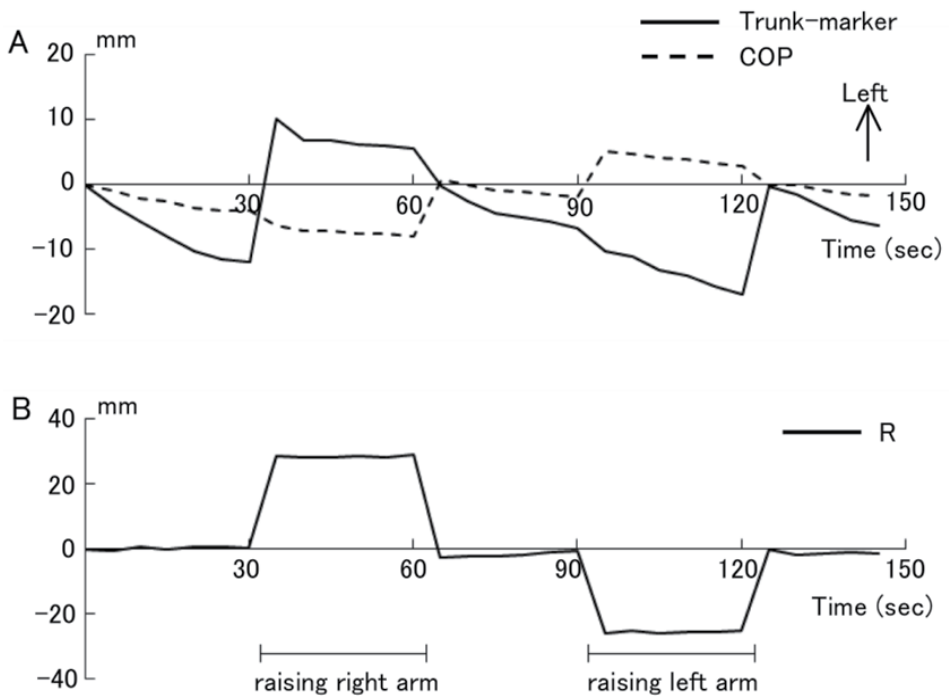


Fig. 4. A: A sequential change of lateral COP displacement (COP) and the value of trunk displacement (Trunk-marker) when one patient raised her arm alternatively. B: The R value change, which was calculated by our proposed equation (see Text).

Patient	Weight (kg)	Sitting height (cm)	Shoulder biacromial breadth (cm)	Bicristal breadth (cm)	Arm length (cm)	Torque (Nm) at rest	Torque (Nm) arm raising
1	46.0	70.0	32.9	23.6	55.0	5.87	39.1
2	60.0	73.6	32.9	26.4	62.9	5.02	44.4
3	44.0	73.6	33.6	28.6	61.4	3.54	42.4
4	37.5	64.3	28.6	25.7	54.3	3.13	37.8
5	48.0	72.9	32.1	28.6	60.0	2.37	42.4
6	61.0	72.9	33.6	25.7	64.3	0.11	43.6
7	43.0	74.3	32.1	26.4	62.1	0.94	43.8
8	60.0	70.0	30.7	25.7	62.9	0.05	43.4
9	44.0	72.9	29.3	25.7	61.4	1.31	43.3
10	47.0	64.3	30.7	27.1	61.4	1.22	43.3
11	57.0	73.6	38.6	27.9	55.7	2.65	38.7
12	54.0	70.0	37.9	27.9	62.9	2.89	43.2
13	44.0	64.3	27.9	26.4	62.1	2.23	43.8
14	34.0	64.3	30.7	21.4	58.6	1.68	41.7
15	51.6	67.9	34.3	26.4	60.7	6.33	45.3
16	45.0	76.4	31.4	27.1	62.1	9.78	42.8
17	65.0	72.9	32.1	27.1	58.6	22.51	41.5

Table 4. Each body segment size or body weight, which were used to estimate the torque, and the estimated value of torque both at rest and arm-raising.

size or body weight, which was used to estimate the torque, is shown in Table 4. There was a tendency toward increased value of the torque in PD patients who experienced falling frequently. The mean value with standard deviation of the torque at rest in non-fallers and less frequent fallers was 2.4 Nm±1.9 Nm, and that of the frequent fallers was 8.6 Nm±8.4 Nm ($p<0.03$). In Figure 5, the relationship between the value of trunk displacement and the estimated torque for each patient is shown. An estimated torque value was calculated using an averaged data value of all 17 patients when our model leaned. The data suggested that the trunk muscle tone was larger in the patients with high falling risk than the patients with less falling risk. In a simulation of the arm-raising, there was no significant difference between the non-fallers (42.9±2.3 Nm) and the fallers (42.1±2.0 Nm) ($p>0.47$).

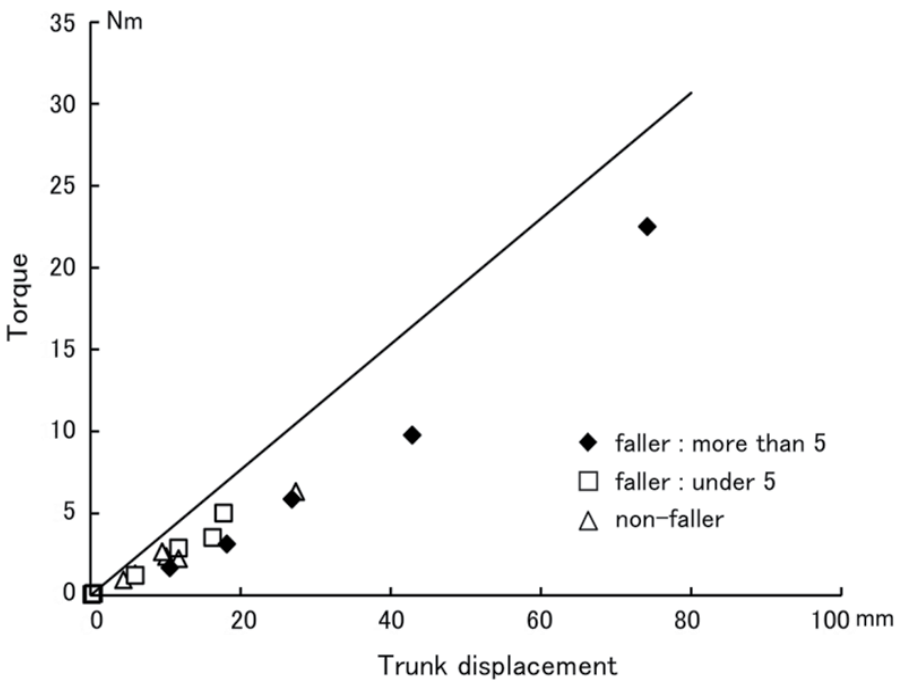


Fig. 5. Relationship between the value of trunk displacement and the estimated torque for each patient. An estimated torque value to the trunk displacement is shown as a straight line: a simulation was conducted using each of the following parameters calculated by averaging the data obtained from each of our 17 patients; body weight (except legs): 49.5 kg; arm weight 3.2 kg; sitting height 70.5 cm; shoulder biacromial breadth 32.3 cm; bicristal breadth 26.3 cm; arm length 60.4 cm.

In Figure 6, both the trunk displacement and the COP displacement were shown when the arm segment of the model was raised up to 90 degrees. Although we observed a transient response when the arm segment moved from a resting posture to a 90-degree arm raising posture or when the arm segment moved from the 90-degree position to the initial position, a constant value was observed when the arm segment was held at the 90-degree position or at the rest position.

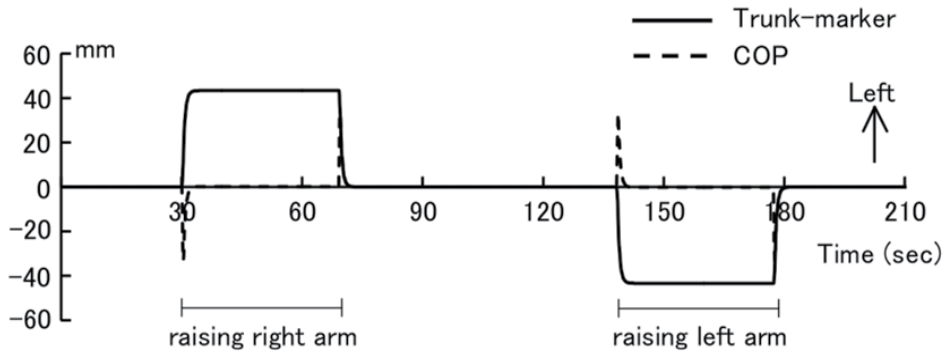


Fig. 6. Simulation representing an arm-raising test. A sequential change of lateral COP displacement and the value of trunk displacement when the model raised an arm alternately. A simulation was conducted using each of the following parameters calculated by averaging the data obtained from each of our 17 patients; body weight (except legs): 49.5 kg; arm weight 3.2 kg; sitting height 70.5 cm; shoulder biacromial breadth 32.3 cm; bicristal breadth 26.3 cm; arm length 60.4 cm.

4. Discussion

In this study, we demonstrated that PD patients who fell frequently tended to have 1) a value of lateral COP displacement greater than the value of control subjects, 2) a geometrical relationship between the arm and the trunk was preserved in PD patients, the same as in control subjects, and 3) a significant difference in postural muscle tone between frequent fallers and non-fallers or less frequent fallers. These results suggest that the measurement of both lateral COP displacement during sitting and arm-raising would be useful in predicting the risk of falling and predicting the trunk rigidity in PD patients.

4.1 Body inclination during sitting and in relation to falling frequency

Postural instability is one of the major symptoms of Parkinson's disease, and the instability in the control of upright stance and posture in PD often results in falling (Bloem et al., 2001; Wood et al., 2002; Grimbergen et al., 2004; Bloem et al., 2006). Several studies reported that postural sway patterns during quiet stance in PD patients are different compared to those of healthy elderly subjects, with PD patients displaying larger lateral excursion compared with anteroposterior excursion (Mitchell et al., 1995; Morris et al., 2000; Van Wegen et al., 2001; Van der Burg et al., 2006). In our study, the same tendency of postural sway pattern during sitting was observed and the excursions in the lateral direction in PD patients were larger than those of control subjects. Regarding postural control during standing, several authors

suggested that instability in the anterior-posterior direction was compensated for by increasing excursion in the lateral direction in PD patients (Schieppati et al., 1994; Mitchell et al., 1995; Van Wegen et al., 2001). These mechanisms might be working during sitting and would have eventually increased the lateral inclination. Van Emmerik et al. (1999) also suggested that lateral impairment in postural control in patients with PD might be a reflection of axial rigidity.

Several studies suggested that increased lateral sway is associated with increased risk of falling in both elderly subjects (Maki et al., 1994) and patients with PD (Mitchell et al., 1995; Rocchi et al., 2002). Our study also showed that the degree of lateral inclination during sitting was significantly larger in PD patients with history of falls than PD patients without history.

Based on these results, we suggest the risk of falls would increase when compensation in the anterior-posterior body sway with the lateral body sway is difficult. Measurement of postural change in the lateral direction during sitting for a relatively long time, 2 minutes in this study, is a simple and effective method that can be used in daily clinical examinations to evaluate the risk of falling.

4.2 Postural change associated with a lateral arm-raising task

A large number of human motor actions cause potential displacement of the body center of gravity (COP) and it is well known that voluntary movement is preceded and accompanied by postural muscular activities. Several studies which fall into this category include activation of posterior trunk and leg muscles when the arms are raised in front of the body (Traub et al., 1980; Zattare & Bouisset, 1988) or when a leg is raised while standing (Lee et al., 1995).

There are several reports that postural adjustments of the upper extremities may also be disrupted in Parkinson's disease. Abnormalities in the timing or amplitude of anticipatory postural adjustments, which occur when rapid voluntary arm movements are made while in the standing position, have been reported in parkinsonian subjects (Dick et al., 1986). Lee and coworkers (1995) studied the preparatory postural adjustments associate with a lateral leg raising task in parkinsonian patients and described the amplitude of the initial displacement of COP was markedly reduced and the interval between the earliest force changes and the onset of leg elevation was prolonged. These authors focused on the initial phase of the preparatory postural adjustments in parkinsonian patients with postural instability. On the other hand, in our study, the postural change after elevating and holding the arm was examined. We found no significant difference in the trunk inclination, associated with arm-raising between normal controls and PD patients, or between raising the right arm and the left arm test in PD patients. These test results indicated that the postural controls during the arm raising were preserved in PD patients we studied.

Adopting an appropriate body orientation, and maintaining this posture to the displacing effects of gravity or external forces is essential for postural control. Patients with Parkinson's disease had difficulty in postural control, especially the control of body vertically (Vaugoyeau et al., 2007; Hayashi et al., 2010). Steiger et al. (1996) reported that PD patients had difficulty in coordinating the orientation of the axial segments along the spinal axis. Several investigators also reported that the proprioceptive feedback information to the static position and movement perception processing decreased in PD patients (Zia et al., 2002; Keijsers et al., 2005; Vaugoyeau et al., 2007). In this study, the body inclination was observed during the arm-raising test, and the R-value was constant. These results suggested that a

geometric relationship between the raised arm and the trunk was preserved during the arm-raising phase even though the trunk inclined.

4.3 Estimation of postural muscle tone in the body axis

Rigidity is a continuous and uniform increase in muscle tone, felt as a constant resistance throughout the range of passive movement of a limb or a neck, and is a cardinal symptom of Parkinson's disease. Clinically, rigidity is usually assessed by passively flexing and extending a patient's limb. Objectively, most previous investigators examined rigidity in the muscles in PD patients, using either torque motor or isokinetic dynamometer (Nuyens et al., 2000; Hayashi et al., 2001). A few studies have done quantitatively to measure of postural muscle tone in the body axis of healthy test subjects (Kumar 2004; Gurfinkel et al., 2006) or to measure of trunk rigidity in parkinsonian patients (Mak et al., 2007). In these studies, the measurement procedures were different; each estimated value of muscle tone was close. Gurfinkel et al. (2006) reported that the value was 2 Nm to 9 Nm in standing, 40 Nm to 80 Nm in sitting (Kumar, 2004). Mak and coworkers (2007) reported PD patients had a significantly higher trunk muscle tone when compared with normal controls in the standing position, in both passive trunk flexion (17-22 Nm・deg in the control group, 27-40 Nm・deg in PD patients) and passive trunk extension (21-26 Nm・deg in the control group, 28-45 Nm ・deg in PD patients).

In this paper, we estimated the postural muscle tone in the body axis based on our model and showed that the positive relationship between the trunk displacement and the estimated torque value at rest condition. The estimated torque value in the high risk PD patients for falls was larger than that of lower risk PD patients. These results were consistent with that reported by Mak and coworkers (2007). In their study, it was reported that unstable PD patients had a tendency to have high trunk muscle tone.

5. Conclusion

Based on these results, we conclude that a measurement of body inclination for an extended period of 2 minutes as in this study is a valuable predictor for the risk of falling and is a simple and easy method to estimate the trunk muscle tone. This study also demonstrates that even PD patients with high falling risk are capable of controlling their postural geometry between the raised arm and the trunk.

6. Appendix

The proposed model, which simplified a sitting posture on a chair, was developed using an ODE (Open Dynamic Engine) simulator. This model is composed of the following 7 parts, including the upper part of the trunk, arm part, shoulder hinge joint, impedance joint set under the upper part, waist hinge joint, lower part of the trunk and the hip hinge joint. Body segment parameters used at the simulator are given by general physical data obtained from our patients, and an estimation value of each body segment was made based on the previous reports (Jensen et al., 1994, Okada et al., 1996).

The unique point of our model is using an "impedance joint", which consist of two parts: "elastic property" and "viscous properties" to artificially reproduce the muscles encompassing the waist.

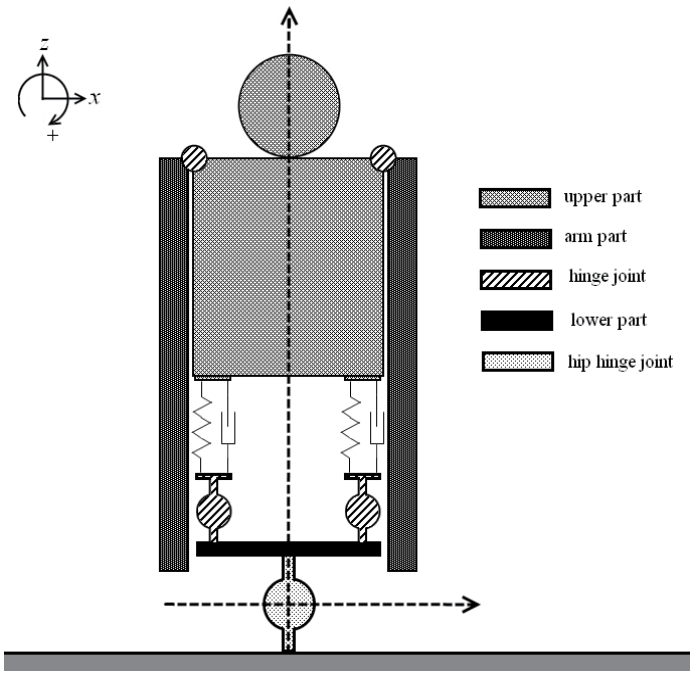


Fig. 7. A proposed model

The mathematical expression of the each impedance joint is shown as:

$$I\ddot{\theta} = \tau - d\dot{\theta} - k\theta$$

where I is the fictitious force, θ is the angle of the joint, τ is the muscle torque around the waist, d is the elastic property and k is the viscous property. By using this impedance joint, it becomes very easy to simulate the behavior of the body. The hinge joints work as an actuator, rotation sprig or a torque motor; which are used in the shoulder, waist and hip joint. It is also possible to obtain the data of each part and the whole body's barycentric coordinates using this simulator.

The procedure of the simulation is thus illustrated as follows: first, each parameter of the model such as weight or height et al. was estimated based on the previous Japanese reports (Okada et al., 1996) and our patients (cf. Table 4). Then a condition was imposed on the model to remain stable while a small disturbance to the body was applied. During this procedure the torque exerted on each of the joints was calculated, and using this data we were able to calculate the optimal solution of the stiffness for each joint.

At the next step, a stiffness condition was imposed on the model, which was evaluated from the previous simulation and then, set the same condition for the model to stay stable. This time, instead of applying a small disturbance, we requested the model to raise their arm up to the 90-degree position in 1 second. Through simulation, we gave careful consideration of the body sway by using the impedance joint and the hinge joints. Tuning the two impedance joints and the stiffness joints through the numerical simulations, we estimated an identified torque, which is needed to maintain posture maintenance.

Winter et al. (1998) reported that a relationship between COP and COM (center of mass or barycenter) was expressed in the following equation in a stiffness control of balance in the quiet standing position.

$$COP - COM = -\frac{I}{mgh}\ddot{x}$$

Where I is the inertial around the mass, m is the mass of the object, g is the acceleration due to gravity, h is the length from the origin coordinates and $\ddot{x}$ is the second derivative of *COM*. At this simulation, thereafter the arm is raised up to the 90-degree position, the body will be stationary; thereby we can consider $\ddot{x} = 0$.
The barycentric coordinate of the full body (P_{tx}, P_{tz}) will be expression as:

$$\begin{aligned} P_{tx} &= (M_{un} \cdot P_{un\_x} + M_{up} \cdot P_{up\_x} + M_{la} \cdot P_{la\_x} + M_{ra} \cdot P_{ra\_x}) / (M_{un} + M_{up} + M_{la} + M_{ra}) \\ P_{tz} &= (M_{un} \cdot P_{un\_z} + M_{up} \cdot P_{up\_z} + M_{la} \cdot P_{la\_z} + M_{ra} \cdot P_{ra\_z}) / (M_{un} + M_{up} + M_{la} + M_{ra}) \end{aligned} .$$

Where $M_{un}, M_{up}, M_{la}, M_{ra}$ is the mathamatical representation of "lower part of the trunk (21.5% of body weight)", "upper part of the trunk (28.5% of body weight)", "left arm (6.5% of body weight)", "right arm (6.5% of body weight)", and $P_{un\_x}, P_{up\_x}, P_{la\_x}, P_{ra\_x}, P_{un\_z}, P_{up\_z}, P_{la\_z}, P_{ra\_z}$ is the barycentric position of each part where x and z represent the horizontal component and the vertical component, respectively.
The angle between "barycentric position" and "hip hinge joint" will be expression as:

$$\text{angle} = \arctan(P_{tx} / (P_{tz} - P_h)) .$$

Where P_h is the length from the home position.

1. to mimic a sitting posture at rest
   The torque applied to the hip hinge joint will be express as:

$$\text{torque}_h = G_{Dh}(0 - R_{Vh}) + G_{Ph}(0 - R_{Ah}) ,$$

   where G_{Dh}, G_{Ph} are a derivative gain and a proportional gain of the torque.
   And R_{Vh}, R_{Ah} are a displacement and an angular rate of the body.
2. to mimic a sitting posture with the right arm raising, we used the right arm hinge torque and the hip hinge torque.
   Right arm hinge torque can be represented excellently by:

$$\text{torque}_{ra} = -G_{Da}(B_{Va} - R_{Va}) - G_{Pa}(B_{Aa} - R_{Aa})$$

   where G_{Da}, G_{Pa} are a derivative gain and a proportional gain of the torque.
   And R_{Va}, R_{Aa} are a displacement and an angular rate and B_{Va}, B_{Aa} are the target trajectories of the arm.

7. References

Bloem, BR., Grimbergen, YAM., Cramer, M., Willemsen, M., Zwinderman, AH. Prospective assessment of falls in Parkinson's disease. *J Neurol.* 248, 2001, pp 950-8.

Bloem, BR., Grimbergen, YAM., van Dijk, JG., Munneke, M. The "posture second" strategy: a review of wrong priorities in Parkinson's disease. *J Neurol Sci.* 248, 2006, pp 196-204.

Dick, JP., Rothwell, JC., Berardelli, A., Thompson, PD., Gioux, M., Benecke, R., Day, BL., Marsden, CD. Associated postural adjustments in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 49, 1986, pp 1378-85.

Duvoisin, RC., Marsden, CD. Note on the scoliosis of Parkinsonism. *J Neurol Neurosurg Psychiatry.* 38, 1975, pp 787-93.

Grimbergen, YAM., Munneke, M., Bloem, BR. Falls in Parkinson's disease. *Curr Opin Neurol.* 17, 2004, pp 405-15.

Gurfinkel, V., Cacciatore, TW., Cordo, P., Horak, F., Nutt, J., Skoss, R. Postural muscle tone in the body axis of healthy humans. *J Neurophysiol.* 96, 2006, pp 2678-87.

Hayashi, R., Hashimoto, T., Tada, T., Ikeda, S. Relation between changes in long-latency stretch reflexes and muscle stiffness in Parkinson's disease comparison before and after unilateral pallidotomy. *Clin Neurophysiol.* 112, 2001, pp 1814-21.

Hayashi, R., Aizawa, J., Nagase, H., Ohara, S. Lateral inclination of the trunk and falling frequency in Parkinson's disease patients. *Electromyogr Clin Neurophysiol.* 50, 2010, pp 195-202.

Hodges, PW., Gurfinkel, VS., Brumagne, S., Smith, TC., Cordo, PC. Coexistence of stability and mobility in postural control: evidence from postural compensation for respiration. *Exp Brain Res.* 144, 2002, pp 293-302.

Jensen, RK., Fletcher, P. Distribution of mass to the segments of elderly males and females. J Biomech. 27,1994, pp 89-96.

Keijsers, NL., Admiraal, MA., Cools, AR., Bloem, BR., Gielen, CC. Differential progression of proprioceptive and visual information processing deficits in Parkinson's disease. *Eur J Neurosci.* 21, 2005, pp 239-48.

Kumar, S. Ergonomics and biology of spinal rotation. *Ergonomics.* 47, 2004, pp 370-415.

Krishnamoorthy, V., Yang, JF., Scholz, JP. Joint coordination during quiet stance: effects of vision. *Exp Brain Res.* 164, 2005, pp 1-17.

Lee, RG., Tonolli, I., Viallet, F., Aurenty, R., Massion, J. Preparatory postural adjustments in parkinsonian patients with postural instability. *Can J Neurol Sci.* 22, 1995, pp 126-35.

Mak, MK., Wong, EC., Hui-Chan, CW. Quantitative measurement of trunk rigidity in parkinsonian patients. *J Neurol.* 254, 2007, pp 202-9.

Maki, BE., Holliday, PJ., Topper, AK. A prospective study of postural balance and risk of falling in an ambulatory and independent elderly population. *J Gerontol*. 49, 1994, pp M72-84.

Mitchell. SL., Collins, JJ., De Luca, CJ., Burrows, A., Lipsitz, LA. Open-loop and closed-loop postural control mechanisms in Parkinson's disease: increased mediolateral activity during quiet standing. *Neurosci Lett*. 197, 1995, pp 133-6.

Morris, M., Iansek, R., Smithson, F., Huxham, F. Postural insatiability in Parkinson's disease: a comparison with and without a concurrent task. *Gait Posture.* 12, 2000, pp 205-16.

Nuyens, G., De Weerdt, W., Dom, R., Nieuwboer, A., Spaepen, A. Torque variations during repeated passive isokinetic movements of the knee in subjects with Parkinson's disease and healthy control subjects. *Parkinsonism Relat Disord.* 6, 2000, pp87-93.

Okada, H., Ae, M., Fujii, N., Morioka, Y. Body segument inertia properties of Japanese elderly. *Biomechanisms* Vol.13, 1996, pp 125-139. The Society of Biomechanisms. ISBN 4-13-060134-3, Japan

Parkinson, J. (1817). *An essay on the shaking palsy.* Sherwood, Neely, and Jones, London.

Rocchi, L., Chiari, L., Horak, FB. Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 73, 2002, pp 267-74.

Schieppati, M., Hugon, M., Grasso, M., Nardone, A., Galante, M. The limits of equilibrium in young and elderly normal subjects and in parkinsonians. *Electroencephalogr Clin Neurophysiol*. 93, 1994, pp 286-98.

Shivitz, N., Koop, MM., Fahimi, J., Heit, G, Bronte-Stewart HM. Bilateral subthalamic nucleus deep brain stimulation improves certain aspects of postural control in Parkinson's disease, whereas medication does not. *Mov Disord*. 21, 2006, pp 1088-97.

Steiger, MJ., Thompson, PD., Marsden, CD. Disordered axial movement in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 61, 1996, pp 645-8.

Traub, MM., Rothwell, JC., Marsden, CD. Anticipatory postural reflexes in Parkinson's disease and other akinetic-rigid syndromes and in cerebellar ataxia. *Brain.* 103, 1980, pp 393-412.

Van der Burg, JCE., van Wegen, EEH., Rietberg, MB., Kwakkel, G., van Dieën, JH. Postural control of the trunk during unstable sitting in Parkinson's disease. *Parkinsonism Relat Disord*. 12, 2006, pp 492-8.

Van Emmerik, REA., Wagenaar, RC., Winogrodzka, A., Wolters, EC. Identification of axial rigidity during locomotion in Parkinson disease. *Arch Phys Med Rehabil.* 80, 1999, pp186-91.

Van Wegen, EEH., van Emmerik, REA., Wagenaar, RC., Ellis, T. Stability boundaries and lateral postural control in Parknson's disease. *Motor Control.* 3, 2001, pp 254-69.

Vaugoyeau, M., Viel, S., Assaiante, C., Amblard, B., Azulay, JP. Impaired vertical postural control and proprioceptive integration deficits in Parkinson's disease. *Neuroscience.* 146, 2007, pp 852-63.

Winter, DA., Patla, AE., Prince, F., Ishac, M., Gielo-Perczak K. Stiffness control of balance in quiet standing. *J Neurophysiol*. 80, 1998, pp-1211-21.

Wood, BH., Bilclough, JA., Bowron, A., Walker, RW. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. *J Neurol Neurosurg Psychiatry*. 72, 2002, pp 721-5.

Zattara, M., Bouisset, S. Posturo-kinetic organisation during the early phase of voluntary upper limb movement. 1. Normal subjects. *J Neurol Neurosurg Psychiatry*. 51, 1988, pp 956-65.

Zia, S., Cody, FW., O'Boyle, DJ. Identification of unilateral elbow-joint position is impaired by Parkinson's disease. *Clin Anat*. 15, 2002, pp 23-3.

Part 3

Multidisciplinary Cognitive Rehabilitation in Parkinson's Disease

13

Cognitive Rehabilitation in Parkinson's Disease Using Neuropsychological Training, Transfer Training and Sports Therapy

I. Reuter[1], S. Mehnert[1], M. Oechsner[2] and M. Engelhardt[3]
[1]Dept. of Neurology, Justus-Liebig University, Giessen, Germany
[2]Neurologisches Rehabilitationszentrum, HELIOS Klinik Zihlschlacht AG,
[3]Dept. of Orthopedic Surgery, Klinikum Osnabrück,
[1,3]Germany
[2]Swiss

1. Introduction

1.1 Cognitive impairment in Parkinson's disease

Idiopathic Parkinson`s disease (PD) is a neurodegenerative disorder characterized by basal ganglia dysfunction frequently being associated with frontostriatal dysfunction and cognitive impairment. The prevalence of PD increases with age and is estimated at 100-200/100000 people (Chen et al., 2001; Schrag et al., 2000) worldwide. The clinical hallmarks of PD are akinesia, rigidity and tremor (Douglas et al., 1999; Hughes et al., 1992). In the past PD has been considered as a pure movement disorder, but in recent years the presence of non-motor symptoms in PD has been recognized. Non-motor symptoms include a variety of autonomic dysfunctions such as orthostatic hypotension, postural tachycardia, bladder dysfunction, sleep disturbances, psychiatric symptoms, i.e. depression, hallucinations or psychosis and cognitive impairment. Non-motor symptoms such as pain, depression or sleep disturbances might precede the onset of motor symptoms in PD and are sometimes even more disabling than motor deficits. For many years cognitive impairment and the occurrence of dementia have been considered as not typical for IPD. James Parkinson (Parkinson, 1817) wrote in his essay on the shaking palsy " the senses are not disturbed". However, there is now enough evidence in the literature that dementia might occur in up to 40% of PD-patients (Emre et al., 2004). PD dementia is the third most common reason for dementia. Dementia in PD has been associated with reduced quality of life, greater sensitivity to medication, higher risk of developing psychosis, shortened survival (Levy, 2002), increased caregivers stress and frequent transfer to nursing homes (Aarsland et al., 2000) compared to PD-patients without dementia. In contrast to dementia mild cognitive impairment might occur early in the course of the disease. Approximately, a quarter of PD-patients without dementia have mild cognitive impairment (PD-MCI) and 20% might have MCI at the time of diagnosis (Aarsland et al., 2011). The cognitive deficits in PD are specific and include executive dysfunction, attentional and visuospatial deficits. Executive functions include control, manipulation, and cognitive flexibility (Funahashi et al., 2001; Lezak, 1995) and is part of working memory (Carpenter et al., 2000). The executive system is thought to

be involved in handling new situations outside the domain of automatic psychological processes (no reproduction of learned schedules or set behaviours). The theoretic model of the executive system has been modified several times over the years. Crucial contributions to the concept of executive functions came from Norman (1980, 2000), Shallice (1982), Baddeley (1986) and Miller & Cohen (2001). In summary, executive functions involve planning and decision making, influence our handling and the processing of information. Furthermore, they are involved in error corrections or troubleshooting, in situations which require new sequences of actions. Components of the executive systems are attention (focusing on relevant information), selective visual attention, inhibition (inhibition of irrelevant information)(Smith & Jonides, 1999), overcoming of strong habitual responses or resisting temptation (Burgess & Shallice, 1996), task and time management, monitoring and coding of information for processing in the working memory, flexibility, set maintenance and set shifting. The executive system can be viewed as a manager enabling the adaptation of the perceptive, cognitive and motor system to new tasks. Some authors have claimed that cognitive control is the primary function of the prefrontal cortex (Miller & Cohens, 2001). Cognitive control is implemented by increasing gain of sensory or motor neurons that are involved in task or goal relevant actions (Miller & Cohen, 2001).

Patients with impaired executive functions face many difficulties in everyday life. They have a low attention span, difficulties in problem solving and decision making, in dual tasking, in set shifting, in visuoconstructive tasks, in adaptation to new tasks and even in verbal learning and delayed recall. Thus, PD-patients with impairment of executive functions have difficulties in simultaneously driving a car and searching for a street or in preparing a meal for several people. They also have difficulties in keeping appointments. Relatives report that patients avoid difficult tasks and retreat from social life. Executive dysfunctions also affect the social components and the interaction with other people (Smith & Jonides, 1999). Patients are reported of being more irritable and having difficulties in suppressing inadequate behaviour.

It has been proposed that executive dysfunction underlies all manifestations of cognitive impairment in PD (Lewis et al., 2005) as part of the 'frontal-executive brain syndrome' (Godefroy, 2003). In accordance Colman et al. (2009) found that executive dysfunction also underlies the performance of PD-patients on verb production.

Pathophysiologically (Leverenz et al., 2009) cognitive impairment in PD might be either associated with catecholaminergic or indolaminergic neurotransmission or with Alzheimer´s disease (AD) related pathology. While the first form manifests mainly with non amnestic features like impaired EF, and might be correlated with Lewy related pathology in limbic and neocortical regions. The second type of CI manifests in amnestic CI and might derive from processes of AD intersecting with PD. 40% of patients develop dementia (Emre et al., 2004).

1.2 Pathophysiology of cognitive impairment in PD

Decline of cognitive performance in PD might result from rupture of nigro-striatum-thalamus cortical circuit interconnecting the striatum to the prefrontal cortex, cholinergic deficits through the differentiation of neurons in the nucleus basalis of Meynert and the pedunculopontine-lateral dorsal tegmental neurons (Calabresi et al., 2006).

In PD the production of dopamine (DA) in the substantia nigra (SN) is decreased. DA is a major neurotransmitter of the basal ganglia, contributing seriously to the development of

frontal-executive dysfunction. Dopaminergic frontal systems play a major role in working memory and executive function (Goldman-Rakic et al., 1992), especially the dorsolateral prefrontal lobe. However, dopaminergic medication has not shown to have a substantial effect on cognitive problems in PD (Fournet et al., 2000; Lewis et al. , 2005,). So far, medical treatment has not been effective enough to prevent PD dementia and restore executive dysfunction.Acetylcholine esterase inhibitors improve cognitive functioning only in some patients.

Furthermore, there is a large body of studies on animals and humans in the literature showing a positive effect of exercise and sports on cognition (Abbott et al., 2004; Colombe et al., 2003a, 2003b, 2006; Laurin et al., 2001; Rolland et al., 2010). Several studies suggest an enhancement of cortical plasticity by exercise. It is assumed that physical exercise mediates increased expression of neurotrophic factors as glial-derived neurotrophic factor (GDNF), basic fibroblast growth factor (FGF-2) , or brain-derived neurotrophic factor (BDNF) (Kleim et al., 2003). BDNF is a member of the neurotrophin family of growth factors vital for trophic support of neurons within both the peripheral and central nervous system. BDNF signals through tyrosine kinase receptor B and through the p75 receptor. Both are expressed by dopamine neurons. Postmortem studies in PD have shown that PD is associated with reduced BDNF levels in the SNC (Howells et al., 2000)

1.3 Treatment options for cognitive decline in PD

Executive functioning was found to be improved by aerobic endurance exercise (Colcombre & Kramer, 2003; Kramer et al., 1999). Motor training was reported to improve cortical plasticity and cortical reorganisation (Nelles 2004; Shepherd 2001). Physical exercise also was found to improve the quality of daily living (Baatile et al., 2000, Reuter et al., 1999) in PD-patients. Furthermore, Hausdorff et al (2005) have shown that higher cognitive functions correlate with gait variability while Ble et al. (2005) reported a close correlation between executive functions and tasks of the lower extremities.

Since patients with mild cognitive impairment have a higher risk to develop dementia, intervention at an early stage of cognitive decline is desirable. Patients who complain of cognitive problems suffer more often from cognitive deficits than patients without complaints (Dujardin et al., 2010). Therefore, these patients should be offered neuropsychological testing and treatment. However, according to our experience, it is difficult to convince patients to participate in cognitive training programmes. PD-patients noting declining cognitive performance are often anxious and ashamed of having cognitive problems. They rather deny their problems and try to avoid situations which make their problems obvious to other people. On the other hand the majority of PD-patients is very interested in exercise- and sport-programmes focusing on improvement of motor skills and mobility. Considering the correlation between cognitive function and motor tasks, it might be possible to improve cognitive function by physical training. Furthermore, achievements in cognitive training performed at a writing desk are often difficult to transfer into daily life. Therefore, we have chosen a comprehensive approach and designed a study using a multimodal cognitive training to improve cognitive functions.

The aim of the present study was to compare the effect of a multimodal cognitive training regime including paper and pencil tasks combined with transfer tasks and a psychomotor training with a cognitive training performed at a writing desk and a cognitive training consisting of various tasks requiring executive functions combined with transfer tasks.

2. Methods

2.1 Subjects

240 patients with idiopathic Parkinson`s disease according to the UK brain bank criteria (Hughes et al., 1991) and complaints about cognitive problems were recruited for the study at the Parkinson clinic Bad Nauheim. Exclusion criteria were severe concomitant diseases, which limit physical performances, and a second neurodegenerative disease. All patients were assessed by a movement disorder specialist. Medical treatment was optimised prior to the study. It was aimed at keeping medication stable during the study. Demographic data included age, body mass index (BMI), duration of disease, weekly sports activity, smoking habits, medication and concomitant diseases (hypertension, chronic obstructive pulmonary disease, thyroid disease, diabetes mellitus, hypercholesterinaemia, osteoarthritis).

2.2 Design

The study was divided into two phases, the first part consisted of a 4-week in-patient stay on a rehabilitation unit with a supervised cognitive training conducted by physiotherapists, occupational therapists and two neuropsychologists.

Patients were randomly allocated to one of the three training groups. Randomisation was conducted by using a computer-generated sequence. All groups received a cognitive training regime using paper and pencil material and a multimedial PC-training. Group A received cognitive training only, while group B took part in a transfer training and a cognitive training. Group C conducted a cognitive training, transfer- and psychomotor training. Patients of group A and B had relaxation training in addition to compensate for the additional training times and occupational therapy without translation training. (Fig. 1) The ethical committee of the Justus-Liebig University has approved the study and all patients gave informed consent. At the baseline visit a medical history was taken and all patients underwent a neurological assessment. Severity of disease was assessed by using the Unified Parkinson`s Disease rating scale (UPDRS).

Demographic data included information about education, profession, family, onset and severity of disease, medication, history of psychosis and impairments in daily living. Patients kept an activity log one week prior to the training programme and one week prior to the third assessment. Sports activities and time spent sitting, doing light, moderate, heavy work were recorded.

2.2.1 Scales used for neurological and neuropsychological assessment of PD

2.2.1.1 UPDRS

For the assessment of the longitudinal course of the disease the Unified Parkinson`s disease rating scale (UPDRS) was applied. The UPDRS is the most frequently used outcome measure in clinical trials in Parkinson`s disease (Fahn et al., 1987). The UPDRS has four subscales: part 1, which has 4 questions on mentation, behaviour and mood (range 0-16 points), part 2, which has 13 questions on activities of daily living (ADL) (range 0-52 points); part 3, which has 14 questions on motor functions (range 0-108 points); and part 4, which has 11 questions on motor and other complications of advanced disease (0-23 points). The UPDRS-Sum score ranges from 0 to 199 points, with a higher score indicating greater problems.

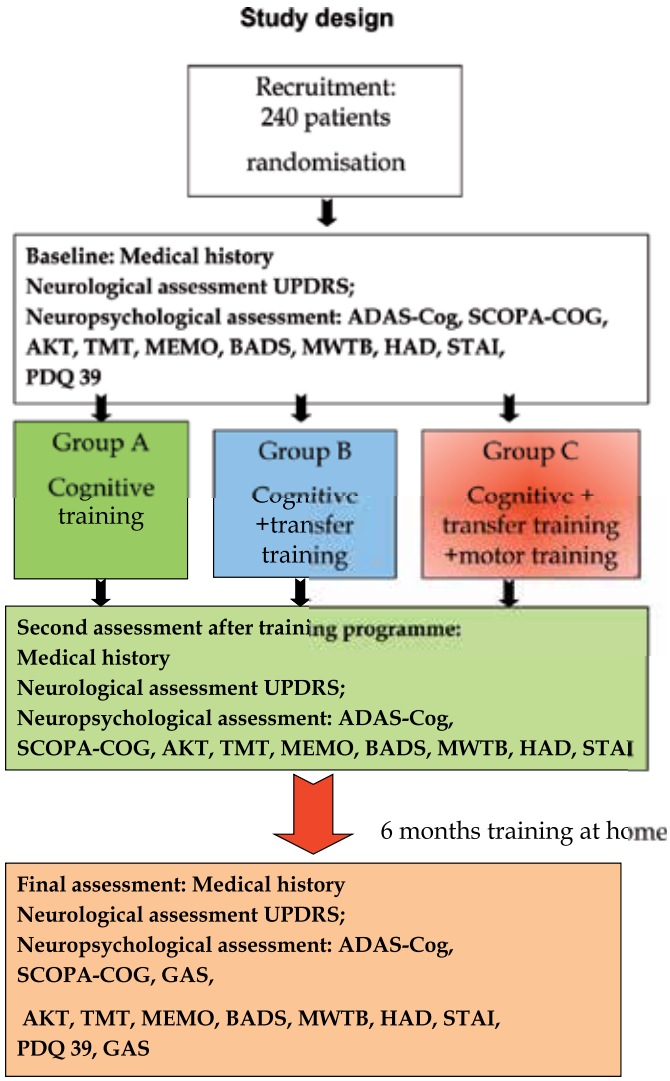


Fig. 1. Study design: First phase of the study: randomisation into three treatment arms, in-patient treatment; second phase of the study: training at home

Posture, postural stability, alternating movements and leg agility were assessed by using the single items of the UPDRS motor scale. The score of each item ranges between 0 to 4 points.

2.2.1.2 Goal attainment scale

The Goal Attainment Scaling (GAS) allows individualisation of realistic and feasible goals according to patient needs and expectations. All patients identified a task they want to improve by the training programme. In this study, GAS was measured using a 6-point scale, where –3 represented function that is worse than at the start of treatment, –2 was no change, –1 represented some improvement but did not meet the expected goal, 0 represented goal achievement and +1 or +2 represented over-achievement or exceeding the defined therapeutic goal (Royal College of Physicians, 2008).

2.2.1.3 Neuropsychological tests:

For neuropsychological assessment all patients underwent a detailed cognitive test battery at the beginning of the study including the ADAS-Cog subscale and the SCOPA-COG as outcome measures.

A: ADAS-Cog (Alzheimer Disease Assessment Scale-Cognition)

Although the ADAS-Cog is not a specific test for cognitive impairment in Parkinson`s Disease the scale was chosen as primary outcome measure in the current study, because it was the primary outcome measure in earlier trials assessing effects of medication on cognitive function in PD (Tab.1).

No	. Task	Characteristics	Score
1	Word recall	The recall task of frequent, easily to imagine words	0-10p
2	Naming	Naming of 12 presented objects and fingers on a hand	0-5p
3	Commands	Task of understanding and fulfilling	0-5p
4	Constructional	Drawing 4 geometric forms using praxis a pattern	0-5p
5	Ideational	The task of ability to perform praxis a familiar but complex sequence of actions	0-5p
6	Orientation	Assessment of time and space orientation	0-8 p
7	Word recognition	The task of discriminating new words from the already presented ones	0-12p
8	Instructions	Ability to remember instructions from remembering the previous recognition task	0-5p
9	Spoken language	Assessment of the quality of patient.s age ability speech	0-5p
10	Word finding	Assessment of patients ability to difficulty communicate verbally	0-5p
11	Comprehension	The patients ability to understand the spoken speech	0-5p

Table 1. Structure of ADAS-Cog scale.

The ADAS-Cog scale was the primary outcome measure in many clinical trials (Rosen WG et al., 1984). The conceptual framework underlying the ADAS-Cog identifies three reproducible factors: memory, language, praxis (Talwalker et al., 1996). The ADAS-Cog score ranges in total from 0 to 70 points with higher scores indicating greater impairment. Language ability is tested by naming objects and fingers, observer rated comprehension of spoken language, expressive language and word finding (range 0-25 points; memoryis tested by recall of instructions, word list recall and recognition (range 0-27 points), test of praxis (range 0-10 points) consists of constructional praxis (copying geometric figures) and ideational praxis (preparing envelope to send to oneself), orientation is assessed for time and space orientation (range 0-8points).

B: SCOPA-COG(Scales for Outcome of Parkinson`s disease-Cognition)

The SCOPA-COG is an instrument which was designed to assess the specific cognitive deficits found in Parkinson`s disease (Marinus et al., 2003). The scale consisting of 10 items covers the domains: memory and recall (verbal recall, digit span backward, indicate cubes), attention (counting backward, months backward), executive function (fist-edge-palm, semantic fluency, dice), visual-spatial functions (assembly pattern) and memory (delayed recall). The score ranges from 0 to 43 points with higher scores reflecting better performance.

Further tests requiring executive and memory functions for assessment of cognitive performance of the PD-patients at baseline, second and final assessment were conducted.

C: Mini Mental test (MMSE)

The Mini mental state examination (Folstein et al., 1975) was used as screening tool for dementia. The test assesses orientation, registration, attention, calculation, recall, language, writing and copying. The maximum score is 30 points; high scores indicate good performance. The cut off criteria for an abnormal result are 24 points and below. Dementia was assumed for less than 20 points.

D: Alters-Konzentrationstest

For assessment of attention the Alters-Konzentrationstest (Gatterer et al., 1989) was applied. Patients are asked to mark specific figures out of other figures alike the target. Time to complete the test, number of correctly marked figures, number and type of mistakes are recorded.

E: Paced auditory serial addition test (PASAT)

The Paced Auditory Serial Addition Test (Gronwall et al., 1977) assesses auditory information processing speed and flexibility and ability to calculate. Single digits are presented either every 3 seconds (trial 1) or every 2 seconds (trial 2). The patient has to add each new digit to the one immediately prior to it. The maximal possible score adds up to 60, the individual test score is equal to the total number of correct sums in each trial. In the current study the slower speed was used.

F: Trail making test

The trail making test (Reitan, 1958) assesses visual attention and task switching. Numbers from 1 to 30 are spread over a sheet, the patient is asked to connect the numbers in ascending order. Time and errors are recorded.

G: MEMO-Test

The MEMO-Test (Schaaf et al., 1994) assesses short-term verbal memory. Ten words are read to the patient. Five trials are performed. Patients are asked to repeat the words immediately, after each trial the words left out are read again. The following assessments are performed: UR: all words produced by short-term memory, ALZS: all words recalled from long term memory, UR + ALZS: all words recalled; KALZS: all words permanently recalled from long term memory; NKALZS: all words inconsistently recalled from long term memory; LZS: all words recalled from long term memory; delayed recall after 15 min..

H: Behavioural assessment of the dysexecutive syndrome (BADS)

The BADS (Wilson et al., 1998) is a battery of tests assessing executive function and comprises several subtests. In this study the Rule Shift Card test was applied to identify perseverative tendencies and mental flexibility, the Zoo Map test assessing was used the ability to plan and the Modified Six Element test, a test of planning, task scheduling and performance monitoring, were applied.

I : Mehrfach-Wortschatz-Test (MWT-B) Multiple choice word test

The MWT-B (Lehrl, 1989) serves as a control factor. A list consisting of 37 rows with 5 words is shown to the patient. Only one of the five words has a real meaning the others are fantasy words. The patients should mark the word with the meaning. The correct answers are added up to the sum-score. Each score is related to a standard score (z) which estimates the IQ of the patient.

K: Hospital anxiety and depression scale

The Hospital anxiety and depression scale (Zigmond & Snaith, 1983) was applied for exclusion of significant depression and anxiety. The scale consists of two subscales, an anxiety scale and a depression scale ranging from 0 to 21 points respectively. Patients are asked to choose one response from the four given for each question. Patients were strongly encouraged to respond promptly. Questions related to anxiety are marked with A and to depression with D. Depression and anxiety are scored separately. On each scale 0 to 7 points indicate a normal, 8 to 10 points a borderline abnormal and 11 or more points an abnormal result.

L: State Trait anxiety inventary (STAI)

The STAI scales (Spielberger et al., 1970) assess the trait anxiety (X2) and the anxiety in a specific situation (X1). Each scale consists of 20 items. Both scales present the answers on a 4 point Likert scale. Both scales range from 20 to 80 points with high scores indicating a high anxiety level.

M: Parkinson`s disease Questionnaire 39 (PDQ 39)

For assessment of health related quality of life patients filled in the PDQ 39 (Jenkinson et al., 1997, Peto et al., 1995). It consists of 8 subscales: subscale 1 mobility (max. 40 points); subscale 2 activities of daily living (max. 24 points), subscale 3 emotional well being (max. 24 points), subscale 4 stigma (max 16 points), subscale 5 social support (max 12 points), subscale 6 cognition (max.16 points), subscale 7 communication (max.12 points), subscale 8 bodily discomfort (max. 12 points) . The sum score of raw data ranges from 0 to 156 points, with high scores indicating lower health related quality of life. For better comparison of the results raw data were transformed and expressed in percentages of maximal possible sum score.

2.2.2 Training programmes

A: Cognitive training

The cognitive training content was individually tailored to patients` requirements based on the results of the baseline tests. Four individual (one to one) lessons took place each week each lasting 60 min. All patients received at least 14 cognitive training sessions.
The training included training of attention, concentration, biographical work, reasoning, memory, working memory, social rules, anticipation, cognitive information speed, prospective memory, cognitive estimation, problem solving, sequencing and planning, associations and coping with disease.
For the training programme a set of tasks requiring executive and memory functions were chosen from a variety of specific tests. Executive tasks of the BADS, which were not used for baseline tests were included in the training. Simple patterns of the "Raven`s Progressive Matrices" were used to establish problem solving strategies in the patients. Picture arrangement tasks, picture completion tasks, block design, and object assembly were adapted from the "Wechsler Intelligence test for children". For improvement of verbal fluency patients were encouraged to tell short stories or discuss short text-passages. Photos were used for training of working memory. Tasks including visual search, rule finding were practised by using a PC-based programme. The training methods were designed to improve the various cognitive deficits, diagnosed at baseline and focused on the executive functions. Task difficulty was adapted to the individual performance level of the patients.

B: Transfer tasks

The aim of the training was to support patients to manage better their daily life and to become more self-confident. Therefore, patients were asked to practise competence in tasks of daily routines. The transfer training programme was composed according to the baseline test results. Special preferences of the patients were considered. The transfer training included a training of concentration, use of mnemonics, strategy (planning), navigational skills, impulse control, decision processes, listening training and memory, behaviour, calculating, handling of money, summarising of articles read or heard and decision making. Typical tasks were to find the way to the supermarket or to prepare a meal, to go to the bank, pay a bill and to use mnemonics. For better evaluation of the training tasks were allocated to different categories: concentration, strategy, improvement of orientation, planning, use of mnemonic devices. The training took place 3 times a week each lasted 90 min. Patients received at least 10 sessions of transfer training.

C: Motor training

Group C performed a motor training resembling psychomotor training lessons applied in children. Psychomotor training (Golubović et al., 2011; Oswald et al., 1996) reflects a relationship between cognitive functions and physical movements. It includes training of co-ordination, strength, speed, perception and orientation. Patients should discover their body and their feelings. The therapeutic approach is multidimensional and based on individual capabilities and needs. The aim of the training was to practise motor sequences, dual tasking (walking and bouncing or throwing a ball, orientation in a space, walking through a parcours to improve anticipation. In summer the training was conducted partly outdoors with inclusion of Nordic walking. Thus, the training combines aerobic and psychomotor components. The training included at least 10, maximal 12 sessions each lasting 60 minutes.

2.2.3 Education of caregivers

A long lasting training effect depends on continuing training. Thus, cognitive training and exercises need to be adapted to the home environment. Consequently, the caregivers most often the patients` family were included in the programme. The education for the caregivers consisted of 5 modules (information about Parkinson`s disease, psychological aspects and the role of a caregiver, information about help aids, information on care instructions, assessment of individual problems, support in cognitive (all groups) and transfer training (group A and B), NW and psychomotor training). Course instructors were a specialist nurse, physiotherapist and a psychologist.

2.2.3.1 Phase II Continuing training

Corresponding to the allocation to the training groups patients got lessons for the cognitive training, transfer training and physical exercises for the training at home. Caregivers were advised how to organise the training but the hospital staff did not organise the training at home.

2.2.3.2 Evaluation of the training

All patients were tested using a neuropsychological test battery: prior to the training and prior to discharge to assess the short term effect and 3 months after the training to assess the long-term effect.

Caregivers were asked regarding their own well being and regarding the cognitive competence of the patients in daily living. Patients and caregivers kept a diary to record training lesions. The diaries were collected and analysed at the 3rd. assessment.

2.3 Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics 18.0 (IBM, Somers, USA) statistical software. Formal power analysis was performed prior to the study. The power analysis was based on an improvement of the ADAS-Cog by 3 points. The results indicated that a sample size of 60 subjects per group was sufficient. Since comprehensive training programmes including several assessments imply drop outs, a drop out rate of 20% was taken into account. Demographic data on ordinal level were analysed by using a non-parametric test (Kruskall-Wallis). The Kruskall-Wallis test was also applied for the analysis of depression and the BADS subscales. Continuous data were analysed by using a One – way-ANOVA. The repeated measure analysis provides information about "between and within subjects" effects. Within subject effects give information about training effects over the assessment period. Linear trends were extracted by orthogonal polynomials and analysed for days and for trials (Memo test). Linear trends showed if there was a systematic change of training effects over time. The interaction between groups and the linear trend of days yielded information about difference in the rate of improvement between groups. The between subject factor compared the overall treatment effect between the groups. Post hoc analysis was done using Bonferroni tests. Parametric data were tested for normal distribution by using the Kolmogorov-Smirnov test. Significance level was set at 0.05.

		Group A (N = 71)	Group B (N = 75)	Group C (N = 76)
gender		F=35 M = 36	F = 36 M = 39	F = 36 M = 40
Duration of PD (months)		98± 8	95 ± 9	100 ± 6
Stage (Hoehn & Yahr)	II	8	6	10
	III	55	59	58
	IV	9	10	8
Medication	L-Dopa	Yes = 68	Yes = 64	Yes = 59
	Dopamine agonist	Yes = 53	Yes = 56	Yes = 59
	MA0 inhibitor	N = 43	N = 38	N = 43
	COMT inhibitor	N = 33	N = 31	N = 34
	Antidepressants	N = 7	N = 8	N = 8
	Neuroleptic drugs	N = 5	N = 8	N = 7
Formal education (years)		10 ± 1.2	11 ± 0.6	11 ± 1.0
Marital status m = married, s = single, c = partner		m = 58 s = 9 p = 5	m = 61 s = 11 p = 3	m = 63 s = 9 p = 4
Home (own home, renting)		Own = 40 Renting = 32	Own = 43 Renting = 32	Own = 40 Renting= 36
BMI		27.5 ± 4	26.8 ± 7	27.2 ± 3
Smoking		Yes = 7 No = 65	Yes = 10 No = 65	Yes = 9 No = 67
Sports activities (min)		∅ 155 ± 17	∅ 163 ± 25	∅ 147 ± 17
Comorbidity	Coronary Heart disease	N = 7	N = 6	N = 8
	Hypertension	N = 32	N = 33	N = 36
	Diabetes mellitus	N = 7	N = 10	N = 8
	COPD	N = 5	N = 6	N = 9
	Thyroid disease	N = 12	N = 10	N = 11
	Hypercholesteriaemia	N = 36	N = 32	N = 27
	Osteoarthritis	N = 27	N = 31	N = 34

Table 2. Demographic data

3. Results

3.1 General results, demographic data and accomplishment of the training

In total 222 patients (97.1%) completed the programme, 71 patients in group A, 75 patients in group B and 76 patients in group C.

The patients were on average 64 ± 4 years old and c. 8 years diagnosed with PD. The patients did not differ significantly in demographic data (Tab. 2). There was no difference in PD specific impairment and in the progress of PD between the groups.

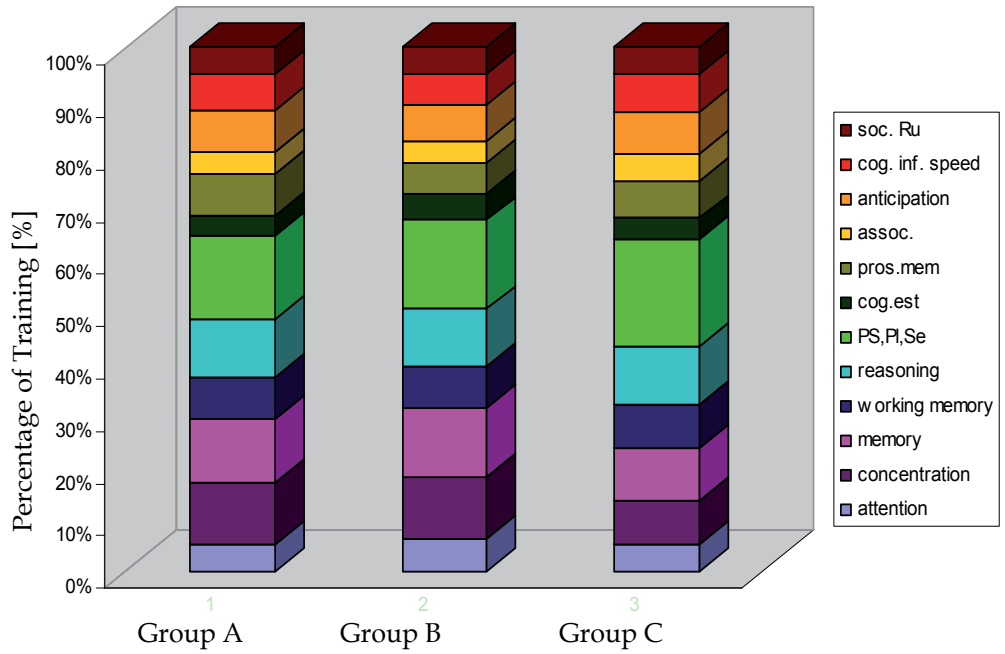
The physical activity of the patients did not differ significantly either.

Patients of group A reported to perform 8.5 ± 2.6 hours very hard work per week, while patients of group B and C reported of 9.2 ± 2.8 and 9.8 ± 2.1hours very hard work respectively. Group A managed 15.2 ± 4.5, Group B 14.9 ± 5 and Group C 15.1 ± 5.5 hard work.

The neuropsychological baseline assessment did not reveal any differences between the groups. The multiple choice word test (MWT-B) was conducted as a measure for premorbid intelligence, the groups did not differ significantly, either. Thus the randomisation process was successful.

A: Cognitive Training:

The groups differed in time of practising concentration tasks and sequencing and planning tasks ($F = 3.60$; $df = 2$; $p < 0.03$). Group A and B spent 12% respectively 15% of the training with concentration training, group c only 8%. In contrast group C spent 22% of the training time with sequencing and planning tasks while group A 16% and group B 17%. The other training areas did not differ significantly between the groups (Fig. 2).



Soc.Ru= social rules; cog.inf.speed= cognitive information speed, assoc.=association; pros.mem= prospecive memory

Fig. 2. Group C spent more time of the training with sequencing and planning tasks, while group A spent more time with concentration tasks.

B: Transfer training

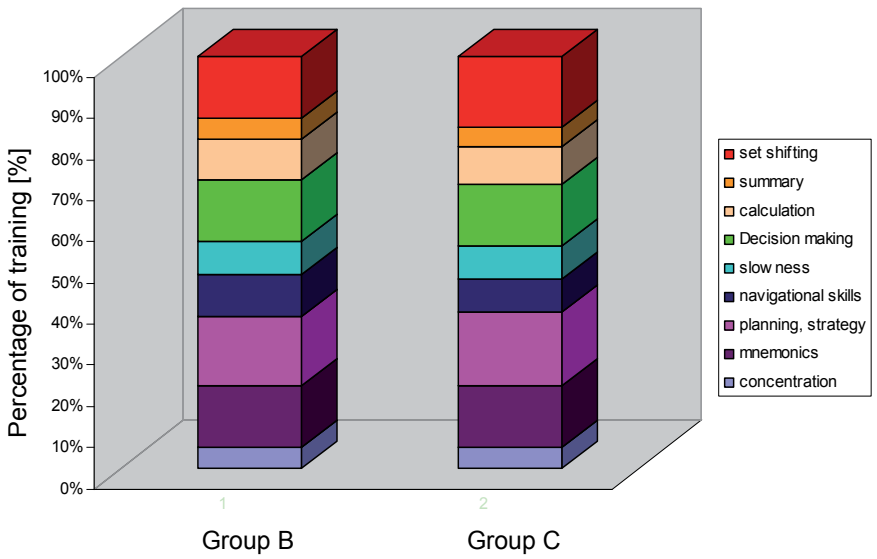


Fig. 3. There was no difference in the quantity and quality of transfer training between group B and C.

C: Motor training

Patients had many difficulties to cope with the tasks. They struggled to find strategies to solve the tasks on their own. The type of tasks and exercises were new to the majority of patients. The character of the tasks challenged the patients since PD-patients have both, deficits in proprioception and in perception of stimuli. The lessons were conducted as individual lessons. It was not possible to conduct group lessons. About 40% of the training took place outdoors, 60% in the gym.

D: Training at home

60% of patients of group A continued practising cognitive tasks 3 times a week, while 40% conducted the training only once or twice per week. All patients of group B tried to continue the transfer tasks learnt during the rehabilitation but further assessment showed that only 60% performed transfer tasks following a regular schedule. 90% of the patients practised cognitive tasks 3 times a week. Patients of Group C spent more time practising cognitive and transfer tasks than the other both groups. Patients conducted the physical training programme most often together with their spouses and very regularly.

E: Assessment of the training by the patients

Patients were asked to evaluate the training programme. Patients of group A felt that the cognitive training was arduous at times. Some patients perceived the training as stressful. Patients of group B and C were asked to compare the training programmes. Patients of group C preferred the motor training to transfer training and cognitive pencil and paper tasks. 80% of patients judged the training as strenuous and felt sometimes exhausted. 30% of patients reported of being frustrated at times but did not ask for help or further explanations.

F: Assessment of the training programme by the caregivers

Caregivers felt more relaxed and competent to handle difficult situation, while patients accepted the guidance of their care, felt more confident and thought that the caregivers were more understanding. Both, patients and caregivers felt competent to continue the training at home.

3.2 Neuropsychological results

Test	Baseline	T1	T2	Significance between groups
MMST				
Group A	27.36 ± 1.76	n.d.	26.4 ± 1.8	n.s.
Group B	27.6 ± 1.89	n.d.	27.1 ± 1.7	
Group C	28.14 ± 1.81	n.d.	28.5 ± 1.8	
ADAS-Cog				
Group A	21.51 ± 2.27	20.81 ± 2.77	20.5 ± 3.6	p< 0.001
Group B	21.37 ± 4.11	18.33 ± 3.67	18.5 ± 4.2	
Group C	22.92 ± 4.02	17.98 ± 2.76	17.4 ± 2.5	
SCOPA-COG				
Group A	29.07 ± 3.8	27.21 ± 3.6	26.86 ± 3.32	p< 0.001
Group B	29.68 ± 2.87	31.32 ± 3.24	30.71 ± 2.9	
Group C	31.83 ± 3.21	39.15 ± 2.9	39.29 ± 2.72	
TMT				
Group A	34.23 ± 16.87	31.7 ± 13.79	32.6 ± 14.5	p < 0.001
Group B	34.19 ± 15.6	32.0 ± 14.5	31.4 ± 13.5	
Group C	33.98 ± 15.8	26.2 ± 13.4	23.12 ± 9.8	
AKT (time)				
Group A	40.76 ± 15.2	42.85 ± 15.2	42.3 ± 14.2	n.s.
Group B	44.96 ± 16.5	41.67 ± 16.4	42.5 ± 15.3	
Group C	41.36 ± 15.23	40.98 ± 16.3	41.3 ± 16.3	
BADS Zoo (profile)				
Group A	2.5 ± 0.95	3.0 ± 1.2	2.4 ± 1.2	T1: Chi-square: 49.31; p < 0.001 T2: Chi-square: 14.421; p > 0.001
Group B	2.4 ± 0.9	2.8 ± 1.1	2.6 ± 1.1	
Group C	2.6 ± 0.98	3.54 ± 0.82	3.43 ± 1.0	
BADS instruction				
Group A	2.8 ± 1.3	3.3 ± 1.1	2.9 ± 0.8	T1: Chi-square: 7.1; p < 0.03 T2: Chi-square: 9.1 p > 0.01
Group B	2.6 ± 1.3	2.9 ± 1.2	3.2 ± 1.1	
Group C	2.7 ± 1.1	3.5 ± 1.1	3.8 ± 0.9	

BADS 6 elements				
Group A	2.8 ± 1.2	3.14 ± 0.89	3.1 ± 0.9	T1:
Group B	2.9 ± 1.2	3.0 ± 1.2	2.9± 1.1	Chi-square: 39.4;
Group C	3.0. ± 0.7	3.55 ± 0.8	3.6 ± 0.9	p < 0.001
				T2:
				Chi-square: 25.3
				p > 0.01
PASAT				
Group A	29.94 ± 14.32	32.8 ± 14.83	32.5 ± 13.87	
Group B	31.00 ± 13.32	37.43 ± 12.72	39.57 ± 13.65	p < 0.001
Group C	30.4 ± 12.98	46.5 ± 11.5	49.2 ± 13.4	
TKS (points)				
Group A	10.1 ± 2.4	11.2 ± 2.2	11.2 ± 2.1	
Group B	10.7 ± 2.5	11.2 ± 2.1	11.24 ± 2	p < 0.01
Group C	11.0 ± 2.5	12.5 ± 2.2	12.8 ± 1.9	
STAI X1				
Group A	44.8 ± 10.9	39.62 ± 10.56	38.98 ± 10.4	
Group B	44.42 ± 11.43	42.43 ± 11.2	38.65 ± 9.87	n.s.
Group C	43.53 ± 9.8	38.76 ± 9.8	36.87 ± 10.0	
STAI X2				
Group A	42.68 ± 10.42	40.03 ± 10.2	41.2 ± 10.1	
Group B	41.84 ± 10.44	39.8 ± 9.8	40.2 ± 9.8	n.s.
Group C	40.72 ± 9.98	38.8 ± 9.6	38.2 ± 10.2	

Table 3. Summary of neuropsychological test results

3.2.1 Primary outcome measure

A: ADAS-Cog

All groups improved on the ADAS-Cog significantly shown by a significant linear trend (F_{lin} [1, 220] = 150; p< 0.001. Group C improved most indicated by a significant interaction between groups and days ($F_{groups \times days}$ [1, 220] = 27.26; p < 0.001) and a significant group difference (F [2,220] = 7.7, p < 0.001). Further analysis showed that 78% of the patients showed some improvement at the second assessment, 51% of patients of group A, 85% of patients of group B and 96% of patients of group C. 50% of the patients reached a reduction of the ADAS-Cog score of 3 or more points, 18% of group A, 54% of group B and 76% of group C. Six months after discharge of the rehabilitation unit 35% of patients (50% of patients of group A, 31% of patients of group B and 28% of group C) showed a deterioration compared to the assessment at the end of the in-patient training programme. Further improvement was observed in 21% patients of Group A, 37% patients of group B and 50% patients of group C.

B: SCOPA-COG

In accordance the SCOPA-COG test showed a significant difference between the groups (Fig. 4). All groups improved, indicated by the linear trend of days (F_{lin}[1, 220) = 46.09; p <

0.001). Group C improved most resulting in a significant difference between the groups ($F[2, 220] = 31.4$, $df = 2$; $p < 0.001$). Since the slopes of the improvements differed between the groups, a significant interaction between days and groups occurred ($F [2, 220] = 65.63$; $p< 0.001$). Post hoc tests revealed a significant difference between all groups ($p< 0.001$). Patients of Group A reached 28.8 ± 3.7 points, Group B 30.3 ± 2.7 points and group C 37.6 ± 3.4 points. After completion of the in-patient training programme 31% of group A, 64% of group B and 88% of group C had shown a significant improvement on the SCOPA-COG, six months later at the final assessment 70% of patients of group A, 80% of patients of group B and 94% of patients of group C had been able to keep their level of performance.

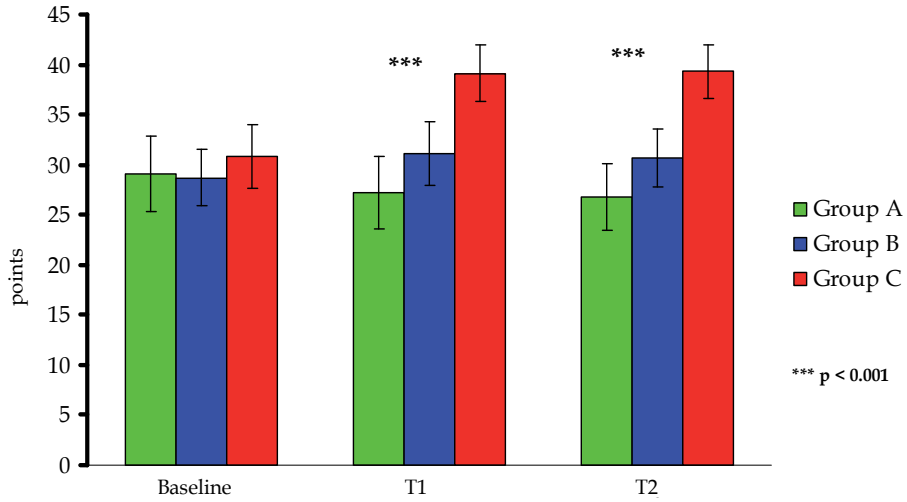


Fig. 4. Group C improved significantly more than group A and B

C: GAS

The GAS was performed on the final assessment. Group C reached more often the main goal than the other groups (Chi-square: 57.1; $p < 0.001$). The detailed analysis of the results is shown in table 4 and 5.

The main cognitive impairments reported by the patients could be attributed to the following domains: dual tasking, planning of complex and sequential tasks, decision making, rule recognition and rule shifting problems with delayed recall, difficulties in finding misplaced items. The patients based the selection of the goals on their individual main impairment. Table 4 shows the goals patients had chosen and if they were obtained.

More patients of group A compared to group B and C did not obtain the chosen goal or deteriorated compared to baseline while 27.6% of patients of group C obtained the goal and 39.4% exceeded the expectations mildly and 7.6% substantially.

D: Concentration

In the Alterskonzentrationstest (AKT) no difference between the groups was detected. Patients did not differ in attention span neither at baseline nor at the final assessment.

E: Information processing

In the ZVT no difference between the groups was detected at baseline assessment. The time to complete the test decreased in all groups after the training (F_{lin} [2,220] = 17.71; $p< 0.001$).

Groups	Goal	Goals chosen		Goals obtained	
		Total number	Percentage [%]	Total number	Percentage [%]
A N = 71	Dual tasking	15	21.1	3	20
B N = 75		14	18.7	9	6.4
C N = 76		15	20	10	67
A N = 71	Planning of complex tasks	15	21.2	3	20
B N = 75		16	21.3	9	56.3
C N = 76		17	22.4	10	58.9
A N = 71	Decision making	10	14.1	4	40
B N = 75		11	14.7	6	54.5
C N = 76		14	18.4	10	71.4
A N = 71	Rule recognition and rule shifting	13	18.3	4	30.8
B N = 75		16	21.3	7	43.8
C N = 76		14	18.4	10	71.4
A N = 71	Delayed recall	12	16.9	3	25
B N = 75		12	16	7	58.3
C N = 76		11	14.5	9	82
A N = 71	Search strategies	6	8.5	4	67
B N = 75		6	8	5	83.3
C N = 76		5	6.6	4	80

Table 4. Goals chosen by the patients

Group C was superior to group A and B ($p < 0.003$) while group A and B did not differ resulting in a significant group difference ($F[2,220] = 7.81$; $p < 0.001$).

In the PASAT test the groups produced on average 50% correct answers at the baseline assessment, group A improved only marginally. Group B and C benefitted from the training programme shown in a significant linear trend for days (F_{lin} [1, 154] = 63.71; $p < 0.001$). Since

GAS	Group A N = 71		Group B N = 75		Group C N = 76		Total	
	Total	Percent	Total	Percent	Total	Percent	Total	Percent
-3	12	16.7	6	8	2	2.6	20	8.9
-2	10	13.8	5	6.7	3	3.9	18	23.7
-1	28	40.3	21	28	18	23.6	67	30
0	13	18.1	19	25.3	23	30.2	55	24.7
1	8	11.1	24	32	24	26.3	56	25,112
2	0	0	0	0	6	7.9	6	2.7
	71		75		76		223	

Table 5. Results of the GAS

the improvement of the groups differed there was also a significant interaction between days and groups (F [2, 154] = 18.99; $p < 0.001$). Group C improved significantly more than group B ($p < 0.03$) and A ($p< 0.001$) (F [2, 154]= 15.46; $p< 0.001$).
Only 157 patients (Group A: 50, Group B: 53, Group C: 54) managed the PASAT test on the first assessment and were included in the statistical model. The other patients did not succeed in finding a strategy to cope with the task. On the second and third assessment 56 patients of group A, 64 of group B and 71 of group C scored on the test.

F: Memory

In the MEMO-Test the recall of words improved in all groups over the trials as well as over the assessment days. The subscales of all words permanently stored in the long-term store (F[2,220] = 2.95; $p< 0.05$).and the total number of words in the long-term store (F[2,220] = 3.27; $p< 0.05$) differed between the groups (Fig 4).

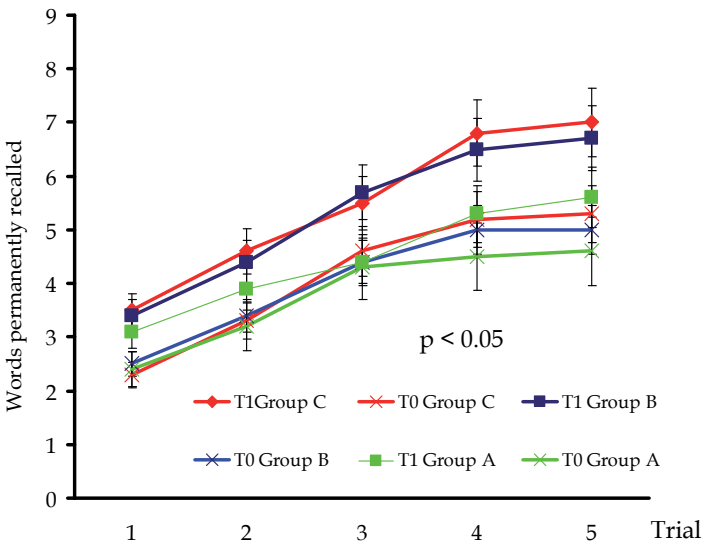


Fig. 5. Group B and C kept more words permanently in memory than group A.

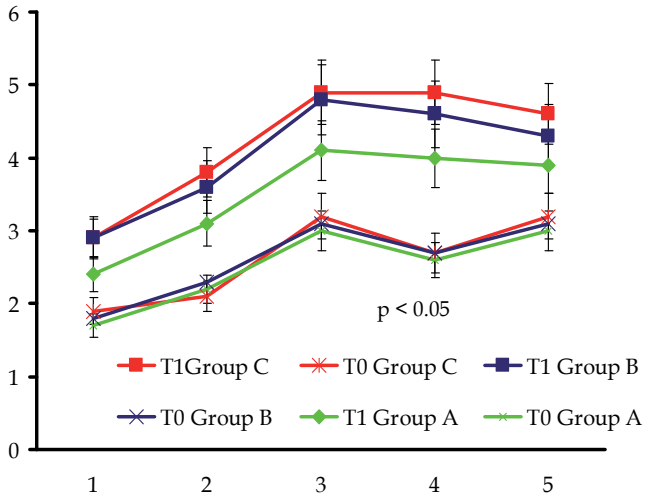


Fig. 6. Group B and C recalled more words than group A.

G: Executive function

The subtests of the BADS (rule shift cards, zoo map, modified 6 elements test) showed the following results:
The baseline scores of the rule shift cards did not differ between the groups. There was a mild but significant difference between the groups at the second assessment (Chi-square = 7.1; $p < 0.03$) and final assessment (Chi-square = 9.1; $p< 0.01$).
At baseline assessment Group C showed a tendency to better performance on the BADS Zoo Test. The mean profile scores of all groups were higher at the second assessment, but significant more patients of group C improved compared to group A and B. There was a clear group difference at the second (Chi-square = 49.31; $p < 0.03$) and third assessment (Chi-square = 14.42; 0.001)
There was no difference in the performance in the 6 elements test or set shifting test. All groups showed an increase of the average profile scores leading to significant group differences at the second (Chi-square = 39.3; $p< 0.001$) and third assessments (Chi-square = 25.3; $p< 0.001$).

H: TKS

The competence in cognitive estimation did not improve in Group A but in group B and C resulting in a significant difference between groups (T1:Chi square = 11.98; df = 2; $p < 0.03$; T2: Chi square = 22.153; df= 2; $p < 0.002$:

3.2.2 Assessment of mental state

15% of the patients in group A, 20% of group B and 18% of patients of group C reported to suffer from depression and received medication. The results on the HADS depression scale indicated in 20% of patients of group A and group C respectively and in 25% of patients of Group B the presence of a mild to moderate depression. The anxiety level was assessed by using the Hamilton anxiety scale and did not differ between the groups. The additional assessments of the current anxiety level at the time of assessment (STAI X1) and of the personality trait anxiety (STAI X2) did not reveal differences between the groups. The anxiety at the time of the assessments decreased mildly from baseline to the final assessment.

3.2.3 PD specific impairment

The PDQ39 shows that patients of group C rated their health related quality of life higher than the other groups. 13.8% of patients of group A, 38% of patients of group B and 52% of patients of group C reported less impairment due to PD. (Fig. 7)

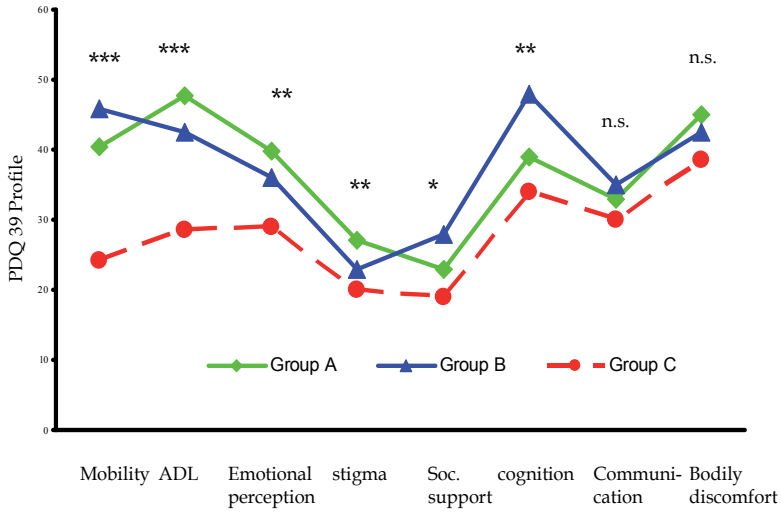


Fig. 7. PD-patients of group C reported less PD-specific impairment at the final assessment. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

The UPDRS score showed a mild improvement in all groups at the final assessment but there was no significant difference between the groups indicating that cognitive improvement was not an unspecific effect resulting from general physical improvement. (Tab. 5)

	Group A N=71	Group B N = 75	Group C N = 76
Baseline			
UPDRS Motor scale	38.56 ± 12.44	37.53 ± 10.76	38.4 ± 11.78
UPDRS Sum-Score	59.20 ± 12.4	60.3 ± 12.4	61.5 ± 12.8
Final assessment			
UPDRS Motor scale	34.1 ± 11.4	34.2 ± 11.2	35.2 ± 12.4
UPDRS Sum-Score	55.4 ± 12.4	56.3 ± 11.5	57.2 ± 11.4

Table 6. UPDRS

3.2.4 Performance in daily living

The patients of Group C reported that they had adapted a more active life style, felt more confident in activities of daily living and had taken over some more chores. They perceived their partners and caregivers as being helpful. They enjoyed the participation of their partners in conjoint sports activities.

Patients of Group B also regarded the training programme as helpful but reported of having still problems with activities of daily living. Patients of group A had more difficulties with transfer of skills into daily life and the carry over effect was smaller than in the other groups.

Sports activities were with 300min/week higher in Group C than in group B (196min/week) and A (176 min/ week).
Patients of group A reported to perform 7.4 ± 3.1 hours very hard work per week, while patients of group B and C reported of 10.4 ± 2.2 and 11.5 ± 2.7 hours very hard work respectively. Group A managed 14.2 ± 3.9, Group B 16.1 ± 4.3 and Group C 17.9 ± 4.1 hard work
In accordance with the patients` reports 65% of the caregivers of patients in Group C found competence and cognition of the patients improved. In group B 54% of caregivers and in group A 49%of caregivers confirmed an improvement. A deterioration of the performance in daily living was reported in 11% of group C, 17% of group B and 25% of group A. In summary patients who conducted a multimodal cognitive rehabilitation programme improved most and continued coping with daily tasks. Patients of group C were more active in daily living and took more often part in sports activities.

4. Discussion

In summary 90 % of patients of group A, 93.8% of patients of group B and 95% of patients of group C completed the training. Data of patients who did not continue with the programme were not included into the statistical analysis. Although patients complained of a lack of concentration, they performed well on the AKT. The second and third assessment did not reveal further improvement. The lack of improvement might be due to a ceiling effect since the performance on this test at baseline was good in all groups. The same might apply for the MMST which did not differ significantly between baseline and follow-up assessments. The training programme did not affect the mood of the patients.
At the baseline assessment patients of all three groups had shown deficits mainly in tests addressing executive functions. Consecutively, the performance of the patients was worse on the subtests of the SCOPA-COG semantic fluency, LURIA, dice and assembly pattern of the SCOPA-COG, Zoo test of the BADS, PASAT and cognitive estimation. The memory tasks such as immediate and delayed word recall were only mildly disturbed. All groups showed some improvements at the assessment immediately after completion of the training programme in the following tests: TMT, BADS Rule shift cards, zoo map, modified 6 elements test, PASAT and TKS. The mean scores of the ADAS-Cog and SCOPA-COG test in group A were not significantly better compared to the baseline assessment although 18% of the patients reached an improvement of 3 or more points on the ADAS-Cog. The findings were similar for the SCOPA-COG test. 31% of the patients showed an improvement on the SCOPA-COG test. Clear differences between the groups were found for the following tests: TMT, BADS zoo map, BADS rule shift cards, BADS 6 elements, PASAT, TKS, 2 subtests of the Memo Test.
At the second outcome assessment, 6 months after completion of the training programme, 21% of the patients of group A showed a further improvement on the ADAS-Cog, on the other hand 50% of patients of group A deteriorated, 31% of patients of group B and 28% of patients of group C within the 6 months after discharge from the rehabilitation unit. Most of the patients of group B and C were able to keep their performance level between the second and third assessment on the SCOPA-COG, while group A deteriorated. Further improvements between the second and the final assessment were obtained in group B and C on the TKS, PASAT and MEMO test.

The BADS subscales especially the zoo map is a very demanding task requiring excellent planning skills. Even patients of group A and B with previously shown improvement on the BADS subscales lost most of that. Only patients of group C managed to keep their level of performance. The performance of group B and A dropped nearly to baseline level. Thus, Group C has been superior to group B and A immediately after completing the training programme and at the second assessment six months later.
The difficulties patients experienced while solving the tasks have been in accordance with the results of other studies (Lewis et al., 2003, 2005). Most improvement has been observed in the LURIA, dice, assembly pattern, MOSAIC test of the SCOPA-COG. Mild improvement has been observed in the ZOO map and the PASAT-test. The pattern of improvement did not differ between the groups but the percentage of subjects showing an improvement differed significantly as well as the speed of recovery. The UPDRS – score improved in all groups slightly. There were no significant differences between the groups and no significant change of medication. Accordingly, the improvement in the neuropsychological tests cannot be referred to a better physical condition of one group and can be attributed to the training programme.
90% of patients of group C pursued the training at home with the same quantity and intensity while only 75% of group B and 50% of group A did so. Patients of group C conducted a motor training programme three times/week and practised cognitive tasks twice a week for 45 min. Patients of group B and C continued with some tasks resembling the transfer tasks they had performed during the training programme. The partners of the patients of group B and C managed to support the patients in practising transfer tasks, they asked them to prepare a meal or to do the shopping. The majority of the spouses of patients of group C joined their partners in the sports programme. The support of the spouses alleviated the home training significantly. As known from a questionnaire sent to the patients social aspects are very important for PD- patients. It is difficult to decide whether the further improvement of cognitive performance which occurred in some tests was due to the quantity of training or the content of the training. However, group C was already superior to the other groups at the second assessment. Since patients were compliant with the programme during the in-patient stay and received the same quantity of training, the different performance might rather be due to the content of the training than to the quantity. The performance of the patients differed between the tasks suggesting that the different training schedules between the groups affect the training outcome. For example the BADS zoo map a very challenging test as mentioned above requires various training approaches to achieve an improvement. As a result only patients of group C obtained an improvement on this test. Depression might also influence the performance in neuropsychological tests. Klepac et al. (2009) had found that depression preceding PD motor signs might favour poorer cognitive abilities. However, there was no significant difference between the groups regarding the percentage of patients being depressed and the onset of depression. Thus, an influence of depression and anxiety on cognitive performance could be ruled out.
Assessment bias in favour for one treatment can be excluded because the movement disorder specialists conducting the tests were blinded to the treatment arms.
Thus, the findings of the study suggest that PD patients benefit from a specific cognitive training and that a multimodal training might be most suitable for improving cognitive performance in PD. As already shown in a previous study (Hullmann et al., 2004) the cognitive training needs to be specific. Therefore, we had chosen an individual approach based on the Patients` results in the neuropsychological test battery. The specificity of the

training for executive functions is also shown in the fact that an other functional domain such as attention was not influenced by the training. Home based cognitive exercises were sufficient to keep the performance of the second assessment in patients of group C. However, patients of group B and C were able to keep some improvements as well. Home based cognitive training without transfer and physical training as performed by group A was less attractive for the patients. However, the poorer results of group A were not due to fewer training lessons since the performance of group A was already poorer on the second assessment. During the in-patient stay the quantity of training lessons were similar in all groups, only the percentage of specific training differed. Thus, the content of the training might be responsible for the different performance of the groups. The superiority of group B compared to group A suggests the efficacy of the transfer tasks. The psychomotor training helps the group C to improve further, especially in the challenging executive tasks regarding rule cognition, set shifting and decision making. However, it is not clear whether patients of group B and C could also cope better with completely new situations.

In contrast to a study by Paris et al. (2011), the present study suggested a translation of improved cognitive performance on the neuropsychological tests into daily living. Group C scored much higher on the PDQ 39 than the other groups. Thus, health related quality of life was improved markedly in these patients. The patients` caregivers also reported an improved competence in real life. In addition the goal attainment scale had been used in the present study. The patients picked the goals according to the cognitive problems they experienced in daily living. Most often the cognitive problem, they suffered most of, was chosen as goal. Half of the patients managed to obtain the goals agreed on prior to the training programme. Patients of group C reached significantly more often the goal than the patients of group B or A

The cognitive training performed in the study of Paris et al. (2011) resembled the training of group A in the current study. Only 29% of patients of group A obtained the goal compared to 69.8% of group C.

Some goals seemed to be more difficult to achieve (see Table 4). Patients faced more difficulties in attaining goals regarding rule generation and rule shifting while goals like dual tasking and memory improvement were easier to obtain. Group C was more successful to achieve an improvement in planning of complex tasks, rule generation and decision finding than group B and C.

Goebel et al. (2010) compared the ability of PD-patients to internally initiate a strategy with their ability to utilize an externally provided strategy in a simple Numerosity judgement task. The data of the study showed a general slowdown after strategy instruction. Furthermore, some patients reported difficulties in applying the strategies. The authors referred the findings to a failure in metacognition. Inferior utilization of metacognitive memory strategies seems to induce problems of PD-patients in real-life situations (Johnson et al., 2005, Shimamura, 2000). External instruction might activate metacognitive control processes and slow down the system. However, when PD-patients had sufficient time to solve the tasks there was no general deficit in the ability to internally generate a cognitive strategy in PD. Patients of group C had sufficient time during the psychomotor training to work out strategies to solve tasks and had time to initiate internal strategies. The combination of the psychomotor training with the transfer training provided the patients with some guidance and instructions to solve the tasks. However, the guidance was not too restrictive, there was enough time to find individual solutions. Additionally, the training was less standardised and strongly tailored to the patients` needs.

Our results are in accordance with the authors` conclusions (Goebel et al., 2008): "Adding training time and scheduling repetitive, cue-initiated learning trials may further improve training effects. Such a procedure may lead to more automated, implicit strategy application that demands less executive control (e.g., Baddeley,1998; Norman & Shallice, 1986; Sammer et al., 2006) whereas instruction alone bears the risk of increasing working memory load".
This is in accord with a work of Sinforiani et al (2004) who showed a significant improvement at verbal fluency, logic memory and Raven's matrices tests after a 6- week cognitive rehabilitiation training including cognitive and physical training. After the completion of the training a carry-over effect has been observed and the authors referred the effects to the combination of a cognitive and physical training. The authors suggested that the cognitive rehabilitation training exerts its positive effects by reinforcing cognitive strategies with improvement of frontal lobe functions.
Therefore, emphasis should be placed on the reduction of cognitive load in psychological training programmes. The combination of cognitive training at the writing table with transfer tasks and a physical training is recommended.
Research over the last decade has shown that cognitive deficits affect motor performance. Patients with cognitive deficits had more difficulties in motor tests than patients without cognitive deficits (Goldmann, 1998). Hausdorff et al (2005) have found a close correlation between walking and executive functions. Yogev et al. (2005) have shown that gait variability in dual tasking is closely associated with the performance in neuropsychological tests of executive tasks.
Therefore, one might speculate that motor functions might affect cognitive performance as well. There is a huge body of literature suggesting a prevention of cognitive decline by life long exercise or even an improvement of cognitive deficits by physical activity. Executive functions may be selectively maintained or improved in people with better physical condition provided by physical training (Churchill et al., 2002). The importance of aerobic physical exercise on cognitive functions, especially on executive functions has been shown (Kramer 1999, Colcombe et al., 2003, 2004, 2006). The studies have been mainly conducted in healthy elderly or patients with dementia. Tanaka et al. (2008) have shown that older people with PD can benefit their executive functions in the same way, as do their peers without PD.
The results of some studies have shown that brain areas undergoing biological aging benefit most from endurance sports. Even structural changes have been observed (Colcombe et al., 2006). Exercise is thought to enhance brain plasticity. Neuroplasticity might be supported by BDNF release, which is exercise regulated. Physical exercise increases the release of growth hormone (GH) which represents the main stimulus for the release of insulin growth factor (IGF-1). IGF-1 is involved in processes regulating learning,, memory, neurogenesis and amyloid degradation (Holzenberger et al., 2003, Carter&Ramsey, 2002). The release of IGF-1 is closely related to the release of BDNF. Several responses of the brain to exercise have been described. In animal studies comparing young and old animals a difference was shown in the location of the BDnF mRNA upregulation in the hippocampus. Young animal showed an increase of BDNF mRNA in dendate gyrus, hilus and Ca3 region, old animals in the Ca1 and Ca2 region. Long term potentiation which is relevant for memory and learning was also found. LTP was correlated with increased expression of mRNA of the NR2B receptor unit of the NMDA (N-methyl-D-aspertate) receptor. Increase of cerebral blood flow and reduction of cardiovascular risk factors might also contribute to the positive effects of sport on cognition. The reduction of cardiovascular risk factors does not play a role in the present study because of the short observation time. The release of dopamine by exercise might also

play a role. An increase in the activity of antioxidant enzymes, and thus increases the capacity to defend against the stress of oxidation in the central nervous system (Rodák et al., 2001) might also support neuroplasticity.
It is not specified so far which type of exercise might be most promising for improving cognitive performance. The role of endurance training has been shown, whether a combination of aerobic training with a cognitive challenging physical training is of advantage needs further research. The physical training in the present study provided both, a training of strategies to solve tasks and an aerobic training. Since intermittent training schedules have been shown to be as effective as daily training, the frequency of training sessions should have been sufficient as well.
It is not clear so far how cognitive training at the writing table might improve cognitive performance. The destruction of the nigrostriatal dopaminergic pathways is often about 75% and involves the ventral tegmental area, which innervates the prefrontal cortex. Therefore, it is unlikely that cognitive training reconstructs the dopaminergic system.
The multimodal training of cognitive functions is time- consuming and put demands on resources. Due to the quantity and quality of the trainings sessions it will also be costly. On the other hand dementia is a risk factor for falls and transfer to nursing –homes, which increases the costs for the patients´ care substantially and jeopardizes the patients` quality of life. Considering the sequelae of dementia such as increased dependence on care givers, high morbidity and increased mortality it is justified to spend more time and effort into prevention of dementia. Therefore, provision of adequate financing is also required.

5. Limitations of the study

One might criticise that we compared three different treatment arms and did not include a control group without cognitive training in this study. Patients were enrolled into the study during their stay in a rehabilitation unit and complained of a deterioration of their cognitive performance. For this reason it was not possible to withhold treatment. Further, we had shown in a previous study (Hullmann et al., 2004) the superiority of a cognitive training compared to standard treatment in control subjects. Therefore, we compared three different treatment arms with increasing stimulus modality.
Another limitation is that there are no evidence based data for the transfer training. Further research is necessary to evaluate and validate which transfer exercises are useful tools. The psychomotor training has been used for many years in children and has been used in patients with dementia (Oswald WP, 1996). However, it has not been validated in PD-patients so far. The selection of tasks had been based on the clinical experience of the therapists and medical staff and the published data based on the work with children.
One might also argue which improvement might be clinically relevant. However, the scales we used are all validated and had been often applied in clinical studies. The clinical relevance of the improvements is also shown by the observed translation into real life. One might criticize that the patients were not tested regarding their performance in completely new situations. Patients, caregivers and the neurologist supervising the treatment agreed on certain goals at the beginning of the study. Hence, situations resembling the agreed goals were trained during the study.
Furthermore, due to the short follow up period of 6 months we cannot report on long-term results. However, studies assessing long-term results are very difficult to conduct since it is very difficult to keep the medication stable. A change in dopaminergic (Fournet et al., 2000)

or antidepressant medication might influence cognitive performance. In order to correct for these confounders a larger sample of patients will be needed.

6. Strengths of the study

To our knowledge, the results of the current study show for the first time, that a multidisciplinary cognitive training in patients with Parkinson`s disease can lead to improvements of cognitive function which translate into everyday life and are not only shown by improvements on neuropsychological scales. We want to emphasize that a blinded randomised design and a standardised neuropsychological test battery were employed. Furthermore, the cohort of patients undergoing the study protocol was big and the dropout rate was low for this type of study. In addition the training of the caregivers guaranteed a supporting environment in all groups. We were able to keep the medication stable avoiding confounding effects by the change of medication.

7. Conclusion

In conclusion, we have shown that PD-patients with cognitive deficits benefit from a multidisciplinary cognitive training. A multimodal training is superior to a paper and pencil based cognitive treatment. We have shown a translation of improvements in cognitive tests into performance in real life. Although the multimodal training is time consuming and requires high motivation, it is worth to pursue the training considering the secondary diseases, loss of quality of life and the costs following the diagnosis of dementia. The role of the caregivers has also to be emphasized, the involvement of the family improves the compliance with the training at home.

8. Acknowledgement

We thank the Dr. Werner Jackstädt-Stiftung, the support made the present study possible.

9. References

Aarsland D, Larsen JP, Tandberg E. & Laake K. (2000). Predictors of nursing home placement in Parkinson`s disease: A population based prospective study. *J Am Geriatr Soc* , 48, pp. 938-942.

Aarsland D, Brønnick K, & Fladby T. (2011 Epub ahead). Mild cognitive impairment in Parkinson`s disease. Curr Neurol Neurosci Rep.

Abbott RD, White LR, Webster R, Masaki KH, Curb JD. & Petrovitch H. (2004). Walking and dementia in physically capable elderly men. *JAMA,* 292 (12), pp. 1447-1453

Baatile J, Langbein WE, Weaver F, Maloney C & Jost MB. (2000). Effect of exercise on perceived quality of life in individuals with Parkinson`s disease. *J Rehabil Res Dev,* 37, pp. 529-534

Baddeley AD (1986). *Working memory*. Oxford: Clarendon Press

Ble A, Volpato S, Zuliani G, Guralnik JM, Bandinelli S, Lauretani F, Bartali B, Maraldi C, Fellin R, & Ferrucci L.(2005). Executive function correlates with walking speed in older persons: the InCHIANTI study.*J Am Geriatr Soc*, 53(3), pp. 410-5.

Brand M, Kalbe E &Kessler J. (2002). Test zum kognitiven Schätzen (TKS). Göttingen: Hogrefe.

Burgess PW& Shallice T. (1996) Response suppression, initiation and strategy use following frontal lobe lesions. Neuropsychologia, 34(4), p.263-72

Calabresi P, Picconi B, Parnetti L &Di Filippo M. (2006). A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine-acetylcholine synaptic balance. *Lancet Neurol,* 5(11), p.974-83

Caradoc-Davies TH, Weatherall M & Dixon GS. (1992). Is the prevalence of Parkinson´s disease in New Zealand really changing? *Acta Neurol Scand* 86, p. 40-44

Carpenter PA, Just MA &Reichle ED. (2000). Working memory and executive function: Evidence from neuroimaging. *Curr opinion in Neurobiol,,* 10,p. 195-199.

Carter S & Ramsey MM. (2002). A critical analysis of the role of growth hormone and IGF-I in aging and lifespan. *Trends genet,* 18 (6), p. 295-301

Chen RC, Chang SF, Su CL, Chen TH, Yen MF, Wu HM, Chen ZY & Liou HH (2001). Prevalence, incidence and mortality of PD: A door-to-door survey in Ilna county, Taiwan. *Neurol,* 57, p. 679-1686

Churchill JD, Calvez R, Colcombe S, Swain RA, Kramer AF & Greenough WT. (2002). .Exercise, experience and the aging brain. *Neurobiol of aging,* 23,p. 941-955.

Colman KSF, Koerts J, Beilen M, Leenders KL, Post WJ& Bastiaanse R. (2009). The impact of executive functions on verb production in patients with Parkinson`s disease. *Cortex* 45, p. 930-942.

Colcombe S&Kramer AF. (2003). Fitness effects on cognitive function of older adults: a meta-analytic study. *Psychol Sci* , 14, p. 125-130

Colcombe S, Erickson KI&Raz N. (2003). Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci* 58A, p. 176-180.

Colcombe S, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, Elavsky S, Marquez DX, Hu L& Kramer AF. (2006). Aerobic exercise training increases brain volume in Aging Humans. *J Gerontology* 61A (11), p. 1166-1170.

Colcombe SJ, Kramer AF, Erickson KI, McAuley E, Cohen NJ, Webb A, Jerome GJ & Marquez DX. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci* 10(9), p. 3316-3321.

Colman KS, Koerts J, van Beilen M, Leenders KL, Post WJ & Bastiaanse R. (2009). The impact of executive functions on verb production in patients with Parkinson's disease.*Cortex,* 45(8), p. 930-42.

Douglas J. Gelb, Eugene Oliver, Sid Gilman (1999) Diagnostic Criteria for Parkinson Disease. *Arch* Neurol, 56, p. 33-39

Dujardin K, Duhamel A, Delliaux M, Thomas-Antérion C, Destée A & Defebvre L. (2010). Cognitive complaints in Parkinson`s disease. Its relationship with objective cognitive decline. J Neurol. 257 (1), p. 79-84

Elgh E, Domello¨ f M, Linder J, Edstrom M, Stenlund H & ForsgrenL. (2009). Cognitive function in early Parkinson's disease: a populationbased study. *Eur J Neurol* 16, p. 1278–1284.

Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, Durif F, Kulisevsky J, van Laar T, Lees A, Poewe W, Robillard A, Rosa MM, Wolters E, Quarg P, Tekin S& Lane R. (2004). Rivastigmine for Dementia associated with Pakinson`s disease. *N Engl J Med,* 351, p. 2509-18.

Fahn S, Elton RL and the members of the UPDRS Development Committee. (1987). Unified Parkinson`s Disease rating scale. In: Fahn S, Marsden CD, Goldstein M et al. Eds. Recent developments in Parkinson`s disease II. New York. McMillan; p. 153-163

Folstein MF& Folstein SE. (1975). "„Mini Mental State". A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res* 12, p. 189-198.

Fournet N, Moreaud O, Roulin J, Naegele B & Pellat J. (2000). Working memory functioning in medicated Parkinson`s disease patients and the effect of withdrawal of dopaminergic medication. *Neuropsychology*, 14, p. 247-253

Fitzpatrick R, Peto V, Greenhall R& Hyman N. (1997). The Parkinson`s diasease Questionnaire (PDQ 39): Development and validation of a Parkinson`s disease summary index score. *Age and Ageing*; 26, p. 1757-1769

Funahashi S. (2001). Neuronal mechanisms of executive control by prefrontal cortex. *Neuroscience Research*, 39,p. 147-165.

Gatterer G, Fischer P, Simany M& Danielczyk W. (1989). The A-K-T (Alters-Konzentrations-Test a new psychometric test for geriatric patients. FunctNeurol; 4 (3), p. 273-276

Goldman-Rakic PS, Lidow MS, Smiley JF & Williams MS. (1992) The anatomy of dopamine in monkey and human prefrontal cortex. *J of Transmission*, suppl. 36, p. 163-177

Godefroy O. (2003).Frontal syndrome and disorders of executive functions. *J Neurol,* 250 (1), p. 1-6.

Goebel S, Mehdorn HM& Leplow B. (2010). Strategy instruction in Parkinson's disease: Influence on cognitive performance.*Neuropsychologia,* 48(2), p. 574-80

Gronwall, D.M.A. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual and Motor Skills*, 44, p. 367-373.

Hausdorff JM, Yogev G, Springer S, Simon ES & Giladi N. (2005). Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. Exp Brain Res. 164 (4); p. 541-8.

Heinz-Martin S., Oberauer K., Wittmann WW, Wilhelm O. & Schulze R. (2002). Working-memory capacity explains reasoning ability and a little bit more. *Intelligence*; 30, p. 261-288.

Hoehn MM, Yahr MR, Parkinsonism: onset, progression and mortality. (1967). *Neurology,* 17,p. 427-442.

Holzenberger M, Dupont J (2000). IGF-I receptor regulates lifespan and resistance to oxidative exercise in mice. *Nature* 421 (6919), p. 182-187

Howells DW, Porrit MJ & Wong JY. (2000). Reduced BDNF mRNA expression in the Parkinson`s disease substantia nigra. *Exp. Neurol*; 166,p. 127-135

Hughes AJ, Daniel SE, Kilford L& Lees AJ. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson`s disease. A clinicopathological study of 100 cases. *JNNP*, 55, p. 181-184

Hullmann K, Sammer G & Reuter I. (2004). Training of executive functions in Parkinson`s disease. *Medimont International Proceedings*, p. 143-148.

Johnson AM, Pollard CC, Vernon PA, Tomes JL& Jog MS. (2005) Memory perception and strategy use in Parlinson`s disease. *Parkinsonism Relat. Disord*. 2005; 1, p. 111-115

Kleim JA, Jones TA& Schallert T. (2003). Motor enrichment and the induction of plasticity before and after brain injury. *Neurochem Res,* 28, p. 1757-1769

Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harisson CR Chason J, Vakil E, Bardell L, Boileau RA & Colcombe A. (1999). Ageing, fitness and neurocognitive function. *Nature*, 400, p. 418-419

Kramer AF, Colcombe SJ, Erickson KI, Paige P. (2006). Fitness training and the brain: From molecules to Minds. *Proceedings of the 206 Cognitive Aging Conference*, Atlanta, Georgia Atlanta GA: Georgia Institute of Technology.

Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P &Kukull W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age or older. *Ann Intern Med,* 144, p. 73-81.

Laurin D., Verreault R., Lindsay J, MacPherson K& Rockword K. (2001). Physical Activity and Risk of Cognitive Impairment and Dementia in elderly persons. *Arch Neurol* ; 58, p. 498-504

Lehrl, S. (1989). Mehrfach-Wortschatz-Intelligenztest: MWT-B. Perimed Fachbuch-Verlagsgesellschaft mbH, Erlangen

Leverenz JB, Quinn JF, Zabetian C, Zhang Jing, Montine K S& Montine T J. (2009). Cognitive impairment and Dementia in Patients with Parkinson Disease. *Curr Top Med Chem,* 9,p. 903-912

Levy G, Tang MX, Louis ED, et al. (2002) The association of incident dementia with mortality in PD. *Neurology,* 59, p. 1708–1713.

Lewis SJG, SlaboszA, Robbins TW, Barker RA & Owen AM. (2005). Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson`s disease. *Neuropsychologica*, 43, p. 823-832

Lezak MF. (1995). Neuropsychological assessment. Oxford: Oxford University Press.

Logsdon RG, McCurry SM, &Teri L. (2005). A home health care approach to exercise for persons with Alzheimer disease. *Care Manage J*, 6 (2), p. 90-97

Norris, G. & Tate, R.L. (2000). The behavioural assessment of the dysexecutive syndrome (BADS): ecological, concurrent and construct validity. *Neuropsychological Rehabilitation,* 10 (1),p. 33-45.

Marinus J, Visser N, Verwey FRJ, Middelkoop HAM, Stiggelbout AM &van Hilten JJ. (2003). Assessment of cognition in Parkinson`s disease. *Neurology,* 61, p. 1222-1228

Mc Curry SM, Gibbons LE, Logsdon RG, Vitiello MV&Teri L. (2005). Nighttime Insomnia Treatment and education for Alzheimner`s disease: A randomised controlled trial. *J Am Geriatr Soc,* 53, p. 793-802.

Miller BT & D'Esposito M (2005). "Searching for "the top" in top-down control". *Neuron,* 48 (4),p. 535–8.

Miller EK & Cohen JD (2001). "An integrative theory of prefrontal cortex function". *Annu Rev Neurosci,* 24 (1), p. 167–202

Nelles G. (2004). Cortical reorganisation – effects of intensive therapy. *Restor Neurol Neurosci*; 22, p. 239-244

Norman DA,&Shallice T (2000). "(1980) Attention to action: Willed and automatic control of behaviour". In Gazzaniga MS. *Cognitive neuroscience: a reader*. Oxford: Blackwell

Parkinson J. An essay on the shaking palsy. 1817London: Sherwood Neely and Jones

Reitan, R. M. (1958) Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills* 8. 271-276

Reuter I, Engelhardt M, Freiwald J& Baas H. (1999) Therapeutic value of exercise training in Parkinson`s disease. *Med & Sci Sports Exerc.* 9: 1544-1549.

Rodák Z, Kaneko T, Tahara S, Nakamoto H, Pucsok J& Sasvari M. (2001). Regular exercise improves cognitive function and decreases oxidative damage in the rat brain. *Neurochenmistry international* 38, 17-23

Rolland Y, v Khan GA & Vellas B. (2010) Healthy brain aging: Role of exercise and physical activity. *Clin Geriatr Med* 26,p. 75-87

Rosen WG, Mohs RC& Davis KL (1984): A new rating scale for Alzheimer's disease. *Am J Psychiatr* , 141, p. 1356-1364

Royal College of Physicians, the Intercollegiate Stroke Working Party. (2008). National clinical guideline for stroke. Third edition. London: RCP

Sammer, G, Reuter, I., Hullmann, K., Kaps, M., & Vaitl, D. (2006). Training of executive. functions in Parkinson's disease. *J Neurol Sci*, 248, p. 115–119.

Schaaf, A., Kessler, J., Grond, M.&Fink, G.R. (1994). Memo-Test. Hogrefe, Goettingen, Germany.

Schrag A, Ben-Shlomo Y& Quinn NP (2000). Cross sectional prevalence survey of idiopathic Parkinson´s disease and Parkinsonism in London. *BMJ,* 321, p. 21-22

Shepherd RB. (2001). Exercise and training to optimise functional motor performance in stroke: driving neural reorganisation. *Neural Plast* 8, p. 121-129

Shallice T. (1982). Specific impairments of planning. Philos Trans R Soc Lond B Biol Sci 25, 298 (1089), p. 199-209.

Shimamura, A. P. (2000). Toward a cognitive neuroscience of metacognition. *Consciousness and Cognition*, 9, 313–323.

Sinforiani, E., Banchieri, L., Zucchella, C., Pacchetti, C. & Sandrini, G. (2004). Cognitive rehabilitation in Parkinson's disease. *Archives of Gerontology and Geriatrics:* Suppl 9, p. 387–391.

Smith EE, Jonides J. (1999). Storage and executive processes in the frontal lobes. *Science,* 283, p. 1657-1661

Spielberger CD, Gorsuch RL, Lushene RE. (1970): STAI; Manual for the State-Trait-Anxiety-Inventory. Consulting Psychologist Press, Palo Alto.

Talwalker S.: Assessment of AD with the ADAS-cog.(1996) . *J. Geriatr. Psychiat. Neurol.*, 9, p. 39.46.

Teri L, Gibbons LE & McCurry SM (2003). Exercise plus behaviour management in patients with Alzheimer disease: A randomised controlled trial. *JAMA* 290 (15), p. 2015-2022

Trejo JL, Carro E, Torres-Aleman EL. (2001). Circulating insulin-like growth factor mediates exercise-induced increases in the number of new neurons in the adult hippocampus, *J Neurosci* 25, p. 1628-1634

Willis SL, Tennstedt S, Marsiske M.Ball K, Ekias J, Koepke KM, Morris JN, Rebok GW, Unverzagt FW, Stoddard AM Wright E, Active Study group. Long-term effects of cognitive training on everyday functional outcomes in elder adults. *JAMa,* ; 296, p. 2805-2814

Wilson BA, Evans JJ, Emslie H,Alderman N & P. Burgess. (1998). The development of an ecologically valid test for assessing patients with a dysexecutive syndrome. *Neuropsychol Rehabilitation 8 (3),* p: 213–228.

Yogev G, Giladi N, Peretz C, Springer S, Simon ES & Hausdorff JM. (2005). Dual tasking, gait rhythmicity, and Parkinson`s Disease: which aspects of gait are attention demanding? *Eur J Neurosci*, 22(5), p. 1248-56.

Zigmond AS& Snaith RP. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatr.Scand,* 67, p. 361-370

14

Mobile Systems as a Challenge for Neurological Diseases Management – The Case of Parkinson's Disease

Laura Pastor-Sanz, Mario Pansera, Jorge Cancela,
Matteo Pastorino and María Teresa Arredondo Waldmeyer
Life Supporting Technologies, Universidad Politécnica de Madrid
Spain

1. Introduction

Nowadays the importance of bio-medical engineering and mobile applications for healthcare is amazingly growing. During the last decades many devices and technological solutions have become available on the market and the interest in applying those technologies to the treatment of several kinds of pathologies has consequently increased. This chapter addresses the problem of continuous monitoring of patients affected by Parkinson's Disease (PD) and proposes a set of technologies to improve the following and management of such subjects.

PD is a neurodegenerative disorder of the central nervous system that affects motor skills and speech (Tolosa, 1998). The primary biochemical abnormality in PD is a deficiency of dopamine due to degeneration of neurons in the substantia nigra pars compact (D. G. Standaert & Young, 2001). The characteristic motor features of the disease include bradykinesia (i.e. slowness of movement), tremor, rigidity (i.e. resistance to externally imposed movements), flexed posture, postural instability and freezing of gait. Furthermore, PD is usually characterised by the loss of normal prosody of the speech (Darkins et al., 1988).

According to the World Health Organisation [WHO], 2002), there are more than six million people worldwide affected by PD. The syndrome typically appears around the age of 60. It affects Europeans and North Americans more often than Asians or Africans and it is more common in men than in women. PD affects about 2% of the population over the age of 65 years, figure that is expected to double by 2020 (de Lau & Breteler, 2006). For those reasons, PD poses a significant public health burden, which is likely to increase in the coming years. Annual medical care, including doctors' visits, physical therapies and treatment for co-occurring illnesses -such as depression- is estimated at $2,000 to $7,000 for people in early stages of the disease, and it is probably much higher for advanced stages. Surgical treatments for PD can cost $25,000 or more. As the disease progresses, institutional care at an assisted-living facility or nursing home may be required, and the related costs can exceed $100,000, per person annually.

Technology in general and specifically ICT might be an affordable alternative for PD's patients' treatment and management. The development of platforms for remote health

status monitoring, the qualitative and quantitative assessment and treatment personalization for people suffering from neurodegenerative diseases is expecting to provide in the future a remarkable improvement in patients' management as well as a substantial cutting-off of the economic burden generated by the disease. New technologies allow monitoring the evolution of the disease through the employment of a wide range of wearable and user-friendly micro-sensors. Moreover, the last advances in data processing and data mining algorithms is bound to provide more accurate information about the diverse aspects of PD evolution. Finally, it is important to highlight the huge potential in costs reduction that such platforms could yield. Furthermore, it is worth mentioning that the reduction in costs of hospitalization and treatment represents an attractive asset for the market forces involved in the development of biomedical applications.

2. Treatment

Current clinical treatment of Parkinson's disease is performed through ersatz dopamine administration or by using Deep Brain Stimulation (DBS) (Singh et al., 2007).

2.1 Dopamine treatment

Current therapy is based on augmentation or replacement of dopamine, using the biosynthetic precursor levodopa or drugs that activate dopamine receptors. These therapies are effective at the beginning of treatment. However, after a variable period of time, this initially excellent response is complicated by the appearance of MRCs. Complications include wearing-off, the abrupt loss of efficacy at the end of each dosing interval and diskinesias (de la Fuente-Fernández et al., 2004). Wearing off and dyskinesias produce substantial disability and frequently interfere with medical therapies (A.E. Lang & A.M. Lozano, 1998). Usually, motor fluctuations appear first, as a shortening of the initially smooth and long lasting dopaminergic response. In the typical case, few hours after drug intake the patients start to realize the re-emergence of signs and symptoms of the disease. This is known as end of dose deterioration or wearing off. This may happen several times a day; therefore the patient may actually several hours per day in the off state (Lees, 1989).

2.2 Deep brain stimulation

DBS is a surgical treatment involving the implantation of a medical device called a brain pacemaker, which sends electrical impulses to specific parts of the brain (Vaillancourt et al., 2003). The introduction of DBS as a therapeutic tool for advanced PD has revolutionised the clinical management of this condition. Due to its safety profile and efficacy, DBS has evolved from a last-resort therapeutic option to a modality that is now routinely offered to patients. Over the years, surgical candidates and the outcome expected with this procedure has become well established (Deuschl et al., 2006). Overall improvement that might be expected with surgery is similar to that provided by levodopa without the associated involuntary movements (Group, 2001). As the diseases progresses, however, non-dopaminergic symptoms (gait, postural instability, sleep disorders and depression, among others) become more prominent, leading to a significant increase in morbidity. To overcome some of the problems, the use of different surgical targets has been advocated. Perhaps the most promising application of DBS on this regards involves the use of Pedunculopontine Nucleus (PPN) stimulation for the treatment of gait and postural instability (Mazzone et al.,

2005). Recent studies suggest that this procedure might be suited for the treatment of falls and freezing. In addition to motor symptoms, an improvement in rapid eye movement sleep in patient with PD treatment with PPN DBS has been reported (Lim et al., 2009). In the future, a tailored approach to patient's specific symptoms may be possible (Lozano, 2009).

3. Assessment - state of the art

The assessment of PD can be performed through clinical and technological methods. Both types of solutions are reviewed.

3.1 Clinical solution

In Europe, each neurologist or general practitioner (GP) normally cares for 50 to 800 patients with PD. The range in workload is a result of diversity both in national health systems and in the availability of clinical resources across Europe. Even at 50 patients per clinician, this represents a serious challenge to homecare monitoring for specialised conditions. PD's patients normally visit their specialised clinician or GP every 4-6 months. As a result, any changes in the patient's conditions may not be recognised for several months, unless the patients themselves make contact (R. Greenlaw et al., 2009).

In clinical practice, information about motor fluctuations is usually obtained by asking patients to recall the number of hours of ON (i.e. when medications effectively attenuate tremor) and OFF time (i.e. when medications are not effective). This kind of self–report is subject to perceptual bias (e.g. patients often have difficulty distinguishing dyskinesia from other symptoms) and recall bias. Another approach is the use of patient diaries, which can improve reliability by recording symptoms as they occur, but does not capture many of the features useful in clinical decision making (Group, 2001).

Certainly for PD there is the additional complication of symptoms which vary throughout the day (swinging between ON and OFF states). During the short office visit in this neurologist the patient may appear very well and he misses to report symptoms of wearing off. As a result, treatment modifications are not undertaken in time. Besides, it is disempowering for the patient to be asked to present a true picture of their disease in a pre-scheduled one hour appointment (R. Greenlaw et al., 2009).

The actual emergence of dyskinesias throughout the day mainly depends on the intermittent dopaminergic drug intake, even in influence by timing and quantity of each individual dose of levodopa. While other phenomena, such as delayed response or no-response depends also on stress, food intake and many other factors. In this case, patients will greatly benefit from quantitative objective assessment of their motor status in daily life in relation to the dosing schedule.

In an attempt to solve these problems and to find more objective assessment, several rating scales have been designed and used. Among them, the Unified Parkinson's Disease Rating Scale (UPDRS) is the most widely used (Goetz et al., 2004). This rating tried to quantify selected symptoms and signs of Parkinsonism in a 5-points scoring system (with 0 for no signal and 4 for a marked severity of the sign). Unfortunately, the use of the UPDRS scale, like any other semi-objective rating scale presents some limitations like intra and inter observer inconsistencies. Besides, it can be time consuming and ca be biased by subjectivity issues related to historical information. Moreover, the pattern and severity of PD symptoms may vary considerably during the day, while clinical rating scales only provide moment-to moment assessment; and finally, measurements of motor fluctuations made in the clinic

may not accurately reflect the actual functional disability experienced by the patient at home.
The accurate assessment of speech quality is a major research problem that has attracted attention in the field of speech communications for many years. Subjective quality measures given by professional personnel who have received special assessment training are necessarily time consuming and costly (Lingyun Gu et al., 2005).

3.2 Technological solution: sensors for motion analysis

Over the past decades various technologies, methodologies and systems have been proposed for the monitoring and the assessment of the Parkinson's disease. A significant number of studies investigated various parameters of the gait of PD patients. Others focused on the evaluation and quantification of the patients' motor status and various disease symptoms by the use of computerized motion tests (e.g. handwriting, inserting pegs, and games). Table 1 describes some features of the human motion, as well as the characteristics which can be measured through the use of wearable sensors.

Features	**Characteristics**	**Sensor**
Gait	Speed of Locomotion	Motion sensor
	Variability of the gait	
	Rigidity of legs	
Posture	Trunk inclination	Motion sensor
Leg movement	Speed	Motion sensor
	Length of Step	Motion sensor
	Step Frequency	Motion sensor
	Stride	Motion sensor
Hand Movement	Speed	Motion sensor
	Angle Amplitude	Motion sensor
Tremor	Amplitude	Motion sensor
	Frequency	
	Duration	
	Asymmetry	
Fall	Fall detection	Motion sensor
Freezing of Gait	Leg movement analysis	Motion sensor
Levodopa-Induced Dyskinesia (LID)	Duration	Motion sensor
	Severity	
Bradykinesia	Duration	Motion sensor
	Severity	
	Asymmetry	
Aphasia	Pitch	Microphone
	EPE	

Table 1. Parkinson's disease – wearable sensors for human motion related measurements

The accuracy of measurements of the parameters above described depends on several technical features that are often in conflict with other needs such as usability, wearability, technical feasibility and the social acceptance of the devices used by the subjects.
In Table 2 a description of these desirable properties along with their conflicts is presented.

Desirable properties	Conflict
Small sensor	The size of sensor is definitely an important factor, especially for portability and mobility matters. However, small sensors may not have enough room for long-lasting battery or storage capacity.
Smart sensor	Sensors possessing many characteristics are often bigger in size, expensive and consume more power
Sensor storage capacity	Due to a limit in storage capacity, sensors have to upload data frequently to the data personal server. So it is important to employ a good wireless communication technology that does not drain excessive power from the sensors.
Sensor processing capability	Because sensors do not often have large processing capability, they may not be able to process all data before the upload to the personal server. This means that large amount of raw data should be stored and eventually sent. Therefore it is important to have an efficient communication channel.
Sensor communication range	Whilst sensors are only able to communicate over short range, it is crucial to define a specific radius of action.

Table 2. Wearable sensors desirable properties & conflicts

3.2.1 Systems for Parkinson's disease monitoring

Most of the research work carried out in the field of PD monitoring focuses on the assessment of the motor status of PD's patients. During the last decade, many research groups have been trying to develop a system able to objectively quantify the severity of the motor disturbances using motion sensors (Patel et al., 2010; 2009; 2007). An important number of these studies is based on the study of various parameters of motor behaviour, in particular features related to the gait (R. Greenlaw et al., 2009; Salarian et al., 2007; 2004).
Other studies focused on the identification of ON/OFF fluctuations through the assessment of tremor (Van Someren et al., 1993), dyskinesias (Keijsers et al., 2003; 2000) and bradykinesia (Papapetropoulos et al., 2010). Some groups are also committed to use electromyogram (EMG) or voice analysis (Kimura et al., 2007).
Additionally, in the literature there are examples of remote monitoring and patient management for PD (Tindall & Huebner, 2009), as well as the use of telematic services to facilitate the performance of motor tests remotely (Das, 2010; Dorsey et al., 2010; Giansanti et al., 2008; Westin et al., 2010).
Even though many advances have been done in the last years, it must be said that there is still a lack of an all-inclusive system able to provide reliable assessment of the status of PD patients being at the same time economically affordable. In particular it is crucial to provide:

- An effective evaluation of PD symptoms through monitoring and testing routines while not interfering with the patient daily life.
- A personalised profile of the patient allowing the correlation between those factors affecting the severity of symptoms (i.e. medication schedule and meals) and the evolution of the disease.
- The clinician with a system able to manage more efficiently the patient by providing timely indications on the effectiveness of the therapy and suggestions on therapy changes.

3.2.2 Available systems in the market/research

There are several products produced by certain research groups or commercially available for the assessment of PD. Some examples follow:

Cleveland Medical Devices

Cleveland Medical Devices Inc. commercialises Kinesia, a compact wireless system for monitoring the severity of PD motor symptoms. The system includes miniature motion sensors worn on the hand and it wirelessly transmits motor symptom information to a personal computer. Data is collected while patients follow computer based video instructions.

Fig. 1. Kinesia, Cleveland Medical Devices Inc. system for PD monitoring based on motor sensors (Jovanov et al., 2001)

Cleveland Medical Devices Inc. also commercialises Kinetisense, a compact wireless system for monitoring gait, posture or upper limb movement. The system integrates two channel Electromyography (EMG) and three orthogonal accelerometers and gyroscopes collecting data on three dimensional movements. The system is wearable and lightweight and is wirelessly connected to a computer for real-time data transmission. As alternative, data can be stored on a memory card for 12 hours recording and transmitted asynchronously. The system can be linked to different software tools for movement and posture analysis, detection of slips and falls and for the performance and monitoring of rehabilitation exercises.

Fig. 2. Kinetisense, Cleveland Medical Devices Inc. system for PD monitoring based on motor sensors and electromyography (Jovanov et al., 2001)

Intel Corporation

Intel Corporation has developed a system called At home Telemonitoring Device (AHTD), based on nonlinear speech single processing methods around the use of discrete variational integrator. It could be used to perform speech analysis detect abnormalities and telemonitor neurological disorders with voice singles.

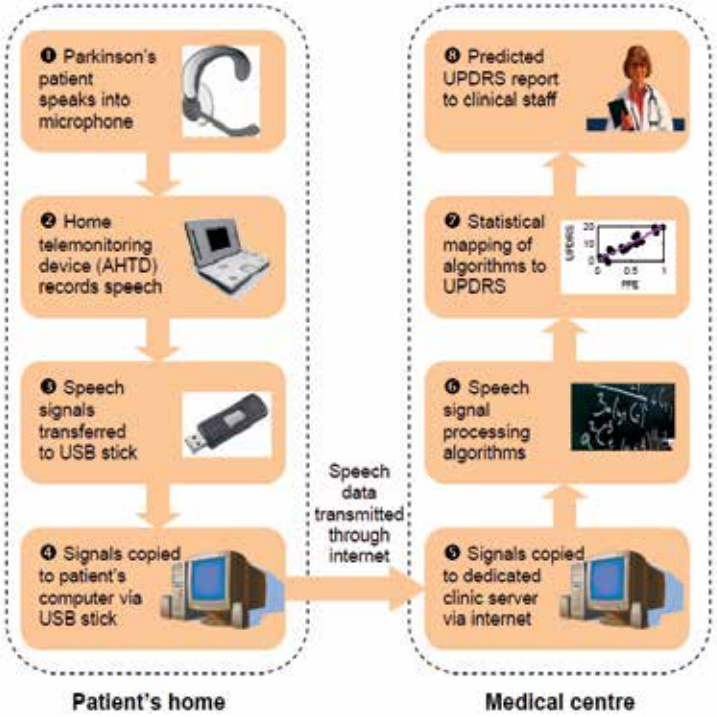


Fig. 3. At Home Telemonitoring Device (AHTD), Intel Corporation system for PD monitoring based on speech processing (Tsanas et al., 2010b)

Karolinska Institute

The Karolinska Institute, Sweden, has developed a prototype test battery for evaluating fluctuation motor symptoms in PD together with a decision support system as part of the Movistar TEVAL project (Westin et al., 2010). The system is based on a handheld device with built-in mobile communication, where combined patient diaries with on-screen motor tests are implemented. The data collected from the patient are transmitted to a central system where they are analysed through Artificial Intelligence methods. Besides, it originates alerts and advice via a web interface.

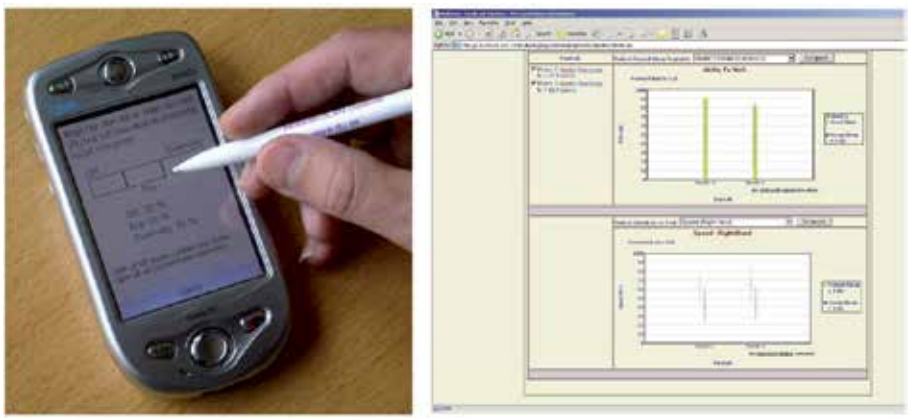


Fig. 4. TEVAL project prototype, Karolinska Institute, Sweden, based on patient diaries together with on-screen motor tests

Twente University

The University of Twente, Enschede, in the Netherlands, has developed a system called SensorShoe that is a mobile gait analysis tool. It is composed by a low-power sensor node equipped with movement sensors (3D accelerometers and 2D gyroscopes) connected to a PDA which provides immediate feedback to the patient while walking and suggest physical

Fig. 5. Sensor Shoe, University of Twente, Enschede, The Netherlands. Gait analysis based on movement sensors (Kauw-A-Tjoe et al., 2007)

exercises based on the personal rehabilitation and training program defined for the patient and stored in the PDA. The system can connect to the hospital or to the physician through the PDA and transmit daily motion data, which can be analysed by physicians and be used to improve the physical therapy.

Federal Polytechnic School of Lausanne

The Federal Polytechnic School of Lausanne, Switzerland, has developed a system for motion monitoring based on a portable data-logger with three body-fixed inertial sensors.

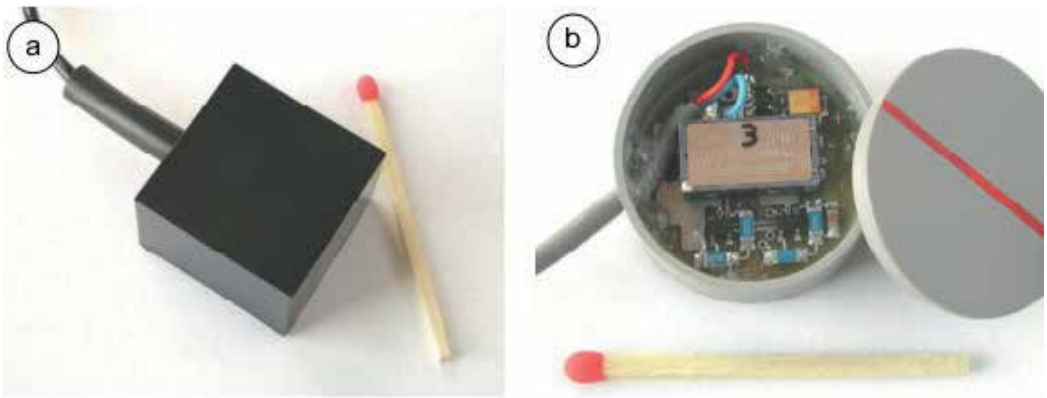


Fig. 6. a) The trunk sensor used for physical activity monitoring b) The uni-axial gyroscopes used for the gait analysis, The Federal Polytechnic School of Lausanne, Switzerland (Salarian et al., 2007).

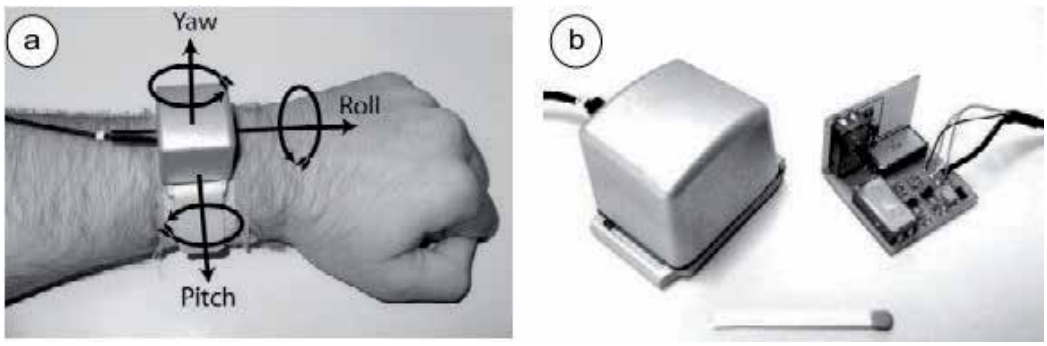


Fig. 7. a) Trunk sensor used for physical activity monitoring b) The uni-axial gyroscopes used for the gait analysis, The Federal Polytechnic School of Lausanne, Switzerland (Salarian, et al., 2007b)

Boston University

The Boston University National Institute of biomedical Imagining and Bioengineering has developed a wearable-sensor system for monitoring motor function. The system is composed by a device that can be worn unobtrusively by patients in their home to automatically detect the presence and severity of movement disorders associated with PD. The onset of the OFF status is based on the motor status of the patient that can be related to

the motor status of the patient with the medications assumptions. The system involves electromyographic (EMG) and accelerometric (ACC) body worn sensors, whose signals are analysed by a system using Artificial Intelligence methods.

Fig. 8. Boston University National Institute of Biomedical Imaging and Bioengineering, PD monitoring system through motor and EMG sensors (UB, 2011)

3.3 Technological solution: non autonomous home based monitoring closed loop systems

Close loop systems are those in which stimulation parameters are adjusted according to recorded signals. Talking about neurodegenerative diseases such as PD, close loop systems imply that medication doses and timing is adjusted based on the measurement of certain biomedical signals. Some examples follow.

3.3.1 PERFORM project

A sophisticated multi-paRametric system FOR the continuous effective assessment and Monitoring of motor status in Parkinson's disease and other neurodegenerative diseases research project has developed an intelligent system that monitors several motor signals of the patients that are analyzed in a medical centre by a medical professional. The system is able to propose treatment changes, based on the clinical assessment. Further explanations are provided later in this chapter (Perform, 2008).

3.3.2 HELP project

The HELP project (Home-based Empowered living for Parkinson's Disease Patients) aims at developing a comprehensive system able to administer drug therapy without patient intervention, in either continuous or on-demand basis in order to manage disease progression and to mitigate PD's symptoms (Help, 2011).

It is based on inertial sensors that capture inertial information about the patient's motion and compute spatiotemporal properties and Parkinson's related symptoms. At the point of care remote supervision of the patient is performed, together with Verification of the infusion algorithm and possible modification of its parameters. An intraoral device continuously administrates dopamine agonists to the mucosa from the mouth. Besides, a subcutaneous pump receives commands adapting the infusion rate of apomorphine, a non-selective dopamine agonist.

4. PERFORM system

4.1 Introduction

PERFORM is a project partially funded by the European Commission under the Seventh Framework Program, aiming at providing an innovative and reliable tool that is able to monitor and evaluate motor neurodegenerative disease patients, such as PD patients.
The PERFORM project is based on the development of an intelligent closed loop system that seamlessly integrates a wide range of wearable micro-sensors constantly monitoring several motor signals of the patients. Data acquired are pre-processed by advanced knowledge processing methods, integrated by fusion algorithms to allow health professionals to remotely monitor the overall status of the patients, adjust medication schedules and personalize treatment. Personalization of treatment occurs through PERFORM's capability to keep track of the timing and doses of the medication and meals that the patient is taking.

4.2 The PERFORM medical and technological vision

The information gathered by the inertial sensors (accelerometers and gyroscopes) is processed by several classifiers. As a result, it is possible to evaluate and quantify the PD symptoms that the patient presents as well as analyze the gait of the patient. Based on this information, together with information derived from tests performed with tests devices (e.g. virtual reality gloves) and information about the medication and food intake, a patient specific profile is built. Next steep is to compare the patient specific profile with his evaluation during the last week and last month, checking whether his status is stable, improving or worsening. Based on that, the system analyses whether a medication change is needed-always under medical supervision- and in this case, information about the medication change proposal is sent to the patient.

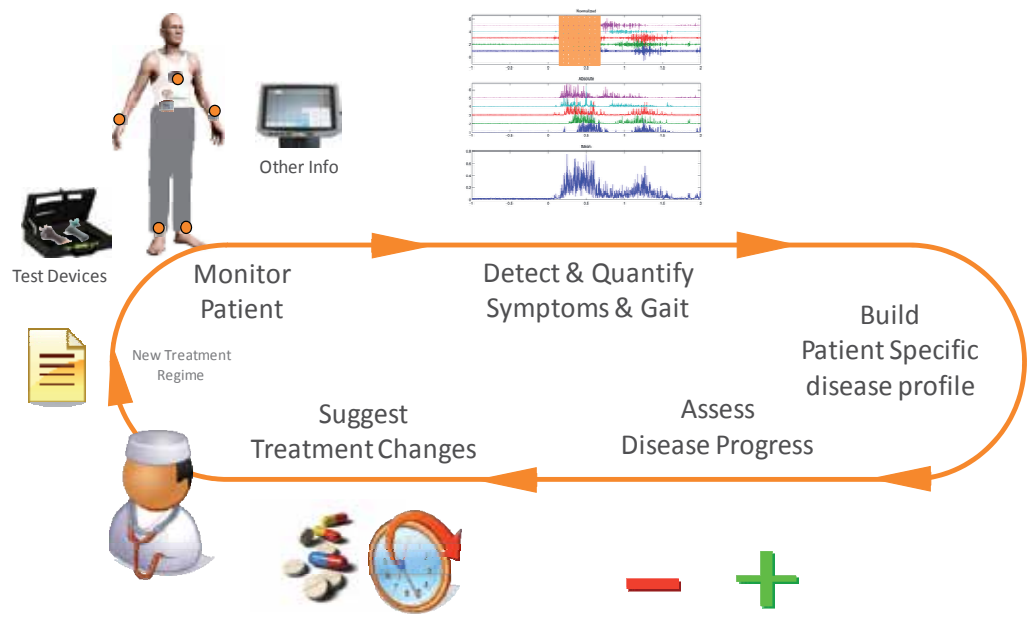


Fig. 9. PERFORM medical and technological vision

4.3 The PERFORM architecture

The system architecture proposed to meet the previously described medical and technological vision is presented in Fig. 10. It consists of two subsystems: the patient-side subsystem and the healthcare centre subsystem.

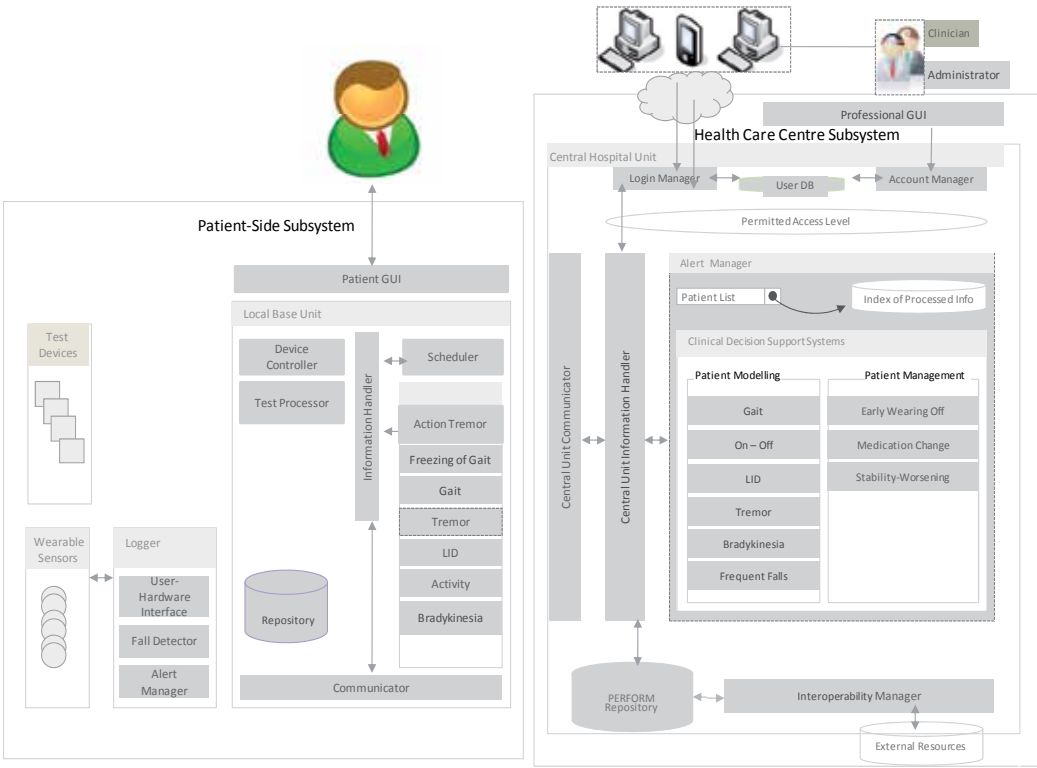


Fig. 10. PERFORM system architecture (R. Greenlaw et al., 2009)

The patient-side subsystem is responsible for the identification and quantification of the patient symptoms and the recording of other useful information for the evaluation of the patient status. The healthcare centre subsystem evaluates the disease progression and suggests appropriate treatment and changes, based on medical knowledge acquired from published medical guidelines.

The patient-side subsystem is composed by the following modules:

Continuous monitoring Module. It is used to monitor the patient motor status through the day. It consists of five accelerometers and a wearable device. The wearable device processes the recorded signals and detects patient falls in real time. The sensors position was hosen after careful examination and research on the targeted disease symptoms.

It is composed of four tri-axial accelerometers used to record the accelerations of the movements at each patient extremity, one accelerometer and gyroscope (on the trunk) used to record body/chest movement accelerations and angular body velocity during trunk and body turning, and a wearable device receiving all recorded signals. The sensors' position was chosen to allow all targeted symptoms detection and quantification with the minimum number of sensors.

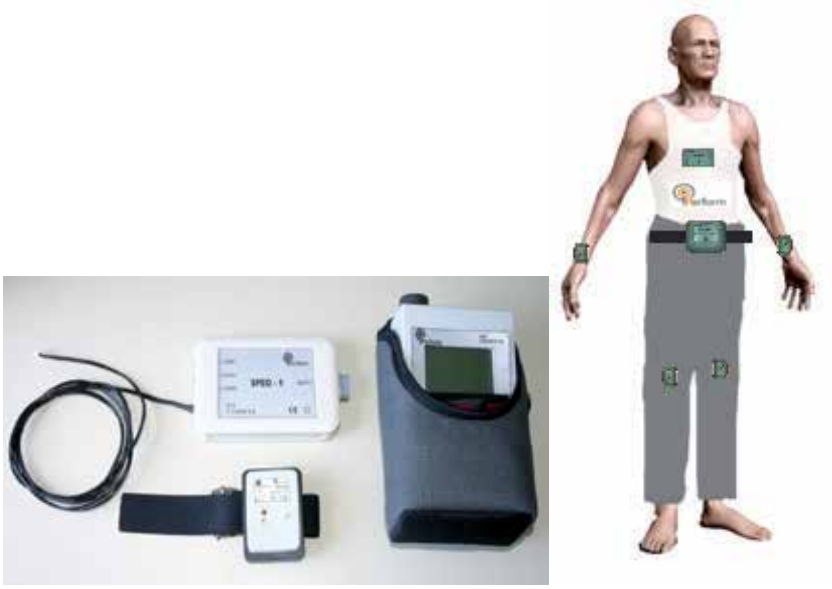


Fig. 11. PERFORM System prototype including accelerometers, gyroscope and data logger (left) System placement on the body (right)

All sensors transmit using Zigbee protocol to the wearable device which is located on the patients' waist thus making up a body sensor network. Special attention is given to the sensors usage and the easy set up by the patient and the caregivers. The sensor size is no bigger than a small matchbox. Sensors on the arms and legs are attached on specially designed elastic Velcro bands, which allow fixation to any wrist or ankle size. The sensors are placed inside an elastic pocket on the band, which secures it firmly on the patient body avoiding motion artefact due to cloth movement. The sensor on the trunk in placed within a zipped elastic pocket on a vest. The vest is also equipped with Velcro straps to firmly adjust the sensor on the patient chest. The selected design allows the easy wearing and attachment/detachment of sensors.

Test Module. It consists of a set of devices (such as virtual reality gloves, microphones or video cameras) used to record patient information, while the patient is performing specific tests, as normally done at the clinician's office during an examination. The patient wears the test devices and performs the tests as instructed from the visual interface of the Base Module (Local Base Unit). The test module records the performed activities and identifies any abnormalities, such as wrong sensor or patient position. Finally, it processes the recorded data and extracts the information about the number of taps and hand movements per second, the detection of hypophonia and neutral face expression.

Patient interface. Emphasis is given in designing an easy to use interface for the patient, considering the patient motor disabilities and limited computer familiarity. The designed interface inherits the feel and tough of the phone dialling pad, and all system choices are based on it. Patient use the interface to declare their subjective estimation of their own status, to gain access to relevant disease information, to receive instructions on life-style interventions, such as medication and good intake and on the execution of tests. Moreover, PD's patients declare medication intake information, which is useful for the patient status assessment.

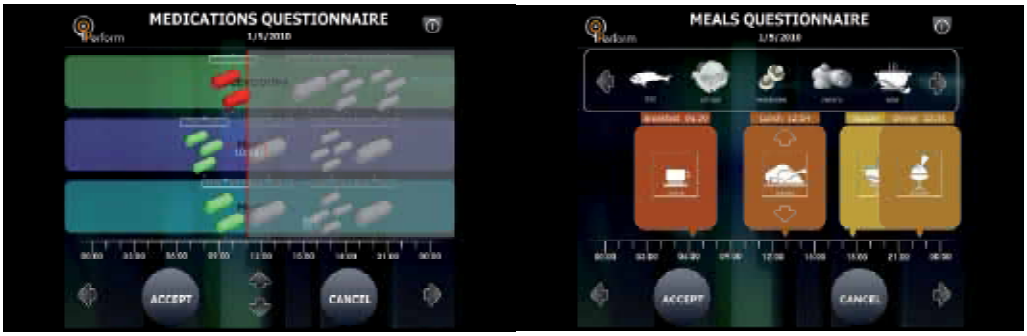


Fig. 12. PERFORM Patient Interface. Medication intake information (left). Food intake information (right)

Communication: the Base Module supports Bluetooth and Zigbee communication with the continuous monitoring system, and fixed line communication to the hospital centre over ISDN and xDSL.

Symptom Detection. This submodule processes received patient signals and detects the targeted patient symptoms (tremor, levodopa induced dyskinesia and off state). For each symptom dedicated submodule processes the relevant signals, detests the symptom episode and quantifies it into a severity scale from 1 to 4, according to the UPDRS scaling for PD patients (Cancela et al., 2010; Keijsers et al., 2000; Pansera et al., 2009). Other features such as duration, frequently and amplitude might also be provided for further clinician review and system evaluation.

The healthcare centre subsystem is composed of the following modules:

Patient Modelling Module. This module exploits the recorded patient information to build a patient symptom profile. For each main symptom (tremor, levodopa induced dyskinesia and on-off states), it produces a patient profile which describes the patient's common symptom features. When a new patient recording is processes, it is checked against the patient symptom profile. If significant differences are found, it might be due to two reasons: either a temporarily patient behaviour abnormality or a change to the patient profile. In the last case, the system checks whether a substantial number of similar situations are identified for the last time period for the specific patient and if that occurs, it creates an alert.

Patient Management Module. This module considers the detected symptoms and their characteristics, combines them with other recorded information and suggests appropriate treatment changes based on the accumulated specialists' knowledge on the management of PD.

Medical Interface: The system can be accessed either locally or remotely by the treating clinician and the general practitioner, using either a large screen access device (e.g. PC, laptop) or a small screen access device (e.g. PDA). Clinicians are directed to the home system screen, which presents the produced patient alerts to the patient specific screen, which provides the information needed to evaluate visually the patient condition. On request, the actual recorded signal and tests are downloaded from the patient-side to the healthcare centre for review. The focus is on the provision of an adequate visual description of the patient status within one screen, minimising the time spend by a clinician. Clinicians will access the system periodically to check patient status, but the option to be alerted when patient status changes are also available.

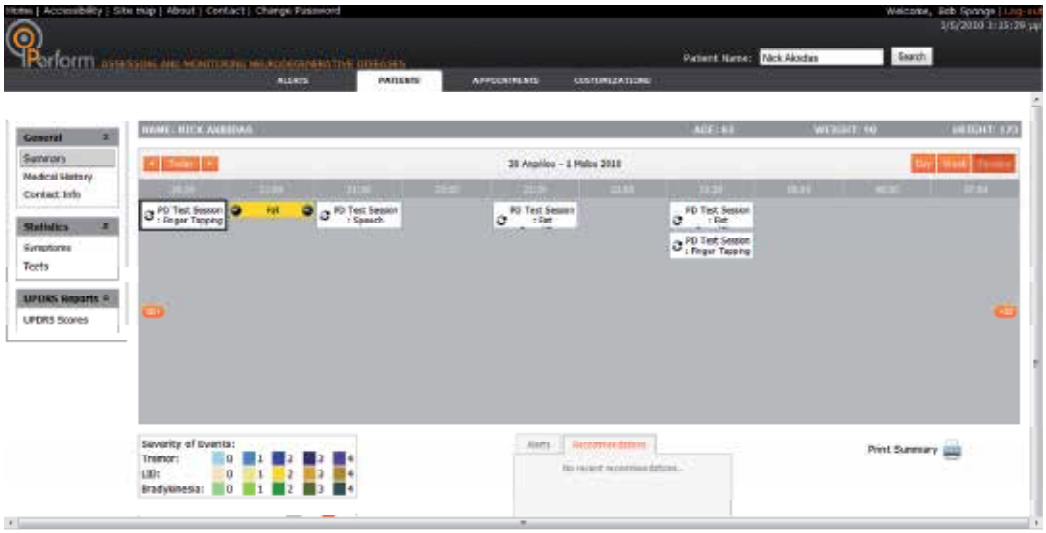


Fig. 13. PERFORM medical interface

Communication. All patient-side data (signal features and patient inserted information) are transmitted to the health-care subsystem once a day, through Internet.

4.4 Evaluation methodology

In order to test PERFORM system, several clinical trials have been arranged into 4 different phases, taking place between 2009 and 2011. Their description follows.

Phase 1: Data collection with SHIMMER

Eight subjects participated in this study, separated in two groups: four PD patients and four healthy subjects. The symptoms were rated by a professional neurologist with more than 20 years of experience with PD patients. Four accelerometers were placed on the right and left forearms and on the right and left calves, with a fifth accelerometer being placed on the trunk, at the base of the sternum. Motion data was collected using the SHIMMER platform (RealTime, 2011). SHIMMER is a small wireless sensor platform designed by Intel as a wearable device for health sensing applications. All sensors provide 3-axis accelerometer signals large storage, and low power-standards based communication capabilities. They also provide a Bluetooth protocol capability that allows SHIIMERs to stream the data to a computer. During the experiment, the accelerometry measurements were complemented by a reflective marker and a camera collection system. This complimentary analysis served as a support tool to validate the data used for this work.

Phase 2: Data Collection with ANCO first release trainer classifier

The data collection was performed with a network of wireless 3-axis ALA-6g sensors (Anco, 2011), located on the limbs, trunk and belt of the patient. During this phase, data were collected during tests with patients in a supervised environment, with the collaboration of the clinic's medical staff. Patients involved in this phase were required to be aged between 18 and 85 years old, suffering from PD, capable of complying with study requirements, receiving dopaminergic treatment and experiencing motor fluctuations. Dementia, Psychosis and significant systemic diseases (such as cancer) were the exclusion criteria

applied when selecting participants. The data set used in this study included trials with twenty PD patients, ten in Navarra (Spain) and ten in Ioannina (Greece). In order to comply with ethical requirements, all procedures were carried with the Clinic Institutional Review Board's permission. Data were collected following a standard clinical protocol in which patients carried out daily basic activities (i.e. walking, lying, sitting, etc.) during two cycles of on-off oscillations in response to levodopa during the same day and under the supervision of a clinician.

Phase 3: Long time recording

Data collection of phase 3 was performed with an updated version of the devices that includes a wearable and programmable logger that gave a better mobility to the patient and new ALA-6g accelerometers sensors equipped with an external battery allowing longer data collection session. Data were collected in a supervised environment and with the collaboration of the medical staff. Furthermore, patients involved in this phase, fulfilled with the age and medical specifications of the previous phase. The data were recorded with twenty-four PD patients, twelve in Navarra and twelve in Ioannina. Data were collected during a six-hour daily session in which patients carried out their normal daily activity. Moreover, four standard clinical protocol sessions were performed during two cycles of on-off oscillations in response to levodopa treatment and under the supervision of a clinician. At the end of the day, data were processed using the train set computed in the previous phase and the output were checked with the results provided by the clinicians

Phase 4: Final system testing

From March 2011, the integrated and final PERFORM system will be introduced to a new group of patients that will perform the final evaluation. The patient group will be constituted by 20 PD patients for regular tests and 4 PD patients for mid-term tests, all recruited from the Neurology Department from the Azienda Unita' Sanitaria Locale di Modena hospital in Modena, Italy.

4.5 Results

PERFORM project has released promising results in patients monitoring and status assessment. Due to the short-term nature of the clinic trials that have been carried out it is difficult to determine the future impact on patient treatment; however it is possible to at least provide a quantification of the performances of the modules of the Patient –Side Subsystem. It is designed to assess the motor status of the patients and establish a direct connection with the physician. Its basic functions are:

- to determine the activity of the subject
- to provide a quantification of symptoms severity based on the UPRDS scale and present such an information to the physician through remote communication
- to gather information about the daily life of the patient

The validation has proved that the first prototype of the Patient Side Subsystem is able to provide a very reasonable assessment of the daily activity of the patients using data classification techniques based on accelerometers. More specifically, the algorithms are able to discriminate activities such as walking, standing, laying or sitting with an accuracy of nearly 99%. The activity recognition is the base information needed to evaluate the symptoms related to movement. Besides, the clinical trials have proved that the algorithms are able to classify with an acceptable degree of accuracy the main symptoms of PD. General

body bradykinesia is quantified with a classification accuracy within the range of 70%-86% (depending on the number of sensors used in the measurements) compared to medical evaluation. Dyskinesia and tremor classification accuracy are respectively 93.6% and 97%. Those results are quite good in comparison with the subjective medical evaluation, with accuracy around 95%. The gait module has also proved to release useful information with acceptable level of accuracy. The gait analysis system provides a measure of stride length with a 7.3% of average error and a measurement of the complexity of movement through an analysis of the entropy of the walking.
Phase IV of the pilots is expected to provide a more accurate validation with long-term recording data.

4.6 Comparison with SoA systems

Compared to Kinesia system, a sophisticated multi-paRametric system FOR the continuous effective assessment and Monitoring of motor status in Parkinson's disease and other neurodegenerative diseases (PERFORM) presents the advantage of integrating other data from patient's monitoring, such as data from normal daily activity Kinesia monitors only upper extremity motor symptoms, while PERFORM is able to monitor the entire motor disorder, involving walking and moving in general, including freezing, falls risks, etc. The system is based on proprietary software and raw data may not be available.
In relation to Kinetisense commercial product, PERFORM links motion monitoring data to other information such as medication assumption, stress situations and historic data of the patient, in order to draw a complete picture and not only a snapshot such as Kinetisense does. The system is based on proprietary software and raw data may not be available. PERFORM integrates more data from continuous monitoring rather than on e-diary and voluntary motion exercises as the TEVAL Movistar system does.
Compared with SensorShoe system, PERFORM provides link to medication and enables complex data interpretation and analysis. On the other hand, PERFORM system is also able to detect abnormalities in motion, which the prototype built by the École Polytechnique Federale de Lausanne is not detecting.
In comparison with the system proposed by Boston university, PERFORM manages data from more devices and is able to correlate different data input.
Finally, in comparison with the project HELP, PERFORM is able to provide an assessment for specific symptoms such as dyskinesia, bradykinesia, tremor and akynesia, delivering a quantification based on the UPDRS scale, which HELP is not taking into consideration. On the other hand, the system is not providing a feedback to adjust the medication directly on the patients. In other word, PERFORM is not closing the loop of monitoring/assessment/medication adjustment in an automatic way, that is what HELP project has tried to do.

5. Conclusions

This chapter has presented a SoA review of the main methods used to monitor and assess PD's patients. On one hand, clinical assessment is usually performed through annotations in diaries and self-reports from the patient during the short office visit in this neurologist the patient may appear very well and he misses to report some symptoms, as a result, treatment modifications are not undertaken in time. The UPDRS is a scale that tries to quantify selected symptoms and signs of Parkinsonism in a 5-points scoring system (with 0 for no

signal and 4 for a marked severity of the sign). Unfortunately, the UPDRS like any other semi-objective rating scale has limitations like intra and inter observer inconsistencies, can be time consuming and ca be biased by subjectivity issues related to historical information.
On the other hand, technological solutions are able to provide quantitative objective information, including the use of motor sensors, electromyography, position transducers, and speech recognition systems.
This chapter has presented PERFORM, a project partially funded by the European Commission under the 7th Framework Program, aiming at providing an innovative and reliable tool that is able to monitor and evaluate motor neurodegenerative disease patients, such as PD patients.
The PERFORM project is based on the development of an intelligent closed loop system that seamlessly integrates a wide range of wearable micro-sensors, constantly monitoring several motor and signals of the patients. Data acquired are pre-processed by advanced knowledge processing methods, integrated by fusion algorithms to allow health professionals to remotely monitor the overall status of the patients and adjust medication schedules and personalize treatment. Personalization of treatment occurs through PERFORM's capability to keep track of the timing and doses of the medication and meals that the patient is taking.
The system architecture has been presented. A comparison with available related systems has been performed.
The system has already been tested in hospitals in Navarra (Spain) and Ioannina (Greece). The integrated tests of the system will be performed in Modena (Italy) from March 2011.
Obtained results so far suggest an overall valid closed loop system, able to detect PD symptoms based on motor signals and additional information, evaluate with a high accuracy level the overall status of the patient and propose medication changes accordingly. However, to achieve more improvements especially in the automation of close-loop mechanism, further improvements are needed in order to provide a complete reliable assessment system for symptoms severity.

6. Acknowledgment

The authors thank PERFORM project Consortium for their valuable contribution to this work, and especially Prof. José Antonio Martín Pereda, Prof. Francisco del Pozo and Prof. Ana González Marcos from the Universidad Politécnica de Madrid for their collaboration and scientific support. PERFORM project (Contract Nr. 215952) is partially funded by the European Commission under the 7th Framework Programme.

7. References

Anco. (2011). Retrieved March 2011, Available from http://www.anco.gr/

Cancela, J, Pansera, M, Arredondo, M T, Estrada, J J, Pastorino, M., Pastor-Sanz, L., (2010). A comprehensive motor symptom monitoring and management system: the bradykinesia case. *Conference proceedings of Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pp. 1008-11. 2010, August 31 – September 4.

Darkins, A. W., Fromkin, V. A., & Benson, D. F. (1988). A characterization of the prosodic loss in Parkinson's disease. *Brain and Language*, 34(2), 315-327. ISSN 0093-934X.

Das, R. (2010). A comparison of multiple classification methods for diagnosis of Parkinson disease. *Expert Systems with Applications*, 37(2), 1568-1572. ISSN 0957-4174 .

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schöfer, H. & Bötzel, K., (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine*, 355(9), 896-908. ISSN 0028-4793.

Dorsey, E., Deuel, L. M., Voss, T. S., Finnigan, K., George, B. P. & Eason, S., (2010). Increasing access to specialty care: A pilot, randomized controlled trial of telemedicine for Parkinson's disease. *Movement Disorders*, 25(11), 1652-1659. ISSN 0885-3185.

Fuente-Fernández, R. de la, Sossi, V., Huang, Z., Furtado, S., Lu, J.-Q. & Calne, D. B., (2004). Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: implications for dyskinesias. *Journal of neurology*, 127(Pt 12), pp. 2747-54. ISSN 1560-9545.

Giansanti, D., Maccioni, G., Cesinaro, S., Benvenuti, F., & Macellari, V. (2008). Assessment of fall-risk by means of a neural network based on parameters assessed by a wearable device during posturography. *Medical engineering & physics*, 30(3), pp. 367-372. ISSN: 1350-4533.

Giansanti, D., Maccioni, G., & Morelli, S. (2008). An Experience of Health Technology Assessment in New Models of Care for Subjects with Parkinson's Disease by Means of a New Wearable Device. *Telemedicine and e-health*, 14(5), 467-472. ISSN 1530-5627

Goetz, C. G., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G. T., Counsell, (2004). Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Movement Disorder*, 19(9), pp.1020-8. ISSN 0885-3185.

Greenlaw, R., Estrada, J., Pansera, M., Konitsiotis, S., Baga, D & Maziewski, P., (2009). PERFORM: Building and Mining Electronic Records of Neurological Patients Being Monitored in the Home. *Proceeding of World Congress on Medical Physics and Biomedical Engineering* (Vol. 25/9, pp. 533-535-535). Munich, Germany. September 7-12.

Group, P. S. (2001). Evaluation of dyskinesias in a pilot, randomized, placebo controlled trial or remacemide in advanced Parkinson disease. *Archives of Neurology*, 58, pp. 1660-1668. ISSN 0003-9942.

Help project (2011). Home Based Empowed Living for Parkinson Disease's Patients. Retrieved March 2011, from http://www.help-aal.com/HELP/

Jovanov, E., Raskovic, D., Price, J., Krishnamurthy, A., Chapman, J., & Moore, A. (2001). Patient monitoring using personal area networks of wireless intelligent sensors. *Biomedical Sciences Instrumentation*, 37, 373-378. ISSN 0067-8856.

Kauw-A-Tjoe, R. G., Thalen, J. P., Marin-Perianu, M., & Havinga, P. J. M. (2007). SensorShoe: Mobile Gait Analysis for Parkinson's Disease Patients. University of Innsbruck public document.

Keijsers, N L W, Horstink, M., Van Hilten, J. J., Hoff, J I, & Gielen, C. (2000). Detection and assessment of the severity of levodopa-induced dyskinesia in patients with Parkinson's disease by neural networks. *Movement Disorders*, 15(6), pp. 1104-1111. John Wiley & Sons. ISSN 0885-3185.

Keijsers, N L W, Horstink, M.W.I.M., & Gielen, S. C. A. M. (2003). Automatic assessment of levodopa-induced dyskinesias in daily life by neural networks. *Movement disorders*, 18(1), 70-80. ISSN 0885-3185.

Keijsers, N. L. W., Horstink, M. W. I. M., Hilten, J. J. van, Hoff, J. I., & Gielen, C. C. A. M. (2000). Detection and assessment of the severity of Levodopa-induced dyskinesia in patients with Parkinson's disease by neural networks. *Movement Disorders*, 15(6), 1104-1111. ISSN 0885-3185.

Kimura, F., Horio, K., Hagane, Y., Yu, W., Katoh, R., Katane, T., (2007). Detecting Perturbation Occurrence during Walking. *Conference proceeding of Towards sysnthesis of Micro-/Nano-systems: The 11th international conference on precision engineering (ICPE)*. Tokyo, Japan, 2007. August 16-18.

Lang, A.E., & Lozano, A.M. (1998). Parkinson's disease: First of two parts. *New England Jorunal of Medicine*, 339, 1044-1053. ISSN 0028-4793

Lau, L. M. L. de, & Breteler, M. M. B. (2006). Epidemiology of Parkinson's disease. *Lancet neurology*, 5(6), 525-35. ISSN 1474-4422.

Lees, A. J. (1989). The on-off phenomenon. Journal of Neurology, *Neurosurgery & Psychiatry*, 52(Suppl), 29. ISSN: 1359-5067.

Lim, A. S., Moro, E., Lozano, A M, Hamani, C., Dostrovsky, J. O., Hutchison, W. D., (2009). Selective enhancement of rapid eye movement sleep by deep brain stimulation of the human pons. *Annals of neurology*, 66(1), pp.110-114. ISSN 0364-5134.

Lingyun Gu, L., J.G, H., Shrivastav, R. M., & Sapienza, C. (2005). Disordered Speech Assessment Using Automatic Methods Based on Quantitative Measures. *EURASIP Journal on Applied Signal Processing*, 9 (pp.1400–1409).ISSN 1110-8657.

Lozano. (2009). Deep brain stimulation: current and future perspectives. *Neurosurgery Focus*, 27(1). ISSN 1092-0684

Mazzone, P., Lozano, A., Stanzione, P., Galati, S., Scarnati, E., Peppe, A., (2005). Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease. *Neuroreport*, 16(17), 1877. ISSN 0959-4965.

Pansera, Mario, Estrada, Juan Jacobo, Pastor, L., Cancela, Jorge, Greenlaw, Reynold, & Arredondo, Maria Teresa. (2009). Multi-parametric system for the continuous assessment and monitoring of motor status in Parkinson's disease: an entropy-based gait comparison. *Conference proceedings of Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2009, pp.1242-5. Minneapolis, USA. September 2-6.

Papapetropoulos, S., Heather, K., Scanlo, B. K., Guevara, A., Singer, C., & Levin, B. (2010). Objective Quantification of Neuromotor Symptoms in Parkinson's Disease: Implementation of a Portable, Computerized Measurement Tool. *Parkinson's Disease*, 010 (Article ID 760196), 6.

Patel, S, Buckley, T., Rednic, R., McClure, D., Shih, L., Tarsy, D., et al. (2010). A Web-Based System for Home Monitoring of Patients with Parkinson's Disease Using Wearable Sensors. *IEEE transactions on bio-medical engineering*, 58(3), 831-836. ISSN 0018-9294.

Patel, S, Lorincz, K, Hughes, R, Huggins, N, Growdon, J. H., Welsh, M, (2007). Analysis of feature space for monitoring persons with Parkinson's Disease with application to a wireless wearable sensor system. Engineering in Medicine and Biology Society,

2007. *Proceeding of EMBS 2007. 29th Annual International Conference of the IEEE* (pp. 6290-6293). Lyon, France, 2007. August 23-26.

Patel, Shyamal, Lorincz, Konrad, Hughes, Richard, Huggins, Nancy, Growdon, J., Standaert, D., (2009). Monitoring motor fluctuations in patients with Parkinson's disease using wearable sensors. *IEEE transactions on information technology in biomedicine*, 13(6), 864-73. ISSN 0018-9294.

Perform. (2008). *Perform Project*. Grant Agreement Nr. 215952.

RealTime. (2011). *Shimmer Research*. Retrieved March 2011, from http://www.shimmer-research.com/

Salarian, A., Russmann, H., Vingerhoets, F. J. G., Burkhard, P. R., & Aminian, K. (2007). Ambulatory monitoring of physical activities in patients with Parkinson's disease. *IEEE Transactions on Biomedical Engineering*, 54(12), pp. 2296-2299. ISSN 0018-9294.

Salarian, A., Russmann, H., Vingerhoets, F. J. G., Dehollain, C., Blanc, Y., Burkhard, P. R., (2004). Gait assessment in Parkinson's disease: toward an ambulatory system for long-term monitoring. *IEEE Transactions on Biomedical Engineering*, 51(8). ISSN 0018-9294.

Singh, N., Pillay, V., & Choonara, Y. E. (2007). Advances in the treatment of Parkinson's disease. *Progress in neurobiology*, 81(1),pp.29-44. ISSN 0301-0082.

Standaert, D. G., & Young, A. B. (2001). Treatment of CNS neurodegenerative diseases. In H. and Limbird (Ed.), *Goodman and Gilman's Pharmacological Basis of Therapeutics* (pp. 549-620). ISBN-10: 0071354697; New Your, Mc Graw-Hill.

Tindall, L. R., & Huebner, R. A. (2009). The Impact of an Application of Telerehabilitation Technology on Caregiver Burden. *International Journal of Telerehabilitation*, 1(1), 3-8.

Tolosa. (1998). *Parkinson's disease and movement disorders*. ISBN 0-7817-7881-6. Baltimore: Lippincott Williams & Wilkins Philadelphia.

Tsanas, A., Little, M. A., McSharry, P. E., & Ramig, L. O. (2010). Enhanced classical dysphonia measures and sparse regression for telemonitoring of Parkinson's disease progression. *Proceeding of Acoustics Speech and Signal Processing (ICASSP), 2010 IEEE International Conference on Biomedical Engineering* (pp. 594-597). Buenos Aires, Argentina, 2010. August 31 – September 4.

UB. (2011). Boston University National Institute of Biomedical Imaging and Bioengineering. Retrieved March 2011, from http://www.bu.edu/bme/

Vaillancourt, D. E., Sturman, M. M., Verhagen Metman, L., Bakay, R. A. E., & Corcos, D. M. (2003). Deep brain stimulation of the VIM thalamic nucleus modifies several features of essential tremor. *Neurology*, 61(7), pp.919-925. ISSN 0340-5354.

Van Someren, E. J. W., Van Gool, W. A., Vonk, B. F. M., Mirmiran, M., Speelman, J. D., Bosch, D. A., (1993). Ambulatory monitoring of tremor and other movements before and after thalamotomy: a new quantitative technique. *Journal of the neurological sciences*, 117(1-2),pp.16-23. ISSN 0022-510X.

Westin, J., Dougherty, M., Nyholm, D., & Groth, T. (2010). A home environment test battery for status assessment in patients with advanced Parkinson's disease. *Computer methods and programs in biomedicine*, 98(1), 27-35. ISSN 0169-2607.

Westin, J., Ghiamati, S., Memedi, M., Nyholm, D., Johansson, A., Dougherty, M., (2010). A new computer method for assessing drawing impairment in Parkinson's disease. *Journal of neuroscience methods*, 190(1), 143-148. ISSN 0165-0270.

WHO. (2002). Integrating prevention into health care. Retrieved 2011, from http://www.who.int/mediacentre/factsheets/fs172/en/index.html

15

An Investigation into the Impact of Parkinson's Disease upon Decision Making Ability and Driving Performance

Jessica Davies[1], Hoe Lee[1] and Torbjorn Falkmer[1,2,3,4]
[1]*School of Occupational Therapy and Social Work, Curtin Health Innovation Research Institute, Curtin University,*
[2]*School of Health Sciences, Jönköping University, Jönköping,*
[3]*Department of Rehabilitation Medicine, IKE, Faculty of Health Sciences Linköping University,*
[4]*School of Occupational Therapy, La Trobe University, Melbourne, VIC,*
[2,3]*Sweden*
[1,4]*Australia*

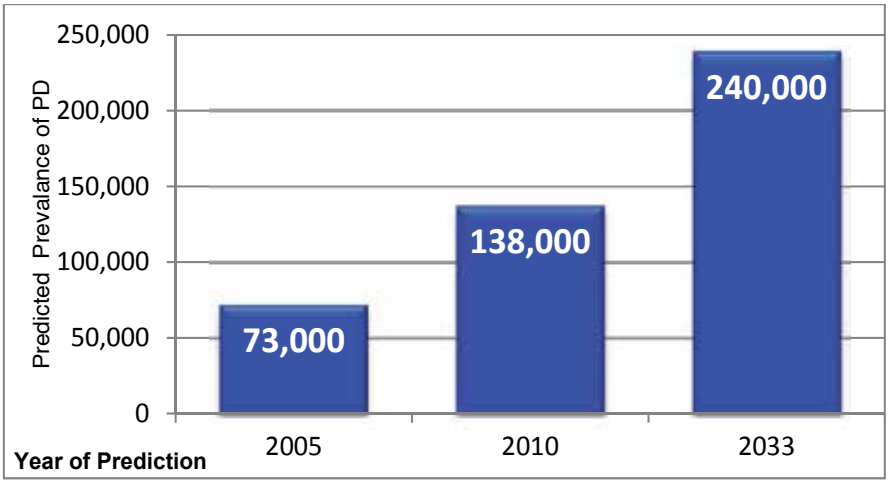
1. Introduction

PD is a severe neurodegenerative disease that can impair functional driving performance and increase the risk of accidents and fatalities on Australian roads (Austroads, 2000). In particular, cognitive symptoms of PD can have a substantial influence on driving performance due to the complicated and demanding nature of the task (Uitti, 2009). PD can affect the neural pathways that facilitate essential cognitive processes; such as attention, information processing speed, memory and risk assessment. These processes are all integral to the decision making process (Cools, et at., 2001). Previous research has highlighted that the ability to make accurate and timely decisions is essential for safe driving performance. However, this has not yet been researched in relation to people with PD (Devos, et al., 2007).

1.1 Prevalence and aetiology of Parkinson's disease

PD is the second most common neurological disease in Australia; causing impairments in motor control, cognitive functioning and sensation (Access Economics, 2010). PD usually affects people over the age of 50 years. However, the rate of disease progression and severity of symptoms can vary greatly between individuals (Australian Bureau of Statistics, 2004). Australia's aging population is expected to increase the prevalence rate of PD by 40% by 2033 (refer to Figure 1) (Access Economics, 2010).

Recent improvements in the medical and psychosocial treatment of PD has dramatically increased life expectancy, as people with PD now live approximately 12 to 20 years past diagnosis (Access Economics, 2010). PD is currently the sixth highest cause of disease-related driving cessation in Australia (Access Economics, 2010). People with PD generally stop driving at the age of 68; eight years earlier than the general population (Access Economics, 2010). Research into the impact of symptoms upon functional ability will enable



Adapted from: Access Economics, 2010

Fig. 1. Predicted prevalence of Parkinson's disease in Australia 2005-2033

the development of better screening tools and allow health professionals to differentiate between capable and unsafe drivers (Adler, et al., 2000). This may allow capable drivers with PD to retain their licences and current quality of life through active participation in occupations (Innes, et al., 2009). As the number of drivers with PD will rapidly increase due to the aging population, such an initiative will assist in improving road safety (Cordell, et al., 2008).

PD is caused by the progressive cellular death of dopaminergic neurons, predominantly in the basal ganglia in the brain (Arias-Carrión & Pöppel, 2007). Symptoms usually occur after the death of 70% of dopaminergic neurons; causing severe depletion of the neurotransmitter, dopamine (Jankovic, 2007). Dopamine has an extensive role in regulating movement, behaviour, mood and motivation; and may influence learning, time estimation, consequence prediction and awareness of the environment (Arias-Carrión & Pöppel, 2007). The cause of PD is unknown and as the disease cannot be detected prior to onset of symptoms, it is not currently possible to cure PD (Cools, et al., 2001). Severity of symptoms and rate of disease progression vary significantly between individuals. For example, some individuals may experience only minor symptoms 10 years after diagnosis, whilst other individuals may require full time high-support care within six months of being diagnosed with PD (Jankovic, 2007). It is not currently possible to predict how the disease will affect each individual's driving performance, and so assessment must be performed on a case-by-case basis (Jankovic, 2007).

1.2 Physical and cognitive symptoms of Parkinson's disease that affect driving

PD can cause a wide range of physical symptoms, which are known to affect driving ability. Common symptoms include motor tremors, bradykinesia, postural instability, rigidity, involuntary movements, generalised slowness and impaired balance (Adler, et al., 2000). People with PD can also experience alterations in sensation; including pain, burning, paresthesia and vestibular dysfunction (Jankovic, 2007). Driving is the most complicated activity of daily living, and even small mistakes can cause severe and potentially fatal crashes (Molnar, Marshall, & Man-Son-Hing, 2006). Driving requires numerous skills and

behaviours to be learnt, coordinated and continuously adapted in a constantly changing environment with time-based pressures (Elvik & Vaa, 2004). Driving therefore places extensive demands upon cognitive abilities, requiring high levels of vigilance, concentration, multitasking, complex reasoning and decision making even when driving over short and/or familiar distances (Devos, et al., 2007).

Physical symptoms of PD have been systematically researched in relation to driving performance. This has contributed to a comprehensive evidence base on the physical effects of PD symptoms upon driving performance (Cordell, et al., 2008; Jankovic, 2007). Drivers with PD have reduced strength and speed of movement, slower reaction times and a diminished ability to turn their head to check mirrors (Adler, et al., 2000; Heikkila, et al., 1997). Drivers with PD also have difficulty in negotiating roundabouts, turning across traffic, driving at high speeds and driving in urban environments (Cordell, et al., 2008; Radford, et al., 2004; Uc, et al., 2009). Drivers with PD are often aware of how their physical limitations influence their driving performance (Kulisevsky & Pagonabarraga, 2009). Consequently, many drivers with PD self-regulate their driving habits by avoiding potentially difficult or risky situations, such as not driving on the freeway, avoiding peak hour or having a co-pilot (Amick, et al., 2007). Factor and Weiner (2002) claimed that the main contributing factors to poor driving performance are PD-related deficits in cognition and visual processing as self-regulating behaviours are very effective in compensating for physical deficits. Uitti (2009) claimed that decline of visual sensitivity, motion perception and cognition are the largest contributing factors to unsafe driving. Further research is required to confirm these claims.

Research into the impact of cognitive symptoms upon driving ability is limited and contradictory. It is difficult to detect the presence of cognitive impairment in PD and to determine the relationship and severity of cognitive impairment on driving performance. The exact prevalence of cognitive impairment amongst drivers with PD is unknown. People with mild to moderate PD have scored significantly lower upon psychomotor and cognitive assessments, showing that PD affects cognition and psychomotor ability at all stages of the disease (Heikkila et al., 1997). However, routine cognitive assessments, such as the Mini Mental Status Examination have low sensitivity, preventing the accurate detection of cognitive deficits in people with PD (Kulisevsky & Pagonabarraga, 2009). Adler and colleagues (2000) stated that 25 to 40% of people in the later stage of PD experience cognitive impairment whilst Factor and Weiner (2002) recorded a lower prevalence rate of 20% amongst another cohort in a similar stage of the disease. Tröster and Woods (2007), however, claimed that cognitive impairment is more common with an earlier onset, occurring in one third of people with only mild to moderate PD.

It is known that the prevalence of cognitive impairment significantly increases with disease progression. However, the number of drivers with PD in Australia who have cognitive impairment is unknown (Amick, et al., 2007). Inability to accurately screen for cognitive impairment is of concern to road safety, since people who are affected may not be aware of it. If drivers with PD are not aware of the need to self regulate driving behaviour and/or compensate for performance alterations, the risk to road safety is increased (Amick, et al., 2007). Drivers may not seek medical advice and/or driving assessments may not be sought as needed, as the potential impacts upon driving performance are poorly understood (Betz & Fisher, 2009). Jones (2009) found that the most frequently self-identified cognitive areas affecting driving amongst people with PD were decision making, complex attention, visual search, impulse control, planning and divided attention. They also conducted a meta-

analysis, and found that these six areas have been associated with previous incidents of unsafe driving and traffic errors (Amick, et al., 2007; Innes, et al., 2009).
In a study of 150 people with PD, it was found that cognitive impairment had a significant impact upon the crash rate per miles driven, irrespective of the actual disease severity (Devos, et al., 2007). Other studies have found that drivers with PD have increased indecision at T-junctions and when changing lanes, as well as a slower information processing speed, reaction time and decision making speed (Heikkila, et al., 1997; Stolwyk, et al., 2006). The current study focuses primarily upon decision making ability, which has been identified as one of the most important contributing factors to safe driving.

1.3 Drivers with Parkinson's disease and road safety

In 2008, traffic collisions caused 1,402 preventable deaths in Australia (Australian Bureau of Statistics, 2008). Deaths and disabilities caused by traffic collisions result in extensive, long term, social and emotional costs to families, friends and communities (Elvik & Vaa, 2004). Traffic collisions have vast financial implications; including healthcare services, insurance premiums, property damage and clean up services (Australian Bureau of Statistics, 2008). Therefore, improving road safety through research is of high importance to save lives and prevent disabilities. Although the majority of traffic collisions are preventable, the number of collisions is actually predicted to increase substantially in the future. Escalating population density in cities, increased usage of vehicles and number of cars per household are resulting in Australian road networks becoming more complicated and demanding (Australian Bureau of Statistics, 2009). The fastest growing population of Australian drivers are aged over 70 years, as improvements in healthcare have enabled drivers, including those with PD, to retain their licences for longer (Australian Bureau of Statistics, 2004). The ageing population demographics, in combination with the increased complexity of road systems, mean that the risk of collision for drivers over 65 years is predicted to triple by 2030 (Australian Bureau of Statistics, 2004). This older population are also more likely to sustain serious injuries or death during collisions due to age-related deterioration of musculoskeletal and cardiovascular systems (Adler, et al., 2000).
Longer licence retention can be very beneficial in improving the quality of life of older Australians, since they are able to maintain independence, access to the community and preserve their self-efficacy (Radford, et al., 2004). However, older drivers must be able to compensate for their age-related deficits, since the increasing complexity of road systems place additional demands on cognitive, physical and sensory systems (Elvik & Vaa, 2004). Drivers with PD face further challenges as the PD symptoms as well as side effects of medication can interfere with driving performance. Research, both on-road and using driving simulators, has shown that drivers with PD commit more risky faults and driving offences, and have a significantly increased number of collisions per kilometre driven when compared to the average population (Devos, et al., 2007; Radford, et al., 2004). Despite the challenges faced by drivers with PD in continuing to drive, it is unethical to cancel their licences based upon diagnosis of the disease alone (Tröster & Woods, 2007). Many drivers with PD are able to overcome barriers using their extensive driving experience and knowledge of road systems or they can compensate for the declining ability through self-monitoring and self-regulation (Stolwyk, et al., 2006). For example, a person who becomes overwhelmed when driving at high speeds may change their route to avoid freeway driving (Tröster & Woods, 2007).

In Australia, like most of the developed countries, the guidelines regulating licence retainment and cancellation are based upon a system of subjective medical expert opinion (Adler, et al., 2000). There are no current national standards or requirements for how clinical driving assessments should be conducted (Innes, et al., 2009). Medical experts are often required to determine driving performance, even though the majority have not been trained in driving assessment, or actually observed their patient driving a car (Adler, et al., 2000). Specific clinical assessment batteries and criteria to renew or cancel driving licences have not been clearly defined in the Australian Assessing Fitness to Drive handbook; the combination of symptoms and/or the severity that could compromise driving ability are not defined (Cordell, et al., 2008). Therefore, the medical practitioner must make a subjective decision on the fitness to drive of their patients, even though they may not have been trained to do so (Cordell, et al., 2008). Most current methods of determining licence retainment or cancellation is through on-road driving tests and/or clinical psychometric assessments (National Road Transport Commission, 2003). On-road assessment is the gold standard. However, the process is costly and time consuming (Bedard, et al., 2010; Bryer, et al., 2006). A person who is unable to undergo a driving assessment as recommended by their medical professional is unlikely to be able to retain their licence (Anceaux, et al., 2008). The high assessment cost and need for drivers with PD to undergo annual driving reviews may contribute to the early cessation of driving (Access Economics, 2010).

The cheapest, most accessible and commonly used method for determining driving ability is through clinical assessment. Tools, such as the Timed Up and Go (measures ability to stand up, walk for 3 metres and return to the chair), Unified Parkinson's Scale and Mini Mental Status Examination (MMSE) are commonly used (Cordell, et al., 2008). However, the predictive validity of using these tools in driving assessment is frequently questioned in the literature (Anceaux, et al., 2008; Betz & Fisher, 2009; Cordell, et al., 2008; Stolwyk, et al., 2006). Radford, Lincoln and Lennox (2004) stated that an objective and reliable assessment tool to measure driving ability do not currently exist. Based upon an extensive literature review, Molnar, Marshall and Man-Son-Hing (2006) concluded that no office-based test had validated cut-off scores that correlated to on-road driving performance amongst people with dementia. Ernst and Paulus (2005) noted that it is difficult to assess risk-taking behaviours in an indoor, clinical setting without actually watching the person drive. In a double blind study using 20 people with PD and 20 age-matched controls; it was found that there was a 35% inconsistency in clinical assessment results conducted by a neurologist, compared to on-road driving assessment results provided by a driving instructor and occupational therapist (Heikkila, et al., 1997). Although these results need to be interpreted with caution due to the small sample size; it does highlight that assessment processes need to be improved. Moreover, the Heikkila el al study (1997) did suggest that visual memory, choice reaction time and information processing speed tests could potentially be used to assess fitness to drive; once more research is conducted to establish validity and reliability. Betz and Fisher (2009) suggested that further research into the detection of cognitive impairment and its potential implications for road safety is becoming more crucial in preventing fatal collisions as the population ages.

1.4 Impact of poor decision making ability of PD drivers on driving performance

PD-related cognitive deficits are believed to occur due the inefficient neurotransmission of dopamine-dependent neural connections between the basal ganglia and other areas of the brain (Tröster & Woods, 2007). The deprivation of dopamine, caused by the damage to the

basal ganglia, can directly affect the cognitive functions that are essential to decision making ability. These include; time estimation, working memory, executive function, compulsion, perseveration, attention, motivation and information processing speed (Cools, et al., 2001). Additionally, priority given to stimuli, error prediction, action planning, learning and interest in the environment are also affected (Ernst & Paulus, 2005). Furthermore, Nieoullon (2002) stated that the reduced amount of dopamine may interfere with a person's ability to perform an activity or behaviour, as well as alter a person's ability to adapt to environmental changes. Making decisions is a high-level cognitive function that involves the caudate nucleus and ventral striatum of the basal ganglia, as well as parts of the prefrontal cortex of the brain (Ernst & Paulus, 2005). The decision making process is reliant upon the neurotransmitter dopamine to transmit information via the mesocortical and mesolimbic pathways to the involved areas of the brain (Cools, et al., 2001). Due to the complexity of the decision making process, multiple high-level cerebral functions contribute to the ability to make a decision within a set period. These include attention, information processing speed and capacity, working memory, concentration, recall memory, planning, complex reasoning and risk assessment (Busemeyer & Stout, 2002; Kalis, et al., 2008). Fatigue, stress, emotions and medication can cause the speed and accuracy of decision making ability to fluctuate (Ernst & Paulus, 2005).

The Decision Making Process Model (see Figure 2) defines three important stages to making a decision: Option Generation, Option Selection and Action Initiation (Kalis, et al., 2008). PD can affect all of the components of decision making, although the severity of deficits vary from person to person (Stolwyk, et al., 2006; Tröster & Woods, 2007). This model has been employed in research to study PD in numerous activities other than driving (Levy & Dubois, 2006). Firstly, in Option Generation the person considers the requirements of the situation and thinks of possible courses of action. Then during the Option Selection stage, the person analyses each potential course of action for probable outcomes. Factors that can influence the selection of one course of action over the alternatives include: probability of the benefits and/or risks, the person's previous experiences, emotional state, values and preferences for one course of action (Ernst & Paulus, 2005). Finally, in Action Initiation, the decision is implemented through physical actions (Kalis, et al., 2008). The person then evaluates the results of the decision to promote learning for future situations. According to Busemeyer and Stout (2002), poor decisions can be due to a failure to anticipate consequences, poor perceptual sensitivity, problems in memory storage or retrieval, inability to determine possible courses of action, fatigue, poor concentration, difficulty in learning from mistakes, and/or impulsivity.

Decision making deficits have been recognised as a key area that could influence driving competence and safety amongst people with PD (Cools, et al., 2001). Dopamine has an important role in facilitating the cognitive processes that enable a person to make a decision. However, what this functionally entails for driving is poorly understood (Arias-Carrión & Pöppel, 2007; Cools, et al., 2001). Deficits in decision making are most apparent during activities, such as driving, that require spontaneous, complex information processing and reasoning within time constraints (Tröster & Woods, 2007). The driver may have to make multiple decisions in quick succession, which place extensive demands upon cognitive processes. The driver must quickly consider all components of the situation, generate and consider options, implement the choice, evaluate the result and then start the decision making process again (Busemeyer & Stout, 2002). The driver may also have to ignore multiple distracting auditory, visual and tactile stimuli from the car's radio, air

conditioning, passengers and the visual environment (Ernst & Paulus, 2005). Medication, fatigue, other PD symptoms, co-morbid conditions and environmental distractions can also intensify the deficits experienced by drivers with PD (Tröster & Woods, 2007).

(Adapted from: Kalis, et al., 2008; Lefy & Dubois, 2006)

Fig. 2. Summary of the decision making process in driving

Decisions can be made either through conscious deliberation, for example, deciding if a parking space is large enough for the car, or through an unconscious process using previously learned behavioural patterns; for instance, automatically using the indicator when leaving a roundabout (Ernst & Paulus, 2005). PD can cause deficits in decision making ability at any of the decision making stages, and the resultant hesitancy, ambivalence or apathy may significantly impact upon road safety for the driver and other road users (Kalis, et al., 2008). As shown in Figure 2, if a driver is indecisive about whether to stop, slow down or to proceed through a roundabout, they could increase the risk of collision due to either incorrect use of signals, inappropriate speed or lane placement, sudden braking without checking review mirrors and/or impulsively increasing speed. All of these actions can directly result in a collision, especially as the other drivers may not be able to anticipate the indecisive driver's actions and react in time.

Numerous studies have identified that hesitancy and indecision contribute to a higher risk of crashing. However, the extent of the contribution is unknown (Bryer, Rapport, & Hanks, 2006; Stolwyk, et al., 2006). Drivers with PD frequently have a lack of cognitive flexibility and difficulty in shifting attention and multi-tasking, particularly when in stressful situations (Arias-Carrión & Pöppel, 2007). Drivers with PD often drive at slower speeds, have reduced reaction times and can fail to notice specific landmarks and traffic signs (Stolwyk, et al., 2006; Uc, et al., 2009). A study that surveyed 5,210 drivers with PD found that cognitive deficits are strongly associated with dangerous driving, with the most common causes of collision being indeciveness at T junctions and reduced usage of mirrors (Meindorfner, et al., 2005). A review of 42 driving studies concluded that the effect of a disease upon driving performance is difficult to determine due to numerous confounding factors. It is not currently possible to conduct an extensive randomised controlled trial into

this area, since there is not yet enough information available to control all confounding variables (Elvik & Vaa, 2004). Therefore, the study reported in this chapter was valuable in trialling alternative assessment methodologies and making recommendations for future research projects. Information from the study may also contribute to the development of a successful assessment protocol for drivers with PD to improve road safety.

2. Methodology

2.1 Purpose of study

The aim of the research was to explore the impact of impaired decision making ability upon the driving performance of people with PD. To address the aim, a quantitative, pre-post case-control study design was employed to assess participants the decision making ability of drivers with PD and healthy controls, as well as their driving performance under time pressure, were examined. The objectives of the study are: **Objective 1:** To assess the decision making ability of drivers with PD using standardised psychometric assessment tools and the E-prime computer based assessment; **Objective 2:** To investigate the relationship between the decision making ability and driving performance of people with PD; and **Objective 3:** To compare the driving performance of people with PD to the healthy control group whilst driving under a time pressure in the driving simulator.

The first objective was addressed by administering an assessment battery of clinical psychometric tests to assess the main cognitive processes that contribute to decision making ability. The assumption was that drivers with PD would have lower scores on the psychometric assessments, due to PD-related cognitive impairments, when compared with the healthy control group. The second objective was addressed by assessing the driving performance of the groups on the driving simulator. The assumption was that drivers with PD would have poorer driving performance at baseline driving (Trial One) as well as driving under time pressure (Trial Two) when compared to the healthy control group. The third objective was addressed by analysing the results from stage one and two to determine if there is a correlation between driving performance and decision making ability. The assumption was that the ability of people with PD to make correct decisions whilst driving under time pressure would be significantly lower than the control group. Ethical approval was granted by the Curtin University Human Research Ethics. Data was collected from Sept 2009 until March 2010 at the Curtin University Driving Rehabilitation Clinic.

2.2 Participants

Convenience sampling was used to recruit participants by displaying advertisement posters at community centres, retirement villages, shopping centres and neurologists' offices. Advertisements were also placed in community newsletters, as well as the Western Australia Parkinson's Association newsletter. Study participants were required to be community living adults, aged 50 to 80 years old with a valid driving licence. They had to be current drivers, driving at least half an hour each week. To ensure adequate binocular acuity, a score of at least 6/12 corrected vision on the Snellen Acuity Chart was required. In the experimental group, each participant's diagnosis of PD had to have been confirmed by a general practitioner or neurologist. Participants were excluded from the study if they had severe hearing impairments or inadequate comprehension of written or verbal English as judged by the researcher, or any co-morbid diagnosis that may interfere with driving ability. Participants with the following conditions were excluded from the study: dementia, severe

cognitive or physical impairment, depression and/or psychiatric conditions. Participants were withdrawn from the study immediately if they requested to do so. A reason for withdrawal was not required. Fifteen drivers with PD and 17 control group participants were recruited were contacted by phone to establish suitability to participate in the study.
To address Study Objectives 2 and 3, baseline-driving performance was established in Trial 1 and then a time constraint was imposed to create pressure upon the participants. In Trial 2, all participants were told to complete the same driving scenario 20% faster than in Trial 1. The percentage of reduction in time was based upon pilot study data. A 20% reduction represented a time that was perceived by the participants as being challenging, yet achievable within the driving assessment parameters. This time pressure forced the participants to make quicker decisions in response to the traffic conditions, without compromising on safety or breaking the road rules. Drivers with PD are more likely to experience decision making deficits whilst making complex decisions under pressure (Amick, et al., 2007). The study assumption is that drivers with PD are capable of making correct decisions; however, they require more time to do so. Important driving behaviours, such as appropriate signalling, use of mirrors and obeying the speed limit potentially could have been affected and/or forgotten as the participants concentrated upon negotiating the scenario faster. The driving performance of participants was measured using Driving Performance Score. A battery of psychometric assessment tools were administered to the participants to assess the cognitive processes that are essential to decision making ability. The cognitive processes included executive function, task switching, sustained, selected and divided attention, attention set shifting, memory, efficiency and accuracy of information processing systems, visual attention and decision making speed and accuracy. All psychometric assessment tools were time based, standardised instruments that measured speed and accuracy of response. The study assumption was that drivers with PD are capable of completing the assessments; however, they will require more time to do so. The confounding variables in the study are presented in Table 1 in next page. Measures have been taken to ensure that the data collected was valid.

2.3 Equipment used in the study

The following section describes the tools used for initial screening of participants, and psychometric assessments for measuring the main components of decision making in driving.

2.3.1 Initial screening of participant medical and driving history

Standardised clinical assessment tools and a Medical History and Driving History Checklist were used to screen for potentially confounding factors (refer to Table 2 and Table 3 for details of assessments). All assessments were administered in a quiet, distraction free room as per the instruction manuals to ensure the reliability of data. The research assistant was trained in administering these assessments prior to commencement of the data collection.

2.3.2 Psychometric assessment

Decision making ability cannot be directly measured. Instead, the main contributing components were all assessed using a battery of psychometric assessments. These components were attention set shifting, visual attention, memory, information processing speed and decision-making speed and accuracy (refer to Table 3). The psychometric

Variable	Potential Impact	Measures taken to improve validity
Medication	- Side effects of medication could affect functional performance. (Radford, et al., 2004).	- Drivers with PD were assessed during periods of optimal function, to ensure that motor and non-motor fluctuations in performance did not affect results (Radford, et al., 2004).
Co Morbid Conditions	- Symptoms and medications for co-morbid conditions could alter functional performance (Radford et al., 2004).	- People with co morbid medical conditions that could affect driving performance were excluded from the study. Refer to Exclusion Criteria and the Screening procedure.
Fatigue	- Fatigue may affect driving performance especially as participants are older (Radford, et al., 2004).	- Assessment periods were held during mid morning and early afternoon and frequent rest breaks with refreshments were offered.
Driving Experience	- People who have been driving either longer or more frequently are likely to be better drivers (Bedard, et al., 2010).	- The Driving History Checklist was used to seek a fair distribution of driving experience across groups. All drivers must have driven at least one half hour a week to ensure the maintenance of skills.
Gender	- Men have a greater risk of having a fatal crash (Adler, et al., 2005).	- A fair distribution of gender between groups was sought. Statistical analysis identified the gender-related difference in performance.
Age	Driving performance usually decreases after the age of 60 years (Adler, et al., 2000)	- A fair distribution of ages between groups was sought. Statistical analysis identified the age-related difference in performance.

Table 1. Confounding variables of the study

assessment battery comprised of the Symbol Digit Modalities Test (Smith, 2007), Digit Vigilance Test (Kelland & Lewis, 1996), Purdue Pegboard (Lafayette Instrument Company, 1985) and Trail Making Test – B (Corrigan & Hinkeldey, 1987).

The assessments were chosen based upon recommendations from literature to ensure high reliability, sensitivity, and/or validity of each test in assessing driving performance. For example, the Trail Making Test-B, Symbol Digit Modalities Test and Digit Vigilance are highly sensitive to detecting differences in cognitive performance (Smith, 2007). The Trail Making Test-B is one of the most frequently used tests in driving research and clinical settings, due to its high reliability and sensitivity to mild cognitive impairment (Arbuthnott & Frank, 2000; Ashendorf et al., 2008). The Symbol Digit Modalities Test was found in a study of 150 people to be the most reliable of 12 assessment tools in detecting mild cognitive impairment (Ashendorf, et al., 2008).

Screening Tool	Purpose of Assessment Tool	Administration and justification for Use
Medical Checklist	- To gather demographic medical information and screen for excluding factors.	- Based on medical screening assessments according to Australian Driving regulations (National Road Transport Commission, 2003).
Driving History Checklist	- To gather demographic driving information and screen for excluding factors.	- Based on current Driving History assessments at the Independent Living Centre and Australian driving regulations (NRTC, 2003).
Snellen Acuity Chart	- A standardised measure frequently used in driving assessment to screen for binocular acuity deficits (Lotfipour, et al., 2010)	- Adequate binocular vision was assumed based upon the ability to read a series of letters on a chart placed 6 metres away. Minimum standard for on road driving is 6/12 corrected vision (NR TC, 2003).
Cognistat (Kiernan, Mueller, Langston, & Van Dyke, 1987)	- Brief screening tool to detect cognitive impairment Subtests of attention, constructional ability, memory, calculations, reasoning and judgement were administered.	- Economical and efficient clinical screening tool that has high sensitivity to cognitive impairment (Adler, et al., 2000)

Table 2. Outline of Screening Tools

2.3.3 E-Prime computer based tool

The E-Prime software has been used in 104 research studies since 2001; including research projects into simulated situations, older adults and neurological conditions (Psychology Software Tools, 2010). The E-Prime software is capable of millisecond precision and is frequently used in research to increase the accuracy and reliability of data (Ranzini, et al., 2009). In the present study, the E-Prime computer program was set up to measure the speed and accuracy of the participants' decision making ability by administering a series of multiple choice questions (refer to Figure 3). The questions were based upon traffic situations in which drivers with PD are known to experience difficulty; such as roundabouts, traffic lights, freeway driving, city driving, over taking and right hand turns (Allen, et al., 2003; Anceaux, et al., 2008; Lee, et al., 2003). It took approximately 10 minutes to complete.

The "red", "yellow" and "green" button system (refer to Figure 3) had buttons that were large, visually distinguishable, and highly sensitive to touch, to enable people, who experienced PD-related physical symptoms to enter their decision as quickly as possible. The computer was placed in front of a blank, white wall and the researcher sat behind the participant, out of sight to prevent potential distractions. The questions were displayed in large, white writing on a black backdrop to improve readability. A black instruction screen was displayed to inform participants about how to answer the following question (refer to Figure 4).

Psychometric Tool	Purpose and Administration	Literature support for tool validity
Trail Making Test B (TMT-B) (Corrigan & Hinkeldey, 1987)	- To assess executive function, visual attention and task switching (Corrigan & Hinkeldey, 1987). Participants join alternating dots of letters and numbers (1, A, 2, B etc.).	- TMT-B is suggested for older driver assessment as a score of over 180 seconds could indicate increased driving risk (Betz & Fisher, 2009). Moderate predictive ability for increased crash risk (Bedard, et al., 2010).
Purdue Peg Board (Lafayette Instrument Company, 1985)	- To assess bilateral gross motor movements and dexterity of the fingers, hands and arms to distinguish between the influence of physical and cognitive PD-symptoms on results.	- Range of norms for people over 65 years available. High test-retest reliability (0.82 to 0.91), moderate sensitivity and moderate predictive ability for driving (Wood, et al., 2005). Suggested for assessing impact of neurological disease upon motor function (Wood, et al., 2005).
Digit Vigilance Test (Kelland & Lewis, 1996)	- To assess sustained, selected and divided attention, and information processing speed and accuracy. Participants scan rows of single digit numbers and circle all of the number sixes.	- High test-retest reliability and has been validated as a measure of sustained attention (Kelland & Lewis, 1996). Determines if participants were able to remember and attend to important information whilst disregarding excess stimuli (Radford, et al., 2004).
Symbol Digit Modalities Test (Smith, 2007)	- To measure the efficiency and accuracy of information processing systems. Participants had to convert geometric shapes into numbers as quickly as possible.	- Substitution tasks are highly sensitive to detecting cerebral dysfunction (Wood, et al., 2005). Norms provided for age and education levels. High test-retest reliability (0.80). Moderate predictive ability for driving ability (Wood, et al., 2005)
E-Prime Computer Based Assessment (Psychology Software Tools, 2010)	To assess decision making accuracy and response time - Multiple-choice questions based upon photographs of different driving scenarios.	- Software is capable of capturing the responses of participants with millisecond precision (Ranzini, et al., 2009). Standardised video instructions used for to improve inter-rater and intra-rater reliability.

Table 3. Outline of the Psychometric Assessment Tools

Fig. 3. The setup of the E-Prime Assessment tool

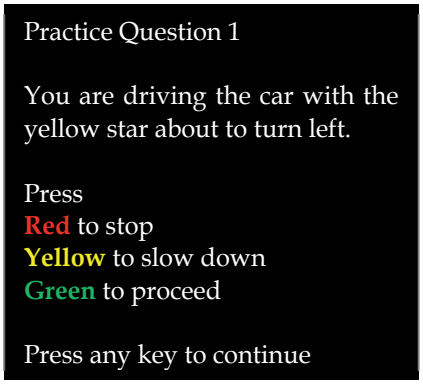


Fig. 4. E-Prime Instruction Screen

Fig. 5. The E-Prime Assessment Tool; displaying an example of a question

In each photograph there was a car labelled with a bright yellow star (refer to Figure 5). Participants were instructed to assume that he or she was the driver of the car with the yellow star and give the most appropriate response for each scenario. The participant had to decide whether they would 'stop', 'slow down' or 'proceed' based upon their interpretation of the hazards as shown in the photograph. Participants responded using one of the three

buttons. The accuracy of answers and response time was automatically recorded by the E-Prime software to determine decision making ability.

2.3.4 Driving simulator in curtin driving rehabilitation clinic

A fixed-base, Systems Technology Incorporated (STI) driving simulator was used to assess driving performance in this study (Lee, et al., 2003). Driving simulators are frequently used in research and clinical practice to assess driving ability, since risk of injury and property damage is eliminated (Bedard, et al., 2010). The STISIM driving simulator enables the development of highly controlled and regulated traffic scenarios (Allen, et al., 2003). The STISIM simulator technology has been used in 61 different studies, whilst the STISIM simulator driving technology in particular has been used in at least 24 studies in the past eight years (Systems Techonology Inc, 2010). Low cost, fixed base driving simulators have been used in research on older drivers and on the effect of fatigue, drugs, cognitive impairment, Alzheimer's disease, PD, traumatic brain injury and numerous other conditions upon driving performance (Bedard, et al., 2010; Lee, et al., 2003). Driving simulators are becoming more affordable options; especially as on-road assessment costs are becoming more prohibitive due to the increasing fuel, car purchase and maintenance costs and higher insurance premiums (Bedard, et al., 2010).

Fig. 6. The Curtin University STISIM Driving Simulator

Simulators are capable of distinguishing between safe and unsafe drivers (De Winter, et al., 2008; Lee, et al., 2003). Numerous studies have found high transferability of simulator-based behaviours to on-road driving behaviours (De Winter, et al., 2008; Lee, et al., 2003). Factor and Weiner (2002) found that driving simulators have a greater accuracy in predicting driving ability than the clinical psychometric assessments currently used by medical practitioners. High inter-rater and intra-rater reliability (correlation coefficients were 0.87 and 0.83 respectively) were recently established by Bedard and colleagues (2010). They used the simulator-recorded data and data manually recorded by a laboratory assistant in a similar STISIM simulator. The validity of the driving simulator used in this study has been established for assessing older adults (Lee, et al., 2003). A photograph of a participant being assessed on the Curtin University STISIM Driving Simulator is shown in Fig. 6.

2.3.5 Development of the STISIM driving scenario

Two driving scenarios were specially designed for the present study. They were based upon the Western Australian licensing standards, in combination with recommendations from

driving simulator literature (Allen, et al., 2003; Factor & Weiner, 2002; Lee, et al., 2003; National Road Transport Commission, 2003). In the present study, the roadway geometry and intersections, position of traffic signals and markings, weather conditions, the responsiveness of vehicle controls, location of other vehicles and road users were all programmed to target decision making ability. The scenarios included small town, city and country driving, simple and complex intersections, curved roads, simulated emergency braking, varied speed control and visually obscured intersections. Auditory instructions were included in the simulator programming to ensure that all of the information and instructions were consistent throughout data collection.

To investigate the impact of PD-related decision making deficits upon driving performance, the scenario in this study was designed to specially assess hazard detection, risk assessment, impulsiveness and decision making ability (Bedard, et al., 2010; Elvik & Vaa, 2004). Traffic situations that are known to be affected by PD, such as driving at high speeds, turning corners, overtaking, merging and complex city intersections were included (Stolwyk, et al., 2006; Radford, et al., 2006). For example, during the scenario, a recorded verbal instruction told each participant to overtake three slow moving trucks whilst avoiding oncoming traffic. A similar process was used in a study by Amick et al., (2007) as they researched cognitive indicators of poor driving performance of drivers with PD. Driving Performance Assessment Guidelines was tabulated in Table 4.

2.4 Data analysis

Data was analysed using the Statistical Package for Social Sciences (SPSS) (SPSS Inc. 2009). Demographic information of participants was presented using descriptive statistics. The difference in total run time and driving performance score between groups was analysed using t-tests; whereas a Chi squared test and Fisher's Exact test was used to analyse ordinal variables, such as gender and number of collisions and infringements. A stepwise Multiple Linear Regression Model was used to analyse the driving performance and E-Prime scores; the driving performance score was the dependent variable and E-Prime (correct answers, time taken and participant group) were the independent variables. The psychometric assessments and the components of the Driving Performance Score were analysed using the non-parametric Wilcoxon 2-sample test. A repeated measure regression analysis was performed using the driving score as a dependent variable and the results of the psychometric assessments, simulator trial run number and group identifier (drivers with PD or control group) as independent variables. The least significant variables were then removed, one at a time, until the p-value associated with each of the remaining variables was less than 0.05. Prior to the analysis, normality of data and the assumptions of the statistical tests were checked to ensure that there were no violations.

3. Study results

3.1 Participant demographics

Seventeen people in the control group and 11 drivers with PD were assessed and their demographic data was tabulated in Table 5. In exploring the characteristics of the participants, it was identified that the number of years of driving experience was different between the comparison groups ($p=0.042$). The drivers with PD group had driven on average 7 years and 8 months longer than the control group. The participants' age, gender, employment status and education level were found to be not significantly different between groups.

Assessment Component	Definition of Required Behaviour/Skill	Assessment Frequency and Scoring Procedure
Frequency of Appropriate Use of Mirrors	- Driver checked left and right mirrors immediately before slowing down, turning or diverging.	- Assessed at 25 locations/events. One point deducted for each omission per mirror
Smooth Manoeuvring around Obstacles	- Driver smoothly manoeuvres around obstacles and maintains a safety buffer around vehicle.	- Assessed at nine locations/events. Up to three points deducted depending on severity of error
Frequency of Appropriate Stopping Distance	- Driver stops at an appropriate distance from traffic lights, stop signs and obstacles.	- Assessed at 20 locations/events. Up to four points deducted depending on severity of error
Maintains Appropriate Vehicle Speed	- Driver maintained vehicle within 9kms of the appropriate speed limit.	- Assessed at 23 locations. Points deducted for excess speed as per national guidelines.
Maintains Correct Lane Position	- Driver stays within the lane markers or to the left on unmarked roads.	- Number of deviations recorded by stimulator. One point deducted for each instance.
Maintains Control of Vehicle on Turns	- Driver kept vehicle stable and adjusted speed as required around turns and on winding roads	- Number of deviations recorded by simulator. One point deducted for each time.
Appropriate Behaviours to Avoid Hazards	- Driver had sufficient room to react, was alert and aware of environment and in control of vehicle	- Number of sudden braking incidents recorded by stimulator. One point deducted for each omission
Appropriate Use of Indicators	- Driver appropriately used indicators to give warning about future diverging movements.	- Assessed at 22 locations/tasks. One point deducted for each omission.
Demonstrates Caution during Manoeuvres	- Driver did not overtake when unsafe, allowed adequate room and stopped at yellow traffic lights.	- Assessed at 27 locations/tasks. Up to three points deducted depending on severity of error
Qualitative Feedback (Bedard, et al., 2010; Elvik & Vaa, 2004)	- Participants comments were recorded verbatim. Clinical observations regarding participant's affect were recorded.	- Information gathered to compliment quantitative data. No points were deducted for clinical observations and feedback

(Bedard, et al., 2010; Bryer, et al., 2006; Elvik & Vaa, 2004; National Road Transport Commission, 2003).

Table 4. Driving Performance Assessment Guidelines

Variable	Drivers with PD n=11 Mean (SD)	Control n=17 Mean (SD)	p-value
Age	68.2 (5.3)	65.6 (8.8)	0.427#
Gender			
– Female	6 (55%)ˇ	7 (41%)ˇ	0.489^
Weekly hours driving			
– Minimum	8.0 (8.5)	13.7 (9.9)	0.162#
– Maximum	9 (8.6)	14.7 (11.3)	0.204#
Years of Driving Experience	50.6 (5.5)	42.9 (9.2)	0.042*
Number of Collisions in last 2 years	0	3 (28%)	0.526+
Number of Infringements in last 2 years	0	2 (12%)	0.515+
Education Level			-
– Tertiary Study	4 (36%)ˇ	8 (47%)ˇ	-
– Year 12 High School	4 (36%)ˇ	6 (35%)ˇ	-
– No answer	3 (28%)ˇ	3 (18%)ˇ	
Disease Symptoms			-
– Tremors in legs	3 (28%)ˇ	-	-
– Tremors in arms	7 (63%)ˇ	-	-
– Mild Rigidity	4 (36%)ˇ	-	-
– Moderate Rigidity	4 (36%)ˇ	-	-
– Severe Rigidity	0	-	-
– Mild Fatigue	2 (18%)ˇ	3 (18%)ˇ	-
– Moderate Fatigue	7 (63%)ˇ	3 (18%)ˇ	-
– Severe Fatigue	0	0	

^ Chi squared test; # T-test; + Fisher's Exact test; *Results were statistically significant ($p<0.05$) and ˇ Categorical frequency (percentage)

Table 5. Results of Participant Demographic Data

The drivers with PD had on average a diagnosis of PD for approximately 8 years and 4 months. Medications that were prescribed to the participants with PD included: Sinemet, Madopar, Cabaser, Sifrol and Selgene. Some participants with PD reported experiencing tremors in arms and legs as well as mild to moderate rigidity and fatigue (refer to Table 5). Six of the control participants reported experiencing mild to moderate fatigue, which was not related to PD. All participants with PD reported they required only minimal assistance to complete self-care activities, whilst none of the participants in the control group required any assistance.

3.2 Psychometric assessment results

The results of four standardised, psychometric assessments and the E-Prime Assessment Tool are shown in Table 6. The only psychometric assessment tool that detected a difference between the groups was the Purdue Pegboard Both Hands subtest and Overall Score. These results indicate that there may be a difference in the speed and dexterity of upper limb

movements between the two groups. There were no statistical differences between groups on the E-Prime Test, Symbol Digit Modalities Test, Digit Vigilance Test and Trail Making Test B.

Psychometric Test	Drivers with PD (n= 11) ** Mean (SD)	Control Group (n=15)** Mean (SD)	Wilcoxon Two-Sample Test) p-value
E-prime			
Correct Answers	12.6 (3.5)	12.7 (3.1)	0.96
Response Time/seconds	126,686 (45,463)	91,482 (34,344)	0.42
Symbol Digit Modalities Test	44.33 (5.63)	49.13 (8.46)	0.18
Digit Vigilance Test			
Page One	3.41 (0.63)	3.37 (0.69)	0.64
Page Two	3.57 (0.71)	3.46 (0.64)	0.87
Trail Making Test B	1.27 (0.65)	1.05 (0.45)	0.84
Purdue Pegboard			
Right Hand	11.75 (2.66)	13.71 (2.02)	0.20
Left Hand	11.25 (2.43)	12.79 (1.67)	0.17
Both Hands	16.25 (5.18)	21.50 (3.72)	0.04*
Assembly Task	12.88 (4.29)	17.43 (4.11)	0.07
Overall Score	39.25 (9.63)	48.00 (5.49)	0.06

*Results were statistically significant ($p<0.05$)
** 8 drivers with PD and 13 control group participants were assessed using the E-Prime Assessment.

Table 6. Participant Psychometric Assessment Results

3.3 Driving simulator results

Two participants, one control and one driver with PD requested additional practice in using the simulator. All other participants began the assessment trials immediately following the practice session. During the assessment process, three drivers with PD and four control participants experienced simulator-induced motion sickness and withdrew. Their partial data was included in the data analyse where appropriate. An Independent t-test was used to determine if there was a difference between each group on the Driving Performance Score and the Scenario Completion Time for each trial. The results are shown in Table 7. The parametric t-test was found to be appropriate for analysing these results as the pre-post nature of assessment doubled the data entries available for analysis; fulfilling the sample size requirements (Hedges, 2009). Of note is that the difference between scenario completion times for Trial 2 had a p-value of 0.014 (refer to Table 7).

This however does not represent a difference between groups as the baseline performance in Trial 1 was dissimilar for each group and this disparity affects the results of Trial 2. The results shown in Table 7 are displayed in two box-and-whisker plots. Figure 7 represents the

change in Driving Performance Score between trials for both groups, whilst Figure 8 shows the change in Scenario Completion Time for each trial.

Variable	Drivers with PD (n=8) Mean (SD)	Control Group (n=13) Mean (SD)	Results p-value
Driving Performance Score			
Trial 1	82.7 (6.0)	76.5 (22.4)	0.36
Trial 2	59.2 (17.9)	67.4 (27.3)	0.47
Between Group Comparison	-23.5 (19.1)	- 9.2 (24.4)	0.17
Comparison between Trials			
- Drivers with PD			0.01*#
			0.02*^
- Control group			0.20#
			0.16^
Scenario Completion Time (seconds)			
Trial 1	864.8 (172)	782 (137)	0.21
Trial 2	776 (110)	674 (64)	0.02*
Between Group Comparison	-88.6 (73.0)	-107.5 (103.8)	0.66
Comparison between Trials			
- Drivers with PD			0.01*#
			0.01^
- Control group			0.01*#
			0.01^

* Results are statistically significant ($p < 0.05$)
^ Wilcoxon Two-sample Signed Rank Test
# Paired T-Test

Table 7. Driving Performance and Scenario Completion Time for Trial One and Two

3.3.1 Comparison between the driving performance of the groups

The Driving Performance Scores of both groups decreased in Trial 2. However, the extent of this decline was significantly greater for the drivers with PD (t-test p=0.01). These results were confirmed by Wilcoxon test (p=0.03) (refer to Table 7). Although the driving performance of the driver with PD was lower under time pressure, the driving performance was not unsafe or dangerous.

The control group had a greater variance in Driving Performance Scores compared with the drivers with PD in both trials, as shown by Figure 7. When under a time pressure, the variance in Driving Performance Scores of the drivers with PD increased.

3.3.2 Group comparison of scenario completion time

Figure 8 shows the difference within each group for the Scenario Completion Time for trial one and trial two. All participants in both groups, except one control participant, completed the second trial faster as required. In trial one, there were four outliers in the control group as shown by the dots in Figure 8. Both groups were able to significantly decrease their Scenario Completion Time; however the control group was able to decrease their score to a greater extent.

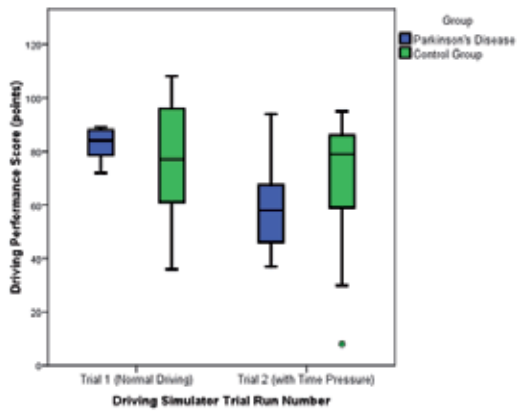


Fig. 7. Change in Driving Performance due to Time Pressure

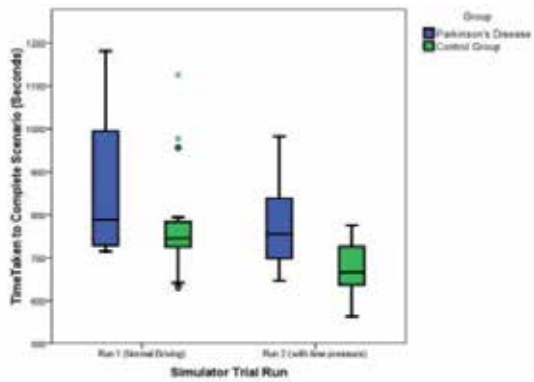


Fig. 8. Change in Scenario Completion Time for Trial One and Two

3.3.3 Group comparison of driving performance score components

As outlined in previous section, the Driving Performance Score comprised of 10 components representing important driving behaviours. Table 8 shows that in trial one, the drivers with PD had a low frequency of appropriate mirror use ($p=0.014$) and had more difficulty in maintaining the vehicle in a correct lane position ($p=0.02$). When under pressure, the drivers with PD continued to demonstrate a low frequency of appropriate mirror use ($p=0.012$) and they were less likely to stop the vehicle an appropriate distance from obstacles ($p=0.02$). The other components of driving were the same between groups (refer to Table 8).

3.4 Impact of decision making ability upon driving performance

To explore the relationship between decision making ability and driving performance, quantitative data and clinical observations that were gathered during Stage 1 and 2 of the study were analysed. A random effects regression model was adopted to analyse the results using the Driving Score as a dependent variable and the Psychometric Assessment Tests, Trial Run Number and group identifier (drivers with PD or control group) as the independent variables. All independent variables were originally included in the analysis,

Variable	Drivers with PD Mean Score n=8 Mean(SD)	Control Mean Score n=13 Mean (SD)	(Wilcoxon Two-Sample Test) p-value
Frequency of Appropriate Use of Mirrors			
Run 1	8.50 (2.67)	4.38 (3.43)	0.014*
Run 2	12.38 (5.95)	5.46 (3.02)	0.012*
Maintains Appropriate Vehicle Speed			
Run 1	6.25 (6.54)	8.08 (9.23)	1.00
Run 2	7.38 (6.50)	12.31 (9.07)	0.31
Demonstrates Caution during Manoeuvres			
Run 1	6.00 (2.98)	6.77 (3.98)	0.47
Run 2	7.00 (3.30)	7.46 (4.52)	0.91
Frequency of Appropriate Stopping Distance			
Run 1	4.50 (2.73)	4.00 (3.87)	0.43
Run 2	5.13 (4.36)	1.77 (2.35)	0.02*
Smooth Manoeuvring around Obstacles			
Run 1	3.50 (2.78)	3.46 (2.22)	1.00
Run 2	6.38 (2.56)	5.00 (2.24)	0.25
Maintains Correct Lane Position			
Run 1	8.13 (3.27)	14.23 (6.00)	0.02*
Run 2	14.50 (3.59)	13.38(6.78)	1.00
Maintains Control of Vehicle on Turns and Winding Roads			
Run 1	1.75 (2.25)	2.54 (2.30)	0.44
Run 2	3.38 (3.74)	3.46 (3.18)	0.83
Appropriate Behaviours to Avoid Hazards			
Run 1	1.75 (2.38)	1.08 (1.89)	0.39
Run 2	2.86 (3.67)	1.54 (2.07)	0.57
Appropriate Use of Indicators			
Run 1	4.63 (1.77)	6.38 (3.33)	0.15
Run 2	9.63 (3.96)	7.92 (5.20)	0.46
Number of Collisions			
Run 1	1.50 (0.53)	1.31 (1.03)	0.79
Run 2	1.25 (0.71)	0.92 (0.86)	0.41

* Results are statistically significant ($p < 0.05$)
Note: a higher score indicates poorer performance

Table 8. Analysis of Driving Performance Score Components

and then the least significant variables were excluded, one at a time, until the p-value associated with each remaining variable was less than 0.05 (refer to Table 9).

The independent variables that were found to be statistically significant were the Driving Simulator Trial Run Number, Purdue Pegboard Both Hands Score and Digit Vigilance Test Page 1 and Page 2. Confidence Intervals (set at 95%) show the reliability of the results by providing a range of scores that the true answer lies within (Hedges, 2009). As shown by the wide confidence intervals in Table 9, the reliability of these results was not convincing. A correlation between the psychometric assessment tools to driving performance therefore

cannot be assumed. Due to the small sample size, it would be misleading to perform individual parametric analysis for each variable.

Variable	Least Squares Mean	Regression coefficient	95% Confidence Interval	p-value
Group				
- Control	76.2	13.0	-3.4 to 29.3	0.114
- Drivers with PD	63.3	0.0		
Trial Run Number				
- 1	76.8	14.2	3.2 to 25.2	0.014*
- 2	62.6	0.0		
Purdue Pegboard Both Hands test				
DVT Page1				
DVT Page2		-1.8	-3.5 to -0.1	0.049*
		-27.4	-51.1 to -3.8	0.025*
		30.2	7.5 to 52.9	0.012*

*Results were statistically significant ($p<0.05$)

Table 9. Multivariable Analysis of Driving Performance Score to Psychometric Assessment Results

3.5 Motion sickness

Three drivers with PD and four control participants experienced symptoms of motion sickness and withdrew from the study. Symptoms included mild dizziness, sweating, nausea and vomiting. The two participants who had requested additional driving simulator practice were amongst the participants who experienced motion sickness.

In all cases, the researcher ceased participation in the study as soon as mild symptoms of motion sickness were experienced. All participants except one driver with PD, recovered within half an hour without residual signs and symptoms of motion sickness. The exception was contacted the following day by the researcher, and reported no residual signs or symptoms.

4. Discussion

4.1 Participant demographics

Eight drivers with PD and 13 control participants were successfully assessed. The volunteer response rate was lower than anticipated. The recruitment process could have been affected by the stated reluctance of medical practitioners to refer clients due to potential legal implications. Legislation for the Compulsory Reporting of Medical Conditions came into effect in Western Australia only one year prior to the commencement of the study, which may have influenced the willingness of drivers with PD to volunteer. It was intended to match participants by gender, driving exposure per week and age, since these factors were identified

by previous studies as having the potential to influence results (Bedard, et al., 2010). Although perfect matching of participants would have been ideal; age, gender and driving exposure per week were not found not to be significantly different between groups. These results concur with a Queensland study using 25 drivers with PD and 21 controls, which also found that age and gender did not appear to affect the results (Wood, et al., 2005).
The only difference between the groups was the number of 'Years of Driving Experience' as the drivers with PD had more experience. This difference may have potentially influenced the results in favour of the drivers with PD having an improved performance, compared with the control group. However, both groups had been driving for over 43 years and there was found to be no difference in the current exposure of the groups to driving. Therefore, the number of years of driving experience may have had a minimal or no impact upon the driving performance results. Elvik and Vaa (2004) investigated 42 different driving studies and found that the years of driving experience was not matched between study cohorts, implying that it is not common practice to do so.

4.2 Psychometric data

In the literature review, it was discussed that decision-making is a complicated process involving many areas of the brain. Dopamine plays an extensive role in enabling these areas to interact and allow a person to make accurate and timely decisions (Ernst & Paulus, 2005). Based upon the prevalence rates of cognitive impairment as discussed; between two and five of the 11 drivers with PD in this study may have had cognitive deficits (Adler, et al., 2000; Factor & Weiner, 2002). If this assumption holds, it was expected that PD-related cognitive deficits would cause drivers with PD to score lower on all of the psychometric assessment tools. The psychometric results however, indicated that there was no difference between the groups upon these decision making components. This may have been due to an inability to detect a difference between groups due to small sample size.
It is possible that a self-selection bias affected the results in favour of the drivers with PD sample performing better than the general population of people with PD. Anceaux et al. (2008) claimed that it is likely that only drivers, who are confident in their ability, tend to volunteer to undergo non-compulsory assessment for research purposes. Participants in the present study were volunteers, more confident drivers, are likely to have influenced the better result of the present study. Results from the Cognistat screening concur with this observation, further supported by the fact that the screening process did not exclude any potential participants due to severe cognitive deficits. Convenience sampling was chosen to recruit participants since a more stringent sampling process would not have been achievable within the time and budget constraints of the study, particularly for recruiting the PD participants (Anceaux, et al., 2008; Elvik & Vaa, 2004). Selection sampling bias due to either snowball or convenience sampling methods is a frequently identified issue in driving studies. Other driving studies, both on-road and using simulators, frequently experience difficulty in assessing large sample sizes due to high costs, the necessity of the participant travelling to the assessment area and high dropout rates (Elvik & Vaa, 2004; Innes, et al., 2009; Kulisevsky & Pagonabarraga, 2009).
A significant difference was found between the groups on the Purdue Pegboard subtest of Both Hand for coordination and speed of bilateral hand movements. The multivariable analysis of driving performance to psychometric assessment results also suggests that the 'Both Hand' subtest may be linked to driving performance. The results reflect findings from an on-road study with 25 PD patients and 21 age matched controls (Wood, et al., 2005).

However, when interpreting the results of the present study, caution should be used due to the wide confidence intervals. Additionally, Bonferroni's correction principle for multiple testing needs to be considered, as the other results, including the overall score on the Purdue Pegboard, were not different. Therefore, the significant results on the Both Hands subtest may be due to random effect and not due to the physical symptoms of PD. It is therefore uncertain if motor performance affected the psychometric assessment results. All of the psychometric tests required physical input of data through pushing a button or writing the answer, which required a physical motor movement. It is therefore worth investigating the validity of the Oral Symbol Digit Modalities test, as well as other motor free tests, on driving performance; especially as the written versions of these assessments are routinely used to assess drivers with PD.

4.3 Driving simulator data

4.3.1 Length of simulator practice time

As previously mentioned, two participants requested additional practice in using the driving simulator. It was noted that both of these participants later experienced motion sickness and withdrew from the study. Kennedy and Fowlkes (2000) found that increased exposure to simulated environments might increase the rate of motion sickness-related participant dropouts. Although this study cannot comment upon this phenomenon, additional research into a possible correlation of exposure time to motion sickness would be useful to provide guidelines for simulator scenario design, especially for older adults or people with PD.

4.3.2 Baseline driving performance

Drivers with PD had a higher mean driving performance than the control group at baseline driving. However this was not statistically different. As shown in Figure 7, all of the scores of the drivers with PD group fell within the interquartile range of the control group. This means that groups cannot be differentiated based upon overall driving performance scores alone. There was also no statistical difference in time to complete trial one; showing that baseline time of the groups was the same. The sub sections of the Driving Performance Score that varied significantly between groups were "Frequency of Appropriate Use of Mirrors" and "Driver Maintains Correct Lane Position". The present study results are similar to the findings of numerous other studies, both on-road and using simulators, that claim that drivers with PD have more errors in these particular aspects of driving (Radford, et al., 2004; Uc, et al., 2009; Uitti, 2009). The present study suggests that although the drivers with PD had a lower driving performance score; this does not necessarily mean that they are 'dangerous' drivers. Similar findings were reported by Uc et al. (2009). Although the 84 drivers with PD in their study committed more lane placement errors, they were still found to be safe drivers overall. Numerous other studies also claim that drivers with PD can be safe drivers (Bryer, et al., 2006; Radford, et al., 2004). The results of the other studies, as with the present study, may have been influenced by self-selection bias as these studies also used convenience sampling and had a small sample size. Therefore, it is possible that people with PD may be safe drivers and so licences should not be cancelled based purely upon having a diagnosis of PD.

4.3.3 Driving with time pressure

When a time pressure was implemented, the median driving performance of both groups decreased; with the drivers with PD experiencing a significant decrease in performance.

The median driving performance of the drivers with PD declined more than the control group, but none of the drivers with PD were found to be unsafe drivers. This indicates that when drivers with PD are under time pressure, they may not be able to compensate for the additional task demands as well as healthy drivers. As previously mentioned, self-selection bias may have affected the results. The drivers with PD in the study may be better or more confident drivers, suggesting that the difference between groups may be more substantial if comparing a more representative sample of drivers with PD to the control group. Findings support the results found by four other studies into PD (Devos, et al., 2007; Factor & Weiner, 2002; Radford, et al., 2004). These results should, however be taken with caution due to the possibility of self-selection bias influencing results. Both groups were able to decrease their individual Scenario Completion Time significantly when instructed to do so in trial two. In addition, it was found that the control group had a significantly greater decrease in driving completion time, compared with the drivers with PD. The difference in Scenario Completion Time does not mean that the drivers with PD are worse drivers. However, it is an interesting trend that has been noticed by other researchers. For example, an on-road study with 77 drivers with PD also found that drivers with PD were slower in completing the route than the control group (Uc, et al., 2009). Reasons for this trend and potential implications for on-road driving performance cannot be established based upon the results of the present study. The reason for the difference in time to complete the trial cannot be ascertained with complete certainty. It is possible that the drivers with PD were unable to increase driving speed whilst maintaining safe driving performance, due to either decision making deficits or other factors. Alternatively, the results could demonstrate that drivers with PD were more cautious and aware of their limitations; making them unwilling to take risks. This information confirmed the assertions made by the drivers with PD about their perception of driving performance since the onset of their PD symptoms. The observation that drivers with PD are more cautious in their driving was also concluded by numerous other studies (Adler, et al., 2000; Devos, et al., 2007). Whether behaviours undertaken by drivers with PD to self-regulate their driving are successful in maintaining safe driving performance is an important area for future research. The results indicate that drivers with PD may be capable of driving safely; showing that research projects such as this study are important in preventing capable drivers from having their licence cancelled, purely due to a diagnosis of PD. The finding that drivers with PD may be safe drivers is supported by other studies into PD and driving (Bryer, et al., 2006; Radford, et al., 2004).

4.4 Methodological considerations and limitations

4.4.1 Reliable protocol

The reliability of the study was improved by using instruction videos, the driving simulator and standardised psychometric assessment tools. Although filming the videos and constructing an appropriate driving scenario were time consuming, these tools increased the repeatability of the study, reduced risk of inter-rater error and can enable the protocol to be generalised to clinical settings in future (Bedard, et al., 2010). Additionally, if this research project were to be repeated on a larger scale, the setting up of the assessment process and training of another researcher could be quickly performed with ease.

4.4.2 Learning effect

It is possible that a learning effect influenced the results, as the participants would have been more familiar with the driving simulator and the scenario during the second trial. However,

this learning effect would have affected participants in both groups equally. Participants were not aware beforehand that they would undergo assessment on the same scenario twice and therefore would not have actively tried to memorise events and hazards during the first trial.

4.4.3 Motion sickness

Motion sickness is a common problem integral in driving simulator assessment (Kulisevsky & Pagonabarraga, 2009). Although the simulator presents a visual appearance of movement, the vestibular and proprioceptive systems do not detect presence of movement. The inconsistencies in sensory information may trigger feelings of nausea, dizziness or elevated temperature. This occurs more commonly in more experienced drivers and in people who have not regularly played computer and video games (Kulisevsky & Pagonabarraga, 2009). The drop out due to motion sickness experienced in this study (25%) was within the range reported by other studies using driving simulators, from 9% (Lee, et al., 2003) to 57% (Kennedy & Fowlkes, 2000), with older drivers being more susceptible to motion sickness. Kulisevsky and Pagonabarraga (2009) found that participants who experienced motion sickness in simulated driving did not have a reduced performance during on-road assessment and suggested that incidence of motion sickness is related to factors other than driving ability.

Potential reasons for the increased rate of motion sickness may include the larger size of the main simulator screen, the addition of side screens, the increased period of exposure and complexity of the driving scenario. The driving scenario in the present study included, right hand turns, driving at high speeds, winding roads, over taking and complex intersections, which were not used in the previous studies (Cordell, et al., 2008; Lee, et al., 2003). These particular elements are known to increase the risk of motion sickness; however, they are also highlighted as driving situations that are known to be challenging for drivers with PD (Kennedy & Fowlkes, 2000). Bedard and colleagues recommended that drivers should be assessed in challenging situations to ensure the detection of poor driving performance. The side screens are smaller than the main screen and consequently, the scenario images do not match up with complete accuracy in real life driving. This discrepancy in scenario images has been found in other studies to increase rates of motion sickness (Kennedy & Fowlkes, 2000). However, Kennedy and Fowlkes (2000) concluded that motion sickness occurs even on very expensive simulators with motion platforms and so purchasing a more expensive simulator will not necessarily be sufficient to address this issue.

Length of exposure to the simulator has been found to increase the risk of motion sickness, particularly among older adults and people with cognitive impairments (Kennedy & Fowlkes, 2000). Good ventilation, low lighting, herbal ginger tea and/or ginger supplements and a gradual introduction to the simulator over a three-day period can also assist to reduce the risk of motion sickness (Kennedy & Fowlkes, 2000).

4.5 Recommendations for future research

It is important to continue to research the cognitive deficits of drivers with PD; particularly decision making ability, as both the complexity of traffic situations, and the prevalence of PD increases (Uitti, 2009). Duplicating study designs of research projects investigating cognitive deficits amongst people with dementia may assist in improving research protocols for drivers with PD (Elvik & Vaa, 2004). A repeat of this study using a larger sample size and including drivers with PD recruited from driving assessment centres is recommended to answer the research question. When using a driving simulator to assess drivers with PD, the researcher needs to consider the implications of potential motion sickness when planning the research methodology.

Elvik and Vaa (2004) suggest that older drivers could be disadvantaged during driving assessment, since their last assessment may be as long as 50 years previously. The stress and anxiety of assessment could potentially affect driving performance, meaning that the assessment results may not represent actual ability (Elvik & Vaa, 2004). In the present study, the average time since participants had had a driving assessment varied from one to 61 years, with 35 years being the average. Participants in the present study commented that having to undergo driving assessment was stressful. As previously discussed, regular on-road assessment is impractical due to long waiting periods and high costs. There is currently no funding available for drivers with PD to undergo neither driving assessment nor driving training. Therefore, the driving simulator could potentially be used as a low cost method to assist drivers with PD to adapt to the assessment process, or to screen for people who may need an on-road review assessment of driving (Lee, et al., 2003).

4.6 Conclusions

This study aimed to explore the impact of impaired decision making ability upon the driving performance of people with PD. There was no difference between the decision making abilities of the groups as measured on the psychometric assessment tools. At normal baseline driving, the drivers with PD used their side mirrors less frequently, had poorer lane placement and took longer to complete the route.

When instructed to finish the scenario faster, both groups were able to have a significant reduction in the scenario completion time. The time pressure also caused a significant reduction in the driving performance scores of the drivers with PD, particularly in their stopping distance from obstacles. However, both groups were able to navigate the driving scenario safely under a time pressure. It is not possible to determine if the difference in completion time was due to the drivers with PD being unable to complete the route faster, or being unwilling to do as they self-regulated their driving. It is important to note, that although there was a difference in driving performance, the drivers with PD were not found to be dangerous or unsafe drivers. As the psychometric assessment results of the groups were the same, the impact of decision making ability upon driving performance cannot be determined at this stage. Information from the chapter is valuable in providing recommendations for further research projects into driving, Parkinson's disease and simulator use.

5. References

Access Economics. (2010). *Federal policy initiatives: a new approach to Parkinson's disease.* Retrieved September 2, 2010, from http://www.parkinsonsnsw.org.au/assets/attachments/media/PA_NewPolicy Initiative.pdf

Adler, G., Rottunda, S., Bauer, M., & Kuskowski, M. (2000). The older driver with Parkinson's Disease. *Journal of Gerontological Social Work, 34*(2), 39 - 49. doi:10.1300/J083v34n02_05

Allen, R. W., Rosenthal, T. J., & Park, G. (2003). Assessment and training using a low cost driving simulator. In *Tenth International Conference on Human-Computer Interaction* (pp. 57-61). Crete, Greece: Systems Technology Inc.

Amick, M. M., Grace, J., & Ott, B. R. (2007). Visual and cognitive predictors of driving safety in Parkinson's disease patients. *Archives of Clinical Neuropsychology, 22*, 957-967. doi:10.1016/j.acn.2007.07.004

Anceaux, F., Pacaux, M. P., Halluin, N., Rajaonah, B., & Popieul, J. C. (2008). A methodological framework for assessing driving behaviour. In L. Dorn (Ed.), *Driver behaviour and training* (Vol. 3, pp. 203 - 213). Hampshire, England: Ashgate Publishing, Ltd.

Arias-Carrión, O., & Pöppel, E. (2007). Dopamine, learning and reward-seeking behaviour. *Acta Neurobiologiae Experimentalis, 67*(4), 481-488. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18320725

Australian Bureau of Statistics. (2004). *The health of older people in Australia, 2001*(Catalogue No. 4827.0). Canberra, Australian Capital Territory: Commonwealth of Australia. Retrieved from http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4827.0.55.001200

Australian Bureau of Statistics. (2008). *Causes of death in Australia, 2008* (Catalogue No. 3303.0). Canberra, Australian Capital Territory: Commonwealth of Australia. Retrieved from http://www.abs.gov.au/ausstats/abs@.nsf/mf/3303.0

Australian Bureau of Statistics. (2009). *Motor Vehicle Census in Australia, 2009* (Catalogue No. 9309.0). Canberra, Australian Capital Territory: Commonwealth of Australia. Retrieved from http://www.abs.gov.au/ausstats/abs@.nsf/mf/9309.0/

Austroads. (2000). Model license re-assessment procedure for older and disabled drivers. Sydney, NSW: Austroads Incorporated.

Bedard, M., Parkkari, M., Weaver, B., Riendeau, J., & Dahlquist, M. (2010). Assessment of driving performance using a simulator protocol: validity and reproducibility. *American Journal of Occupational Therapy, 64*, 336-340. doi:10.5014/ajot.64.2.336

Betz, M. E., & Fisher, J. (2009). Trail making test B and driver screening in emergency departments. *Traffic Injury Prevention, 10*(5), 415-420. doi:10.1080/15389580903132819

Bryer, R. C., Rapport, L. J., & Hanks, R. A. (2006). Determining fitness to drive: neuropsychological and psychological considerations. In J. M. Pellerito (Ed.), *Driver Rehabilitation and Community Mobility: Principles and Practice* (pp. 165-181). St. Louis, Missouri: Elsevier Mosby.

Busemeyer, J. R., & Stout, J. C. (2002). A contribution of cognitive decision models to clinical assessment: decomposing performance on the Bechara gambling task. *Psychological Assessment, 14*(3), 253-262. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12214432

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cerebral Cortex, 11*, 1136-1047. doi:10.1093/cercor/11.12.1136

Cordell, R., Lee, H. C., Granger, A., Vieira, B., & Lee, A. H. (2008). Driving assessment in Parkinson's disease: a novel predictor of performance. *Movement Disorders, 23*(9), 1217-1222. doi:10.1002/mds.21762

Corrigan, J. D., & Hinkeldey, M. S. (1987). Relationships between parts A and B of the trail making test. *Journal of Clinical Psychology, 43*(4), 402-409. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3611374

De Winter, J. C., deGroot, S., Mulder, M., Wieringa, P. A., Dankelman, J., & Mulder, J. (2008). Relationships between driving simulator performance and driving test results. *Ergonomics, 28*, 1-24. doi:10.1080/00140130802277521

Devos, H., Vandenberghe, W., Nieuwboer, A., Tant, M., Baten, G., & De Weerdt, W. (2007). Predictors of fitness to drive in people with Parkinson's disease. *Neurology, 69*(14), 1434-1441. doi:10.1212/01.wnl.0000277640.58685.fc

Elvik, R., & Vaa, T. (2004). Concepts of road safety research. In R. Elvik, A. Høye, T. Vaa & M. Sørensen (Eds.), *Handbook of Road Safety Measures* (pp. 15-33). Oslo: Elsevier.

Ernst, M., & Paulus, M. P. (2005). Neurobiology of decision-making: a selective review from a neurocognitive and clinical perspective. *Biological Psychiatry, 58*, 597-604. doi:10.1016/j.biopsych.2005.06.004

Factor, S. A., & Weiner, W. J. (2002). Driving. In S. A. Factor & W. J. Weiner (Eds.), *Parkinson's disease: Diagnosis and Clinical Management* (pp. 647-703). London: Demos Medical Publishing.

Hedges, L. V. (2009). Statistical Considerations. In H. M. Cooper, L. V. Hedges & J. C. Valentine (Eds.), *The handbook of research synthesis and meta-analysis* (pp. 37-50). New York: Russell Sage Foundation.

Heikkila, V. M., Turkka, J., Korpelainen, J., Kallanranta, T., & Summala, H. (1997). Decreased driving ability in people with Parkinson's Disease. *Journal of Neurology Neurosurgery and Psychiatry, 64*(325-30). Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2170019/

Innes, C. R. H., Jones, R. D., Anderson, T. J., Hollobon, S. G., & Dalrymple-Alford, J. C. (2009). Performance in normal subjects on a novel battery of driving related sensory-motor and cognitive tests. *Behaviour Research Methods, 41*(2), 284-894. doi:10.3758/BRM.41.2.284

Jankovic, J. (2007). Pathophysiology and clinical assessment. In R. Pahwa & K. E. Lyons (Eds.), *Handbook of Parkinson's Disease* (4th ed., pp. 49-76). Kansas City, Missouri: Informa Healthcare.

Kalis, A., Mojzisch, A., Schweizer, T. S., & Kaiser, S. (2008). Weakness of will, akrasia, and the neuropsychiatry of decision making: An interdisciplinary perspective. *Cognitive, Affective & Behavioural Neuroscience, 8*(4), 402-417. doi:10.3758/CABN.8.4.402

Kelland, D. Z., & Lewis, R. F. (1996). The digit vigilance test: reliability, validity, and sensitivity to diazepam. *Archives of Clinical Neuropsychology, 11*(4), 339-344. Retrieved from http://www.sciencedirect.com/science/article/B6VDJ-3Y2G16K-8/2/f4ed9a85da96e69b69ff7be

Kennedy, R. S., & Fowlkes, J. E. (2000). Duration and exposure to virtual environments: sickness curves during and across sessions. *Presence, 9*, 463-472. doi:10.1162/105474600566952

Kiernan, R. J., Mueller, K., Langston, J., & Van Dyke, C. (1987). The neurobehavioural cognitive status examination: a brief but differentiated approach to cognitive assessment. *Annals of Internal Medicine, 107*, 481-485. doi: http://www.annals.org/content/107/4/481.short

Kulisevsky, J., & Pagonabarraga, J. (2009). Review of cognitive impairment in Parkinson's disease: tools for diagnosis and assessment. *Movement Disorder Society, 24*(8), 1103-1110. doi:10.1002/mds.22506

Lafayette Instrument Company. (1985). *Instruments and normative data for the Model 32020, Purdue Pegboard*. IN: Lafayette Instrument Company.

Lee, H. C., Cameron, D., & Lee, A. (2003). Assessing the driving performance of older adult drivers: on-road versus simulated driving. *Accident Analysis & Prevention, 35*(5), 797-803. Retrieved from http://www.sciencedirect.com/science/article/B6V5S-47K2G65-/9309ee8116ccc84a88849d985bb715bc

Lotfipour, S., Patel, B., Grotsky, T., Anderson, C. L., Carr, E. M., Ahmed, S. S., et al. (2010). Comparison of the visual function index to the Snellen visual acuity test in

predicting older adult self-restricted driving. *Traffic Injury Prevention, 11*, 503-507. doi: 10.1080/15389588.2010.488494

Meindorfner, C., Körner, Y., Möller, J. C., Stiasny-Kolsterm, K., Oertel, W. H., & Kruger, H. P. (2005). Driving in Parkinson's disease: mobility, accidents and sudden onset of sleep at the wheel. *Movement Disorder, 20*(7), 832-842. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/mds.20412/pdf

Michon, J. A. (1985). A critical review of driver behaviour models: what do we know, what should we do? In L. Evans & R. C. Schwing (Eds.), *Human Behaviour and Traffic Safety* (pp. 485-520). New York: Plenum.

Molnar, A., Marshall, H. L., & Man-Son-Hing, K. (2006). Clinical utility of office based cognitive predictors of fitness to drive in persons with dementia: a systematic review. *Journal of American Geriatrics Society, 54*, 1809-1824. doi:10.1111/j.1532-5415.2006.00967.x

National Road Transport Commission. (2003). *Assessing fitness to drive* (3rd ed.). Sydney, NSW: Austroads Incorporated.

Nieoullon, A. (2002). Dopamine and the regulation of cognition and attention. *Progress in Neurobiology, 67*, 52-83. doi:10.1016/S0301-0082(02)00011-4

Psychology Software Tools, I. (2010). E-Prime 2: selected publications and other works. Retrieved October, 12, 2010, from http://www.pstnet.com/eprimepublications.cfm

Radford, K. A., Lincoln, N. B., & Lennox, G. (2004). The effects of cognitive abilities on driving in people with Parkinson's disease. *Disability and Rehabilitation, 26*(2), 65-70. doi:10.1080/09638280310001629633

Ranzini, M., Dehaene, S., Piazzaa, M., & Hubbard, E. M. (2009). Neural mechanisms of attentional shifts due to irrelevant spatial and numerical cues. *Neuropsychologia, 47*(12), 2615-2624. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19465038

Smith, A. (2007). *Symbol digit modalities test* (10 ed.). Los Angeles, CA: Western Psychological Services.

Stolwyk, R. J., Charlton, J. L., Triggs, T. J., Lansek, R., & Bradshaw, J. L. (2006). Neuropsychological function and driving ability in people with Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 28*(6), 898 - 913. Retrieved from http://www.informaworld.com/10.1080/13803390591000909

Systems Techonology Inc. (2010). System techonology software. Retrieved September, 3, 2010, from http:/www.systemstech.com

Tröster, A. I., & Woods, S. P. (2007). Neuropsychological aspects. In R. Pahwa & K. E. Lyons (Eds.), *Handbook of Parkinson's disease* (4th ed., pp. 109-130). New York: Informa Healthcare.

Uc, E. Y., Rizzo, M., Johnson, J. E., Dastrup, E., Anderson, S. W., & Dawson, J. (2009). Road safety in drivers with Parkinson's disease. *Neurology, 73*, 2112-2119. Retrieved from http://www.neurology.org/cgi/content/abstract/73/24/2112

Uitti, R. J. (2009). Parkinson's disease and issues related to driving. *Parkinsonism & Related Disorders, 15S3*, S122-125. Retrieved from http://www.sciencedirect.com.dbgw.lis.

Wood, J. M., Worringham, C., Kerr, G., Mallon, K., & Silburn, P. (2005). Quantitative assessment of driving performance in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 76*, 176-180. doi:10.1136/jnnp.2004.047118

16

Effects of a Multimodal Exercise Program on Clinical, Functional Mobility and Cognitive Parameters of Idiopathic Parkinson's Disease Patients

L.T.B. Gobbi, F.A. Barbieri, R. Vitório, M.P. Pereira and C. Teixeira-Arroyo
on behalf of the PROPARKI Group*
UNESP – Univ Estadual Paulista, Rio Claro, SP, Brazil

1. Introduction

This chapter has as main objective to present the effects of a multimodal exercise program on major signs/symptoms, functional mobility and cognitive parameters of people with Parkinson's disease (PD). This program is developed to improve all functional capacity components (strength, balance, aerobic resistance, coordination and flexibility) in order to increase patients' independence, autonomy and quality of life. As main result, we found maintenance of clinical status and memory after the exercise program with an increase in functional mobility. These results can be attributed to neuro-protection mechanisms enhanced by exercise and to an increase in functional capacity.

Parkinson's Disease (PD) is the second most incident neurodegenerative pathology in subjects over 60 years old (Olanow et al., 2009). PD has been described to affect approximately 0.3% of the population and 1% to 2% of those older than 60 years (de Lau & Breteler, 2006). It is a neurodegenerative pathology characterized by progressive degeneration of the dopamine-producing neurons in the substantia nigra pars compacta. The neuromotor impulses in the subcortical to cortical pathways, responsible for accurate control of muscle activation, are compromised with the decreased amount of dopamine. As a consequence, people with PD show motor (e.g. resting tremor, rigidity, postural instability, mobility and others) and non-motor (e.g. executive functions, depression, memory, humor alterations, dementia and others) (Taylor et al., 1986; Chaudhuri et al., 2006; Martinez-Martin, 2006; Olanow et al., 2009) signs/symptoms. Clinical parameters of PD patients tend to get worse progressively (Karlsen et al., 2000) even though pharmacological interventions associated with non pharmacological therapies have shown some benefits to patients (Sage & Almeida, 2009, 2010).

Motor signs/symptoms related to PD can contribute to the decline in balance control and mobility (Christofoletti et al., 2006), which subsequently can lead to a reduction in functional

*A.P.T. Alves, R.A. Batistela, P.M. Formaggio, E. Lirani-Silva, L.C. Morais, P.H.S. Pelicioni, V. Raile, N.M. Rinaldi, P.C.R. Santos, C.B. Takaki, F. Stella and S. Gobbi

independence. As a consequence, individuals with PD experience an increase in both the difficulties in performing daily activities, such as rising from a chair or walking, that are directed related to impoverishment in balance control (Hong & Steen, 2007), and in the risk of falls (Grimbergen et al., 2004). Together with motor disturbances, cognitive deficits in PD are detectable in the early stages (Stella et al., 2007) and are evidenced primarily by impairments in executive functions, i.e., the ability to generate spontaneous action as well as to develop motor strategies in specific planning for the performance of a given task (Taylor et al., 1986; Chaudhuri et al., 2006). Although the people with PD have the ability to decode, store and consolidate new information preserved, they present difficulty in retrieving these information (Dubois & Pillon, 1997; Dujardin & Laurent, 2003; Costa et al., 2008). These tasks involve transient working memory (handling, maintenance and temporary activation of the memory) and episodic memory (conscious recollection of individual events, reported within a specific context of space and time) (Dujardin & Laurent, 2003). Executive functions are regulated by both the prefrontal areas and the frontostriatal circuitry (Dujardin et al., 2003; Owen, 2004). In the prefrontal cortex, the transmission of dopamine by the dopamine receptors (D1) plays an important role in the functioning of working memory and learning (Cropley et al., 2006; Rashid et al., 2007), while the frontostriatal circuitry is related to motor planning (Olanow et al., 2009).

One possibility for the treatment of PD is the pharmacological therapy, i.e., the administration of synthetic dopamine (levodopa). Studies in patients with early stage of the disease have shown antagonistic effects during the *on phase* of the medication. Positive effects have been observed in locomotor (Pieruccini-Faria et al., 2006) and cognitive (Cools, 2006; Pascual-Sedano et al., 2008) parameters. However, over the years as the disease progresses, the effect of drug decreases and higher doses are needed for treatment. As a result, patients start to present motor fluctuations and dyskinesias (involuntary movements), which are side effects associated with long-term drug treatment (Obeso et al., 2000). Associated with drug therapy, non-pharmacologic therapies related to PD, such as physical exercises and nutrition, helped to attenuate the disease's severity or reduce its progression (Hirayama et al., 2008; Morris et al., 2009). The regular practice of physical exercise is effective to provide improvements in quality of life of this group of patients (White et al., 2006; Hirayama et al., 2008). Forced aerobic exercise affected both the scores in motor sub-section of the UPDRS and the performance in manual skills (Ridgel et al., 2009) while the sensory focused exercise program improved functional mobility and the motor symptoms (Sage & Almeida, 2010) in people with PD. The physical exercise can act as a protector factor generating brain changes due to a greater cerebral oxygenation, such as neuroplasticity, brain repairing and an increase of the dopaminergic cells (Smith & Zigmond, 2003; Fox et al., 2006). Besides, when the exercise is introduced in the early stages of the disease, the disease progression can slow down (Fox et al., 2006).

Physical exercise is an important factor that can improve functional capacity in the elderly (Cyarto et al., 2008). Crizzle and Newhouse (2006), reviewing the literature, concluded that, through exercise, patients with PD improve their physical performance and the performance of activities of daily living. Recently, some evidences have been showed positive changes after the exercise program not only in balance and mobility (Gobbi et al., 2009; Hackney & Earhart, 2010) but also for the motor (Sage & Almeida, 2009; Sage & Almeida, 2010) and non-motor signs/symptoms (Tanaka et al., 2009) in PD patients. Therefore, systematic participation in physical exercise programs can help individuals with PD to maintain their motor repertories and their cognitive ability to perform daily living activities.

Any type of physical exercise is better than no exercise to improve the level of functional capacity (Brach et al., 2004). However, little is known about the effect of exercise on cognitive function in patients with PD. For healthy elderly, without PD, studies have shown positive results of exercise on cognitive functions, especially on memory (Chiari et al., 2010). Aerobic exercises are the more effective ones to improve memory parameters of older people when compared to cognitive exercises and the ones that combine aerobic and cognitive exercises (Fabre et al., 2002). The positive results found for the elderly population may suggest that people with PD also benefit from physical exercise practice. Physical exercise programs for people with PD that focus on improvements in functional capacity and mobility vary according to the type of proposed activity, whether it will be practiced individually or in a group, the program's duration, the frequency and duration of the weekly sessions, and the means of evaluation. Such programs include intensive sports training (Reuter et al., 1999), treadmill training with body weight support (Miyai et al., 2000), resistance training (Scandalis et al., 2001; Dibble et al., 2009), aerobic exercise (Bergen et al., 2002), alternative forms of exercise (Hackney & Earhart, 2009), home-based exercise intervention (Nocera et al., 2009), and the practice of movement strategies (Morris et al., 2009).

The results of our group, using a multimodal exercise program based on the improvement of the functional capacity components (strength, balance, aerobic resistance, coordination and flexibility) revealed a positive effect on the executive functions (Tanaka et al., 2009) and on the functional mobility and balance (Gobbi et al., 2009). Tanaka et al. (2009) analyzed the effects of an aerobic exercise program on executive functions in older people with PD. We found significant improvements in executive functions in people with PD after six months of participation in aerobic exercise program. Such benefits were expected to play an important role on independence, autonomy and quality of life of such population. Gobbi et al. (2009) investigated the effects of two intervention programs, a multi-mode exercise program and an adaptive program, on the mobility and functional balance in people with PD. We found that both the intensive and adaptive exercise programs improved balance and mobility in patients with PD.

Within this context, the purpose of this chapter is to demonstrate the effectiveness of a long-term multimodal exercise program in improving clinical parameters, functional mobility and cognitive function in people with PD. We analyzed the benefits of the long-term exercise interventions in motor and non motor signs/symptoms in a more holistic point of view, since this type of physical exercise intervention for people with PD have not been reported.

2. Methods

This study adhered to the guidelines of the Declaration of Helsinki, and was approved by the local Ethics Committee. All patients signed informed consent forms before involvement in the study.

2.1 Participants

Fifteen idiopathic PD patients were enrolled in the study. All had a diagnosis of idiopathic PD, with no other major neurological problems. Inclusion criteria were: disease in Stages I–III of the Hoehn and Yahr Rating Scale (H&Y; Hoehn & Yahr, 1967), independent walker, and no cognitive impairment, as judged by Brucki et al.'s (2003) suggestions for utilization

of the Mini-Exam of Mental Status (MEMS; Folstein et al., 1975) in Brazil. Demographic data of PD patients are outlined in Table 1.

Subject	Gender	Age (years)	Body height (cm)	Body mass (kg)	H&Y (stage)	Years since diagnosis
A	female	66	162.2	85.5	1	3
B	female	60	163	56.7	2	2
C	female	67	153	47.5	1	3
D	female	59	154.4	67	1	2
E	female	60	142.8	57.5	1	2
F	female	82	153	71.7	3	4
G	female	65	151.8	39.5	1.5	4
H	female	60	162	70.4	1	3
I	male	75	176.5	62.5	1.5	4
J	male	64	161.8	85.1	3	19
L	male	69	174	69.7	1	3
M	male	59	165.5	88.7	1	2
N	male	78	165.5	88.7	2	1
O	male	65	163.3	77.9	1	1
P	male	73	165.5	91.6	1	4
Mean		**67**	**161.0**	**70.7**	**1.5**	**3.8**
SD		**7.28**	**8.74**	**15.87**	**0.7**	**4.33**

Table 1. Demographic characteristics of the participants.

2.2 Intervention

The aim of the multimodal exercise program was to develop the patients' functional capacity, cognitive functions, posture, and locomotion through a program that is primarily aerobic. It was composed of a variety of activities that simultaneously focus on the components of functional capacity, such as muscular resistance (specific exercises for large muscle groups), motor coordination (rhythmic activities), and balance (recreational motor activities). These components were selected because they seem to be those most affected by PD. The multimodal program took place over a six-month period (72 sessions, 3 times a week, and 60 minutes per session). Each session consisted of five components (warm-up, pre-exercise stretching, the main exercise session, cool-down and post-exercise stretching). All sessions were conducted in the morning, in the ''on medication'' state, between 1 and 1½ h after participants' first morning dose of medication. The program was designed in six phases and each phase was composed of 12 sessions and lasting approximately one month. At the end of each phase there was a progressive increase of load (Chart 1). Heart rate during the sessions remained between 60% and 80% of maximum heart rate (220 minus the participant's age in years), which characterizes training with aerobic predominance. The exercise program was supervised by at least three physical education professionals at any

one time. Each participant was required to attend at least 70% of the sessions in order to be included in the data analysis. This protocol has been previously described by Tanaka et al. (2009).

Phases	Capacities		
	Coordination	*Muscular Resistance*	*Balance*
Phase 1	Upper and lower limbs movements.	Exercises without weights.	Recreational activities that stimulated the vestibular system.
Phase 2	Trunk movements were added to upper and lower limbs movements.	Light-weight equipment (hoops, ropes and batons).	Recreational activities that stimulated the visual and vestibular systems.
Phase 3	Trunk movements were substituted by head movements.	Heavier equipments (barbells, ankle weights, medicine balls).	Recreational activities that stimulated the visual and somatossensorial systems.
Phase 4	Head, trunk and upper and lower limb movements.	Load was again increased with heavier equipment for resistance training (increase of intensity) or increased repetitions (increased volume).	Recreational activities integrated the vestibular, visual and somatossensorial systems.
Phase 5	Four different movement sequences, two of which were the same for upper and lower limbs and two other sequences that alternated movements for upper and lower limbs in place and in movement.	Exercises were done with weights: leg press, pulley, seated cable rows, pecdeck, and bench press, in two series of 15 repetitions.	Recreational activities included static balance, dynamic balance, half-turn and complete turn (all with visual cues).
Phase 6	Four sequences of different movements, two sequences of alternating movement for upper and lower limbs and two sequences of different movement for upper and lower limbs, with or without trunk movement and equipment (balloons, balls, hoops and rope).	Series of 15 repetitions were added.	Recreational activities were composed of activities with tactile cues.

Chart 1. Designed phases of the 6-month intervention protocol with progressive increments on load and complexity for people with Parkinson's disease (adapted from Tanaka et al., 2009).

2.3 Evaluation protocol for the dependent variables

Participants were tested before commencing the multimodal program (pre-test), and upon completion (post-test). All assessments were carried out in the morning, in the ''on medication'' state, at least 1 h after participants' first morning dose of medication. The participants were evaluated by the same trained assessor (blinded as to the study purpose) under the same conditions in both moments (pre- and post-tests).

2.3.1 Clinical evaluation

A neuropsychiatrist performed a clinical assessment by means on the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987), MEMS, and H&Y. Higher scores on the UPDRS and H&Y represent higher commitment levels of the disease. Conversely, higher scores on the MEMS indicate a more preserved cognitive function. For data analysis, scores on the UPDRS sub-sections I (Mentation, Behavior, and Mood), II (Activities of Daily Living), and III (Motor) were considered separately.

2.3.2 Functional mobility evaluation

Basic functional mobility was assessed by means of the Timed Up and Go Test (TUG; Podsiadlo & Richardison, 1991) and the Postural Locomotion Manual test (PLM; Steg et al., 1989).

i. TUG: The task consisted of the participant to stand up from a sitting position in an armless chair with a seat height of 46.5 cm, walk a distance of 3 m, circumvent a cone, return, and sit back down in the chair. Participants were instructed to perform the test as quickly as possible, but without running. At least one practice trial was offered to the participants at the beginning of the procedure so that they could become familiar with it. Three trials were performed for testing purposes, and the time to perform the task was measured in seconds. Time was recorded from the instant the person's buttocks left the chair (standing up) until the next contact with the chair (sitting down). The mean value of the three attempts was considered for statistical analysis.
ii. PLM: This test measures postural control, locomotion and a goal directed reaching arm movement and the efficacy with which these movements compose a smooth dynamic action of the whole-person. To perform the PLM test, the participants were asked to move a small squared object (500 g), from a clearly marked starting place on the floor, to a stand located at eyes level, 1.82 m away in front of the starting place. Subjects had to deal with postural changes during the different phases of the test (to bend the upper body to pick up the object, walk forward and place the object on the stand). Time to perform the task was recorded from the "go" sign to the first contact of the object with the stand. The mean value of the three attempts was considered for statistical analysis.
iii. Since each subject performed three attempts of each task, we also compared these attempts (Attempt 1 vs Attempt 2 vs Attempt 3) before and after the training program.

2.3.3 Cognitive evaluation

The following tests were applied for cognitive function assessment:

i. Executive Functions, by the Wisconsin Card Sorting Test – WCST (Heaton et al., 1993; Paolo et al., 1995). This test specifically assesses abstraction, mental flexibility and attention. It consists of 4 stimulus cards and 128 response cards that must be combined with the stimulus cards by following the hints "right" or "wrong" provided by the evaluator. From this hint, without pre-established rule, the participant must find the right combination (according to color, shape or number). Every 6 consecutive hits, the evaluator changes the mix and the participant must change his or her strategy. The test continues until the participant completes 6 categories of combinations or the 128 attempts. The WCST was chosen due to: a) its good construct validity for people with PD; b) it assesses three executive functions at the same time (abstraction, mental flexibility, attention) and; c) it does not require high level of schooling and this also

makes it appropriate for the population involved in our study. Within the executive functions, mental flexibility was the variable of interest for this study. It was assessed based on the number of perseverative errors made by patients.

ii. The subtest Logical Memory I and II, Wechsler Memory Scale Revised – WMS-R (Wechsler, 1997) was used to measure the short-term memory (logical memory I) and episodic declarative memory (logical memory II). In this subtest two stories are told separately. Immediately after hearing each story, the patient states what was remembered and the amount of linguistic units remembered is computed for logical memory I. After 30 minutes, participants are asked to retell the two stories and the points concerning linguistic units remembered are computed for logical memory II.

3. Results

Clinical, functional mobility and cognitive data from pre- and post-tests are outlined in Table 2. The Wilcoxon test did not show significant differences between pre- and post-intervention for H&Y, UPDRS-I, UPDRS-III, MEMS, perseverative errors and episodic logic memory I. The multimodal exercise program was effective in improving UPDRS-II scores, episodic declarative memory II, TUG and PLM.

Dependent variable	Pre-test	Post-test	*P* value
Clinical			
H&Y (stage)	1.47±0.72	1.53±0.72	0.157
UPDRS-I (score)	3.67±2.69	3.33±2.44	0.301
UPDRS-II (score)	11.07±6.36	9.73±6.04	0.022
UPDRS-III (score)	20.13±12.26	21±14.53	0.728
MEMS (score)	26.2±3.47	25.9±4.35	0.778
Functional mobility			
TUG (s)	10.37±4.54	8.41±2.27	0.002
PLM (s)	4.03±1.42	3.58±0.76	0.013
Cognitive			
Perseverative errors (errors)	6.87±6.83	5.13±7.52	0.151
Logic memory I (score)	14.8±5.02	17.07±5.93	0.132
Logic memory II (score)	8.6±5.95	13.8±6.38	0.005

Table 2. Means and standard deviations for each clinical dependent variable at pre and post-test and *P* value.

Figures 1 and 2 show respectively times to complete all attempts of the TUG and the PLM tests at pre- and post-intervention. The Friedman test showed a significant effect for attempts on TUG at pre-test ($p=0.019$) and post-test ($p=0.047$; not confirmed by the Wilcoxon test, $p>0.05$) and PLM at pre-test ($p<0.001$). Therefore, at pre-test a significantly increase in time to complete TUG (Attemp1 vs Attempt 3 - $Z=2.240$; $p=0.025$) was observed.

During the PLM, patients reduced their time at pre-test (Attempt 1 vs Attempt 3 - Z=3.678; p<0.001), showing a learning effect. No differences were observed on Attempt 1 and Attempt 2 in all cases.

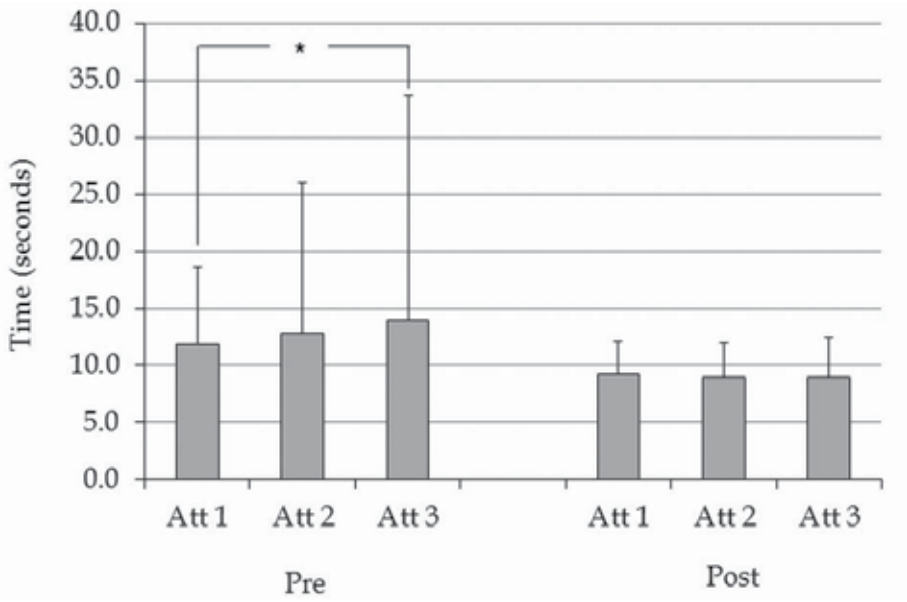


Fig. 1. Mean (+SD) time to complete attempts 1 to 3 (Att1 – Att3) of TUG test at pre- and post-intervention. * p<0.05

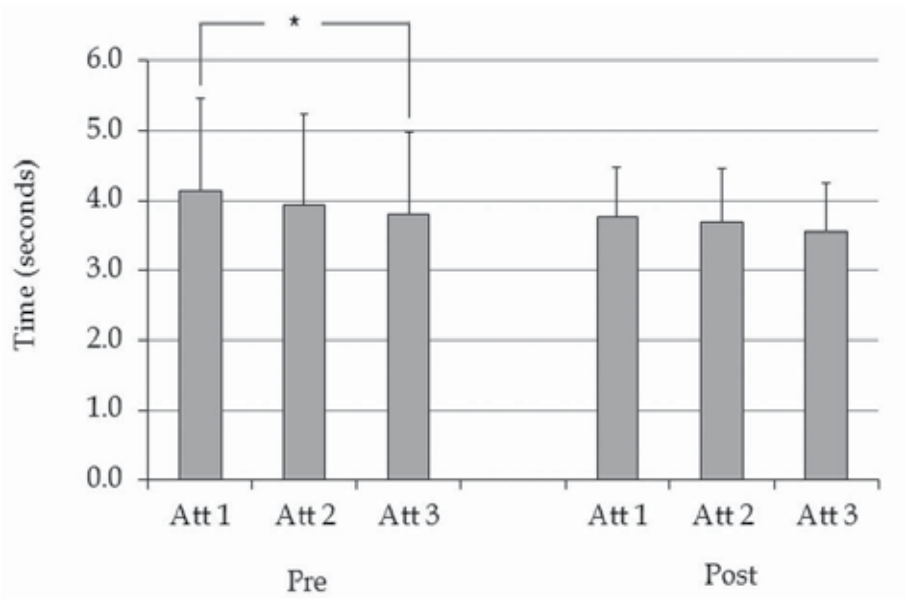


Fig. 2. Mean (+SD) time to complete attempts 1 to 3 (Att1 – Att3) of PLM test at pre- and post-intervention. * p<0.05

4. Discussion

The purpose of this chapter was to demonstrate the effectiveness of a long-term multimodal exercise program in improving clinical parameters, functional mobility and cognitive function in people with PD. Our results show a clear maintenance in the disease stage and severity with an increase on balance control and functional mobility. Also, the maintenance of both the executive functions and the short-term memory was observed.

Even with an expected increase in the disease stage and severity (H&Y scale), patients that were enrolled in our 6-moths multimode exercise program maintained their disease and motor impairments (Table 1). Since PD is a neurodegenerative and progressive disorder (Olanow et al., 2009) it would be expected that after the intervention period these patients would present a reduction in their motor performance as also observed by others (Hackney & Earhart, 2010). Alves et al. (2005) found an increase of 3.2% in the H&Y score for each year. However, as shown in Table 2, our multimode training program was successful to maintain both UPDRS I and UPDRS III sub-scores and to decelerate the increment in H&Y score, since it was observed only a 0.04% raise in 6-months.

In this way, we can speculate that exercise promotes at least in part, a protective role on dopaminergic neuronal loss and on the disease impairments. Several studies had pointed out a positive exercise effect on brain function, as neural growth (Zigmond et al., 2009), higher neurotransmissors use efficiency (Petzinger et al., 2010) and angiogenesis (Hirsch & Farley, 2009). According to Tajiri et al. (2010), exercise can enhance synaptic plasticity with a re-construction of cortical path network on PD induced rat models. Therefore we can suggest that exercise played some role, not yet fully understand (Hirsch & Farley, 2009), in the protection of dopaminergic neural loss.

The characteristics of the multimodal exercise program were responsible for increase stability of these patients. All exercises were focused on the patients' impairments, as bradkynesia, unbalance, difficulties to perform sequential movements and changing movement directions. Therefore, we can affirm that the 10-20% of reduction in time to complete TUG and PLM tests (Table 2) was due, at least in part, to the intervention features, such as the group sessions and long-term duration. The program effect was enough to approach the patients' performance to healthy elderly (8.8 to 9.1 seconds – Alfieri et al., 2010). The reduction presented by our subjects is highly superior to that observed on both healthy elderly (Alfieri et al., 2010: 8-12%; Arai et al., 2009: 8%) and people with PD (Sage & Almeida, 2009: 6-8%). In this way, our data are particularly important, since the improvement in balance control reduces the risk of falling and therefore, reduces patients' mortality and morbidity (Lee & Chou, 2006).

It is believed that physical capacities such as strength, flexibility, aerobic resistance and others were worked properly during our multimode exercise program, allowing subjects to improve functional capacity and decrease their time spent to perform the TUG and PLM tests. We can also suggest that aerobic resistance was also improved by our intervention program. Before the program, subjects presented an increase on time to complete TUG in different attempts, suggesting the presence of fatigue (Garber & Friedman, 2003). However, after the 6-months intervention period, this time was maintained during different attempts (Figure 1). Also, subjects performed TUG and PLM tests with a lower variability at post-test in comparison to pre-test (Figures 1 and 2), showing an improvement on stability.

The multimodal exercise program also improved the episodic declarative memory, despite the physical exercise did not change the executive function and short-term memory

performance. However, studies have shown that the annual rate of clinical decline in people with PD is between 3.5% (Alves et al., 2005) and 11.2% (García-Ruiz et al., 2004). So, the maintenance of the scores in executive functions and short-term memory in the period of six months is also an important outcome for the patient.

The different memory systems depend on different anatomical structures. The short-term memory is located in the hippocampus and adjacent cortical areas of the temporal lobe, while episodic declarative memory is related to the medial temporal lobe, anterior thalamic nucleus, mammillary bodies, fornix, and prefrontal cortex (Robertson, 2002; Budson & Price, 2005). People with PD do report declarative memory loss but they do not report implicit memory loss, which suggests a problem of memorization strategy (Appollonio et al., 1994). To retrieve some information, people can use declarative memory, which requires conscious effort and attention, or implicit memory (typically unconscious), which is automatically accessed (Johnson et al., 2005). Due to degeneration of dopaminergic and cholinergic neurons in the nigrostriatal pathway in PD, cognitive behavior and the control of motor action are impaired. Therefore, the anatomical damages due to the disease can explain why episodic memory is the most affected (Calabresi et al., 2006). Our results showed that the episodic declarative memory (logical memory II) was more sensitive for the exercise. Perhaps, the exercise may achieve most impaired memory areas in PD patients.

As a study limitation we can not forget that all these results are applicable for subjects in the inital stages of the disease as those evaluated by our group. Also, it is important to remeber that a control group was not assessed and therefore there is a need to evaluate if some of these results were not related to learning or aging effects. However, our research group is already performing another study to fullfil this need.

5. Conclusion

As conclusion we can affirm that exercise as proposed by our group – a multimodal exercise program of long duration – plays an important role on the quality of life in people with PD by improving or maintaining their clinical parameters, functional mobility and cognitive function. This program has the capacity to decelerate the disease advance. This is particularly true when the disease stage and impairments are considered, as also seen in memory. These exercise effects are believed to be due to neuroprotection mechanisms no yet fully understudied and to an increase of all components of the functional capacity.

6. Acknowledgments

This study was supported in part by the PROEX/UNESP Univ Estadual Paulista and by the FAPESP – Fundação de Amparo à Pesquisa do Estado de São Paulo throughout scholarships (contract # 2010/07040-0, 2010/50532-0, 2009/02862-4 and 2007/06261-0).

7. References

Alfieri, F.; Riberto, M.; Ribeiro, C.; Lopes, J.; Santarém, J. & Battistella, L. (2010). Functional mobility and balance in community dwelling elderly submitted to multisensory versus strength exercises. *Clinical Interventions in Aging*, Vol. 5, pp.1810-185.

Alves, G.; Wentzel-Larse, T.; Aarsland, D. & Larsen, J. (2005). Progression of motor impairment and disability in Parkinson disease: a population-based study. *Neurology*, Vol. 65, pp. 1436-1441.

Appollonio, I.; Grafman, J.; Clark, K.; Nicheli, P.; Zeffiro, T. & Hallet, M. (1994). Implicit and explicit memory in patients with Parkinson's disease with and without dementia. *Archives of Neurology,* Vol. 51, No. 4, pp. 359-367.

Arai, T.; Obuchi, S.; Inaba, Y.; Shiba, Y. & Satake, K. (2009). The relationship between physical condition and change in balance functions on exercise intervention and 12-month follow-up in Japanese community-dwelling older people. *Archives of Gerontology and Geriatrics*. Vol. 48, pp. 61-66.

Bergen, J.; Toole, T.; Elliott III, R.; Wallace, B.; Robinson, K. & Maitland, C. (2002). Aerobic exercise intervention improves aerobic capacity and movement initiation in Parkinson´s disease patients. *NeuroRehabilitation*; Vol. 17, pp. 161-168.

Brach, J.; Simonsick, E.; Kritchevsky, S.; Yaffe, K. & Newman, A. (2004). The association between physical function and lifestyle activity and exercise in the Health, Aging and Body Composition Study. *Journal of the American Geriatrics Society*, Vol. 52, pp. 502-509.

Brucki, S.; Nitrini, R.; Caramelli, P.; Bertolucci, P. & Okamoto, I. (2003). Suggestions for utilization of the mini-mental state examination in Brazil. *Arquivos de Neuropsiquiatria*, Vol. 61, pp. 777–781.

Budson, A. E. & Price, B. H. (2005). Memory Dysfunction. *The New England Journal of Medicine*, Vol. 352, No. 7, pp. 692- 699.

Calabresi, P.; Picconi, B.; Parnetti, L. & Di Filippo, M. (2006). A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine–acetylcholine synaptic balance. *The Lancet Neurology*, Vol. 5, pp. 974-983.

Chaudhuri, K.; Healy, D. & Schapira, A. (2006). Non-motor symptoms of Parkinson's diseases: diagnosis and management. *The Lancet Neurology*, Vol. 5, pp. 235-245.

Chiari, H.; Mello, M.; Rezeak, P. & Antunes, H. (2010). Physical exercise, physical activity and the benefits of the memory of elderlys. *Revista Psicologia e Saúde*, Vol. 2, pp. 42-49.

Christofoletti, G.; Oliani, M.; Gobbi, L.; Gobbi, S. & Stella, F. (2006). Risk of falls among elderly people with Parkinson's disease and Alzheimer's dementia: A cross-sectional study. *Brazilian Journal of Physical Therapy*, Vol. 10, pp. 429-433.

Cools, R. (2006). Dopaminergic modulation of cognitive functionimplications for L-DOPA treatment in Parkinson's disease. *Neuroscience and Biobehavioral Reviews,* Vol. 30, pp. 1-23.

Costa, A.; Peppe, A.; Brusa, L.; Caltagirone, C.; Gatto, I. & Carlesimo, G. (2008). Levodopa improves time-based prospective memory in Parkinson's disease. *Journal of the International Neuropsychological Society*, Vol. 14, pp. 601-610.

Crizzle, A. & Newhouse, I. (2006). Is physical exercise beneficial for persons with Parkinson's disease? *Clinical Journal of Sport Medicine*, Vol. 16, pp. 422-425.

Cropley, V.; Fujita, M.; Innis, R. & Nathan, P. (2006). Molecular imaging of the dopaminergic system and its association with human cognitive function. *Biological Psychiatry*, Vol. 59, pp. 898-907.

Cyarto, E.; Brown, W.; Marshall, A. & Trost, S. (2008). Comparison of the effects of a home-based and group-based resistance training program on functional ability in older adults. *American Journal of Health Promotion*, Vol. 23, No. 1, pp.13-17.

de Lau, L. & Breteler, M. (2006). Epidemiology of Parkinson's disease. *The Lancet Neurology*, Vol. 5, pp. 525–535.

Dibble, L.; Hale, T.; Marcus, R.; Gerber, J. & LaStayo, P. (2009). High intensity eccentric resistance training decreases bradykinesia and improves quality of life in persons with Parkinson's disease: A preliminary study. *Parkinsonism and Related Disorders*, Vol. 15, No. 10, pp. 752-757.

Dubois, B. & Pillon, B. (1997). Cognitive deficits in Parkinson's disease. *Journal of Neurology*, Vol. 244, pp. 2-8.

Dujardin, K. & Laurent, B. (2003). Dysfunction of the human memory systems: Role of the dopaminergic transmission. *Current Opinion in Neurology*, Vol. 16 (Suppl. 2), pp. S11-S16.

Dujardin, K.; Defebvre, L.; Krystowiak, P.; Degreef, J. & Destee, A. (2003). Executive function differences in multiple system atrophy and Parkinson's disease. *Parkinsonism and Related Disorders*, Vol. 9, pp. 205-211.

Fabre, C.; Chamari, K.; Mucci, P.; Massé-Biron, J. & Préfaut, C. (2002). Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. *International Journal of Sports Medicine*, Vol. 23, No. 6, PP. 415-421.

Fahn, S.; Elton, R. & Members of the UPDRS Development Committee. (1987). Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. *Recent Developments in Parkinson's Disease*. Florham Park, NJ: Macmillan Health Care Information, pp. 153–63.

Folstein, M.; Folstein, S. & McHugh, P. (1975). Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, Vol. 12, pp. 189–198.

Gobbi, L.; Oliveira-Ferreira, M. D.; Caetano, M. J.; Lirani-Silva E.; Barbieri, F.; Stella, F. & Gobbi, S. (2009). Exercise programs improve mobility and balance in people with Parkinson's disease. *Parkinsonism and Related Disorders*, Vol. 15, pp. S49-52.

Grimbergen, Y.; Munneke, M. & Bloem, B. (2004). Falls in Parkinson's disease. *Current Opinion in Neurology*, Vol. 17, pp. 405–415.

Hackney, M. & Earhart, G. (2009). Health-related quality of life and alternative forms of exercise in Parkinson disease. *Parkinsonism and Related Disorders*, Vol. 15, No. 9, pp. 644-648.

Hackney, M.. & Earhart, G.. (2010). Effects of dance on gait and balance in Parkinson's disease: a comparison of partnered and nonpartnered dance movement**.** *Neurorehabilitation and Neural Repair, Vol.* 24,No. 4, pp. 384-392.

Heaton, R.; Chelune, G.; Talley, J.; Kay, G. & Curtiss, G. (1993). *Wisconsin card sorting test manual*. USA: Psychological Assessment Resources.

Hirayama, M.; Gobbi, S.; Gobbi, L. & Stella, F. (2008). Quality of life (QoL) in relation to disease severity in Brazilian Parkinson's patients as measured using the WHOQOL-BREF. *Archives of Gerontology and Geriatrics*, Vol. 46, pp. 147-160.

Hirsch, M. & Farley, B. (2009). Exercise and neuroplasticity in persons living with Parkinson's disease. *European Journal of Physical and Rehabilitation Medicine,* Vol. 45, No. 2, pp. 215-229.

Hoehn, M. & Yahr M. (1967). Parkinsonism: onset, progression and mortality. *Neurology*, Vol. 17, pp. 573–581.

Johnson, A. M.; Pollard, C.; Vernon, P.; Tomes, J. & Jog, M. (2005). Memory perception and strategy use in Parkinson's disease. *Parkinsonism and Related Disorders*, Vol. 11, pp. 111-115.

Karlsen, K.; Tandberg, E.; Arsland, D. & Larsen, J. (2000). Health related quality of life in Parkinson's disease: a prospective longitudinal study. *Journal of Neurology, Neurosurgery and Psychiatry*, Vol. 69, pp. 584–589.

Lee, H. & Chou, L. (2006). Detection of gait instability using the center of mass and center of pressure inclination angles. *Archives of Physical and Medicine Rehabilitation*, Vol. 87, pp. 569-575.

Miyai, I.; Fujimoto, Y.; Ueda, Y.; Yamamoto, H.; Nozaki, S.; Saito, T. & Kang, J. (2000). Treadmill training with body weight support: its effect on Parkinson's disease. *Archives of Physical Medicine and Rehabilitation*, Vol. 81, pp. 849-852.

Morris, M.; Iansek, R. & Kirkwood, B. (2009). A randomized control trial of movement strategies compared with exercise for people with Parkinson's disease. *Movement Disorders, Vol.* 24, pp. 64-71.

Nocera, J.; Horvat, M. & Ray, C. (2009). Effects of home-based exercise on postural control and sensory organization in individuals with Parkinson disease. *Parkinsonism and Related Disorders*, Vol. 15, No. 10, pp. 742-745.

Obeso, J.; Olanow, C. & Nutt, J. (2000). Levodopa motor complications in Parkinson's disease. *Trends in Neurosciences*, Vol. 23, pp. S2-S7.

Owen, A. (2004). Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. *Neuroscientist*, Vol. 10, pp. 525-537.

Olanow, C.; Stern, M. & Sethi, K. (2009). The scientific and clinical basis for the treatment of Parkinson disease. *Neurology*, Vol. 72, No. 4S, pp. S1-S136.

Paolo, A.; Troster, A.; Axelrod, B. & Koller, W. (1995). Construct validity of the WCST in normal elderly and persons with Parkinson's disease. *Archives of Clinical Neuropsychology*, Vol. 10, No. 5, pp. 463-473.

Pascual-Sedano, B.; Kulisevsky, J.; Barbanoj, M.; García-Sánchez, C.; Campolongo, A.; Gironell, A.; Pagonabarraga, J. & Gich, I. (2008). Levodopa and executive performance in Parkinson's disease: A randomized study. *Journal of the International Neuropsychological Society*, Vol. 14, pp. 832-841.

Petzinger, G.; Fisher, B.; Van Leewmen, J.; Vucovik, M.; Akopian, G.; Meshul, C.; Holschneider, D.; Nacca, A; Walsh, J. & Jakowec, M. (2010). Enhancing neuroplasticity in the basal ganglia: the role of exercise in Parkinson's disease. *Movement Disorders*, Vol. 25, p. S141 – S145.

Pieruccini-Faria, F.; Menuchi, M.; Vitório, R.; Gobbi, L.; Stella, F. & Gobbi, S. (2006). Kinematic parameters for gait with obstacles among elderly patients with Parkinson's disease, with and without Levodopa: a Pilot Study. *Brazilian Journal of Physical Therapy*, Vol. 10, No. 2, pp. 233-239.

Podsiadlo, R. & Richardison, M. (1991). The Timed "Up & Go": A Test of Basic Functional Mobility for Frail Elderly Persons. *Journal of the American Geriatrics Society*, Vol. 39, pp. 142–148.

Rashid, A.; So, C.; Kong, M.; Furtak, T.; El-Ghundi, M.; Cheng, R.; O'Dowd, B. & George, S. (2007). D1-D2 dopamine receptor heterooligomers with unique pharmacology are

coupled to rapid activation of Gq/11 in the striatum. *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 104, No. 2, pp. 654-659.

Reuter, I.; Engelhardt, K. & Baas, H. (1999). Therapeutic value of exercise training in Parkinson's disease. *Medicine and Science in Sports and Exercise*, Vol. 31, pp. 1544-1549.

Ridgel, A.; Vitek, J. & Alberts, J. (2009). Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabilitation and Neural Repair*, Vol. 23, pp. 600-608.

Robertson, L. T. (2002). Memory and the brain. *Journal of Dental Education*, Vol. 66, No. 1, pp. 30-42.

Sage, M. & Almeida, Q. (2009). Symptom and gait changes after sensory attention focused exercise vs aerobic training in Parkinson's disease. *Movement Disorders,* Vol. 24, pp. 1132–1138.

Sage, M. & Almeida, Q. (2010). A positive influence of vision on motor symptoms during sensory attention focused exercise for Parkinson's disease. *Movement Disorders,* Vol. 25, pp. 64-69.

Scandalis, T.; Bosak, A.; Berliner, J.; Helman, L. & Wells, M. (2001). Resistance training and gait function in patients with Parkinson's disease. *American Journal of Physical Medicine and Rehabilitation,* Vol. 80, pp. 38-43.

Steg, G.; Ingvarsson, P.; Johnels, B.; Valls, M. & Thorselius M. (1989). Objective measurement of motor disability in Parkinson's disease. *Acta Neurologica Scandinavica*, Vol. 126, pp.67–75.

Stella, F.; Gobbi, L. T. B.; Gobbi, S.; Oliani, M. M. & Tanaka, K.; Pieruccini-Faria, F. (2007) Early impairment of cognitive functions on Parkinson's disease. *Arquivos de Neuropsiquiatria*, Vol. 65, pp.406-410.

Tanaka, K.; Quadros Jr, A. C.; Santos, R.; Stella, F.; Gobbi, L. & Gobbi, S. (2009). Benefits of physical exercise on executive functions in older people with Parkinson's disease. *Brain and Cognition*, Vol. 69, pp. 435–441.

Taylor, A.; Saint-Cyr, J. & Lang, A. (1986). Frontal lobe dysfunction in Parkinson's disease: The cortical focus of neostriatal outflow. *Brain*, Vol. 109, pp. 845-883.

Wechsler, D. (1997). *The Wechsler Memory Scale – III Revised (Manual)*. Santo Antonio Texas: Psychological Corporation.

White, D.; Wagenaar, R. & Ellis, T. (2006). Monitoring activity in individuals with Parkinson's disease: a validity study. *Journal of Neurological Physical Therapy*, Vol. 30, No. 1, pp. 12-21.

Zigmond, M.; Cameron, J.; Leak, R.; Mirnics, K.; Russell, V.; Smeyne, R. & Smith, A. (2009). Triggering endogenous neuroprotective processes through exercise in models of dopamine deficiency. *Parkinsonism and Related Disorders*, Vol 15, No S3, pp. S42-S45.

17

Rehabilitation of Patients Suffering from Parkinson's Disease by Normotensive Therapy

Gilles Orgeret
Regional Hospital,
Poissy/Saint Germain en Laye,
France

1. Introduction

Neurodegenerative injuries lead to disabilities, such as sensory and motor disturbances, with patients often losing their balance, and falling as a consequence. Moreover, capsulo-ligamentary adhesions often occur, which create stiffness and secondary retractions due to the lack of mobilization of the periarticular structures. These complex clinical pictures, when interlinked, are even more important when simultaneously the patients suffer from recurrent diseases, such as degenerative rheumatism.

Parkinson's disease, this public health issue, is evaluated through clinical criteria, as there are as many forms of Parkinson's disease as there are various cases. Personalized and adaptable physiotherapist option is therefore necessary. The syndrome associated with Parkinson's disease is characterized by a motor disorder, an akinesia combined with one of the following symptoms: extra pyramidal stiffness, tremor and postural instability. A depressive syndrome, a cognitive decline, and more or less disabling pain, come on top of the clinical picture. The patients frequently suffer from cramps or painful contractions, which mainly affect (74%): calves, neck, lumbar rachis, and which are more or less combined with dystonia. Comorbidities make the treatment even more complex. And it is always difficult to know, when considering the symptoms and their origin, whether it is Parkinson's or other illnesses which are to blame. These comorbidities should always be taken very seriously, and be properly treated, as they have an influence on the patient's mobility fluctuations *(1)*.

Normotensive Therapy reinitiates the movement, it treats stiffness, pain, and lack of mobility. 68% of patients, whatever the stage of the disease they are in, suffer from concomitant illnesses such as: arthritis which can affect shoulders and knees and make the postural syndrome even worse, undefined chronic pain, arterial hypertension or heart pathologies. Unfortunately taking drugs often triggers rheumatism symptoms, and either contributes to their development, or keeps them going and makes them worse *(2)*. The drugs intake is, on top of that, one of the main risk factors of fall among the elderly, and therefore complicates the rehabilitation. These drugs intake is a real risk factor whatever the patient's residence, autonomy and independence level are, as it underlines poor health condition and pre-existent fragility. The drugs classes which are mostly to blame are :

psychotropic substances (most of the time the first to be cited), as well as hypnotic, sedative, antihypertensive, antalgic and opiate drugs (3).
Mepronizine, a treatment for accidental insomnia, is to be avoided in the elderly, especially when over 75 years old, as it may cause falls and intoxications. At the opposite, some other drugs like Dopamine might help the patient suffering from Parkinson's disease, especially at the beginning of the illness as it has a protective role, which is not so obvious when the illness is more developed.
An increase in the L-Dopa dose, the first intention drug, might lead to motor fluctuations after a two year treatment, such as diskinesia and akinesia.
Furthermore, the end of dose of L-Dopa is to be taken into account versus akinesia *(4)*. A well trained Normotensive Therapy physiotherapist will consider the stage of the patient's illness before making his choice among the different maneuvers. Should the Physiotherapist consider a maneuver for the patient, if it proves inadequate, he would easily switch to another one. For example, he could switch from an active exercise which involves the patient's participation to a passive and gentler manoeuver. The NT (Normotensive Therapy) is a very adaptable physiotherapist option, but it requires the patient's total acceptance, in order to avoid situations of conflict which might cause confusion and/or diskinesia. The NT must be carried out at fixed time, so that the patient is physically and mentally well prepared, and available (never disturb a family visit for instance, wait until toilet is over). The NT will be more effective in favorable conditions: correct heating of the room, well adapted clothes and shoes. The after-meal times should be avoided as the digestion might disturb the course of the exercises. Abrupt exercises are to be avoided.

2. Successive stages of the illness

Parkinson's disease takes on three different main stages: the honeymoon period, the stage when the illness gets settled, and the dependency stage.
In the initial phase of the illness, the symptoms are usually mild and the NT attempts to keep and reinforce the patient's balance, while trying to improve the pain and functional impotency resulting from degenerative rheumatism. Back pain is frequently shown as the main preexisting handicap, often disturbing the thoracic amplitude and therefore the cardiorespiratory system.
In the second phase, and during the "on" period, the patient's balance will be improved by exercising on the Klein balloon, wearing an elastic bandage for other specific exercices, and by foot-stimulation with TENS (Transcutaneus electro-neuro-stimulation) as described further on (new treatments). The patient will be encouraged to keep a straight and upright position as long as possible, and the NT will help the joints to stay supple and the breathing to keep its former amplitude thanks to anti-kyphosis and anti-flessum NT maneuvers.
During the "off" period, the postural, articular, and muscular pain increase, due to motor deficit, depressive syndrome, and medication (5) . That is why it is very important to keep using the Klein balloon during that period (under supervision) while the patient's physical movements are usually limited. The physiotherapist will try to make the muscles relax in order to facilitate the movements and the NT maneuvers will deaden the pain.
In the third phase, when the dependency becomes complete, the physiotherapist will try to prevent the patient from becoming utterly bedridden, in carrying on NT maneuvers (relaxing maneuvers), and the pain treatment. An appropriate use of the Klein balloon in handicapped patients, will be encouraged under strict supervision.

3. The *Normotensive Therapy*: An alternative method to reinitiate the movement

NT is not a medicine, although it depends on a personalized morpho-staturo-dynamic examination. It is based on a medical diagnosis, and is carried out in close collaboration with the medical staff (general practitioner, psychologist, nutritionist, occupational therapist, speech therapist, relaxation therapist). NT is not symptomatic and treats the whole body, focusing on zones which seem essential to treat, even if these zones have not been mentioned by the consultant.

Two main poles of intervention :

1. Atraumatic manual normalization of the tissues which should correct stiffness and allow mobility to be restored without any pain.
2. Control and correction of the posture thanks to specific exercises.

The NT is a manual atraumatic therapy with no articular thrust beyond physiological amplitude. It is an important source of somesthetic afferences, as the patient suffering from Parkinson's is particularly receptive to the neuro-informational sensory component of this kind of specific massage.

The word "Normotensive" is a contraction of two words: "normalization and tension". It is a myofascial and neurosensorial therapy which doesn't imply hooking the tendons. During the session, the patient is kept in an active postural activity all the time, the passive maneuvers on the tissues being carried out before and after the exercises. In the Parkinson's case, NT helps restore scapulothoracic mobility, reduce kyphosis, improve ventilation often disturbed by thoracic tightening, and improve the functional clinical picture: postural reactions, balance, walking. It treats the pain due to bad postures, or the after-effects of concomitant disorders such as degenerative rheumatism. No excess stress or fatigue can arise from NT, as it is quite a soft therapy.

The manual normalization of the tissues depends on two maneuvers: *the triggering touch* and the *relaxing touch*.

These maneuvers are not to be carried out in case of inflammation or injuries whether superficial or deep.

3.1 The triggering touch

It is a sustained vibrating proprioceptive therapeutic maneuver, which is less than one minute long, and can be manual (most of the time) or instrumental, according to two distinct methods. In the Parkinson's, the plastic hypertonia expresses itself in a resistance to the passive stretching of the muscles. It is therefore essential to control the muscular contraction, so that it is more effective, and the *triggering touch* is part of it, being a soft stretching method encouraging the muscular relaxation. Indeed, in central neurology, the response to the vibrations is more easily recognized than some other finer tactile perceptions.

The *triggering touch* is based on two methods:

The first maneuver called *static triggering touch*, aimed at the soft tissues. It is a long lasting transcutaneous vibration under soft traction of the dysfunctional myofascial structure.

The vibratory intensity is modulated according to the local thickness of the teguments, to the more or less deep situation of the above-mentioned soft tissues, and to the wish not to be algogenic.

The second maneuver called *dynamic triggering touch*, aimed at the joints. The physiotherapist will give the regarded joint a soft passive vibratory movement of limited amplitude (flexion-extension, rotation, or adduction-abduction, according to the contingent possibilities). If possible this gesture is backed up by a very gentle segmental traction-decoaptation.

Tissue traction

In order to properly understand the interest of the superficial tissue traction, let's cite *Rabishong:* "the identification of rachidial posture and position is made by tractions on the skin". This traction gives to the central nervous system a feeling of muscular stretching. Then, the vibration made on highly tendinous zones, makes the treated muscle relax by activation of the antagonist (Sherrington Law).
Besides, the Golgi tendon organs, neuronal endings surrounded by a connective capsule, are situated at the junction between the smooth muscle fibers and the tendinous tissue. The Golgi tendon organs, could help monitor muscle strengths in order to fight gravity. Mechanoreceptors, Ruffinian corpuscules, Golgi corpuscules, are situated inside the articular capsules and the ligaments. And this is precisely where the NT is efficient.

Vibrations

Vibrations have been used since antiquity as therapeutic means. Transcutaneous mechanoreceptors are very sensitive to transcutaneous vibrations. These vibrations result in a mainly sensorimotor neuronal message, facilitate the sliding plans, relieve the pain, and reinforce the *gate control* (6). The primary endings of the neuromuscular spindles are activated too, especially when the source of the vibratory impact is close to the tendons. So, proprioceptive information can easily be rigged by a vibration, and this one, if its intensity and frequency are well adapted, leads to a modification in the information coming from the fibers Ia, and therefore will be read by the neuronal system as a muscular stretching (7, 8, 9). This misinterpretation from the central nervous system gives the illusion that the joint is moving, and that the vibrated muscle is contracting, which leads to a change in the patient's postural control. Using this information, several studies have analyzed the effect of a vibration upon the muscles of different joints on the postural control (10, 11, 12). Results show that the nervous system interprets the signal coming from the vibrated muscles differently according to its location. Applying a vibration to the pelvic limbs leads to corrective reactions from the whole body in an opposite direction of the perceived movement, whereas above the pelvis the reaction occurs in the same direction as the perceived movement. For some authors (13, 14, 15), this is due to the strong interaction between the vestibular and proprioceptive cervical informations while the information is being treated by the central nervous system, because of the necessity to know the relative position of the head and the trunk to use the vestibular information in a satisfying way. For other authors (16, 17, 18), it is due to the functional role of the proprioceptive messages coming from different body parts. For instance, it is possible to give a function of opposition to the destabilization of the body to the proprioceptive messages coming from the lower body, whereas they give the function of orientation of the body to the information coming from the cervical region. These items of scientific research help the Normotensive treatment determine how to correct the posture. They always involve a cephalocervical treatment.

3.2 The relaxing touch

It always takes place after the triggering touch and takes into consideration the fact that a disruption in the articular micro-movements leads to a loss of performance in great amplitude movements. The *relaxing touch*, according to two modes, will allow the tissue mobility to be restored and the pain to be soothed, by working on the *tensive lesions*, a few millimeters long pathogenic threadlike cords, or tight strings. In case of a skeletal muscle being contracted, they are very easily recognizable in a softer surrounding myofascial structure. It is explained by the comprehension of the myotatic reflex, and of the effect of the motoneurons. The alpha and beta motoneurons, are equipped with an inhibition system called recurrent inhibition. Golgi receptors which are scattered at the muscle-tendon or muscle-aponeurosis junction, are receptive to their stretching. They have a direct role in the control of the contraction and in the feed-back of the normal myotatic reflex. And this zone is precisely the one which interests the NT (19). Furthermore, about the nature of the collagen, the late Eric Viel used to describe an ogive shape which overlaps, with *cross-linkage* contacts between the fibers beams. These *cross-linkages* can turn into points which become hardened because of: an immobilization, an attitude syndrome, a trauma, or any deep or superficial injury. The great anatomist Xavier Bichat used to call these *cross-linkages* : "hardened tissues". The stiffness of the collagen tissue being a sign of ageing, and making the spine tissues harder. The physiotherapist fingers, used to the NT, can detect these points where collagen sticks, and set it free (20).

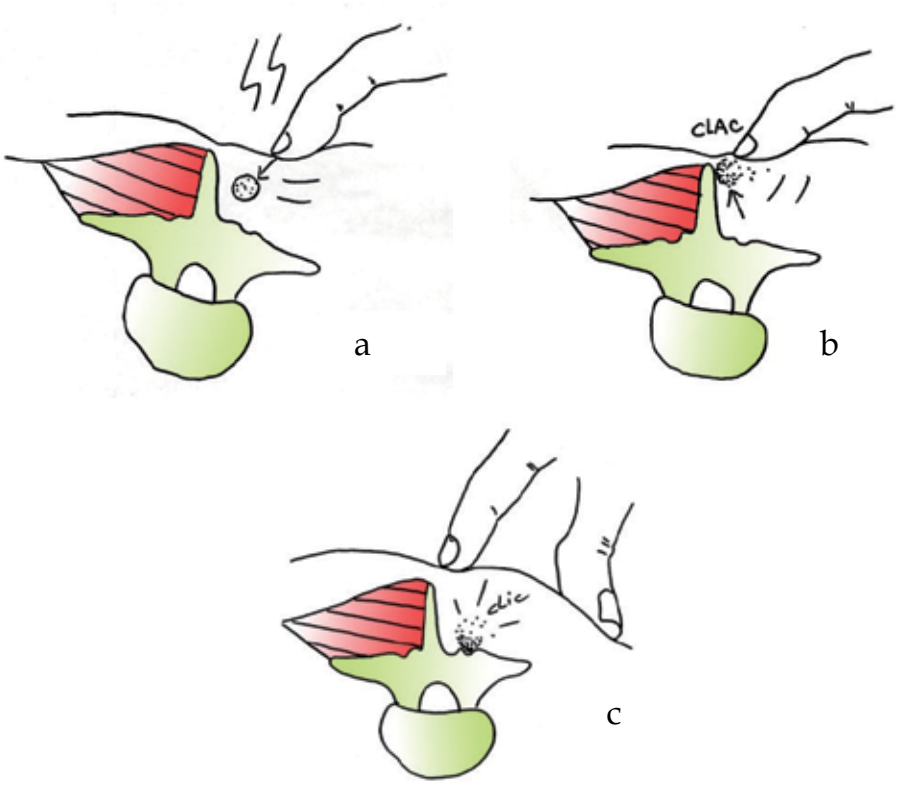


Fig. 1. The two modes of the *relaxing touch*

When they are close to a bone relief, the physiotherapist sharply pushes away the *tensive lesions* against this bone (Fig 1, a). He crushed them on the bone and makes them crack (Fig 1, b). If there is no close bone relief around, the therapist strongly squeezes them between thumb and index, as if they were a guitar string. This gesture is to be made two or three times at a go.
The second gesture consists in making the treated soft structures bulge while vibrating. It looks like the "roll and lift" method, but it is longitudinal instead of being transversal (Fig 1, c). It aims to make the tissues become detached, and to allow them to slide on each other again.

4. Control and normotensive postural corrections

4.1 The functions of the postural system

The sensorimotor control of our postures and movements, is subject to fluctuations in the course of our existence. Unfortunately, it turns out not to be very effective for most people, whether they are ill or not. Should this control be disturbed on a long term basis, some signs might appear such as: tiredness, pain, tendonitis, degenerative arthralgia, discal hernia. Four sensorial entries are mainly to blame: internal ear, podal afference, vision, jaw.
Very soon in life, from the age of 35, the postural extensive muscles weaken, which leads to some difficulties for the rachis to adapt to verticality. Besides, when an elderly has a bad fall, his balance can be definitely disturbed (clinical picture of "post fall" and dysexecutive syndrome).
In the Parkinson's disease, where sensorial afferences are highly disturbed, especially the graviceptive somesthetic information, it is essential that the balance be taken therapeutically into account. The habits in the use of the body are progressively disturbed. If the patient is elderly, myogene or neurogene atrophy can occur and lead to a muscular unbalance, whatever the gravity of the illness.
The human motor behavior is organized in reference to a biological vertical line, which is built by the brain from visual and graviceptive informations (otolithic and somesthetic). Evocating the notion of position in an environment implies a system of reference. The system of reference based on the gravity vertical line, is mainly informed by the vestibular system, whereas the one which is based on landmarks in the space is mainly informed by the vision. As for the one which is peculiar to the individual, it is based on information coming from the somesthetic system (one of the base of the NT treatment).
The search for balance is the decisive factor of the postural control. Some cerebral injuries can alter the ability to keep a certain position, or to change it, in the three fundamental postures: reclining, sitting and vertical position. Sometimes, serious abnormalities of the sense of verticality can occur from a tactile, visual, or postural perception of the vertical line. In neuronal (or vestibular) pathology, the abnormalities of the subjective vertical line consist in the existence of a slantwise direction, and/or an uncertainty about the verticality. Any cerebral injury concerning a zone which is involved in the graviceptive vestibular or somesthetic perception can lead to a disturbance in the construction of the subjective vertical line. An injury of the vestibular tracts affecting the graviceptive somesthetic tracts will give an angle to the subjective vertical line concerning the postural perception of the vertical line. The posterolateral thalamus is not only an intermediary for the vestibular tracts, but it could be a fundamental structure for the control of the upright position as well. In the patients suffering from Parkinson's, the postural mode of the subjective vertical line is disturbed.

The vestibular, somesthetic, and visceral graviceptors, contribute to the actualization of this subjective vertical line (21).
However, if the contribution of the visual and somesthetic information to the control of the biped posture is well determined, the one regarding the vestibular informations remains a controversial issue. A study mention sensitivity thresholds of the upper semicircular canal, to the quickening of the classic postural fluctuations observed in an undisturbed upright static position (22).
Our tactile sensitivity is conveyed by different mechanoreceptors (Meissner, Pacini and Ruffini corpuscules, Merckel discs…). They provide informations about the outer world to the central nervous system, mainly thanks to the hands and the feet. That is why the NT is seriously taking them into consideration. The tactile receptors of the plantar sole are quite important, but the other cutaneous informations should not be overlooked. From feet to head, the continuity of the sensorial information which allows our balance, relies on numerous muscles and joints which are associated in chains. The plantar arches give informations about the variety of supports, eyes give information about the position into the space. There is a direct link between jaw and neck, and between eyes and neck muscles. The stability of the head relies on the balance between the jaw joints (23). Some scientific studies suggest, on the one hand, that the central and peripheral visions play a complimentary role in the control of the biped posture, and, on the other hand, that the relative contribution of each of these visions depends on the information given by the other sensorial systems, especially the somatosensorial informations coming from the foot-ankle segment (24, 25). If the sensorial captors are situated in different parts of the body, the information they provide converge to common cortical or subcortical structures, which control the postural system through different reflexes. The vestibulo-ocular reflex allows the stabilization of the eyes, the vestibulo-spinal and vestibulo-oculo-cervical reflexes allow the global control and the maintenance of the posture by their action upon the myostatic reflex.
In the patient suffering from Parkinson's, the visual stimulation is usually shown as being supportive to the reconstruction of the motor activity. Nothing is less certain. The whole day long, the patient is aware of the risks due to his pathology, and the result is not conclusive. The movements with the eyes open are inefficient and ill adapted to the real needs of the patient, who is under constant stress while performing his daily routine. During the NT session, the vision is sometimes occulted in order to reinforce the patient's confidence in his other senses, as he often perceives the environment as hostile and full of potential and insurmountable difficulties. It is not possible for the patient to control everything: balance, postural correction, lengthening of the step. If the eyes are closed, and the therapist around, the patient can relax and focus on the reinforcement of his other senses, which later on will allow him to adapt better to the variations of his environment. In his everyday life, the extrinsic factors which are factors of falls such as: faulty lighting, carpets or furniture, will be more easily grasped, the vision becoming an asset adding to the other reinforced senses, instead of just being a substitute.

4.2 Posturo-normo-regulator examination

It is inspired by the medical clinical examination, and by the anamnesis. It is important to appreciate the comorbidity which could alter the conclusions of the examination: medical history of cardiovascular accident, heart failure, myocardial infarction, infectious illness, hypoglycemia if diabetic patient. The posturo-normo-regulator examination involves many

maneuvers, which cannot all be mentioned in this paper which does not aim to be exhaustive.
The patient is examined when in underwear. The examination should not be more than 5/10 minutes long, as the patient will rapidly adopt wrong corrective postures which will alter the conclusions. It is important to look for faulty postures and maladjusted movements which might pose problems.
The examination regarding the balance control consists in checking the patient's ability to stay in a stable position when sitting, then standing, with the eyes wide open, then closed. The static and dynamic bipodal then unipodal phases are assessed (there is an abnormality if the patient cannot stand more than 5 seconds on his favorite foot, with his eyes wide open (26). The *Get-up-and-go test* consists in asking the patient, sitting on a chair which is 3 meters from a wall, to stand up, stay immobile for a few seconds, walk up to the wall, turn round and go back to the chair and sit again in no particular hurry. Between the age of 65 and 85, it normally takes the patient about 12 seconds to perform the exercise. If the exercise takes him more than 30 seconds, the patient is said to be highly dependent. The inability to stand on one foot for less than 5 seconds is said to be pathologic (27).

4.2.1 Postural bearing test

It aims to detect the degree of global corporal instability. This test is to be carried out both at the beginning and at the end of the physiotherapy session. The end of session test is expected to be better than the one carried out at the beginning of the session. In case it is not so, the following session must be optimized by either changing the time of the session, or by reinforcing the balance control exercises. All these sessions will be interrupted with NT normalization of the tissue maneuvers.

Fig. 2. Postural bearing test

The patient is standing up, eyes closed. Without any warning, the therapist is exerting a thrust in the popliteal space. The therapist can check the reaction of the different body segments, and then evaluate the restoration of the balance component, and the arms swing (Fig 2).

4.2.2 Test in the trunk diagonal with focus on the fluctuating effect

It is about the closing chain of the locomotion muscular chains, and it tests the mobility of the scapular and pelvic belt with each other.

This examination is to be carried out on both sides, as a comparison test. The therapist lays one hand on the patient's shoulder, and the other one on the opposite hip. Then he exerts a sudden thrust with his two hands, in order to test the articular mobility. For instance a thrust on the shoulder may harmoniously drag down the lateral hemithorax, whereas the opposite hip remains blocked in the high position, which evokes a flaw in the lombo-pelvic cinematic (Fig 3).

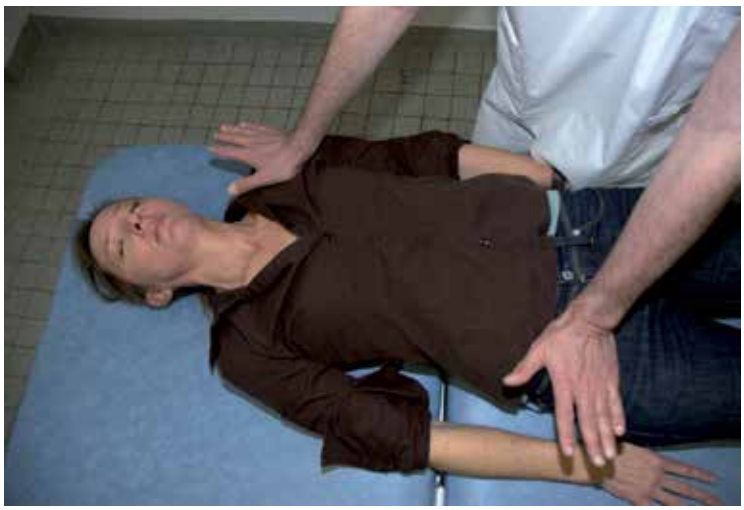


Fig. 3. Test in the trunk diagonal with focus on the fluctuating effect

5. Rehabilitation

In the patient suffering from Parkinson's, the poor speed and amplitude of the movements are to be seriously taken into consideration before any other parameter. The NT treatment is a combination of different balance control exercises on a Klein balloon and when wearing an elastic bandage, and also normotensive correction of the tissues carried out either before or during or even after the exercises. The sessions must be quite short in duration, interrupted with phases of rest. It is indeed important to hold the patient's attention during the session and even to make sure he enjoys it.

5.1 About the obstacle of dystonia

Dystonia is movements in profusion which is difficult to control. When walking, the patient takes long strides and swerves, and might easily fall. However disturbing they might be, this dystonia should not prevent the rehabilitation session to be carried out in a satisfactory

way, even if they are painful or if they disturb the patient's balance because of their impact on the joints, or on any other body segment.
If the exercise in process is definitely disturbed, it is then necessary to carry on the session with other active or passive maneuvers, and to come back later on to the previously planned exercise, at a more convenient time.

5.2 The walking ability

We know that some factors predispose to falls, such as : being over 80, being a woman, depressed, suffering from a loss of strength or a bad coordination of movements, or from feet abnormality or ill-fitting shoes. In the patient suffering from Parkinson's, the main problem with the walking ability is that not only is the walking faulty, but it moreover lacks stimulation. Over the years, walking becomes slower, with a shortened step, a lengthening of the time when the two feet are supportive, a loss in the arms swing, and a tendency to stand with the trunk leaning backwards (28).

5.3 Improvement in walking by foot stimulation by TENS (Transcutaneous electro-neuro-stimulation)

Most of the patients suffering from Parkinson's are suffering from their feet. As a consequence the neuro-informational podal component, which is essential to the balance control, is disturbed. This leads to falls in the patients. However it is possible to improve the postural vertical component, thanks to a low frequency ambulatory transcutaneous neurostimulation. This stimulation improves the foot somesthetic perception. It stimulates the walking. The power reinforces the foot afferences, giving the patient a better perception of the support.

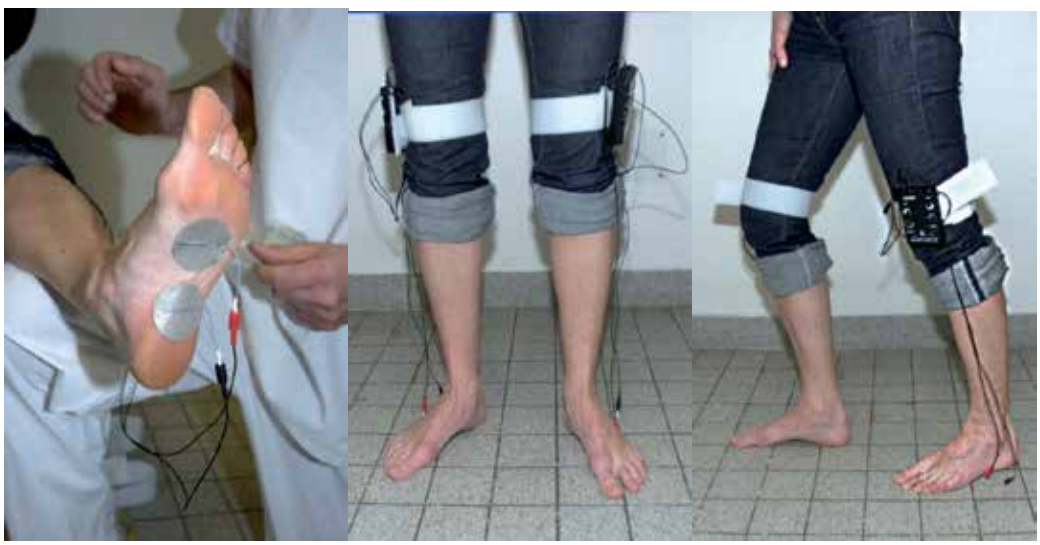


Fig. 4. The electrodes are installed in medioplantar. The stimulation must not be excitomotor. The power must be of a low intensity, just enough to be perceptible, and no algogenic. If one of the feet is less responsive, we must increase the stimulation on the less responsive side. It is possible to vary the treatment, for instance in stimulating only one of the feet, or in modifying the electrodes position, in order to get a better motor reaction.

5.4 Exercices and walking with an elastic bandage

It has been proved that wearing elastic adhesive bandages on different body parts, or Velcro bandages, could increase the intensity of tactile informations (29, 30). Taking this information as a starting point, I had the idea to initiate the occasional wearing of an elastic bandage (60mm wide coarsely woven flat elastic band, 10 m long roll), to be worn directly on the clothes. It is especially recommended in case of: weakness of a lower limb, osteoporosis, arthritis, backache, very old age, Alzheimer, hemiplegia, Parkinson's. This extensor system allows the patient to better apprehend his body from every angle. It helps him to feel the joints interaction, forces him to stretch his body, encourages the proprioception, and re-educates the vertebral erectors in restoring the balance of the chains of movements. In the Parkinson's case, the equinism of the ankle pushes the patient back even more. The elastic bandage partly makes up for that. It must be on while exercising, and even for a few hours a day if necessary. It is not to be kept on too long, nor when sleeping, sitting, or lying down.

Place the elastic bandage in the middle of the foot, and then pull it up to the shoulders, folding it tightly and firmly across the body. (Figures 5, 6, 7 and 8)

Fig. 5. Standing up after sitting. To restore the gravity line forward (its tendency being backward), the patient pull on his "suspenders".

Fig. 6. Putting forward an upper limb or exaggeratedly lifting a lower limb, in making sure the movement doesn't push the patient backward, might be enough to initiate the step. The patient is asked to pull on the elastic bandage as he would do with suspenders (that he should wear later on, for the same use). When stepping over an obstacle, it is first the therapist who pulls on the bandage to help the patient move, and then it should be the patient himself who does it, as soon as he/she is able to.

Fig. 7. Half a turn, initiated by the therapist (then by the patient), in waddling alternately to the left and to the right, in order to alight the body weight so that the foot can move forward

Fig. 8. Harmonization of the movements of the shoulder and pelvic girdle, during the moving

5.5 Specific exercises on the Klein balloon

"An active sitting position should be encouraged whereas a passive position should be avoided !"

Generally speaking, we should all sit on a balloon instead of using a chair, as a passive sitting position is very aggressive for our back, alter our balance, and doesn't make sense on the postural point of view.

A posture which is too long maintained is always harmful, especially when regarding elderly people or people who seldom move. It is the same problem with the patients suffering from Parkinson's. The elderly women who spend more than 9 hours a day sitting have one and a half more risks of suffering from a broken hip than the women who sit less

Fig. 9. Exercise of transfer of the body weight from one foot to the other one, a phase which is essential for the initialization of the step. The therapist can give a rhythm to the exercise. For example he claps his hands to help the patient change his support, and the exercise can be carried out more or less rapidly

Fig. 10. Make a ball roll on a long table when walking alongside it. At the end of the table, change hands and go back to the starting point. Accelerate the pace progressively

than 6 hours a day (31). Unfortunately elderly people are most of the time made sitting in a chair the whole day long, especially in old people's homes. Because of that, the motor deprogramming is quick which makes the rehabilitation even more difficult. It would be much better to encourage the elderly, if their health condition allows it, to sit on the Klein balloon in order to reinforce their balance.
In the case of the patients suffering from Parkinson's, the balance of the head, as well as the setting of the body weight forward, should be thoroughly checked, as the akinesia leads to the gestures being scarce, to the body coiling itself up, and to retractions. The exercises while sitting on the balloon, backed up with manual maneuvers, try to make up for these problems.

6. Normotensive normalization of the tissues

The patient is checked according to the pattern of the above-mentioned posturo-normo-regulator examination. And then early corrective manual maneuvers are carried out for quite a short time (about ten minutes). Next, the patient performs some exercises on an oscillating board, with the eyes closed, for the same duration. Eventually, following a new normo-postural examination, ultimate corrections are made.

6.1 Example of manual treatment

The Normotensive Therapy is quite rich in different maneuvers and the therapist can pick up any of them , according to the specific need of the patient.
Here are some of them:
In this example, the patient shows up with a fixed facies. The walk is awkward: bent shoulders, accentuated cervical lordosis, accentuated and stiff kyphosis which lead to

cervical and scapular bilateral pain. Furthermore the right ankle is scarcely mobile which causes the support to be faulty. The thoracic expansion is limited, and the respiratory amplitude affected. The patient can easily fall. In the Parkinson's stiffness very usually predominates on the flexors, when in flexion.

6.2 Myofascial Normotensive treatment

6.2.1 Treatment of the facies

There are close links between cervical biomechanics and manducator function. Only if the jaw joints are well balanced can the head remains stable. If the patient shows a fixed facies and a poor facial expression, it is necessary to treat him in order to soften the expression. The manducator function is quite important for the general balance of the body. The very specific NT massage increases the biting force and allows the peripheral muscles of the neck to relax, while they usually make the patient adopt a very poor posture in the severe phase of the illness. It has been proved that vibrating friction massage could improve the biting force (32).

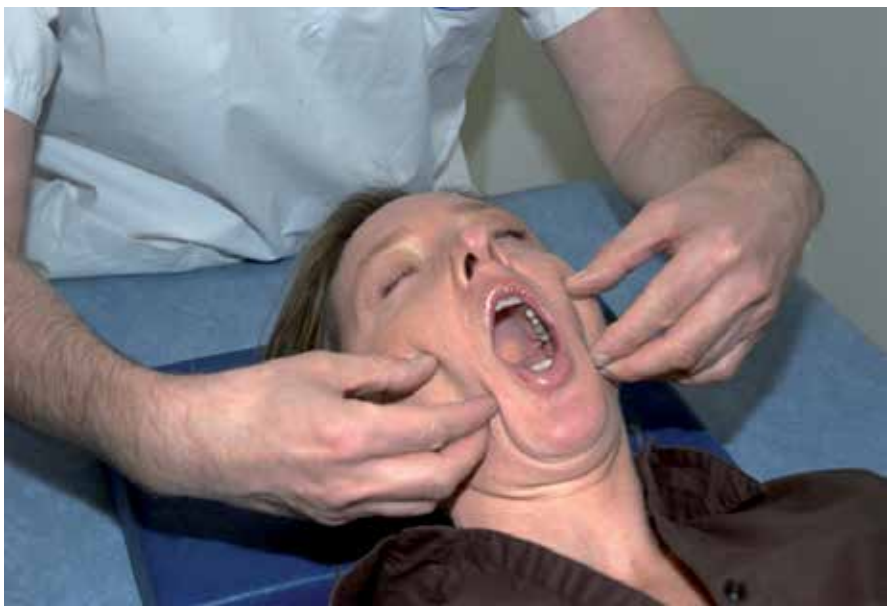


Fig. 11. Treatment of masseter muscles

This treatment mainly applies to the masseter and lateral pterygoid muscles, very much involved in the dysfunctions of temporo-mandibular joints.

The patient is asked to firmly and quickly close his mouth, whereas the therapist tries to prevent the movement with the tip of his fingers (Fig 11). Next the therapist carries out a *triggering touch* without the patient's participation, with thumb and forefinger first joined together, then, moving apart from each other, several times at a go. Maneuver to be carried out on both sides.

Then, the patient is asked to move his chin sideways, in opposition to the treated muscle while the therapist prevent the movement, and then carries out a *triggering touch* in separating thumb and forefinger on this muscle(Fig 12). Maneuver to be carried out on both sides.

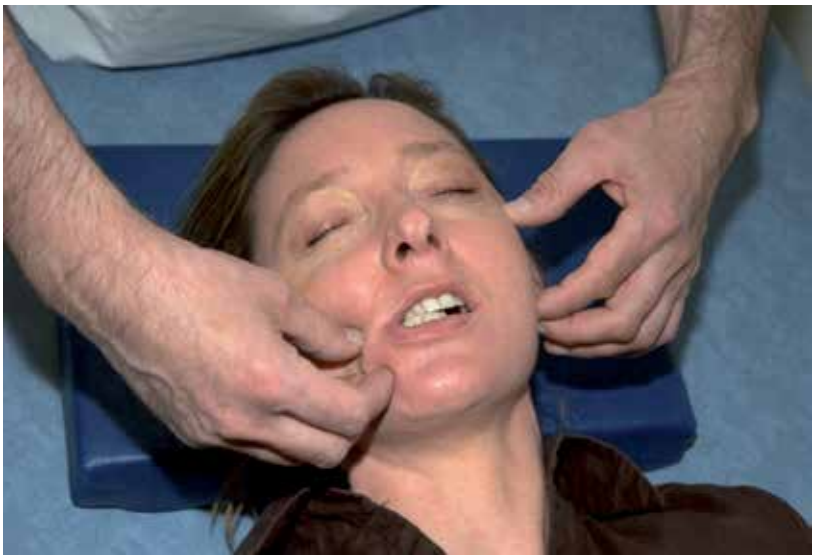


Fig. 12. Treatment of lateral pterygoid muscles

6.2.2 The Twist maneuver

It is a global NT maneuver which aims to the softening of the vertebral column.

(1) (2)

Fig. 13. The *twist maneuver*

The patient puts his shoulder forward and raises his knee in a rotary outward movement, whereas the therapist resists it (Fig 13 -1). Next the patient relaxes and follows the therapist who triggers a spiral movement while firmly holding the pelvis which must remain immobile (Fig 13 - 2). Maneuver to be carried out on both sides. If it is only a thoracic amplitude gain which is to be obtained, the hand which holds the pelvic should be placed slightly higher.

6.3 Cervical treatment

The cervicothoracic treatment always comes before the treatment of the shoulder as it relies on it. The balance of the head is to be thoroughly monitored. The cervical rachis should be softened, functional, and harmoniously following the eyes, as the vestibulo-ocular and

vestibulo-oculo-cervical reflexes have an important role in the preservation of a correct posture.

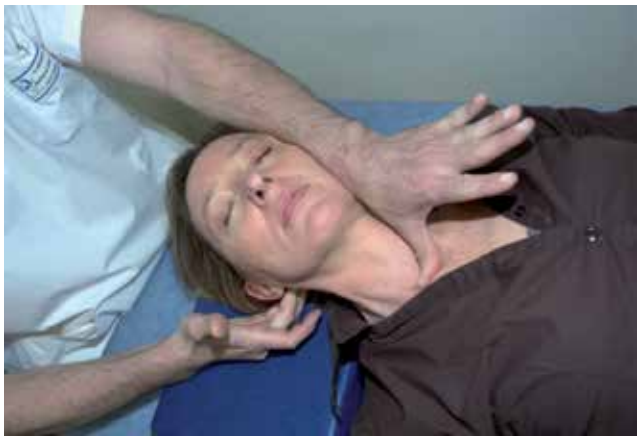


Fig. 14. *Dynamic triggering touch* on sternocleidomastoid muscle

The patient is in decubitus. The therapist resists to a contraction (isometric movement) of the muscle in rotation of head and neck, of the opposite side of the contraction (sternal head), and then in homolateral inclination (clavicular head). Next, he pulls on the extended muscle by a soft occipital traction, while gently rotating the head to and fro (Fig 14).

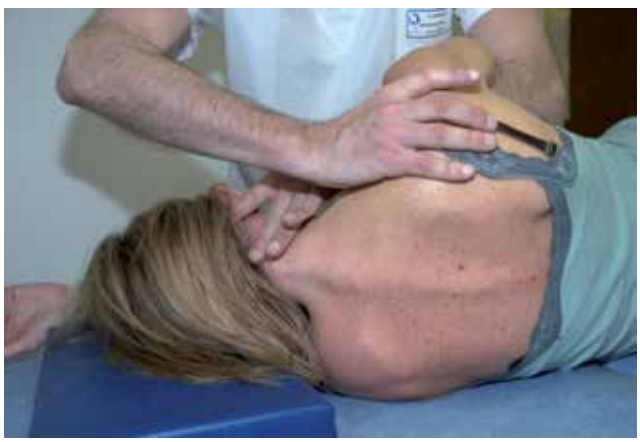


Fig. 15. Cervical maneuver in *nutcracker*

The patient is in lateral decubitus (Fig 15). He is asked to raise the shoulder three or four times, slightly backward, in opposition to a manual resistance (isometric movement). Next, the therapist makes the superior trapezius muscle stretch with hands apart, while simultaneously carrying out a static triggering touch with both hands. And then he carries out the same *static triggering touch*, then *relaxing touch* on the scapular insertion of the levator scapulae muscle, after the shoulder blade has been raised in the opposite direction. A regional *relaxing touch* is then carried out if needed, especially if there are *tensive lesions* left, the therapist's hands being placed the same way.

6.4 Thoracic treatment

Although deformations appear quite late, emphasis must be put on their prevention. Moreover, there is quite frequently a feeling of thoracic oppression occurring during the periods of *block*. Spinal or scapular pain often occur at the same time.

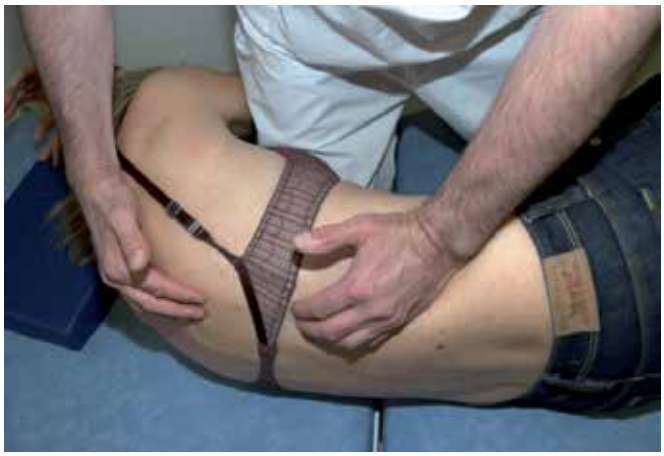


Fig. 16. Vertebral thoracic treatment

The patient is in lateral decubitus, with his back bent (Fig 16). While he is breathing out, the therapist's hands, moving apart from each other, exert *triggering touch traction* along the paravertebral thoracic muscles, on the side which doesn't lean on the table. At the same time, his knee placed in the thoracic zone exerts a pressure so that the treated zone is stretched. A relaxing maneuver is to be carried out if *tensive lesions* are detected. To be repeated in the opposite lateral decubitus.

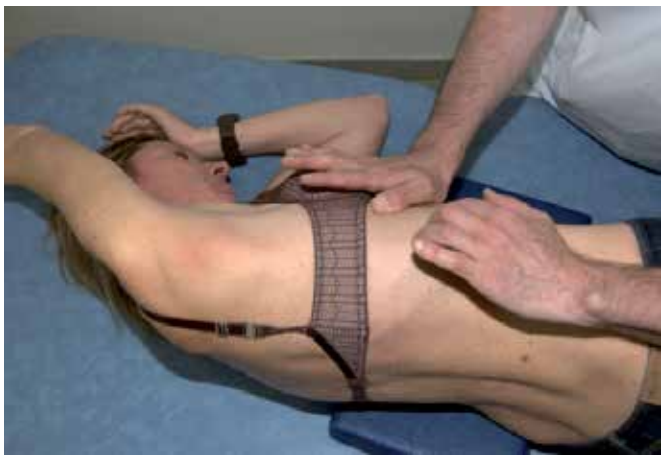


Fig. 17. Costal treatment

The therapist puts his fingers successively in each intercostal space, insisting on the area where the thoracic expansion is limited (Fig 17). The patient is asked to "breathe inside his ribs". The therapist carries out small stretching movements in *triggering touch*, with the hands moving apart while the patient breathes out.

Then, relaxing treatment, if necessary, mainly in the posterior thoracic zone, near the vertebras.

Fig. 18. Shoulder treatment

The patient being in dorsal decubitus, the therapist keeps stretching the upper limb of the patient along his back, while he gently pulls the head of humerus in decoaptation with his thigh (Fig 18). He uses the heel of the hand to push backward and downward the head of humerus with a *triggering touch.* This maneuver which is never painful, is to be repeated for two or three minutes at a go.

6.5 Lumbar treatment: Specific treatment of Iliopsoas muscle

The Iliopsoas muscle is often to blame in any lumbar mechanical pathology, even sometimes the only one to blame. It is necessary to check it or correct it, if necessary.
The patient finds it difficult to straighten up. His muscles are stiff and hypertonic, partly because of his posterior muscles "in flessum".

Fig. 19. Lumbar Iliopsoas treatment

The patient is in decubitus at the end of the table, with the thigh folded on the abdomen (Fig 19). The therapist tests the elastic resistance of the two Iliopsoas through a palpation of the abdomen (inferolateral part of the abdomen, rectus abdominis excluded) with the patient's hip bent in opposition (isometric movement), his hand being below the groin fold. And then he treats the lesional Iliopsoas: the patient bends his hip against resistance, the other being tucked up on the abdomen, and the therapist carries out a *triggering touch*, with both hands vibrating at the same time.

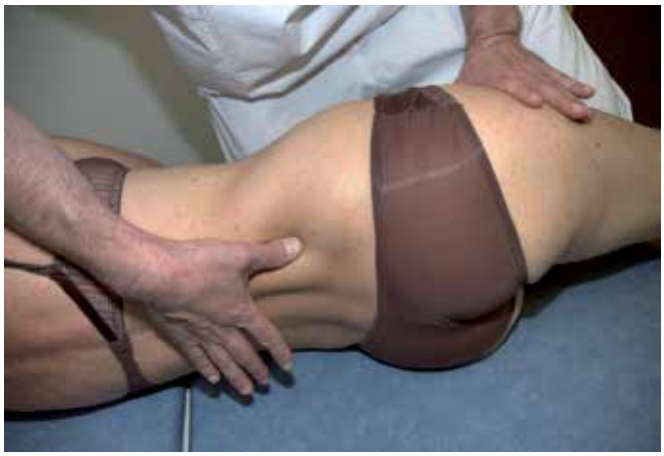


Fig. 20. Lumbar Iliopsoas treatment

Immediately after the maneuver before, the patient positions himself in laterocubitus, with the trunk in rotation (Fig 20). On the side which is to be treated, the thigh is kept in extension. The patient bends his hip (isometric) with opposition from the therapist, and then the therapist carries out a *relaxing touch* on the patient's lumbar rachis while pushing his shoulder back to the table.

6.6 Tibiofibular treatment

Treatment of the tibiofibular syndesmosis when blocked, in order to ease the flexion-extension movement of the ankle and to restore the support.

Fig. 21. and 22. Tibiofibular treatment

The patient is sitting on the Klein balloon (Fig 21, 22). He makes it roll from right to left (so that the ankle is mobile, which is the dynamic element of the maneuver) while the therapist carries out a *triggering touch* on the tibiofibular syndesmosis, followed by a *relaxing touch* if needed. It must lead to a mobility gain in the flexion-extension of the ankle. Otherwise, the maneuver must be repeated.

6.7 Minor joints

The different rehabilitation maneuvers often overlook the minor joints. However, the illness seriously alters the way they work, which can handicap the patient in all his daily activities, so he ends up forgetting to use them. Thanks to the NT, he realizes how important it is to reintegrate them in his body scheme, being aware that taking care of them will give him back a freedom of movement.

The tactile foot captors give very valuable information on the body oscillations in relation to the vertical line. However the skin sensitivity decreases over the course of years, and it can alter the balance, especially in the case of Parkinson's disease whereas it is important to keep a good support.

The graviceptive somesthetic tactile information brought by the *triggering touch* on the plantar soles, improves the patient's postural stability. Each session should include a *triggering touch* on the plantar soles just before the equilibration exercises on the oscillating board. When the skin receptors are stimulated by vibrations, the control of the biped posture is improved.

The patient is sitting on the balloon. He bents the hallux against slight resistance, then the therapist exerts a traction in line in *triggering touch.* Again the patient is asked to bend the hallux against resistance (Fig 23). Then, he can relax whereas the therapist keep the hallux bent while he carries out a *triggering touch* on the upper side of the joint. The maneuver is to be repeated between the proximal and the distal phalanges.

Fig. 23. *Triggering touch* on the hallux between head of first metatarsal bone and base of proximal phalange, on a Klein balloon

The patient suffering from Parkinson's tends to lose his sensitivity and his foot mobility. Nevertheless the plantar sole is an important sensorial entry for the body balance.
One hand is grabbing the calcaneus, the other one is picking the metatarsal bones, with the patient being asked to bend his foot (Fig 24). A *triggering touch* is being carried out on the plantar sole, in longitudinal stretching, with hands moving apart from each other.

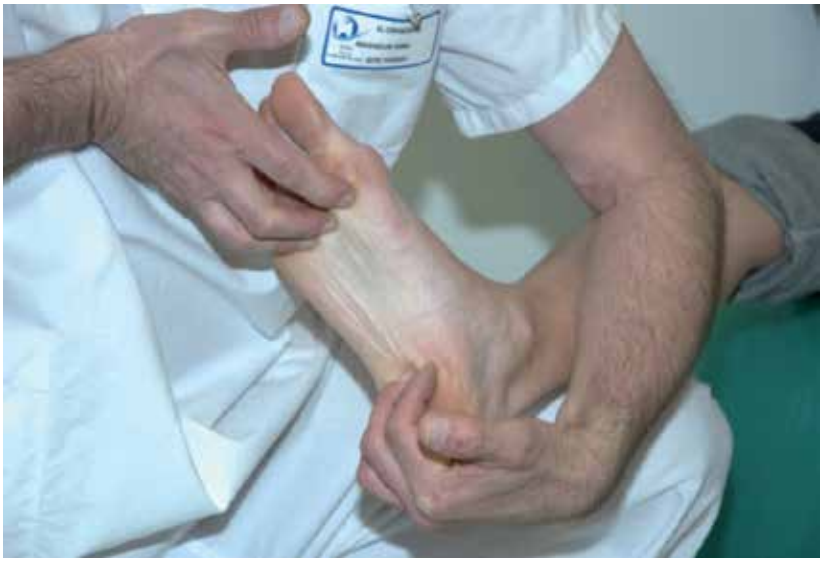


Fig. 24. Maneuver on the plantar sole

7. Late phase

When in the late phase of the illness, the NT maneuvers can still improve the patient's comfort, by easing the pain and improving the vertebral (spiral maneuvers) and thoracic mobility (thoracic amplitude and cardio respiratory capacity). Besides, the *normo-triggering touch* (which is antalgic) will allow the muscles to relax. (Figure 25)

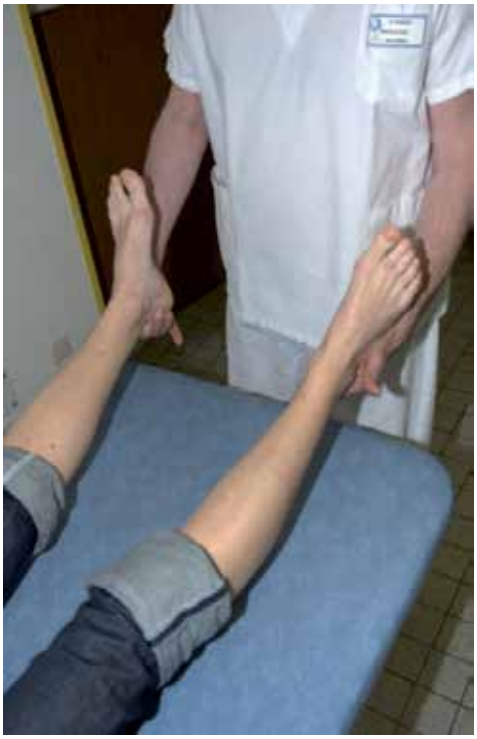


Fig. 25. Gentle shaking of the legs in order to make the muscles relax, and to ease the blood circulation. Shaking of the lower then upper limbs

8. Conclusion

The Normotensive Therapy doesn't stand in the way of other traditional rehabilitative methods. It just adds its personal touch, its *triggering and relaxing touches*. The NT not only treats the symptoms but also the patient in his complexity, without forgetting the comorbidities. Dystonia and diskinesia, unpredictable, often very disturbing in rehabilitation, are attenuated and less frequent, thanks to the gentle and adaptable side of the NT, which can adjust if necessary, if the patient's health is changing, so that his confidence is restored without any added stress.

The central neurology patient is usually a little deprived of physical contact. Consequently his loss of body marks gets worse, and he is even more depressed. It is important to assess his postural problems regularly, by using well chosen therapeutic tools, in order to avoid being overwhelmed by difficulties. The therapist must be ready to adapt quickly. His finger must be at the right place, at the right moment, where and when it hurts. It must be a *vibrating finger,* a *relaxing finger,* a *gentle finger* and a *stroking finger*… A finger which "recognizes the needs of the body", a neuro-informational finger. That is the point of the Normotensive Therapy, which consists in stimulating the patient's balance, his walk and consequently his autonomy, by closely associating manual therapy and original exercises with an elastic bandage and also the Klein balloon during the same session.

9. Acknowledgement

Special thanks to Roselyne De Waele my translator (rosydenys@yahoo.fr), and to Patrice Jones my photograph.

10. References

[1] Amarenco G, Césaro P, Chevrie-Muller C,Cornu Ph, Damier Ph, Destée A, Fabre N, Fénelon G, Laumonnier A, Mahieux F, Marion M-H, Rascol O, Roubeau B, Senard J-M, Tison F. Parkinson's Disease. Acanthe, Masson Smithkline Beecham, Paris, 1998. PP 41-43; 108-110.

[2] Bannwarth B, Bertin P, Trèves R, Dehais J. Affections articulaires induites par les médicaments. Le Concours Médical. 04. 12. 99. 121-39. P 3066-3070.

[3] Jego M et Viallet F. Maladie de Parkinson du sujet âgé. Prise en charge thérapeutique : médicaments à prescrire et médicaments à éviter. La Revue de Gériatrie. 2009.1; 34(1). A8-A11.

[4] Stacy M, Bowron A, Guttman M, Hauser MD, Hughes K, Petter J, Larsen MD, Lewitt P, Oertel W, Niall Quinn, Kapil Sethi, Stocchi F. Identification of motor and nonmotor wearing-off in Parkinson's disease : comparison of a patient questionnary versus clinician assessment. Mov disorders. 2005 ; 20(6) : 726-33.

[5] Bleton JP. Maladie de Parkinson et qualité de vie - 1ère et 2ème parties. Kinésithérapie Scientifique. 1999 ; 387: 56-388.55.

[6] Neiger H, Gilhodes JC, Roll JP. Méthode de rééducation motrice par assistance proprioceptive vibratoire. Kinésithérapie Scientifique.1986; 252: 6-21.

[7] Burke D, Hagbarth K. E. & Lofstedt L. & Wallin,B.G The responses of human muscle spindle endings to vibration during isometric contraction. J Physiol. 261, 695-711.

[8] Lackner J.R and Levine M.S. Changes in apparent body orientation and sensory localization induced by vibration of postural muscles: vibratory myesthetic illusions. Aviat Space Environ Med.1979. 50(4) : 346-54.

[9] Roll JP, Vedel JP, Ribot E. Alteration of propioceptive messages induced by tendon vibration in man : a microneurographic study. Exp Brain Res. 1986. 76 :203-222.

[10] Eklund G. Further studies of vibration-induced effects on balance. J Med Sci. 78. (1973) : 65-72.

[11] Bove M, Nardone A, Schieppatin M. Effects of leg muscle tendons vibration on group Ia and group II reflex responses to stance perturbation in humans. J Physiol Lond. 550. 2003. 617-630.

[12] Smetanin BN, Popov KE, Kozhina GV. Human postural responses to vibratory stimulation of calf muscles under conditions of visual inversion. Human Physiol 28. 2002. 554-558.

[13] Lekhel. H, Popov. K, Anastasopoulos D, Bronstein A, Bhatia K, Marsden CD, Gresty M. Postural responses to vibratin of neck muscles in patients with idiopathic torticolis. Brain. 1997; 120 : 583-91.

[14] Ivanenko YP, Talis VL and Kazennikov OV. Support stability influences postural responses to muscle vibration in humans. Eur J Neurosci. 1999 ; 11 (2) : 647-654.

[15] Ivanenko YP, Grasso R and Lacquantini F. Neck muscle vibratin makes walking humans accelerate in the direction of gaze. J Physiol. 2000 ; 525: 803-814.

[16] Kavounoudias A, Gilhodes JC, Roll R, Roll JP. From Balance regulation to body orientation : two goals for muscle propioceptive information processing ? Exp Brain Res. 1999. 124 : 80-88.

[17] Kavanoudias A, Roll R , Roll JP. Specific whole-body shifts induced byfrequency-modulated vibrations of human plantar soles. Neurosci Lett. 2000. 281 : 99- 102.

[18] Bloem B.R, Allum J.H, Carpenter M.G, Honegger F. Is lower leg propioception essential for triggering human automatic postural responses ? Experimental Brain Research. 2002. 130(3): 375-391.

[19] Polak J. Contractures persistantes: l'hypothèse d'une boucle beta. Kinésithérapie Scientifique. N°360. Octobre 1996. P 9.

[20] Orgeret G, Viel E. Thérapie manuelle du système myofascial. Coll. Bois Larris. Masson, Paris, 2000. P 57.

[21] Perennou D. Postural disorders and spatial neglect in stroke patients ; a strong association. Restor Neurol Neurosci. 2006. 24: 319-334.

[22] Fitzpatrick and MacCloskey. Propioceptive, visual and vestibular thresholds for the perception of sway during standing in humans. J Physiol. 1994, 478, 1, 173-186.

[23] Bogumila Sobczak. Influence de la kinésithérapie sur l'état fonctionnel des articulations temporo-mandibulaires, de la colonne vertébrale et des membres ; Kinésithérapie Scientifique. N° 328. Novembre 1993. P11-25.

[24] Amblard B. Les descripteurs du contrôle postural. Ann Réadaptation Méd. Phys. 1998, 41, 225-237.

[25] Uchiyama M, Demuras S. Low visual acuity is associated with the decrease in postural sway. Tohoku J Exp Med. 2008 nov ; 216 (3) : 277-85.

[26] Naudin-Rousselle P. Les chutes répétées des personnes âgées. Le Généraliste. Septembre 2009. N° 2495. P21.

[27] Podsiadlo D, Richardson S. The timed up and go: a test of basic functional mobility for frail elderly persons. J Am Geriat Soc 1991 ; 39 : 142-148.

[28] Kemoun G, Defevre L, Watelain E et al. Maladie de Parkinson comme modèle de vieillissement: analyse prospective des troubles de la marche. Revue Neurologique 2003; 159; 1028-37.

[29] Vaillant J, Barthalais N, Vuillerme N. Ankle strapping and postural control : Effetc of underwrap. Science & Sports. 23. 2008. 78-82.

[30] Menz HB, lord SR, Fitzpatrick R. A tactile stimulus applied to the leg improves postural stability in young, old and neuropathic subjects. Neuroscience Letters. Volume 406, Issues 1-2, 2 octobre 2006. P 23-26.

[31] Zouch M, Alexander Ch, Vico L. L'activité physique dans l'ostéoporose, avec modération. Impact Medecine. Exercice. N°215. 18 Octobre 2007. P 28.

[32] Iwatsuki h, Ikuta y, Shinoda K, Deep friction massage on the masticatory muscles, in stroke patients increases biting force. J Phy; Ther Sci; 2001; 1: 17-20.

18

Potentials of Telehealth Devices for Speech Therapy in Parkinson's Disease

Lilian Beijer[1] and Toni Rietveld[1,2]
[1]*Sint Maartenskliniek Nijmegen, Section Research, Development & Education*
[2]*Radboud University Nijmegen, Faculty of Arts, Department of Linguistics*
The Netherlands

1. Introduction

Rapidly evolving technological developments have been influencing our daily lives for a few decades now. In particular information and communication technologies enable more sophisticated and faster ways of communication than ever before. These developments have far reaching consequences for professional, domestic and leisure activities. Use of computers, whether or not with an internet connection, has become very common also in the field of education and health care. The primary benefits in these areas are believed to lie in cost reduction and enhanced efficiency.
In this chapter we will focus on the possibilities of technological developments in health care, particularly for patients with Parkinson's disease. This patient group is believed to benefit considerably from innovative applications of information and communication technologies since the number of parkinsonian patients is dramatically growing due to demographic developments. Moreover, Parkinson's disease pre-eminently concerns a chronic and progressive illness, increasingly disabling these patients in almost all domains of their lives. In this chapter we will explore how telehealth technology and speech technology relates to the maintenance of their communicative competence.

2. General aspects of speech disorders associated with Parkinson's disease

2.1 General motor functions and oral motor control

Parkinson's disease is caused by the progressive impairment of neurons in an area of the brain known as substantia nigra. This is due to an imbalance in two brain chemicals (i.e. dopamine and acetylcholine) which are responsible for the transmission of nerve messages from the brain to the motor nerves in the spinal cord which control muscle movement. As a result, the communication between the substantia nigra and the corpus striatum, required for coordinating smooth and balanced muscle movement, is distorted.
The diminished functioning and coordination of respiratory, laryngeal and supralaryngeal muscles obviously affects speech, swallowing and saliva control in parkinsonian patients (Ziegler, 2003). As a consequence, the quality of speech in patients with Parkinson's disease tends to be deteriorated to some degree. As it is, dysarthria is a common manifestation of Parkinson's disease (PD) which increases in frequency and intensity with the progress of the

disease (Streifler, 1984). Hypokinetic dysarthria is mainly associated with PD; mixed dysarthria tends to occur in atypical parkinsonism.
General motor symptoms such as rigidity, bradykinesia (reduced speed of muscles), tremors or trembling are reflected in typical speech symptoms of hypokinetic dysarthria. Bradykinesia associated with Parkinson's disease causes difficulty in the initiation of voluntary speech. This can result in delay in starting to talk as well as very slow speech. According to Duffy (1995), there may be freezing of movement during speech. Rigidity can also occur. Additionally, parkinsonian patients have reduced loudness, imprecise consonant production, reduced pitch variability and festinating speech. The latter can result in extremely fast speech together with short rushes of speech (Ferrand and Bloom, 1997). Perceptual features of parkinsonian speech associated with hypokinetic dysarthria, are a weak, breathy (hoarse) voice, monotone and monoloud speech, low volume, articulatory imprecision and rate disturbances (Darly et al., 1969). The syndrome of parkinsonian dysarthria is by no means homogeneous with respect to speech rate. This might be due to different consecutive stages in the development of parkinsonian dysarthria or to different degrees of impairment (Ackermann & Ziegler, 1991). In general, more pronounced phonatory than articulatory disturbances tend to occur as far as clinical-perceptual ratings are observed.

2.2 Speech intelligibility

As a consequence of distorted oral motor functions and coordination, speech intelligibility in patients with PD obviously tends to be reduced. Prevalence studies point out that about 70% of patients living at home with Parkinson's disease have speech complaints (Kalf et al., 2008a), which are mainly associated with hypokinetic dysarthria. Diminished communication skills, in addition to the fact that these patients are increasingly disabled in their physical condition and motor abilities in the course of their disease, frequently lead to patients experiencing a deteriorating quality of life (Slawek et al., 2005). Improving or at least maintaining speech quality as long as possible is essential to enable optimal social participation and to maintain relationships. As a consequence, patients with PD are often eager to practice and improve their speech quality.
Although the majority of patients with PD are dysarthric speakers, only a minority of this group with diminished speech quality receives speech therapy (20-30%). The small percentage of PD patients under 'speech therapeutical control' might be partially due to the fact that a majority of speech language therapists consider themselves not capable to adequately treat dysarthric speakers with PD. Another reason might be the fact that speech therapy often is provided to patients that have only recently been diagnosed with PD. Therapists lose sight of their patients once face-to-face therapy sessions have been completed. Thus, dysarthric patients tend to be deprived of speech therapy in the chronic and deteriorating course of their disease. As it is, this tendency of 'undertreatment' of dysarthric patients with PD is likely to continue in the course of the coming years. That is, the incidence and prevalence of PD will increase due to our aging population. It is estimated that in 2030 about 30% of our population will be 65 years of age or older.

2.3 Guidelines for diagnostic and treatment procedures

Apart from the observed 'undertreatment' of patients with PD, large variability exists in therapeutical approaches of this patients group. In the Netherlands, evidence based guidelines for diagnostic and treatment procedures for patients with PD were developed in order to

provide speech-language therapists with recommendations for their clinical practice (Kalf et al., 2008b). It should be noted that methodological quality of comparative studies is often insufficient to meet the conditions of highest level of evidence (Deane et al., 2001). Therefore, evidence is mainly based on comparative studies of less methodological quality, noncomparative studies or experts' opinions. Five key points for treating dysarthric speech in patients with PD were formulated in the evidence based guidelines (Kalf et al., 2008b):

1. Patients with PD have basically normal motor skills, requiring to be elicited in an adequate way.
2. Hypokinesia increases when duration and complexity of motor acts increase. Therefore, complex acts should be divided into more simple acts.
3. Separate acts should therefore compensate for failing automatic motor acts
4. External cues could support initiation and continuation of motor acts.
5. Simultaneous execution of motor and cognitive tasks should be avoided, since execution of motor tasks already puts considerable demands on cognitive functions.

For diagnosis and treatment of dysarthria in patients with PD, two procedures are strongly recommended. 1) As far as diagnostic procedures are concerned, the initial situation should be assessed by documenting spontaneous speech and establishing to what extent speech can be stimulated by means of maximum performance tests. 2) For treatment, the Lee Silverman Voice Treatment (LSVT) (Ramig et al., 2001) and the Pitch Limiting Voice Treatment (PLVT) (de Swart et al., 2003) are strongly recommended. The LSVT focuses on tasks to maximize respiratory and phonatory functions in order to improve respiratory drive, vocal fold adduction, laryngeal muscle activity and synergy, laryngeal and supralaryngeal articulatory movements, and vocal tract configuration. The PLVT also aims at increasing loudness but at the same time sets vocal pitch at an adequate level. The LSVT and the PLVT produce the same increase in loudness but PLVT limits an increase in vocal pitch and claims to prevent a strained or stressed voicing (de Swart et al., 2003). Both therapy programs concern intensive training periods of four sessions weekly during a training period of four weeks. Intensive speech therapy is preferred if diagnostic results allow highly intensive and frequent training. That is, voice quality, intrinsic motivation, physical condition and cognitive abilities are vital conditions for intensive training of newly acquired speech techniques. In case a patient's condition does not allow intensive training, augmentative and alternative procedures or devices could provide a solution to the communication problems experienced by dysarthric speakers with PD.

In the next sections, we will go into more detail with respect to current trends in speech therapy for patients with PD. These result from rapidly evolving developments in information-, communication- and speech technology. Not only will these developments provide patients with new therapy facilities; they are also expected to bring about some crucial changes for health care providers (i.e. speech therapists) and influence health care processes.

3. Current trends in the therapy of speech disorders related to Parkinson's disease

3.1 Increased need for speech training

A considerable percentage of PD patients experience oral motor disorders, causing problems with swallowing, speech and saliva control. With 70% of PD patients being dysarthric, it is obvious that therapeutical interventions are required. That is, the speech of PD patients with

predominantly hypokinetic dysarthria, needs treatment in order to improve speech intelligibility. Since communication skills are vital for adequate social participation, improvement of these abilities can significantly contribute to quality of life.
A number of current trends seem to influence the developments in speech therapy for parkinsonian patients. Firstly, there is an increased attention for dysarthria and its treatment. This is partially due to the results of scientific research in the field of PD, enhancing care givers' awareness of the relevance for long lasting communication skills in parkinsonian patients. Secondly, recent social and demographic developments have caused patients to be more aware of possibilities for treatment and to be more assertive in their call for adequate information. Patient centred health care has even gained considerable importance for reimbursement companies that find themselves increasingly confronted with clients searching for the best quality of care. Apart from this, the economic instability in this decade urges the health care community to treat the growing number of elderly patients with neurological diseases with less financial means. It is obviously a challenge to maintain a sound balance between the need (and call) for speech training on the one hand, and the availability of professionals and financial means for speech training on the other hand. Particularly with current speech training programs for PD such as the LSVT (Ramig et al., 2001) and the Dutch PLVT (de Swart et al., 2003), involving intensive speech training for several weeks to enhance speech intelligibility, it becomes clear that traditional speech therapy does no longer meet the actual needs of our current society.

3.2 Telehealth in the field of speech-language pathology

Telehealth applications, resulting from recently developed information and communication technologies in health care, could provide solutions to overcome barriers of access to therapy services caused by factors such as decreasing financial resources, shortage of professionals and increasing number of clients. The terms 'telemedicine' and 'telehealth' are sometimes used interchangeably. Telemedicine is considered a subset of telehealth. Telemedicine uses communication networks for delivery of healthcare services and medical education from one geographical location to another, primarily to address challenges like uneven distribution and shortage of infrastructural and human resources (Sood et al., 2007). 'Telehealth' is a broader term and does not necessarily involve clinical services. It can be defined as the use of telecommunication technologies both to provide health care services and to enable access to medical information for training and educating health care professionals and consumers. As such, telehealth concerns all applications of information and communication technologies, enabling the retrieval, recording, management and transmission of information to support health care. In this chapter, we refer to this latter definition when discussing telehealth.
Mashima and Doarn's (2008) overview of telehealth activities in the field of speech-language pathology provide a strong foundation for broader applications of telehealth technologies in this area. Also telehealth applications for treatment of patients with neurogenic communication disorders have been reported. Theodoros et al. (2006) report an online speech training for PD patients which turned out to be effective. Ten patients with PD followed the LSVT online using video conferencing, during a four-week program of intensive training, involving 16 therapy sessions. Comparison of sound pressure level, pitch measurements and perceptual ratings from audio recordings pre- and posttreatment, containing participants' reading and conversational monologue, showed significant

improvements, comparable to previously reported outcomes for the LSVT when delivered face-to-face. This example shows that remote diagnosis and treatment of speech in parkinsonian patients has vital benefits, in particular for patients who are less mobile and easily fatigued due to their deteriorated physical condition. Ziegler and Zierdt (2008) report an online version of a computer-based intelligibility assessment tool: the Munich Intelligibility Profile. The web based MVP-version is reported to have potentials for dysarthric speech of patients with PD and other underlying neurological diseases such as stroke.

3.3 E-learning based Speech Therapy (EST)

Quite recently, in the Netherlands a web based speech training device 'E-learning based Speech Therapy' (EST) has been developed (Beijer et al., 2010a). EST primarily aims at patients with dysarthric speech resulting from acquired neurological impairment such as stroke and Parkinson's disease. According to our clinical experience, these patients suffer from their deteriorating quality of speech. Particularly in the chronic phase of their disease, once therapy sessions have been completed, the lack of practice results in diminished speech intelligibility. With verbal communication being a vital condition for adequate social participation, diminished abilities in this field can be considerably invalidating. A vital benefit of EST is the possibility to follow a tailor-made speech training program in the patients' home environment. That is, time, energy and costs normally involved with speech training can be reduced for these patients who tend to be less mobile and easily fatigued due to their physical condition. In addition, the possibility to practice speech in the home environment at any moment, allows intensive speech training, which is known to be effective in patients with acquired neurological diseases (Kwakkel et al., 1999). Repetitive training in chronic phases also has been proven to have positive effects on speech intelligibility (Rijntjes et al., 2009).

Since telehealth applications tend to differ in many respects, Tulu et al., (2007) made an effort to provide insight into the large number of innovative web based devices that are available. They introduced a taxonomy of telehealth applications along five dimensions: communication infrastructure, delivery options, application purpose, application area and environmental setting. According to this classification, EST concerns a store-and-forward web application for treatment (i.e. training) purposes in the area of speech pathology that is commonly used in the home environment.

The keystone of the EST infrastructure is formed by a central server. The server hosts two types of audio files: target speech files in MP3 format and recorded speech files uploaded by patients in wav format (Figure 1). A desktop computer or a laptop with internet connection provides users with access to the server. Using their EST therapist account, therapists are able to, at a distance, provide their patients with a tailor-made speech training program, which is compiled from audio examples of target speech, stored at a central server.

Patients have access to this program using their client account. In the EST training procedure patients listen to audio examples of target speech which is downloaded from the server. Subsequently they imitate the audio example, in order to approach the target speech. The target and the own speech are then aurally compared. Finally the patients' speech is uploaded and stored at the server (Figure 2).

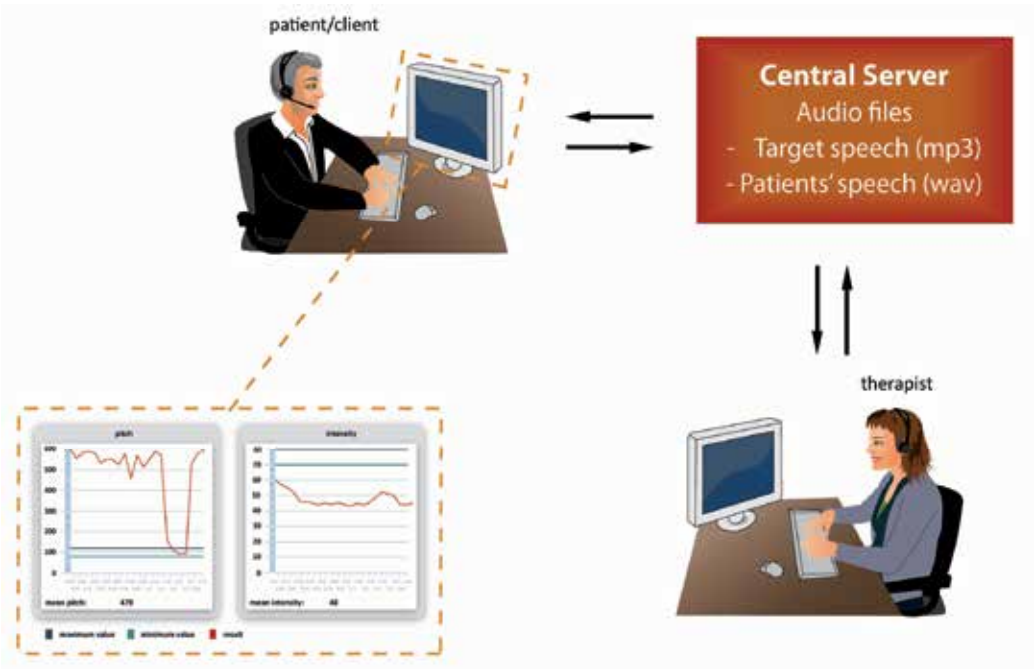


Fig. 1. Infrastructure of E-learning based Speech Therapy (EST). (Reproduced with credit of the Telemedicine and eHealth journal)

Obviously, this training procedure puts considerable demands on patients' auditory speech discrimination skills. However, indications have been reported that patients with PD experience problems with estimating the own speech volume (Ho et al., 2000) and with auditory speech discrimination (Beijer, Rietveld & van Stiphout, in press). Although this diminished auditory discrimination might be caused by cognitive problems and hearing loss, these patients would benefit from additional visual feedback on their own speech realization. That is, visualization of speech might support them in the auditory discrimination task of the EST training procedure. Although this visualization is already implemented in EST, the abstract graphs (Figure 1) and the delayed, post hoc display of visual feedback did not appear suitable for all patients (Beijer et al., 2010b). Therefore, the development of an intuitive visualisation of loudness and pitch is currently underway in order to apply to patients with various backgrounds (i.e. educational levels, age, gender). Not only should the graphic form of the visual feedback apply to the patients, indicating into what direction a new speech attempt should be adjusted to approach the target. It should also be assessed to what extent different visualisations contribute to the improvement of speech intelligibility. In section 4.4. we will go into some detail with respect to visual feedback on pitch and intensity (loudness).

Therapists are allowed to download audio files of their patient's speech from the server. Thus, they are able to listen to their patient's speech at different points across time. In addition they may analyze the acoustic speech signal for objective measures of speech dimensions that are relevant for an individual patient.

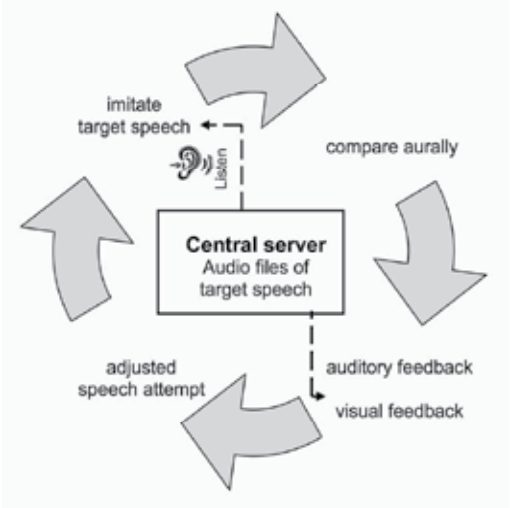


Fig. 2. EST training procedure. (Reproduced with credit of Telemedicine and eHealth)

Despite the improvements to be made, a case study conducted with a male patient with PD suggested that EST is a suitable web based speech training device with potential efficacy for patients with PD (Beijer et al., 2010b). The patient had completed face-to-face sessions of PLVT practice, and was able to conduct the training program that he was already familiar with, independently at home. He followed an intensive, protocolized four-week program, involving the PLVT (de Swart et al., 2003) by means of EST. His speech intelligibility had significantly improved immediately after the EST training period. Speech intelligibility was measured by the percentage correctly (orthographically) transcribed words in semantically unpredictable sentences (SUS). After several weeks without practice, the patient's speech intelligibility declined. Apparently, practice of speech maintained speech quality. As mentioned in section 1.3, the PLVT primarily aims at improving speech intensity (the acoustical correlate of perceived loudness) with, for vocal hygiene reasons, limited vocal pitch raise and laryngeal tension. It appeared that the participant appreciated weekly contact via telephone with his speech therapist. Apparently there was a need for additional therapeutical suggestions and a therapeutical relationship. Nevertheless, the results of this case study are hopeful. Currently, the efficacy and the user satisfaction of the web application EST are subject of investigation.

3.4 Research issues for EST

It will be clear that innovative web based applications for diagnostic and treatment purposes should be evaluated from several perspectives. First of all, the technological feasibility should be proven. Secondly, patients as well as therapists should be able to operate the web based devices. Hence, user satisfaction should be evaluated since this is obviously vital for successful implementation. The term 'user satisfaction' needs to be accurately defined to ensure comparison of user satisfaction across time and across different web based devices. This brings us to the need to establish minimum user requirements regarding physical condition, motor coordination skills and auditory or cognitive abilities. Assessing these conditions for successful use of web based devices is vital for parkinsonian patients who tend to experience constraints in more domains than communication or speech alone. Thirdly the efficacy and the

effectiveness of EST should be evaluated. This brings us to the vital issue of reliable outcome measures for treatment outcomes. In the case of parkinsonian speech, these treatment outcomes primarily concern speech intelligibility. Most of these outcome measures concern subjective, perceptual measures of speech quality (FDA, rate scaling, etc.). Along with health care reimbursers' call for objective outcome measures however, current trends point into the direction of objective acoustical measures of speech quality as a vital outcome measure for speech intelligibility in addition to traditional perceptual measures.
Employment of web based applications for diagnosis and treatment tend to go perfectly along with the need for speech technological developments. That is, speech data can be easily collected, thus generating an automatic data base of pathological speech. We will elaborate on this in section 4.5.

4. The role of speech technology in speech therapy

4.1 Introduction

For more than 25 years phoneticians, speech technologists and speech therapists have systematically investigated the phonetic correlates of speech disorders. These investigations were carried out with a number of explicit or implicit objectives: a) to corroborate subjective judgements of speech therapists, b) to find objective evidence for progress as a result of therapy, c) to facilitate the distinction of subgroups of pathologies, and d) to find evidence for theories on the nature of pathologies, which could not be obtained on the basis of subjective measurements. As has been the case in phonetics sciences, the progress of computer and information technology made available a number of additional applications, which form the core of the current chapter:

a. Gathering objective evidence based on acoustic and/or physiological data,
b. The development of systems which can be used by patients to obtain direct or indirect feedback on their realizations in a training program,
c. The implementation of feedback systems in telehealth applications in order to facilitate intensive training at home.

In the following we will focus on a number of applications of speech technology to be used in the assessment and treatment of dysarthria in general and that of dysarthria associated with Parkinson's disease in particular. We should be aware of the fact that phonetics and the associated speech technology are language bound, that is to say that phenomena which are relevant in one language, may be irrelevant in another.
Kent et al. (1999) published a seminal overview of acoustic correlates of quite a number of phenomena associated with dysarthria. The overview distinguishes the conventional phonetic components of the speech production process: Initiation, Phonation, Articulation, Velopharyngeal functioning and Prosody. As is the case with most acoustic correlates of speech disorders, stochastic relations between perceptually distinctive disorders on one side and acoustic correlates on the other are more evident than inferential procedures which boil down to statements like: the F1 and F2 (first and second formants) of segment X are higher/lower than 'normal', so we can be sure that this segment was not realized in a canonical way. The fact that trade-off relations exist between speech production and speech perception is the nuisance factor. Trade-off relations in phonetics occur when an effect in one domain – say segment duration – can compensate for the absence of a feature in another domain, say voicing. In English, for instance, a relatively long pre-consonantal vowel can perceptually compensate for an obstruent which is incorrectly realized as voiceless.

The presence of this kind of trade-off relations is an obstacle in finding clear and unambiguous acoustic correlates of the perception of speech and speech disorders. This fact is not a direct problem in group studies, which aim at finding tendencies in signal characteristics between pathological groups and a control group. In set-ups in which the aim is to provide stable and robust feedback to a patient, the presence of trade-offs can be disturbing.

Providing instrumental feedback to speakers has quite a long history. As a matter of fact, there are two parallel developments. One development focuses on learning a foreign language ("L2"), and the other on correcting speech disorders. It is quite obvious why these developments are parallel: the dimensions on which deviations of target speech can be projected are – most of the time – equal or similar: prosodic dimensions, dimensions of segmental quality, phonatory dimensions and dimensions of velopharyngeal functioning. Like in speech pathology, it is hardly ever the case that all dimensions are equally relevant. For French as L2, nasality is more important than for English or Dutch. Intonation and tone is extremely important for languages like Chinese, and much less important for English, French or Dutch. These facts have directed research both in systems which provide feedback in L2 learning and in speech therapy. Until now, it has proven not to be worth the effort in this context to assess all characteristics of speech which are imitations of target speech. It is better to direct efforts to specific segments which are known to be vulnerable and/or relevant in L2 learning and speech pathology. This brings us to two different lines in feedback:

a. Direct, quasi real time feedback on the realization of global parameters like intensity, tempo and intonation and parameters associated with segmental quality, and
b. Indirect, post-hoc feedback on the realization of speech parameters.

Direct feedback is meant to help the patient in non-face-to-face training sessions; indirect, post-hoc feedback is often only needed when the therapist has to have access to assessment scores; it is only available after quite a number of speech materials have been collected.

There might be a misunderstanding when it is decided to provide web based speech therapy, in the sense that it is often assumed that a computer system which provides feedback is immediately applicable in an e-health application. That is not true. Supervised training/learning often cannot be directly applied in an environment in which direct assistance is absent. Supervised learning is much more robust than its non-supervised counterpart. An example is provided by Carmichael (2007). In his study, which aimed at the development of objective acoustic measures for the Frenchay Dysarthria Assessment Procedure (Enderby, 1980), the calibration of the 'loudness' measurements might be somewhat complicated to be performed at home. It involves the use of a Sound meter at a standard distance. In his set-up the test administrator performs the calibration procedure. In order to avoid this kind of calibration at home, we opted in our telehealth application for the production of a long nasal consonant [*mmmm*]. As the production of this consonant does not involve any mouth opening and variable jaw movements, the radiated sound can be assumed to be quite constant, and to function as a reliable calibration.

Speech technology in the context of speech pathology can be divided in a number of approaches, which also depend on the objectives to be achieved. In this chapter we restrict our review to applications in assessment, therapy and training. We distinguish five dimensions on which the approaches can vary:

Dimension I: Either the parameters focus on global parameters like intensity, tempo and pitch, or on characteristics which reflect segmental quality.

Dimension II: There are two types of results to be obtained, viz. global assessment, or direct feedback.
Dimension III: Types of speech: the assessment of free speech, or the assessment of read, known speech.
Dimension IV: The inclusion of physiological parameters, like reflexes and respiration.
Dimension V: The inclusion of facial expressions as parameter(s).
A more general dimension is the user-interface. Of course, the interface for the therapist requires less attention, but the one for the patient asks for robustness and psychological validity.
Dimension I: In specific therapies, like the PLVT (de Swart et al., 2003), global parameters are of great importance. As explained in section 1.3 of this chapter, it involves two therapy goals: "speaking loud" while not increasing pitch at the same time. The rationale is that speaking loud generally leads to an increase of articulatory precision, while increasing pitch above habitual level may harm the vocal cords.
Dimension II: Global assessment – not to be confused with global parameters – involves the assessment of speech on a long-term scale. That is, direct feedback is not provided, only feedback after some amount of speech materials has been realized, recorded and analyzed. In an application for direct feedback, the user is provided with quasi real time feedback on the quality of the speech parameters at issue: global parameters like intensity and F0, or feedback on specific segments, like vowels or consonants.
Dimension III: Very often, known and consequently read speech will be used in assessment and therapy sessions. The automatic recognition of speech and the detection of deviations from it, are enormously facilitated by the use of this kind of texts (it implies what is called forced recognition). The drawback is that the use of read speech may decrease the ecological validity of the measures and indices thus obtained.
Dimension IV: As is well-known, the initiation phase in speech, which refers mainly to respiration, is crucial for the generation of speech. There are, to our knowledge, no applications available yet which provide assessment and feedback on initiation (respiration) parameters.
Dimension V: In a number of speech pathologies the assessment of facial expressions is a relevant issue. This is also the case with dysarthria. The recognition and assessment of facial expression demand dedicated software, which is quite difficult to tune to the demands of the patient and/or therapist.

4.2 Realization of assessment and feedback systems

For the realization of feedback and assessment on global parameters (F0, Intensity), relatively simple algorithms are needed, often implemented in current software packages for signal analysis, like PRAAT (Boersma & Weenink, 2011). The problem there is not the analysis of the parameters itself, but the display of the results and the feedback on deviations from the goal values. No significant changes in the detection of the global speech parameters are to be expected, but work has to be done in order to provide displays which facilitate insight in possible errors and stimulate improvements.
For the realization of feedback and assessment of segmental quality, speech technology comes to play. There are a number of approaches, depending again, on the objectives of the application: direct/indirect feedback on the realization of each target speech sound

(phoneme), direct/indirect feedback on the realization of single words, direct/indirect feedback on the realization of a short text, direct/indirect feedback on fixed or free texts, and feedback on the overall intelligibility of words and texts. The two main technical approaches are: the analysis of speech based on Automatic Speech Recognition (ASR) and ASR-free analysis of speech (Middag et al., 2010). If ASR is used, the Hidden Markov Model (HMM) is the main tool. HMMs constitute the default tool for automatic speech recognition, although other approaches are also possible (Middag et al., 2010). Hidden Markov Models are based on probabilities of states of speech segments and transitions from one state to another, or to the same state. In light of the popularity of HMMs we present a short account of this approach below. To illustrate HMMs we give a fictitious example of the use of an HMM for the recognition of the vowel /i/. The acoustic parameter used is the second formant (F2) only. In that respect the example is already fictitious: HMMs hardly ever use formants as acoustic parameters, let alone just one formant. The default parameters used to reflect the spectra of the sound segments are Mel-Frequency-Cepstral Coefficients (MFCCs), which also take into account human perception (Davis & Mermelstein, 1980).

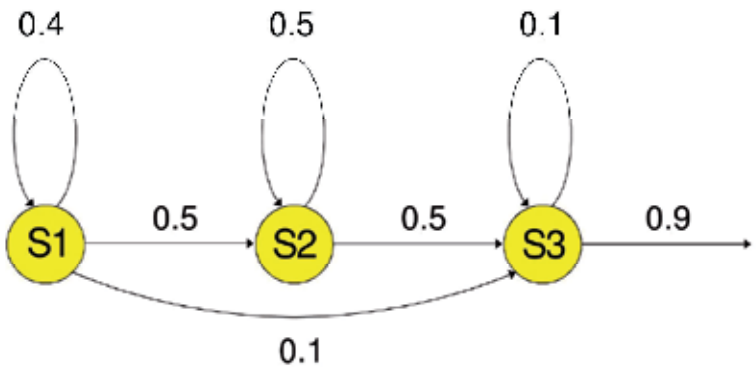


Fig. 3. A hypothetical Hidden Markov Model of the vowel /i/. (Reproduced from Rietveld & van Heuven, 2009, with permission).

In the above figure we display a model of the second formant (F2) of the vowel /i/. We see an inner loop from state 2 to state 2, which occurs with a probability of 0.5; this means that the model has a relatively high probability of staying in state 2, which boils down to the realization of a long vowel. The probability of going from state 1 (initial state) to the final state (S3) is small, only 0.1. The probabilities of obtaining discrete values of F2 for state 2 (low, rather low, rather high and high: E1, E2, E3, E4) are 0.05, 0.10, 0.15 and 0.70 respectively. Thus the probability of finding a high value of F2 in the middle of the vowel /i/is rather high.

In reality we observe small speech frames, with – in our restricted and hypothetical example – only values of F2. The sequence of values of the F2, for instance E2, E4, E4, E4, E3 (each frame covering 20 ms), has to be compared with the probabilities implied by the model. The model which has the largest probability of having generated the observed sequence of

states, will be labelled as the 'realized segment'. Of course, there will be differences in confidence that a sequence X should be labelled as segment /x/.
A confidence index is a possible measure of the quality of the realized segment. This procedure is used in an ASR application for the detection of errors in L2 (Cucchiarini et al., 2009). There is a complication. In most speech recognition algorithms, a so-called 'language model' plays a role. That language model contains transitional probabilities of going from one word to another. In Dutch, for instance, the probability of finding a word with the neutral gender – like '*house*' – is extremely low after the non-neutral determiner 'de' ('the'). In some ASR approaches language models even pertain to phoneme sequences. In Dutch, for instance, the sequence /l r/ is very low, whereas the probability of observing a sequence /s t/ is relatively high. Of course, this language knowledge should be used in speech recognition, but not in a system that aims at assessing the quality of speech segments. Knowledge of the language model is a well-known obstacle to the subjective assessment of speech. We all know that in '*the cat p...*' '*p*' will be followed with a high probability by '*urrs*'. That is why subjective measurement has an intrinsic problem: the expectation of the listener.
HMMs are used in a number of formats, depending on:

- the number of states used in modelling speech segments,
- the amount of training material needed,
- the dimensionality of the statistical distributions of the parameters used.

A word-based account of errors is often not informative, even if the language model in the HMM is "switched off". The reason is that segment mispronunciations have to be weighted in order to obtain a valid error score for an utterance (Preston, Ramsdell, Oller, Edwards & Tobin, 2011). That is why most systems developed for providing feedback on the adequacy of pronunciation are segment based. Before a robust ASR system can be set up to provide feedback on speech performance, it has to be established to which extent target speech segments meet the following criteria, which, as a matter of fact, are quite similar to the criteria used in systems for error detection in second language acquisition (see Cucchiarini et al. 2009).

a. The influence of an incorrect realization has an impact on intelligibility and communication; this implies that for every language different segments and features are important. Tonal movements are less important for languages like English or German, but crucial in Chinese.
b. The errors are perceptually salient;
c. The errors are frequent;
d. The errors occur in the speech of relatively many speakers;
e. The errors are persistent;
f. Robust automatic error detection is possible;
g. Unambiguous feedback is available.

4.3 Speech materials to be used

An often neglected subject is the nature of the speech materials to be used. Of course, the materials should contain language samples which are prone to be incorrectly realized – see above -, but there are also other aspects which should be considered. There are a multitude of factors which affect the realization of speech segments and global parameters

of speech. We mention: the prosodic position: in the English word *rhododendron,* for example, '*den*' carries word stress. Word stress affects duration, intensity and spectral characteristics, the length of the utterance: the longer an utterance is, the shorter the speech segments which make it up are (the 'i' in '*stride*' is shorter than in '*side*', the distinction between function words and content words (for instance '*in*' vs. '*bin*') is influential in speech tempo, intensity and spectral characteristics. If speech materials are to be used in subsequent assessment procedures, it is worthwhile to have the speech segments realized in balanced conditions.

4.4 Technical requirements

The American Telemedicine Association published a valuable list of "Core Standards for Telemedicine Operations" (2007). For speech applications an additional number of technical requirements have to be met, as a function of the goals of the application. Most of them are self-evident. We mention a number of requirements, and will give some more information on requirements which are less self-evident:

1. *The presence of a reliable and robust server*, with personnel that can answer technical questions at well-defined time intervals and can update the system as required by IT-developments (firewalls, browsers etc.);
2. *A cross-platform browser-based application* which delivers uncompromised viewing of applications;
3. *A clear distribution of roles* with an associated system for authorizations: user, therapist and administrator;
4. *Quick uploading* of target utterances;
5. *A psychologically valid and quick presentation of feedback with sufficient screen resolution.*
   The configuration of visual feedback for speech is not self-evident, and needs some scrutiny in order to adapt it to the user population. In this domain, speech technologists should be supplemented with experts in the integration of auditory and visual perception (Sadakata et al., 2008). For patients with neurogenic communication disorders such as PD, who are likely to suffer from other disorders than distorted speech alone, visual or cognitive distortions might be a serious constraint in the perception of visual displays that aim at providing feedback on different speech dimensions, such as pitch and intensity (loudness). This is particularly the case when two or more speech dimensions of a dysarthric speaker are displayed, such as pitch and intensity in the case of the PLVT for parkinsonian speakers. Rather than abstract graphs, which are difficult to interpret for a large number of predominantly elderly speakers, visualization should be simple and intuitive. That is, the form of visual feedback should apply to patients and give cues for approaching and adequate realization of speech.
   An example: how should one display the time course of pitch and intensity, as a simple graph (see Figure 4a), or as a picture which might intuitively be more appealing (Figure 4b)? The solution might obviously lie in an integrated, multidimensional picture of more speech dimensions.
   Currently, in the Netherlands, web based experiments are set up in order to evaluate what graphic form appeals to healthy controls. In addition, it will be evaluated whether or not preferences for visual forms in healthy controls also goes for neurological patients such as speakers with PD or after stroke.

Fig. 4a. Separate displays of the time course of pitch and intensity (female speaker)

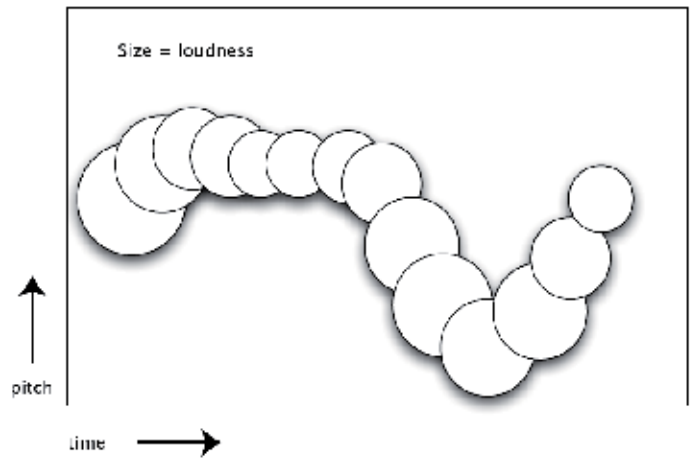
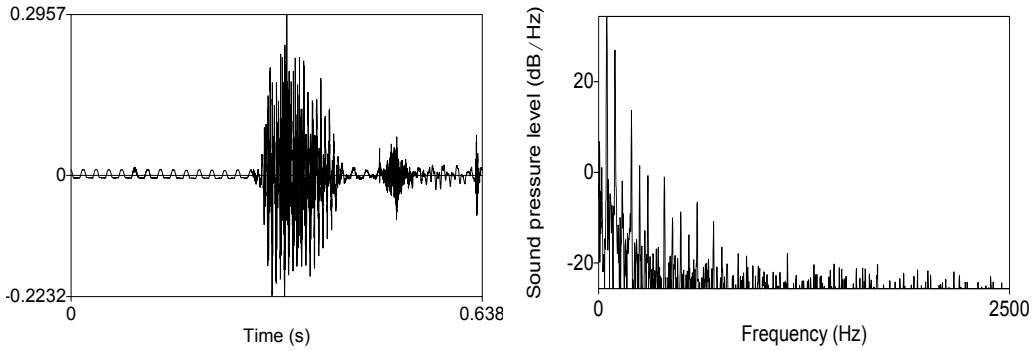


Fig. 4b. Integrated display of the time course of pitch and intensity

6. *Easy use of the PC/laptop;*
7. *Adjustable text fonts;*
8. Possibility to *personalize* protocols for exercises;
9. *Privacy guarantees;*
10. *Adequate format of speech files.*
    If (subsets of) realized utterances are stored for subsequent assessment by a speech therapist or an automated computer procedure, the format of the speech files should be suited for those procedures. The main element of the format is the sampling frequency (22.05 kHz or 44.1 kHz). Preferably no signal coding should be used to reduce the amount of data. MP3 coding and the associated data reduction (with bit rates of 128 or 192) does not have any effects on perception, but may lead to some effects on the

spectral representation. WAV-files have an advantage: they are files without any data-coding. Important factors in the decision on the sampling frequency and the possible data reduction are the characteristics of the parameters to be extracted from the signal. The upper bound of the frequency range relevant for the acoustic description of vowel-like sounds is around 3 kHz. For the analysis of fricatives – for instance speech sounds like /s/ and /ʃ/ - we need a wider frequency range, with an upper bound of at least 6 kHz (Olive et al., 1993).

11. *Robust and well-defined recording conditions.*
The basic principle underlying eHealth applications is that patients can use the application at home. Conditions at home vary to a great extent. Some people will use the application in a quiet office, others in a kitchen with neon tubes, or in a garden with traffic noise in the background. In the following figure we show the waveform of an utterance with an added 50 Hz-signal; the latter is not a pure sinus wave. The sinusoidal signal might hinder subjective judgement, and create biases in the spectral representation of the realized utterances, see panel (b) in Figure 5, where a strong 50 Hz component and the associated harmonics are displayed. The presence of the harmonics is due to the fact that the sinus wave was not 'pure'.



(a) (b)

Fig. 5. (a) Waveform of a fragment of the Dutch word 'buitenboord' ([bœytəb...]:'English: 'outboard') with an added 50 Hz signal generated by an external source and
(b) spectrum of the (intended silent) initial part of the waveform.

In many approaches to the (semi-automatic) assessment of the segmental quality of speech segments, the silent interval associated with the closing phase of stop consonants like /p, t, k/ is relevant. If this interval is filled with some 'humming' it may be an indication that the speaker was not able to firmly close his/her lips for the stop consonant (Kent et al., 1999).

4.5 Secondary outcomes of telehealth applications for speech technology

Apart from therapeutical aims, which mainly focus on the benefits for clients and therapists, telehealth applications such as EST provide a vital source of data for researchers in the field of speech pathology and speech technology. That is, uploading patients' speech by means of web based systems, automatically generates a data base of pathological speech (Figure 6). This data base is vital for clinical outcome research in the field of speech pathology. That is, a data base allows perceptual and acoustical measurements of speech across time in order to evaluate therapy outcomes. This will increasingly gain importance in the context of

decreasing financial resources for health care, where evidence based treatments finally will prevail. Although guidelines for diagnosis and treatment have been formulated (section 2.3), these are not based on the highest level of evidence. Objective outcome measures on the basis of a central data base of pathological speech are likely to enhance evidence based guidelines. Government policies and hence requirements of health care reimbursers will be based on objective therapy results, to be derived from data sources as generated by web based applications such as EST. For therapists the objective speech data over time of an individual patient is expected to provide useful information to evaluate therapy results and to adjust therapy focus if necessary.

In addition to its relevance for clinical outcome research, a data base of pathological speech contains vital information for speech technological and language technological research. In general, speech and language technology has considerably gained importance in health care during the last few decades. Particularly for patients with communicative problems this research area is of vital importance. These problems can be due to cognitive disorders (e.g. aphasia or dyslexia), sensory disorders (blindness or hearing loss) or voice and speech disorders (e.g. dysarthria, stuttering, dysphonia). Speech and language technology also applies to the needs of patients with communication problems in a broader sense. That is, constraints in the interaction with their environment as a result of motor system disorders such as Repetitive Strain Injury (RSI) or movement disorders such as paralysis after stroke or distorted arm movement coordination due to PD. Only recently, a report on needs and future possibilities for speech and language technologies for patients with communicative problems appeared (Ruiter et al., 2010).

Applications of speech and language technology are expected to contribute to more efficient and more effective health care. Patients can stay longer in their home environment without putting demands on health care givers and, hence, on financial resources. For example, patients with PD could benefit from speech synthesis applications for text-to-speech conversions, facilitating patients with severely diminished speech intelligibility in their verbal communication. Automatic error detection could provide parkinsonian patients who are eager to practice their speech in their home environment using web applications such as EST, with automatic feedback on segmental speech quality (i.e. articulation of speech sounds). An ASR application in dysarthric speech for example would lie in the field of domotica. PD patients with severe motor constraints could gain considerable independence from remotely (i.e. speech) controlled domestic equipment.

In general, speech synthesis, as applied in text-to speech conversions, is usually relatively simple and is not dependent on features of pathological speech. Automatic speech recognition (ASR) and automatic error detection of pathological speech however, are complex issues in the field of speech technology. This is primarily due to the large variability within and between pathological speakers, in particular in the case of neurogenic speech disorders such as dysarthria. Hence, large amounts of data are required for the development of ASR and automatic error detection in pathological (i.e. dysarthric speech). Applications of automatic error detections concern for instance feedback on segmental speech quality in EST, in addition to feedback on loudness and overall pitch. This would enhance patients' independent web based speech training.

Obviously, apart from research in the field of speech technology, an automatically generated data base of pathological speech, is an essential source for additional fundamental research into acoustical features of parkinsonian dysarthria for instance. Outcomes of acoustical studies might even lead to adjustments of speech training programs for patients with PD.

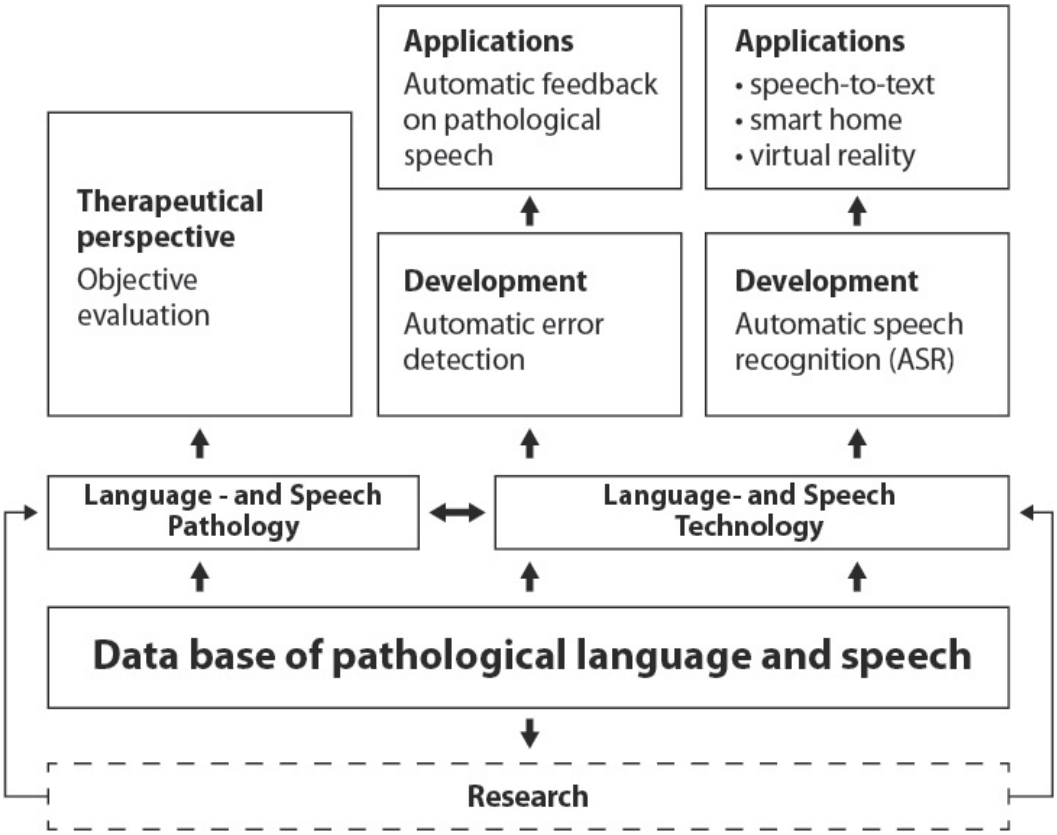


Fig. 6. A data base of pathological speech as a vital source for clinical outcome research and speech and language technological research.

A data base of pathological speech should contain speech at various linguistic levels. Audio recordings stored at the data base should be adequately annotated. That is, identification of standardized speech tasks, orthographic and phonetic annotation and linguistic level should be well documented. In addition, anonymous speaker identification should be ensured. An adequately structured data base should facilitate researchers' search for audio files of pathological speech. In Belgium, the Corpus of Pathological and Normal Speech (COPAS) (Middag et al., 2010) has been collected. Researchers employ the COPAS data base for the development of an automated intelligibility assessment, based on phonological features. These phonological features refer to articulatory dimensions. This information should reveal underlying articulation problems in dysarthric speakers. The Nemours Data Base of Dysarthric Speech is another example of a corpus of pathological speech (Menendez-Pidal et al., 1996). It should be noticed however that the COPAS and the Nemours data bases were not generated by a web based system, whereas a data base generated by means of EST involves upload and storage of audio files by means of a telehealth application. Vital conditions must be met to ensure audio recordings with adequate quality for perceptual and acoustical assessment. Obviously, a data base of pathological speech is language specific. Cross-language comparisons however should be enabled by similar structures of speech data bases for different languages.

5. Research areas with respect to the development, implementation and evaluation of telehealth applications for speech training of patients with Parkinson's disease

Telerehabilitation has a potential in a large number of fields. We are still in the first phase of a development which may revolutionize medical care and cure. The heterogeneous applications – be they in psychiatry, asthma or diabetes care, speech and language therapy – share a number of factors which have to be fulfilled in order to warrant success, but which are not always met yet. A dangerous aspect of the phase we are in now is that we focus on technology and just admire its realized or promised possibilities. Thus we might overlook the key human factors for telerehabilitation applications in general as reviewed by Brennan and Barker (2008). In this section we give an overview of the four research areas formulated by the American Telemedicine Association (Krupinsky et al., 2007), and will zoom in on those aspects which are relevant for telehealth applications for people with Parkinson's disease.

a) Attention should be paid to definition of infrastructure and integration of various infrastructural components of web based devices

Of course, the definition of infrastructure and the integration of various infrastructural components of web based devices is a prerequisite for the application and evaluation of results obtained with web based devices (see section 3.3), but the central component of the applications in our field remains the availability of robust speech recognition and/or error detection systems, if at least providing automatic feedback on realized utterances in speech training is (one of) the goal(s) of the web-application. Both speech and language pathology and speech and language technology are language bound. That is, they share underlying principles (HMMs, for instance, are used for very diverse languages like Chinese, English or Russian), and pathological reduction of vowels, consonants and pitch excursions occur in all languages, but the details of the technologies have to be developed for every specific language and the phenomena associated with speech pathology of specific languages have to be studied. In this context much attention has to be paid to the form of feedback, as was already pointed out in section 4.4.
Speech disorders and the associated symptoms may show considerable variability between and within speakers. While intensive training may help some patients to partially recover and improve their speech skills, other patients will show no improvement or perhaps even deterioration. Therefore, novel speech recognition and natural language processing techniques will have be developed that can cope with the dynamics of the speech disorder.

b) Clinical utility of telehealth should be established

The establishment of the clinical utility of a telehealth application for speech therapy of patients with PD is not a simple one. The first prerequisite is the presence of a robust infrastructure and a robust feedback system. While students using a feedback system on the quality of their pronunciation of a second language may be "robust" themselves, we cannot assume the same extent of robustness in patients with PD. That is why a very small number of studies have been conducted on the clinical utility of eHealth applications in our field. In order to test the clinical utility in phase III or phase IV studies, quite a number of conditions have to be fulfilled:

- A clear definition of the effect one wants to attain with the application. There are different possible and/or positive effects: (1) after a pre-specified time interval the

speech quality of the telehealth group has improved more than that of the control group, (2) after the time interval the speech quality of the telehealth group was more stable than that of the control group, (3) in the long run, maintenance of achieved results is made possible by the telehealth application. Each of these possible outcomes has to be crossed with outcomes regarding the cost-effectiveness of the treatment (see under d) and user satisfaction.

- Relatively large numbers of patients are needed in order to ensure sufficient power to detect possible differences between a treatment and a control group. In light of the heterogeneity of the patients with respect to a large number of relevant background variables (age, SES, cognitive and motor skills, hearing and vision, computer skills, mobility, home situation), matching on these variables is a crucial issue in the effect studies to be carried out. As it is not very simple to include large numbers of patients, it is difficult to obtain a complete overview of the importance of these variables (see under c).
- An important aspect of effect studies is a clear definition of the outcome variables to be used. For telehealth applications for patients with Parkinson's disease we mention five variables which are directly related to speech dimensions:
  - Articulatory precision
  - Intelligibility
  - Naturalness of speech
  - Speech effort
  - Listening comfort

  Much research is needed to find generally accepted operationalizations of the above-mentioned variables. Reviewing the relevant international journals in this domain makes clear that research is still going on, and that final results are not in view. This is in contrast to related questions on the intelligibility and naturalness of synthesized speech, where researchers agreed on a number of well-documented protocols to assess these aspects of computer speech (see the Blizzard Challenge, a yearly competition among speech synthesis systems based on corpora, see http://www.cs.cmu.edu/~awb/). For a review of problems encountered in subjective methods to assess intelligibility we refer to Beijer, Clapham & Rietveld (submitted) and Hustad (2006).

  Even if the correct operationalizations are available, a number of other questions have to be answered before ecologically valid effectiveness studies can be carried out. Here are two examples of the questions still to be answered: (1) Articulatory precision can be achieved at the cost of naturalness ("speak loud", the message of the Lee-Silverman therapy): what is more important: articulatory precision or naturalness? (2) Intelligibility is obvioulsy related to articulatory precision, but to what extent can outcomes of current intelligibility tests and tests of articulatory precision be generalized to daily life?

c) Human and ergonomic factors should be taken into account in research activities.

At first sight the condition under c) is stating the obvious; however, enthusiasm for technology might obscure the importance of these factors. It is well known that diseases like PD may come with other problems: comorbidity is not uncommon (Lowit et al., 2005). The problems may be such that a telehealth application is not suitable for a patient, neither in daily practice, nor in a research setting. For a research setting which aims at finding evidence for the effectiveness of an application itself – out of the social/psychological

context - the problem may be that some of the participants are not suited to fully appreciate the application. There are a multitude of possible reasons for this; we mention impaired auditory processing and impaired vision as possible and obvious obstacles to the use of a telehealth application. In section 3.3 we describe an Auditory Discrimination Test on a number of speech dimensions (Beijer, Rietveld, & van Stiphout, in press) to assess participants' suitability to use auditory feedback.
There are also less obvious factors which should be taken into account, and which are often also region-determined. In densely populated areas like the Netherlands, with short distances, a patient has the choice to opt for face-to-face sessions or to stay at home with an eHealth application. A number of aspects may influence the choice: (1) finances – in the Dutch context hardly ever a factor for a patient, as even taxi expenses will often be reimbursed, (2) the wish to see other people at a regular basis; this opportunity is provided by face-to-face sessions and not by a telehealth application, (3) mobility; some people are home-bound, while others may be mobile, (4) the need to be intelligible for people others than direct partners.

d) Economic analysis should point out whether the balance of costs and benefits is beneficial to the actual economic and social situation.

This research area becomes an important one against the background of an ageing population and limited financial resources. A prerequisite for cost-effectiveness studies is the availability of effectiveness measures accepted by the community of speech and language pathologists and therapists. The question how to decide whether a number of beneficial units of web based speech therapy (less effort for a listener, less repetitions needed to achieve complete understanding, less absence from home, less transport, better maintenance of communication etc.) are in a positive trade-off relation with additional costs (implementation and maintenance of infrastructure, availability of a help-desk etc.) is a matter of politics and society.

6. Conclusion

Employment of telehealth devices for dysarthric patients with PD seems promising with respect to their possibilities to practice their speech independently. As such, they might provide a solution for the foreseen imbalance between the need (and call) for speech training on the one hand, and the reduced availability of therapeutical resources on the other hand. Although technological feasibility of various web based training devices has been established, user requirements for parkinsonian patients with frequently observed deficits in cognitive and motor functioning demand further adjustments. Apart from therapeutical goals, web based training devices such as EST provide the possibility of generating a data base of pathological speech. This data base not only provides required information for clinical outcome research. It is also of vital importance for the development of automatic speech recognition and automatic error detection of pathological (i.e. parkinsonian) speech.

7. Acknowledgement

The authors wish to thank Dike Ottoy for her corrections of the English text and Gaetano Ambrosino for his assistance with the illustrations.

8. References

Ackermann, H. & Ziegler, W. (1991). Articulatory deficits in parkinsonian dysarthria: an acoustic analysis. *Journal of Neurology, Neurosurgery & Neuropsychiatry*, 54 (12), pp. 1093-1098, ISSN 00223050.

American Telemedicine Association. http://atmeda.org/news/definition.html. Last accessed 20.2.2011.

Beijer, L.J., Clapham, R.P., & Rietveld, A.C.M. 'Evaluating the suitability of orthographic transcription and intelligibility scale rating of semantically unpredictable sentences (SUS) for speech training efficacy research in dysarthric speakers with Parkinson's disease.' *Journal of Medical Speech-Language Pathology* (Accepted for publication, November 2011).

Beijer, L., Rietveld, T., van Beers, M, Slangen, R., van den Heuvel, H., de Swart, B. & Geurts, S. (2010a). E-learning based Speech Therapy (EST) as a web application for speech training. *Telemedicine and e-Health*, 16(2), pp. 177-180, ISSN 1530-5627.

Beijer, L., Rietveld, T., Hoskam, V., Geurts, A. & de Swart, B. (2010b). Evaluating the feasibility and the potential efficacy of e-Learning-Based Speech Therapy for speech training in dysarthric patients with Parkinson's disease: a case study. *Telemedicine and e-Health*, 16(6), pp. 732-738, ISSN 1530-5627.

Beijer. L., Rietveld, A. & van Stiphout, A. (in press). Auditory discrimination for E-learning based Speech Therapy: a proposal for an Auditory Discrimination Test (ADT) for adult dysarthric speakers. *Journal of Communication Disorders*, ISSN 0021-9924.

Blizzard Challenge: http://www.cs.cmu.edu/~awb/).

Boersma, P. & Weenink, D. (2011). *Praat: Doing Phonetics by Computer*. www.praat.org. Downloaded 8.3.2011.

Brennan, D.M. & Barker, L.M. (2008). Human factors in de the development and implementation of telerehabilitation systems. *Journal of Telemedicine and Telecare,*14, pp. 55-58, ISSN 1758-1109.

Carmichael, J.N. (2007) *Introducing Objective Acoustic Metrics for the Frenchay Dysarthria Assessment Procedure*, Unpublished PhD-thesis, University of Sheffield.

Cucchiarini, C., Neri, A., Strik, H. (2009). Oral Proficiency Training in Dutch L2: the Contribution of ASR-based Corrective Feedback. *Speech Communication*, 51(10), pp. 853-863, ISSN 0167-6393.

Davis, S. & Mermelstein, P. (1980). Comparison of parametric representations for monosyllabic word recognition in continuously spoken sentences. *IEEE Transactions on Acoustics, Speech, and Signal Processing*, 28, pp. 357-366, ISSN 0096-3518.

Darly, F.L., Aronson, A.E., & Brown, J.R. (1969). Differential diagnostic patterns of dysarthria. *Journal of Speech and Hearing Research, 12*, pp. 246-269, ISSN 1092-4388.

Deane, K.H.O., Whurr, R., Playford, E.D., Ben-Shlomo, Y., Clarke, C.E. (2001). Speech and language therapy versus placebo or no intervention for dysarthria in Parkinson's disease. Cochrane *Database of Systematic Review*s, Issue 2. Art. No.: CD002814, ISSN 1469-493x.

Duffy, J.R. (1995). *Motor Speech Disorders: Substrates, Differential Diagnosis and Management.* Mosby-Year Book, ISBN 0801669448, St. Louis.

Enderby, P. (1980). Frenchay Dysarthria Assessment, *British Journal of Disorders of Communication*, 21, pp.165-173, ISSN 0007-098x.

Ferrand, C. & Bloom, R. (1997). *Introduction to Organic and Neurogenic Disorders of Communication.* Allyn and Bacon, ISBN10: 0205168671, Needham Heights, MA.

Ho, A.K., Bradshaw, J.L. & Iansek, R. (2000).Volume perception in parkinsonian speech. *Movement Disorders* 15 (6), pp. 1125-1131, ISSN 1531-8257.

Hustad, K.C. (2006). Estimating the intelligibility of speakers with dysarthria. *Folia Phoniatrica et Loopaedica,* 58, pp. 217-228, ISSN 1021-7762.

Kalf, J.G., de Swart, B.J.M., Zwarts, M.J., Munneke, M., Bloem, B.R. (2008a). Frequency of oral motor impairments in Parkinson's disease and implications for referral to speech therapists. *Movement Disorders*; 23:S328, ISSN 1531-8257.

Kalf, J.G., de Swart, B.J.M., Bloem, B.R., Munneke, M. Guidelines for speech-language therapy in Parkinson's disease (2008b). *Movement Disorders*; 23:S328, ISSN 1531-8257.

Kent, R.D., Weismer, G., Kent, J.F., Vorperian, H.K. & Duffy, J.R. (1999). Acoustic studies of dysarthric speech: methods, progress, and potential. *Journal of Communication Disorders*, 32, pp. 141-186, ISSN 0021-9924.

Krupinsky, E, Dimmick, S., Grigsby, J., Mogel, G., Puskin, D., Speedie, S., Stamm, B., Wakefield, B., Whited, J., Whitten, P., Yellowlees, P. Research recommendations for the American Telemedicine Association. *Telemedicine and e-Health*, 12(5), pp. 579-589, ISSN 1530-5627.

Kwakkel, G., Wagenaar, R.C., Twisk, J.W.R., Lankhorst G.J., Koetsier, J.C. (1999). Intensity of leg- and arm-training after primary middle-cerebral- artery stroke. Lancet, 354 (9174), pp.191-196, ISSN 0140-6736.

Lowit, A., Howell, P. & Brendel, B. (2005). Cognitive impairment in Parkinson's disease. Is it a unfied phenomenon? *Journal of Brain Impairment*, 6 (3), pp. 191-204, ISSN 1443-9646.

Mashima, P. & Doarn, C. (2008). Overview of telehealth activities in speech-language pathology. *Telemedicine and e-Health,* 14, pp. 1101-1109, ISSN 1530-5627.

Menéndez-Pidal, X., Polikoff, J.B., Peters, S.M., Leonzio, J.E. & Bunnell, H.T. (1996). The Nemours Database of Dysarthric Speech. *Proceedings of the Fourth International Conference on Spoken Language Processing.* Philadelphia, PA, USA.

Middag, C., Saeys, Y. & Maryens, J-P. (2010). Towards an ASR-free objective analysis of pathological speech. *Proceedings Interspeech 2010, Makuhari, Japan*, pp. 294-297 ISSN 1990-9772.

Neri, A., Cucchiarini, C. & Strik, H. (2006). Selecting segmental errors in L2 Dutch for optimal pronunciation training. *International Review of Applied Linguistics in Language Teaching*, 44, pp.357-404, ISSN 1613-4141.

Olive, J.P., Greenwood, A. & Coleman, J. (1993). *Acoustics of American English Speech: A Dynamic Approach*. Springer Verlag, ISBN 0-387-97984, New York.

Preston, J.L., Ramsdell, H.L., Oller, D.K, Edwards, M.L. & Tobin, S.J. (2011). Developing a Weighted Measure of Speech Sound Accuracy. *Journal of Speech, Language, and Hearing Research*, 54, pp.1-18, ISSN 1558-9102.

Ramig, L.O., Sapir, S. Countryman, S., Pawlas, A.A., O'Brien, C., Hoehn, M. & Thompson, L.L. (2001). Intensive voice treatment (LSVT) for patients with Parkinson's disease:

a 2 year follow up. *Journal of Neurology Neurosurgery and Psychiatry*, 71, pp. 493-498, ISSN 00223050.

Rietveld, T. & Stoltenberg, I. (2005). *Taal- en spraaktechnologie en communicatieve beperkingen*. ('Language and speech technology for people with communication disorders', in Dutch). Dutch Language Union, ISBN-13: 9789070593063, The Hague.

Rietveld, T. & van Heuven, V.J. (2009). *Algemene Fonetiek ('General Phonetics', in Dutch)*, 3rd edition. Coutinho, ISBN 978 90 469 0163 2, Bussum.

Rijntjes M, Haevernick K, Barzel A, van den Bussche H, Ketels G, Weiller C.(2009). Repeat therapy for chronic motor stroke: a pilot study for feasibility and efficacy. *Neurorehabilitation & Neural Repair*. 23(3), pp. 275-80, ISSN 0888-4390.

Ruiter, M.B., Rietveld, Toni C.M., Cucchiarini, C., Krahmer, E.J. & Strik, H. (2010). Human Language Technology and Communicative Disabilities: Requirements and Possibilities for the Future in Dutch. *Proceedings Seventh International Conference of Language Resources and Evaluation* (LREC), pp. 2839-2846, ELRA: ISBN 2-9517408-6-7, Malta.

Sadakata, M., Hoppe, D., Brandmeyer, A., Timmers, R. & Desain, P. (2008). Real-Time Visual Feedback for Learning to Perform Short Rhytms with Variations in Timing and Loudness. *Journal of New Music Research*, 37, pp. 207-220, ISSN 1744-5027.

Sanders, E., Ruiter, M., Beijer, L. & Strik, H. (2002). Automatic recognition of Dutch dysarthric speech: A pilot study. *Proceedings of ICSLP-2002*, Denver, USA, pp. 661-664.

Slawek, J., Derejko, M., Lass, P. (2005). Factors affecting the quality of life of patients with idiopathic Parkinson's disease – a cross-sectional study in an outpatient clinic attendees. *Parkinsonism & Related Disorders*, 11 (7), pp. 465-468, ISSN 1353-8020.

Sood, S., Mbarika V., Jugoo, S., Dookhy, R., Doarn, C.R., Prakash, N., Merrell, R.C. (2007). What is telemedicine? A collection 104 peer-reviewed perspectives and theoretical underpinnings. *Telemedicine and e-Health*,13 (5), pp. 573-590, ISSN 1530-5627.

Strik, H., Truong, K., de Wet, F., Cucchiarini, C. (2009). Comparing different approaches for automatic pronunciation error detection. *Speech Communication*, Volume 51, Issue 10, October 2009, pp. 845-852, ISSN 0167-6393.

Swart, B.J.M. de, Willemse, S.C., Maassen, B.A.M. & Horstink, M.W.I.M. (2003). Improvement of voicing in patients with Parkinson's disease by speech therapy. *Neurology*, 60, pp. 498-500, ISSN 0028-3878.

Streifler, M. & Hofman, S. (1984). Disorders of verbal expression in parkinsonism. *Advances in Neurology*, 40, pp. 385, ISSN 0091-3952.

Teasell, R.W. & Kalra, L. (2004). Advances in stroke 2003. What's new in stroke rehabilitation? *Stroke*, February, pp. 383-385, ISSN 1524-4628.

Von Campenhausen, S., Bornschein, B., Wick, R., Botzel, K., Sampaio, C., Poewe, C., et al. (2005). Prevalence and incidence of Parkinson's disease in Europe. *European Neuropsychopharmacology*, 15(4), pp. 473-490, ISSN 0924-977x.

Theodoros, D.G., Constantinescu, G., Russell, T.G., Ward, E.C., Wilson, S.J.& Wootton, R.(2006). Treatin the speech disorder in Parkinson's disease online. *Journal of Telemedicine and Telecare*, 12: S3, pp. 99-91, ISSN 1758-1109.

Tulu, B. Chatterjee, S. and Maheshwari, M. (2007). Telemedicine Taxonomy: a classification tool. *Telemedicine and e-Health*, 13 (3), pp.349-358, ISSN 1530-5627.

Ziegler, W. (2003). Speech motor control is task-specific: Evidence from dysarthria and apraxia of speech. *Aphasiology*, 17 (1), pp. 3-36, ISSN 1464-5041.

Ziegler, W. & Zierdt , A. (2008). Telediagnostic assessment of intelligibility in dysarthria: A Pilot investigation of MVP-online. *Journal of Communication Disorders,* 41(6), pp. 553-577, ISSN 0021-9924.

19

Rehabilitation Versus no Intervention – Only a Continued Intensive Program Conducted Statistically Significant Improvements Motor Skills in Parkinson's Disease Patients

Jesús Seco Calvo and Inés Gago Fernández
University of León,
Spain

1. Introduction

Parkinson's disease (PD) is a degenerative disease characterised by movement disorder, which consists of bradykinesia (movement slowness), hypokinesia (reduced movement), tremor, rigidity and alterations in gait and posture; mood changes also constitute a main component of PD (Marsden, 1994), which is also related to postural instability and often to cognitive deficits (Carne, et al., 2005). Working memory —which is defined as the capacity to maintain, supervise and use inner information for behavioural self-control— is an essential cognitive skill which works as base for other more complex and executive functions affected by PD (Baddeley, 1992). Since 1987, the Parkinson Study Group has undertaken a series of random controlled tests. In these studies, researchers used standardized clinical scales to examine the impact of pharmaceutical interventions on the progression of PD symptoms (Carne, et al., 2005). Other authors (Hiroyuki, et al. 2003) have studied modifications in balance, demonstrating that balance exercises lead to improvement in the function of static balance and that gait exercises improve dynamic balance and wandering functions in fragile or dependent elderly patients(Hiroyuki, et al. 2003). Quantitative reduction of muscular strength in the back, hips, ankles, with damage in propioception —visual sense and the lowest support base— are the main cause of instability in patients with Parkinson's disease. Motor complications caused by the disease have an important effect on physical and functional capacity.

Regarding gait, Herman et al., (Herman, et al. 2007), have evaluated the effects of 6 weeks of treadmill exercises, which allow rhythmic training of gait, functional mobility and quality of life in PD patients; the results obtained show the exercises' potential to improve gait rhythmically in PD patients and suggest that a progressive and intensive training program in treadmill may be used to reduce gait alterations and falling risk, and increase the quality of life of such patients[5]. In this sense, some authors (Brichelto, et al. 2006) showed potential short-term effectiveness of gait-slowness training in PD patients. Positive results were documented by clinic position scales and gait objective evaluation. Quick loss of clinical advantage suggests that further researches are necessary for a more precise definition of optimum frequency and treatment duration (Brichelto, et al. 2006). In order to reduce bradykinesia, the combination of motor imagery and real practice of motor movement might

turn out to be efficient in PD treatment. Putting into practice such treatment regime allows improving quality of life involving non-significant risks and low cost (Tamir & Huberman, 2007). Several standard guidelines as well as interdisciplinary measures have been established with the purpose of achieving overall improvement of personal wellbeing, such as physical exercise, occupational and speech therapies, and psychological, food and social guidance, obtaining encouraging results (Quality Standars Subcommitte, American Academy of Neurology, 1993; Köler, et al., 1994). According to observations, occupational and behavioural therapies based on psychological and motivational aspects might induce improvements in movement initiation and quality (Muller, et al., 1997). Treatment by functional recovery or physiotherapy has already shown its effectiveness in PD patients (Comella, et al., 1994; Formisano, et al., 1992; Franklyn, et al., 1981; Gibberd, et al., 1981; Pederson, et al., 1990), although such evidence is questioned in several reports (Ellgring, et al., 1990). Physical therapy generally works as reinforcement for the motor program, but such kind of intervention generally lacks of motivational and emotional spheres which might explain why physiotherapy traditionally achieves little influence on mood condition and is not easily incorporated into the patient's way of life (Ellgring, et al., 1990). On the other hand, it is also well-known that psychosocial variables such as emotional or psychosocial tension have a strong influence on gait and postural anomalies, as well as on other motor functions (Carne, et al., 2005; O´Shea, et al., 2002).

In order to quantify improvement in patient's motor condition and be able to show variations in his/her quality of life, the use of the Unified Parkinson's Disease Rating Scale (UPDRS) has prevailed (Movement Disorder Society Task Force on Ratio Scales for Parkinson´s Disease, 2003). Pellecchia et al. (Pellecchia, et al., 2004) observed that —after a physiotherapy protocol— a significant improvement of UPDRS scoring took place in the section of daily-life activities and the motor section, but also in the Self-rating Scale for PD Incapacity, the 10-metre walking test and Zung Self-rating Depression Scale; after three months such clinic improvements were maintained to a great extent (Pellecchia, et al., 2004). In the same way, Ellis et al. (Ellis, et al., 2005) found out that total scoring within the mental and motor sections was not much different among different groups and that significant differences were only found three months after treatment in the UPDRS section devoted to daily-life activities and its total scoring (Ellis, et al., 2005), observing that PD patients obtain short-term benefits from physiotherapeutic group treatment and long-term advantages in UPDRS total scoring, although significant variations were found among different groups(Ellis, et al., 2005). Therefore, it seems to be evident that sustained improvement in motor skills can be achieved in PD patients through a physiotherapy program within a reasonable long term time-period (Pellecchia, et al., 2004; Ellis, et al., 2005).

Therefore, the aim of the present study is to demonstrate the effectiveness of a physiotherapy protocol in PD patients, quantified in terms of improvement in UPDRS scoring within its motor subscale.

2. Material and methods

2.1 Sample

27 PD patients (12 females and 15 males), members of the PD Patient Association from Astorga and its Region (Spain), of 69.50± 10.34 years of age —ranging from 55 to 80 years of age— and with an average number of disease evolution years of 11.39±1.614, ranging from 10 to 15 evolution years.

All subjects met the following inclusion criteria: Stable reaction to anti-Parkinson medication; Hoehn and Yahr stage I, II or III; At least one mobility-related activity limitation within the core areas of physiotherapy practice in PD (gait, balance and posture); No severe cognitive impairtment, defined by Mini-Mental State Examination, score ≥24; No other severe neurologic, cardiopulmonary, or orthopedic disorders and not having participated in a physical therapy or rehabilitation program in the previous 4 month.
We divided our patient into two groups: control group (n=9, received only medication therapy) and experimental group (n=18, received physical therapy and medication therapy).

2.2 Kind of study

Descriptive study which consists of analysis —within the particular context of a PD association— of the relation between physiotherapeutic treatment and scoring obtained through motor examination in UPDRS scale; and Transversal study, since two measurements are carried out within two particular time periods (beginning and end of physiotherapeutic treatment).

2.3 Method

Qualitative: carried out on a reduced population (n=27), analysing physiotherapeutic strategy; and Quantitative: analysis of data obtained through motor examination in UPDRS scale.

2.4 Data collection process

We interview each patient and one of his/her relatives, who were provided with a complete description of the project. Through the following weeks we undertook data collection of the study variables composing the section of motor examination in the UPDRS scale (O´Shea, et al., 2002; Movement Disorder Society Task Force On Ratio Scales For Parkinson´s Disease, 2003) with each patient in both on and off phases. The physical therapist involved in conducting UPDRS was not involved in performing the intervention. All subjects were required to take their medications at the same time of day for all assesment sessions. All subjects usage: L-dopa, dopamine –agonist and amantadine. It should be pointed out that —during study development— we decided to carry out greater incidence on physical work focused on the variables of neck rigidity, posture, postural stability and gait in each patient; as a consequence of such approach, we analyse —apart from results of global scoring in motor examination in UPDRS scale— the results of these four variables.

2.5 Intervention protocol

For the application of the study, we undertook a program of physiotherapeutic treatment according to protocol (Ellis, et al., 2005; Keus, et al., 2007; Morris, 2000; Scandalis, et al., 2001), in which all patients in the sample received physiotherapy group sessions.
The group sessions took 90 minutes. All treatment sessions occurred at the same time of the day throughout the study. The physiotherapist involved in performing the intervention was not involved in conducting UPDRS scale.
The treatment consisted of cardiovascular warm-up activities (5min), stretching exercises (15min), strengthening exercises in a functional context (15min), functional training (15min), gait training overground and on a treadmill with external auditory cueing (15min), balance training and recreational games (15min), and relaxation exercise (10min).

According to the frequency of attendance to such sessions, we divided our experimental group (n=18) into four different subgroups: Subgroup 1 (from 1 to 3 monthly sessions), Subgroup 2 (from 4 to 6 monthly sessions), Subgroup 3 (from 7 to 9 monthly sessions) and Subgroup 4 (from 10 to 12 monthly sessions); each group will obtain different scores in motor examination, as it will be demonstrated in the section corresponding to result analysis.
We also undertook program revision after 32 weeks, in that the physical therapist entrusted to gather to the beginning of the study the punctuations in the subscale engine of the scale UPDRS with every subject of the study so much in the stadium on as (like) in the off, returns to gather the corresponding punctuation in identical conditions to those of the beginning of the study (at the same hour in two interviews). All the subjects finished the study, so much those of the group control as those of the experimental group.

2.6 Statistical analysis

These study design was a Prospective, Randomized, Placebo-Controlled, Double-Blinded Study. For data analysis we use statistical software SPSS® in its 16.0 version.
We calculate measures for central trend (mean, median, mode, standard deviation, minimum and maximum value); we use Student's t-test to analyse the existing relation among the four study variables. Significance level was fixed with $p<0.05$ and $p<0.01$, with a confidence interval of 95% and 99%, respectively.

3. Results

3.1 Experimental group

Regarding measures of central trend of global scoring obtained in the section of motor examination in the UPDRS scale achieved in pre- and post-intervention stages, it is obtained in the on phase that the value of the mean comes from 64.22 ±16.383 before physiotherapeutic intervention to 50.89±19.499 after intervention; in the off phase the value of such mean comes from 85.78±12.549 to 75.78±17.745.
If one compares data obtained in the pre- and post-intervention stages, apart from the decrease in global average scoring, it is also obtained a decrease in the values of the means of the central trend in variables of neck rigidity, posture, postural stability and gait (Table1).
In the neck-stiffness variable, it is where greatest difference among mean values of pre- and post-intervention are obtained, for both on (from 3.33 to 2.11) and off (from 3.72 to 2.94) phases.
The Table2 shows study-variable changes in the different modalities in on phase; by comparing data (expressed in percentages) obtained in pre- and post-intervention stages, it can be pointed out: a decrease in normal-posture modality from 0% to 11.1%;an increase postural stability (recovered without help) from 11.1% to 50% and a decrease in severe-gait-condition modality from 38% to 22.2%.
Table 3 shows study-variable changes in different modalities in off phase; by comparing data (expressed in percentages) obtained in pre- and post-intervention stages, it can be pointed out: a decrease of severe-rigidity modality from 72.2 % to 27.8 %; a variation in slight-rigidity modality or only in neck activity from 0% to 11.1% after physiotherapeutic intervention; a decrease in postural stability (unable to stand) from 38.9% to 22.2% and a decrease in severe-gait-condition modality from 55.6% to 16.7%.

	Valid N	Missing N	Mean	Median	Mode	Standard deviation	Min.	Max.
PHASE ON								
Pre-intervention								
Neck rigidity	18	0	3,33	3,00	3	,594	2	**4**
Posture	18	0	2,33	2,50	3	,907	1	**4**
Postural stabillity	18	0	2,33	2,00	2	,686	1	**3**
Gait	18	0	2,33	2,00	2	,840	1	**4**
Post-intervention								
Neck rigidity	18	0	2,11	2,00	2	,900	1	**4**
Posture	18	0	1,89	2,00	2	1,231	0	**4**
Postural stabillity	18	0	1,50	1,00	1	,985	0	**3**
Gait	18	0	1,94	2,00	2	,938	0	**3**
PHASE OFF								
Pre-intervention								
Neck rigidity	18	0	3,72	4,00	4	,461	3	**4**
Posture	18	0	3,11	3,00	3	,676	2	**4**
Postural stabillity	18	0	3,22	3,00	3	,732	2	**4**
Gait	18	0	3,11	3,00	3	,676	2	**4**
Post-intervention								
Neck rigidity	18	0	2,94	3,00	3	,938	1	**4**
Posture	18	0	2,72	2,00	3	,958	1	**4**
Postural stabillity	18	0	2,56	3,00	2	,984	1	**4**
Gait	18	0	2,78	3,00	4	1,166	1	**4**

Table 1. Experimental group, measures of central trend in on and off stages in pre- and post-intervention stages.

			Fq	%	Valid %	Cumulative %
Neck rigidity pre-intervention.	Valid	mild/moderate.	1	5,6	5,6	**5,6**
		marked, but full range of motion easily achieved.	10	55,6	55,6	**61,1**
		severe.	7	38,9	38,9	**100,0**
		Total	18	100,0	100,0	

			Fq	%	Valid %	Cumulative %
Neck rigidity post-intervention.	Valid	slight or only with activation.	4	22,2	22,2	**22,2**
		mild/moderate.	7	38,9	38,9	**61,1**
		marked, but full range of motion easily achieved.	4	22,2	22,2	**83,3**
		severe.	3	16,7	16,7	**100,0**
		Total	18	100,0	100,0	
Posture pre-intervention.	Valid	slightly stooped posture.	4	22,2	22,2	**22,2**
		moderately stooped posture.	5	27,8	27,8	**50,0**
		severely stooped posture with kyphosis.	8	44,4	44,4	**94,4**
		marked flexion with extreme abnormality of posture.	1	5,6	5,6	**100,0**
		Total	18	100,0	100,0	
Posture post-intervention.	Valid	normal erect.	2	11,1	11,1	**11,1**
		slightly stooped posture.	5	27,8	27,8	**38,9**
		moderately stooped posture.	8	44,4	44,4	**83,3**
		severely stooped posture with kyphosis.	2	11,1	11,1	**94,4**
		marked flexion with extreme abnormality of posture.	1	5,6	5,6	**100,0**
		Total	18	100,0	100,0	
Postural stability pre-intervention.	Valid	recovers unaided.	2	11,1	11,1	**11,1**
		would fall if not caught by examiner.	8	44,4	44,4	**55,6**
		falls spontaneously.	8	44,4	44,4	**100,0**
		Total	18	100,0	100,0	
Postural stability post-intervention.	Valid	normal.	1	5,6	5,6	**5,6**
		recovers unaided.	9	50,0	50,0	**55,6**
		would fall if not caught by examiner.	4	22,2	22,2	**77,8**
		falls spontaneously.	2	11,1	11,1	**88,9**
		unable to stand.	2	11,1	11,1	**100,0**
		Total	18	100,0	100,0	
Gait pre-intervention.	Valid	walks slowly.	3	16,7	16,7	**16,7**
		walks with difficulty, but requires little or no assistance.	7	38,9	38,9	**55,6**
		severe disturbance of gait, requiring assistance.	7	38,9	38,9	**94,4**
		cannot walk.	1	5,6	5,6	**100,0**
		Total	18	100,0	100,0	
Gait post-intervention.	Valid	normal .	2	11,1	11,1	**11,1**
		walks slowly.	6	33,3	33,3	**44,4**
		walks with difficulty, but requires little or no assistance.	5	27,8	27,8	**72,2**
		severe disturbance of gait, requiring assistance.	4	22,2	22,2	**94,4**
		cannot walk.	1	5,6	5,6	**100,0**
		Total	**18**	**100,0**	**100,0**	

Table 2. Experimental group, modifications in scores of variables neck rigidity, posture, postural stability and gait in the *on* phase of the pre- and post-intervention stage.

			Fq	%	Valid %	Cumulative %
Neck rigidity pre-intervention	Valid	marked, but full range of motion easily achieved.	5	27,8	27,8	**61,1**
		severe.	13	72,2	72,2	**100,0**
		Total	18	100,0	100,0	
Neck rigidity post-intervention	Valid	slight or only with activation.	2	11,1	11,1	**11,1**
		mild/moderate.	2	11,1	11,1	**22,2**
		marked, but full range of motion easily achieved.	9	50	50	**72,2**
		severe.	5	27,8	27,8	**100,0**
		Total	18	100,0	100,0	
Posture pre-intervention	Valid	moderately stooped posture.	3	16,7	16,7	**16,7**
		severely stooped posture with kyphosis.	10	55,6	55,6	**72,2**
		marked flexion with extreme abnormality of posture.	5	27,8	27,8	**100,0**
		Total	18	100,0	100,0	
Posture post-intervention	Valid	slightly stooped posture.	2	11,1	11,1	**11,1**
		moderately stooped posture.	5	27,8	27,8	**38,9**
		severely stooped posture with kyphosis.	7	38,9	38,9	**77,8**
		marked flexion with extreme abnormality of posture.	4	22,2	22,2	**100,0**
		Total	18	100,0	100,0	
Postural stability pre-intervention	Valid	would fall if not caught by examiner.	3	16,7	16,7	**11,1**
		falls spontaneously.	8	44,4	44,4	**61,1**
		unable to stand.	7	38,9	38,9	**100,0**
		Total	18	100,0	100,0	
Postural stability post-intervention	Valid	recovers unaided.	2	11,1	11,1	**11,1**
		would fall if not caught by examiner.	9	44,4	44,4	**55,6**
		falls spontaneously.	4	22,2	22,2	**77,8**
		unable to stand.	2	22,2	22,2	**100,0**
		Total	18	100,0	100,0	
Gait pre-intervention	Valid	walks with difficulty, but requires little or no assistance.	3	16,7	16,7	**16,7**
		severe disturbance of gait, requiring assistance.	7	55,6	55,6	**72,2**
		cannot walk.	7	27,8	27,8	**100,0**
		Total	18	100,0	100,0	
Gait post-intervention	Valid	walks slowly.	3	16,7	16,7	**16,7**
		walks with difficulty, but requires little or no assistance.	5	27,8	27,8	**44,4**
		severe disturbance of gait, requiring assistance.	3	16,7	16,7	**61,1**
		cannot walk.	7	38,9	38,9	**100**
		total	**18**	**100,0**	**100,0**	

Table 3. Experimental group, modifications in scores of variables neck rigidity, posture, postural stability and gait in the *on* phase of the pre- and post-intervention stage.

Thus, as it can be observed in Tables 2 and 3, better results were obtained in on phases than in off phases after physiotherapeutic intervention.

According to attendance to group sessions, different results were obtained for the four study-variables:

The results obtained by applying Student's t-test with a $p<0.05$ significance level were: Subgroup 1: the difference among the four variables —in on phase and pre- and post-intervention stages— is not statistically significant ($p>0.05$) and t-test could not be calculated in the off phase since the standard error of the difference equals zero; Subgroup 2: the difference among the four variables in both on and off phases of the pre- and post-intervention stages is not statistically significant; Subgroup 3: in the on stage, the difference between stiffness in pre- and post-intervention stages is statistically significant ($p<0.05$), as well as the difference in posture between pre- and post-intervention stages. However, the difference regarding balance in pre- and post-intervention stages could not be calculated, since the standard error of the difference equals zero; regarding posture and gait in pre- and

	Mean	Standar desviation	Standard error of mean	95% confidence interval		t-value	Degrees of freedom	Critical level
				Min	Max			
PHASE ON								
Neck rigidity pre-intervention_ neck rigidity post-intervention.	1,875	,354	,125	1,579	2,171	15,000	7	,000
Posture pre-intervention_ posture post-intervention.	1,250	,463	,164	,863	1,637	7,638	7	,000
Retropulsion test pre-intervention_ retropulsion test post-intervention.	1,375	,518	,183	,942	1,808	7,514	7	,000
Gait pre-intervention_ gait post-intervention.	,875	,354	,125	,579	1,171	7,000	7	,000
PHASE OFF								
Neck rigidity pre-intervention_ neck rigidity post-intervention.	1,375	,744	,263	,753	1,997	5,227	7	,001
Posture pre-intervention_ posture post-intervention.	1,000	,535	,189	,553	1,447	5,292	7	,001
Retropulsion test pre-intervention_ retropulsion test post-intervention	1,500	,535	,189	1,053	1,947	7,937	7	,000
Gait pre-intervention_ gait post-intervention.	1,000	,535	,189	,553	1,447	5,292	7	,001

Table 4. Experimental group: Student's t-test fro Subgroup 4 in on and off phase between pre- and post-intervention stages with a 95 % confidence interval.

post-intervention stages, statistical difference is not significant. T-test could not be calculated for stiffness in the on phase since standard error of the difference equals zero; differences were not either significant in the other three variables; and Subgroup 4: the difference among the four variables in the on and off phases in pre- and post-intervention stages is statistically significant (Table 4).

The results obtained by applying Student's t-test with a $p<0.01$ significance level, were:

Subgroups 1, 2 and 3: No statistically significant difference was obtained among the four study variables in on or off phases ($p>0.01$) and Subgroup 4: the difference among the four variables in on and off phases in pre- and post-intervention stages is statistically significant (Table 5 and Figure 2).

	Mean	Standar desviation	Standard error of mean	99% confidence interval		t-value	Degrees of freedom	Critical level
				Min.	Max.			
PHASE ON								
Neck rigidity pre-intervention_ neck rigidity post-intervention.	-,556	,527	,176	-1,145	,034	-3,162	8	**,000**
Posture pre-intervention_ posture post-intervention.	-,556	,726	,242	-1,368	,257	-2,294	8	**,000**
Retropulsion test pre-intervention_ retropulsion test post-intervention.	-,444	,726	,242	-1,257	,368	-1,835	8	**,000**
Gait pre-intervention_ gait post-intervention.	-,556	,527	,176	-1,145	,034	-3,162	8	**,000**
PHASE OFF								
Neck rigidity pre-intervention_ neck rigidity post-intervention.	-,556	,726	,242	-1,368	,257	-2,294	8	**,001**
Posture pre-intervention_ posture post-intervention.	-,444	,726	,242	-1,257	,368	-1,835	8	**,001**
Retropulsion test pre-intervention_ retropulsion test post-intervention	-,333	,707	,236	-1,124	,458	-1,414	8	**,000**
Gait pre-intervention_ gait post-intervention.	**-,444**	**,726**	**,242**	**-1,257**	**,368**	**-1,835**	**8**	**,001**

Table 5. Experimental group: Student's t-test fro Subgroup 4 in on and off phase between pre- and post-intervention stages with a 99 % confidence interval.

3.2 Control group

The results obtained by applying Student's t-test with a $p<0.05$ significance level were: the difference among the four variables —in on and off phases and pre- and post-intervention stages— is not statistically significant. The results obtained by applying Student's t-test with a $p<0.01$ significance level were: the difference among the four variables —in on and off phases and pre- and post-intervention stages— is not statistically significant (Table 6).

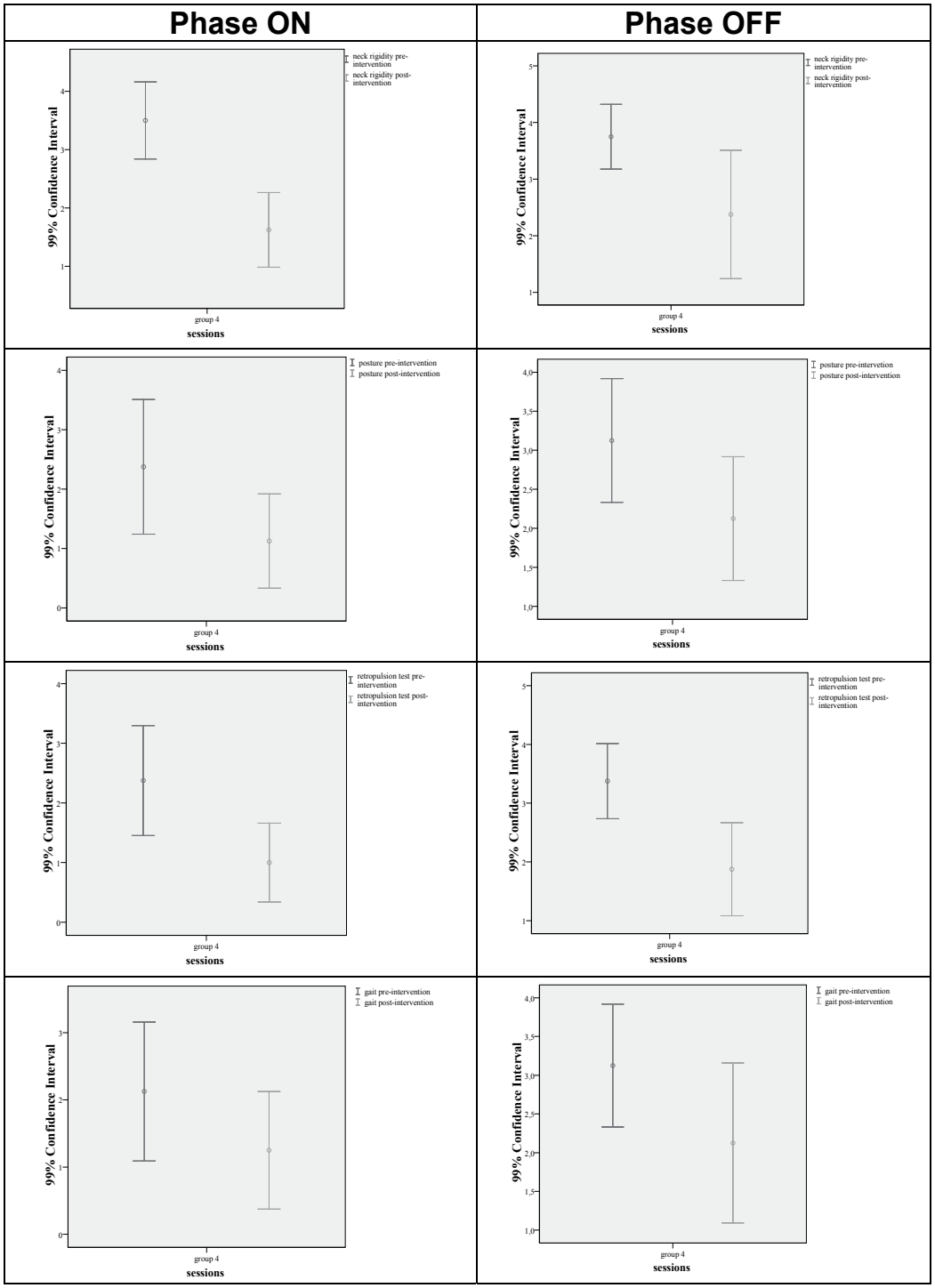


Fig. 1. Experimental group, Subgroup 4: mean values of clinical measurements (99% confidence Interval).

	Mean	Standar desviation	Standard error of mean	99% confidence interval		t-value	Degrees of freedom	Critical level
				Min.	Max.			
PHASE ON								
Neck rigidity pre-intervention_ neck rigidity post-intervention.	-,556	,527	,176	-,961	-,150	-3,162	8	**,013**
Posture pre-intervention_ posture post-intervention.	-,556	,726	,242	-1,114	,003	-2,294	8	**,051**
Retropulsion test pre-intervention_ retropulsion test post-intervention.	-,444	,726	,242	-1,003	,114	-1,835	8	**,104**
Gait pre-intervention_ gait post-intervention.	-,556	,527	,176	-,961	-,150	-3,162	8	**,013**
PHASE OFF								
Neck rigidity pre-intervention_ neck rigidity post-intervention.	-,556	,726	,242	-1,114	,003	-2,294	8	**,051**
Posture pre-intervention_ posture post-intervention.	-,444	,726	,242	-1,003	,114	-1,835	8	**,104**
Retropulsion test pre-intervention_ retropulsion test post-intervention	-,333	,707	,236	-,877	,210	-1,414	8	**,195**
Gait pre-intervention_ gait post-intervention.	**-,444**	**,726**	**,242**	**-1,257**	**,368**	**-1,835**	**8**	**,104**

Table 6. Student´s t-test fro control group in on and off phase between pre- and post-intervention stages with a 95% confidence interval

4. Discussion

As Morris et al. (Morris, 2000) state, there is a need to devise and evaluate locomotor training programs for both the on an off phases of the levodopa cycle. The effects of PD medications on movement and functional capacity should not be overlooked.

Following Jacobs et al. (Jacobs & Horak, 2006), greater validity and sensibility is achieved in balance valuation in PD patients by supplementing the retropulsion test of the UPDRS scale with the test on postural stability developed. Our work achieves global improvement in motor capacity in PD patients, as it is demonstrated by the decrease of average scores in motor examination and by significant modifications regarding the variables of neck rigidity, posture, postural stability and gait. Regarding the effectiveness of physiotherapy programs, we agree with De Goede et al. (De Goede, et al., 2001) and Ellis et al. (Ellis, et al., 2005), who demonstrate the benefits of a physiotherapy program supplementary to medical treatment; however, we have observed a significant increase in the improvement of the four variables studied in patients belonging to the Subgroup 4 of the present study.

It has been studied (Lun, et al., 2005) the effect of a self-supervised home exercise program and a therapist-supervised exercise program on motor symptoms in PD; Lun et al., (Lun, et al., 2005), —through an evaluator-blinded clinical trial— observed that (confidence intervals at 95 % were calculated for change in secondary results measures with an 8-week duration) a statistically significant decrease took place in the motor-examination section of UPDRS during those scarce 8 weeks in both treatment groups; no difference was found in the confidence interval at 95 % of secondary results measures (Lun, et al., 2005). Although patients in our work have followed the protocol under strict professional guidance (undertaken by the physiotherapist in charge of their treatment), it can be found in the bibliographical references that the validity of a self-supervised home exercise program is similar to that of a physiotherapist-supervised program regarding improvement of motor symptoms in PD patients (Lun, et al., 2005). Such finding is important for advising PD patients with regard to co-adjuvant treatment through exercise (movement) of DP motor symptoms.

Apart from traditional treatments, a series of supplementary methods are also applied, such as Qigong. Studies in such line by Schmitz-Hübsch et al., (Schmitz-Hübsch, et al., 2006) demonstrated —after 3, 6 and 12 months— that there were more patients whose symptoms improved in the Qigong group than in control group within a 3 and 6-month period ($P = 0.0080$ for 3 months and $P = 0.0503$ for 6 months; using the Fisher's exact test); depression scores diminished in both groups, while the incidence of non-motor symptoms only diminished in the treatment group (Schmitz-Hübsch, et al., 2006). Nallegowda et al. (Nallegowda, et al., 2004), showed that medication improves muscular strength, gait-speed and ankle optimization when gaiting, and did not observe worsening of the propioceptive sense. However, it was observed a correlation among muscle strength, static and dynamic balance, and gait in both on and off phases (Nallegowda, et al., 2004).

5. Conclusions

In short, quantitative reduction of muscle strength in back, hip and ankle —with damage to propioception and visual sense, and lower supporting base— are the main causes for

postural instability in PD patients. We have observed in the present study that when increasing the number of sessions up to 7-12 (subgroups 3 and 4), scoring in motor subscale is higher, which indicates that neck rigidity, posture, postural stability and gait improve, and that such improvement is longer lasting; such fact is demonstrated establishing significance level at $p < 0.01$, for which subgroup 4 is the only group obtaining statistically significant improvements.

Definitively, since Jöbges et al., (Jöbges, et al., 2007) demonstrated the clinical relevance of rehabilitation programs for patients of PD is estimated to be sufficient if the following seven criteria are met: effectiveness, everyday life relevance, long-term effect, therapy frequency+setting, duration of therapy units, quality of live, timing of assessment+medication; for it, we conclude that the relevant of our work is to have demonstrated the long-term efficiency of a physiotherapy protocol in PD.

6. Acknowledgements

The authors would like to thank the members of the Association of PD Patients from Astorga and its Region (Spain) for their interest and collaboration, and of the physicians and physical therapists who participated in the study.

No sources of funding were used to assist in the preparation of this text. The authors have no conflicts of interest, that are directly relevant to the content of this text.

7. References

Baddeley, A. (1992). Working memory: the interface between memory and cognition. *Journal of Cognitive Neuroscience*, Vol.4, No.3, (Summer 1992), pp. 281–288, ISSN 898-929

Brichetto,G; Pelosin, E.; Marchese, R.& Abbruzzese, G. (2006). Evaluation of physical therapy in parkinsonian patients with freezing of gait: a pilot study. *Clinical Rehabilitation,* Vol.20, No.1, (January 2006), pp. 31–35, ISSN 02692155

Carne, W.; Cifu, DX.; Marcinko, P.; Baron, M; Pickett, T.; Qutubuddin, A.; Calabrese, V.; Roberge, P.; Holloway, K. & Mutchler, B.(2005) Efficacy of multidisciplinary treatment program on long-term outcomes of individuals with Parkinson's disease. *Journal of Rehabilitation Research and Development,* Vol.42, No.6, (November-December 2005), pp. 779–86, ISSN 0748-7711

Comella, JC.; Stebbins, GT.; Brown-Tomas, N. & Goetz, CG.(1994) Physical therapy and Parkinson's disease: a controlled clinical trial. *Neurology,* Vol.44, No.3, (March 1994), pp. 376–78, ISSN 0028-3878

De Goede, CJ.; Zeus, S.; Kwakkel, G. & Wagenaar, R. (2001). The effects of physical therapy in Parkinson's disease: a research synthesis. *Archives of Physical Medicine and Rehabilitation,* Vol.82, No.4, (April 2001), pp.509–15, ISSN 0003-9993

Ellgring, H.; Seiler, S.; Nagel, U.; Perleth, B.; Gassr, T. & Oertel, WH. (1990). Psychosocial problems of Parkinson patients: approaches to assessment and treatment. *Advances in Neurology*, Vol.53, (June 1990), pp. 349–353, ISSN 0091-3952

Ellis, T.; de Goede, CJ.; Feldman, RG.; Wolters, EC.; Kwakkel, G. & Wagenaar, RC. (2005). Efficacy of a physical therapy program in patients with Parkinson's disease: a randomized controlled trial. *Archives of Physical Medicine and Rehabilitation,* Vol.86, No.4, (April 2005), 2005, pp.626-632, ISSN 0003-9993

Formisano, R.; Pratesi, L.; Modarelli, F.; Bonifanti, V. & Meco, G. (1992). Rehabilitation and Parkinson's disease. *Scandinavian Journal of Rehabilitation Medicine*, Vol.24, No.3, (September 1992), pp. 157–160, ISSN 0036-5505

Franklyn, S.; Kohout, IJ.; Stern, GM. & Dunning, M. (1981). Physiotherapy in Parkinson's disease, In: *Research progress in Parkinson's disease,* Rose, FC. & Capildeo, R. (Ed.), pp. 397-400, Pitman Medical, ISBN 9780272796016, Kent, UK

Gibberd, FB.; Page, GR. & Spencer, KM. (1981). A controlled trial in physiotherapyfor Parkinson's disease, In: *Research progress in Parkinson's disease,* Rose, FC. & Capildeo, R. (Ed.), pp. 401-403, Pitman Medical, ISBN 9780272796016, Kent, UK

Goetz, CG.; Fahn, S.; Martínez-Martín, P.; Poewe, W.; Sampaio, C.; Stebbins, GT.; Stern, MB.; Tilley, BC.; Dodel, R.; Dubois, B.; Holloway, R.; Jankovic, J.; Kulisevsky, J.; Lang, AE.; Lees, A.; Leurgans, S.; Lewitt, PA.; Nyenhuis, D.; Olanow, CW.; Rascol, O.; Schrag, A.; Teresi, JA.; Van Hilten, JJ. & LaPelle, N. (2007). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. *Movement Disorders*, Vol.22, No.1, (January 2007), pp. 41–47, ISSN 0885-3185

Herman, T.; Giladi, N.; Gruendlinger, L. & Hausdorff, JM. (2007). Six weeks of intensive treadmill training improves gait and quality of life in patients with Parkinson's disease: a pilot study. *Archives of Physical Medicine and Rehabilitation*, Vol. 88, No.9, (September 2007), pp. 1154-1158, ISSN 0003-9993

Hiroyuki, S.; Uchiyama, Y. & Kakurai, S. (2003). Specific effects of balance and gait exercises on physical function among the frail elderly. *Clinical Rehabilitation,* Vol.17, No.5. (August 2003), pp. 472–479, ISSN: 02692155

Jacobs, JV. & Horak, FB. (2006). An alternative clinical postural stability test for patients with Parkinson's disease. *Journal of Neurology,* Vol.253, No.11, (November 2006), pp. 1404-1413, ISSN: 0340-5354

Jöbges, E.; Spittler-Schneiders, H.; Renner, C. & Hummelsheim, H. (2007). Clinical relevance of rehabilitation programs for patients with idiopathic Parkinson syndrome. II: symptom-specific therapeutic approaches. *Parkinsonism & Related Disorders,* Vol.13, No.4, (May 2007), pp. 203-213, ISSN 1353-8020

Keus, S.; Bloem, BR.; Hendriks, E.; Bredero-Cohen, A. & Munneke, M. on behalf of the Practice Recommendations Development Group. (2007). Evidence-based analysis of physical therapy in Parkinson's disease with recommendations for practice and research. *Movement Disorders,* Vol.22, No.4, (March 2007), pp. 451-460, ISSN 0885-3185

Köller, WC.; Silver, DE. & Lieberman, A. (1994). An algorithm for the management of Parkinson's disease. *Neurology,* Vol.44, No.12 Suppl 10 (December 1994), pp. 51-52, ISSN 0028-3878

Lun, V.; Pullan, N.; Labelle, N.; Adams, C. & Suchowersky, O. (2005). Comparison of the effects of a self-supervised home exercise program with a physiotherapist-

supervised exercise program on the motor symptoms of Parkinson's disease. *Movement Disorders,* Vol.20, No.8,(August 2005) pp. 971-75, ISSN 0885-3185

Marsden, CD. (1994). Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry,* Vol.57, No.6 (June 1994), pp. 672-681, ISSN 00223050

Morris, ME. (2000) Movement disorders in people with Parkinson's disease: a model for physical therapy. *Physical Therapy*, Vol.80, No.6, (June 2000), pp. 578-597, ISSN 2079-9209

Movement Disorder Society Task Force on Ratio Scales for Parkinson's Disease. (2003). The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. *Movement Disorders*, Vol.18, No.7, (July 2003), pp. 738-750, ISSN 0885-3185

Muller, V.; Mohr, B.; Rosin, R.; Pulvermuller, F.; Muller, F. & Birbaumer, N. (1997). Short-term effects of behavioral treatment on movement initiation and postural control in Parkinson's disease: a controlled clinical study. *Movement Disorders,* Vol.12, No.3, (May 1997), pp. 306-314, ISSN 0885-3185

Nallegowda, M.; Singh, U.; Handa, G.; Khana, M.; Wadhwa, S.; Yadav, SL.; Kumar, G. & Behari, M.(2004). Role of sensory input and muscle strength in maintenance of balance, gait and posture in Parkinson's disease: a pilot study. *American Journal of Physical Medicine & Rehabilitation,* Vol.83, No.12, (December 2004), pp. 898-908, ISSN 0894-9115

O'Shea, S.; Morris, ME. & Iansek, R. (2002). Dual task interference during gait in people with Parkinson disease: effects of motor versus cognitive secondary tasks. *Physical Therapy,* Vol.82, No.9, (September 2002), pp. 888-897, ISSN 2079-9209

Pederson, SW.; Oberg, B.; Insulander, A. & Vretman A. (1990). Group training in Parkinsonism: quantitative measurements of treatment. *Scandinavian Journal of Rehabilitation Medicine,* Vol.22, No.4, (October 1990), pp. 207-211, ISSN 0036-5505

Pellecchia, MT.; Grasso, A.; Biancardi, LG.; Squillante, M.; Bonavita, V. & Barone, P. (2004). Physical therapy in Parkinson's disease: an open long-term rehabilitation trial. *Journal of Neurology,* Vol.251, No.5, (May 2004), pp. 595-598, ISSN 0340-5354

Quality Standards Subcommittee, American Academy of Neurology. (1993). Practice parameters: initial therapy of Parkinson's disease. *Neurology*, Vol.43, No.7, (July 1993), pp. 1296-1297, ISSN 0028-3878

Scandalis, TA.; Bosak, A.; Berliner, JC.; Hellman, LL. & Wells, MR. (2001). Resistance training and gait function in patients with Parkinson's disease. American Journal of physical Medicine & Rehabilitation, Vol.80,No.1, (January 2001), pp. 38-46, ISSN 0894-9115

Schmitz-Hübsch, T.; Pyfer, D.; Kielwein, K.; Fimmers, R.; Klockgether, T. & Wüllner, U. (2006) Qigong exercise for the symptoms of Parkinson's disease: a randomized, controlled pilot study. *Movement Disorders,* Vol.21, No.4, (April 2006), pp. 543-548, ISSN 0885-3185

Tamir, R.; Dickstein, R. & Huberman, M. (2007). Integration of motor imagery and physical practice in group treatment applied to subjects with Parkinson's disease. *Neurorehabilitation and Neural Repair,* Vol.21, No.1, (January-February 2007), pp. 68-75, ISSN 1545-9683

20

Improving Transfer of Parkinson's Disease Patients – Sit-to-Stand Motion Assistance

Yoshiyuki Takahashi[1], Osamu Nitta[2] and Takashi Komeda[3]
[1]Toyo University,
[2]Tokyo Metropolitan University,
[3]Shibaura Institute of Technology,
Japan

1. Introduction

In many areas of the world, population aging is steadily increasing. Japan became an aged society in 1995 and the numbers of Japanese citizens aged 65 years and above (elderly) continues to increase. In 2010, the percentage of elderly people in Japan reached 23.1%. In such a "super-aged" society, health maintenance, along with the prevention and treatment of diseases, are important long-term social care issues affecting elderly people.
Because the incidence of Parkinson's disease (PD) onset increases among persons over 50 years of age, it can be considered an age-related ailment, and there were approximately 145,000 confirmed PD patients in Japan at the time of this research. PD is caused by the death of dopamine-containing cells in substantia nigra of the brain. Common symptoms of PD are tremors, muscle stiffness, slow movement and poor balance, as well as other movement-related problems. When walking and during sit-to-stand motions, persons afflicted with such symptoms face increased risks from falls and subsequent injuries.
Ensuring efficient and safe transfer motions helps ensure self-reliant lifestyles, especially among elderly and physically disabled people, including PD patients. Transfer motions are among the basic activities of daily life. To help such persons, there are a number of commercially available sit-to-stand assistance devices on the market today, most of which assist users in rising from chairs by means of a lift seat that reduces the load on their lower limbs. However, from the viewpoint of maintaining lower muscle strength, excessive assistance is undesirable. Because of this, we have developed an effective sit-to-stand assistance system that provides the minimum assistance necessary.
In this paper, an outline of our developed sit-to-stand assistance system is introduced and experiments with this system involving individuals diagnosed with PD are described. It was found that the proposed system effectively permitted individuals to rise from a seated position.

2. Research background

There are numerous different tools and devices designed to assist transfer maneuvers. Most commonly, handrails are provided for individuals who have problems standing up and walking. However, handrails are difficult to adjust once installed. This can pose difficulties

in situations where an individual's physical abilities change over a short period of time due to age and/or disease, because such changes often require that the position of an installed handrail be modified.
Such modifications often require reconstruction of the facilities. The typical position of a handrail that meets industrial standards e.g. Japanese Industrial Standard (JIS) is not suitable for all people because of differences in body size and physical abilities. Accordingly, the primary purpose of this research was the development of a moveable handrail system that provides sit-to-stand assistance that can be personalized to individual users.

Fig. 1. Typical handrail installation

Previous handrail studies focused primarily on finding generalized heights and shapes, and no reports discussing active handrails for stand-up assistance were found. However, a number of active stand-up assistance devices have been developed. These include the Rehabilitation Robot Cell for Multimodal Stand-Up Motion Augmentation and the Stand-Up Motion Assistance System. Furthermore, the following devices are already available commercially: a seat lift chair, a lifting cushion, and a toilet seat lift. Such devices, which are not aimed at rehabilitation efforts, assist users in getting up from chairs by means of a lift seat that reduces the load on their lower limbs.
However, from the viewpoint of maintaining the lower muscle strength of a patient, excessive assistance is undesirable. Based on observations of the standing motions of large numbers of PD patients and elderly persons, it is clear that a significant percentage of such individuals would be able to stand up, despite poor motor function, if the transfer motion could be assisted in some ways. Therefore, we attempted to develop an effective sit-to-stand assistance system that provides the minimum degree of assistance necessary.

3. Sit-to-stand motion assistance system

Our prototype sit-to-stand assistance system was designed for elderly and disabled persons, including PD patients, who find it difficult to stand up from a sitting position. Figure 2 shows an overview of this sit-to-stand assistance system, which consists of two 650 mm stroke AC servo motor driven linear actuators combined in a square configuration and a handrail installed at the intersection of these actuators. When a user begins to stand from a seated position on a chair, the handrail moves to lead his or her motions. A personal computer was used to control the handrail movements, which was designed to move a 490 N load at a maximum velocity of 125 mm/s.

Figure 3 shows the system diagram. A six-axis force sensor (100M40A, JR3, Inc., California, USA) was attached to the base of the handrail. Figure 4 shows the six-axis force sensor coordinate system. The control program of the system calculates the trajectory of the handrail, and the force exerted on the handrail can be used to actuate the handrail movement. The direction and the actuating speed can be set on the control panel.

In our experiment, two force detection plates were positioned under the feet of the users, as shown in Figure 5. Each plate was 400 mm in length and 300 mm wide. The plates were designed to detect the floor reaction force exerted as the subject was standing up. A maximum force of 1500 N could be measured at a resolution lower than 2.5 N.

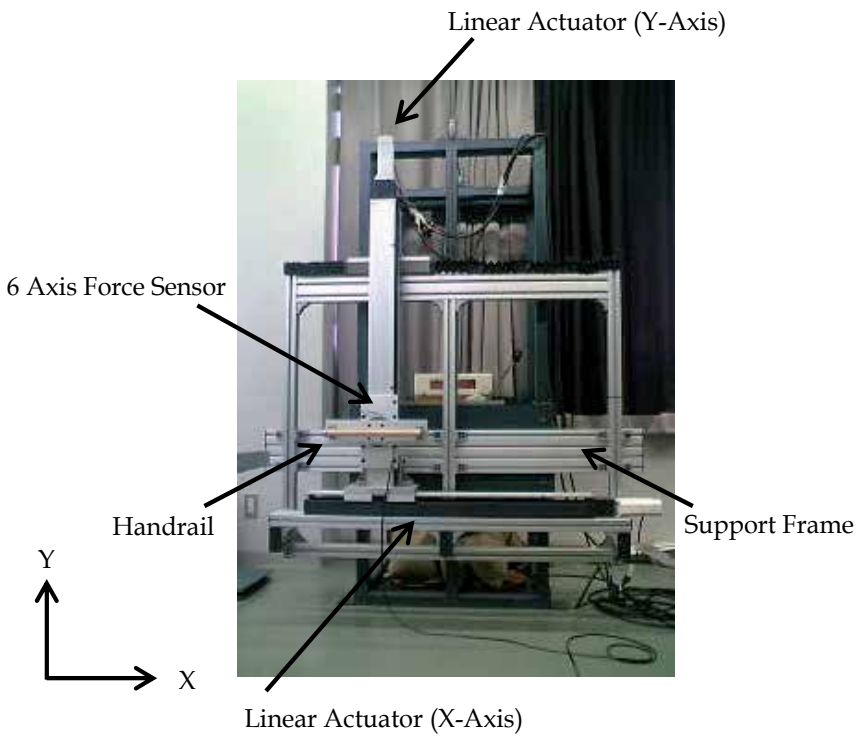


Fig. 2. Experimental sit-to-stand assistance system

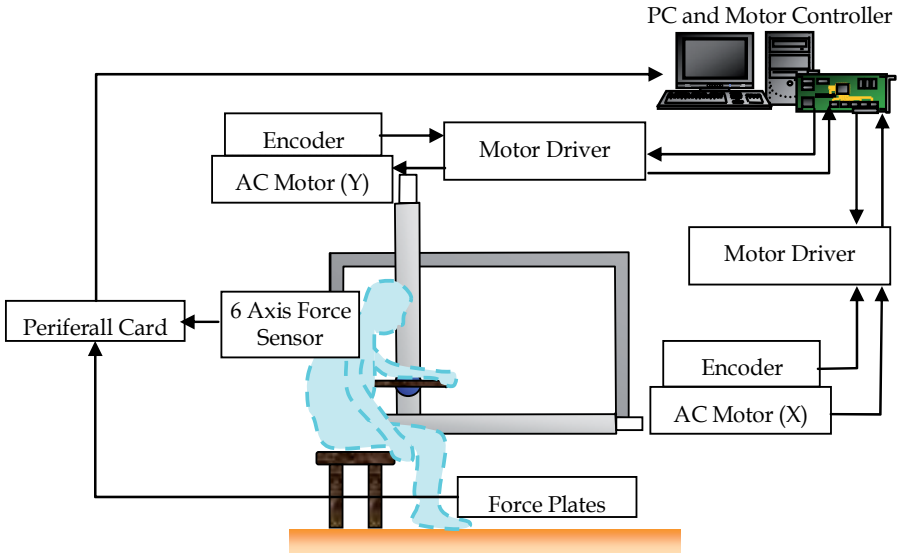


Fig. 3. Overview of the sit-to-stand motion assistance system

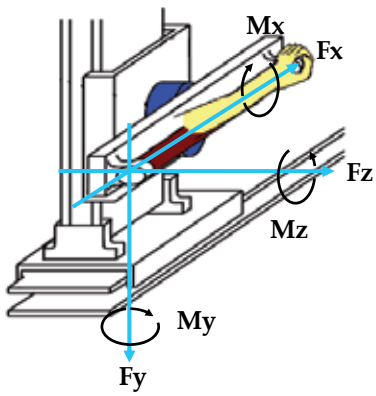


Fig. 4. 6 Axis force sensor coordinate system

Fig. 5. Force detection plates for measuring feet pressure

4. Handrail motion

4.1 Concept of the sit-to-stand motion assistant strategy

People normally utilize two different strategies when executing a sit-to-stand maneuver. One is a sudden, rapid torso bend-and-straighten motion that generates and utilizes inertia to propel the person to a standing position. The other involves moving the person's center of gravity (CG) position slowly forward, balancing on the legs, and then straightening into the standing position. Normal healthy people can flex their torsos very rapidly, so they do not need to make excessive motions. In contrast, elderly people with low muscle strength are unable to make rapid torso motions. As a result, they normally move their torso forward to shift their CG, and then straighten up using the muscle strength of their legs.

In case of PD patients, it is often difficult for such persons to flex their torsos forward and back quickly enough to execute the first method and (due to increased muscle tone) they lack the knee joint extension power and flexibility needed to rise to the standing position, which is necessary for the second method. Furthermore, since their CG position does not move forward sufficiently, it is easy for such persons to fall backwards, as shown in Figure 6. Therefore, to assist such persons' sit-to-stand motions, the following method was considered to be effective. First, pulling their torso forward slowly until their CG positions moved onto their base of support and then leading their torsos upwards in a straight motion.

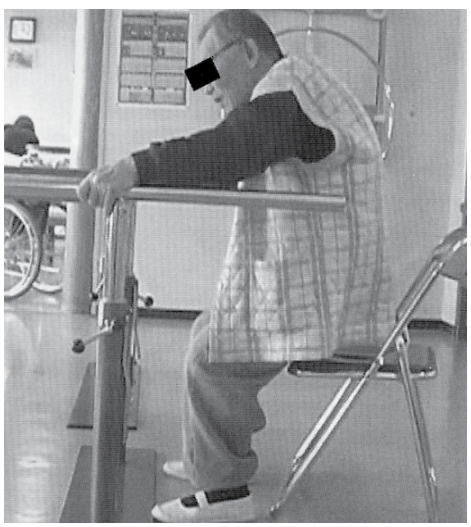


Fig. 6. Elderly PD patient standing up from a chair

4.2 Design of the individualized handrail trajectory system

In previous experiments, we examined three different handrail trajectories for PD patient sit-to-stand motion assistance. These included a horizontal motion, a diagonal motion and a curvature motion that was based on the shoulder motions of a normal healthy adult. Our examinations indicated that, in most cases, a trajectory based on the shoulder motion of a normal healthy individual in the process of standing up was effective for PD patient sit-to-stand motion assistance because it successfully assisted patients who were unable to stand using a fixed handrail. In these experiments, it was confirmed that the patient CG

moved onto the base of support before the seat-lift and the handrail pulling force was decreased.

However, the curvature trajectory was not suitable for all PD patients. We then examined a fixed trajectory and determined that it would not be able to accommodate different user heights. Finally, we designed a new approach, which was to adjust the timing of the handrail motions using measurements of the force applied to the floor beneath the patient's feet in order to determine whether the CG had moved onto the base of support.

In this evolution, the handrail first moves slowly forward and downward to bend the patient's torso and shift his or her CG onto the base of support. Then, when the force under the patient's feet exceeds the preset threshold, the handrail begins moving upwards and slightly backwards to extend the patient's torso vertically. The original curvature trajectory was segmented and set to an approximate curve. Figure 7 shows a typical handrail trajectory and its formula.

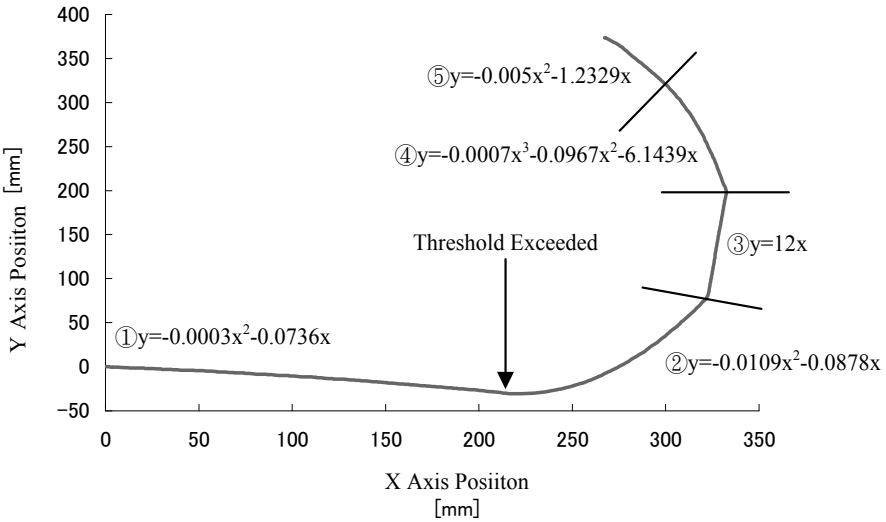


Fig. 7. Typical handrail trajectory

5. Materials and methods

The prototype sit-to-stand assistance system was designed and tested in conjunction with the handrail trajectory control program, and experiments were conducted to evaluate the sit-to-stand motion of PD patients as compared with normal healthy subjects.

5.1 Subjects

Two PD patients and two healthy adults (selected as the control subjects) participated as text subjects in this experiment. Both PD test subjects were diagnosed as Stage 4 patients based on the Hoehn and Yahr Scale. The mean age of the PD test subjects was 73.5 years (SD, 1.5 years). Their average weight was 48.5 kg (SD 5.5 kg); average height was 1.60 m (SD 0.03 m). Neither subject could stand up from a chair unassisted. The average weight of the control subjects was 70.5 kg (SD, 1.5 kg). The average height was 1.73 m (SD, 0.01 m). Informed consent was obtained from all test subjects.

5.2 Tasks and protocols

The initial posture of the subjects is shown in Figure 8. The X axis of the coordinate system is horizontal and the Y axis is vertical. Test subjects were positioned on a height-adjustable stool with an initial lower limb posture as follows: hips were flexed at 90° and knees were flexed at 80°. The height of the stool was set between approximately 370 and 390 mm. The height of the stool and the posture of the test subject were selected to simulate the position of a user on a toilet seat, as set in the Japanese Industrial Standard. The handrail was set to fit initial upper limb posture: the elbow position was 110°.

The PD test subjects were asked to perform sit-to-stand motions from a stool using the proposed sit-to-stand assistance system. Figure 7 shows an example of the handrail trajectories. Here, it can be seen that the handrail moves forward (X axis) and then curves upward (Y axis). In this experiment, the reaction force exerted on the floor under the feet of the test subjects was used to switch the handrail motion direction. Three different levels of reaction force, equal to 50%, 70% and 80% of the test subjects' body weight were used as thresholds. Each subject was asked to perform the sit-to-stand motion two times.

5.3 Measurements

A total of 11 optical markers were placed on key points of the subjects (the head of the 5th metatarsal bone, the lateral malleoluses, knee joints, hip joints, shoulders, top of the head, elbow, and wrist) and on the edge of the handrail. The locations of the optical markers are shown in Figure 5. A Vicon motion analysis system (Vicon 370, Oxford Metrics, Ltd. Oxford, UK) operating at a rate of 60 Hz was used to measure the various positions and calculate the posture of the subjects. Four floor-mounted force detection plates were used to measure the reaction force exerted on the chair and floor. The six-axis force sensor, operating at a rate of 30 Hz, measured the force exerted on the handrail and the two floor mounted force detection plates were used to determine when to switch the handrail motion direction. The marker positions, along with the pressures applied to the handrail and force detection plates, were all measured simultaneously. The corrected data was low-pass filtered using a 7 Hz Butterworth filter.

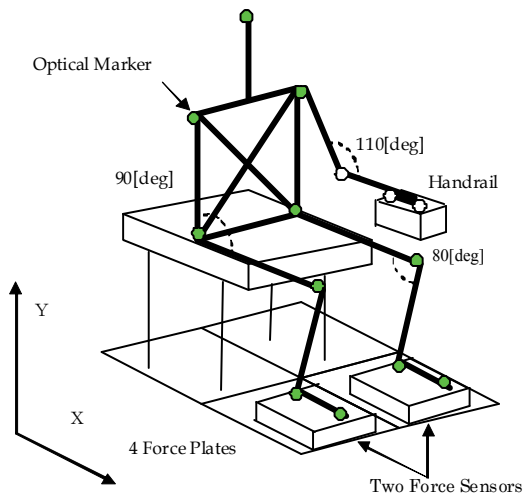


Fig. 8. Initial posture of the subject and the force sensor locations

The position of the test subject's CG was calculated by the positions of the 11 optical markers. A rigid link model, which consisted of the feet, lower legs, thighs, torso and head of the test subject, was used. The values used for the moment of inertia and the center of mass of body parts were taken from a database of body part characteristics for Japanese elderly people.
The timing of the seat-off event was set at the point when Y-axis force on the floor mounted force plates became 0 N. Figure 9 shows a PD test subject participating in the experiment.

Fig. 9. PD test subject participating in the experiment

6. Results

6.1 CG position

Figure 10 shows examples of the handrail trajectories. The origin is set to the initial position of the handrail. Table 1 shows the average handrail positions that were moving direction switching position in X axis. The handrail trajectory was programmed to switch movement directions at certain points. Measurements equal to 50%, 70% and 80% of the test subject's body weight were set as thresholds. For the 80% threshold, the handrail was extended further forward than when the 50% and 70% threshold were set.
Figure 11 shows the CG trajectories. The X and Y axes positions were divided by the subject's body height and normalized. Table 2 shows the average CG positions when the seat-off point and maximum forward position occurred. The CG positions were then divided by the subject's foot length and normalized.
For healthy test subjects that did not use the handrail, the CGs were found to have moved forward and slightly down at first, following which, they moved upward in a curve. The seat-off position was designated at the point when the CG moved 10% of the test subject's foot length. At the 50% threshold, the maximum forward position of the CG was -18% of the test subject's foot length, at which point the PD test subjects were unable to stand. Therefore, it was considered likely that the CG had not moved onto the base of support. In the case of the 70% threshold, the subject could stand, however when the CG started to rise its movement distance was found to be less than that of a normal healthy test subject. At the 80% threshold, the test subject was able to stand smoothly and the CG trajectory was similar to that of a healthy test subject. The maximum recorded forward position of the CG was 54% of the test subject's foot length, which was roughly similar to that of a healthy test subject.

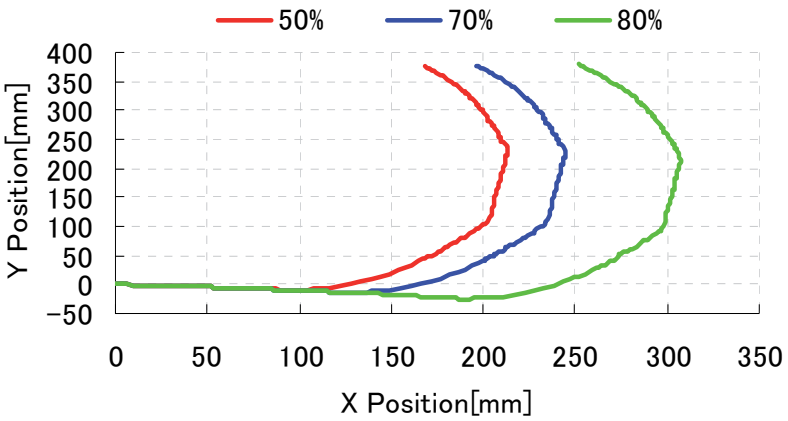


Fig. 10. Handrail trajectories

Threshold (% of body weight)	Handrail Position [mm]
50%	92
70%	232
80%	272

Table 1. Average handrail positions actuated by the handrail trajectory

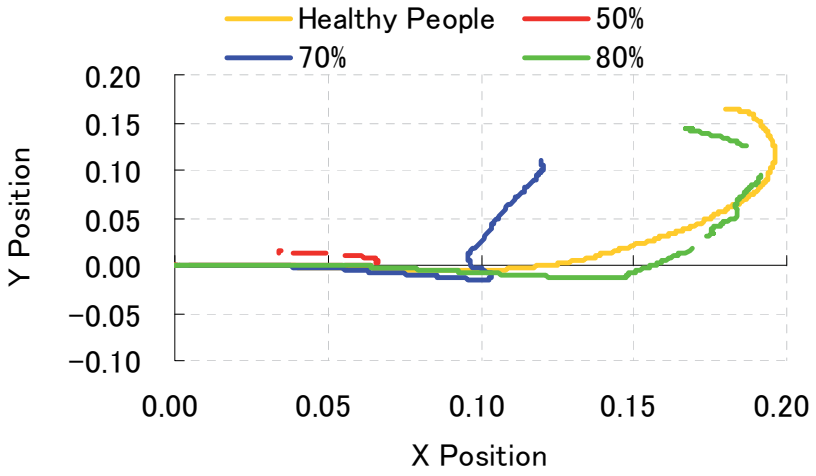


Fig. 11. CG trajectories

Threshold (% of body weight)	Seat-off Position [% of foot length]	Max. Forward Position [% of foot length]
Control (Healty Subject)	10	54
50%	–	−18
70%	16	37
80%	20	54

Table 2. Maximum forward CG position

6.2 Torso and thigh angle

Figure 12 shows the torso and thigh angles of the healthy test subjects. Figures 13 and 14 show the torso angle, thigh angle and X axis position of the handrail for the PD subjects at the 70% and 80% thresholds. The horizontal axis indicates the timeline, which was divided by the total time and normalized. The origin of the torso angle is set on the horizontal line that extends through the hip joints. The origin of thigh angle is set on the horizontal line that extends through the knee joint. The initial position of the handrail is set as the origin point.
For the healthy test subjects, thigh angles increased before seat-off occurred, after which the torso angles also increased. For the 70% and 80% thresholds, the torso angle increased after the handrail moved backward in the horizontal direction. In the case of the 80% threshold, the torso angle began increasing after seat-off occurred, at which time the handrail began moving backwards. This indicates that, in the case of 80% threshold, the test subject's body bent forward during the standing motion and the CG remained within the base of support. This motion assistance allowed the achievement of a stable sit-to-stand motion.

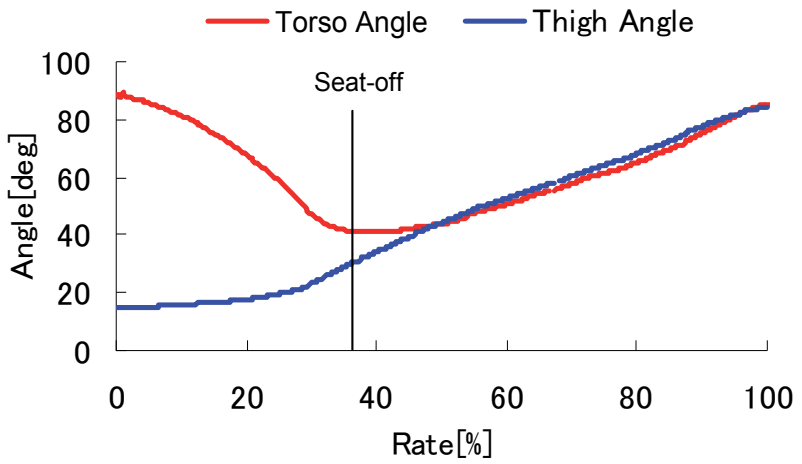


Fig. 12. Torso angle and thigh angle of a normal healthy subject

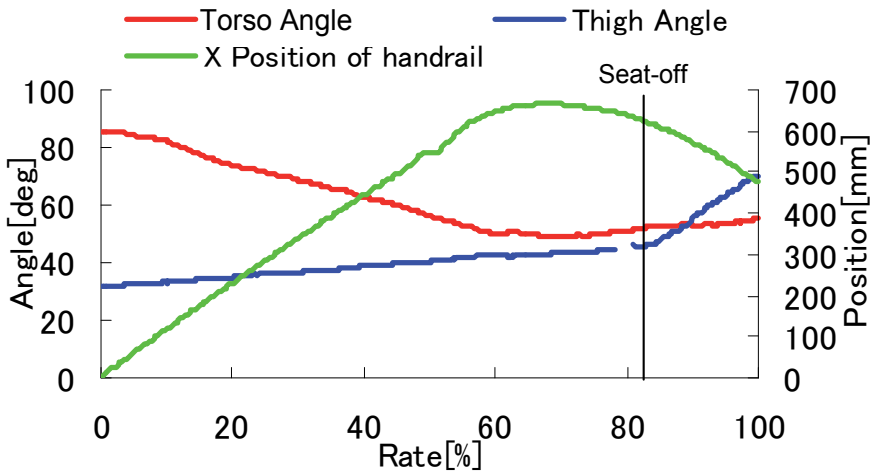


Fig. 13. Torso angle, thigh angle and handrail position of a PD subject at the 70% threshold

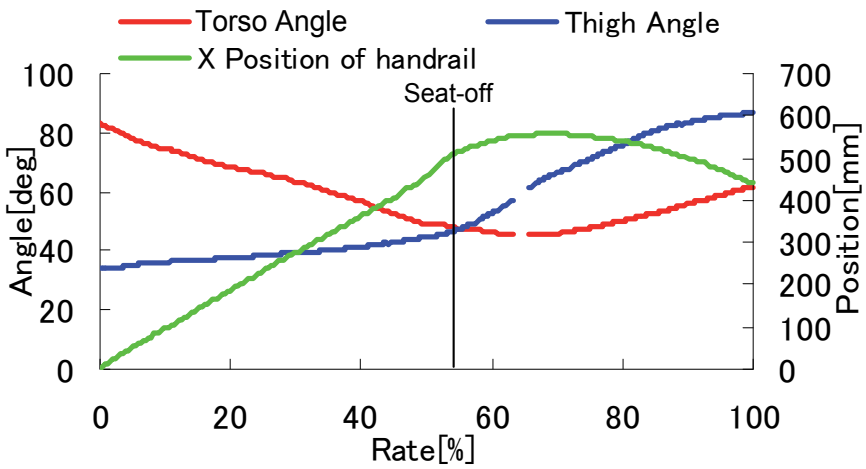


Fig. 14. Torso angle, thigh angle and handrail position of a PD subject at the 80% threshold

Threshold (% of body weight)	Minimum Trunk Angle [deg]
Control (Healthy Subject)	43
50%	58
70%	47
80%	43

Table 3. Minimum torso angle

6.3 Knee joint moment

Figure 15 shows the knee joint moment. Here, it can be seen that the flexion direction is positive and the extension direction has a negative value. This measurement was divided by the subject's height and normalized. The time for sit-to-stand motion was divided by the total time and normalized. Table 4 shows the maximum knee joint moment.

The variation of knee joint moment for healthy test subjects was larger than those measured for PD subjects in extension. At the 50% threshold, the subject could not achieve seat-off and the variation of the knee joint moment changed only fractionally. At the 70% and 80% thresholds, no significant difference was found in the maximum values. However, the timing of peak was different it caused by the different timing of seat-off.

Threshold (% of body weight)	Maximum Knee Joint Moment [Nm/kg]
Control (Healthy Subject)	−1.19
50%	−0.26
70%	−0.98
80%	−0.94

Table 4. Maximum knee joint moment

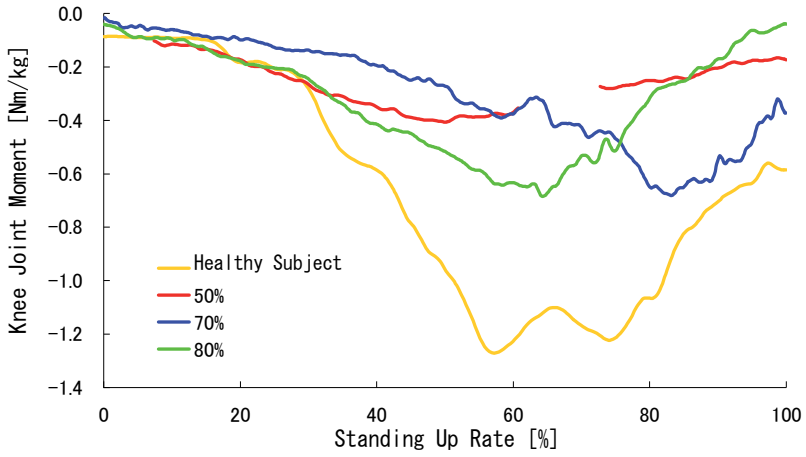


Fig. 15. Knee joint moment

6.4 Force exerted on the handrail

Figures 16 and 17 show the force exerted on the handrail on the X and Y axes. Here, the forward and down directions were positive (Figure 4). The X and Y axes of Table 5 and 6 show the maximum force exerted on the handrail.

There were no significant differences between the 50%, 70% and 80% thresholds on the X axis. However, in the case of the 80% threshold, the maximum force exerted on the handrail on the Y axis was less than the 50% and 70% thresholds.

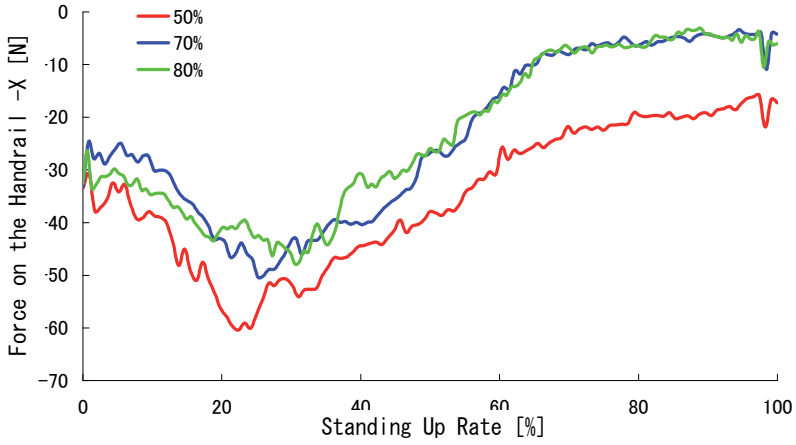


Fig. 16. Force exerted on the handrail as plotted on the X Axis

Threshold (% of body weight)	Max. Force on the Hnadrail -X [N]
50%	-60
70%	-65
80%	-61

Table 5. Maximum force exerted on the handrail as plotted on the X axis

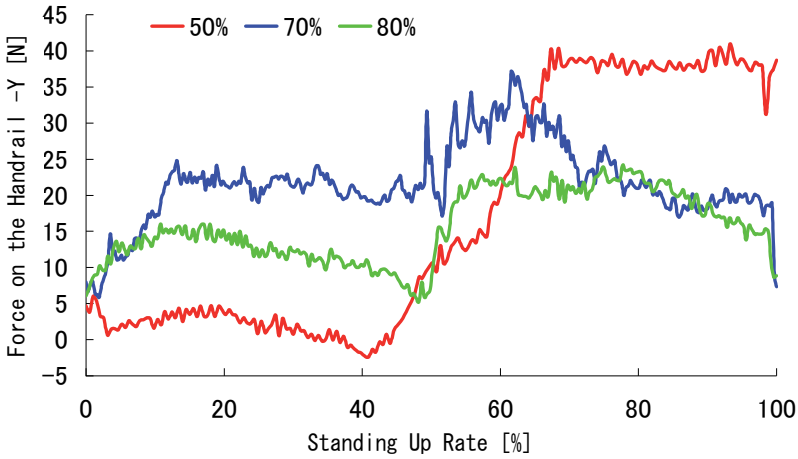


Fig. 17. Force exerted on the handrail on the Y Axis

Threshold (% of body weight)	Max. Force on the Hnadrail -Y [N]
50%	30
70%	32
80%	17

Table 6. Maximum force exerted on the handrail as plotted on the Y Axis

7. Discussion

The CG trajectory of a normal healthy test subject increased in a curve after seat-off. At that time, the torso was angled forward. After seat-off, the angle of the torso increased as the subject straightened into a standing posture. The CG was found to have shifted forward a maximum of 54% of the subjects' foot length, and the knee joint moment was measured at 1.19 Nm/kg in the extension direction.

The PD test subjects were unable to stand up at the 50% threshold assistance level. In that situation, the CG shift was -18% and the CG did not enter the base of support.

At the 70% threshold level, the PD test subject was able to stand, but the CG trajectory was different from that of a normal healthy subject, and the timing of the straightening motion was earlier than that for a normal healthy subject. When the handrail started to move backward, the subject's torso angle shifted to vertical. Additionally, it was found that the handrail had moved backward and torso angle had shifted to vertical before seat-off occurred. Thus, it was determined that the CG and posture transition sequence of PD subjects was different from that of normal healthy subjects, and that the PD subjects straightened their torsos before their CG had moved sufficiently forward. They also used stronger downward pushing pressure on the handrail than was exerted at the 80% threshold.

At the 80% threshold, PD subjects were able to stand successfully and the CG trajectory was similar to that of a normal healthy subject. It was also determined that PD subjects straightened their torsos after the CG had moved forward onto their base of support. When the subject seat-off occurred, the CG had moved forward approximately 20% of the subject's foot length and the maximum CG position was 54% of the foot length.

These results indicate that moving the handrail forward until the normal force under the feet exceeds 80% of total body weight, and then actuating the vertical rise of the handrail to perform seat-off could assist PD subjects in performing the sit-to-stand motion in a stable manner.

8. Conclusions

A sit-to-stand assistance system was developed and experiments with PD test subjects were performed. The results indicate that a moveable handrail with a forward trajectory (X axis) and upward curve motion (Y axis) could be used to assist individuals as they transition from a seated to a standing position. The motion direction was actuated by the reaction force exerted on the floor under the feet of the subject, and it was found that the 80% threshold was the most effective point for initiating assistance to their standing up motion.

9. Acknowledgment

I would like to acknowledge the generous support received from Mr. Tomuro, Dr. Takagi and students of the Tokyo Metropolitan University who joined the experiments conducted during this research.

10. References

Oshima T., Ito A., Endo Y. (2000). Research of a taste of "diameter and height" of handrail. *Proceedings of Architectural Institute of Japan,* pp. 1031-1032, ISSN 13414518

Takashima T., Nakanishi Y., Higaki H. (2005). Study of Design of Handrail, Proceedings of the Japan Society of Mechanical Engineers. *Proceedings of the Japan Society of Mechanical Engineers, Bioengineering Division,* 2005(18), pp. 315-316

Kamnik R., Bajd T., Williamson J., Murray-Smith R. (2005). Rehabilitation Robot Cell for Multimodal Standing-Up Motion Augmentation. *Proceedings of the 2005 IEEE International Conference on Robotics and Automation, ICRA 2005,* pp. 2277-2282, ISSN 0-7803-8914-X

Chugo D., Okada E., Kawabata K., Kaetsu H., Aasama H., Miyake N. (2005). Force Assistance System for Standing-Up Motion: 1st Report: Required Assistance Power for Standing-Up Motion: 1st Report: Required Assistance Power for Standing-Up. *The JSME Symposium on Welfare Engineering Vol.2005(20051207),* pp. 257-260

Hoehn M.M, Yarh D. M. (1967). Parkinsonism: onset, progression and mortality. *Neurology 17*, pp. 427-442

Ichirou H. (2001). *Living climate of welfare coordinator second class text*, The Tokyo Chamber of Commerce and Industry, ISBN 978-4924547476

Takahashi Y, Osamu N, Komeda T. (2008). Development of a Sit-to-Stand Assistance System. *Lecture Notes in Computer Science, 2008, Volume 5105/2008,* pp. 1277-1284, ISSN 0302-9743

Uplift Technologies Inc., 17.04.2011, Available from http:// www.up-lift.com/

TOTO LTD., 17.04.2011, Available from http:// www.toto.co.jp/

Part 4

Invasive Methods Examine in Patients with Parkinson's Disease

21

Human Central Nervous System Circuits Examined in Patients with Parkinson's Disease Using the Electrodes Implanted for Deep Brain Stimulation

Joao Costa[1,2], Francesc Valldeoriola[2] and Josep Valls-Sole[2]
[1]*Institute of Molecular Medicine, Lisbon Faculty of Medicine*
[2]*Neurology Department, Hospital Clínic, Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED) and Institut d'Investigacio Biomedica August Pi i Sunyer (IDIBAPS), Facultad de Medicina, Universitat de Barcelona*
[1]*Portugal*
[2]*Spain*

1. Introduction

Epidural or subdural electrodes are often used in humans in order to identify eloquent structures by stimulation or recording. Neurosurgeons are able to use the motor maps gathered more than 50 years ago by Penfield and Jasper (1954) for delineation of the functions of non-lesioned cortical tissue. These and other contributions have been made during surgical procedures in humans by either applying direct cortical stimulation (Woolsey et al., 1979; Burke and Hicks, 1998) or recording from the spinal cord tracts after cortical or peripheral nerve stimulation (Burke and Hicks, 1998; Di Lazzaro et al., 2006). Peroperatory neurophysiological monitoring offers also great opportunities for learning from using neurophysiological techniques, at the same time as helping the surgeon to reach a better outcome (Rainov et al., 1997; Horikoshi et al., 2000; Deletis and Sala, 2008).
These procedures have not only helped to improve the surgical procedure but they have allowed the use of neurophysiological tests to expand our knowledge on human central nervous system circuitry and functional connectivity. Nowadays, stereotactically placed electrodes with therapeutic aims such as deep brain stimulation (DBS), offer the possibility to reach structures that could not be otherwise targeted in humans and investigate further physiological aspects of brain circuits. For these purposes, authors have used the DBS electrodes inserted either in the nucleus ventralis intermedius of the thalamus (Vim), the globus pallidus internus (GPi), the subthalamic nucleus (STN), the pedunculopontine nucleus (PPN) or others in which the results of research are still scarce (Weinberger et al., 2008; Galati et al., 2008; Shimamoto et al., 2010; Alessandro et al., 2010). The information brought by these studies has already shed some light on the functioning of some central nervous system circuits. However, many questions remain to be answered and further research on the subject is required to 1) understand fully the physiological mechanisms underlying the beneficial effects of chronic repetitive high frequency DBS, and 2) strengthen our knowledge on human brain circuitry and connectivity.

In this chapter, we revise the contributions that have been made to various physiological questions by the use of the electrodes implanted for therapeutic purposes in patients with Parkinson disease (PD) or dystonia. We have not included works on clinical effects of deep brain stimulation or clinical correlations, unless they were considered relevant for understanding physiological processes. The reader interested on clinical aspects may look for recent reviews on the topic (Limousin and Martinez-Torres, 2008; Lozano and Schneider, 2008; Benabid et al., 2009; Foltynie et al., 2010).

2. Recording

2.1 Neuronal spikes and local field potentials

2.1.1 Localization of targets

During the surgical procedure, at the operating room, it is possible to perform direct microelectrode recording of neuronal activity along the structures crossed by the electrode to reach the target nucleus. This is part of routine practice in most centers to help in localizing the target basal ganglia (Hutchison et al., 1998; Benazzouz et al., 2002; Sterio et al., 2002a; Molinuevo et al., 2003; Mrakic-Sposta et al., 2008). An example of such recordings taken from a patient along the trajectory of the electrode to the STN is shown in Figure 1.

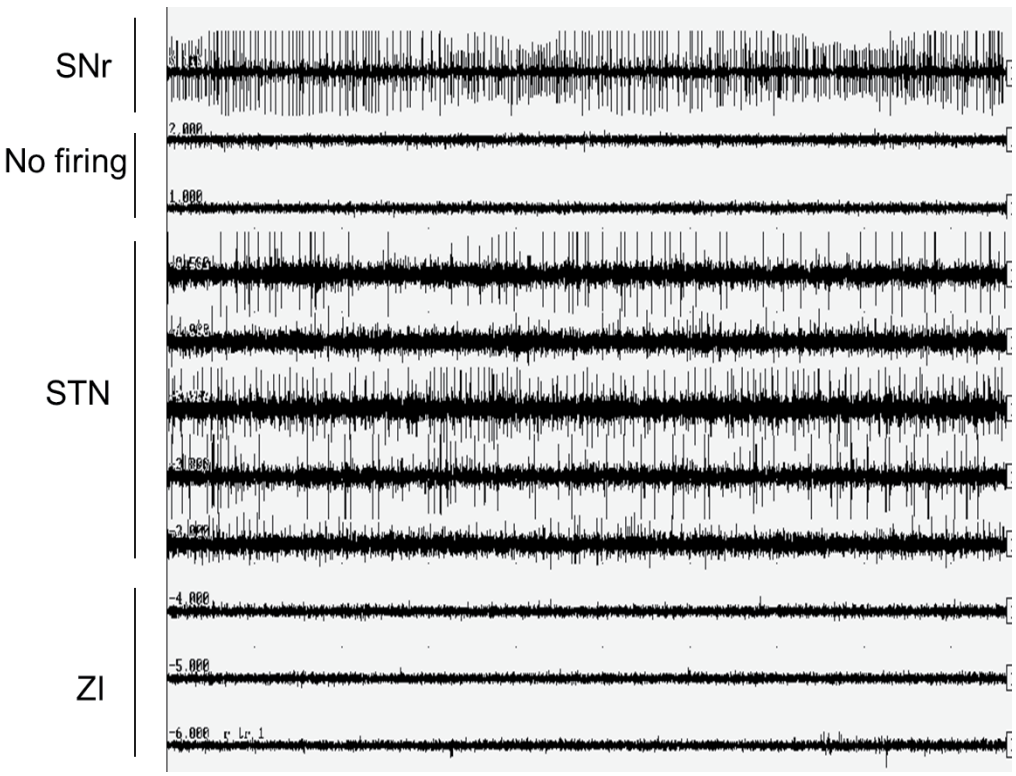


Fig. 1. Neurophysiological recording of various sites while inserting the electrode. From the bottom to the top: The electrode in the zona incerta (ZI) records almost no activity. When it enters the subthalamic nucleus (STN), the spikes become grouped in various bursts. Exiting the nucleus, there is a zone with no activity and then a continuous firing of spikes at a relatively high frequency, when the electrode enters the substantia nigra pars reticulata (SNr).

The possibility exists of recording from different nuclei in the circuitry. It is known, for instance, that the globus pallidus externus (GPe) shows a typical pauser neuronal firing, with activity in bursts. Sani et al. (2009) hypothesized that the characteristics of such firing might be different in patients with different disorders. They examined pause characteristics in 224 GPe units in patients with primary generalized dystonia, PD and secondary dystonia. The results showed that the characteristics of the pauses recorded in the GPe in awake humans distinguished primary dystonia from PD and secondary dystonia. Patients with primary dystonia had longer pause length, shorter interpause interval and higher mean pause frequency than PD patients. Interpause interval was also shorter in primary than in secondary dystonia. These results indicated an increased phasic input from striatal D2 receptor positive cells in primary dystonia.

A method to help localizing the border between the STN and the substantia nigra pars reticulata (SNr) has been shown by Lafreniere-Roula et al. (2009). These authors stimulated at low and high frequency through the electrode intended for the STN. When the electrode was at the border area between the STN and the SNr, they observed that high frequency stimulation caused a long lasting pause in the SNr firing but not in the STN. This is, therefore, an interesting technique to be used as a landmark for the STN electrode positioning. The same authors found inhibition in the GPi, similar to that induced in the SNr, although there were differences in threshold (Lafrenière-Roula et al., 2010), and suggested that such activity depression could contribute to the therapeutic effects of high frequency stimulation. A wavelet-based measure for quantitative assessment of neural background was used by Snellings et al. (2009) to show increase background levels within the STN that would help in identifying better the nucleus boundaries.

In our institution, we use the following criteria to consider electrode placement: For the GPi or the STN we consider signs of appropriate placement: 1) the observation of neuronal activity linked to limb movements, 2) a good therapeutic response such as improvement of bradykinesia, rigidity or tremor with intraoperatory high frequency stimulation, and 3) the absence of capsular, visual or ocular effects with the high frequency stimulation or its presence only when the stimulus intensity is increased above therapeutic threshold. For the Vim, we consider the finding of tremor cells within the boundaries of the nucleus and the disappearance of tremor when stimulating in the absence of motor or sensory side effects.

In 2002, various authors reported their observations on the preferred technical approach to reach the anatomical location for the electrodes to be implanted in the STN, GPi or Vim (Benazzouz et al., 2002; Lanotte et al., 2002; Starr et al., 2002; Saint-Cyr et al., 2002). However, good outcome measures of the surgical procedure should consider not only the precise localization of the appropriate target but, also, the lowest occurrence of residual symptoms and the lowest occurrence of side effects (Guehl et al., 2007).

Recognizing the target structure is a very important task at the time of electrode implantation. Knowing where the stimuli are actually applied or where they are more effective is another important piece of information for feedback. An attempt at knowing where the stimuli were actually applied through the STN electrode for the best clinical outcome was made by Maks et al. (2009). These authors used neuroimaging to measure the theoretical volume of tissue activated (VTA) by clinically defined best therapeutic stimulation parameters. They showed that therapeutic benefit was mainly achieved when the majority of VTA was in the area of the STN, mainly at its dorsal region, but outside the atlas defined boundaries of the nucleus. This, therefore, underlines the importance of the axons surrounding the STN for therapeutic efficacy. A similar observation was made by

Herzog et al. (2007) using electrodes implanted in the thalamus for the treatment of tremor. These authors observed a better effect on tremor using leads that were located closer to the STN rather than in the thalamus itself.

2.1.2 Assessment of activity and connectivity

Once in the target nucleus, the microelectrode can record both neuronal spikes and local field potentials (LFPs) originating in the same nucleus or in neighbouring neuronal groups. Such recordings have been used to characterize the physiological relationship between the target nuclei and its surroundings, as well as to provide evidence for disease-related neurophysiological abnormalities and their modulation by treatment (pharmacological and/or DBS).

Microelectrode recordings from within the STN show relatively rich background and spontaneously firing single neurons. Interestingly, however, if spikes are removed (obtaining a 'despiked' trace), the analysis of the STN signal still provides for the possibility to identify a pattern of activity typical of the STN (Danish et al., 2008). Various authors have reported high firing rates of neuronal spikes in PD patients in both, the STN (Rodríguez-Oroz et al., 2001; Sterio et al., 2002a), and the GPi (Hutchison et al., 1997; 2003), fitting well with the hypothesized hyperactivity of the indirect circuit of the basal ganglia in PD patients (Alexander and Crutcher, 1990; Wichmann and DeLong, 1996). An interesting finding has been recently reported by Novak et al. (2009) to provide a cue to understand why patients with unilateral STN DBS show bilateral benefit. These authors found that during high frequency STN DBS, there was an increase in multiunit spiking activity in the contralateral STN, an observation that provides also many questions to be answered in future studies. Apart from increased firing frequency, Levy et al. (2001; 2002) observed that neuronal spikes recorded from PD patients with tremor showed a prominent oscillatory pattern, which was substantially modified under dopaminergic activity. In the case of dystonia, however, the hypothesized low frequency firing rate of the GPi neurons has not always been found. While Vitek et al. (1999) reported firing rates lower than in PD in 3 patients with dystonia and one patient with hemiballismus, other authors have suggested that anesthesia played an important role in decreasing neuronal firing rate (Hutchison et al., 2003). The effect of anesthesia has not always been confirmed (Sanghera et al., 2003) and, according to Pralong et al. (2005), the lower firing rate of GPi neurons is independent of the type of anesthetic drug used.

Tremor is usually treated with thalamic high frequency stimulation both in PD and in essential tremor (ET). To see if there were differences between the two disorders in regard to the spontaneous neuronal firing in thalamic neurons, Chen et al., (2010) analyzed the recordings from the ventral oral posterior and the ventral intermediate nuclei. These authors concluded that there were significant differences between the two disorders, with decreased ventral oral posterior firing frequency in ET and increased neuronal firing rates in the ventral intermediate nucleus in patients with PD. The authors speculated on the possible pathophysiological implications of their findings.

Neuronal activity can be recorded also as LFPs, which have been confirmed to be time-locked to spikes generated in neighbouring neurones by recording spike-triggered LFP averages (Kuhn et al., 2005a) or examining coherence with multiunit recordings (Weinberger et al., 2006). The analysis of the LFPs may help confirming that the electrode is between the dorsal and ventral borders of the STN (Miyagi et al., 2009).

The LFPs can be recorded from the macroelectrode leads left externalized after surgery prior to connection to the impulse generator and, therefore, they can be analyzed while patients perform cognitive or motor tasks (Brown and Williams, 2005). Three prevailing frequency bands have been identified in the LFPs recorded from the basal ganglia: <8, 8-30 and >60 Hz. The band dominating the spectrum in the 'off' medication stage is the frequency in the alpha-beta range (8-25 Hz), while in the 'on' medication state baseline frequencies are higher (70-80 Hz). Brown et al. (2002) reported an increase in the amplitude of the frequency band of 25 Hz in the GPi of 2 PD patients that occurred prior to completion of a bimanual timing task. Because of a strong correlation between band amplitude changes and task duration, the authors suggested that modulation of this GPi frequency band could be involved in the prediction of movement timing. The band of 8-30 Hz predominates in the STN and GPi of PD patients withdrawn from their dopaminergic medication and is, therefore, considered antikinetic, likely contributing to the bradykinesia.

The high frequency LFP oscillations can only be recorded with normal levels of dopaminergic activity, while the band of 8-30 Hz is suppressed by dopaminergic treatments, behaviourally relevant stimuli and voluntary movement. Therefore, it seems that the subthalamo-pallidal-thalamo-cortical circuit undergo an opposite modulation by dopaminergic activity that may be a fundamental feature of the pathophysiological mechanisms of bradykinesia in PD (Brown, 2003). Actually, a correlation has been reported between the efficacy of the pair of leads used for chronic stimulation and the energy of the beta and gamma frequency band detected initially with LFP recordings during movements (Ince et al., 2010; Zaidel et al., 2010).

Foffani et al. (2003; 2005) described a distinct 300 Hz band in the STN that was more consistently seen during movement than at rest and more robust after apomorphine treatment. The authors suggested that such high frequency band represented a distinct mode of operation of the STN that could be a pathophysiological clue for PD. However the same group reported a similar high frequency band in the STN of two patients with diagnosis other than PD (one with dystonia and another with ET), hence suggesting that this finding may represent a broader feature of human STN function rather than being specific for PD (Danish et al., 2007).

Various loops are likely to run between the cortex and the basal ganglia that can be segregated by the amplitude of the frequency band. Williams et al. (2002) examined coherence between neuronal oscillatory activity recorded from electrodes inserted into the STN (8 patients) or the GPi (2 patients) and the EEG activity. They found significant coherence in three major frequency bands: 2-10 Hz, 10-30 Hz and 70-85 Hz, which differed in their cortical topography. Cortical activity led by around 20 ms the basal ganglia activity in frequencies <30 Hz, while it was the other way around with frequencies in the 70-85 Hz band.

An exaggerated synchronization in the band between 8 and 35 Hz (alpha/beta) might be implicated in the pathophysiology of Parkinson's disease. The power in this band decreased with dopamine treatment, as shown by several authors in the analysis of STN-LFP oscillations (Giannicola et al., 2010). The same effect has been obtained with STN DBS (Kuhn et al., 2008; Bronte-Stewart et al., 2009; Giannicola et al., 2010) although the intensity of the effect has not been the same in all reports. The abnormally enhanced beta band oscillations are encountered in certain sites of the STN and some authors have found a correlation between localization of the electrode in sites of the STN where there was a predominating beta band and the efficacy of STN DBS in alleviating the patient's symptoms (Ince et al.,

2010; Zaidel et al., 2010). Interestingly, the activity was transiently suppressed between 200 and 600 ms after transcranial magnetic stimuli (TMS), regardless of it being applied to the motor cortex or to the supplementary motor area (Gaynor et al., 2008). The effect was seen even with subthreshold intensity for elicitation of a motor evoked potential and, therefore, the authors dismissed the possibility for peripheral reafferentation as the cause of the transient interruption. This observation could underline the beneficial effects of repetitive TMS (rTMS) in patients with PD but the differences between L-Dopa, STN DBS and rTMS point out to the existence of other contributory mechanisms.

The high frequency oscillatory activity (gamma band) is more prominently recorded in patients treated with L-Dopa, suggesting that this may be an important correlate of dopaminergic activity. Although initially considered to be related to the L-Dopa induced dyskinesias, an increase power in the gamma band was actually seen at movement onset in patients in the OFF medication state, to increase significantly in the 'on' medication state (Androulidakis et al., 2007). Therefore, there is evidence that the L-Dopa related increase in gamma band power is a sign of restoration of physiological pattern of oscillatory activity in Parkinson's disease. An abnormally low ratio between beta and gamma activity has been found in the STN during tremor (Weinberger et al., 2009), suggesting that the balance between these two oscillatory frequency bands may be associated with the clinical manifestation of tremor.

Kuhn et al. (2006a) examined event-related desynchronization (ERD) by recording LFPs from the STN region in 8 PD patients 'off' dopaminergic medication. Patients were instructed to either extend the wrist or to imagine performing the same task without any overt movement. They found that imagining a motor action was accompanied by ERD of oscillatory beta activity in the region of the STN that was similar in frequency, time course and degree to the ERD occurring during real execution of movement. The event-related synchronization (ERS) occurring after completion of movement was significantly smaller in movement imagination than in movement execution. According to these observations, neuronal activity in an area around the STN might have a role in trial-to-trial motor learning and in the re-establishment of postural set after movement.

In dystonia, Chu Chen et al. (2006), using a multielectrode that combined 4 platinum-tungsten fibers in a glass insulation with 4 circular contacts, reported the finding of a high power 3-12 Hz band in the analysis of LFP from the GPi, which has been considered relevant in the pathophysiology of dystonia (Silberstein et al., 2003; Liu et al., 2006). Again, computed spike-triggered averages demonstrated that the oscillations were actually generated by GPi neuronal spikes. Consistent with the expected basal ganglia functional activity, a significantly lower firing rate was found in the GPi neurons in dystonic patients than in PD patients (Tang et al., 2007). When recording from the STN of dystonic patients, Schrock et al. (2009) found a frequency of firing of 26.3 Hz (SD 13.6), which was lower than that in the PD patients (35.6 Hz, SD 15.2), but higher than published values for subjects without basal ganglia dysfunction. In Tourette's syndrome, Marceglia et al. (2010) reported the observation of bursting neuronal activity in the ventralis oralis (VO) complex of the thalamus, known to improve tics in patients with Tourette's syndrome. These bursts occurred at low frequencies (2-7 Hz) and in the alpha-band (8-13 Hz), while there was virtually absent beta band activity. Microelectrode recording was performed in the GPi by Zhuang et al. (2009) to explore the relationship between basal ganglia output and electromyographic activity during tics and demonstrate that the basal ganglia motor circuit is involved in tic movements. In 232 neurons, these authors found 45% of them that were related to either a burst of activity or a pause in ongoing tonic activity.

The correlation between LFP oscillatory changes and movements has been reported by many authors, supporting the hypothesis that the GPi and the STN are somehow involved in movement preparation in humans. An increase in high frequency activity (>60 Hz) has been found to occur before voluntary movement (Cassidy et al., 2002). Alegre et al. (2005) reported bilateral changes in the neuronal oscillatory activity of the STN during voluntary unilateral hand movements, suggesting that movement-related activity in the STN has a bilateral representation and probably reflects cortical input. Alegre et al. (2010) also reported, during movement observation, a bilateral beta reduction in subthalamic power, similar to that observed in the EEG, , and decreased cortico-STN coherence, suggesting that the basal ganglia might be engaged by the activity of the human mirror system. Likely, there are multiple circuits linking the motor cortex with the basal ganglia that are segregated by not only topography but also frequency (Lalo et al., 2008).

Interestingly, Paradiso et al. (2003) reported the finding of pre-movement potentials recorded from the STN similar to those recorded from the scalp. These authors found a bilateral slow rising negative pre-motor potential beginning at a latency of more than 2 seconds before onset of self-paced wrist extension movements. Further support for the implication of the cortico-basal ganglia-thalamocortical circuit in movement preparation has been brought recently by the same group. Purzner et al. (2007) reported a phase reversal of the pre-movement potential when simultaneously recorded the activity preceding self-paced or externally cued movements with scalp electrodes and STN electrodes. The possibility that rhythms of neuronal oscillatory activity determine the participation of the basal ganglia on movement preparation, movement execution and post-movement recovery was pointed out by Foffani et al. (2005), while Marceglia et al. (2006) suggested that the key factor could be the interaction between rhythms generated in different neuronal circuits.

There is some evidence for the human STN area to be involved in the processing or transmission of emotional information: Kuhn et al. (2005b) recorded LFPs through the STN electrode in 10 PD patients while viewing pleasant and unpleasant emotionally arousing and neutral pictures. They found a significant, unspecific, ERD in the alpha power (8 to 12 Hz), starting at about 0.5 seconds after stimulus presentation, and a later ERD (at about 1 to 2 seconds post-stimulus), that was larger in trials containing pleasant or unpleasant images than in those with neutral stimuli. These findings suggest some kind of link between the STN and limbic structures that could be a clue for understanding the pathophysiology underlying the mood changes observed in patients with PD and high frequency STN stimulation. The basal ganglia may be involved in the evaluation of changes in the environment and their significance, which could explain the behavioural impairment that can follow basal ganglia lesions or dysfunctions (Sauleau et al., 2009).

2.1.3 Responses of nearby neuronal groups

In search for an explanation of the effects of high frequency stimulation, investigators have used microelectrode recording of neuronal spikes and LFPs in response to local stimuli. Technical development has brought up the possibility of recording from one contact while stimulating by another at a few hundred microns distance only, allowing for the construct of a functional stereotactic mapping around the microelectrode. Dostrovsky et al. (2000) reported inhibition of the GPi neurons by high frequency stimulation through another electrode inserted in the same nucleus, between 250 and 600 microns apart. This was re-examined in 2007 by Pralong et al., who reported opposite effects of high frequency stimulation (100 Hz) over neurones located in different parts of the GPi nucleus, with a

pattern of local inhibition and distant excitation. A similar study was done in STN neurons by Filali et al. (2004), who reported an inhibitory effect of stimulation applied through another electrode located in the same nucleus at a distance of about 600 microns. Welter et al. (2004) reported that stimulation at frequencies over 40 Hz decreased firing frequency and increased burst-like activity of STN neurons in patients with PD. Montgomery (2006) reported on microelectrode recordings in the posterior VO nucleus of the thalamus during high frequency GPi DBS in a patient with dystonia. Eighty-eight percent of neurons showed brief but highly consistent increased firing in the first 1ms following stimulation. This was followed by inhibition in about half of the neurons, which occurred at about 3.5 to 5 ms, and a post-inhibitory rebound of enhanced activity in 25% of neurons.
The importance of stimulus intensity in determining effects on neuronal firing was demonstrated by Maurice et al. (2003) who reported that the firing rate of the SNr neurons increased with high intensity, and decreased with low intensity STN DBS. This observation suggests that the fibers connecting STN to SNr neurons may carry inhibitory or excitatory inputs depending on the firing frequency. Sterio et al. (2002b) demonstrated that the STN neurons were activated by stimuli applied to the GPi, with two different main effects: reduction of firing rate in neurons of the dorsal region of the STN, and facilitation in those of the ventral region of the STN. The latter had a behavior similar to that of the SNr neurons. The authors point out that this finding is just one example of the complexity of the basal ganglia loops, which overshadows the relatively simple and linear, although still useful, schematic connections predicted after the classical circuitry (Alexander and Crutcher, 1990; Wichmann and DeLong, 1996).

2.1.4 Effects of disease and treatment on neuronal activity in the basal ganglia

The possible association between characteristics of the neuronal firing in the STN and GPi and tremor, dyskinesias and other movement dysfunctions of PD patients has been studied by many authors in 'off' and 'on' medication state. The high frequency STN rhythm at about 300 Hz described by Foffani et al. (2003) was dopamine-dependent. It was more robust and larger after apomorphine, suggesting that modulation of this high frequency band may be underlying beneficial therapeutic effects in PD. The authors suggested that an absent 300-Hz STN rhythm during movement could be a pathophysiological clue for PD. Priori et al. (2004) reported that the main effects of L-Dopa and apomorphine were an increase in the power of the low frequency bands (2-7 Hz), and a decrease in the power of low-beta activity (13-20 Hz). Their findings were compatible with at least two STN neuronal oscillatory rhythms, separately modulated by antiparkinsonian medication: one at low frequencies and one in the beta range. Alonso-Frech et al. (2006) found basically the same results and suggested that the increase in the power of the 4-10 Hz frequency band could account for dopamine-induced dyskinesias in PD patients. This has been also pointed out more recently by Lee et al. (2007) who observed that a decrease in neuronal firing rate in the GPi preceded the onset of dyskinesias induced by the administration of apomorphine.
Kuhn et al. (2006b) calculated in 9 PD patients the STN LFP power over the frequencies of the most prominent spectral peak within the 8-35 Hz frequency band and of any peak in the 60-90 Hz band. They observed a dopamine-related reduction in peak activity in the 8-35 Hz band, which was positively correlated with the contralateral hemibody improvement on motor aspects of the unified Parkinson's disease rating scale (UPDRS) and with hemibody subscores of akinesia-rigidity, but not tremor. They also found a trend for negative correlations between peak 60-90 Hz LFP power and UPDRS hemibody score, suggesting

that positive correlations were relatively frequency specific. Peak amplitude or power of the frequency band may be not the only relevant aspect for the function of basal ganglia.
A few authors have examined whether STN DBS have the same effects as dopamine on neuronal firing and LFP oscillations. This has been assessed immediately after switching off the stimulator, when patients still benefit from STN DBS but there is no ongoing stimulation (Foffani et al., 2003; Priori et al., 2006). In those studies, the effects were limited to an increase in the power of very low frequency bands (1-1.5 Hz), while no effects were seen in the low beta band (13-20 Hz), high beta band (20-35 Hz), gamma band (60-90 Hz) or in the 300 Hz oscillations. However, Wingeier et al. (2006) were able to document in two patients a significant attenuation of the power of the beta band oscillatory activity recorded from the STN immediately after DBS, an effect that lasted for 15-25 s after DBS had been turned off. Therefore, more work is needed in this area to establish whether or not the effects induced by DBS on the neuronal oscillatory activity of the STN are the same or not as those induced by dopaminergic treatment.
The mechanisms by which DBS is effective in the symptomatic treatment of PD remain not fully elucidated. A prevailing theory is that, instead of just blocking the activity, the electrical stimuli interfere with the output from the STN, in such a way that the pathological activity is jammed. Carlson et al. (2010) found results consistent with this hypothesis when recording from the STN during therapeutically effective stimulation. These authors saw that the spontaneous firing was not arrested but the firing patterns were altered, with a predominant shift toward random firing.

2.1.5 Discussion

Neurophysiological recordings during surgery are routine practice for most departments carrying out stereotactic procedures for treatment of Parkinson's disease. Recording neuronal spikes helps in the assessment of the trajectory and, together with the magnetic resonance imaging (MRI) correlate of the electrode and the relevant anatomical structures, has provided cues for the assessment of the electrode position with most effective clinical results. Although landmarks have been defined and are helpful for orientation of the target, modification of the first tract is done in about 1/3 of patients in order to reach better outcomes for the specific individual. The relationship between movements of specific body parts and STN neuronal activity has led to recognize topographic specificity of neuronal groups within the STN, which may lead in the future to modification of the target to better suit specific purposes. One example is speech, a complex function that is not always improved and many times even worsens when the STN DBS has been implanted in the best location for improvement of motor function (Rodriguez-Oroz et al., 2005; Tornqvist et al., 2005). At present, when morbidity is low and patients can be relatively assured of an outstanding clinical benefit, the challenge for specialized teams is to search for alternatives that lead to still larger benefit by improving as many functions as possible and avoiding unwanted effects. The neurophysiological mapping of neuronal groups in the STN and other target nuclei could help to better locate the leads in the somatosensory area of the STN, avoiding associative and limbic areas.
Unfortunately, the findings on frequency of spike recordings, band power of LFPs, or even cortico-STN oscillations cannot have a direct correlation with the pathophysiological mechanisms of the disease, since the setup in which these features are recorded implies the presence of interfering factors such as anesthetics, surgery-related stress, and others that may influence brain activity in general. However, measurements of neuronal firing and

LFPs allow for understanding better the effects of medication and repetitive stimulation on the behaviour of local neuronal activity and oscillatory loops. Many authors agree in that frequency bands at about the beta range decrease with dopamine. However, it is not always clear whether repetitive STN DBS modifies the recordings in the same way, and further work is certainly needed in this regard.

2.2 Intracranial recording through the implanted electrode

2.2.1 Characteristics of the evoked potentials

Intracranial electrodes can be used to record relatively large volume conduction action potentials from distant sources. The electrodes inserted in the thalamus, mainly with the purposes of arresting tremor in patients with PD or severe ET, are likely the most appropriate for recording the evoked potentials (EP) after somatosensory stimuli (). In general, the EPs recorded from DBS electrodes are polyphasic and of a latency 2 to 3 ms shorter than the cortical EPs (Figure 2). In most occasions, the subcortical EPs have been recorded from the thalamic Vim, where the electrodes are close to the source of activity. Klosterman et al. (2003) recorded the median nerve EPs from various sites along the pathway of the electrode. When recording from sites along the tract to the STN or the Vim, the EPs were of low amplitude with no high frequency oscillations (HFO). These characteristics did not change when the electrode entered the STN, while entering the Vim it

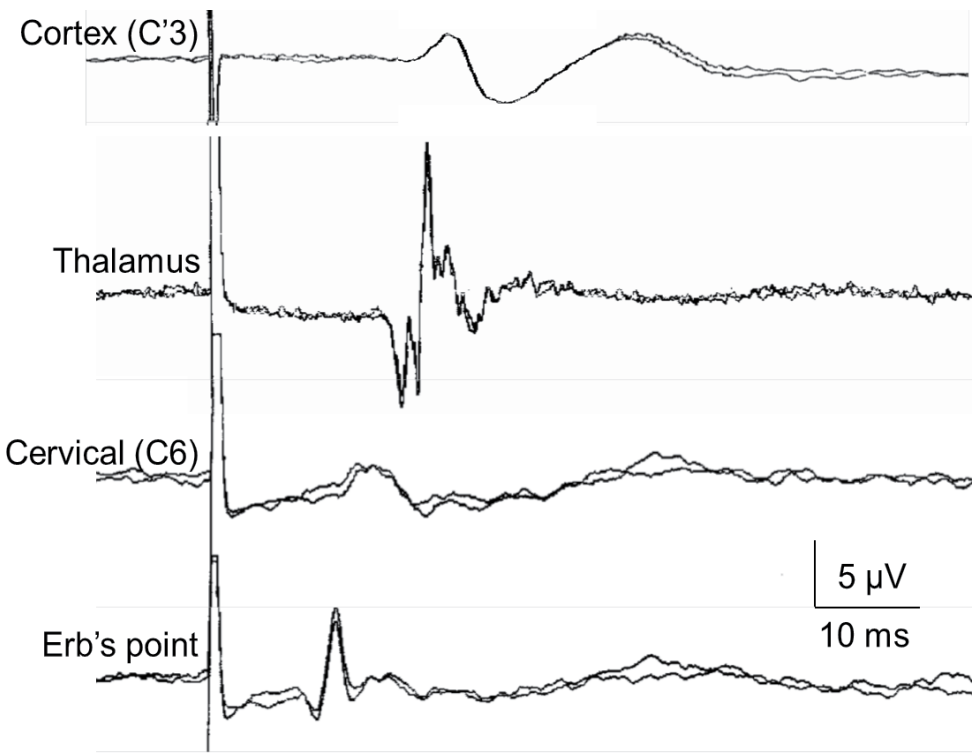


Fig. 2. Somatosensory evoked potentials recorded from Erb's point (Erb), cervical spinal cord (cervical), the nucleus ventral intermedius of the thalamus (thalamus) and the cortex to median nerve stimulation at the wrist.

was recognized by a sharp amplitude increase and the observation of HFOs. The latter were characterized by Hanajima et al. (2004a), who identified them with intrathalamic neuronal firing at intervals between 0.8 and 1.2 ms (a frequency of about 1000 Hz) and found the site of phase reversal at about the nucleus ventralis caudalis. The same authors (Hanajima et al., 2004b) recorded from the thalamic electrode a large somatosensory EP with a mean latency of 17.9+/-1.7 ms, which had a phase reversal at the level of the inter-commissural line. Assessment of phase reversal with bipolar recordings from two electrode leads may be potentially useful intraoperatory to establish the optimal position of the contacts relative to the sensory pathways, contributing to the choice of contacts for chronic stimulation. Laser stimulation has been reported recently to induce also intrathalamic evoked potentials (Kobayashi et al., 2009; Valeriani et al., 2009).

The small EPs recorded from the STN or along the tract are likely to be volume conduction from non-local generators, although Pesenti et al. (2003) proposed that the STN EPs can also be due to local field potentials elicited by muscle afferent inputs to the STN or to activity in thalamo-subthalamic projections. A few articles have been published on intracerebral recording from other nuclei than the thalamus. However, Kitagawa et al. (2007) recorded the somatosensory EPs from the thalamus and the subthalamic area, indicating that this could be a way to refine target localization. Balaz et al. (2008) recorded the P300 wave from the STN, suggesting that this nucleus is involved in cognitive executive functions.

2.2.2 Efferent and afferent gating in subcortical structures

Efferent or centrifugal gating is understood as the modulatory effect of movement on incoming sensory volleys (Grunewald et al., 1984; Cohen and Starr, 1987), while afferent or centripetal gating is understood as the competition between incoming afferent volleys to the brain (Schmidt et al., 1990; Nakajima et al., 2005). Both types of gating of EPs in humans have been documented to occur in part in subcortical structures by recording from the DBS electrodes. However, all authors agree in that a significantly larger effect is seen in scalp recordings than in subcortical recordings.

Regarding efferent gating, Valeriani et al. (2001) recorded the subcortical EPs during voluntary movement of the stimulated foot and saw a significant reduction of amplitude in all DBS recordings and in cortical somatosensory EP components following the P30 potential at the vertex but not at the contralateral temporal and ipsilateral parietal recordings. The authors speculated on the possibility that posterior tibial nerve stimulation generates two differently oriented dipoles in the contralateral hemisphere, one perpendicular to the mesial cortex and another radial to the convexity. Insola et al (2004) also reported that the movement-induced gating of somatosensory EPs occurs at a subcortical level by recording from the STN and GPi electrodes in 9 PD patients. The EPs recorded in those nuclei were triphasic (P1-N1-P2) and their latency ranged from 14 to 22 ms. When they were recorded during voluntary flexo-extension movements of the stimulated wrist, the subcortical EPs significantly decreased in the same way as the scalp N20, P22 and N30 potentials, while the response recorded in the Erb's point remained unchanged. Klosterman et al. (2002) investigated gating of intrathalamic somatosensory EPs in 10 PD patients during the surgical procedure. These authors applied median nerve stimuli to record EPs simultaneously with the intrathalamic and scalp electrodes in patients anesthetized with propofol. They compared conditions before and after application of the depolarising muscle blocker succinylcholine, i.e., with and without reafferent somatosensory inflow from background muscular tone and the repetitive muscle twitches

caused by the median nerve stimulation needed to induce the EPs. The authors found no changes in the sensory nerve action potentials recorded at the upper arm, but the primary cortical component (N20) was significantly increased under succinylcholine (+17%). This cortical release from gating was not paralleled, however, by an increased thalamic response; rather, the primary thalamic response (P16) showed a significant (-9%) amplitude reduction. Thus, the findings reported by these authors suggest a thalamo-cortical dissociation in the phenomenon of gating, when tested by causing muscle relaxation, with significantly more effect in the primary somatosensory cortex than in the thalamus.

Regarding afferent gating, Hsieh et al. (1995) performed a very early study in 5 patients with PD and one with Meige's syndrome undergoing thalamotomy. These authors examined the afferent gating induced by simultaneous stimulation of two fingers. Apart from intrathalamic recordings, these authors obtained direct recordings also from the sensory and motor cortices, and the cuneate nucleus. Electrical stimulation was applied to the II, III or V fingers individually, and also to pairs of either the II and III fingers or the II and V fingers simultaneously. The authors calculated the interaction between afferent volleys as the ratio of amplitude attenuation of the EP caused by the simultaneous stimulation to two fingers compared with the amplitude of the arithmetically summed EPs to the individual stimulation of each finger. The largest interaction was observed in the responses recorded in the scalp (P25 and P22), but a significant effect was also seen in the thalamic recordings. We have examined another form of afferent gating, i.e., the simultaneous activation of fibers by two different stimulus modalities: mechanical taps to the muscle and electrical stimulation to the digital nerves. Interactions between inputs of different sensory modality occur along the sensory pathway, including the thalamus. We investigated the interactions between mechanical taps and electrical nerve stimuli in 8 patients who had an implanted electrode for deep brain stimulation for symptomatic treatment of ET or PD (Costa et al., 2008). A hand-held electronic reflex hammer was used to deliver a mechanical tap to the skin overlying the first dorsal interosseous muscle, and trigger an ipsilateral digital median nerve electrical stimulus time-locked to the mechanical tap with a variable delay of 0 to 50ms. There were significant time-dependent interactions between the two sensory volleys at subcortical level. Thalamic SEPs were decreased in amplitude at inter-stimulus intervals (ISIs) from 10 to 40ms with maximum effect at 20ms, with no changes in peripheral responses. Our results are in line with those reported in other forms of gating and indicate that gating among two different somatosensory afferent volleys occurs at various levels of the central nervous system, and although it is predominating in cortical circuits there is already a significant effect taking place at a subcortical level.

2.2.3 Discussion

Having electrodes implanted in the basal ganglia and particularly in thalamic nuclei called for investigating physiological mechanisms involving sensory events. Most of the research in this area has dealt with thalamic EPs. Although the Vim does not contain the second order neurons activated by somatosensory inputs, the EPs to median or tibial nerve stimulation show consistently reproducible HFOs thought to reflect neuronal activity in the nearby nucleus ventralis caudalis of the thalamus. A few authors have used the electrodes in the STN or GPi to record EPs. In most instances, the authors agree in the fact that the EPs recorded in these nuclei have the same characteristics as those recorded outside the thalamus and are probably volume-conducted from distant sources.

Many investigators have devoted their efforts to examine the phenomenon of gating at the thalamic level. All authors coincide in that the two main forms of gating reported in the EPs (afferent and efferent) can already be demonstrated at thalamic level. However, gating increases in more rostral structures, in such a way that the EPs recorded from scalp electrodes show more effect than those of the thalamus. The whole picture indicates that gating is a multilevel effect that begins at a point caudal to the thalamus and increases along the path up to the site of generation of the scalp EPs.
Interestingly, while nerve stimulation causes well defined EPs in the Vim, we were unable to record such EPs to mechanical muscle taps. Only a slow shift of the baseline time-locked to the mechanical stimulus was apparent in some recordings, indicating that the afferent volley has reached a central nervous system structure where it generated an action potential that is volume conducted towards the electrode. A series of studies may be necessary to determine, for instance, whether or not direct electrical stimulation of muscle afferents does or does not generate Vim EPs. It would be interesting also to use other more natural forms of stimulation to assess their effects on thalamic neurons either by direct recording of EPs or by assessing the effects that such stimuli may induce in thalamic EPs generated by electrical stimuli. In the same line, research has not been done yet in other afferent pathways, such as visual or auditory. Challenges for future investigations using intrathalamic electrodes involve not only deepening in the mechanisms of gating but also in the role of the thalamus in mediating and processing the input from different sources of information.

3. Stimulation

3.1 Experimental procedures

3.1.1 Effects due to activation of circuits and tracts

Because patients are kept awake during most of the surgical time during implantation of electrodes for DBS, the immediate beneficial effects of electrical stimulation can be evaluated in situ by clinical neurological observations and tests. Nevertheless, Liu et al. (2005) have drawn the attention to the usefulness of monitoring the effects of DBS with surface electromyography from the affected muscles to assist electrode implantation and lesioning. According to the authors, there are several potential uses of intraoperative EMG monitoring. EMG can be used as the reference signal for other events, such as the oscillatory LFPs simultaneously recorded via the implanted electrodes, to quantify the effects of acute electrical stimulation on the motor symptoms and to detect unwanted muscle responses induced by direct stimulation of the motor tract.
The effects of stimulation through the DBS electrode may be evaluated in a neurophysiological environment that is more convenient than the operating room if the electrodes are left available for a few days for further testing before implantation of the stimulator. It is understood that the electric field generated by the current delivered through the electrode spreads beyond the target nuclei and affects surrounding structures (McIntyre et al., 2004; Butson et al., 2007). According to the general principles of the effects of stimulation of the neuropil (Nowak and Bullier 1998; Ashby et al., 1999), electrical stimuli are more likely to activate axons than cell bodies, fibers near the cathode than those near the anode, and fiber tracts that run parallel rather than those that run perpendicular to the electrode. Indeed, the effects obtained with just a single stimulus at the weakest possible intensity are usually those due to activation of axons in long tracts located in the vicinity of the target nuclei. Ashby and Rothwell (2000) have summarized nicely the possibilities for

neurophysiological studies using deep brain electrodes. Two structures have been used for recording: the brain and the muscle.

3.1.2 Effects on cortical activity

The EEG activity is modulated by stimuli applied through the electrodes inserted in the STN (Ashby et al., 2001). Single stimuli elicited a negative potential with an onset latency of approximately 3 ms, followed by later potentials at 5 and 8 ms, which were usually largest over the frontal region in 9 out of 11 sides. Medium latency (18-25 ms) and long latency (longer than 50 ms) responses were also reported. Short latency EPs had short chronaxie and refractory period, implying that they arose from the activation of low threshold neural elements, possibly myelinated axons. They were maintained without blocking at stimulation frequencies as high as 100 Hz. Cortical responses likely due to direct stimulation of axons running close to the electrode were reported by Baker et al. (2002) with latencies ranging from 8 to 400 ms. Medium-latency EPs, with an average onset of 14 +/- 3 ms and peak at 23 +/- 4 ms, were reported by MacKinnon et al. (2005) to low frequency STN stimulation (5-10 Hz). These authors showed that the distribution of the EPs recorded by scalp electrodes to stimuli applied through the STN electrode was similar to that of the EPs elicited by median nerve stimuli. One likely axonal bundle that may generate the EEG potentials after electrical stimulation through the electrode inserted in the STN is the pallido-thalamic tract, which contains highly myelinated axons and traverses the dorsal aspect of the STN. These authors, did not find a positive correlation between the cathodal contact that produced the largest EEG response and the one that produced the optimal clinical benefit, suggesting that the neural elements mediating the medium-latency EP are different from those responsible for clinical effects. However, Kuriakose et al. (2010) have recently suggested that one of the mechanisms by which the STN DBS causes a beneficial effect is through cortical activation. These authors examined the time course of cortical activation after controlled stimulation at the STN and suggested that cortical activation could be due to short-latency antidromic stimulation of cortico-subthalamic projections and the medium-latency facilitatory basal ganglia-thalamo-cortical interactions. No significant changes were observed in event related potentials in regard to amplitude in a standard oddball auditory paradigm (Kovacs et al., 2008), in spite of the improvement in the accuracy of the task. Interestingly, the P300 was recorded from the STN or its vicinity in 8 out of 14 leads examined by Balaz et al. (2008).

A few other observations of the effects of DBS have been reported in circuits involving the cortex. Fraix et al. (2008) reported a tendency to normalization of the contralateral silent period to TMS and short-interval intracortical facilitation during STN DBS. Herzog et al. (2008) reported improvement of integration of sensory inputs from the bladder with STN DBS 'on'. Using positron emission computed tomography (PET) they showed that urinary bladder filling led to an increased regional cerebral blood flow (rCBF) in the periaqueductal grey, the posterior thalamus, the insular cortex as well as in the right frontal cortex and the cerebellum bilaterally. These authors suggest that STN DBS facilitates the discrimination of different bodily states by supporting sensory perception and the underlying neural mechanisms.

Neuroimaging techniques have given some cues for understanding the relationship between basal ganglia nuclei and regions of the cortex using functional MRI (fMRI) (Jech et al., 2001; Perlmutter et al., 2002; Karimi et al., 2008) or rCBF with PET (Payoux et al., 2004, Grafton et al., 2006; Thobois et al., 2002; Strafella et al., 2003; Vafaee et al., 2004). In these studies, high frequency stimulation decreased the abnormal hyperactivity of the motor cortex at rest and increased activity in premotor areas during movement in PD patients. Measuring rCBF,

Payoux et al. (2009) showed opposite effects of GPi and GPe over the ipsilateral primary sensorimotor cortex. Using PET, Arai et al. (2008) observed effects of unilateral thalamic stimulation on the motor cortex of the side stimulated and on the GPi of the contralateral side, which could underline the observation of bilateral improvement after unilateral stimulation.

3.1.3 Muscle responses

Ashby et al. (1998; 1999) were the first to report the effects of controlled external stimuli using the artifact of the implanted stimulator, picked up by cutaneous electrodes, as the trigger of the recording device a few months after the stimulator had been implanted. Single stimuli modulated voluntary EMG activity of contralateral muscles, inducing a short-latency facilitation, followed by a longer latency inhibition. The authors hypothesized that facilitation was due to activation of descending axons in the corticospinal tract of the capsula interna, which lies at a mean distance of about 4.5 mm in the mediolateral plane and 2 mm in the antero-posterior plane from the tip of the electrode implanted in the STN (Schaltenbrand and Wahren, 1977; Voges et al., 2002; Molinuevo et al., 2003). Ashby et al. (1999) reported also an inhibitory effect of DBS on the ongoing voluntary activity, revealed by a decrease ('dip') in the level of EMG activity. This silent period (SP) was thought to arise from the activation of large-diameter inhibitory thalamo-cortical fibres running parallel to the electrode. Hanajima et al., (2004c) observed that 3 ms after STN stimulation, the Motor Evoked Potential (MEP) amplitudes produced by TMS-induced anterior-posterior directed currents were significantly larger than control responses, while the responses to lateral-medial currents were unchanged. Similar facilitation also occurred after GPi stimulation, but not with thalamic stimulation. Therefore, single pulse STN DBS had a short latency facilitatory effect on motor cortex, which may be due to antidromic excitation of the cortico-STN fibers or transmission through the basal ganglia-thalamocortical pathway.

Kuhn et al. (2004) compared motor effects of activation of corticospinal neurons using either subcortical (direct electrical stimulation through the DBS electrode) or cortical (indirect stimulation of cortical neurons by TMS) stimuli. The study was done in 8 dystonic patients that underwent GPi DBS, using again the artifact of the stimuli issued by the implanted electrodes as triggers for the recording. Single pulse DBS activated a fast conducting monosynaptic pathway to alpha motoneurones. The contralateral MEPs had a significantly shorter onset latency and shorter duration compared to the responses induced by TMS. They reported the observation of a contralateral SP of short duration and no ipsilateral facilitatory or inhibitory motor effects. These results suggest that DBS of the GPi activates the corticospinal neurons at the level of the internal capsule to account for the MEP, and the thalamic fasciculus or cerebellothalamic fibers to account for the SP (see also Strafella et al., 1997 and Ashby et al., 1999). The absence of ipsilateral inhibition is consistent with a transcallosal pathway for the ipsilateral SP. In contrast, our group (Compta et al., 2006), who used the electrode implanted in the STN, reported ipsilateral SP with two short duration phases. This challenged the possibility that the ipsilateral SP is mediated through the corpus callosum since the stimuli were applied caudal to the transcallosal fibers. However, the possibility still exists that some parts of the ipsilateral SP are indeed mediated through transcallosal collaterals activated antidromically.

We found a long duration contralateral SP that had the peculiarity of having a burst separating it into two parts (Figure 3). The characteristics of the contralateral SP were explained on the bases of collision between the antidromic impulses generated through the DBS electrode and the descending volleys related to voluntary activity. Collision would have freed some neurons

from antidromic invasion of inhibitory collaterals and precisely the firing of these neurons with new premotor inputs would account for the burst of EMG activity breaking through the SP. Methodological differences could account for the different results reported by Kuhn et al. (2004) and our group (Compta et al., 2006). Kuhn et al. (2004) used electrodes inserted in the GPi, which is slightly more rostral, anterior and lateral than the STN, and could activate a different bunch of corticospinal axons than the electrode inserted in the STN. The same differences apply to the volley reaching the axons responsible for inhibitory effects via the thalamus. Whereas Compta et al. (2006) studied patients with Parkinson's disease, Kuhn et al. (2004) studied patients with generalized dystonia who are known to have a disorder of inhibition and an abnormally shorter SP (Ridding et al., 1995; Chen et al., 1997). Finally, Kuhn et al. (2004) applied the stimuli at a frequency of 5 Hz from the implanted generators, which allows for a relatively short time for analysis between two consecutive stimuli.

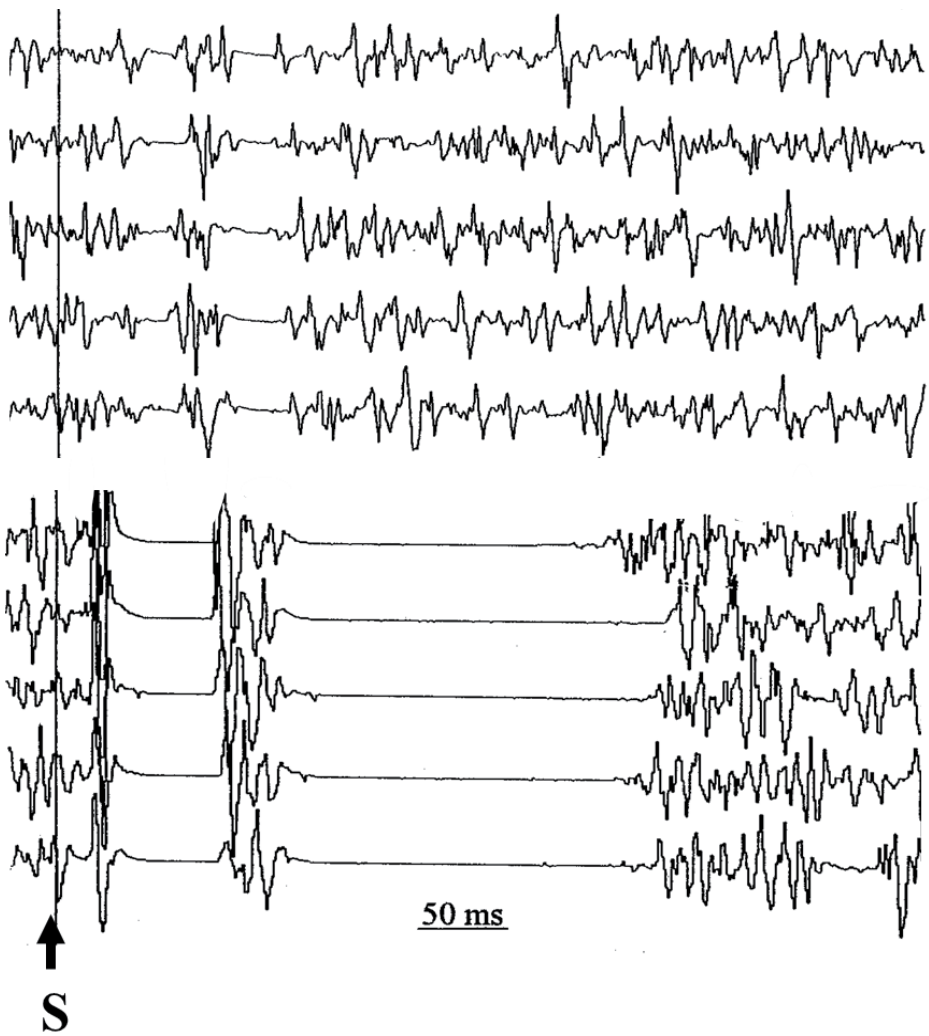


Fig. 3. Contralateral and ipsilateral silent periods induced by a single unilateral suprathreshold stimulus through the electrode inserted in the STN

Obviously, MEPs are not only obtained in hand muscles but in all muscles receiving innervation through fibers running in the capsula interna. This includes the cortico-bulbar tract. Fibers of the cortico-bulbar tract run in the genu of the capsula interna and are readily accessible to stimuli applied through the DBS electrode. Our knowledge of the distribution of cortical innervation to muscles innervated by cranial nerves is less accurate than for limb muscles because of various drawbacks of cortical stimulation such as the generation of large artefacts and the unavoidable elicitation of direct and reflex responses to activation of cranial nerves in the posterior fossa. We studied responses of cranial nerve innervated muscles to single STN DBS in 14 PD patients (Costa et al., 2007). The stimulus intensity used was 130% the resting threshold for an MEP in the thenar muscles. The inhibitory effects were also examined during sustained voluntary contraction of about 20% of maximum. As expected, unilateral stimuli induced strictly contralateral responses in thenar muscles at a mean latency of 20.1±2.0 ms. The MEPs obtained in the trapezius, deltoid and biceps muscles were also present in only the contralateral side, but the same stimulus induced always (i.e., a probability of 100%) bilateral MEPs in orbicularis oculi, orbicularis oris, masseter and sternocleidomastoid. The mean MEP latency ranged from 6.0 to 9.1 ms. The MEP latencies were significantly longer in facial nerve innervated muscles than in masseter and sternocleidomastoid muscles (Figure 4).

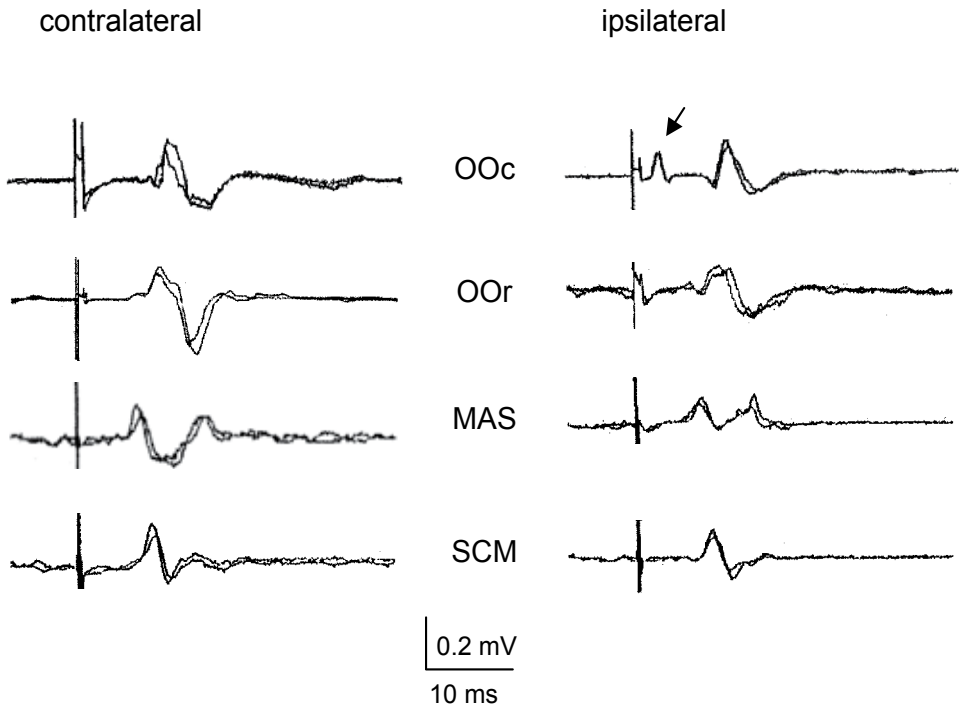


Fig. 4. Motor evoked potentials of cranial nerve innervated muscles to unilateral STN DBS electrode stimulation. Responses in the contralateral muscles are on the left side column while those of the ipsilateral muscles are on the right side column. OOc= Orbicularis oculi; OOr=Orbicularis oris; MAS= Maseter; SCM= sternocleidomastoid. Note the small short latency potential in the ipsilateral orbicularis oculi (inclined arrow)

Well defined SPs to single unilateral STN stimuli were present in both sides in the orbicularis oculi and masseter muscles in all patients, probably due to transient alpha motoneuron refractoriness after synchronized firing, blocking of the arrival of excitatory inputs to the motoneurons (Compta et al., 2006), and activation of thalamocortical inhibitory projections (Strafella et al., 1997). The amplitude of the MEP elicited during contraction was higher, and the duration of the SP was significantly longer, in the contralateral with respect to the ipsilateral sides. However, duration of the SP had no significant correlation with amplitude of the MEP.

3.1.4 Discussion

It seems obvious that chronic high frequency DBS causes its therapeutic effects by changing neuronal excitability in the area covered by the electrical field. Therefore, several authors have studied the effect in neurons in the vicinity. However, the mechanism of action of high frequency DBS is far from being clarified. Instead, the analysis of the effects of stimulation through one electrode lead and recording with a nearby electrode has brought new evidences for interconnections between nuclei of the basal ganglia. As expected, the observations suggest a more complex circuitry than a simple chain of nuclei with excitatory and inhibitory connections. In at least some connections, the frequency of inputs determines the sign of the effect while in others the exact site of the nucleus receiving the inputs is what makes a difference. This is likely reflecting that we are beginning to establish the temporal and spatial characteristics of the connectivity between basal ganglia nuclei and from the basal ganglia to output structures.

STN DBS induces consistent changes in cortical metabolism that can be summarized as a decrease of motor cortical activity at rest and an increase in cortical activity of the supplementary motor area and premotor cortex during active movements. However, the changes in metabolism do not necessarily show the function of the neurons undergoing such change, because they may involve both facilitatory and inhibitory neurons. Unfortunately, a good correlation between neuroimaging studies reflecting changes in metabolism and neurophysiology studies showing changes in cortical excitability has not yet been done.

There are effects of STN DBS on tracts with long projections that run close to the position of the electrode. We do not know if activation of those tracts contributes somehow to the clinical effects of DBS. Corticonuclear and corticospinal fiber tracts can be activated at relatively low intensity through the electrodes inserted in the STN or in the GPi. It is noteworthy that the effects on the motor tract of stimuli applied through the STN electrode seem not to be the same as those induced by stimuli applied through the GPi electrode (Kuhn et al., 2004; Compta et al., 2006). If these differences hold true in future works, they may be a hint to further understand the differential mechanisms of action of electrodes inserted in the two nuclei.

As with the MEPs elicited in hand muscles, the most likely physiological mechanism accounting for the generation of the MEPs in cranial nerve innervated muscles is activation of axons of the corticonuclear tracts within the internal capsule. However, in the case of the facial nucleus, Morecraft et al. (2001) have reported up to 5 projections from motor cortical areas to subsectors of the facial nucleus. Therefore, the MEPs obtained in cranial nerve innervated muscles by single pulse STN DBS could result from activation of just one of the many descending corticonuclear pathways, the function of which is largely unknown.

3.2 Effects of DBS on neurophysiological tests of clinical use

Several studies have demonstrated that high frequency DBS improves the symptoms of PD patients. These effects have been documented and quantified using clinical scales. For instance, a clinical significant effect of the treatment is usually considered when there is more than 30% improvement in the UPDRS score. However, researchers have been interested in knowing how DBS modifies certain clinical neurophysiological abnormalities that may not have a direct clinical correlate but support in part pathophysiological mechanisms underlying parkinsonian symptoms and signs (Hallett, 1998; Rossini et al., 1998; Deecke, 2001; Valls-Solé and Valldeoriola, 2002). This has a double advantage: One is the quantitation and documentation of improvement through objective scales; the other is the determination of the neurophysiological abnormalities that are more closely related to clinical changes. Usually, the clinical and neurophysiological effects of DBS are compared with those of dopaminergic medication in a quadruple comparison: 'on' vs. 'off' medication and 'on' vs. 'off' stimulation.

3.2.1 Cortical physiology

One of the first observations on the neurophysiological effects of DBS was the change in contingent negative variation reported by Gerschlager et al. (1999) with bilateral STN DBS in PD patients. The contingent negative variation is a slow negative potential shift reflecting cognitive processes associated with the preparation and/or anticipation of a response that has been found to be reduced over the frontal and frontocentral regions in PD (Deecke, 2001). The increase in amplitude of the contingent negative variation with STN DBS 'on' (Gerschlager et al., 1999) suggests improvement of the impaired cortical functioning in PD, particularly within the frontal and premotor areas.

In a series of works on ERD preceding movement and ERS at movement termination, Devos et al. (2003, 2004, 2006) showed that STN DBS had also effects on the abnormally reduced and delayed cortical oscillatory activity patterns of PD patients, which have been considered a correlate of bradykinesia (Magnani et al., 1998; Brown and Marsden, 1999). The effects shown by Devos et al. with STN DBS (2003, 2004) were similar to those of an acute administration of L-Dopa. Interestingly, when recording ERD and ERS from the electrode inserted in the STN, the contacts that produced the best clinical results were also those showing the earliest mu and beta ERD and the strongest beta and gamma ERS.

The effects of STN or GPi DBS on motor cortex excitability have been studied by many authors. Chen et al. (2001) reported the effects of GPi DBS on several brain circuits that may exhibit functional abnormalities when examined with neurophysiological methods in PD patients. These included motor threshold, MEP recruitment curve, SP duration, short interval intracortical inhibition (SICI), long interval intracortical inhibition, and intracortical facilitation. The stimulators were set at the optimal parameters, at half the optimal stimulus intensity or switched off, in random order, while patients remained in their usual medication condition. No significant differences were found in most tests among the three conditions, the only exception being a reduction in the SP duration. Similar absence of modification of SICI was reported by Kuhn et al. (2003) during GPi DBS in patients with dystonia. However, switching off GPi stimulation led to an increase in motor threshold, and reduced the size of contralateral responses in the stimulus-response curves in relaxed muscles. On top of that, the authors reported no STN DBS related changes in spinal excitability, assessed by the H-reflex in the forearm muscles.

A different result was reported by Cunic et al. (2002) who examined the effects of STN DBS on cortical excitability in 9 PD patients, using the same protocol that Chen et al. (2001) and Kuhn et al. (2003) used for the GPi. These authors found that resting SICI, studied with paired-pulse TMS at the interstimulus interval of 2 ms, was restored to normal levels in the 'on' condition. Opposite to the results reported with GPi DBS, STN DBS did not induce changes in SP duration, motor threshold or MEP recruitment curve. Thus, in parallel to the differences found when recording hand muscle responses (Kuhn et al., 2004; Compta et al., 2006), it seems that the effects of STN DBS are different from those of the GPi DBS on motor cortex excitability changes accessible to neurophysiological testing with TMS. The effects of STN DBS on resting SICI were confirmed by Pierantozzi et al. (2002), who found an increase in SICI at intervals of 2 ms with STN and 2 and 3 ms with GPi. The improvement was similar to the one provided by apomorphine infusion. The authors suggest that improvement of SICI may be related to a recovery in modulation of thalamo-cortical motor pathway.

3.2.2 Subcortical circuits

Tisch et al. (2006a) measured changes in the excitability of the blink reflex after GPi DBS in 10 patients with dystonia. The abnormally enhanced excitability recovery after a conditioning stimulus (Kimura, 1973) was found to decrease progressively at intervals of 1, 3, and 6 months after surgery, suggesting that GPi DBS results in functional reorganization of the nervous system and a long-term increase in brainstem inhibition. Another dysfunction seen in the recording of the blink reflexes in PD patients is reduced prepulse inhibition (Schicatano et al., 2000; Valls-Solé et al., 2004). The pathophysiology of this phenomenon is not clarified but the abnormalities observed in PD may be due to a dysfunction in the connections between the basal ganglia and the brainstem nuclei, particularly the PPN (Pahapill and Lozano, 2000). We investigated the prepulse effects of single electrical STN DBS on the blink reflex induced in orbicularis oculi muscle by supraorbital electrical nerve stimulation in 7 PD patients (Costa et al., 2006). Five of them had an abnormally reduced prepulse inhibition to auditory and somatosensory stimuli. In all 7 patients, stimuli applied through the STN electrodes induced significant inhibition of the R2 at inter-stimuli intervals between 10 and 30 ms, with a mean percentage inhibition of 92% at 20 ms. Therefore, dysfunction of auditory and somatosensory prepulses in PD patients cannot be due to the machinery activated by DBS. We proposed that either the abnormal reduction in prepulse inhibition lies in a point of the circuit before reaching the structures activated by DBS, or STN DBS causes the prepulse by a different circuit than auditory and somatosensory stimuli.

The effects of DBS on spinal cord excitability have been reported for propriospinal circuits in the forearm (Tisch et al., 2006b) and in the leg (Potter et al., 2004). Tisch et al. (2006) reported a progressive improvement of the reciprocal inhibitory effect of a radial nerve stimulus on the median nerve H reflex, at 1,3, and 6 months of GPi DBS in patients with dystonia, and suggested that DBS causes functional reorganization of the nervous system that includes the spinal machinery. Potter et al. (2004) reported an increase of autogenic inhibition of the soleus H reflex, a propriospinal inhibitory phenomenon that has been found to be abnormal in PD (Delwaide et al., 1991). The authors measured the soleus H-reflex alone or conditioned by previous gastrocnemius nerve stimulation at ISIs of 2 to 10 ms in 10 PD patients. STN DBS induced an increase in the inhibitory effect of the conditioning stimulus that was significantly correlated with the clinical improvement of gait and posture. In a more recent work, the same group (Tisch et al., 2007) reported the absence of long-term potentiation-like

effect in patients with dystonia and GPi DBS. This has been considered a sign of abnormal plasticity in patients with dystonia (Quartarone et al., 2003). Therefore, this negative result could be reflecting the mechanism of action of pallidal DBS in dystonia.
Activity in descending tracts facilitates the soleus H reflex but such facilitation is abnormally decreased in patients with PD. This has been shown for auditory stimuli (Delwaide et al., 1993) and for TMS (Valls-Sole and Valldeoriola, 2002). Potter-Nerger et al. (2008) reported an improvement of the descending modulation of the H reflex by continuous high frequency STN DBS. Using single pulse STN DBS, we found in 11 PD patients that it modulates the amplitude of the soleus H reflex and therefore the net influence of the various mechanisms determining the excitability of the spinal alpha-motoneuron pool (Costa et al., 2011). Furthermore, the modulation of the H reflex was different according to the site of stimulation (ipsilateral vs. contralateral). In the case of contralateral single pulse STN DBS, the modulation of the soleus H reflex is distributed in an early and late facilitation phases, while in the case of ipsilateral single pulse STN DBS, there is a single early facilitation phase. Whether the modulation of the H reflex by STN DBS is the consequence of direct or indirect effects on the reticulospinal motor system is presently unknown.
The work of Tisch et al. and Potter et al. are just illustrative studies of one of the many positive effects reported during continuous high frequency STN DBS in the various abnormalities described in patients with PD, dystonia or ET (Sailer et al., 2007 for afferent inhibition; Potter et al., 2008 for audiospinal reactions; Yugeta et al., 2010, for the initiation and inhibition of saccades; Kronenbuerger et al., 2010 for eyeblink conditioning).

3.2.3 Discussion

In general terms, DBS causes changes in neurophysiological tests of clinical use that consist in a tendency to normalization, although in many occasions differences remain between patients with DBS 'on' and control subjects. This is consistent with clinical observations and points to a good correlate of some neurophysiological tests. This is particularly true for those tests related to planning and execution of voluntary movements such as the ERD or the cognitive negative variation. Changes in these tests demonstrate the influence of basal ganglia on cortical reactivity.
Less straightforward are the results of the assessment of motor cortical excitability at rest or during tonic voluntary contraction. Although there is no complete agreement among all authors, changes in SICI and in the SP duration seem not to result from activation of the same structure since most studies show that when there is reduction in SICI there is no effect on SP duration and viceversa. Interestingly, GPi and STN seem to give different results, reinforcing the possibility to identify distinctive neurophysiological outcome from the two nuclei.
The effects of DBS on subcortical circuits, including the brainstem and spinal levels, indicate a tendency to normalization of the results of neurophysiological tests. One of the subcortical circuits of interest in PD is the one responsible for prepulse inhibition (Fendt et al., 2001). The abnormally reduced prepulse inhibition in PD patients (Schicatano et al., 2000; Valls-Solé et al., 2004) reflects in part disturbed sensorimotor integration, but the normality of the effects when DBS is used as prepulse indicate that the defect does not lie ahead of the structures activated by the stimulus. We cannot assume that the circuit of prepulse inhibition is the same with DBS and with auditory or somatosensory stimuli. Actually, the STN is not part of the circuit of the prepulse. However, fibers connecting the GPi and the

PPN run close to the STN (Swerdlow et al., 2001) and might have been activated by the stimulus through the STN electrode. If this was the case, two explanations should be considered: One is that the dysfunction responsible for the loss of prepulse inhibition by acoustic and somatosensory inputs lies in circuits rostral to the PPN. One such possibility is the nucleus reticularis pontis caudalis, which receives inputs from the acoustic and somatosensory stimuli, and has reciprocal connections to the PPN. Another is that STN DBS induces its effects at a point beyond the PPN in the prepulse circuit. In favour of the first hypothesis is the fact that PD patients have an abnormal startle reaction due to dysfunction in nuclei of the reticular formation. In favour of the second hypothesis is the fact that STN DBS is known to cause inhibitory effects by way of activating afferents to the thalamic nuclei. Only further work in the area may help in answering the questions that remain unsolved by the findings reported so far.

4. Conclusion and future perspectives

The outstanding clinical neurophysiological investigation that is currently ongoing makes probably superfluous the task of guessing what can be expected in future years in this field. Nevertheless, the rapid growing understanding of both, the physiology and pathophysiology mechanisms of the different subcortical-cortical circuits, as well as the underlying clinical neurophysiological mechanisms of DBS, points to the possibility in the near future to: (1) Change the paradigm of DBS to another one were patients are treated with electrodes placed simultaneous in different nuclei (e.g. STN and PPN); (2) Allow for the simultaneous assessment of neuronal activity through recording of LFPs from DBS electrode leads and the consequent change in DBS stimulation parameters delivered by other DBS electrode leads, in a kind of real time individualised DBS therapy; (3) Begin to explore the possibility of improving non-motor symptoms through identification of new targets and stimulation parameters.

Many more studies than those reported here dealing with the effects of DBS have been published, bringing small or large pieces of information to increase our understanding of how the basal ganglia participate in the very many tasks that they are assigned. In this review, we attempted to focus on neurophysiological aspects of DBS not necessarily correlated with therapeutic effects. Understanding the physiological mechanisms accounting for some of the events seen with DBS is a growing field in which relevant contributions appear often in the literature and some of them might have done so while this chapter was in the review or publication processes. We hope, however, that this review reflects the state of our knowledge at the beginning of a new era in neurophysiology: that of direct recording and stimulation from deep brain electrodes. We hope also that it stimulates research in the field, the only way to eventually understand at least partially the function of the basal ganglia and subcortical motor circuits.

5. References

Alegre M, Alonso-Frech F, Rodriguez-Oroz MC, Guridi J, Zamarbide I, Valencia M, Manrique M, Obeso JA, Artieda J. Movement-related changes in oscillatory activity in the human subthalamic nucleus: ipsilateral vs. contralateral movements. Eur J Neurosci 2005;22:2315-2324.

Alegre M, Rodríguez-Oroz MC, Valencia M, Pérez-Alcázar M, Guridi J, Iriarte J, Obeso JA, Artieda J. Changes in subthalamic activity during movement observation in Parkinson's disease: is the mirror system mirrored in the basal ganglia? Clin Neurophysiol 2010;121:414-425.

Alessandro S, Ceravolo R, Brusa L, Pierantozzi M, Costa A, Galati S, Placidi F, Romigi A, Iani C, Marzetti F, Peppe A. Non-motor functions in parkinsonian patients implanted in the pedunculopontine nucleus: focus on sleep and cognitive domains. J Neurol Sci 2010;289:44-48.

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 1990;13:266-271.

Alonso-Frech F, Zamarbide I, Alegre M, Rodriguez-Oroz MC, Guridi J, Manrique M, Valencia M, Artieda J, Obeso JA. Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. Brain 2006;129:1748-1757.

Androulidakis AG, Kühn AA, Chen CC, Blomstedt P, Kempf F, Kupsch A, Schneider GH, Doyle L, Dowsey-Limousin P, Hariz MI, Brown P. Dopaminergic therapy promotes lateralized motor activity in the subthalamic area in Parkinson's disease. Brain 2007;130:457-468.

Arai N, Yokochi F, Ohnishi T, Momose T, Okiyama R, Taniguchi M, Takahashi H, Matsuda H, Ugawa Y. Mechanisms of unilateral STN-DBS in patients with Parkinson's disease: a PET study. J Neurol 2008;255:1236-1243.

Ashby P, Strafella A, Dostrovsky JO, Lozano A, Lang AE. Immediate motor effects of stimulation through electrodes implanted in the human globus pallidus. Stereotact Funct Neurosurg 1998;70:1-18.

Ashby P, Kim JY, Kumar R, Lang AE, Lozano AM. Neurophysiological effects of stimulation through electrodes in the human subthalamic nucleus. Brain 1999; 122: 1919-1931.

Ashby P, Rothwell JC. Neurophysiologic aspects of deep brain stimulation. Neurology 2000;55(Suppl 6):S17-20.

Ashby P, Paradiso G, Saint-Cyr JA, Chen R, Lang AE, Lozano AM. Potentials recorded at the scalp by stimulation near the human subthalamic nucleus. Clin Neurophysiol 2001;112:431-437.

Baker KB, Montgomery Jr EB, Rezai AR, Burgess R, Lüders HO. Subthalamic nucleus deep brain stimulus evoked potentials: Physiological and therapeutical implications. Mov Disord 2002;17:969-983.

Baláz M, Rektor I, Pulkrábek J. Participation of the subthalamic nucleus in executive functions: An intracerebral recording study. Mov Disord 2008;23:553-557.

Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 2009;8:67-81.

Benazzouz A, Breit S, Koudsie A, Pollak P, Krack P, Benabid AL. Intraoperative microrecordings of the subthalamic nucleus in Parkinson's disease. Mov Disord 2002;17 Suppl3:S145-149.

Bronte-Stewart H, Barberini C, Koop MM, Hill BC, Henderson JM, Wingeier B. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation.Exp Neurol 2009;215:20-28.

Brown P, Marsden CD. Bradykinesia and impairment of EEG desynchronization in Parkinson's disease. Mov Disord 1999;14:423-429.

Brown P, Williams D, Aziz T, Mazzone P, Oliviero A, Insola A, Tonali P, Di

Lazzaro V. Pallidal activity recorded in patients with implanted electrodes predictively correlates with eventual performance in a timing task. Neurosci Lett 2002;330:188-192.

Brown P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord 2003;18:357-363.

Brown P, Williams D. Basal ganglia local field potential activity: character and functional significance in the human. Clin Neurophysiol 2005;116:2510-2519.

Burke D, Hicks RG. Surgical monitoring of motor pathways. J Clin Neurophysiol 1998;15:194-205.

Butson CR, Cooper SE, Henderson JM, McIntyre CC. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. Neuroimage 2007;34:661-670.

Carlson JD, Cleary DR, Cetas JS, Heinricher MM, Burchiel KJ. Deep brain stimulation does not silence neurons in subthalamic nucleus in Parkinson's patients. J Neurophysiol 2010;103:962-967.

Cassidy M, Mazzone P, Oliviero A, Insola A, Tonali P, Di Lazzaro V, Brown P. Movement-related changes in synchronization in the human basal ganglia. Brain 2002;125:1235-1246.

Chen R, Wassermann EM, Canos M, Hallett M. Impaired inhibition in writer's cramp during voluntary muscle contraction. Neurology 1997; 49: 1054-1059.

Chen R, Garg RR, Lozano AM, Lang AE. Effects of internal globus pallidus stimulation on motor cortex excitability. Neurology 2001;56:716-723.

Chen H, Zhuang P, Miao SH, Yuan G, Zhang YQ, Li JY, Li YJ. Neuronal firing in the ventrolateral thalamus of patients with Parkinson's disease differs from that with essential tremor. Chin Med J 2010;123:695-701.

Chu Chen C, Kuhn AA, Trottenberg T, Kupsch A, Schneider GH, Brown P. Neuronal activity in globus pallidus interna can be synchronized to local field potential activity over 3-12 Hz in patients with dystonia. Exp Neurol 2006;202:480-486.

Cohen LG, Starr A. Localization, timing and specificity of gating of somatosensory evoked potentials during active movement in man. Brain 1987;110:451-467.

Compta Y, Valls-Sole J, Valldeoriola F, Kumru H, Rumia J. The silent period of the thenar muscles to contralateral and ipsilateral deep brain stimulation. Clin Neurophys 2006;117:2512-2520.

Costa J, Valls-Sole J, Valldeoriola F, Pech C, Rumia J. Single subthalamic nucleus deep brain stimuli inhibit the blink reflex in Parkinson's disease patients. Brain 2006;129:1758-1767.

Costa J, Valls-Sole J, Valldeoriola F, Rumia J, Tolosa E. Motor responses of muscles supplied by cranial nerves to subthalamic nucleus deep brain stimuli. Brain 2007;130:245-255.

Costa J, Valls-Solé J, Valldeoriola F, Rumià J. Subcortical interactions between somatosensory stimuli of different modalities and their temporal profile. J Neurophysiol 2008;100:1610-1621.

Costa J, Guzmán J, Valldeoriola F, Rumià J, Tolosa E, Casanova-Molla J, Valls-Solé J. Modulation of the soleus H reflex by electrical subcortical stimuli in humans. Exp Brain Res 2011 (in press).

Cunic D, Roshan L, Khan FI, Lozano AM, Lang AE, Chen R. Effects of subthalamic nucleus stimulation on motor cortex excitability in Parkinson's disease. Neurology 2002;58:1665-1672.

Danish SF, Moyer JT, Finkel LH, Baltuch GH, Jaggi JL, Priori A, Foffani G. High-frequency oscillations (>200 Hz) in the human non-parkinsonian subthalamic nucleus. Brain Res Bull 2007;74:84-90.

Danish SF, Baltuch GH, Jaggi JL, Wong S. Determination of subthalamic nucleus location by quantitative analysis of despiked background neural activity from microelectrode recordings obtained during deep brain stimulation surgery. J Clin Neurophysiol 2008;25:98-103.

Deecke L. Clinical neurophysiology of Parkinson's disease. Bereitschaftspotential and contingent negative variation. Adv Neurol 2001;86:257-271.

Deletis V, Sala F. Intraoperative neurophysiological monitoring of the spinal cord during spinal cord and spine surgery: a review focus on the corticospinal tracts. Clin Neurophysiol 2008;119:248-264.

Delwaide PJ, Pepin JL, Maertens de Noordhout A. Short-latency autogenic inhibition in patients with Parkinsonian rigidity. Ann Neurol 1991;30:83-89.

Delwaide PJ, Pepin JL, Maertens de Noordhout A. The audiospinal reaction in Parkinsonian patients reflect functional changes in reticular nuclei. Ann Neurol 1993; 33: 63–9.

Devos D, Labyt E, Cassim F, Bourriez JL, Reyns N, Touzet G, Blond S, Guieu JD, Derambure P, Destée A, Defebvre L. Subthalamic stimulation influences postmovement cortical somatosensory processing in Parkinson's disease. Eur J Neurosci 2003;18:1884-1888.

Devos D, Labyt E, Derambure P, Bourriez JL, Cassim F, Reyns N, Blond S, Guieu JD, Destée A, Defebvre L. Subthalamic nucleus stimulation modulates motor cortex oscillatory activity in Parkinson's disease. Brain 2004;127:408-419.

Devos D, Szurhaj W, Reyns N, Labyt E, Houdayer E, Bourriez JL, Cassim F, Krystkowiak P, Blond S, Destée A, Derambure P, Defebvre L. Predominance of the contralateral movement-related activity in the subthalamo-cortical loop. Clin Neurophysiol 2006;117:2315-2327.

Di Lazzaro V, Pilato F, Oliviero A, Dileone M, Saturno E, Mazzone P, Insola A, Profice P, Ranieri F, Capone F, Tonali PA, Rothwell JC. Origin of facilitation of motor-evoked potentials after paired magnetic stimulation: direct recording of epidural activity in conscious humans. J Neurophysiol 2006;96:1765-771.

Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol 2000;84:570-574.

Fendt M, Li L, Yeomans JS. Brain stem circuits mediating prepulse inhibition of the startle reflex. Psychopharmacology 2001;156:216-224.

Filali M, Hutchison WD, Palter VN, Lozano AM, Dostrovsky JO. Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus. Exp Brain Res 2004;156:274-281.

Foffani G, Priori A, Egidi M, Rampini P, Tamma F, Caputo E et al. 300-Hz subthalamic oscillations in Parkinson's disease. Brain 2003;126:2153-2163.

Foffani G, Bianchi AM, Baselli G, Priori A. Movement-related frequency modulation of beta oscillatory activity in the human subthalamic nucleus. J Physiol 2005;568:699-711.

Foltynie T, Hariz MI. Surgical management of Parkinson's disease. Expert Rev Neurother 2010;10:903-914.

Fraix V, Pollak P, Vercueil L, Benabid AL, Mauguière F. Effects of subthalamic nucleus stimulation on motor cortex excitability in Parkinson's disease. Clin Neurophysiol. 2008;119:2513-2518.

Galati S, Scarnati E, Mazzone P, Stanzione P, Stefani A. Deep brain stimulation promotes excitation and inhibition in subthalamic nucleus in Parkinson's disease. Neuroreport 2008;19:661-666.

Gaynor LM, Kühn AA, Dileone M, Litvak V, Eusebio A, Pogosyan A, Androulidakis AG, Tisch S, Limousin P, Insola A, Mazzone P, Di Lazzaro V, Brown P. Suppression of beta oscillations in the subthalamic nucleus following cortical stimulation in humans. Eur J Neurosci. 2008;28:1686-1695.

Gerschlager W, Alesch F, Cunnington R, Deecke L, Dirnberger G, Endl W, Lindinger G, Lang W. Bilateral subthalamic nucleus stimulation improves frontal cortex function in Parkinson's disease. An electrophysiological study of the contingent negative variation. Brain 1999;122:2365-2373.

Giannicola G, Marceglia S, Rossi L, Mrakic-Sposta S, Rampini P, Tamma F, Cogiamanian F, Barbieri S, Priori A. The effects of levodopa and ongoing deep brain stimulation on subthalamic beta oscillations in Parkinson's disease. Exp Neurol 2010;226:120-127.

Grafton ST, Turner RS, Desmurget M, Bakay R, Delong M, Vitek J, Crutcher M. Normalizing motor-related brain activity: subthalamic nucleus stimulation in Parkinson disease. Neurology 2006;66:1192-1199.

Grunewald G, Grunewald-Zuberbier E, Schuhmacher H, Mewald J, Noth J. Somatosensory evoked potentials to mechanical disturbances of positioning movements in man: gating of middle-range components. Electroencephalogr Clin Neurophysiol 1984;58:525-536.

Guehl D, Edwards R, Cuny E, Burbaud P, Rougier A, Modolo J, Beuter A. Statistical determination of the optimal subthalamic nucleus stimulation site in patients with Parkinson disease. J Neurosurg 2007;106:101-110.

Hallett M. The neurophysiology of dystonia. Arch Neurol 1998;55:601-603.

Hanajima R, Chen R, Ashby P, Lozano AM, Hutchison WD, Davis KD, Dostrovsky JO. Very fast oscillations evoked by median nerve stimulation in the human thalamus and subthalamic nucleus. J Neurophysiol 2004a;92:3171-3182.

Hanajima R, Dostrovsky JO, Lozano AM, Hutchison WD, Davis KD, Chen R, Ashby P. Somatosensory evoked potentials (SEPs) recorded from deep brain stimulation (DBS) electrodes in the thalamus and subthalamic nucleus (STN). Clin Neurophysiol 2004b;115:424-434.

Hanajima R, Ashby P, Lozano AM, Lang AE, Chen R. Single pulse stimulation of the human subthalamic nucleus facilitates the motor cortex at short intervals. J Neurophysiol 2004c;92:1937-1943.

Herzog J, Hamel W, Wenzelburger R, Pötter M, Pinsker MO, Bartussek J, Morsnowski A, Steigerwald F, Deuschl G, Volkmann J. Kinematic analysis of thalamic versus subthalamic neurostimulation in postural and intention tremor. Brain 2007;130:1608-1625.

Herzog J, Weiss PH, Assmus A, Wefer B, Seif C, Braun PM, Pinsker MO, Herzog H, Volkmann J, Deuschl G, Fink GR. Improved sensory gating of urinary bladder

afferents in Parkinson's disease following subthalamic stimulation. Brain 2008;131:132-145.

Horikoshi T, Omata T, Uchida M, Asari Y, Nukui H. Usefulness and pitfalls of intraoperative spinal motor evoked potential recording by direct cortical electrical stimulation. Acta Neurochir 2000;142:257-262.

Hsieh CL, Shima F, Tobimatsu S, Sun SJ, Kato M. The interaction of the somatosensory evoked potentials to simultaneous finger stimuli in the human central nervous system. A study using direct recordings. Electroencephalogr Clin Neurophysiol 1995;96:135-142.

Hutchison WD, Levy R, Dostrovsky JO, Lozano AM, Lang AE. Effects of apomorphine on globus pallidus neurons in parkinsonian patients. Ann Neurol 1997;42:767-775.

Hutchison WD, Allan RJ, Opitz H, Levy R, Dostrovsky JO, Lang AE, Lozano AM. Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann Neurol 1998;44:622-628.

Hutchison WD, Lang AE, Dostrovsky JO, Lozano AM. Pallidal neuronal activity: implications for models of dystonia. Ann Neurol 2003;53:480-488.

Ince NF, Gupte A, Wichmann T, Ashe J, Henry T, Bebler M, Eberly L, Abosch A. Selection of optimal programming contacts based on local field potential recordings from subthalamic nucleus in patients with Parkinson's disease.Neurosurgery 2010;67:390-397.

Insola A, Le Pera D, Restuccia D, Mazzone P, Valeriani M. Reduction in amplitude of the subcortical low- and high-frequency somatosensory evoked potentials during voluntary movement: an intracerebral recording study. Clin Neurophysiol 2004;115:104-111.

Jech R, Urgosik D, Tintera J, Nebuzelsky A, Krasensky J, Liscak R, Roth J, Růzicka E. Functional magnetic resonance imaging during deep brain stimulation: a pilot study in four patients with Parkinson's disease. Mov Disord 2001;16:1126-1132.

Karimi M, Golchin N, Tabbal SD, Hershey T, Videen TO, Wu J, Usche JW, Revilla FJ, Hartlein JM, Wernle AR, Mink JW, Perlmutter JS. Subthalamic nucleus stimulation-induced regional blood flow responses correlate with improvement of motor signs in Parkinson disease. Brain 2008;131:2710-2719.

Kimura J. Disorder of interneurons in Parkinsonism. The orbicularis oculi reflex to paired stimuli. Brain 1973; 96: 87-96.

Kitagawa M, Murata J, Uesugi H, Hanajima R, Ugawa Y, Saito H. Characteristics and distribution of somatosensory evoked potentials in the subthalamic region. J Neurosurg 2007;107:548-554.

Klostermann F, Gobbele R, Buchner H, Curio G. Dissociation of human thalamic and cortical SEP gating as revealed by intrathalamic recordings under muscle relaxation. Brain Res 2002; 958: 146-151.

Klostermann F, Vesper J, Curio G. Identification of target areas for deep brain stimulation in human basal ganglia substructures based on median nerve sensory evoked potential criteria. J Neurol Neurosurg Psychiatry 2003;74:1031-1035.

Kobayashi K, Winberry J, Liu CC, Treede RD, Lenz FA.A painful cutaneous laser stimulus evokes responses from single neurons in the human thalamic principal somatic sensory nucleus ventral caudal (Vc). J Neurophysiol 2009;101:2210-2217.

Kovacs N, Balas I, Kellenyi L, Janszky J, Feldmann A, Llumiguano C, Doczi TP, Ajtay Z, Nagy F. The impact of bilateral subthalamic deep brain stimulation on long-latency event-related potentials. Parkinsonism Relat Disord 2008;14:476-480.

Kronenbuerger M, Tronnier VM, Gerwig M, Fromm C, Coenen VA, Reinacher P, Kiening KL, Noth J, Timmann D. Thalamic deep brain stimulation improves eyeblink conditioning deficits in essential tremor. Exp Neurol. 2008;211:387-396.

Kuhn AA, Meyer BU, Trottenberg T, Brandt SA, Schneider GH, Kupsch A. Modulation of motor cortex excitability by pallidal stimulation in patients with severe dystonia. Neurology 2003;60:768-774.

Kuhn AA, Brandt SA, Kupsch A, Trottenberg T, Brocke J, Irlbacher K et al. Meyer BU. Comparison of motor effects folllowing subcortical electrical stimulation through electrodes in the globus pallidus internus and cortical transcranial magnetic stimulation. Exp Brain Res 2004; 155: 48-55.

Kuhn AA, Trottenberg T, Kivi A, Kupsch A, Schneider GH, Brown P. The relationship between local field potential and neuronal discharge in the subthalamic nucleus of patients with Parkinson's disease. Exp Neurol 2005a;194:212-220.

Kuhn AA, Hariz MI, Silberstein P, Tisch S, Kupsch A, Schneider GH, Limousin-Dowsey P, Yarrow K, Brown P. Activation of the subthalamic region during emotional processing in Parkinson disease. Neurology 2005b;65:707-713.

Kuhn AA, Doyle L, Pogosyan A, Yarrow K, Kupsch A, Schneider GH, Schneider GH, Hariz MI, Trottenberg T, Brown P. Modulation of beta oscillations in the subthalamic area during motor imagery in Parkinson's disease. Brain 2006a;129:695-706.

Kuhn AA, Kupsch A, Schneider GH, Brown P. Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. Eur J Neurosci 2006b;23:1956-1960.

Kühn AA, Kempf F, Brücke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, Trottenberg T, Kupsch A, Schneider GH, Hariz MI, Vandenberghe W, Nuttin B, Brown P. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. J Neurosci 2008;28:6165-6173.

Kuriakose R, Saha U, Castillo G, Udupa K, Ni Z, Gunraj C, Mazzella F, Hamani C, Lang AE, Moro E, Lozano AM, Hodaie M, Chen R. The nature and time course of cortical activation following subthalamic stimulation in Parkinson's disease. Cereb Cortex 2010;20:1926-36.

Lafreniere-Roula M, Hutchison WD, Lozano AM, Hodaie M, Dostrovsky JO. Microstimulation-induced inhibition as a tool to aid targeting the ventral border of the subthalamic nucleus. J Neurosurg 2009;111:724-728.

Lafreniere-Roula M, Kim E, Hutchison WD, Lozano AM, Hodaie M, Dostrovsky JO. High-frequency microstimulation in human globus pallidus and substantia nigra. Exp Brain Res 2010;205:251-261.

Lalo E, Thobois S, Sharott A, Polo G, Mertens P, Pogosyan A, Brown P. Patterns of bidirectional communication between cortex and basal ganglia during movement in patients with Parkinson disease. J Neurosci. 2008;28:3008-3016.

Lanotte MM, Rizzone M, Bergamasco B, Faccani G, Melcarne A, Lopiano L. Deep brain stimulation of the subthalamic nucleus: anatomical, neurophysiological, and

outcome correlations with the effects of stimulation. J Neurol Neurosurg Psychiatry 2002;72:53-58.

Lee JI, Verhagen Metman L, Ohara S, Dougherty PM, Kim JH, Lenz FA. Internal pallidal neuronal activity during mild drug-related dyskinesias in Parkinson's Disease: decreased firing rates and altered firing patterns. J Neurophysiol 2007;97:2627-2641.

Levy R, Dostrovsky JO, Lang AE, Sime E, Hutchison WD, Lozano AM. Effects of apomorphine on subthalamic nucleus and globus pallidus internus neurons in patients with Parkinson's disease. J Neurophysiol 2001;86:249-260.

Levy R, Hutchison WD, Lozano AM, Dostrovsky JO. Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. J Neurosci 2002;22:2855-2861.

Limousin P, Martinez-Torres I. Deep brain stimulation for Parkinson's disease. Neurotherapeutics 2008;5:309-319.

Liu X, Aziz TZ, Bain PG. Intraoperative monitoring of motor symptoms using surface electromyography during stereotactic surgery for movement disorders. J Clin Neurophysiol 2005;22:183-191.

Liu X, Yianni J, Wang S, Bain PG, Stein JF, Aziz TZ. Different mechanisms may generate sustained hypertonic and rhythmic bursting muscle activity in idiopathic dystonia. Exp Neurol 2006;198:204-213.

Lozano AM, Snyder BJ. Deep brain stimulation for parkinsonian gait disorders. J Neurol. 2008;255 Suppl 4:30-31.

MacKinnon CD, Webb RM, Silberstein P, Tisch S, Asselman P, Limousin P, Rothwell JC. Stimulation through electrodes implanted near the subthalamic nucleus activates projections to motor areas of cerebral cortex in patients with Parkinson's disease. Eur J Neurosci 2005; 21: 1394-1402.

Magnani G, Cursi M, Leocani L, Volonte MA, Locatelli T, Elia A, Comi G. Event-related desynchronization to contingent negative variation and self-paced movement paradigms in Parkinson's disease. Mov Disord 1998;13:653-660.

Maks CB, Butson CR, Walter BL, Vitek JL, McIntyre CC. Deep brain stimulation activation volumes and their association with neurophysiological mapping and therapeutic outcomes. J Neurol Neurosurg Psychiatry 2009;80:659-66.

Marceglia S, Foffani G, Bianchi AM, Baselli G, Tamma F, Egidi M, Priori A. Dopamine-dependent non-linear correlation between subthalamic rhythms in Parkinson's disease. J Physiol 2006;571:579-591.

Marceglia S, Servello D, Foffani G, Porta M, Sassi M, Mrakic-Sposta S, Rosa M, Barbieri S, Priori A. Thalamic single-unit and local field potential activity in Tourette syndrome. Mov Disord. 2010;25:300-308.

Maurice N, Thierry AM, Glowinski J, Deniau JM. Spontaneous and evoked activity of substantia nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. J Neurosci 2003;23:9929-9936.

McIntyre CC, Mori S, Sherman DL, Thakor NV, Vitek JL. Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. Clin Neurophysiol 2004;115:589-595.

Miyagi Y, Okamoto T, Morioka T, Tobimatsu S, Nakanishi Y, Aihara K, Hashiguchi K, Murakami N, Yoshida F, Samura K, Nagata S, Sasaki T. Spectral analysis of field potential recordings by deep brain stimulation electrode for localization of

subthalamic nucleus in patients with Parkinson's disease. Stereotact Funct Neurosurg 2009;87:211-218.

Molinuevo JL, Valldeoriola F, Valls-Solé J. Usefulness of neurophysiologic techniques in stereotactic subthalamic nucleus stimulation for advanced Parkinson's disease. Clinical Neurophysiology 2003;114:1793-1799.

Montgomery EB Jr. Effects of GPi stimulation on human thalamic neuronal activity. Clin Neurophysiol 2006; 117: 2691-2702.

Morecraft RJ, Louie JL, Herrick JL, Stilwell-Morecraft KS. Cortical innervation of the facial nucleus in the non-human primate: a new interpretation of the effects of stroke and related subtotal brain trauma on the muscles of facial expression. Brain 2001;124: 176–208.

Mrakic-Sposta S, Marceglia S, Egidi M, Carrabba G, Rampini P, Locatelli M, Foffani G, Accolla E, Cogiamanian F, Tamma F, Barbieri S, Priori A. Extracellular spike microrecordings from the subthalamic area in Parkinson's disease. J Clin Neurosci 2008;15:559-567.

Nakajima T, Endoh T, Sakamoto M, Komiyama T. Nerve specific modulation of somatosensory inflow to cerebral cortex during submaximal sustained contraction in first dorsal interosseous muscle. Brain Res 2005;1053:146-53.

Novak P, Klemp JA, Ridings LW, Lyons KE, Pahwa R, Nazzaro JM. Effect of deep brain stimulation of the subthalamic nucleus upon the contralateral subthalamic nucleus in Parkinson disease. Neurosci Lett 2009;463:12-16.

Nowak LG, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter I. Evidence from chronaxie measurements. Exp Brain Res 1998;118: 477–88.

Pahapill PA, Lozano AM. The pedunculopontine nucleus and Parkinson's disease. Brain 2000; 123: 1767-1783.

Paradiso G, Saint-Cyr JA, Lozano AM, Lang AE, Chen R. Involvement of the human subthalamic nucleus in movement preparation. Neurology 2003;61:1538-1545.

Payoux P, Remy P, Damier P, Miloudi M, Loubinoux I, Pidoux B, Gaura V, Rascol O, Samson Y, Agid Y. Subthalamic nucleus stimulation reduces abnormal motor cortical overactivity in Parkinson disease. Arch Neurol 2004;61:1307-1313.

Payoux P, Remy P, Miloudi M, Houeto JL, Stadler C, Bejjani BP, Yelnik J, Samson Y, Rascol O, Agid Y, Damier P. Contrasting changes in cortical activation induced by acute high-frequency stimulation within the globus pallidus in Parkinson's disease. J Cereb Blood Flow Metab 2009;29:235-243.

Penfield W, Jasper HH. Epilepsy and the functional anatomy of the human brain. Boston: Little Brown, 1954.

Perlmutter JS, Mink JW, Bastian AJ, Zackowski K, Hershey T, Miyawaki E, Koller W, Videen TO. Blood flow responses to deep brain stimulation of thalamus. Neurology 2002;58:1388-1394.

Pesenti A, Priori A, Locatelli M, Egidi M, Rampini P, Tamma F, Caputo E, Chiesa V, Barbieri S. Subthalamic somatosensory evoked potentials in Parkinson's disease. Mov Disord 2003;18:1341-1345.

Pierantozzi M, Palmieri MG, Mazzone P, Marciani MG, Rossini PM, Stefani A, Giacomini P, Peppe A, Stanzione P. Deep brain stimulation of both subthalamic nucleus and internal globus pallidus restores intracortical inhibition in Parkinson's disease

paralleling apomorphine effects: a paired magnetic stimulation study. Clin Neurophysiol 2002;113:108-113.

Potter M, Illert M, Wenzelburger R, Deuschl G, Volkmann J. The effect of subthalamic nucleus stimulation on autogenic inhibition in Parkinson disease. Neurology 2004;63:1234-1239.

Pötter M, Herzog J, Siebner HR, Kopper F, Steigerwald F, Deuschl G, Volkmann J. Subthalamic nucleus stimulation modulates audiospinal reactions in Parkinson disease. Neurology. 2008;70:1445-1451.

Pötter-Nerger M, Ilic TV, Siebner HR, Deuschl G, Volkmann J. Subthalamic nucleus stimulation restores corticospinal facilitation in Parkinson's disease. Mov Disord 2008;23:2210-2215.

Pralong E, Pollo C, Coubes P, Bloch J, Roulet E, Tetreault MH, Debatisse D, Villemure JG. Electrophysiological characteristics of limbic and motor globus pallidus internus (GPI) neurons in two cases of Lesch-Nyhan syndrome. Neurophysiol Clin 2005;35:168-173.

Pralong E, Pollo C, Villemure JG, Debatisse D. Opposite effects of internal globus pallidus stimulation on pallidal neurones activity. Mov Disord 2007;22:1879-1884.

Priori A, Foffani G, Pesenti A, Tamma F, Bianchi AM, Pellegrini M, Locatelli M, Moxon KA, Villani RM. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. Exp Neurol 2004;189:369-379.

Priori A, Ardolino G, Marceglia S, Mrakic-Sposta S, Locatelli M, Tamma F, Rossi L, Foffani G. Low-frequency subthalamic oscillations increase after deep brain stimulation in Parkinson's disease. Brain Res Bull 2006;71:149-154.

Purzner J, Paradiso GO, Cunic D, Saint-Cyr JA, Hoque T, Lozano AM, Lang AE, Moro E, Hodaie M, Mazzella F, Chen R. Involvement of the basal ganglia and cerebellar motor pathways in the preparation of self-initiated and externally triggered movements in humans. J Neurosci 2007;27:6029-6036.

Quartarone A, Bagnato S, Rizzo V, Siebner HR, Dattola V, Scalfari A, Morgante F, Battaglia F, Romano M, Girlanda P. Abnormal associative plasticity of the human motor cortex in writer's cramp. Brain 2003; 126, 2586–2596.

Rainov NG, Fels C, Heidecke V, Burkert W. Epidural electrical stimulation of the motor cortex in patients with facial neuralgia. Clin Neurol Neurosurg 1997;99:205-209.

Ridding MC, Sheean G, Rothwell JC, Inzelberg R, Kujirai T. Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. J Neurol Neurosurg Psychiatry 1995; 59: 493-498

Rodriguez-Oroz MC, Rodriguez M, Guridi J, Mewes K, Chockkman V, Vitek J, DeLong MR, Obeso JA. The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics. Brain 2001;124:1777-1790.

Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S, Kulisevsky J, Albanese A, Volkmann J, Hariz MI, Quinn NP, Speelman JD, Guridi J, Zamarbide I, Gironell A, Molet J, Pascual-Sedano B, Pidoux B, Bonnet AM, Agid Y, Xie J, Benabid AL, Lozano AM, Saint-Cyr J, Romito L, Contarino MF, Scerrati M, Fraix V, Van Blercom N. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. Brain 2005;128:2240-2249.

Rossini PM, Filippi MM, Vernieri F. Neurophysiology of sensorimotor integration in Parkinson's disease. Clin Neurosci 1998;5:121-130.

Sailer A, Cunic DI, Paradiso GO, Gunraj CA, Wagle-Shukla A, Moro E, Lozano AM, Lang AE, Chen R. Subthalamic nucleus stimulation modulates afferent inhibition in Parkinson disease. Neurology 2007;68:356-363.

Saint-Cyr JA, Hoque T, Pereira LC, Dostrovsky JO, Hutchison WD, Mikulis DJ, Abosch A, Sime E, Lang AE, Lozano AM. Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging. J Neurosurg 2002;97:1152-1166.

Sanghera MK, Grossman RG, Kalhorn CG, Hamilton WJ, Ondo WG, Jankovic J. Basal ganglia neuronal discharge in primary and secondary dystonia in patients undergoing pallidotomy. Neurosurgery 2003;52:1358-1370.

Sani S, Ostrem JL, Shimamoto S, Levesque N, Starr PA. Single unit "pauser" characteristics of the globus pallidus pars externa distinguish primary dystonia from secondary dystonia and Parkinson's disease. Exp Neurol 2009;216:295-299.

Sauleau P, Eusebio A, Thevathasan W, Yarrow K, Pogosyan A, Zrinzo L, Ashkan K, Aziz T, Vandenberghe W, Nuttin B, Brown P. Involvement of the subthalamic nucleus in engagement with behaviourally relevant stimuli. Eur J Neurosci 2009;29:931-942.

Schaltenbrand G, Wahren W. Atlas for stereotaxy of the human brain. 2nd ed. Stuttgart, Germany. Thieme Medical Publishers, 1977.

Schicatano EJ, Peshori KR, Gopalaswamy R, Sahay E, Evinger C. Reflex excitability regulates prepulse inhibition. J Neurosci 2000;20:4240-4247.

Schmidt RF, Torebjork HE, Schady WJ. Gating of tactile input from the hand. II. Effects of remote movements and anaesthesia. Exp Brain Res 1990;79:103-108.

Schrock LE, Ostrem JL, Turner RS, Shimamoto SA, Starr PA. The subthalamic nucleus in primary dystonia: single-unit discharge characteristics. J Neurophysiol 2009;102:3740-3752.

Shimamoto SA, Larson PS, Ostrem JL, Glass GA, Turner RS, Starr PA. Physiological identification of the human pedunculopontine nucleus. J Neurol Neurosurg Psychiatry 2010;81:80-86.

Silberstein P, Kuhn AA, Kupsch A, Trottenberg T, Krauss JK, Wohrle JC, Mazzone P, Insola A, Di Lazzaro V, Oliviero A, Aziz T, Brown P. Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. Brain 2003;126:2597-2608.

Snellings A, Sagher O, Anderson DJ, Aldridge JW. Identification of the subthalamic nucleus in deep brain stimulation surgery with a novel wavelet-derived measure of neural background activity. J Neurosurg 2009;111:767-774.

Starr PA, Christine CW, Theodosopoulos PV, Lindsey N, Byrd D, Mosley A et al. Implantation of deep brain stimulators into the subthalamic nucleus: technical approach and magnetic resonance imaging-verified lead locations. J Neurosurg 2002;97:370-387.

Sterio D, Zonenshayn M, Mogilner AY, Rezai AR, Kiprovski K, Kelly PJ, Beric A. Neurophysiological refinement of subthalamic nucleus targeting. Neurosurgery 2002a;50:58-67.

Sterio D, Rezai A, Mogilner A, Zonenshayn M, Gracies JM, Kathirithamby K, Berić A. Neurophysiological modulation of the subthalamic nucleus by pallidal stimulation in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002b;72:325-328.

Strafella A, Ashby P, Munz M, Dostrovsky JO, Lozano AM, Lang AE. Inhibition of voluntary activity by thalamic stimulation in humans: Relevance for the control of tremor. Mov Disord 1997;12:727-737.

Strafella AP, Dagher A, Sadikot AF. Cerebral blood flow changes induced by subthalamic stimulation in Parkinson's disease. Neurology 2003;60:1039-1042.

Swerdlow NR, Geyer MA, Braff DL. Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. Psychopharmacology 2001;156:194-215.

Tang JK, Moro E, Mahant N, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Neuronal firing rates and patterns in the globus pallidus internus of patients with cervical dystonia differ from those with Parkinson's disease. J Neurophysiol 2007;98:720-729.

Thobois S, Dominey P, Fraix V, Mertens P, Guenot M, Zimmer L, Pollak P, Benabid AL, Broussolle E. Effects of subthalamic nucleus stimulation on actual and imagined movement in Parkinson's disease: a PET study. J Neurol 2002;249:1689-1698.

Tisch S, Limousin P, Rothwell JC, Asselman P, Quinn N, Jahanshahi M, Bhatia KP, Hariz M. Changes in blink reflex excitability after globus pallidus internus stimulation for dystonia. Mov Disord 2006a;21:1650-1655.

Tisch S, Limousin P, Rothwell JC, Asselman P, Zrinzo L, Jahanshahi M, Bhatia KP, Hariz MI. Changes in forearm reciprocal inhibition following pallidal stimulation for dystonia. Neurology 2006b;66:1091-1093.

Tisch S, Rothwell JC, Bhatia KP, Quinn N, Zrinzo L, Jahanshahi M, Ashkan K, Hariz M, Limousin P. Pallidal stimulation modifies after-effects of paired associative stimulation on motor cortex excitability in primary generalised dystonia. Exp Neurol 2007;206:80-85.

Tornqvist AL, Schalen L, Rehncrona S. Effects of different electrical parameter settings on the intelligibility of speech in patients with Parkinson's disease treated with subthalamic deep brain stimulation. Mov Disord 2005;20:416-423.

Vafaee MS, OStergaard K, Sunde N, Gjedde A, Dupont E, Cumming P. Focal changes of oxygen consumption in cerebral cortex of patients with Parkinson's disease during subthalamic stimulation. Neuroimage 2004;22:966-974.

Valeriani M, Insola A, Restuccia D, Le Pera D, Mazzone P, Altibrandi MG, Tonali P. Source generators of the early somatosensory evoked potentials to tibial nerve stimulation: an intracerebral and scalp recording study. Clin Neurophysiol 2001;112:1999-2006.

Valeriani M, Truini A, Le Pera D, Insola A, Galeotti F, Petrachi C, Mazzone P, Cruccu G. Laser evoked potential recording from intracerebral deep electrodes. Clin Neurophysiol 2009;120:790-795.

Valls-Sole J, Valldeoriola F. Neurophysiological correlate of clinical signs in Parkinson's disease. Clin Neurophysiol 2002;113:792-805.

Valls-Sole J, Munoz JE, Valldeoriola. Abnormalities of prepulse inhibition do not depend on blink reflex excitability: a study in Parkinson's disease and Huntington's disease. Clinical Neurophysiology 2004;115:1527–1536.

Valls-Solé J, Compta Y, Costa J, Valldeoriola F, Rumià J. Human central nervous system circuits examined through the electrodes implanted for deep brain stimulation. Clin Neurophysiol 2008;119:1219-31.

Vitek JL, Chockkan V, Zhang JY, Kaneoke Y, Evatt M, DeLong MR et al, Mewes K, Hashimoto T, Bakay RAE. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. Ann Neurol 1999; 46:22-35.

Voges J, Volkmann J, Allert N, Lehrke R, Koulousakis A, Freund HJ, Sturm V. Bilateral high frequency stimulation in the subthalamic nucleus for the treatment of Parkinson's disease: correlation of therapeutic effect with anatomical electrode position. J Neurosurg 2002; 96:269-279.

Weinberger M, Mahant N, Hutchison WD, Lozano AM, Moro E, Hodaie M, Lang AE, Dostrovsky JO. Beta oscillatory activity in the subthalamic nucleus and its relation to dopaminergic response in Parkinson's disease. J Neurophysiol 2006;96:3248-3256.

Weinberger M, Hamani C, Hutchison WD, Moro E, Lozano AM, Dostrovsky JO. Pedunculopontine nucleus microelectrode recordings in movement disorder patients. Exp Brain Res 2008;188:165-174.

Weinberger M, Hutchison WD, Lozano AM, Hodaie M, Dostrovsky JO. Increased gamma oscillatory activity in the subthalamic nucleus during tremor in Parkinson's disease patients. J Neurophysiol 2009;101:789-802.

Welter ML, Houeto JL, Bonnet AM, Bejjani PB, Mesnage V, Dormont D, Navarro S, Cornu P, Agid Y, Pidoux B. Effects of high-frequency stimulation on subthalamic neuronal activity in parkinsonian patients. Arch Neurol 2004;61:89-96.

Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol 1996; 6:751-758.

Williams D, Tijssen M, Van Bruggen G, Bosch A, Insola A, Di Lazzaro V, Mazzone P, Oliviero A, Quartarone A, Speelman H, Brown P. Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. Brain 2002;125:1558-1569.

Wingeier B, Tcheng T, Koop MM, Hill BC, Heit G, Bronte-Stewart HM. Intra-operative STN DBS attenuates the prominent beta rhythm in the STN in Parkinson's disease. Exp Neurol 2006;197:244-251.

Woolsey CN, Erickson TC, Gilson WE. Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. J Neurosurg 1979;51:476-506.

Yugeta A, Terao Y, Fukuda H, Hikosaka O, Yokochi F, Okiyama R, Taniguchi M, Takahashi H, Hamada I, Hanajima R, Ugawa Y. Effects of STN stimulation on the initiation and inhibition of saccade in Parkinson disease. Neurology 2010;74:743-748.

Zaidel A, Spivak A, Grieb B, Bergman H, Israel Z. Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. Brain 2010;133:2007-2021.

Zhuang P, Hallett M, Zhang X, Li J, Zhang Y, Li Y. Neuronal activity in the globus pallidus internus in patients with tics. J Neurol Neurosurg Psychiatry 2009;80:1075-1081.

22

Estimation of Electrode Position with Fused Images of Preoperative MRI and Postoperative CT Using the Mutual Information Technique After STN DBS in Patients with Advanced Parkinson's Disease

Sun Ha Paek
Movement Disorder Center, Department of Neurosurgery, Seoul National University Hospital, Seoul National University College of Medicine, South Korea

1. Introduction

Since the introduction of deep brain stimulation (DBS) by Benabid and colleagues in 1987, this technique has become the preferred treatment for patients with various movement disorders including Parkinson's disease (Benabid et al., 1987). Patients with advanced Parkinson's disease (PD) who have intolerable drug-induced side effects or motor complications following the long-term use of dopaminergic drugs have shown significant improvement in symptoms such as motor fluctuation and dyskinesia following subthalamic nucleus (STN) deep brain stimulation (DBS), facilitating reductions in dosages of levodopa (Limousin et al., 1998). Significant improvements in motor function have been documented in both short-term and long-term periods (Krack et al., 2003; Benabid et al., 2005; Lyons & Pahwa, 2005; Rodriguez-Oroz et al., 2005; Deuschl et al., 2006; Kleiner-Fisman et al., 2006; Tsai et al., 2009). However, variable improvement of symptoms has been observed after STN DBS even in well-selected patients with advanced PD (Paek et al., 2008). Such individual variation was not predictable before surgery and its cause is not obvious. Differences in the extent of disease progression or constitutional differences in response to STN DBS might lead to such variation; alternatively, it might be caused by differences in the accuracy of electrode positioning in relation to the STN.

The precise positioning of the electrodes in the STN is considered an important factor in achieving good clinical outcome following STN DBS. To achieve precise targeting of electrodes, many approaches have been taken; these include direct targeting based on fused images of CT-MRI, MRI-MRI, and MRI-brain atlas, as well as intra-operative microelectrode recording and intra-operative stimulation (Bejjani et al., 2000; Benazzou et al., 2002; Hamid et al., 2005; Godinho et al., 2006; Cho et al., 2010). However, many unexpected factors, such as possible brain shift due to CSF leakage, electrode artifacts in the MRI, and error in the manipulation of instruments, make it difficult to precisely position electrodes in the center of the STN (Martinez-Santiesteban et al., 2007; Miyagi et al., 2007; Halpern et al., 2008; Khan et al., 2008). Thus, following surgery, not all patients have electrodes positioned exactly in

the STN. This might lead to different clinical outcomes following STN DBS in advanced PD patients. However, the existing literature contains few reports on the possible correlation between clinical outcome and electrode position confirmed at a stable period after bilateral STN stimulation.

The foregoing considerations suggest that it is necessary to determine the exact location of DBS electrodes after surgery in order to accurately predict clinical outcomes and to program appropriate stimulation parameters for STN DBS. The Movement Disorder Center of Seoul National University Hospital (SNUH MDC) was launched in March, 2005; at that time, DBS began to be covered by the National Health Insurance system in Korea. During the past six years, we have systematically approached the analysis of clinical outcome in terms of electrode position after bilateral STN stimulation (Heo et al., 2008; Kim et al., 2008a; Kim et al., 2008b; Lee et al., 2008; Kim et al., 2009; Kim et al., 2010; Lee et al., 2010a; Lee et al., 2010b; Paek et al., 2010).

In this chapter, I would like to briefly touch on these issues based on a review of the literature as well as on our own experience. I would also like to introduce the DBS Electrode Localization Analysis System (DELAS), an internet on-line service to estimate electrode positions with fused images of pre-operative MRI and post-operative CT using mutual information technique following STN DBS surgery in patients with advanced Parkinson's disease.

2. Image fusion using the mutual information technique and plotting of electrode positions with reference to the human brain atlas of Schaltenbrand and Wahren

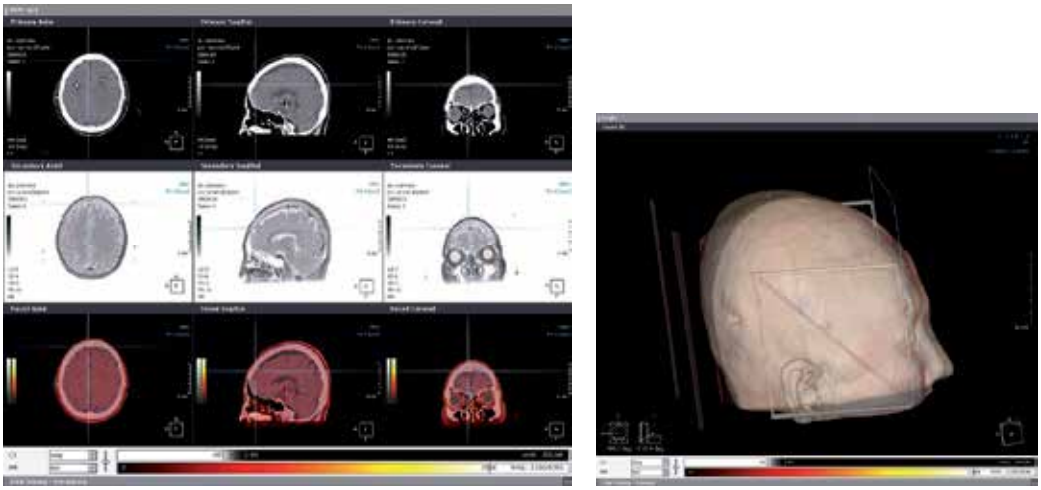
2.1 Image-to-image registration using the mutual information technique

The mutual information technique is a commonly used image registration technique (Wells et al., 1996; Christensen et al., 1997; Maes et al., 1997). Fig. 1 (Lucion, Cybermed Inc., Korea) shows an instance of accurate registration between CT and MR images. The first image was obtained by preoperative MRI and the second by postoperative CT. The process of image-to-image registration using the mutual information technique can be briefly described as follows. Consider the 2D histogram of 3D images A and B for a given transform T between the two images: if the images have their discrete values m and n in [0…M], the 2D histogram is a function h(m,n) from [0…M]x[0…N] to ln that associates every pair of image values (m,n) with the number of occurrences in which image A equals n at the same spatial point x in 3D (for the given transform T, the number of such occurrences depends on parameters p:m=a(x) and n=B(T(x)). If we consider 3D images A and B to be from the same modality, then when the images are registered, the histogram h(m,n) is an array that has accumulation points on the line m=n. These accumulation points are therefore very concentrated.

A possible way to characterize the complexity of a 2D histogram is to consider entropy. Entropy, e(p), is minimal when the histogram is concentrated on very few accumulation points. It is given by the following equation:

$$e(p) = -\int P(m,n)\ln(P(m,n))dm\,dn \tag{1}$$

When images are registered, the entropy will be minimized. Equation 1.1 is now replaced by the expression of mutual information, which has to be maximized, as follows:



(a) (b)

Fig. 1. Registration of multimodality images using entropy-based methods. (a) The different CT slices are shown with the edges of the registered and reformatted MR data overlaid. (b) A rendering of the 3D models constructed from different MR acquisitions that were registered together: anatomic information (the skin, the brain, the vessels, the ventricles) was generated from the post-contrast gradient echo (SPGR) MR images.

$$h(m,n) = -\int_S P(m)\ln(P(m))dm - \int_S P(n)\ln(P(n))dn + \int P(m,n)\ln(P(m,n))dm\,dn \quad (2)$$

The method of Wells et al. (1996) implements this principle very efficiently. In practice, images do not need to be of the same modality; they merely need to "look similar." Obviously, there are some limitations to the method and many aspects remain to be explored; however, the technique has yielded very efficient results in a variety of instances (Pluim et al., 2003).

2.1.1 Calculation of mutual information (MI)

Calculation of MI is performed by employing formula (3) below. First, we need to obtain the mutual histogram, ***g(a,b)***, of two volumetric images; then, by using the following equation, the normalized mutual information is obtained. As the optimization procedure proceeds, the value of MI gradually decreases. The optimization procedure terminates when the change in the MI value is below a threshold,

$$MI = \sum_{a,b} p_{u,v}(a,b)\log_2 \frac{p_{uv}(a,b)}{p_u(a)p_v(b)}, \text{ where}$$

$$p_u(x) = \sum_b p_{uv}(x,b),\ p_v(y) = \sum_a p_{uv}(a,y), \text{ and } p_{uv}(x,y) = \frac{g(x,y)}{\sum_{a,b} g(a,b)}. \quad (3)$$

In this equation, ***g(a,b)*** represents the mutual histogram, ***x*** represents the intensity index of the primary image, and ***y*** represents the intensity index of the secondary image.

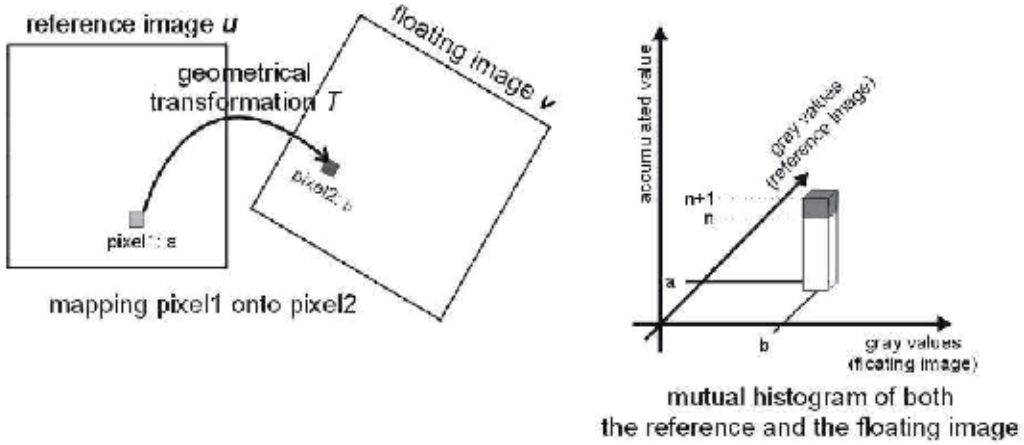


Fig. 2. Mutual histogram of two different images.

When the final screw vector is obtained, we can register the two volumetric images by applying the transformation to the secondary volume.

2.2 Image fusion of preoperative brain MRI and postoperative brain CT/MRI images and plotting of electrode positions with reference to the human brain atlas

Image fusions are performed using the mutual information technique with the preoperative brain MRI and the brain CT/MRI images taken after STN DBS. Window level and width are adjusted to best visualize the STN in the T2-weighted MRI and to best visualize the electrodes in the CT/MRI. The preoperative T2-weighted axial images are fused with the postoperative 3-D spiral CT scan images or T2-weighted axial images at the data set of 1-mm thickness reformatted images, aligned to the anterior commissure-posterior commissure

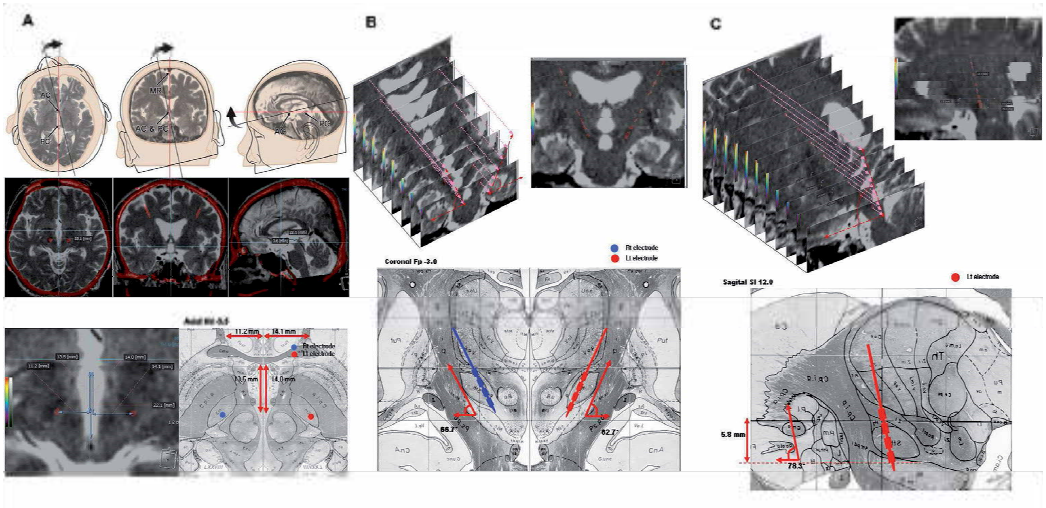


Fig. 3. Image fusion of preoperative MRI and postoperative brain CT.

(AC-PC) line. For the correction of head-rotation error, the midline of the reformatted coronal images is positioned to intersect the midsagittal plane. The length of the AC-PC line and the width of the third ventricle are taken into consideration for the proportional localization of electrode position with reference to the human brain atlas of Schaltenbrandt and Wahren (1998). In the reformatted axial images, the lateral distance from the midline and the antero-posterior distance from the mid-commissural line to each electrode are measured (Fig 3-A). In the reformatted coronal images in which the electrode trajectory is best visualized, the lateral angles of the electrode trajectory from the midline are measured for each electrode in every patient (Fig 3-B). In the reformatted sagittal images in which the electrode trajectory is best shown, the antero-posterior angle of the electrode trajectory from the line perpendicular to the AC-PC line and the depth of the electrodes are also measured for each electrode in every patient (Fig 3-C).

3. Comparison study of estimated electrode locations obtained using various image fusion techniques

3.1 Comparison study of CT and MRI for the localization of electrodes following subthalamic nucleus deep brain stimulation

Despite the wide use of MRI in stereotactic neurosurgical procedures, the potential for distortion of normal anatomical structures in MRI in comparison with brain CT scans has been noted. Several studies focused on the reliability of MRI in target localization and concluded that though some differences were identified, they were not significant and that MRI alone may be used for target localization (Kondziolka et al., 1992; Holtzheimer et al., 1999). Relatively less attention has been paid to the accuracy of MRI in localization of electrode position, and the results have been controversial. However, by calculating magnetic field perturbations using a Fourier-based method for various wire microelectrodes, one study showed that significant artifact is produced depending on the magnetic susceptibility of the material used and on the size, shape, and orientation of the electrodes with respect to the primary magnetic field (Martinez-Santiesteban et al., 2007). This study concluded that the platinum–iridium microwire commonly used for DBS shows a complete signal loss that covers a volume 400 times larger than the actual volume occupied by the microelectrode. Thus, artifacts caused by electrode interference with local magnetic fields can make it difficult to precisely localize the center of the electrodes in MRI.

We found that there is a considerable difference in the estimated electrode position obtained using postoperative CT and that obtained using MRI. Figure 4 shows fused images of a brain CT and a brain MRI from one patient, both taken 6 months after bilateral subthalamic stimulation. The fused images obtained from the MRI and the CT are aligned along the AC-PC line at the level of the AC and the PC in the axial, sagittal, and coronal planes. The red signal represents the position of the electrode extracted from brain CT images obtained six months after surgery, and the gray signal represents the position of the electrode extracted from brain MRI images obtained six months after surgery. The centers of the red and gray areas, representing the center of the electrode as extracted from brain CT and brain MRI images, respectively, do not coincide but instead show significant discrepancy in their positions in the axial, coronal, and sagittal planes of the fused images (Fig 4-A). With the adjustment of window level and width of the fused images, only the electrodes in red color are superimposed in 3-D reconstructive rendering brain MR images of the superior anterior view (Fig 4-B), the left anterior superior oblique view (Fig 4-C), and the anterior posterior view (Fig 4-D). The discrepancy in the electrode position extracted

from the brain CT and the center of the electrode artifact from the brain MRI taken 6 months after surgery is remarkable in all three (axial, sagittal, and coronal) planes.

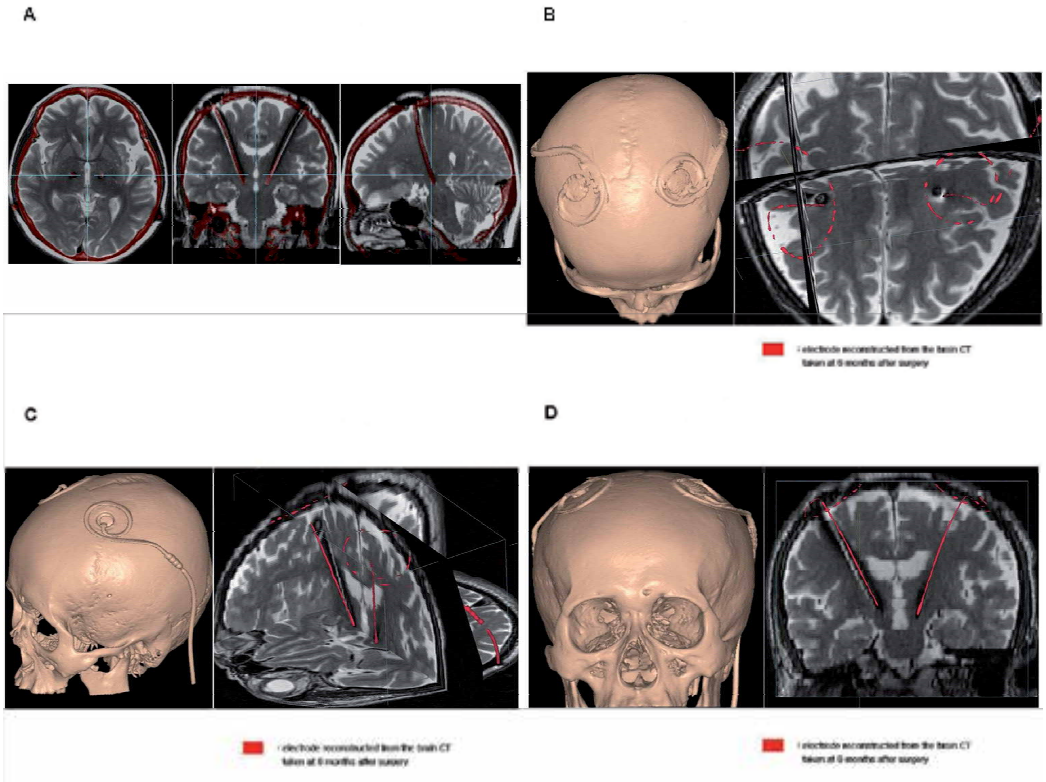


Fig. 4. Fused images of brain CT and brain MRI, both taken 6 months after bilateral subthalamic nucleus stimulation.

To validate the accuracy of MRI in electrode localization in comparison with CT scanning, we compared the X-, Y-, and Z- coordinates of the centers of the electrodes estimated by MRI and CT in 61 patients who received both MRI and CT at least six months after bilateral STN DBS (Lee et al., 2010b). The x- and y-coordinates of the centers of the electrodes shown by CT and MRI were compared in the fused images, and the average difference at five different levels was calculated. The difference in the location of the tips of the electrodes, designated as the z coordinate, was also calculated.

The average distance between the centers of the electrodes in the five levels estimated in the fused images of brain CT and MRI taken at least 6 months after STN DBS was 1.33 mm (0.1–5.8 mm). The average discrepancy of the x coordinates for all five levels between MRI and CT was 0.56±0.54 mm (0–5.7 mm); the discrepancy of the y coordinates was 1.06±0.59 mm (0–3.5 mm) and that of the z coordinates was 0.98±0.52 mm (0–3.1 mm) (all p values <0.001). Notably, the average discrepancy of x coordinates at 3.5 mm below the AC–PC level, i.e., at the level of the STN, was 0.59±0.42 mm (0–2.4) between MRI and CT; the discrepancy of the y coordinates at this level was 0.81±0.47 mm (0–2.9) (p values<0.001). It is suggested that the electrode location evaluated by postoperative MRI may show significant discrepancy with that estimated by brain CT scan.

3.2 Comparison of electrode location measured on the immediate postoperative day and six months after bilateral STN DBS

Despite the wide use of brain CT scans during and immediately after DBS surgery, unexpected circumstances during surgery, such as electrode bending and possible brain shift due to CSF leakage, have not been seriously considered in the estimation of electrode position using brain CT in the immediate postoperative period after DBS surgeries. One study, which used brain CT to evaluate and correct geometrical error due to brain shift during stereotactic brain surgery (van den Munckhof et al., 2010), showed that the stereotactically implanted DBS electrodes were displaced in an upward direction with time and that this displacement was significantly correlated with the amount of air in the subdural space. This study calculated the displacement of the electrode on the fusion image of preoperative and postoperative images. However, the fiducial points for the fusion of different images were not associated with brain structures but with the skull. The migration of metallic material in the parenchyma of the central nervous system has also been reported (Ott et al., 1976; Sorensen & Krauss, 1991). We observed considerable brain shift when comparing immediate postoperative CT scans and CT scans taken 6 months after surgery. We also found considerable discrepancy in the apparent electrode position on immediate postoperative CT scans and brain CT scans taken 6 months after surgery (Fig. 5).

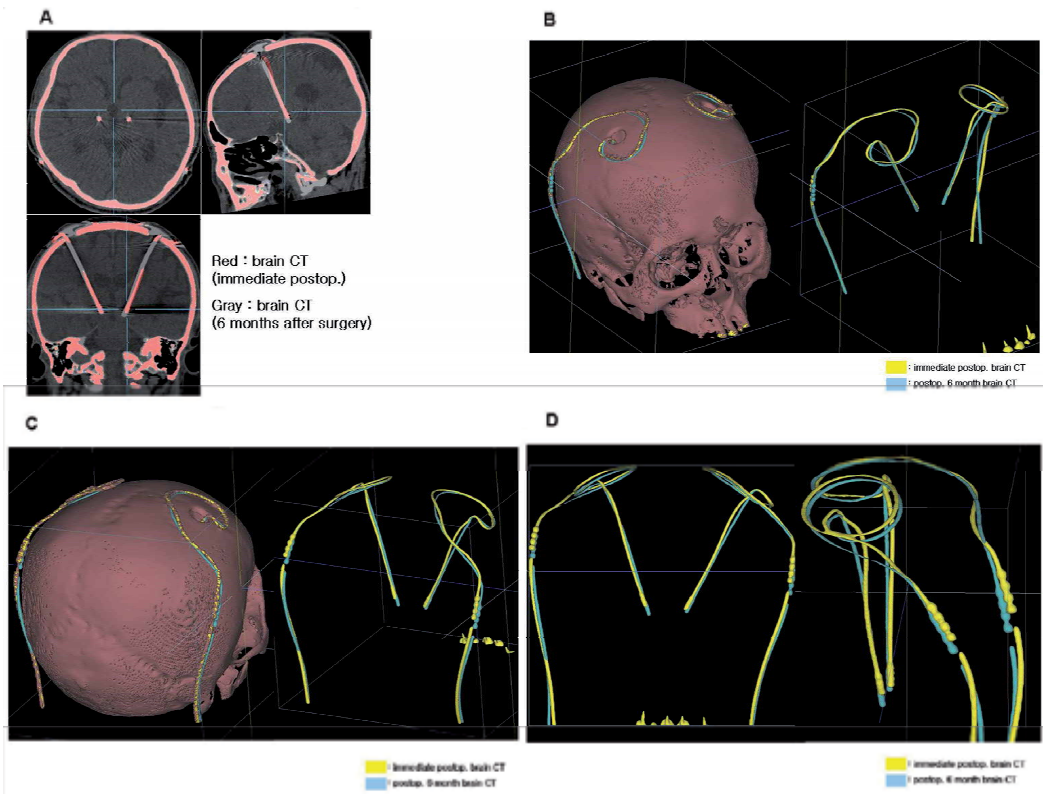


Fig. 5. Fused images of an immediate postoperative brain CT and a brain CT taken 6 months after bilateral subthalamic nucleus stimulation.

In Fig. 5, fused images obtained from two CT scans are aligned along the AC-PC line at the level of the AC and the PC in the axial, sagittal, and coronal planes. The red area represents the position of the electrode extracted from brain CT images obtained immediately after surgery, and the gray area represents the position of the electrode extracted from brain CT images taken six months after surgery. The red and the gray areas do not coincide, exhibiting significant discrepancy in their positions in the axial and coronal planes (Fig 5-A). With the adjustment of window level and width of the fused images, only the shadow of both electrodes is extracted in 3-D reconstructive rendering images of the right superior oblique view (Fig 5-B), the right posterior oblique view (Fig 5-C), and the AP and lateral views (Fig 5-D). In these views, the yellow area represents the position of the electrode extracted from brain CT images obtained immediately after surgery, and the sky-blue area represents the position of the electrode extracted from brain CT images taken six months after surgery. The discrepancy in the electrode position between the two CT scans is remarkable and significant.

We compared the positions of subthalamic nucleus (STN) deep brain stimulation (DBS) electrodes estimated during the immediate postoperative period with those estimated 6 months after surgery. Brain CT scans were taken immediately and 6 months after bilateral STN DBS in 53 patients with Parkinson's disease (Fig 5.). (Kim et al., 2010). The two images were fused using the mutual information technique. The discrepancies in electrode position in three coordinates were measured in the fused images, and the relationship with the pneumocephalus was evaluated.

The average discrepancies of the x- and y-coordinates of the electrode position at the level of the STN (3.5 mm below the anterior commissure–posterior commissure line) were 0.6± 0.5 mm (range, 0-2.1 mm) and 1.0±0.8 mm (range, 0~5.2 mm), respectively. The average discrepancy of the z-coordinate of the electrode tip in the fused images was 1.0±0.8 mm (range, 0.1~4.0 mm). The volume of pneumocephalus (range, 0-76 ml) was correlated with the y-coordinate discrepancies ($p<0.005$).

We found that there was significant discrepancy in the implanted electrode position measured during the immediate postoperative period and that measured 6 months after DBS surgery. The discrepancy was greatest when the amount of pneumocephalus measured in the immediate postoperative CT scan was large. We think that the stabilization of the electrode position may require at least one month following surgery.

4. Analysis of clinical outcome dependence on electrode position following subthalamic nucleus stimulation

4.1 Data management system in a movement disorder center

When evaluating patients with movement disorders such as Parkinson's disease (PD), most neurologists observe patients only during a limited period at the outpatient clinic. Such limited periods of observation may be less than optimal for precise evaluation of patients with varying and unexpected patterns of movement and for supporting the development of optimal treatment plans for such patients. In order to have a good DBS program, a system that can handle the vast amount of data generated by a DBS program is required (Lee et al., 2008). Data include information on patients' pre- and postoperative clinical condition (including videos), medications and stimulation-related parameters. For proper management of patients, easy access to these data is essential . For this reason, we designed a specialized monitoring unit and data management system with systematic storage and

easy access for use in deep brain stimulation programs for patients with movement disorders (Paek et al., 2010). All patients were monitored and evaluated in a specialized 24-hour monitoring system, postoperatively as well as preoperatively, in order to provide information for making accurate diagnoses and thorough evaluation of surgical candidates, as well as to provide them with the best care based on a consistent management protocol and an organized follow-up system. We digitized all of the data and developed a data management system that allowed systematic storage and easy access to the data on demand by users in the offices and outpatient clinics. We describe our data management system and how it provides benefit to patients (Fig. 6), so that others may use it as a template for designing their own data management systems. The details have been described previously (Paek et al., 2010).

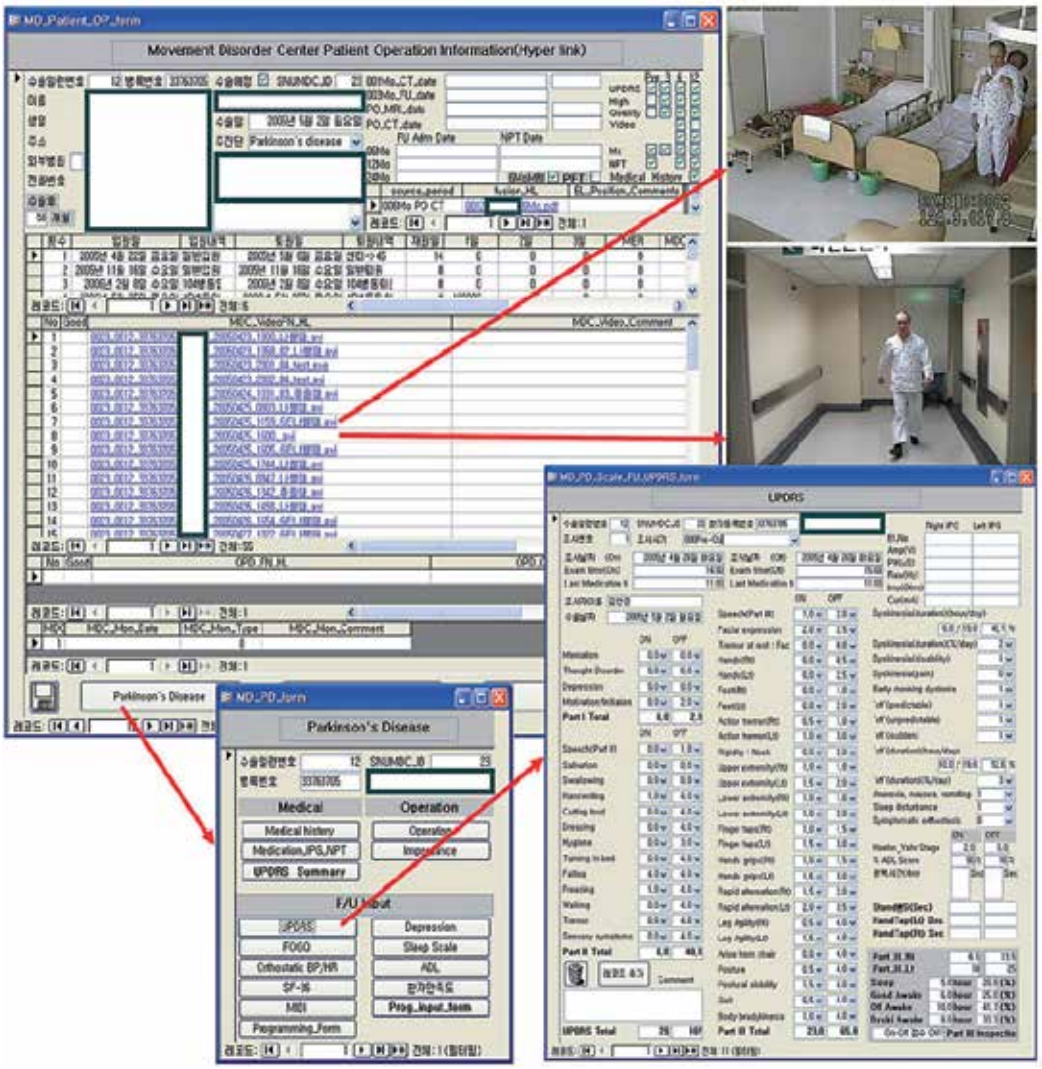


Fig. 6. Data management system in the Movement Disorder Center of SNUH.

The easy accessibility and the outstanding convenience for users of the stacked information in our data management system are useful in many ways.
First, they can improve the quality of patient management. Our specialized 24-hour monitoring system can provide more precise preoperative evaluation of patients with various movement disorders, including advanced PD, and can show various and unexpected side effects including the severe wearing-off phenomenon, dyskinesia and motor fluctuation during their 24-hour daily lives. The systematic management system can be useful not only for the selection of surgical candidates but also for dose adjustment of stimulation parameters before and after surgery.
Second, our data management system can be a useful tool for the education for patients and their caregivers. Many patients with PD have difficulty differentiating between off tremor, dystonia and dyskinesia. Video recordings were helpful in educating the patients about the conditions seen in the videos and in teaching them how to describe their symptoms correctly for future communication.
Third, we can use the data to continually review our performance and to perform standardized outcome analysis. With our data management system, we can access all the collected data representing integrated clinical information on all our patients and carry out a statistical evaluation of our performance.

4.2 Short-term outcome dependence on electrode position as determined by fused images of preoperative and postoperative brain MRI following bilateral subthalamic nucleus stimulation

STN DBS improves motor symptoms and daily activities in patients with advanced PD (Krack et al., 2003; Benabid et al., 2005; Lyons & Pahwa, 2005; Rodriguez-Oroz et al., 2005; Deuschl et al., 2006; Kleiner-Fisman et al., 2006; Tsai et al., 2009). However, variable improvement of symptoms has been observed after STN DBS, even in well-selected patients with advanced PD (Krack et al., 2003; Ford et al., 2004). Such individual variation was not predictable before surgery and no obvious explanation for it is evident; it might have resulted from differences in the extent of disease progression, constitutional differences in individual patients' responses to STN DBS, or the relative accuracy of electrode positioning. Many studies have discussed the technical details of electrode localization in postoperative magnetic resonance imaging (MRI) and have described the anatomical locations of clinically effective electrode contacts (Saint-Cyr et al., 2002; Schrader et al., 2002; Starr et al., 2002; Yelnik et al., 2003; Hamid et al., 2005; Plaha et al., 2006; Pollo et al., 2007). However, most reports do not include a comparison of electrode location and surgical outcome. Plaha et al. (2006) stated that electrodes located in the zona incerta resulted in greater improvement in contralateral motor scores than those located in the STN or dorsomedial/medial to the STN after STN DBS. These authors used guide tubes and plastic stylets implanted in the target point and performed intraoperative MRI to verify the electrode position. Postoperative confirmation of the electrode location was not carried out. McClelland et al. (2005) calculated the electrode tip coordinates in x, y, and z planes relative to the midcommissural point from fused MRI scans of postoperative and preoperative planning images in 26 consecutive patients and compared electrode tip location with clinical outcome. Yokoyama et al. (2006) compared the clinical improvement of Parkinsonian symptoms after monopolar stimulation using four electrode contacts, the locations of which were determined using intraoperative x-rays obtained after placing the DBS electrode in the STN. In both of these studies, the positions of the electrodes were determined by intraoperative x-ray or by using

fused images from immediate pre- and postoperative MRI. Possible brain shift during the operation and/or the immediate postoperative period could be a concern regarding the accuracy of the electrode localization. Both studies assessed electrode position relative to the AC–PC line or to the midcommissural point, but neither demonstrated a 3-dimensional relationship between the electrode and the STN.

We evaluated the clinical outcomes of 53 advanced PD patients at three and six months after bilateral STN DBS with respect to electrode position estimated from fused pre- and postoperative magnetic resonance images (Paek et al., 2008). Patients were evaluated using the Unified Parkinson's Disease Rating Scale, Hoehn and Yahr staging, Schwab and England Activities of Daily Living, L-dopa equivalent dose, and the Short Form-36 Health Survey before surgery and at 3 and 6 months after surgery. Brain magnetic resonance imaging (1.5-T) was performed in all 53 patients at 6 months after STN DBS.

In this group of patients, the Unified Parkinson's Disease Rating Scale, Hoehn and Yahr staging, Schwab and England Activities of Daily Living, and Short Form-36 Health Survey scores all improved at 3 and 6 months after STN DBS, while the L-dopa equivalent dose decreased by 60%. The electrode position was classified according to its relationship to the STN and the red nucleus. The off-medication speech subscale score improved only in patients whose electrodes were correctly bilaterally positioned in the STN; however, the improvement of Parkinsonian symptoms other than speech and stimulation side effects did not vary with the variation of electrode locations found. It seems that there is a significant target volume in the region of the STN that provides equivalent clinical efficacy.

Despite these correlations, we found that there is a significant difference in electrode position determined from the fused images of postoperative MRI and CT scans taken six months after surgery and those measured immediately following bilateral STN DBS surgery. Thus, we again compared the clinical outcomes of 57 advanced PD patients at six and twelve months following bilateral STN DBS according to electrode positions estimated using fused preoperative magnetic resonance images and postoperative computed tomography obtained six months after surgery. Electrode positions were determined in the fused images of preoperative magnetic resonance images and postoperative computed tomography taken at six months after surgery. The patients were divided into three groups: group I, both electrodes in the subthalamic nucleus; group II, only one electrode in the subthalamic nucleus; group III, neither electrode in the subthalamic nucleus. Unified Parkinson's Disease Rating Scale, Hoehn and Yahr Stage, Schwab and England Activities of Daily Living were prospectively evaluated before and at 6 and 12 months after surgery.

In Groups I and II, the Unified Parkinson's Disease Rating Scale, the Hoehn and Yahr Stage, and the Schwab and England Activities of Daily Living scores significantly improved with a reduced l-dopa equivalent daily dose at 6 and 12 months after subthalamic nucleus stimulation. The patients of group I, especially those in whom the electrodes were located in the middle third of both subthalamic nuclei 3.5 mm below the anterior-posterior commissural line, had better outcome in speech with a smaller L-dopa equivalent daily dose than that of the two other groups.

The LEDD of 13 of the 57 patients was zero at their last follow up. The preoperative characteristics of this group were not different from those of the other patients. Their total UPDRS scores, H&Y Stage, SEADL, and dyskinesia disability scores improved dramatically at 12 months after STN DBS. Their off-time UPDRS part III subscores, including speech, were significantly improved at 12 months after surgery. On investigating electrode positioning in these patients, it was found that all had both electrodes positioned in or close

to the middle one third of the STN on axial view, at a level of 3.5 mm below the AC-PC line. It is suggested that the best symptom relief, including improved speech with reduced LEDD, was observed in the patients whose electrodes were accurately positioned in both STN. Thus, a good long-term outcome of subthalamic nucleus stimulation is predicted when the electrodes are positioned in the middle third of the subthalamic nucleus (Fig. 7). However, the improvement of Parkinsonian symptoms, LEDD, neuropsychological changes other than speech, and stimulation side effects did not vary with the variation of electrode location found in this series of patients. This study thus supports the idea proposed by McClelland et al. (2005) that there is a significant target volume in the region of the STN that provides equivalent clinical efficacy.

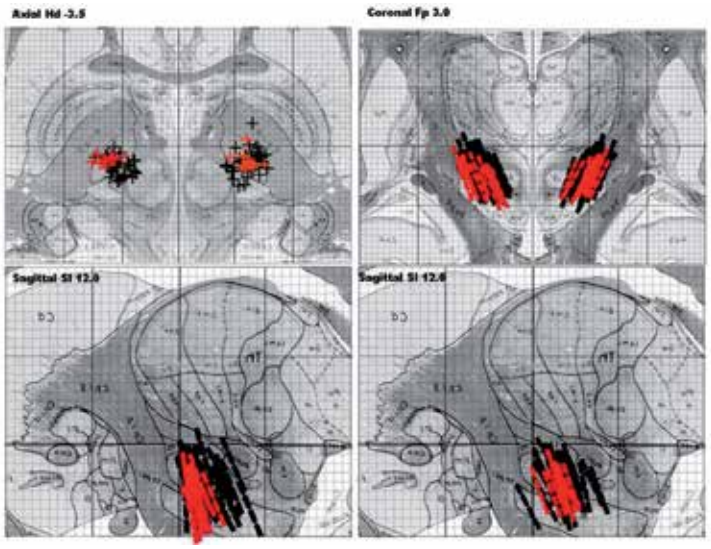


Fig. 7. Locations of the electrodes based on fused images obtained from 13 patients who showed significant clinical improvement in UPDRS part III including speech with nil LEDD (shown in red) and on fused images obtained from the remaining 44 patients (shown in black) at the last follow-up period more than one year after surgery. Most of the electrodes in the 13 patients who showed improvement are positioned in the middle one third of the subthalamic nucleus (in the axial view) at a level of 3.5 mm below the AC-PC line (upper left); they are also positioned in the subthalamic nucleus in the coronal view at a level of 3.0 mm posterior to the midcommissural point (upper right) and in the sagittal view at a level of 12 mm lateral to the midline (lower panels).

4.3 Three-year long-term outcome following bilateral STN DBS with respect to electrode position

Although many studies have addressed the relationship between patients' clinical outcomes and prognostic factors, few studies have analyzed the long-term clinical outcome of STN DBS as a function of inserted electrode positioning (Tsai et al., 2009). Many studies have shown stable improvement in patients' UDPRS scores after bilateral STN DBS (Krack et al., 2003; Liang et al., 2006; Ostergaard & Sunde., 2006; Piboolnurak et al., 2007; Wider et al., 2008; Tsai et al., 2009), although the scores were observed to diminish over time due to disease progression (Olanow et al., 1995; Louis et al., 1999; Jankovic et al., 2001; Krack et al.,

2003; Rodriguez-Oroz et al., 2005; Tsai et al., 2009). In a review of the literature, Benabid et al. (2009) found that improvements in UDPRS III scores after STN DBS were reasonably stable over time, decreasing from 66% improvement at one year to 54% improvement five years after surgery (Benabid et al., 2009). It is suggested that the progression of symptoms over time after STN DBS closely resembles the natural history of PD on medically-treated PD but motor complications, which was thought to represent disease progression. Piboolnurak et al. (2007) investigated the long-term levodopa response after bilateral STN DBS and the predictive value of preoperative L-dopa response in 33 patients with PD (Piboolnurak et al., 2007). They found a trend of decreasing DBS response and observed that preoperative L-dopa responsiveness was not predictive of long-term DBS benefit. Wider et al. (2008) have described the long-term outcomes of 50 consecutive PD patients up to five years after bilateral STN DBS. They noted that a highly significant improvement in UPDRS part III sub-scores with stimulation was maintained at five years; however, this tended to diminish over time due to disease progression. They suggest that the observation of worsening symptoms in these cases argues against the neuroprotective effect hypothesis of STN DBS and actually reflects disease progression (Olanow et al., 1995; Louis et al., 1999; Jankovic et al., 2001; Krack et al., 2003). Unfortunately, there is little information available in the literature on how patients' long-term outcomes relate to electrode position measured in a stable period following bilateral STN stimulation.

We investigated the three-year outcomes of 42 PD patients following bilateral STN DBS and related the outcomes to electrode position as determined by means of fused preoperative MRI and postoperative CT images. Forty-two advanced PD patients were followed for three years after bilateral STN DBS using a prospective protocol. Patients were evaluated before surgery and one, two, and three years after surgery using the Unified Parkinson's Disease Rating Scale, Hoehn and Yahr staging, Schwab and England Activities of Daily Living, and the Short Form-36 Health Survey. The patients were divided into two groups according to electrode position; group I included patients who had both electrodes in the STN (n=31), whereas group II included patients who did not have both electrodes in the STN (n=11).

The UPDRS, Hoehn & Yahr staging, Schwab and England Activities of Daily Living, and the Short Form-36 Health Survey scores showed significant improvements with decreased L-dopa equivalent daily doses (LEDDs) in both groups, as well as in the patient cohort as a whole, up to three years following bilateral STN DBS (Fig 8). However, for patients in group II, the off-medication UPDRS total and motor (part III) scores significantly deteriorated with increased LEDDs three years after STN DBS in comparison to patients in group I (Fig. 8).

It is suggested that electrode positioning influences the long-term outcome of advanced PD patients following STN DBS. Accurate electrode positioning and documentation thereof should be considered in long-term assessment following STN DBS.

5. Programming/reprogramming guided by the use of fused images from preoperative MRI and postoperative CT following STN DBS

5.1 DBS Electrodes Location Analysis System (DELAS)

We developed an on-line service called "DBS Electrode Localization Analysis System (DELAS)", (http://delas.ondemand3d.com) that can be used to estimate the location of an individual patient's electrodes following STN DBS. Based on our previous experience, estimation of electrode positions at a stable period (around one month) following STN DBS can provide a useful basis for predicting the surgical outcome of each patient and for programming appropriate IPG parameters for each advanced PD patient treated with STN DBS.

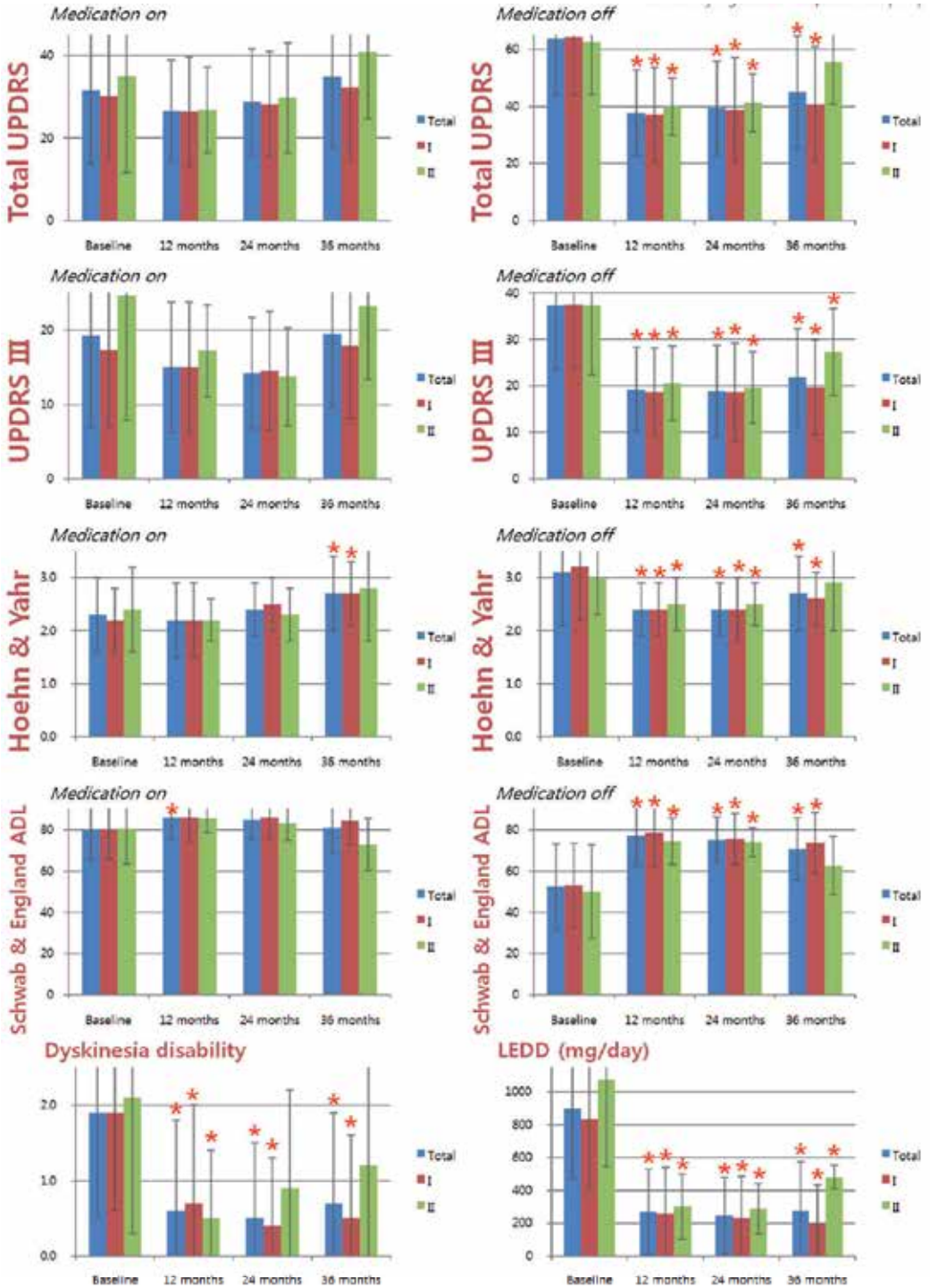


Fig. 8. On-time and off-time scores in 42 patients at 1, 2, and 3 years after subthalamic nucleus stimulation.

5.2 Programming/reprogramming guided by the use of fused images

An examination of the effectiveness and side effects of each of the four contacts of the electrodes used in DBS was performed using an N'vision® programmer (Medtronic, Minneapolis, WI) in all patients to select the best contact of the electrodes and electrical settings for chronic stimulation by the neurologist. After beginning stimulation at the minimal available level (around 1.0 volts), the medication and stimulation parameters were optimized to the demand for the best status of motor functions in harmony with the DBS programming via a 24-hour monitoring unit. Using this method and the electrode position identified by CT-MRI fused images, the stimulation parameters can be carefully adjusted with the selection of the best or the closest contacts of the stimulation electrodes.

5.2.1 Fusion-image-based programming

Subthalamic nucleus (STN) deep brain stimulation (DBS) is a standard therapy for patients with advanced Parkinson's disease (PD) and intolerance for long-term use of medication (Krack et al., 2003; Benabid et al., 2005; Lyons & Pahwa, 2005; Rodriguez-Oroz et al., 2005; Deuschl et al., 2006; Kleiner-Fisman et al., 2006; Tsai et al., 2009). DBS programming is a time-consuming task, however, that requires the patient to undergo a long period of adjustment after surgery (Moro et al., 2002; Deuschl et al., 2006a; Volkmann et al., 2006). Traditionally, DBS programming follows a standardized step-by-step approach (14, 19). The basic algorithm for DBS programming comprises (i) initial programming during the postoperative period; (ii) initiation of long-term stimulation; (iii) stimulation adjustment during the stabilization period (first 3–6 months after surgery) (Deuschl et al., 2006a; Volkmann et al., 2006). This approach tests each electrode individually to determine the most effective stimulation parameters. Generally, the starting point is set at a pulse width of 60 us and a frequency of 130 Hz. Subsequently, the amplitude thresholds for the induction of clinical responses and side effects are determined using monopolar stimulation for each electrode contact with stepwise increases in amplitude of 0.2–0.5 V. If clinical improvement is observed without side effects, the amplitude is increased further to determine the threshold of onset of adverse effects. If no beneficial or adverse effects are observed within the available amplitude range, the next contact is selected and tested. The electrode contact with the lowest threshold that induces a benefit and the largest therapeutic width (i.e., highest threshold for side effects) is selected for long-term stimulation.

We deemed that the determination of the best electrode contacts closest to the STN can be performed more easily and quickly via the use of fused preoperative magnetic resonance imaging (MRI) and postoperative computed tomography (CT) images. We proposed fusion-image-based programming to effectively adjust DBS parameters for patients with advanced Parkinson's disease (PD) after subthalamic nucleus (STN) deep brain stimulation (DBS) (Paek et al., 2011). Thirty-eight patients with advanced PD were consecutively treated with STN DBS between January 2007 and July 2008. The electrode positions and information regarding their contacts with the STN were determined via fusion of images obtained by preoperative magnetic resonance imaging (MRI) and postoperative computed tomography (CT) carried out 1 month after STN DBS (Fig. 9). Postoperative programming was performed using the information on electrode position acquired from the fused images.

All patients were evaluated using a prospective protocol of the Unified Parkinson's Disease Rating Scale, Hoehn and Yahr Staging, Schwab and England Activities of Daily Living, levodopa equivalent daily dose (LEDD), the Short Form-36 Health Survey, and neuropsychological tests prior to and at 3 and/or 6 months after surgery.

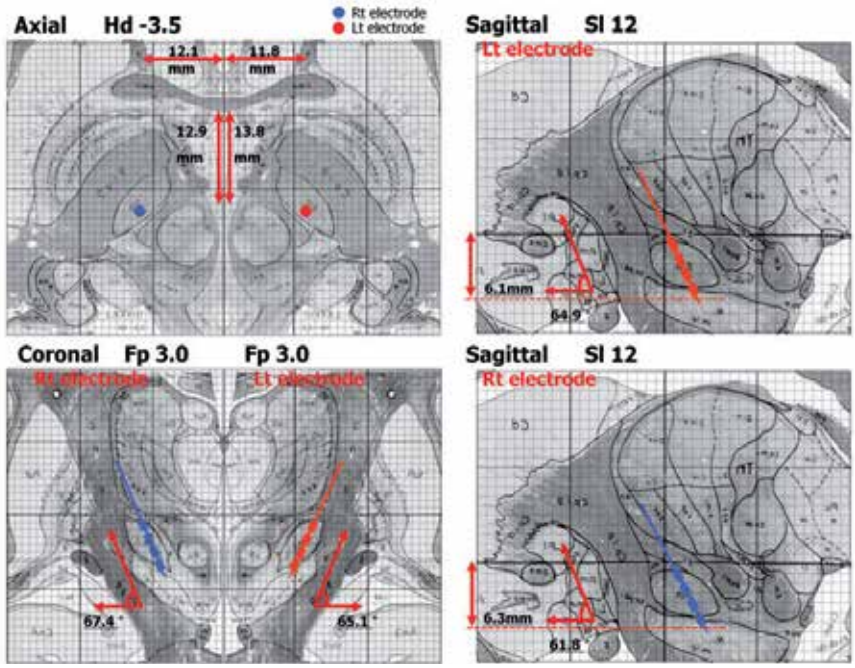


Fig. 9. Electrode positions plotted with reference to the human brain atlas of Schaltenbrandt and Wahren. The electrode positions are based on information obtained from fused images of preoperative MRI and postoperative CT taken one month after surgery.

After STN stimulation, there was rapid and significant improvement of motor symptoms, especially tremor and rigidity, with low morbidity. Stimulation led to an improvement in the off-medication UPRSR III scores of approximately 55% of the patients at 3 and 6 months after STN DBS. Dyskinesia was also significantly improved (74% at 3 months and 95% at 6 months) (Table 1).

In addition, LEDD values decreased to 50% of the level observed before surgery within 1 month after STN DBS surgery (Fig. 10).

When information from the fused images of preoperative MRI and postoperative CT was used to ascertain electrode position, the time spent selecting the stimulation contacts and appropriate stimulation parameters was markedly shortened, and patients were able to avoid prolonged experience of the unnecessary adverse effects caused by the selection of inappropriate contacts far from the STN target. With this approach, the selection of stimulation contacts with appropriate stimulation parameters can be achieved soon after surgery, in harmony with reduced dosages of antiparkinsonian drugs. When the fused images were used, the time and effort expended by physicians in the selection of the stimulation contacts and appropriate stimulation parameters were also markedly reduced, and the long-term trial-and-error rounds caused by the step-by-step selection of the contacts, which frequently occurred even with experienced specialists (Moro et al., 2002; Deuschl et al., 2006a; Volkmann et al., 2006), could be avoided. Thus, it is suggested that programming based on fused images of preoperative MRI and postoperative CT scans after STN DBS can often be carried out quickly, easily, and efficiently.

	Medication	DBS	Baseline	3 months	6 months	P-value 3 months vs. baseline	P-value 6 months vs. baseline
Total UPDRS	On	Off	30.8 ± 14.4				
	Off		65.7 ± 18.1				
	On	On		24.5 ± 12.8	25.3 ± 10.4	p=0.015	p=0.038
	Off			33.7 ± 16.4	33.4 ± 14.2	p<0.001*	p<0.001*
UPDRS III	On	Off	20.3 ± 11.7		33.4 ± 14.8		p<0.001*
	Off		40.9 ± 13.4		38.0 ± 13.6		P=0.203
	On	On		14.4 ± 8.3	14.5 ± 6.1	p=0.004*	p=0.005*
	Off			18.6 ± 8.4	18.1 ± 8.0	p<0.001*	p<0.001*
H & Y	On	Off	2.4 ± 0.5				
	Off		3.1 ± 0.9				
	On	On		2.4 ± 0.5	2.5 ± 0.5	p=0.729	p=0.337
	Off			2.6 ± 0.4	2.6 ± 0.5	p=0.001*	p<0.001*
SEADL	On	Off	83.3 ± 10.1				
	Off		64.2 ± 13.6				
	On	On		86.1 ± 9.9	86.6 ± 9.7	p=0.185	p=0.085
	Off			80.6 ± 13.7	80.5 ± 14.3	p<0.001*	p<0.001*
Dyskinesia disability			2.1 ± 1.5	0.5 ± 1.1	0.3 ± 0.8	p<0.001*	p<0.001*
LEDD (mg/day)			793.4 ± 527.0	285.3 ± 387.2	246.5 ± 322.1	p<0.001*	p<0.001*

Table 1. Clinical outcome in 38 patients after subthalamic nucleus stimulation. * Asterisks indicate p<0.01 and statistical significance with use of the Bonferroni correction method to avoid a Type I error when conducting multiple analyses over time.

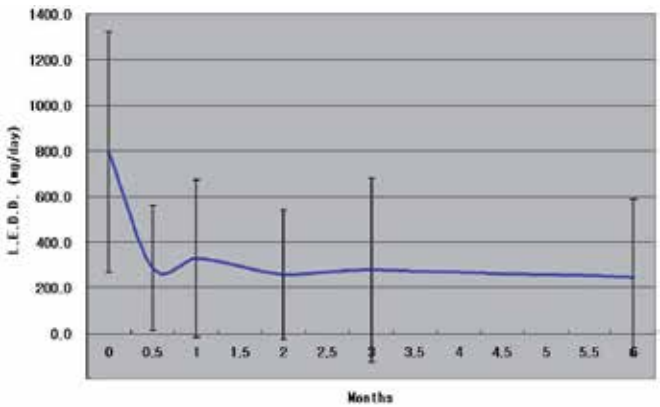


Fig. 10. Levodopa equivalent daily dose (LEDD) changes in 38 patients after subthalamic nucleus stimulation.

5.2.2 Fusion-image-based reprogramming

Published guidelines for DBS programming in PD recommend that the contact for chronic stimulation be selected after testing the efficacy of each electrode separately to evaluate its effective threshold and therapeutic width (Volkmann et al., 2002; Volkmann et al., 2006). Although the established guidelines provide a systematic approach, several practical

difficulties are encountered in DBS programming. First, the responses from stimulating each contact serially at several-minute intervals can be confounded by the effects of the previously stimulated electrode. Second, it is time-consuming to stimulate each electrode separately and to evaluate the threshold of each parameter. Third, adequate patient cooperation, which can be easily affected by the patients' subjective feelings and motivation, is essential to determining the thresholds. The placebo effect is yet another difficulty. Therefore, the outcome of DBS programming is highly dependent on the physician's capability and the capacity of the DBS care facility (Moro et al., 2002; Moro et al., 2006).

We have developed a fusion method that combines images of pre-operative magnetic resonance imaging (MRI) and postoperative computed tomography (CT) (Kim et al., 2008a; Kim et al., 2008b; Lee et al., 2008; Kim et al., 2009; Kim et al., 2010; Paek et al., 2010). This fusion method enabled us to determine the 3-dimensional (3D) location of the leads and each contact in relation to the STN.

Assuming that use of this visual information would improve the outcomes of DBS programming, we reprogrammed the stimulator based on the fused images of MRI and CT in patients who had been stably managed on the STN-DBS for at least 6 months. To evaluate the usefulness of the visual information about the location of the contacts in deep brain stimulation (DBS) programming, we compared the outcomes of subthalamic nucleus (STN) stimulation before and after reprogramming guided by the fused images of MRI and CT (Lee et al., 2010a).

Of 65 patients with Parkinson's disease who underwent bilateral STN-DBS surgery between March 2005 and September 2006 and had been managed for at least 6 months with conventional programming based only on physiological responses from the patients, 54 patients were reprogrammed based on the 3D anatomical location of the contacts revealed by the fused images of preoperative MRI and post-operative CT scans taken 6 months after surgery. A total of 51 patients completed the evaluation after reprogramming.

Reprogramming significantly improved the patients' UPDRS part III scores during both on- and off-medication conditions. The daily levodopa-equivalent dose was significantly reduced. Improvement in the UPDRS part III scores after reprogramming was greater in the patients with electrodes in the STN than in patients with electrodes located outside the STN (Table 2).

Characteristics	Pre-reprogramming	Post-reprogramming	*p*-Value
Primary outcomes			
UPDRS – III (0–108)			
Off-medication	22.5 ± 10.5	19.1 ± 11.5	0.0137†
On-medication	17.0 ± 9.2	14.0 ± 7.9	0.0006†
Secondary outcomes			
UPDRS – I (0–16)			
Off-medication	4.5 ± 3.4	4.2 ± 2.5	0.5535
On-medication	2.8 ± 2.6	3.1 ± 2.3	0.2415
UPDRS – II (0–52)			
Off-medication	17.8 ± 7.9	16.3 ± 7.3	0.1455
On-medication	10.0 ± 6.4	12.3 ± 6.9	0.0130†
UPDRS – III subscores for axial symptoms (0–20)			
Off-medication	4.9 ± 2.2	5.0 ± 2.7	0.8645
On-medication	3.9 ± 2.0	4.0 ± 2.4	0.8812
Dyskinesia disability (0–4)	0.9 ± 1.3	0.6 ± 1.0	0.0598
Dyskinesia duration (0–4)	0.4 ± 0.6	0.3 ± 0.6	0.3991
Off-duration (0–4)	1.4 ± 1.1	1.1 ± 1.0	0.0549
Hoehn and Yahr stage (0–5)			
Off-medication	2.6 ± 0.5	2.6 ± 0.7	0.6465
On-medication	2.4 ± 0.6	2.5 ± 0.7	0.2620
LEDD (mg/day)	355.6 ± 321.3	276.7 ± 283.0	0.0155†

Table 2. Outcomes before and after reprogramming in 51 patients.

It is suggested that CT-MR fusion images helped physicians reprogram stimulation parameters with ease and confidence in a time-saving manner and resulted in further clinical improvement. This method could complement the conventional method of adjusting stimulation parameters after bilateral STN-DBS.

6. Conclusion

In STN DBS, precise positioning of electrodes within the STN is important for good clinical outcome after surgery. Many approaches, including image fusion of CT-MRI, MRI-MRI, use of an MRI brain atlas, intraoperative microelectrode recording, and stimulation, have been used in efforts to achieve precise targeting of electrodes. However, many unexpected factors such as possible brain shift due to CSF leakage, electrode artifacts in the MRI, and error in the manipulation of instruments, make it difficult to have electrodes precisely positioned in the center of the STN. Thus, not all patients have electrodes positioned exactly in the STN after surgery. This might result in different clinical outcomes following STN DBS in advanced PD patients. Knowledge of the exact location of DBS electrodes may be important in the prediction of clinical outcomes as well as in the programming of stimulation parameters following STN DBS.

We developed the DBS Electrode Localization Analysis System (DELAS) to estimate the location of electrodes following STN DBS. We demonstrated that electrode location can influence long-term clinical outcome in advanced PD patients following STN DBS. Hence, electrode positioning in relation with the STN and documentation thereof should be emphasized when adjusting long-term management plans and assessing the long-term effects of DBS on disease progression in advanced PD patients following STN DBS. We believe that the DELAS system makes it possible to try a new approach of programming or reprogramming after STN DBS that consists of fusing images of preoperative MRI and postoperative CT using the mutual information technique. This technique allows the identification of the 3-D location of the leads and of each contact in relation to the STN. Using information on the 3-D location of the electrodes and their contacts based on fused images of preoperative MRI and postoperative CT scans acquired 1 month after surgery, programming can be quickly, easily, and efficiently performed after STN DBS.

7. Acknowledgements

This work was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea (A092052-0911-000100).

8. References

Bejjani BP, Dormont D, Pidoux B, Yelnik J, Damier P, Arnulf I, Bonnet AM, Marsault C, Agid Y, Philippon J, Cornu P.(2000) Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance. *J Neurosurg* 92(4):615-625. ISSN: 0022-3085

Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. (1987) Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl Neurophysiol* 50(1-6):344-346 ISSN: 0302-2773

Benabid AL, Chaardes S, Mitrofanis J, Pollak P. (2009) Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol* 8 :67-81. ISSN: 1474-4422

Benabid AL, Chabardès S, Seigneuret E. (2005) Deep-brain stimulation in Parkinson's disease: Long-term efficacy and safety—What happened this year? *Curr Opin Neurol* 18:623–630. ISSN: 1350-7540

Benazzouz A, Breit S, Koudsie A, Pollak P, Krack P, Benabid AL. (2002) Intraoperative microrecordings of the subthalamic nucleus in parkinson's disease. *Mov Disord* 17:S145-149. ISSN: 0885-3185

Cho ZH, Min HK, Oh SH, Han JY, Park CW, Chi JG, Kim YB, Paek SH, Lozano AM, Lee KH. (2010) Direct visualization of deep brain stimulation targets in Parkinson disease with the use of 7-tesla magnetic resonance imaging. *J Neurosurg* 113(3):639-647. ISSN: 0022-3085

Christensen GE, Joshi SC, Miller MI. (1997) Volumetric transformation of brain anatomy. *IEEE Trans Med Imaging* 16:864–877. ISSN: 0278-0062

Deuschl G, Herzog J, Kleiner-Fisman G, Kubu C, Lozano AM, Lyons KE, Rodriguez-Oroz MC, Tamma F, Troster AI, Vitek JL, Volkmann J, Voon V. (2006a) Deep brain stimulation: postoperative issues. *Mov Disord* 21(Suppl 14):S219-S237. ISSN: 0885-3185

Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, Daniels C, Deutschländer A, Dillmann U, Eisner W, Gruber D, Hamel W, Herzog J, Hilker R, Klebe S, Kloss M, Koy J, Krause M, Kupsch A, Lorenz D, Lorenzl S, Mehdorn HM, Moringlane JR, Oertel W, Pinsker MO, Reichmann H, Reuss A, Schneider GH, Schnitzler A, Steude U, Sturm V, Timmermann L, Tronnier V, Trottenberg T, Wojtecki L, Wolf E, Poewe W, Voges J; German Parkinson Study Group, Neurostimulation Section. (2006b) A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 355:896–908. ISSN: 0028-4793

Ford B, Winfield L, Pullman SL, Frucht SJ, Du Y, Greene P, Cherinqal JH, Yu O, Cote LJ, Fahn S, McKhann GM 2nd, Goodman RR. (2004) Subthalamic nucleus stimulation in advanced Parkinson's disease: Blinded assessments at oneyear follow-up. *J Neurol Neurosurg Psychiatry* 75:1255–1259. ISSN: 0022-3050

Godinho F, Thobois S, Magnin M, Guenot M, Polo G, Benatru I, Xie J, Salvetti A, Garcia-Larrea L, Broussolle E, Mertens P. (2006) Subthalamic nucleus stimulation in Parkinson's disease: anatomical and electrophysiological localization of active contacts. *J Neurol* 253:1347-1355. ISSN: 0885-3185

Halpern CH, Danish SF, Baltuch GH, Jaggi JL. (2008) Brain shift during deep brain stimulation surgery for Parkinson's disease. *Stereotact Funct Neurosurg* 86:37-43. ISSN: 1011-6125

Hamid NA, Mitchell RD, Mocroft P, Westby GW, Milner J, Pall H. (2005) Targeting the subthalamic nucleus for deep brain stimulation: technical approach and fusion of pre-and postoperative MR images to define accuracy of lead placement. *J Neurol Neurosurg Psychiatry* 76:409-414. ISSN: 0022-3050

Heo JH, Lee KM, Paek SH, Kim MJ, Lee JY, Kim JY, Cho SY, Lim YH, Kim MR, Jeong SY, Jeon BS. (2008) The effects of bilateral Subthalamic Nucleus Deep Brain Stimulation (STN DBS) on cognition in Parkinson disease. J Neurol Sci. 273(1-2):19-24. ISSN: 0022-510X

Holtzheimer PE 3rd, Roberts DW, Darcey TM (1999) Magnetic resonance imaging versus computed tomography for target localization in functional stereotactic neurosurgery. *Neurosurgery* 45:290–297. ISSN: 0148-396X

Jankovic J & Kapadia AS. (2001) Functional decline in Parkinson disease. *Arch Neurol* 2001;58:1611–1615. ISSN: 0003-9942

Khan MF, Mewes K, Gross RE, Skrinjar O. (2008) Assessment of brain shift related to deep brain stimulation surgery. *Stereotact Funct Neurosurg* 86:44-53. ISSN: 1011-6125

Kim HJ, Lee JY, Kim JY, Kim DG, Paek SH, Jeon BS.(2008a) Effect of bilateral subthalamic deep brain stimulation on diphasic dyskinesia. *Clin Neurol Neurosurg* 110(4):328-332. ISSN: 0303-8467

Kim HJ, Paek SH, Kim JY, Lee JY, Lim YH, Kim MR, Kim DG, Jeon BS. (2008b) Chronic subthalamic deep brain stimulation improves pain in Parkinson disease. *J Neurol.* 255(12):1889-1894. ISSN: 0885-3185

Kim HJ, Paek SH, Kim JY, Lee JY, Lim YH, Kim DG, Jeon BS. (2009) Two-year follow-up on the effect of unilateral subthalamic deep brain stimulation in highly asymmetric Parkinson's disease. *Mov Disord* 15;24(3):329-335. ISSN: 0885-3185

Kim HJ, Jeon BS, Paek SH, Lee JY, Kim HJ, Kim CK, Kim DG. (2010) Bilateral subthalamic deep brain stimulation in Parkinson disease patients with severe tremor. *Neurosurgery* 67(3):626-632 ISSN: 0148-396X

Kim YH, Kim HJ, Kim C, Kim DG, Jeon BS, Paek SH. (2010) Comparison of electrode location between immediate postoperative day and 6 months after bilateral subthalamic nucleus deep brain stimulation. *Acta Neurochir (Wien*) 152(12):2037-2045. ISSN: 0001-6268

Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, Lang AE, Deuschl G. (2006) Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Mov Disord* 21(Suppl.14): S290–S304. ISSN: 0885-3185

Kondziolka D, Dempsey PK, Lunsford LD, Kestle JR, Dolan EJ, Kanal E, Tasker RR (1992) A comparison between magnetic resonance imaging and computed tomography for stereotactic coordinate determination. *Neurosurgery* 30:402–406. ISSN: 0148-396X

Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, Le Bas JF, Benabid AL, Pollak P. (2003) Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 349:1925–1934. ISSN: 0028-4793

Lee JY, Han JH, Kim HJ, Jeon BS, Kim DG, Paek SH. (2008) STN DBS of Advanced Parkinson's Disease Experienced in a Specialized Monitoring Unit with a Prospective Protocol J Korean Neurosurg Soc. 44(1):26-35. ISSN: 2005-3711

Lee JY, Jeon BS, Paek SH, Lim YH, Kim MR, Kim C. (2010a) Reprogramming guided by the fused images of MRI and CT in subthalamic nucleus stimulation in Parkinson disease. *Clin Neurol Neurosurg* 112(1):47-53. ISSN: 0303-8467

Lee JY, Kim JW, Lee JY, Lim YH, Kim C, Kim DG, Jeon BS, Paek SH. (2010b) Is MRI a reliable tool to locate the electrode after deep brain stimulation surgery? Comparison study of CT and MRI for the localization of electrodes after DBS. *Acta Neurochir (Wien)* 152(12):2029-2036. ISSN: 0001-6268

Liang GS, Chou KL, Baltuch GH, Jaggi JL, Loveland-Jones C, Leng L, Maccarone H, Hurtig HI, Colcher A, Stern MB, Kleiner-Fisman G, Simuni T, Siderowf AD. (2006) Long-term outcomes of bilateral subthalamic nucleus stimulation in patients with

advanced Parkinson's disease. Stereotact Funct Neurosurg 84 :221-227. ISSN: 1011-6125

Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, Benabid AL. (1998) Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 339:1105–1111. ISSN: 0028-4793

Louis ED, Tang MX, Cote L, Alfaro B, Mejia H, Marder K. (1999) Progression of parkinsonian signs in Parkinson disease. *Arch Neurol* 56:334–337. ISSN: 0003-9942

Lyons KE, Pahwa R. (2005) Long-term benefits in quality of life provided by bilateral subthalamic stimulation in patients with Parkinson disease. *J Neurosurg* 103:252–255. ISSN: 0022-3085

Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P. (1997) Multimodality image registration by maximization of mutual information. *IEEE Trans Med Imaging* 16:187–198. ISSN: 0278-0062

Martinez-Santiesteban FM, Swanson SD, Noll DC, Anderson DJ. (2007) Magnetic field perturbation of neural recording and stimulating microelectrodes. *Phys Med Biol* 52:2073-2088. ISSN: 0031-9155

McClelland S 3rd, Ford B, Senatus PB, Winfield LM, Du YE, Pullman SL, Yu Q, Frucht SJ, McKhann GM 2nd, Goodman RR. (2005) Subthalamic stimulation for Parkinson disease: Determination of electrode location necessary for clinical efficacy. *Neurosurg Focus* 19:E12. ISSN: 1092-0684

Miyagi Y, Shima F, Sasaki T. (2007) Brain shift: an error factor during implantation of deep brain stimulation electrodes. *J Neurosurg* 107:989-997. ISSN: 0022-3085

Moro E, Esselink RJ, Xie J, Hommel M, Benabid AL, Pollak P. (2002) The impact on Parkinson's disease of electrical parameter settings in STN stimulation. Neurology 59:706-713. ISSN: 0028-3878

Moro E, Poon YW, Lozano AM, Saint-Cyr JA, Lang AE. (2006) Subthalamic nucleus stimulation; improvements in outcome with reprogramming. *Arch Neurol* 63:1266–1272. ISSN: 0003-9942

Olanow CW, Hauser RA, Gauger L, Malapira T, Koller W, Hubble J, Bushenbark K, Lilienfeld D, Esterlitz J. (1995) The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol* 38:771–777. ISSN: 0364-5134

Ott K, Tarlov E, Crowell R, Papadakis N (1976) Retained intracranial metallic foreign bodies. Report of two cases. *J Neurosurg* 44:80-83. ISSN: 0022-3085

Ostergaard K, Sunde NA. (2006) Evolution of Parkinson's disease during 4 years of bilateral deep brain stimulation of the subthalamic nucleus. *Mov Disord* 21 :624-631. ISSN: 0885-3185

Paek SH, Han JH, Lee JY, Kim C, Jeon BS, Kim DG. (2008) Electrode position determined by fused images of preoperative and postoperative magnetic resonance imaging and surgical outcome after subthalamic nucleus deep brain stimulation. *Neurosurgery* 2008; 63:925-937. ISSN: 0148-396X

Paek SH, Kim JW, Lim YH, Kim MR, Kim DG, Jeon BS. (2010) Data Management System in a Movement Disorder Center: Technical Report. *Stereotact Funct Neurosurg* 88(4):216-223. ISSN: 1011-6125

Paek SH, Kim HJ, Yoon JY, Heo JH, Kim CY, Kim MR, Lim YH, Kim KR, Han JH, Kim DG, Jeon BS. (2011) Fusion image-based programming after subthalamic nucleus deep brain stimulation. *World Neurosurgery* [Epub ahead of print]. ISSN:1878-8750

Piboolnurak P, Lang AE, Lozano AM, Miyasaki JM, Saint-Cyr JA, Poon YY, Hutchison WD, Dostrovsky JO, Moro E (2007) Levodopa response in long-term bilateral subthalamic stimulation for Parkisnon's disease. Mov Disord 22 : 990-997. ISSN: 0885-3185

Plaha P, Ben-Shlomo Y, Patel NK, Gill SS. (2006) Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. *Brain* 129:1732–1747. ISSN: 0006-8950

Pluim JP, Maintz JB, Viergever MA. (2003) Mutual-information-based registration of medical images: a survey. *IEEE Trans Med Imaging* 22:986–1004. ISSN: 0278-0062

Pollo C, Vingerhoets F, Pralong E, Ghika J, Maeder P, Meuli R, Thiran JP, Villemure JG. (2007) Localization of electrodes in the subthalamic nucleus on magnetic resonance imaging. *J Neurosurg* 106:36–44. ISSN: 0022-3085

Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S, Kulisevsky J, Albanese A, Volkmann J, Hariz MI, Quinn NP, Speelman JD, Guridi J, Zamarbide I, Gironell A, Molet J, Pascual-Sedano B, Pidoux B, Bonnet AM, Agid Y, Xie J, Benabid AL, Lozano AM, Saint-Cyr J, Romito L, Contarino MF, Scerrati M, Fraix V, Van Blercom N. (2005) Bilateral deep brain stimulation in Parkinson's disease: a multicenter study with 4 years follow-up. *Brain* 128:2240–2249. ISSN: 0006-8950

Saint-Cyr JA, Hoque T, Pereira LC, Dostrovsky JO, Hutchison WD, Mikulis DJ, Abosch A, Sime E, Lang AE, Lozano AM. (2002) Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging. *J Neurosurg* 97:1152–1166. ISSN: 0022-3085

Schaltenbrand G & Wharen W. (1998) Atlas of Stereotaxy of the Human Brain, 2nd ed. New York: Thieme. ISBN (Americas): 9780865770553, ISBN (EUR, Asia, Africa, AUS): 9783133937023

Schrader B, Hamel W, Weinert D, Mehdorn HM. (2002) Documentation of electrode localization. *Mov Disord* 17 [Suppl 3]:S167–S174. ISSN: 0885-3185

Sorensen N & Krauss J (1991) Movement of hemostatic clips from the ventricles through the aqueduct to the lumbar spinal canal. Case report *J Neurosurg* 74:143–146. ISSN: 0022-3085

Starr PA, Christine CW, Theodosopoulos PV, Lindsey N, Byrd D, Mosley A, Marks WJ Jr. (2002) Implantation of deep brain stimulators into the subthalamic nucleus: Technical approach and magnetic resonance imaging-verified lead locations. *J Neurosurg* 97:370–387. ISSN: 0022-3085

Tsai ST, Lin SH, Chou YC, Pan YH, Hung HY, Li CW, Lin SZ, Chen SY. (2009) Prognostic factors of subthalamic stimulation in Parkinson's disease: a comparative study between short- and long-term effects. *Stereotact Funct Neurosurg* 87:241-248. ISSN: 1011-6125

van den Munckhof P, Contarino MF, Bour LJ, Speelman JD, de Bie RM, Schuurman PR (2010) Postoperative curving and upward displacement of deep brain stimulation electrodes caused by brain shift. *Neurosurgery* 67:49–53. ISSN: 0148-396X

Volkmann J, Herzog J, Kopper F, Deuschl G. (2002) Introduction to the programming of deep brain stimulators. *Mov Disord* 17:S181–5187. ISSN: 0885-3185

Volkmann J, Moro E, Pahwa R. (2006) Basic algorithms for the programming of deep brain stimulation in Parkinson's disease. *Mov Disord* 21:S284-S289. ISSN: 0885-3185

Wells WM 3rd, Viola P, Atsumi H, Nakajima S, Kikinis R. (1996) Multimodal volume registration by maximization of mutual information. *Med Image Anal* 1:35–51. ISSN: 1361-8415

Wider C, Pollo C, Bloch J, Vingerhoets FJ. (2008) Long-term outcome of 50 consecutive Parkinson's diease patients treated with subthalamic deep brain stimulation. *Parkinsonism and Relat Disord* 14 :114-119. ISSN: 1353-8020

Yelnik J, Damier P, Demeret S, Gervais D, Bardinet E, Bejjani BP, Francois C, Houeto JL, Arnule I, Dormont D, Galanaud D, Pidoux B, Cornu P, Aqid Y. (2003) Localization of stimulating electrodes in patients with Parkinson disease by using a three-dimensional atlas-magnetic resonance imaging coregistration method. *J Neurosurg* 99:89–99. ISSN: 0022-3085

Yokoyama T, Ando N, Sugiyama K, Akamine S, Namba H. (2006) Relationship of stimulation site location within the subthalamic nucleus region to clinical effects on parkinsonian symptoms. Stereotact Funct Neurosurg 84:170–175. ISSN: 1011-6125

23

Electrical Stimulation of Primary Motor Cortex for Parkinson's Syndrome

Naoki Tani[1] and Youichi Saitoh[1,2]
[1]Department of Neurosurgery,
Osaka University Graduate School of Medicine,
[2]Department of Neuromodulation and Neurosurgery,
Osaka University,
Japan

1. Introduction

Deep brain stimulation (DBS) of several nuclei at the basal ganglia, mainly globus pallidus interna (GPi), and subthalamic nucleus (STN) is highly effective in controlling motor symptoms in patients with advanced Parkinson's disease (PD) (Krack et al., 1998; Limousin et al., 1998) However, several complications have been published by different groups with a large experience in DBS (Lyons et al., 2004; Umemura et al., 2003), and patients with poor response to levodopa or those with cognitive impairment, advanced age, considerable brain atrophy, cerebral ischemic foci in the white matter or Unified Parkinson's Disease Rating Scale (UPDRS) part III < 30 to 40 in the *off* condition are considered unsuitable patients for DBS, because of the increased surgical risk (Lopiano et al., 2002; Pahwa et al., 2005). On the other hand, STN DBS may improve axial symptoms at the beginning, but results are less rewarding at long-term follow-up (Bejjani et al., 2000; Kleiner-Fisman et al., 2003).
At the early of the 1990s, Tsubokawa introduced electrical motor cortex stimulation (EMCS) for the relief of central pain (Tsubokawa et al., 1991a, b). Its use has been extended to peripheral neuropathic pain conditions, and very recently to patients with movement disorders. EMCS might represent an alternative in patients who would not fulfill all DBS inclusion criteria. There has been some evidence that EMCS may relieve motor symptoms of patients with PD (Canavero et al., 2002; Pagni et al., 2005). However, there have also been a number of contradictory reports regarding the efficacy of EMCS in patients with PD. A number of reasons could account for the apparent discrepancies among different studies which may include different selection criteria, different surgical (i.e. extradural vs. subdural electrode) or methodological (i.e. stimulation frequencies) approaches, and importantly, different way of motor performance assessments. This report attempts to summarize current evidence on these topics.

2. Transcranial magnetic stimulation on primary motor cortex

Several studies have shown the transient benefit of the stimulation of primary motor cortex (M1) using repetitive transcranial magnetic stimulation (rTMS) for the symptoms of patients

with PD, such as akinesia, tremor, rigidity and depression. The benefits depend on stimulus frequency and the site of the stimulation; high frequency rTMS of M1 (5-25 Hz) improved the motor performance (Khedr et al., 2006; Lefaucheur et al., 2004), rTMS of the supplementary motor area (SMA) worsened performance of motor tasks at high frequencies (5-10 Hz) or improved UPDRS (Hamada et al, 2008) but reduced levodopa-induced dyskinesias at low frequency (1 Hz) (Boylan et al., 2001; Koch et al., 2005), and 5 Hz rTMS of the dorsolateral prefrontal cortex (DLPFC) demonstrated the benefit on depression of patients with PD (Pal et al., 2010). Recently, rTMS on M1 is expected to predict the efficacy of EMCS for patients with PD, for instance, we experienced a patient with akinesia in whom high frequency rTMS on M1 showed similar beneficial effect on motor symptom to the subsequent EMCS. In the patients with intractable pain, Andre-Obadia demonstrated that 20 Hz rTMS on M1 predicted the efficacy of subsequent EMCS for pain reduction (Andre-Obadia et al., 2006) and Hosomi et al reported that there is good correlation between the pain reduction with 5 Hz rTMS and that with EMCS (Hosomi et al, 2008). Thus, the rTMS technique might be used to better define the targets and the parameters of stimulation subsequently applied in chronic EMCS.

3. Surgical procedure

Basically, the surgical procedure of EMCS for Parkinson's Syndrome is same as that for intractable pain. Because of the small number of the reported case of EMCS for PD, there is still controversy, such as unilateral stimulation or bilateral stimulation, epidural electrode or subdural electrode. Detailed procedure of EMCS will be mentioned in this session. Previously the detailed methods were reported (Saitoh and Hosomi, 2009).

3.1 Pre-surgical preparation

Prior to the surgical procedure, the hand motor area is identified as a target of EMCS using fMRI or anatomical MRI. Because the lower limb motor area locates in the inter-hemispheric fissure, implanting an electrode on the lower limb motor area is difficult. Functional MRI (fMRI) (Figure 1) is useful to precisely localize the site of the M1, otherwise some anatomical landmarks can help to identify the central sulcus. The central sulcus is characterized by the lack of sulcal branches, and lies just anterior to the pars marginalis of the cingulate sulcus on the interhemispheric surface (Naidich et al., 2001; Naidich et al., 1995). The precentral knob sign corresponding to the hand motor area is easily identified on surface view of MRI (Figure 2).

3.2 Neuronavigation

After the identification of targeted area, neuronavigation is used to precisely identify M1 intraoperatively. Several kinds of navigation systems for neurosurgical assistance can be used to estimate the position of the central sulcus from skin surface (Tirakotai et al., 2007). Neuronavigation combined with fMRI data help to decide the best position for craniotomy and for placement of the stimulating paddle (Rasche et al., 2006). A drawback of neuronavigation is the requirement that the patient's head be fixed in a 3-point pin holder or vacuum headrest (Tirakotai et al., 2007), which several patients may not tolerate under local anesthesia. For this reason, other surgeons prefer not to fix the patient's head and operate without neuronavigation, and use the Taylor-Haughton instead of neuronavigation lines (Figure 3) (Greenberg, 2010).

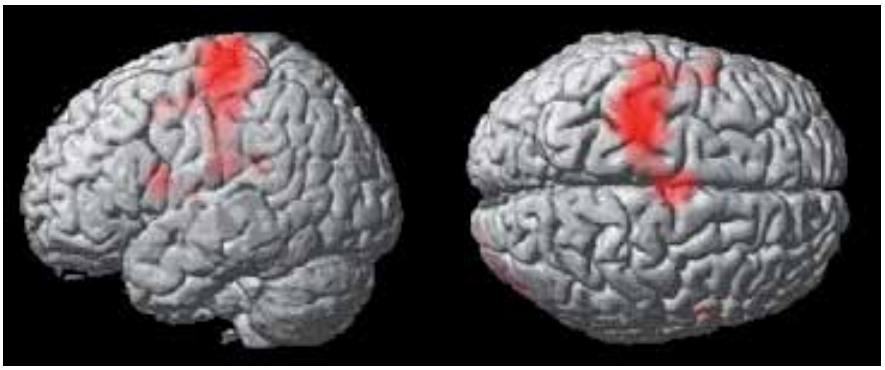


Fig. 1. Motor cortex localization using fMRI. During the acquisition of fMRI data (echo planar imaging), the patient perfomed twelve 30-second epocks of right hand grasp with identical rest epochs. Data analysis was performed in MATLAB 2008a (Math Works, Inc., Natick, MA) using Statistical Parametric Mapping software (SPM@; Wellcome Department of Imaging Neuroscience, London, England).

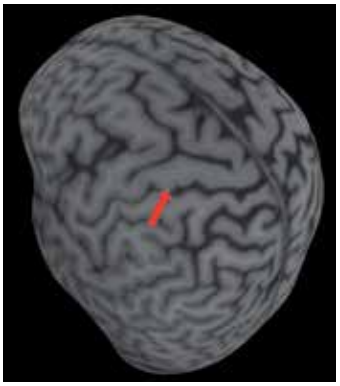


Fig. 2. Brain surface view of MRI. Red arrow indicates the left primary motor cortex hand area.

3.3 Anethesia

Implantation of electrode is done under local anesthesia or general anesthesia. General anesthesia is induced with a loading dose of Remifentanil 3–4 ng/ml in continuous infusion followed after 5–8 min by Propofol 5.5 μg/ml as induction dose (Total intravenous anesthesia, TIVA). Endotracheal intubation is facilitated by vecuronium bromide 0.1 mg/kg; no further doses of muscle relaxants are administered throughout surgery. The lungs are mechanically ventilated with a 50% O2 in air mixture, in order to maintain end tidal concentrations of CO2 (ETCO2) at 30–35 mmHg. Anesthesia is maintained with Remifentanil (5–6 ng/ml, up to 7-8 ng/ml if necessary) and Propofol (2.5-3.0 μg/ml). At the end of the surgical procedure, all patients are awakened within 15–30 min from cessation of TIVA.

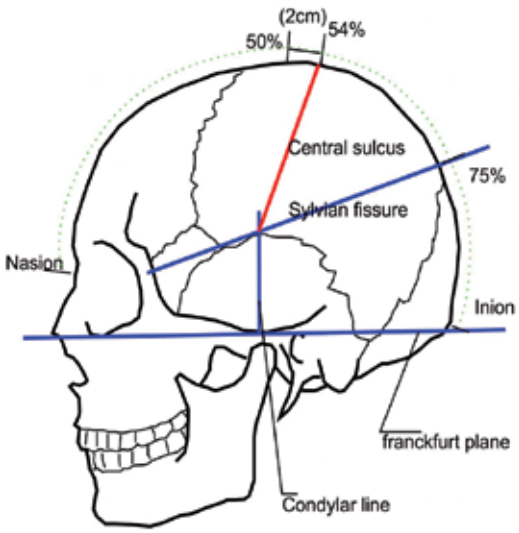


Fig. 3. Taylor-Haughton line indicates the position of the central sulcus from the scalp. The Frankfurt plane is the line from the inferior margin of the orbit through the upper margin of the external auditory meatus. The distance from the nasion to the inion is measured across the top of the calvaria and is divided into quarters. The condylar line runs perpendicular to the baseline through the mandibular condyle (intersecting the line representing the sylvian fissure). The Sylvian fissure is approximated by a line connecting the lateral canthus to the point 3/4 of the way posterior along the arc running over convexity from nasion to inion. Central sulcus is drawn from 54% point on naso-inoin line to the point where the Sylvian line cuts the condylar line.

3.4 Electrophysiological localization of hand motor area

For localizing central sulcus, most neurosurgeons employ somatosensory evoked potential (SSPE) using contralateral median nerve stimulation. The phase reversal of the N20 (sensory cortex) /P20 (motor cortex) waves is used to confirm the location of the central sulcus (Wood et al., 1988), using a multi-contact grid and the central scalp EEG leads or directly using the definitive 4-contact strip overlying the dura matter (Figure 4). Recently, an enlarged and displaced motor map for the hand area was described in patients with PD. Map shifts were found in the majority of the patients (Thickbroom et al., 2006). Therefore, electrode placement only with SSEP is often inadequate or impossibles. According to Velasco et al. (Velasco et al., 2002), recording corticocortical evoked responses (CCER) is simple and reliable and superior to SSEPs. M1 stimulation elicits negative CCER over the frontal scalp, whereas the stimulation of primary sensory cortex (S1) elicits positive responses over parietal and occipital scalp regions.

Most neurosurgeons attempt intraoperative test stimulation by using the quadripolar or the grid electrodes. Test bipolar stimulation (210-1000 μs –generally 400-500-μs, 1-5 Hz up to 500Hz, at increasing voltage or intensity –up to 50 mA, anodally, but also cathodally) is applied by means of the contacts situated over M1. In general, the amplitude needed to produce motor responses is higher using epidural rather than subdural stimulation. Motor contraction can be elicited at relatively lower amplitudes when general anesthesia is not employed. 1Hz stimulation is preferred to higher frequencies, since the former does not

habituate and has less potential to trigger seizures. Muscle responses are recorded from muscle bellies of the contralateral upper limb, with EMG electrodes or visually.

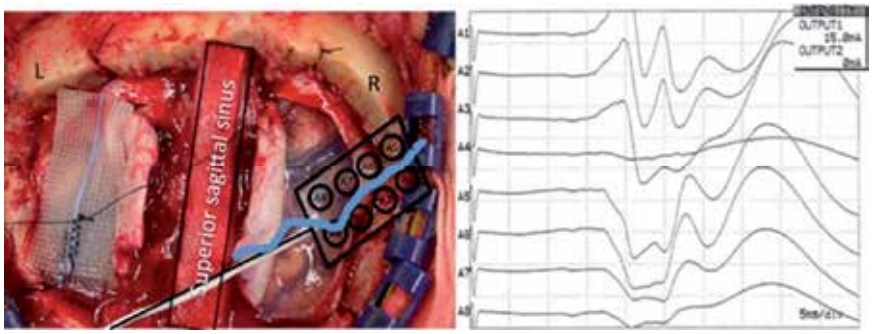


Fig. 4. SSEP recording on the right central sulcus using an eight contact subdural electrode. An eight-polar plate electrode (Specify Lead, 3998; Medtronic, Minneapolis, MN) was placed on the right central sulcus. Left median nerve was stimulated at wrist with stimuli consist of single shocks (0.5 ms, 4.7 Hz, 20 mA) to produce a small, but consistent contraction of the thumb. SSEPs were recorded from each cortical electrode referenced to the ipsilateral ear lobe. Individual SSEP signals were differentially amplified and filtered: 200 were averaged through a digital signal analyzer with sample interval of 100 msec. Blue line indicates the central sulcus confirmed by SSPE.

3.5 Electrode implantation

For EMCS, the great majority of investigators prefer epidural electrode to subdural electrode. This attitude is attributed largely to the greater risk of developing complications with subdural EMCS, such as cerebrospinal fluid leakage, difficulty in fixing the electrode, hemorrhage, and iatrogenic seizures. However, according to the physical model suggested by Holsheimer et al. (Holsheimer et al., 2007) and Manola et al. (Manola et al., 2007), subdural EMCS appears to be more energy-efficient, as compared with epidural EMCS. In some patients with brain atrophy, the cortical surface and the dura mater are wide apart, in which case patients may fail to respond to extradural stimulation: a subdural approach may be considered in selected cases.

There is no direct comparison study between unilateral EMCS and bilateral EMCS. Some investigator reported the bilateral effects in clinical outcome by unilateral EMCS (Cilia et al., 2008; Pagni et al., 2005). These bilateral effects of unilateral cortical stimulation are probably due to bilateral afferent and efferent connections between cortical and subcortical structures (Leichnetz, 1986).

The four-contact electrode array or 2 side-by-side 4-contact electrode strips is placed on the hand motor area. Some surgeons place the electrode perpendicular to the central sulcus above the precentral (cathode) and postcentral (anode) gyri for the supposed improved selectivity (Nguyen et al., 1999), others in a parallel fashion, i.e. with all contacts on the M1 or S1 (Canavero and Bonicalzi, 2002; Rasche et al., 2006). Moreover, no polarity-related difference in pain relief is seen for most patients with epidural electrodes (Katayama et al., 1998).

3.5.1 Epidural electrode

Canavero (Canavero et al., 2002, 2003) makes an oblique linear skin incision (6-10cm) parallel to and 1 cm ahead of or behind the projection of the central sulcus and then drills

two burr holes at a distance of 2-4 cm (plus a bony groove parallel to the paddle to accommodate the connector between the looping lead and the extension). A stimulating paddle is inserted from the edge of one burr hole into the epidural space overlying the precentral gyrus contralateral to more disabled side for movement disorders. The bony bridge between the two holes will then hold the plate in place and simultaneously reduce the durocortical gap (Figure 5). This technique entails no risk of epidural hematoma, and accidental displacement of the electrode has never been observed (S Canavero, personal communication)

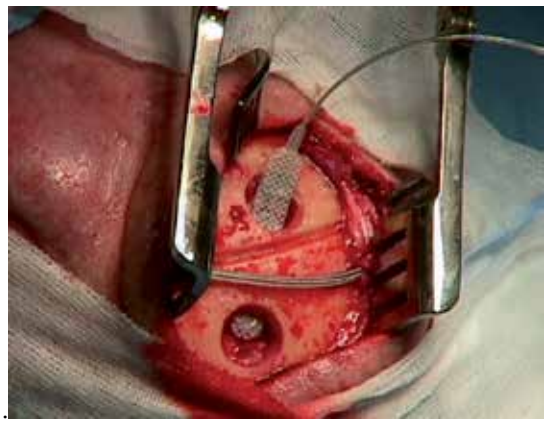


Fig. 5. Two burr-hole surgery is shown. The locations of burr holes are marked on the scalp depending on the anatomical landmarks (courtesy of Prof. Canavero).

3.5.2 Subdural electrode

In patients with advanced cortical atrophy, epidural stimulation may fail due to the duro-cortical separation. The cortical surface and interhemispheric surfaces subdurally may be elected as targets for stimulation. However, large bridging veins sometimes interfere with implantation on the interhemispheric surface. We performs bilateral craniotomy over superior sagittal sinus. After the opening of dura mater, the location of central sulcus is confirmed using phase reverse of the N20 component upon stimulation of the median nerve. A subdural quadripolar electrodes (Resume II, model 3587A; Medtronic, Minneapolis, MN) are then placed bilaterally on the M1 adjacent to the superior sagittal sinus. At the end of surgery, the lead extension is fixed to the dura or the border of the burr hole with a silk suture to prevent dislocation. However, migration of the electrodes seems to be more of a problem with a subdural than an extradural approach. A meticulous, watertight dural closure is mandatory to minimize the risk of cerebrospinal fluid leakage.

3.6 Test stimulation

After closure of the craniotomy, the electrode cable(s) is/are connected to trial stimulator. After 3 to 14 days period of test stimulation, the best stimulation parameters and electrodes are decided. There is considerable variation in the stimulation parameters; amplitudes range from 2 V to 6 V, rates from 10 Hz to 130 Hz, and pulse widths from 60 μsec to 450 μsec (Canavero et al., 2003; Canavero et al., 2002; Cilia et al., 2007; Cilia et al., 2008; Fasano et al., 2008; Gutierrez et al., 2009; Pagni et al., 2005; Strafella et al., 2007; Tani et al., 2007). The best

location and orientation of the electrode array are generally determined in such a way that bipolar stimulation with an appropriate pair of electrodes. Once the pulse width and frequency have been optimized, most investigators will increase stimulus intensities during the trial using a percentage of the motor threshold as a guide. Many investigators begin by increasing the intensity by 20% of the motor threshold and then increase by 20% increments thereafter to 80% of motor threshold.

3.7 Implantation of IPG

If the test stimulation improves the motor symptom, patients would be returned to the operating room and the electrode(s) is/are connected to implanted pulse generator(s) (Itrel III IPG; Medtronic Inc., Minneapolis, MN, USA), usually placed subcutaneously over the pectoralis muscle under general anesthesia (Figure 6).

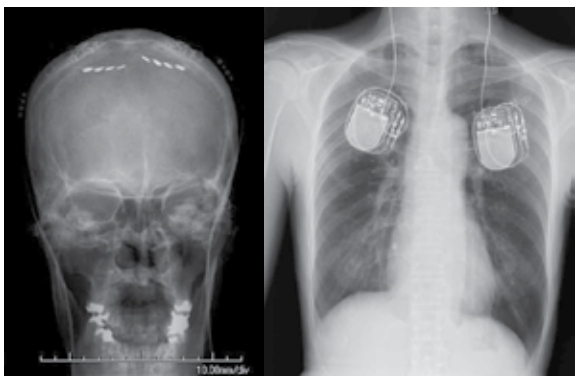


Fig. 6. Subdural electrodes implanted bilaterally on the primary motor cortex and pulse generators. The two Resume II electrodes are connected to pulse generators (Itrel III; Medtronic) that are implanted in the bilateral anterior chests.

4. Clinical outcome

Clinical outcomes from several studies were summerised in Table 1. Variable clinical outcomes after EMCS have been reported in the patients with PD. The limited case series available on literature and the differences in patient selection criteria and stimulus parameters may partly account for the variable clinical benefit reported so far. Basically, the degree of the clinical improvement obtained with EMCS is lower than that reported with DBS (Cilia et al., 2008; Gutierrez et al., 2009). Most of EMCS studies did not find significant mean changes between stimulation-on and stimulation-off in UPDRS part II and III (Cilia et al., 2008; Gutierrez et al., 2009; Strafella et al., 2007). On the other hand, motor evaluation in individual patients revealed clinical improvement during stimulation in comparison to STIM-OFF condition (Cilia et al., 2008; Fasano et al., 2008; Gutierrez et al., 2009; Strafella et al., 2007; Tani et al., 2007). These published data must be interpreted very cautiously, because they are from open labelled studies that involved only small numbers of patients from a few centres. The clinical benefits from EMCS were observed mainly in axial symptoms, such as gait, stooped posture and postural instability. Because axial symptom has small proportion in UPDRS-III (20/108), the benefit of EMCS for axial symptom does not change a lot in UPDRS-III score. Additionally, clinical improvement by EMCS occurs

Authors	Cases	Stimulation condition	clinical outcome
Cilla	6	epidural, unilateral, monopolar, 40-60 Hz, 3.0 ± 0.67 V, 180 -210 μsec	No significant mean changes in UPDRS-II (40% improvement), UPDRS-III (20% improvement), as well as medication dose (15% reduction) between baseline, 6-month STIM-ON and 6-month STIM-OFF. Objective motor benefit was observed mainly in axial symptoms, such as gait, stooped posture and postural instability.
Pagni	6	epidural, unilateral, bipolar, 25-40 Hz, 2.5-6 V, 100-180 μsec	UPDRS: tremor;bilateraly more than 80% reduction in 3 of 4 cases, rigidity; more than 50% reduction in 5 of 6 cases in contralateral side and in 4 of 6 cases in ipsilateral side, activityies of daily living; more than 50 % reduction in 3 of 6 cases, axial symptom.; more than 50% reduction in 3 of 6 cases, dyskinesia; more than 50% reduction in 4 of 5 cases, 11-70 % reduction of L-dapa daily dose
Strafella	4	subdural, unilateral, 50 or 130 Hz, 3-5 V, 60-90 μsec	No reduction of daily L-dopa dose, no significant difference in the UPDRS motor score between OFF stimulation (43.0 ± 7.9) and ON stimulation (39.5 ±12.5).
Gutierrez	6	epidural, unilateral, bipolar, 10-30 Hz, 3-4.5 V, 330-450 μsec	Mild improvement in 2 of 6 cases (14.7% and 7.3% improvement in UPDRS-III)(on stimulation on medication vs off stimulation on medication), 17.1 ± 11.1% reduction of L-dopa daily dose.
Canavero	3	epidural, unilateral, bipolar, 20-31 Hz, 2-3.5 V, 90-330 μsec	Case 1; independent walk, absence of rigidity, trochlea, and tremor to all four limbs, 80% reduction of L-dopa daily dose. Case 2; 50% improvement of UPDRS-III, absense of freezing gait, tremor, improvement of bradykinesia, 70% reduction of L-dopa daily dose. Case 3; absence of tremor, rigidity, improvement of gait and speech.
Fasano	1	epidural, bilateral, bipolar, 130 Hz, subthreshold intensity, 120 μsec	20% improvement of UPDRS-III, mainly in Axial score (UPDRS items 27-30).
Tani	1	subdural, bilateral, bipolar, 100 Hz, 1.8 V, 210 μsec	50% improvement of UPDRS-III and dramatic improvement in walking

Table 1. Summery of clinical outcomes

after a variable time interval - most often several days up to 4 weeks - after stimulation parameters modifications (Cilia et al., 2008). Several investigators reported that rigidity and tremor were abolished within several minutes of stimulation, but the full effect on bradykinesia and axial symptom, especially gait disturbance, were appreciated only after a longer period of stimulation, with a slow worsening over more than 2 days period after stimulation-off (Canavero et al., 2002; Cilia et al., 2008; Pagni et al., 2003; Tani et al., 2007). In some studies, the motor symptom assessments were done in shorter period after the modification of stimulation parameter, so the benefit in motor symptom could be underestimated.

5. Mechanisms of action

The exact mechanisms of action of EMCS are poorly understood. It is noteworthy that, whereas the effects of EMCS on rigidity and tremor are almost immediate (observed within the first minute of stimulation), the clinical benefit on akinesia and axial symptom necessitate a longer stimulation time to become detectable. The latency of the clinical effects of high-frequency STN-DBS is also known to vary from one type of parkinsonian motor symptoms to another with short latency benefit (less than 1 min) observed for rigidity and tremor and longer time delay (a few minutes, up to a few days) observed for other symptoms such as bradykinesia and akinesia (Krack et al., 2002). As discussed by others, the delays of clinical benefits observed with EMCS may be due to synaptic plasticity, long-term potentiation, long-term depression, expression of secondary messengers or polarization of brain tissue (Drouot et al., 2004; Krack et al., 2002; Priori and Lefaucheur, 2007), and the immediate effects may be due to the dual effect - imposing a specific pattern of activity and suppress abnormal, disease-associated rhythmicity of oscillation in corticobasal ganglia-cortical circuit (Brown, 2006; Fasano et al., 2008; Garcia et al., 2003; Priori and Lefaucheur, 2007).

Studies of rTMS of M1 reveal that PD is associated with excess excitability or reduced inhibition at the M1 (Cantello et al., 2002), and rigidity and tremor might be caused by hyperactivity of the M1 (Haslinger et al., 2001; Rodriguez-Oroz et al., 2009). In the patients with PD, during production of a voluntary output, its activation is inadequately modulated, owing, for instance, to reduction of intracortical inhibitory mechanisms mediated by γ-aminobutyric acid A (GABA) and GABA receptors (Cantello et al., 2002). Canavero et al. suggests that EMCS increases the cortical GABA in patients affected by central pain syndromes (Canavero and Bonicalzi, 1995, 1998). EMCS might reduce cortical hyperactivity, increasing GABA concentration and activating inhibitory neurons (Hanajima et al., 2002). Indeed, ECD SPECT data demonstrated a resting state reduction of neuronal activity in motor cortical areas during EMCS (Cilia et al., 2008).

Finally, functional neuroimaging studies showed a significant increase of cerebral perfusion in the SMA and the DLPFC in STIM-ON condition (Drouot et al., 2004; Fasano et al., 2008; Tani et al., 2007). The SMA and the DLPFC are known to be under-active in patients with PD, probably underlying bradykinesia (Haslinger et al., 2001; Jahanshahi et al., 1995; Rascol et al., 1992), and these cortical metabolic abnormalities can be reversed by antiparkinsonian therapies such as dopaminergic treatment (Jenkins et al., 1992), pallidotomy (Grafton et al., 1995), STN-DBS (Limousin et al., 1997) or GPi-DBS (Fukuda et al., 2001). The similarity of these results suggests that these strategies may induce a similar therapeutic benefit in the patients with PD and might have some common mechanism.

Authors	Cases	Stimulation	Modality	Neuroimaging
Cilla	6	unilateral, 40-60 Hz	Tc-SPECT STIM-ON vs STIM-OFF under rest	Decrease in bilateral M1, bilateral premotor cortex, left DLPFC, right caudate nucleus and left middle occipital gyrus Increase in right cerebellar lobe, left inferior occipital gyrus, left cerevellar lobe and vermis.
Strafella	4	unilateral, 50 or 130 Hz	[^{15}O] H_2O PET movement vs rest	the changes in rCBF were not significantly different when comparing across different stimulation setting (OFF vs 50 Hz vs 130 Hz).
Canavero	3	unilateral, 20 - 31 Hz	IBZM-SPECT	Before EMCS, asymmetrical binding (right less than left) in the basal ganglia During EMCS, renormalization of basal ganglia anomalies
			ECD-SPECT	Before EMCS, bilateral parieto-temporal hypoperfusion. During EMCS, renormalization of cortical metabolism on the side of stimulation but not contralaterally.
Fasano	1	bilateral, 130 Hz	ECD-SPECT STIM-OFF vs STIM-ON (medication off)	increase in the right frontal, right parietal cortex and left frontal cortex.
Tani	1	bilateral, 100 Hz	[^{15}O] H_2O PET STIM-OFF vs STIM-ON (medication on)	increase in the left SMA and right DLPFC.

Table 2. Summery of the functional neuroimaging

6. Complication

The only complication reported concerning EMCS for PD was misplaced electrode (Pagni et al., 2005). Because of the small number of the cases of EMCS for PD, we summarize the reported complication of EMCS for intractable pain patients in this section.

While a majority of studies have reported no adverse events with EMCS (Gharabaghi et al., 2005; Saitoh et al., 2000; Tsubokawa et al., 1991b), serious complications have been reported. Montes et al. (Montes et al., 2002) analyzed event-related potentials (ERPs) and behavioral performance during an auditory target-detection task in 11 consecutive patients obtained during EMCS and 10 minutes after switching off stimulation. While sensory responses remained unaffected by EMCS, there was a significant delay of brain potentials reflecting

target detection in the older patients, rapidly reversible after EMCS discontinuation. No effect was observed in patients younger than 50 years. Cognitive effects of EMCS appeared as mild and non-specific, directly related to the stimulation period (i.e. with no post-effect), in a manner reminding of cognitive effects reported during rTMS on M1. Thus, EMCS may interfere with relatively simple cognitive processes such as those underlying target detection, notably in the elderly and in the presence of preexistent cerebral lesions.

Occurrence of epileptic seizures has been reported during test stimulation in a minority of patients. The low rate of epileptic seizures during chronic stimulation (0.2%) means that stimulation of M1 within an appropriate range of parameters is reasonably safe. The most serious reported complications are epidural or subdural hematomas. These are definitely exceptional with an extradural approach, and some surgeons never observed one, making the risk of peri-operative hemorrhage much lower compared to DBS.

Some wound infections have been reported by most neurosurgeons. If the infection occurs, all devices including the paddle, extension leads, and pulse generators must be removed temporally. The implanted pulse generator (IPG) can accidentally turn off due to electromagnetic interference from household devices in close (<10 cm) proximity, such as electric appliances of any kind, but also anti-theft devices and metal detectors or magnets in loudspeakers.

At impedances >2000 Ω, a connection problem, such as a broken cable or a lead fracture, must be suspected. The operator should thus measure impedance in a unipolar configuration in order to assign a value to the single contact.

7. Conclusion

EMCS can provide some different benefit for the patients with PD from STN-DBS. Although the degree of clinical improvement of EMCS is lower than that of DBS, the fact that EMCS can improve axial symptom of PD, which is difficult even with STN-DBS, is an irreplaceable gift for some part of patients with PD, and its less surgical invasiveness than DBS can make the surgery safer for the patients with advanced age or sever brain atrophy.

8. References

Andre-Obadia, N., Peyron, R., Mertens, P., Mauguiere, F., Laurent, B., Garcia-Larrea, L. (2006). Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. *Clin Neurophysiol*, 117, 1536-1544, ISSN 1388-2457

Bejjani, B.P., Gervais, D., Arnulf, I., Papadopoulos, S., Demeret, S., Bonnet, A.M., Cornu, P., Damier, P., Agid, Y. (2000). Axial parkinsonian symptoms can be improved: the role of levodopa and bilateral subthalamic stimulation. *J Neurol Neurosurg Psychiatry*, 68, 595-600, ISSN 0022-3050

Boylan, L.S., Pullman, S.L., Lisanby, S.H., Spicknall, K.E., Sackeim, H.A. (2001). Repetitive transcranial magnetic stimulation to SMA worsens complex movements in Parkinson's disease. *Clin Neurophysiol*, 112, 259-264, ISSN 1388-2457

Brown, P. (2006). Bad oscillations in Parkinson's disease. *J Neural Transm Suppl*, 27-30, ISSN 0303-6995

Canavero, S., Bonicalzi, V. (1995). Cortical stimulation for central pain. *J Neurosurg*, 83, 1117, ISSN 0022-3085

Canavero, S., Bonicalzi, V. (1998). The neurochemistry of central pain: evidence from clinical studies, hypothesis and therapeutic implications. *Pain*, 74, 109-114, ISSN 0304-3959

Canavero, S., Bonicalzi, V. (2002). Therapeutic extradural cortical stimulation for central and neuropathic pain: a review. *Clin J Pain*, 18, 48-55, ISSN 0749-8047

Canavero, S., Bonicalzi, V., Paolotti, R., Castellano, G., Greco-Crasto, S., Rizzo, L., Davini, O., Maina, R. (2003). Therapeutic extradural cortical stimulation for movement disorders: a review. *Neurol Res*, 25, 118-122, ISSN 0161-6412

Canavero, S., Paolotti, R., Bonicalzi, V., Castellano, G., Greco-Crasto, S., Rizzo, L., Davini, O., Zenga, F., Ragazzi, P. (2002). Extradural motor cortex stimulation for advanced Parkinson disease. Report of two cases. *J Neurosurg*, 97, ISSN 1208-1211

Cantello, R., Tarletti, R., Civardi, C. (2002). Transcranial magnetic stimulation and Parkinson's disease. *Brain Res Brain Res Rev*, 38, 309-327, ISSN 0165-0173

Cilia, R., Landi, A., Vergani, F., Sganzerla, E., Pezzoli, G., Antonini, A. (2007). Extradural motor cortex stimulation in Parkinson's disease. *Mov Disord*, 22, 111-114, ISSN 0885-3185

Cilia, R., Marotta, G., Landi, A., Isaias, I.U., Vergani, F., Benti, R., Sganzerla, E., Gerundini, P., Pezzoli, G., Antonini, A. (2008). Cerebral activity modulation by extradural motor cortex stimulation in Parkinson's disease: a perfusion SPECT study. *Eur J Neurol*, 15, 22-28, ISSN 1468-1331

Drouot, X., Oshino, S., Jarraya, B., Besret, L., Kishima, H., Remy, P., Dauguet, J., Lefaucheur, J.P., Dolle, F., Conde, F., Bottlaender, M., Peschanski, M., Keravel, Y., Hantraye, P., Palfi, S. (2004). Functional recovery in a primate model of Parkinson's disease following motor cortex stimulation. *Neuron*, 44, 769-778, ISSN 0896-6273

Fasano, A., Piano, C., De Simone, C., Cioni, B., Di Giuda, D., Zinno, M., Daniele, A., Meglio, M., Giordano, A., Bentivoglio, A.R. (2008). High frequency extradural motor cortex stimulation transiently improves axial symptoms in a patient with Parkinson's disease. *Mov Disord*, 23, 1916-1919, ISSN 1531-8257

Fukuda, M., Mentis, M., Ghilardi, M.F., Dhawan, V., Antonini, A., Hammerstad, J., Lozano, A.M., Lang, A., Lyons, K., Koller, W., Ghez, C., Eidelberg, D. (2001). Functional correlates of pallidal stimulation for Parkinson's disease. *Ann Neurol*, 49, 155-164, ISSN 0364-5134

Garcia, L., Audin, J., D'Alessandro, G., Bioulac, B., Hammond, C. (2003). Dual effect of high-frequency stimulation on subthalamic neuron activity. *J Neurosci*, 23, 8743-8751, ISSN 1529-2401

Gharabaghi, A., Hellwig, D., Rosahl, S.K., Shahidi, R., Schrader, C., Freund, H.J., Samii, M. (2005). Volumetric image guidance for motor cortex stimulation: integration of three-dimensional cortical anatomy and functional imaging. *Neurosurgery*, 57, 114-120; discussion 114-120, ISSN 1524-4040

Grafton, S.T., Waters, C., Sutton, J., Lew, M.F., Couldwell, W. (1995). Pallidotomy increases activity of motor association cortex in Parkinson's disease: a positron emission tomographic study. *Ann Neurol*, 37, 776-783, ISSN 0364-5134

Greenberg, M., (2010). *Handbook of neurosurgery*, (5 ed), Thieme, ISBN 1604063262, New York

Gutierrez, J.C., Seijo, F.J., Alvarez Vega, M.A., Fernandez Gonzalez, F., Lozano Aragoneses, B., Blazquez, M. (2009). Therapeutic extradural cortical stimulation for Parkinson's Disease: report of six cases and review of the literature. *Clin Neurol Neurosurg*, 111, 703-707, ISSN 1872-6968

Hamada, M., Ugawa, Y., Tsuji, S., (2008) High-frequency rTMS over supplementary motor area for treatment of Parkinson's disease. Mov Disord 23, 1524-1531

Hanajima, R., Ashby, P., Lang, A.E., Lozano, A.M. (2002). Effects of acute stimulation through contacts placed on the motor cortex for chronic stimulation. *Clin Neurophysiol*, 113, 635-641, ISSN 1388-2457

Haslinger, B., Erhard, P., Kampfe, N., Boecker, H., Rummeny, E., Schwaiger, M., Conrad, B., Ceballos-Baumann, A.O. (2001). Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. *Brain*, 124, 558-570, ISSN 0006-8950

Holsheimer, J., Nguyen, J.P., Lefaucheur, J.P., Manola, L. (2007). Cathodal, anodal or bifocal stimulation of the motor cortex in the management of chronic pain? *Acta Neurochir Suppl*, 97, 57-66, ISSN 0065-1419

Hosomi, K., Saitoh, Y., Kishima, H., Oshino, S., Hirata, M., Tani, N., Shimokawa, T., Yoshimine, T. (2008). Electrical stimulation of primary motor cortex within the central sulcus for intractable neuropathic pain. *Clin Neurophysiol,* 119, 993-1001, ISSN 1388-2457

Jahanshahi, M., Jenkins, I.H., Brown, R.G., Marsden, C.D., Passingham, R.E., Brooks, D.J. (1995). Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain*, 118 (Pt 4), 913-933, ISSN 0006-8950

Jenkins, I.H., Fernandez, W., Playford, E.D., Lees, A.J., Frackowiak, R.S., Passingham, R.E., Brooks, D.J. (1992). Impaired activation of the supplementary motor area in Parkinson's disease is reversed when akinesia is treated with apomorphine. *Ann Neurol*, 32, 749-757, ISSN 0364-5134

Katayama, Y., Fukaya, C., Yamamoto, T. (1998). Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response. *J Neurosurg*, 89, 585-591, ISSN 0022-3085

Khedr, E.M., Rothwell, J.C., Shawky, O.A., Ahmed, M.A., Hamdy, A. (2006). Effect of daily repetitive transcranial magnetic stimulation on motor performance in Parkinson's disease. *Mov Disord*, 21, 2201-2205, ISSN 0885-3185

Kleiner-Fisman, G., Fisman, D.N., Sime, E., Saint-Cyr, J.A., Lozano, A.M., Lang, A.E. (2003). Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson disease. *J Neurosurg*, 99, 489-495, ISSN 0022-3085

Koch, G., Brusa, L., Caltagirone, C., Peppe, A., Oliveri, M., Stanzione, P., Centonze, D. (2005). rTMS of supplementary motor area modulates therapy-induced dyskinesias in Parkinson disease. *Neurology*, 65, 623-625, ISSN 1526-632X

Krack, P., Fraix, V., Mendes, A., Benabid, A.L., Pollak, P. (2002). Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. *Mov Disord*, 17 Suppl 3, S188-197, ISSN 0885-3185

Krack, P., Pollak, P., Limousin, P., Hoffmann, D., Xie, J., Benazzouz, A., Benabid, A.L. (1998). Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. *Brain*, 121 (Pt 3), 451-457, ISSN 0006-8950

Lefaucheur, J.P., Drouot, X., Von Raison, F., Menard-Lefaucheur, I., Cesaro, P., Nguyen, J.P. (2004). Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease. *Clin Neurophysiol*, 115, 2530-2541, ISSN 1388-2457

Leichnetz, G.R. (1986). Afferent and efferent connections of the dorsolateral precentral gyrus (area 4, hand/arm region) in the macaque monkey, with comparisons to area 8. *J Comp Neurol*, 254, 460-492, ISSN 0021-9967

Limousin, P., Greene, J., Pollak, P., Rothwell, J., Benabid, A.L., Frackowiak, R. (1997). Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Ann Neurol*, 42, 283-291, ISSN 0364-5134

Limousin, P., Krack, P., Pollak, P., Benazzouz, A., Ardouin, C., Hoffmann, D., Benabid, A.L. (1998). Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med*, 339, 1105-1111, ISSN 0028-4793

Lopiano, L., Rizzone, M., Bergamasco, B., Tavella, A., Torre, E., Perozzo, P., Lanotte, M. (2002). Deep brain stimulation of the subthalamic nucleus in PD: an analysis of the exclusion causes. *J Neurol Sci*, 195, 167-170, ISSN 0022-510X

Lyons, K.E., Wilkinson, S.B., Overman, J., Pahwa, R. (2004). Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. *Neurology*, 63, 612-616, ISSN 1526-632X

Manola, L., Holsheimer, J., Veltink, P., Buitenweg, J.R. (2007). Anodal vs cathodal stimulation of motor cortex: a modeling study. *Clin Neurophysiol*, 118, 464-474, ISSN 1388-2457

Montes, C., Mertens, P., Convers, P., Peyron, R., Sindou, M., Laurent, B., Mauguiere, F., Garcia-Larrea, L. (2002). Cognitive effects of precentral cortical stimulation for pain control: an ERP study. *Neurophysiol Clin*, 32, 313-325, ISSN 0987-7053

Naidich, T.P., Blum, J.T., Firestone, M.I. (2001). The parasagittal line: an anatomic landmark for axial imaging. *AJNR Am J Neuroradiol*, 22, 885-895, ISSN 0195-6108

Naidich, T.P., Valavanis, A.G., Kubik, S. (1995). Anatomic relationships along the low-middle convexity: Part I--Normal specimens and magnetic resonance imaging. *Neurosurgery*, 36, 517-532, ISSN 0148-396X

Nguyen, J.P., Lefaucheur, J.P., Decq, P., Uchiyama, T., Carpentier, A., Fontaine, D., Brugieres, P., Pollin, B., Feve, A., Rostaing, S., Cesaro, P., Keravel, Y. (1999). Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. *Pain*, 82, 245-251, ISSN 0304-3959

Pagni, C.A., Zeme, S., Zenga, F. (2003). Further experience with extradural motor cortex stimulation for treatment of advanced Parkinson's disease. Report of 3 new cases. *J Neurosurg Sci*, 47, 189-193, ISSN 0390-5616

Pagni, C.A., Zeme, S., Zenga, F., Maina, R. (2005). Extradural motor cortex stimulation in advanced Parkinson's disease: the Turin experience: technical case report. *Neurosurgery*, 57, E402; discussion E402, ISSN 1524-4040

Pahwa, R., Wilkinson, S.B., Overman, J., Lyons, K.E. (2005). Preoperative clinical predictors of response to bilateral subthalamic stimulation in patients with Parkinson's disease. *Stereotact Funct Neurosurg*, 83, 80-83, ISSN 1011-6125

Pal, E., Nagy, F., Aschermann, Z., Balazs, E., Kovacs, N. (2010). The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: a randomized, double-blind, placebo-controlled study. *Mov Disord*, 25, 2311-2317, ISSN 1531-8257

Priori, A., Lefaucheur, J.P. (2007). Chronic epidural motor cortical stimulation for movement disorders. *Lancet Neurol*, 6, 279-286, ISSN 1474-4422

Rasche, D., Ruppolt, M., Stippich, C., Unterberg, A., Tronnier, V.M. (2006). Motor cortex stimulation for long-term relief of chronic neuropathic pain: a 10 year experience. *Pain*, 121, 43-52, ISSN 0304-3959

Rascol, O., Sabatini, U., Chollet, F., Celsis, P., Montastruc, J.L., Marc-Vergnes, J.P., Rascol, A. (1992). Supplementary and primary sensory motor area activity in Parkinson's disease. Regional cerebral blood flow changes during finger movements and effects of apomorphine. *Arch Neurol*, 49, 144-148, ISSN 0003-9942

Rodriguez-Oroz, M.C., Jahanshahi, M., Krack, P., Litvan, I., Macias, R., Bezard, E., Obeso, J.A. (2009). Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms. *Lancet Neurol*, 8, 1128-1139, ISSN 1474-4465

Saitoh, Y., Shibata, M., Hirano, S., Hirata, M., Mashimo, T., Yoshimine, T. (2000). Motor cortex stimulation for central and peripheral deafferentation pain. Report of eight cases. *J Neurosurg*, 92, 150-155, ISSN 0022-3085

Saitoh Y, Hosomi K: Chapter 2. From localization to surgical implantation. In Textbook of therapeutic cortical stimulation Ed: Sergio Canavero, Nova Science Publishers, Inc. Hauppauge NY, 2009

Strafella, A.P., Lozano, A.M., Lang, A.E., Ko, J.H., Poon, Y.Y., Moro, E. (2007). Subdural motor cortex stimulation in Parkinson's disease does not modify movement-related rCBF pattern. *Mov Disord*, 22, 2113-2116, ISSN 0885-3185

Tani, N., Saitoh, Y., Kishima, H., Oshino, S., Hatazawa, J., Hashikawa, K., Yoshimine, T. (2007). Motor cortex stimulation for levodopa-resistant akinesia: case report. *Mov Disord*, 22, 1645-1649, ISSN 0885-3185

Thickbroom, G.W., Byrnes, M.L., Walters, S., Stell, R., Mastaglia, F.L. (2006). Motor cortex reorganisation in Parkinson's disease. *J Clin Neurosci*, 13, 639-642, ISSN 0967-5868

Tirakotai, W., Hellwig, D., Bertalanffy, H., Riegel, T. (2007). Localization of precentral gyrus in image-guided surgery for motor cortex stimulation. *Acta Neurochir Suppl*, 97, 75-79, ISSN 0065-1419

Tsubokawa, T., Katayama, Y., Yamamoto, T., Hirayama, T., Koyama, S. (1991a). Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir Suppl (Wien)*, 52, 137-139, ISSN 0065-1419

Tsubokawa, T., Katayama, Y., Yamamoto, T., Hirayama, T., Koyama, S. (1991b). Treatment of thalamic pain by chronic motor cortex stimulation. *Pacing Clin Electrophysiol*, 14, 131-134, ISSN 0147-8389

Umemura, A., Jaggi, J.L., Hurtig, H.I., Siderowf, A.D., Colcher, A., Stern, M.B., Baltuch, G.H. (2003). Deep brain stimulation for movement disorders: morbidity and mortality in 109 patients. *J Neurosurg*, 98, 779-784, ISSN 0022-3085

Velasco, M., Velasco, F., Brito, F., Velasco, A.L., Nguyen, J.P., Marquez, I., Boleaga, B., Keravel, Y. (2002). Motor cortex stimulation in the treatment of deafferentation pain. I. Localization of the motor cortex. *Stereotact Funct Neurosurg*, 79, 146-167, ISSN 1011-6125

Wood, C.C., Spencer, D.D., Allison, T., McCarthy, G., Williamson, P.D., Goff, W.R. (1988). Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. *J Neurosurg*, 68, 99-111, ISSN 0022-3085

24

Joint Replacement Surgery in Parkinson's Disease

Adrian J. Cassar Gheiti, Joseph F. Baker and Kevin J. Mulhall
Orthopaedic Research and Innovation Foundation
Republic of Ireland

1. Introduction

Parkinson Disease affects 4 million people worldwide and it is the second most common neurological disorder after Alzheimer disease (Huse et al. 2005). It occurs in 1% of the population over the age of 60 years (Adams et al. 1997). The annual incidence of Parkinson's disease is 20.5 per 100,000 (Rajput et al. 1984) and can result in numerous symptoms including tremor, muscular rigidity and abnormalities of gait, posture and facial expression. Despite optimal pharmacological treatment, progression of Parkinson's disease normally results in a decline in general mobility and ability to ambulate safely.

Rigidity secondary to Parkinson's Disease often aggravates joint pain from osteoarthritis (Adams et al. 1997). The outcome of joint arthroplasty in these patients is effective in relieving pain, but the overall functional results have been found to be variable (Oni et al. 1985; Vince et al. 1989; Duffy et al. 1996; Koch et al. 1997; Weber et al. 2002; Shah et al. 2005; Kryzak et al. 2009; Kryzak et al. 2010). A report from the Scottish joint registry has found an annual prevalence of Parkinson's disease of 5% to 8% in patients undergoing total hip arthroplasty (Meek et al. 2006). Optimal management of the disease before, during and after surgery is a challenge due to the neurological disturbances in Parkinson's disease including tremor, rigidity, contractures and gait abnormalities.

We will firstly provide an overview of the difficulties faced when planning surgery in patients with Parkinson's disease before discussing specific pre-, intra- and post-operative measures that should be taken. Finally we will provide an overview of the evidence available for arthroplasty in Parkinson's disease specific to the three major joints replaced – hip, knee and shoulder.

2. Parkinson's disease and surgery

Patients with Parkinson's disease usually suffer from rigidity, contractures, tremor and gait abnormalities. People with Parkinson's disease who undergo surgery have longer hospital stays and increased mortality (Pepper et al. 1999). Preoperative fasting regimes can unnecessarily result in reduced or missed administration of dopaminergic medications and subsequent serious complications (Reed et al. 1992). Patients with mild Parkinson's disease are able to tolerate the fasting period but those patients with advanced Parkinson's disease, who are under high doses of levodopa are susceptible to the condition Neuroleptic Malignant Syndrome with associated fever, confusion, raised concentration of muscle

enzymes and even death (Ueda et al. 1999). The disease itself predisposes these patients to increased risk of aspiration pneumonia and urinary tract infection compared to patients without the disease (Pepper et al. 1999).
Discharge from hospital after surgery is more difficult in those with Parkinson's disease. Patients are more likely to suffer from intra – operative and post-operative complication including falls and fractures. A longer duration of hospital stay than in patient without Parkinson's disease can be anticipated and appropriate planning is necessary (Mueller et al. 2009). Planning consists of medical and surgical optimisation and also appropriate consideration to prehabilitation, rehabilitation and convalescent requirements.

2.1 Pre – operative management

2.1.1 Pharmacologic management

Patients with Parkinson's disease require advance planning, appropriate medication and specialist neurological advice for optimisation of pharmacological management of the disease before, during and after surgery (Brennan et al. 2010). Ideally these patients are screened at the pre – assessment clinic, and advice should be sought from a neurologist or geriatrician. The neurologist can give advice about the patient treatment regimen for the period around the operation and to consider any additional measures required. Brennan and Genever have reported that oral medications should be continued until time of anaesthetic induction and that patients with Parkinson's disease are ideally placed at the start of the operating list. This facilitates greater predictability over the time of fasting and surgery.
Alternative Parkinson's drugs such as apomorphine and rotigontine can be used in the post-operative period, when post-operative ileus or delayed gastric emptying can be anticipated. Apomorphine is a potent dopamine agonist which is delivered subcutaneously, but can cause severe emesis and need the concomitant use of an anti-emetic such as domperidon. Rotigontine is delivered transdermally; it has ease of use and tolerability but may not provide adequate treatment in patients with severe Parkinson's disease (Brennan et al. 2010).
Parkinsonian medication should not be withheld prior to surgery. Although some can tolerate missed doses, there are reports of Neuroleptic Malignant Syndrome in cases where the regular dose has been omitted (Ueda et al. 1999). Mason et al have provided a detailed list of pre-anaesthetic assessments that should be carried out prior to surgery (Mason et al. 1996). This list details a number of features to look for by system and appropriate investigations (Table 1, page 511).
Respiratory complications are possible as a significant number of patients with Parkinson's Disease have an obstructive picture on pulmonary function testing (Neu et al. 1967). Orthostatic hypotension is a potential problem and agents that cause or contribute to peripheral vasodilatation can exacerbate this. Hypovolaemia secondary to surgical blood loss needs to be attended to as this can clearly contribute to lower blood pressure and risk of subsequent fall. Administration of medications such as tricyclic anti-depressants may also contribute to a fall in blood pressure and should be used with caution in this patient population (Nicholson et al. 2002).

2.1.2 Bone mineral density

Several studies have shown that patient with Parkinson's disease have decreased bone mineral density (BMD) and are prone to vitamin D deficiency when compared to the general

System	Assessment by history	Tests
Head and neck	Pharyngeal muscle dysfunction Dysphagia Sialorrhoea Blepharospasm	
Respiratory	Respiratory impairment from rigidity, bradykinesia or uncoordinated involuntary movement of the respiratory muscles	Chest radiograph Pulmonary function tests Arterial blood gases
Cardiovascular	Orthostatic hypotension Cardiac arrhythmias Hypertension Autonomic dysfunction	ECG
Gastrointestinal	Weight loss Poor nutrition Susceptibility to reflux	Serum albumin/transferrin Skin test allergy
Urological	Difficulty in micturition	
Endocrine	Abnormal glucose metabolism (selegiline)	Blood glucose concentration
Musculoskeletal	Muscle rigidity	
Central Nervous System	Muscle rigidity Akinesia Tremor Confusion Depression Hallucinations Speech impairment	

Table 1. Recommended assessment of the patient with Parkinson's disease(Mason et al. 1996)

population (Kao et al. 1994; Sato et al. 1997; Fink et al. 2005; Sato et al. 2005). Patients with Parkinson's disease tend to be less active than patients without the disease, and lack of sunlight absorption makes these patients more likely to be ostopenic. Rigidity and bradykinesia result in reduction in spontaneous movements, rendering the patient less mobile and active. Lack of mobilization stimulates bone calcium resorption, secondary to disuse and lack of weight bearing (Clouston et al. 1987; Gross et al. 1995; Inoue 2010). Patients with Parkinson's disease with low BMD are have twice as much the risk of fractures when compared with osteoporotic patients without the disease(Taylor et al. 2004).

Those with poor bone quality are at an increased are at increased risk of intraoperative fracture during joint arthroplasty particularly during femoral stem insertion in uncemented THA when hoop stresses are at their greatest (Hernigou et al. 2006). In an experimental *in vitro* study Thomsen et al found that patients with poor bone quality treated with uncemented THA are at higher risk of periprosthetic fracture and recommended that cemented stems should be used in this group of patients(Thomsen et al. 2008). Improving

the patient bone density or preventing continuing bone loss is therefore important before joint arthroplasty is considered in patient with PD.

All patients with Parkinson's disease referred for orthopaedic assessment for possible joint arthroplasty should be screened for osteoporosis and treated appropriately. Bisphosphonates are known to reduce osteoclastic activity and immobilization induced bone loss has been successfully treated with these agents (Yates et al. 1984; Sato et al. 2007). In a randomized control trial in patients undergoing cemented TKA, Hilding et al. showed that daily treatment with 400mg of clodronate reduced tibial component migration by 25% when compared with placebo at 6 months following surgery(Hilding et al. 2000). Friedl et al. have identified reduced migration of cementless acetabular cups in THA over 2 years following a single dose of intravenous zoledronate in patients undergoing THA for avascular necrosis(Friedl et al. 2009). However, other authors have found the effect of bisphosphonates less promising with no beneficial effect of systemic bisphosphonates seen over 2 years after hybrid THA and cementless TKA(Wilkinson et al. 2005; Hansson et al. 2009).

Patients with PD are also reported to have abnormal bone metabolism(Sato et al. 2005) resulting from reduced parathyroid hormone. Recent studies using teriparatide, a recombinant human parathyroid hormone, for the treatment of reduced BMD are showing promising results (Aspenberg et al. 2010; Ma et al. 2011; Moricke et al. 2011) but so far none of the studies are related to patients with PD.

2.1.3 Physiotherapy

Physiotherapy has proven functional improvements in patients with PD and this needs to be considered in the planning for arthroplasty surgery (Formisano et al. 1992). Physiotherapy should not be left for the post-operative phase and emerging evidence suggests that it should play a greater role prior to surgery than we realize. Prehabilitation is fast growing to be a recognized as a potential key element in arthroplasty pathways and this has been particularly noted in patients undergoing total knee arthroplasty (Jaggers et al. 2007; Topp et al. 2009; Swank et al. 2011). Patients with PD should not be exempt from this more of preparation, and given the potential for poor mobility, loss of muscle mass and bone mineral density in this cohort, it may be even more prudent to direct these individuals for prehabilitation prior to surgery.

Nocera et al have found that knee extensor strength has a negative correlation with disease severity in PD and a positive correlation with dynamic stability (Nocera et al. 2010). Specific physical therapy programs for PD have been shown to be effective for mild to moderate disease severity(Ebersbach et al. 2010) . Allen et al in a randomized controlled trial setting have shown that a prescribed exercise program results in increased muscle strength and a reduced fear of falling in those with PD(Allen et al. 2010). While a painful degenerate joint can prohibit some prescribed exercises, gains made prior to surgery will be transcribed to potential gains made following surgery.

2.2 Intra – operative management

According to the literature, regional anaesthesia is preferred to general anaesthesia, especially in patients who require continues infusion of levodopa/carbidopa therapy during the procedure(Burton et al. 2004). Backus et al have reported a case of post-extubation laryngospasm in an un-anaesthetised patient(Backus et al. 1991). General anaesthesia has

been shown to contribute to post-operative confusion, which adversely affects patient outcomes and prolongs hospital stay (Duffy et al. 1996; Koch et al. 1997; Weber et al. 2002) Propofol which is commonly used to induce general anaesthesia may temporarily supress the tremor associated with Parkinson's disease but it has been also shown to exacerbate dyskinesia (Anderson et al. 1994; Krauss et al. 1996). Wright et al have suggested that low dose ketamine may represent an alternative sedative for use pre-operatively as it reduces dyskinesia and controls Parkinsonian tremor(Wright et al. 2009).
Of the commonly used analgesics during surgery fentanyl and morphine can both result in increased muscular rigidity (Klausner et al. 1988; Berg et al. 1999). Alfentanil has been reported to have resulted in dystonic reactions(Mets 1991)
Succinylcholine can result in hyperkalaemia and should be avoided(Muzzi et al. 1989). Non-depolarizing muscle relaxants are considered safe(Nicholson et al. 2002).

2.2.1 Peri-articular infiltration

A number of randomized control studies (Andersen et al. 2007; Toftdahl et al. 2007; Andersen et al. 2010) show the effectiveness of intra operative local infiltration analgesia (LIA) in the post - operative period. LIA has been used both during TKA and THA with equal effectiveness in pain reduction and reduction in analgesic use in the post - operative period. In a randomized, double blinded, placebo controlled study, LIA was used in hip arthroplasty (Andersen et al. 2007). Patients treated with local infiltration analgesia experienced less pain up to two weeks postoperatively and resulted in less joint stiffness and better function one week after the procedure(Andersen et al. 2007).
Multimodal anaesthetic infiltration around the hip joint has been trialled and reports to date suggest that this is an efficacious way of controlling post-operative pain whilst reducing requirements for rescue analgesia. Busch et al have shown that peri-articular infiltration of a multi-modal analgesic regime has a positive effect on subjective pain following THA and results in a reduced requirement for rescue opiate use via PCA(Busch et al. 2010). Lee et al reported similar results noting that peri-articular infiltration conferred no increased risk for the patient in the post-operative setting. Their multi-modal injection consisted of morphine, ropivacaine and methylprednisolone. Parvataneni et al reported superior control of post-operative pain using peri-articular infiltration of bupivacaine, epinephrine, methylprednisolone, cefuroxime and morphine(Parvataneni et al. 2007). Use of periarticular infiltrations such as these, particularly in hip arthroplasty can minimise subsequent use of opiate based analgesics and reduce the risk of adverse events associated with opiate usage.
Recent studies show that periarticular infiltration at the end of TKA has several advantages over other approaches. In a randomized controlled study by Venditoli et al 42 patients who underwent TKA were randomized either to receive an intraoperative infiltration with ropivacaine followed by an infusion of ropivacaine through 16 gauge catheter on the first post-operative day or control group. Narcotic consumption was less in the first 40 hours post op with improved pain scores during rest and exercise for the first forty eight hours and fewer nausea symptoms during the first five post-operative days than the control group(Vendittoli et al. 2006). It is well known that morphine exerts its analgesic effect by binding to opioid receptors in the central nervous system and peripherally (Stein et al. 1989). In a double blinded, randomized clinical trial Tanaka et al. have shown that patient who were administered intra-articular morphine and bupivacaine had reduced pain scores, a much smaller requirement of systemic analgesia, longer duration between the operation

and the first requirement of systemic analgesia and improvement in the range of motion of the knee joint at time of discharge(Tanaka et al. 2001). Andersen et al. have used a combination intraoperative infiltration of ropivacaine ketorolac and epinephrine combined with and intra-articular infusion of ropivacaine and ketorolac for the first 48 hours post operatively. They found out that peri and intra-articular analgesia with multi modal drugs provided superior pain relief and reduced opioid consumption compared with continuous epidural infusion with ropivacaine combined with intravenous ketorolac(Andersen et al. 2010). These protocols can be used in patients with Parkinson's disease to help reduce the use of opioids in the post-operative period and reducing the risk of multi drug interaction and side effects. Further studies are required, to assess the effectiveness of these protocols in patients with Parkinson's disease.

2.3 Post – operative management

2.3.1 Analgesic management

In joint arthroplasty, pain control after the procedure is one of the major elements in early mobilizations. Most patients are managed with opioid analgesics for the first 24 hours after surgery including the use of patient controlled analgesia (PCA). Opioid analgesics are well known to cause confusion especially in elderly patients.

This type of analgesics effect patients' mental state and can exacerbate Parkinsonian symptoms through the dopaminergic pathway (Chudler et al. 1995; Burton et al. 2004). Opioid analgesic has also been shown to increase the length of stay in hospital in a nationwide study done in Denmark(Husted et al. 2010).

Multimodal analgesia with non-steroidal anti-inflammatory drugs in patients with adequate renal function is reported to be as effective as opioid analgesia with fewer side effects (O'Hara et al. 1997; Post et al. 2010). When using multimodal analgesia, it is especially important to take early advice from the patient's neurologist for potential adverse interaction between the type of analgesic protocol used and the neurological medication regime.

2.3.2 Respiratory function

Post-operative nursing care and rehabilitation are an important factor in patients with Parkinson's disease because these patients are at high risk of for falls and fractures (Melton et al. 2006; Camicioli et al. 2010). Close attention to the respiratory status in this patient cohort following surgery is mandatory. As eluded to earlier, Parkinson's Disease is associated with an obstructive respiratory pattern. This is likely due to the incoordination of the upper airway seen in extra-pyramidal disorders(Vincken et al. 1984). Musculature around the larynx is likely to be affected by the neuromuscular abnormalities in Parkinson's disease. Patients are therefore prone to atelectasis, retained secretions and respiratory tract infections(Easdown et al. 1995). It has been noted that aspiration pneumonia is a not infrequent cause of death(Hughes et al. 1993). Pulmonary physiotherapy and early commencement of ambulation are essential components to help minimise the risk of these complications.

2.3.3 Physiotherapy

Patients with Parkinson's disease require more intensive monitoring than patients without the disease in order to prevent complications such as pressure sores. Earlier mobilization

and physiotherapy regimes improve motor function, respiratory function and may help in preventing muscle contractures (Gobbi et al. 2009; Dereli et al. 2010). The Royal Dutch Society for Physical Therapy (KNGF) has published evidenced based clinical practice guidelines in order to be able to deliver optimal care to patients with PD. These guidelines have been also adopted by the Association of Physiotherapist in Parkinson's disease Europe(Keus et al. 2007). The two treatment strategies recommended in these guidelines are cognitive movement strategies and cueing strategies. These guidelines also emphasize on training joint mobility and training strength which are essential in both the pre- and post-operative period. Hurwitz et al. showed that an exercise program focused on improving joint mobility, in combination with improving mobility and self-care also improved memory(Hurwitz 1989). In a randomized control trail, Schenkman et al. showed that an exercise program focused at improving joint mobility and coordinated moving incorporated in activities of daily living (ADL) improves functional axial rotation and reach(Schenkman et al. 1998). Exercise programs which are, focused on improving muscle strength, may also improve muscle strength in patients with PD (Toole et al. 2000; Hirsch et al. 2003).
Again, in the post-operative phase it is important to remain cognizant of the potential pharmacological interactions that may precipitate orthostatic hypotension and lead to a reduced mobility or increased risk of falling.

3. Parkinson's disease and arthroplasty

There is limited literature focusing on joint arthroplasty in patients with Parkinson's disease and so far there are only 17 studies. Seven studies dealt with fractures of the femoral neck treated with hemi-arthroplasty(Rothermel and Garcia 1972; Coughlin and Templeton 1980; Eventov, Moreno et al. 1983; Staeheli, Frassica et al. 1988; Turcotte, Godin et al. 1990; Clubb, Clubb et al. 2006; Kryzak, Sperling et al. 2010), 6 studies dealt with total knee arthroplasty in Parkinson's disease(Oni and Mackenney 1985; Vince, Insall et al. 1989; Fast, Mendelsohn et al. 1994; Duffy and Trousdale 1996; Erceg and Maricevic 2000; Shah, Hornyak et al. 2005), 2 studies dealt with total hip arthroplasty(Weber, Cabanela et al. 2002; Meek, Allan et al. 2006) and 2 dealt with total shoulder arthroplasty. In this section we will provide an overview of the evidence available for arthroplasty in PD specific to the three major joints replaced – hip, knee and shoulder.

3.1 Hip

3.1.1 Hemiarthroplasty for femoral neck fractures

The 7 studies (Rothermel et al. 1972; Coughlin et al. 1980; Eventov et al. 1983; Staeheli et al. 1988; Turcotte et al. 1990; Clubb et al. 2006; Kryzak et al. 2010), that discussed the outcome of hemi-arthroplasty in Parkinson's disease are not strictly applicable since the procedure is usually undertaken as an emergency or semi-elective procedure, but some inferences can be taken in terms of rates of dislocation and post-operative complications(Table.2. Page 516). However, it must be remembered that the biomechanics of a hemiarthroplasty are different to those in THA.
Turcotte, et al(Turcotte et al. 1990) reported that out of 41 patients undergoing 47 hemi-arthroplasty for a Garden III – IV fracture , five subsequently dislocated and four of these within the first month of surgery. Four patients had wound infections, one subsidence of the stem, one acetabular protrusion, one femoral shaft fracture, three decubitus ulcers on the operated limb and one patient died within the first 6 months. Four patients never walked

Study authors	Study type	Arthroplasty (type + numbers)	Mean age (yrs, range)	Length of follow up (yrs)	Implant type/surgical technique	Outcome
Weber et al	retrospective	THR(107)	72 (57 - 87)	7.1 (2 - 21)	94 acetabular cups and 103 femoral stems were cemented, 13 acetabular cups and 4 stems were uncemented	93% pain free, 6% dislocations, 3% aseptic loosening, 26% post oprative medical complication rate
Meek et al	retrospective	THR(2394)	N/A	N/A	N/A	0.46 annual dislocation rate
Kryzak et al	retrospective	Hemi hip		0.5 - 6 years	posterior approach, various types of endo prosthesis	6 month mortality 75%, 37% dislocation, 8.3% deep wound infection
Clubb et al	Literature review	Hemi hip	N/A	N/A	N/A	N/A
Eventov et al	retrospective	Hemi hip (62)	74 (61 - 90)	N/A	34 patients had a hemiarthroplasty using the posterolateral approach, 11 underwent plate and nail fixation , the rest were treated non operativly	31% mortality at 3 months, pneumonia most frequent cause of dead, complications highest in the operated group.
Rothermel et al	retrospective	Hemi hip (16)	63.5	N/A	7 treated with hemiarthroplasty, 3 McLaughlin nail, plate and screws, 1 miltiple pins 2 nail and plate and 2 on traction	12.5% flexion contractures,
Coughlin et al	retrospective	Hemi hip (13)	78	0.5 - 6 years	posterior approach, various types of endo prosthesis	6 month mortality 75%, 37% dislocation, 8.3% deep wound infection
Staeheli et al	retrospective	Hemi hip (50)	74.3 (47 - 92)	7.3 years	50% anterolateral approach, 40% posterior approach and 10 % trans trochanteric approach, various prosthesis used	2% dislocation, 20% mortality at 6 months, pneumonia was the most frequent cause of dead
Turcotte et al	retrospective	Hemi hip (47)	74 (51 - 89)	N/A	posterior approach	8.5% wound infection, 11% dislocated, , 2.1% subsidence, 2.1% protrusio acetabuli, 2.1% femoral shaft fracture, 6.4% decubitus ulcers, 15% mortality at 6 months

Table 2. Summary of the studies in patient with Parkinson's disease undergoing THR or Hemiarthroplasty.

again despite being ambulatory prior to surgery. Overall mortality in these patients was 15%(Turcotte et al. 1990) mainly due to increased medical complications.
Other studies had better outcomes with Staeheli et al(Staeheli et al. 1988) reporting only one dislocation out of a series of 49 patients undergoing hemi-arthroplasty for femoral neck fracture, while Eventov et al have reported a 3% dislocation rate (Eventov et al. 1983).
Some studies have reported mortality rates as high 47% within the first 6 months after hemi-arthroplasty of the hip(Coughlin et al. 1980). As in other studies the high mortality rate was mainly due to increased medical complications including myocardial infarction, urosepsis and pneumonia (Staeheli et al. 1988; Turcotte et al. 1990). Aggressive physiotherapy and early mobilization was advised for patients with Parkinson's disease undergoing hemi-arthroplasty(Coughlin et al. 1980; Eventov et al. 1983; Staeheli et al. 1988; Turcotte et al. 1990). Some of these studies have also advised that patients with Parkinson's disease should be treated with internal fixation of the fracture and that hemi-arthroplasty may be contraindicated (Coughlin et al. 1980; Turcotte et al. 1990).

3.1.2 Total hip arthroplasty

Total Hip Arthroplasty (THA) is usually performed in patients with osteoarthritis (OA) (Fig.1. Page 518 & Fig.2. Page 519) to relieve pain and improve joint function. In a review of total hip arthroplasty (THA) in patient with neurological conditions , Queally et al found only two studies in the literature which report the results of THA in patients with Parkinson's disease(Queally et al. 2009). These studies reported lower rates of dislocation than those noted in reported cohorts of hemiarthroplasty in the trauma setting. Meek et al have reported only two dislocations in 1467 patients with Parkinson's disease who underwent THA between 1996 and 2004 as reported in the Scottish National Arthroplasty Registry(Meek et al. 2006). They also found an annual incidence of Parkinson's disease 5% to 8% in patients undergoing THA (Meek et al. 2006).
Weber et al reported a high rate of post-operative complications (26%) in 98 patients with Parkinson's disease after THA at mean follow up at 7.1 years(Weber et al. 2002). An anterolateral approach was used in 56 patients, trans-trochanteric in 36, postero-lateral in 12, and direct lateral in three patients. No dislocations or wound infections were noted. They did note that THA provided a high level of long lasting pain relief and initial improvement in ambulation. Functional decline in the individuals was related to the neurological disease and was not joint specific. There were 6 dislocations in the revision THA group, which included 1 from the trans-trochanteric approach, 1 from the direct lateral and 4 from the anterolateral approach. The low rate of dislocation seen in these 2 studies is mostly related to both advancement in medical management of Parkinson's disease developed in recent years and the wider choice of biomaterials such as constrained liners and larger femoral heads which improve stability at the hip joint. These 2 studies are summarised in Table. 2 (page 516).
General decline in mobility in Parkinson's disease can lead to weakness in abductor muscle function. Application of biomechanical principles suggests that increasing the offset can optimize abductor function by lengthening the abductor lever arm. Contractures may develop in any individual after hip arthroplasty, limiting functional gains. This potential case is probably more likely in PD due to the lower mobility and associated problems with rigidity. Bhave et al have found that administration of botulinum toxin to the contracted muscle groups can help alleviate this problem. Injection to a variety of muscle group including the adductors, abductors and hip flexors resulted in lasting improvement in range of movement for 20 months or more(Bhave et al. 2009).

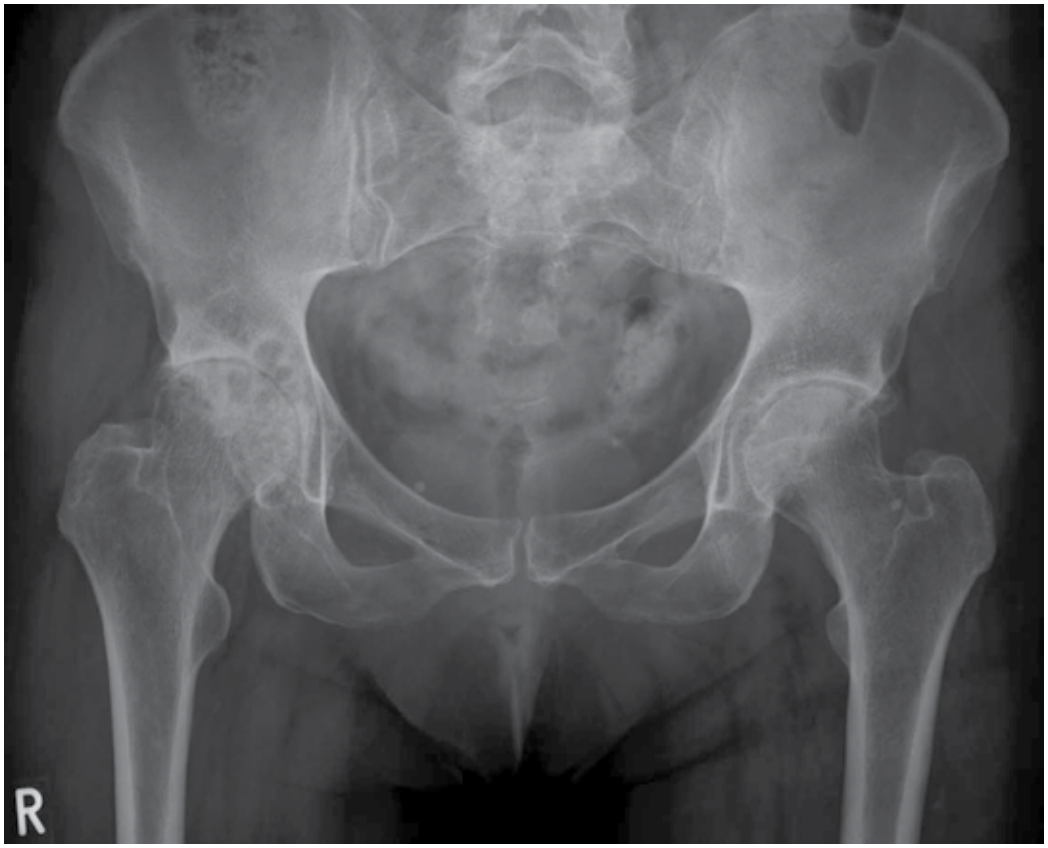


Fig. 1. Anteroposterior radiograph of the pelvis showing, right hip osteoarthritis with a triad of joint space narrowing, subchondral cysts and osteophyte formation.

3.2 Knee

3.2.1 Knee Arthroplasty

Total Knee Arthroplasty (TKA) has been condemned for patients with Parkinson's disease by Oni et al in 1985 when they reported 3 cases of TKA complicated by a persistent flexion contracture of the hamstrings induced by the operation itself(Oni et al. 1985). Quadriceps tendon rupture was also seen in two patients. All three patients died within six months of surgery.

Vince et al reported 13 TKA in 9 patients with Parkinson's disease at time of surgery(Vince et al. 1989). All knees showed fixed flexion before the arthroplasty. Ten joints had a posterior stabilised implant; one revision joint arthroplasty required a customized stem implant and the other two cases underwent a total condylar I and II. Nine of 12 primary knee replacement achieved excellent scores Hospital for Special Surgery knee rating system within the first year and the other 3 had good scores. Even though complications such as urinary tract infections, deep vein thrombosis and pulmonary embolism were common, all patients recovered. The authors' advice that with careful consideration of age and severity of disease TKA; may improve the function of patients with Parkinson's disease by alleviating the pain, correcting flexion deformity and restoring movement.

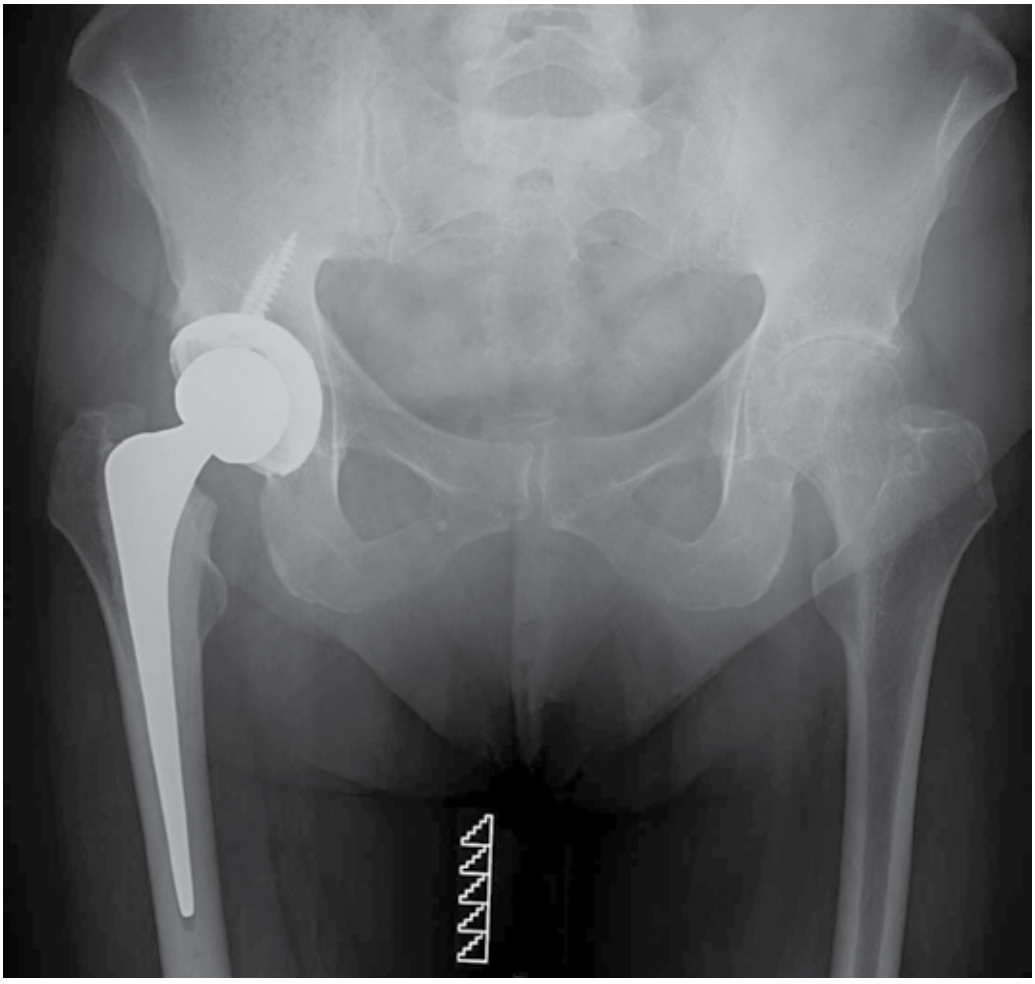


Fig. 2. Anteroposterior radiograph of the pelvis showing a right Hybrid (cemented stem/uncemented acetabular cup)THA and osteoarthritic left hip joint.

Duffy et al reported results from a retrospective review of 24 patients (33 knees) with Parkinson's disease who underwent TKA with patellar resurfacing(Duffy et al. 1996). All patients in this study continued levodopa/carbidopa up to the day of surgery and restarted it within 24 hours of surgery. Knee scores were assessed according to the Knee Society system at 2 months one year and mean follow up of 2.8 (2.2 - 6) years. Pain scores as determined by The Knee society scoring system, improved from a mean of 34 points before surgery to 89 points at the last follow up. On the other hand functional scores did not improve that much with 42 points pre – operatively to 68 points post operatively. Poor functional scores where reported due to progression of Parkinson's disease with increased imbalance, decreased muscle control, and increased rigidity(Duffy et al. 1996). In view of this the authors agree with Vince et al and recommend TKA in reliving the pain of arthritic knees in patient with Parkinson's disease(Vince et al. 1989; Duffy et al. 1996).

Two case reports have highlighted potential problems following TKR (Erceg et al. 2000; Shah et al. 2005). Erceg et al reported a case of recurrent dislocation with a posterior

stabilized TKA in a patient with Parkinson's disease(Erceg et al. 2000). According to the authors, the recurrent posterior dislocation was mainly due to destruction of the cam of the polyethylene tibial insert caused by entrapped cement rather than progression of Parkinson's disease. Flexion contracture seems to be one of the most common complications after TKA in patients with Parkinson's disease (Oni et al. 1985; Duffy et al. 1996; Shah et al. 2005).

Shah et al describe a case which was effectively managed with a manipulation under anaesthesia and motor point blocks of the long head of the biceps femoris and semitendinosus with botulinum toxin type A(Shah et al. 2005). The authors recommend that motor block injection with Botulinum toxin type A may be a viable alternative to open hamstring release in treating flexion contractures in patients with Parkinson's disease(Shah et al. 2005). A summary of these papers is shown in Table. 3 (page 520).

Study authors	Study type	Arthroplasty (type + numbers)	Mean age (yrs, range)	Length of follow up (yrs)	Implant type/surgical technique	Outcome
Oni et al	case series	TKR(3)	76(72 - 83)	2	1 Stanmore , 2 Oxford meniscal TKA	Flexion contracture(3), quads rupture (2), death in 2 years(3)
Shah et al	case series	TKR(1)	61	6.5 months	N/A	Flexion contracture
Vince et al	retrospective	TKR(13)	70(64 - 75)	4.3(1-8)	Condylar type resurfacing arthroplasty, posterior stabilised TKA(10), Custom prosthetic (1), Total conylar I(1), total condoylar II(1), all cemented and all patella resurfaced	flexion contracture (5), patellar fracture 1, patellar subluxation(1), DVT(4), PE(2)
Erceg et al	case series	TKR(1)	65	1	PFC	Recurrent posterior tibial dislocation
Duffy et al	retrospective	TKR(33)	71	2.8(2.2 - 6)	cemented condylar TKA of a single design (press-fit condylar), Johnson & Johnson.	patellar subluxation (2), deep vein thrombosis (2), superficial infection (2), myositis ossificans (1), reoperation (4), patellar fracture (2), deep wound infection(2)

Table 3. Summary of the studies in patient with Parkinson's disease undergoing TKR.

Macauley et al have suggested a list of contraindications for total knee arthroplasty. These include any level of preoperative delirium, any contraindication to regional anaesthesia, re-operative fixed flexion deformity of greater than 25 degrees, a lack of a multidisciplinary team, and a Hoehn and Yahr rating greater than, or equal to, 3 (Table. 4. page 521)(Hoehn et al. 1967). They also propose that failure to respond to a diagnostic intra-articular infiltration

of bupivacaine as a contraindication(Macaulay et al. 2010). Specific pre-operative planning should include appropriate implant selection. Cruciate retaining rather than cruciate substituting prostheses should be used. In severe disease constrained knees or hinged prostheses should be considered. The need for these considerations has been highlighted by the reports of dislocated prostheses (Macauley et al, 2010).
Femoral nerve blockade is contraindicated following knee arthroplasty – early quadriceps motor block could predispose to early development of a knee flexion deformity. Continuous Passive Motion (CPM) is not recommended as this can exacerbate the rigidity experienced.

3.3 Shoulder

3.3.1 Shoulder hemiarthroplasty for proximal humeral fractures

One report has assessed the outcomes of shoulder hemiarthroplasty for proximal humerus fractures (Kryzak et al. 2010). Their retrospective review of seven patients with a minimum of two years follow-up suggested that the surgical outcomes for patients with Parkinson's disease are poor. Mean achievable abduction was 97 degrees, external rotation 38 degrees and internal rotation to the level of the sacrum. Although there was one non-union and one mal-union no patient required revision surgery. On a scale of 1-5 the mean pain score remained as high as 2.5 and the authors concluded that the benefit of this surgical procedure in patients with Parkinson's disease is marginal. Consequently patients need to be counselled regarding the poor prognosis in surgery with anticipated persistent pain and restriction of movement.

Stage 1	Not disabling, mild, unilateral symptoms (e.g. tremor, posture, locomotion, and facial expression).
Stage 2	Bilateral involvement, without impairment of balance. Possibly already a light kyphotic posture, slowness and speech problems. Postural reflexes are still intact.
Stage 3	Significant slowing of body movements, moderate to severe symptoms, postural instability, walking is impaired, but still possible without help, physically independent in ADL
Stage 4	Severe symptoms, rigidity and bradykinesia, partly disabled, walking is impaired, but still possible without
Stage 5	Fully disabled, walking and standing impossible without help, continuous nursing care is necessary

Table 4. The Hoehn and Yahr scale for staging Parkinson's disease (Hoehn et al. 1967).

3.3.2 Total shoulder arthroplasty

There are two studies reviewing patients with Parkinson's disease that underwent a total shoulder arthroplasty (TSA)(Koch et al. 1997; Kryzak et al. 2009)(Table 5. Page 522).
The first study by Koch et al, reviewed 15 patients between 1979 and 1990 who underwent TSA in the Mayo clinic, Rochester(Koch et al. 1997). There were 16 TSA performed in 15 patients suffering from Parkinson's disease that were prospectively monitored as part of the total shoulder arthroplasty registry with average length of follow up of 5.3 years. Six of the patients in the study group were deceased at the most recent review and the average follow up was 2.1 years. The authors report that only 25% of the group achieved excellent results, 12.5% were rated satisfactory and 62.5% rated unsatisfactory. They also reported a

significant reduction in external rotation after surgery. Three patients out of 15 required revision surgery, two for painful subluxation and one for glenoid loosening. The authors concluded that despite careful rehabilitation and medical management of Parkinson's disease, functional results are poor, particularly in patients older than 65 years of age.

Recently Kryzak et al have reported a series of 49 TSA performed in patients with Parkinson's disease for osteoarthritis of the shoulder(Kryzak et al. 2009). Mean age of patients at time of surgery was 69.7 years and 17 TSA were done in women while 32 were in men. Mean age of follow up was 8 years. Eight out of 49 shoulders were revised, three were revised in less than one year due to instability, four were revised due to loosening of the components and one due to periprosthetic fracture(Kryzak et al. 2009). The authors report a significant relief of pain with the average pain score decreasing from 4.6 pre-op to 1.8 post-op at last follow up. Overall they had 10 excellent (23%) results, 13 satisfactory (30%) results and 20 unsatisfactory (47%) results. The most common reason for unsatisfactory results were insufficient abduction, external rotation or a combination of both, instability requiring revision and continued pain.

Study authors	Study type	Arthroplasty (type + numbers)	Mean age (yrs, range)	Length of follow up (yrs)	Implant type/surgical technique	Outcome
Kryzak et al	retrospective	TSA (49)	69.7 (54 - 87)	8 years	31 Cofield (Smith and Nephew, Memphis, TN), 13Neer (Kirschner Medical, Fairlawn, NJ), 4 Tornier (Grenoble,France), and 1 Biomet humeral components (Warsaw, IN), 26 Cofield (Smith and Nephew), 18 Neer (KirschnerMedical), 4 Tornier (Grenoble, France), and 1 Biomet glenoidcomponents (Warsaw, IN)	16.3% of shoulders revised, 88% survival free of revision, 23% had excellent results, 30% satisfactory and 47% unsatisfactory
Koch et al	retrospective	TSA (16)	49 - 84 years	5.3 (1.2 - 15) years	standard deltopectoral approach was used, 12 cases used Neer (Kirschner Medical, Fairlawn, NJ), 4 cases treated with Cofield (Smith and Nephew, Memphis, TN)	40% of patient were dead at the most recent review, 25% rated as excellent, 12.5% rated as satisfactory and 62.5% rated as unsatisfactory results. 3 patients required revision 2 for subluxation and 1 for aseptic loosening

Table 5. Summary of the studies in patient with Parkinson's disease undergoing TKR.

4. Summary

Parkinson's disease affects a not inconsiderable proportion of the population and it is inevitable that the orthopaedic surgeon encounters these patients in practice. Arthroplasty of the hip, knee and shoulder are frequently used to alleviate pain from numerous arthropathies and hip and shoulder arthroplasty utilized in selected fracture patterns around the respective joints.

We have highlighted specific areas that require attention in the pre-, intra-, and post-operative management of patient with Parkinson's disease undergoing arthroplasty procedures. Although outcomes following elective arthroplasty procedures are promising, outcomes after shoulder hemiarthroplasty for trauma are less than encouraging.

Despite this, there is a distinct lack of evidence in the literature for many facets of care. We encourage physicians and surgeons alike to optimise the medical and surgical management of patients with Parkinson's disease to ensure best possible outcomes.

5. References

Adams, R. D., M. Victor and A. H. Ropper (1997). Principles of neurology. New York ; London, McGraw-Hill, Health Professions Division.

Allen, N. E., C. G. Canning, C. Sherrington, S. R. Lord, M. D. Latt, J. C. Close, S. D. O'Rourke, S. M. Murray and V. S. Fung (2010). "The effects of an exercise program on fall risk factors in people with Parkinson's disease: a randomized controlled trial." Mov Disord 25(9): 1217-1225.

Andersen, K. V., M. Bak, B. V. Christensen, J. Harazuk, N. A. Pedersen and K. Soballe (2010). "A randomized, controlled trial comparing local infiltration analgesia with epidural infusion for total knee arthroplasty." Acta Orthop 81(5): 606-610.

Andersen, K. V., M. Pfeiffer-Jensen, V. Haraldsted and K. Soballe (2007). "Reduced hospital stay and narcotic consumption, and improved mobilization with local and intraarticular infiltration after hip arthroplasty: a randomized clinical trial of an intraarticular technique versus epidural infusion in 80 patients." Acta Orthop 78(2): 180-186.

Andersen, L. J., T. Poulsen, B. Krogh and T. Nielsen (2007). "Postoperative analgesia in total hip arthroplasty: a randomized double-blinded, placebo-controlled study on peroperative and postoperative ropivacaine, ketorolac, and adrenaline wound infiltration." Acta Orthop 78(2): 187-192.

Anderson, B. J., P. V. Marks and M. E. Futter (1994). "Propofol--contrasting effects in movement disorders." Br J Neurosurg 8(3): 387-388.

Aspenberg, P. and T. Johansson (2010). "Teriparatide improves early callus formation in distal radial fractures." Acta Orthop 81(2): 234-236.

Backus, W. W., R. R. Ward, S. A. Vitkun, D. Fitzgerald and J. Askanazi (1991). "Postextubation laryngeal spasm in an unanesthetized patient with Parkinson's disease." J Clin Anesth 3(4): 314-316.

Berg, D., G. Becker and K. Reiners (1999). "Reduction of dyskinesia and induction of akinesia induced by morphine in two parkinsonian patients with severe sciatica." J Neural Transm 106(7-8): 725-728.

Bhave, A., M. G. Zywiel, S. D. Ulrich, M. S. McGrath, T. M. Seyler, D. R. Marker, R. E. Delanois and M. A. Mont (2009). "Botulinum toxin type A injections for the

management of muscle tightness following total hip arthroplasty: a case series." J Orthop Surg Res 4: 34.

Brennan, K. A. and R. W. Genever (2010). "Managing Parkinson's disease during surgery." BMJ 341: c5718.

Burton, D. A., G. Nicholson and G. M. Hall (2004). "Anaesthesia in elderly patients with neurodegenerative disorders: special considerations." Drugs Aging 21(4): 229-242.

Busch, C. A., M. R. Whitehouse, B. J. Shore, S. J. MacDonald, R. W. McCalden and R. B. Bourne (2010). "The efficacy of periarticular multimodal drug infiltration in total hip arthroplasty." Clin Orthop Relat Res 468(8): 2152-2159.

Camicioli, R. and S. R. Majumdar (2010). "Relationship between mild cognitive impairment and falls in older people with and without Parkinson's disease: 1-Year Prospective Cohort Study." Gait Posture 32(1): 87-91.

Chudler, E. H. and W. K. Dong (1995). "The role of the basal ganglia in nociception and pain." Pain 60(1): 3-38.

Clouston, W. M. and H. M. Lloyd (1987). "Immobilization-induced hypercalcemia and regional osteoporosis." Clin Orthop Relat Res(216): 247-252.

Clubb, V. J., S. E. Clubb and S. Buckley (2006). "Parkinson's disease patients who fracture their neck of femur: a review of outcome data." Injury 37(10): 929-934.

Coughlin, L. and J. Templeton (1980). "Hip fractures in patients with Parkinson's disease." Clin Orthop Relat Res(148): 192-195.

Dereli, E. E. and A. Yaliman (2010). "Comparison of the effects of a physiotherapist-supervised exercise programme and a self-supervised exercise programme on quality of life in patients with Parkinson's disease." Clin Rehabil 24(4): 352-362.

Duffy, G. P. and R. T. Trousdale (1996). "Total knee arthroplasty in patients with parkinson's disease." J Arthroplasty 11(8): 899-904.

Easdown, L. J., M. J. Tessler and J. Minuk (1995). "Upper airway involvement in Parkinson's disease resulting in postoperative respiratory failure." Can J Anaesth 42(4): 344-347.

Ebersbach, G., A. Ebersbach, D. Edler, O. Kaufhold, M. Kusch, A. Kupsch and J. Wissel (2010). "Comparing exercise in Parkinson's disease--the Berlin LSVT(R)BIG study." Mov Disord 25(12): 1902-1908.

Erceg, M. and A. Maricevic (2000). "Recurrent posterior dislocation following primary posterior-stabilized total knee arthroplasty." Croat Med J 41(2): 207-209.

Eventov, I., M. Moreno, E. Geller, R. Tardiman and R. Salama (1983). "Hip fractures in patients with Parkinson's syndrome." J Trauma 23(2): 98-101.

Fink, H. A., M. A. Kuskowski, E. S. Orwoll, J. A. Cauley and K. E. Ensrud (2005). "Association between Parkinson's disease and low bone density and falls in older men: the osteoporotic fractures in men study." J Am Geriatr Soc 53(9): 1559-1564.

Formisano, R., L. Pratesi, F. T. Modarelli, V. Bonifati and G. Meco (1992). "Rehabilitation and Parkinson's disease." Scand J Rehabil Med 24(3): 157-160.

Friedl, G., R. Radl, C. Stihsen, P. Rehak, R. Aigner and R. Windhager (2009). "The effect of a single infusion of zoledronic acid on early implant migration in total hip arthroplasty. A randomized, double-blind, controlled trial." J Bone Joint Surg Am 91(2): 274-281.

Gobbi, L. T., M. D. Oliveira-Ferreira, M. J. Caetano, E. Lirani-Silva, F. A. Barbieri, F. Stella and S. Gobbi (2009). "Exercise programs improve mobility and balance in people with Parkinson's disease." Parkinsonism Relat Disord 15 Suppl 3: S49-52.

Gross, T. S. and C. T. Rubin (1995). "Uniformity of resorptive bone loss induced by disuse." J Orthop Res 13(5): 708-714.

Hansson, U., S. Toksvig-Larsen, L. Ryd and P. Aspenberg (2009). "Once-weekly oral medication with alendronate does not prevent migration of knee prostheses: A double-blind randomized RSA study." Acta Orthop 80(1): 41-45.

Hernigou, P., G. Mathieu, P. Filippini and A. Demoura (2006). "[Intra- and postoperative fractures of the femur in total knee arthroplasty: risk factors in 32 cases]." Rev Chir Orthop Reparatrice Appar Mot 92(2): 140-147.

Hilding, M., L. Ryd, S. Toksvig-Larsen and P. Aspenberg (2000). "Clodronate prevents prosthetic migration: a randomized radiostereometric study of 50 total knee patients." Acta Orthop Scand 71(6): 553-557.

Hirsch, M. A., T. Toole, C. G. Maitland and R. A. Rider (2003). "The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease." Arch Phys Med Rehabil 84(8): 1109-1117.

Hoehn, M. M. and M. D. Yahr (1967). "Parkinsonism: onset, progression and mortality." Neurology 17(5): 427-442.

Hughes, A. J., S. E. Daniel, S. Blankson and A. J. Lees (1993). "A clinicopathologic study of 100 cases of Parkinson's disease." Arch Neurol 50(2): 140-148.

Hurwitz, A. (1989). "The benefit of a home exercise regimen for ambulatory Parkinson's disease patients." J Neurosci Nurs 21(3): 180-184.

Huse, D. M., K. Schulman, L. Orsini, J. Castelli-Haley, S. Kennedy and G. Lenhart (2005). "Burden of illness in Parkinson's disease." Mov Disord 20(11): 1449-1454.

Husted, H., H. C. Hansen, G. Holm, C. Bach-Dal, K. Rud, K. L. Andersen and H. Kehlet (2010). "What determines length of stay after total hip and knee arthroplasty? A nationwide study in Denmark." Arch Orthop Trauma Surg 130(2): 263-268.

Inoue, D. (2010). "[Musculoskeletal rehabilitation and bone. Mechanical stress on the skeletal system]." Clin Calcium 20(4): 503-511.

Jaggers, J. R., C. D. Simpson, K. L. Frost, P. M. Quesada, R. V. Topp, A. M. Swank and J. A. Nyland (2007). "Prehabilitation before knee arthroplasty increases postsurgical function: a case study." J Strength Cond Res 21(2): 632-634.

Kao, C. H., C. C. Chen, S. J. Wang, L. G. Chia and S. H. Yeh (1994). "Bone mineral density in patients with Parkinson's disease measured by dual photon absorptiometry." Nucl Med Commun 15(3): 173-177.

Keus, S. H., B. R. Bloem, E. J. Hendriks, A. B. Bredero-Cohen and M. Munneke (2007). "Evidence-based analysis of physical therapy in Parkinson's disease with recommendations for practice and research." Mov Disord 22(4): 451-460; quiz 600.

Klausner, J. M., J. Caspi, S. Lelcuk, A. Khazam, G. Marin, H. B. Hechtman and R. R. Rozin (1988). "Delayed muscular rigidity and respiratory depression following fentanyl anesthesia." Arch Surg 123(1): 66-67.

Koch, L. D., R. H. Cofield and J. E. Ahlskog (1997). "Total shoulder arthroplasty in patients with Parkinson's disease." J Shoulder Elbow Surg 6(1): 24-28.

Krauss, J. K., E. W. Akeyson, P. Giam and J. Jankovic (1996). "Propofol-induced dyskinesias in Parkinson's disease." Anesth Analg 83(2): 420-422.

Kryzak, T. J., J. W. Sperling, C. D. Schleck and R. H. Cofield (2009). "Total shoulder arthroplasty in patients with Parkinson's disease." J Shoulder Elbow Surg 18(1): 96-99.

Kryzak, T. J., J. W. Sperling, C. D. Schleck and R. H. Cofield (2010). "Hemiarthroplasty for proximal humerus fractures in patients with Parkinson's disease." Clin Orthop Relat Res 468(7): 1817-1821.

Ma, Y. L., F. Marin, J. Stepan, S. Ish-Shalom, R. Moricke, F. Hawkins, et al. (2011). "Comparative effects of teriparatide and strontium ranelate in the periosteum of iliac crest biopsies in postmenopausal women with osteoporosis." Bone.

Macaulay, W., J. A. Geller, A. R. Brown, L. J. Cote and H. A. Kiernan (2010). "Total knee arthroplasty and Parkinson disease: enhancing outcomes and avoiding complications." J Am Acad Orthop Surg 18(11): 687-694.

Mason, L. J., T. T. Cojocaru and D. J. Cole (1996). "Surgical intervention and anesthetic management of the patient with Parkinson's disease." Int Anesthesiol Clin 34(4): 133-150.

Meek, R. M., D. B. Allan, G. McPhillips, L. Kerr and C. R. Howie (2006). "Epidemiology of dislocation after total hip arthroplasty." Clin Orthop Relat Res 447: 9-18.

Melton, L. J., 3rd, C. L. Leibson, S. J. Achenbach, J. H. Bower, D. M. Maraganore, A. L. Oberg and W. A. Rocca (2006). "Fracture risk after the diagnosis of Parkinson's disease: Influence of concomitant dementia." Mov Disord 21(9): 1361-1367.

Mets, B. (1991). "Acute dystonia after alfentanil in untreated Parkinson's disease." Anesth Analg 72(4): 557-558.

Moricke, R., K. Rettig and T. D. Bethke (2011). "Use of Recombinant Human Parathyroid Hormone(1-84) in Patients with Postmenopausal Osteoporosis: A Prospective, Open-Label, Single-Arm, Multicentre, Observational Cohort Study of the Effects of Treatment on Quality of Life and Pain - the PROPOSE Study." Clin Drug Investig 31(2): 87-99.

Mueller, M. C., U. Juptner, U. Wuellner, S. Wirz, A. Turler, A. Hirner and J. Standop (2009). "Parkinson's disease influences the perioperative risk profile in surgery." Langenbecks Arch Surg 394(3): 511-515.

Muzzi, D. A., S. Black and R. F. Cucchiara (1989). "The lack of effect of succinylcholine on serum potassium in patients with Parkinson's disease." Anesthesiology 71(2): 322.

Neu, H. C., J. J. Connolly, Jr., F. W. Schwertley, H. A. Ladwig and A. W. Brody (1967). "Obstructive respiratory dysfunction in parkinsonian patients." Am Rev Respir Dis 95(1): 33-47.

Nicholson, G., A. C. Pereira and G. M. Hall (2002). "Parkinson's disease and anaesthesia." Br J Anaesth 89(6): 904-916.

Nocera, J. R., T. Buckley, D. Waddell, M. S. Okun and C. J. Hass (2010). "Knee extensor strength, dynamic stability, and functional ambulation: are they related in Parkinson's disease?" Arch Phys Med Rehabil 91(4): 589-595.

O'Hara, D. A., G. Fanciullo, L. Hubbard, T. Maneatis, P. Seuffert, L. Bynum and A. Shefrin (1997). "Evaluation of the safety and efficacy of ketorolac versus morphine by patient-controlled analgesia for postoperative pain." Pharmacotherapy 17(5): 891-899.

Oni, O. O. and R. P. Mackenney (1985). "Total knee replacement in patients with Parkinson's disease." J Bone Joint Surg Br 67(3): 424-425.

Parvataneni, H. K., V. P. Shah, H. Howard, N. Cole, A. S. Ranawat and C. S. Ranawat (2007). "Controlling pain after total hip and knee arthroplasty using a multimodal protocol with local periarticular injections: a prospective randomized study." J Arthroplasty 22(6 Suppl 2): 33-38.

Pepper, P. V. and M. K. Goldstein (1999). "Postoperative complications in Parkinson's disease." J Am Geriatr Soc 47(8): 967-972.

Post, Z. D., C. Restrepo, L. K. Kahl, T. van de Leur, J. J. Purtill and W. J. Hozack (2010). "A prospective evaluation of 2 different pain management protocols for total hip arthroplasty." J Arthroplasty 25(3): 410-415.

Queally, J. M., A. Abdulkarim and K. J. Mulhall (2009). "Total hip replacement in patients with neurological conditions." J Bone Joint Surg Br 91(10): 1267-1273.

Rajput, A. H., K. P. Offord, C. M. Beard and L. T. Kurland (1984). "Epidemiology of parkinsonism: incidence, classification, and mortality." Ann Neurol 16(3): 278-282.

Reed, A. P. and D. G. Han (1992). "Intraoperative exacerbation of Parkinson's disease." Anesth Analg 75(5): 850-853.

Rothermel, J. E. and A. Garcia (1972). "Treatment of hip fractures in patients with Parkinson's syndrome on levodopa therapy." J Bone Joint Surg Am 54(6): 1251-1254.

Sato, Y., Y. Honda and J. Iwamoto (2007). "Risedronate and ergocalciferol prevent hip fracture in elderly men with Parkinson disease." Neurology 68(12): 911-915.

Sato, Y., Y. Honda, J. Iwamoto, T. Kanoko and K. Satoh (2005). "Abnormal bone and calcium metabolism in immobilized Parkinson's disease patients." Mov Disord 20(12): 1598-1603.

Sato, Y., M. Kikuyama and K. Oizumi (1997). "High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease." Neurology 49(5): 1273-1278.

Schenkman, M., T. M. Cutson, M. Kuchibhatla, J. Chandler, C. F. Pieper, L. Ray and K. C. Laub (1998). "Exercise to improve spinal flexibility and function for people with Parkinson's disease: a randomized, controlled trial." J Am Geriatr Soc 46(10): 1207-1216.

Shah, S. N., J. Hornyak and A. G. Urquhart (2005). "Flexion contracture after total knee arthroplasty in a patient with Parkinson's disease: successful treatment with botulinum toxin type A." J Arthroplasty 20(8): 1078-1080.

Staeheli, J. W., F. J. Frassica and F. H. Sim (1988). "Prosthetic replacement of the femoral head for fracture of the femoral neck in patients who have Parkinson disease." J Bone Joint Surg Am 70(4): 565-568.

Stein, C., M. J. Millan, T. S. Shippenberg, K. Peter and A. Herz (1989). "Peripheral opioid receptors mediating antinociception in inflammation. Evidence for involvement of mu, delta and kappa receptors." J Pharmacol Exp Ther 248(3): 1269-1275.

Swank, A. M., J. B. Kachelman, W. Bibeau, P. M. Quesada, J. Nyland, A. Malkani and R. V. Topp (2011). "Prehabilitation before total knee arthroplasty increases strength and function in older adults with severe osteoarthritis." J Strength Cond Res 25(2): 318-325.

Tanaka, N., H. Sakahashi, E. Sato, K. Hirose and S. Ishii (2001). "The efficacy of intra-articular analgesia after total knee arthroplasty in patients with rheumatoid arthritis and in patients with osteoarthritis." J Arthroplasty 16(3): 306-311.

Taylor, B. C., P. J. Schreiner, K. L. Stone, H. A. Fink, S. R. Cummings, M. C. Nevitt, P. J. Bowman and K. E. Ensrud (2004). "Long-term prediction of incident hip fracture risk in elderly white women: study of osteoporotic fractures." J Am Geriatr Soc 52(9): 1479-1486.

Thomsen, M. N., E. Jakubowitz, J. B. Seeger, C. Lee, J. P. Kretzer and M. Clarius (2008). "Fracture load for periprosthetic femoral fractures in cemented versus uncemented hip stems: an experimental in vitro study." Orthopedics 31(7): 653.

Toftdahl, K., L. Nikolajsen, V. Haraldsted, F. Madsen, E. K. Tonnesen and K. Soballe (2007). "Comparison of peri- and intraarticular analgesia with femoral nerve block after total knee arthroplasty: a randomized clinical trial." Acta Orthop 78(2): 172-179.

Toole, T., M. A. Hirsch, A. Forkink, D. A. Lehman and C. G. Maitland (2000). "The effects of a balance and strength training program on equilibrium in Parkinsonism: A preliminary study." NeuroRehabilitation 14(3): 165-174.

Topp, R., A. M. Swank, P. M. Quesada, J. Nyland and A. Malkani (2009). "The effect of prehabilitation exercise on strength and functioning after total knee arthroplasty." PM R 1(8): 729-735.

Turcotte, R., C. Godin, R. Duchesne and A. Jodoin (1990). "Hip fractures and Parkinson's disease. A clinical review of 94 fractures treated surgically." Clin Orthop Relat Res(256): 132-136.

Ueda, M., M. Hamamoto, H. Nagayama, K. Otsubo, C. Nito, T. Miyazaki, A. Terashi and Y. Katayama (1999). "Susceptibility to neuroleptic malignant syndrome in Parkinson's disease." Neurology 52(4): 777-781.

Vendittoli, P. A., P. Makinen, P. Drolet, M. Lavigne, M. Fallaha, M. C. Guertin and F. Varin (2006). "A multimodal analgesia protocol for total knee arthroplasty. A randomized, controlled study." J Bone Joint Surg Am 88(2): 282-289.

Vince, K. G., J. N. Insall and C. E. Bannerman (1989). "Total knee arthroplasty in the patient with Parkinson's disease." J Bone Joint Surg Br 71(1): 51-54.

Vincken, W. G., S. G. Gauthier, R. E. Dollfuss, R. E. Hanson, C. M. Darauay and M. G. Cosio (1984). "Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation." N Engl J Med 311(7): 438-442.

Weber, M., M. E. Cabanela, F. H. Sim, F. J. Frassica and W. S. Harmsen (2002). "Total hip replacement in patients with Parkinson's disease." Int Orthop 26(2): 66-68.

Wilkinson, J. M., A. C. Eagleton, I. Stockley, N. F. Peel, A. J. Hamer and R. Eastell (2005). "Effect of pamidronate on bone turnover and implant migration after total hip arthroplasty: a randomized trial." J Orthop Res 23(1): 1-8.

Wright, J. J., P. D. Goodnight and M. D. McEvoy (2009). "The utility of ketamine for the preoperative management of a patient with Parkinson's disease." Anesth Analg 108(3): 980-982.

Yates, A. J., T. H. Jones, K. I. Mundy, R. V. Hague, C. B. Brown, D. Guilland-Cumming and J. A. Kanis (1984). "Immobilisation hypercalcaemia in adults and treatment with clodronate." Br Med J (Clin Res Ed) 289(6452): 1111-1112.

Edited by Juliana Dushanova

Diagnostics and Rehabilitation of Parkinson's Disease presents the most current information pertaining to news-making topics relating to this disease, including etiology, early biomarkers for the diagnostics, novel methods to evaluate symptoms, research, multidisciplinary rehabilitation, new applications of brain imaging and invasive methods to the study of Parkinson's disease. Researchers have only recently begun to focus on the non-motor symptoms of Parkinson's disease, which are poorly recognized and inadequately treated by clinicians. The non-motor symptoms of Parkinson's disease have a significant impact on patient quality of life and mortality and include cognitive impairments, autonomic, gastrointestinal, and sensory symptoms. In-depth discussion of the use of imaging tools to study disease mechanisms is also provided, with emphasis on the abnormal network organization in parkinsonism. Deep brain stimulation management is a paradigm-shifting therapy for Parkinson's disease, essential tremor, and dystonia. In the recent years, new approaches of early diagnostics, training programmes and treatments have vastly improved the lives of people with Parkinson's disease, substantially reducing symptoms and significantly delaying disability. Written by leading scientists on movement and neurological disorders, this comprehensive book should appeal to a multidisciplinary audience and help people cope with medical, emotional, and practical challenges.

ISBN 978-953-51-6598-9

Photo by KatarzynaBialasiewicz / iStock

IntechOpen