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Parkinson's Disease and Beyond

A Neurocognitive Approach

Edited by Sara Palermo, Mario Stanziano and Rosalba Morese

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Published in London, United Kingdom







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http://dx.doi.org/10.5772/intechopen.79277
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First published in London, United Kingdom, 2019 by IntechOpen
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, The Shard, 25th floor, 32 London Bridge Street
London, SE19SG – United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

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

Parkinson's Disease and Beyond – A Neurocognitive Approach
Edited by Sara Palermo, Mario Stanziano and Rosalba Morese
p. cm.
Print ISBN 978-1-83962-648-7
Online ISBN 978-1-83880-869-3
eBook (PDF) ISBN 978-1-83880-870-9

Meet the editors

Sara Palermo has an MSc in Clinical and Community Psychology and a PhD in Experimental Neuroscience. Currently she is a postdoc research fellow at the University of Turin (Italy). She is a research member of the Center for the Study of Movement Disorders and the Placebo Responses Mapping Group at the Department of Neuroscience. She is also a research member of the Neuropsychology of Cognitive Impairment and CNS Degenerative Diseases Group at the Department of Psychology.
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Mario Stanziano is a physician, currently resident in Diagnostic Imaging at the University of Milan, cooperating with the Brain Imaging Center and the Trauma Center of Turin. He has been working with the neural network morphology lab of the University of Naples Vanvitelli in the Human Anatomy Department.
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Rosalba Morese holds a Bachelor's degree in Psychology from the University of Parma, Italy, and a PhD in Neuroscience from the University of Turin, Italy, to develop new techniques and approaches in cognitive and social neuroscience.
She is an expert in cognitive and social neuroscience, neuroeconomics, psychophysiology, and psychology. She performs neuroimaging studies in social contexts in order to investigate neural correlates involved during social interactions, such as social exclusion, social support, empathy, communicative intention, and social decision making. She is currently working at Università della Svizzera italiana, Switzerland.

Contents

Preface

This book aims to bring together in a single publication the knowledge on diagnosis and characterization of the clinical and neuropsychological profile in Parkinson's disease. The strong impulse to research this topic has produced in recent years a large literature that documents the high level of complexity of the issue. Due to this complexity, a reasoned multidimensional analysis able to integrate expertise of different disciplines (neurology, neuropsychology, neuroradiology, and neuroscience) is necessary.

The authors offer original contributions to develop new perspectives in the field of Parkinson's disease research thanks to the originality of their ideas, theories, research, scientific results, and discussions.

The *introduction* opens with the fundamental question of how to recognize unmet needs in clinical and research settings. Patients fight against a range of physical motor symptoms. However, this is the not the full story. They also experience many other non-motor symptoms that affect their daily living, sometimes in ways that are just as important to them as the cardinal motor symptoms of the disease. However, clinicians often regard non-motor symptoms and their management as peripheral to that of the motor symptoms. A person-centered perspective is suggested and strongly supported.

The *first chapter* deals with the etiopathogenesis of the disease. The *second chapter* presents an interesting perspective of analyzing the hypothesis of oxidative stress and mitochondrial changes as the apparent most relevant cause of Parkinson's disease. It also discusses the neuroprotective role played by Kir6.2, a potassium-ATP channel and calcium voltage-gated v1.3. The *third chapter* describes the contribution of the brain-derived neurotrophic factor (BDNF) as one of the causes of neurodegeneration and neuroinflammation. It also discusses the participation of this neurotrophic factor in the development of cognitive dysfunction, and presents novel BDNF-based therapies for Parkinson's disease.

The *fourth chapter* describes the radiological anatomy, sequencing, and imaging appearances of the disease. It also discusses new approaches with potential applicability to clinical practice.

The *last chapter* outlines the clinical phenomenology of the pathology according to a neurocognitive approach. It also presents motor and non-motor symptoms, therapies of the advanced phase, and role of the neuropsychological evaluation. Particular attention is paid to the side effects of advanced therapy; dyskinesias and dyskinesia-reduced-self-awareness are widely discussed. The chapter addresses new findings concerning the association between executive functions and the neural correlates of this phenomenon.

This book offers an excellent synopsis and an interesting expression of different perspectives, methods, empirical evidences, and international references. Therefore

this book represents an extraordinary opportunity to target challenging unmet needs and to outline new horizons in Parkinson's disease research.

> *"The moment I understood this - that my Parkinson's was the one thing I wasn't going to change - I started looking at the things I could change, like the way research is funded."*
>
> *Michael J. Fox*

> *"As a practicing neurologist, I can tell you first hand that working with Parkinson's patients offers clinical challenges. But from an emotional perspective, this disease can border on overwhelming."*
>
> *David Perlmutter*

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Chapter 1

Introductory Chapter: Targeting Unmet Needs in Parkinson's Disease

Sara Palermo, Rosalba Morese and Mario Stanziano

1. Introduction

About 20 years ago, actor Michael J. Fox—well known for the trilogy "Back to the Future" and at the time at the height of his success and of his youth—declared to the public that he had received the unexpected diagnosis of Parkinson's disease (PD) 7 years before. On the same occasion, Michael announced the decision to put his image at the service of what would become one of the most lasting and decisive campaigns of hope, information, awareness, and fundraising for research in the fight against PD. About 20 years later, what progress has actually been made?

As is known, Parkinson's disease does not yet have a cure. The fundamental therapy is still the pharmacological one, which is implemented today with the administration of various active ingredients in addition to levodopa which remains the most powerful drug, but which presents marked side effects after a few years. 2018 was a special year for people with Parkinson's and their loved ones. It started in January with the shocking news of the decision by the pharmaceutical company Pfizer to suspend all research related to treatments for Parkinson's and Alzheimer's because they were too expensive, to continue with the announcement by researchers at Johns Hopkins University to have obtained results, still preliminary but extremely encouraging, with the drug called NLY01. With regard to non-pharmacological interventions, we note the progress of neuronal stem cell experimentation carried out in Australia by the International Stem Cell Corporation (ISCO), which, according to what the company reported, looks very promising. These are the first steps and the path will still be long, but these are just some of the researches that keep hope for the future alive.

Innovative ideas and therapies for PD go far beyond a single drug or stem cell. There is a broader and more exciting picture. Innovative ideas include drugs, cells, vaccine, ICT-IoT devices, genetics, social care, and cognitive-behavioral enhancement. The most recent therapeutic approaches have highlighted the importance of the multidisciplinary perspective and the usefulness of rehabilitation, both in its "classic" form as physiotherapy and in one or more of the so-called "complementary therapies" (indicating that they complement but do not replace approaches that are more conventional). Patients and their families should be kept informed and updated on all potential innovative therapies. Above all, their needs should be at the center of the healthcare process and the research initiatives. Some of the most frequent questions we receive from parkinsonian patients and families are "How can I be cured?," "What will be the next breakthrough?," and "For everything else what do I do now?"

Because of the complexity of the disease, each patient has a different combination of motor and non-motor symptoms, of difficulties in daily life. This complexity therefore means that the answer to the next possible innovative therapy will vary from patient to patient—and could be an innovation in care, as well as, possibly, a new ICT-IoT device or a new cocktail of drugs. We will need to expand our notion of innovation, and we will need to exploit this knowledge to reduce the burden of Parkinson's patients. This introductory chapter therefore aims to answer the fundamental question: *What are the unmet needs in Parkinson's disease?*

2. Unmet needs in Parkinson's disease: new horizons in the clinic and in research

PD patients fight against a range of physical motor symptoms including slowness of movement, rigidity, tremor, and postural instability. However, this is the not the full story. They also experience many other non-motor symptoms, which affect their daily living, sometimes in ways that are just as important to them as the cardinal motor symptoms of the disease.

The awareness has now been reached that non-motor symptoms burden is a key determinant of quality of life of patients and their primary caregivers [1, 2].

Treating these kinds of symptoms that negatively influence the lives of patients—and in particular those that are responsive to the dopaminergic replacement therapy—automatically translates into improvements in quality of life and reduction of the associated burden [3].

However, clinicians often regard non-motor symptoms and their management as peripheral to that of the motor symptoms. Just for an example, the 2011 Parkinson's UK report showed non-motor symptoms recorded in only 21% of elderly care and 9% of neurology services in the UK.

Nevertheless, Hatano and collaborators [4] suggested that PD patients have unmet needs in their treatment and standards of care already in 2009. In particular, the authors suggested focusing on the development of better treatment for motor symptoms, the development of new treatments for non-motor symptoms and improved two-way communication between patient and physician.

Chaudhuri et al. reported a few years later: "Key medical unmet needs in PD include the need for better animal models replicating the parkinsonian process, slowing of disease progression/neuroprotection, improved biomarkers (imaging, genetic, clinical or other modality), improved 24-h control of motor fluctuations in moderate to advanced disease and more effective treatment of non-motor symptoms (NMS). Nocturnal symptoms as well as early morning fluctuations remain also neglected" ([5], p. 52). To confirm the above, in their study on Palliative Needs of Parkinson's Patients, Prizer and colleagues [6] have shown that among the palliative needs most frequently reported by patients, there were: healthcare education, care coordination, support groups, spirituality/religion, and the greater presence of the neurologist.

How to address the unmet needs of people living with Parkinson's disease? We need a person-centered perspective.

It is proposed this year an interesting approach called the "Voice of the Costumer" [7], which includes three successive phases of gathering information on the real needs due to the experience of the disease: (1) capturing patient needs by means of semi-structured interviews with patients, relatives, and healthcare providers in their private environment; (2) preparing a comprehensive summary of the contents discussed in the interviews; and (3) prioritizing needs in a consensus meeting, in which all parties participate. Vlaanderen and collaborators [7] suggested that patients were more concerned about the impact of PD on their daily

lives than about the bio-medical aspects of the disease. The authors have found that top unmet needs of the parties involved were: more self-management; better interdisciplinary collaboration between different healthcare professionals; more time to discuss the future and possible scenarios; and a healthcare professional acting as a single point of access, acting as personal case manager, either to solve problems directly or to direct patients to the professional best equipped to address the problem at hand.

Another useful tool could be the *Parkinson's Well-Being Map™*—developed in partnership with the European Parkinson's Disease Association (EPDA), the Cure Parkinson's Trust, and the Spanish Federation of Parkinson's Disease—which takes a holistic approach, allowing patients to track both motor and underlying symptoms. The map helps PD patients to prepare for consultations with their healthcare team, so that they can help to understand how living with Parkinson's disease affects them. The map covers all aspects of Parkinson's, so that a patient can highlight the symptoms that are of most concern to him/her and list the most important questions to ask at his/her next consultation. It was made available free online and in paper form.

Approaches of this kind can help clinicians and researchers to better plan their activities so that in the future, gaps in the current methods of management are filled and research topics are expanded based on a patient-centered approach.

3. The nature and purpose of the book

The volume aims to bring together in a single publication the knowledge on the topic of diagnosis, characterization of the clinical and neuropsychological profile in Parkinson's disease. The strong impulse given to research on this topic has produced in recent years a large literature that documents the high level of complexity of the issue, for which a reasoned multidimensional analysis able to integrate expertise of different disciplines (neurology, neuropsychology, neuroradiology, and clinical neuroscience) is necessary.

The volume illustrates the neuropathological characteristics that define Parkinson's disease. Subsequent contributions focus on the diagnostic characterization and monitoring of Parkinson's disease, considering also the contribution of neuropsychology, morphological and functional imaging techniques.

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Chapter 2

Mitochondrial K_{ATP} Channel and Dopaminergic Vulnerability Neurons in Parkinson's Disease

Gesivaldo Santos, Julita Maria Pereira Borges, Marcos Avilla-Rodriguez, Érika Pereira Rubio, Cattiúscia Batista Bromochenkel, Djalma Menezes Oliveira, Jane Lima dos Santos, Rosane Moura Aguiar, Milena Mascarenhas Ferraz, Silvana Batista Gaino, Francisco Capani and George E. Barreto

Abstract

The motor deficiency control commonly characterizes Parkinson's disease (PD), resulting in impairment of neuromuscular command, because of basal ganglia nuclei degeneration and late formation of Lewy's bodies in the remaining dopaminergic (DA) neurons. Motor signals are triggered in high cortical motor areas and go toward the midbrain regions, where the final tuning movement takes place. PD is characterized primarily by the death of dopaminergic neurons in the regions known as *substantia nigra compacta* (STNc). Mutations in a couple of genes, such as Parkin1 and DJ1, correspond to the usual familial form of the disease, due to its association with oxidative stress and depolarization of mitochondrial membrane. However, this form does not explain the selective pattern of apoptosis between the neuronal dopaminergic areas of midbrain regions. In this chapter, we are putting forward the hypothesis of oxidative stress and mitochondrial changes as the apparent most relevant cause in PD, as well as the neuroprotective role played by Kir6.2, a potassium-ATP channel and calcium voltage-gated v1.3.

Keywords: Parkinson's disease, potassium-$_{ATP}$ channel, calcium v1.3 channel, mitochondria ETC impairments, oxidative stress

Glossary:

1. PD nonhuman animal model: simulation of PD may be acquired using rotenone and MPTP, two pesticides whose use leads to impairments in mitochondrial complex-I and in consequence an outburst of oxidative species and free radicals.

2. Kir6.2/SUR1: during oxidative stress, potassium-ATP channel may act as a neuroprotector factor, by inducing GABA release in subcortical areas, thereby preventing neuronal glutamatergic overexcitation.

1. Introduction

Parkinson's disease (PD) is related to the selective loss of neurons, which contain dopamine (DA) in *substantia nigra compacta* (STNc) and late formation of Lewy's bodies in the remaining dopaminergic (DA) neurons [1]. PD is one of the most conditions, falling behind only Alzheimer's disease. Parkinson's disease prevalence is progressive, ranging from 1% in people >60 years old until 2–4% in people >70 years old.

PD is commonly known by the disease of the motor deficiency process [2]. Due to its association with impairments in basal ganglia, the presence of resting tremor, muscular rigidity, bradykinesia, sleep disturbances, gait impairment, and difficulties with balance [3–5] became the most prominent footprint in PD characterization (see **Figure 1**) [4].

In humans, movements are coordinated by a series of high-precision steps that begin in the regions of the prefrontal cortex and go toward the areas directly related to movement coordination, such as supplementary area and primary motor area [6]. From the start point, the signal follows pathways from inside the brain into the subcortical regions and reaches the spinal cord and finally the skeletal muscle [7]. However, it is not enough to simply generate the motor signal and deliver it to the muscle; it is necessary to coordinate and control the accuracy of the process generated in high cortical regions. That is the point where basal ganglia take place on this process as a stakeholder (**Figure 1**) [8].

Basal ganglia are composed of a series of subcortical nuclei scattered for the midbrain regions, whose role extends from the motor fine-tuning, initialization, and finalization of the movement (processes supported by the *substantia nigra pars compacta* (STNc)), as well as the development of cognitive functions such as learning, reward, and emotions, mostly supported by the ventral tegmental area (VTA) and

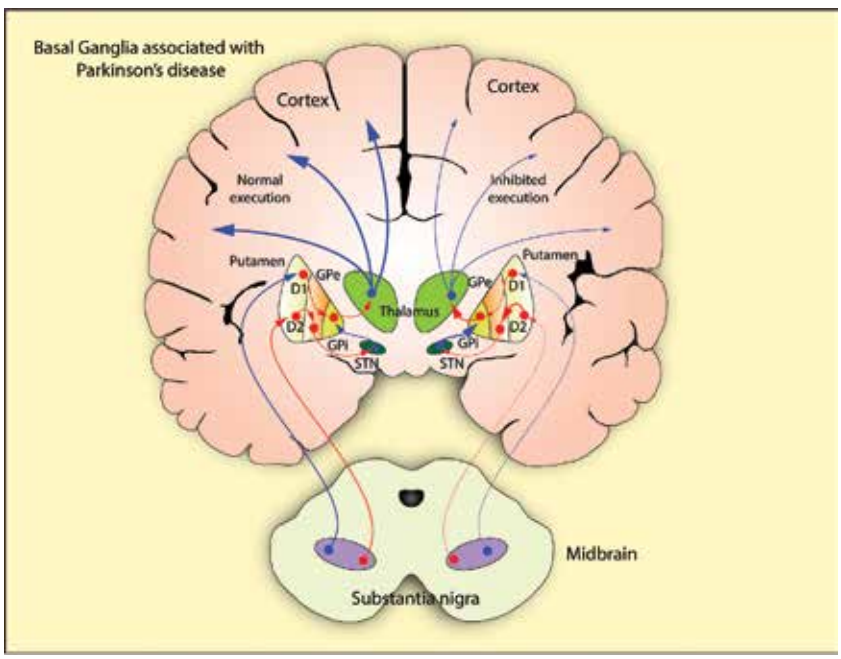

Figure 1.
The basal ganglia and a series of subcortical nuclei responsible for the motor fine-tuning in health brain (right) and in PD (left). Direct pathway provides the disinhibition of the thalamus (D1 signaling in blue). Indirect pathway, in red, will stop the movement, previously initiated. D1, dopamine receptor 1; D2, dopamine receptor 2; GPi, globus pallidus internus*; GPe,* globus pallidus external.

nucleus *accumbens* (NC). Together, they are functionally known as the ventral and dorsal *striatum*, respectively [9].

As one can see in **Figure 1**, in parkinsonism, the striatum plays an important role in the pathophysiology of the disease, and the substantia *nigra* compacta (STNc) emerges as the main nucleus responsible for the core mechanism related to the initialization of the movement, assigned to the direct pathway [10]. Direct pathway provides the disinhibition of the thalamus by the dopamine D1 signaling, performed by STNc [11]. In opposite side, the indirect pathway will stop the movement, previously initiated by the release of GABA from the external *globus pallidus* (GPe) and *substantia nigra pars reticulata* (STNr) [12].

James Parkinson did the first description of the disease in 1817 in his book: *An Essay on the Shaking Palsy* [13]. PD is characterized primarily by the death of

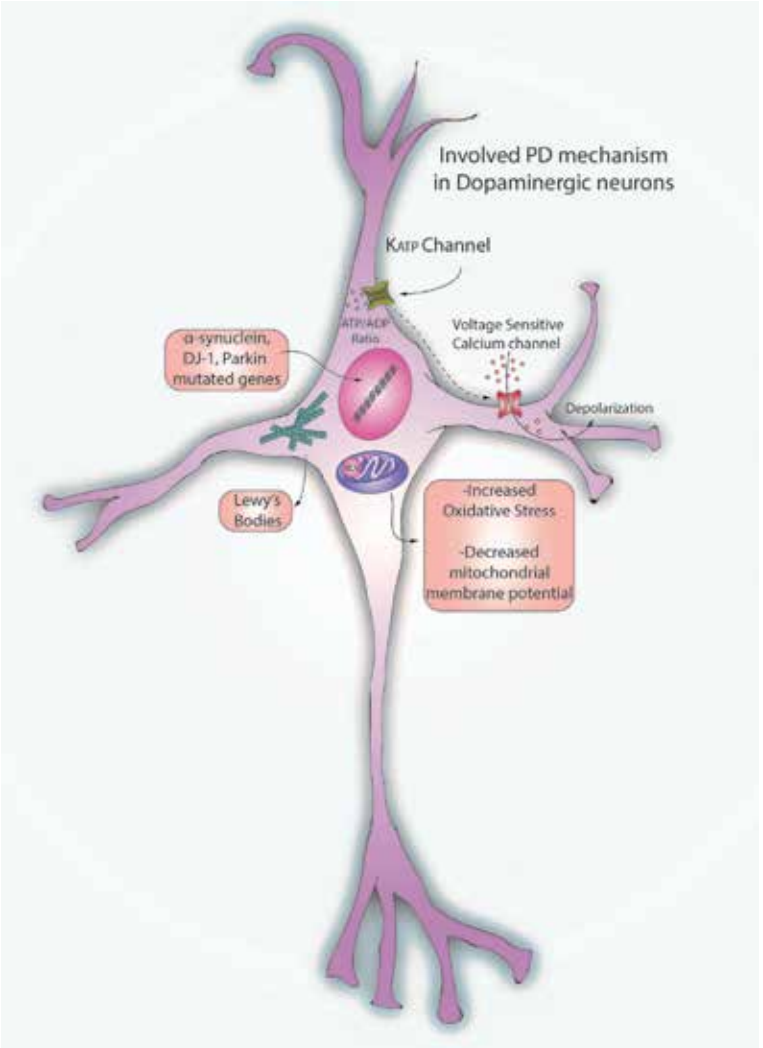

Figure 2.
Dopaminergic neurons undergo several mechanisms that may explain in part the selective cell death in substantia nigra*. Mutations associated with major PD related genes such as α-synuclein, DJ-1 and Parkin are well characterized. It is possible that the mutated genes induced a protein imbalance that lead to the aggregation of proteins to form the so-called Lewy's bodies. Another key mechanism studied is the ROS imbalance in mitochondria resulting in a diminished ATP that affect the ability of dopaminergic neuron to reach its main functions. A plausible mechanism to be explored is the role of K-ATP channel that is sensitive to ATP/ADP changes to govern the depolarization in GABAergic neuron.*

dopaminergic neurons in the STNc resulting in defective control of the movements in the basal ganglia (**Figure 1**) [14]. However, in addition to dopamine metabolism impairment, another pathological process implicated in the etiology of the disease is the aggregation of alpha-synuclein (a-syn), resulting in Lewy's body formation in the remaining dopaminergic neurons, characterizing the non-motor symptoms of the disease (**Figure 2**) [4, 5, 15].

Despite the dominant prevalence of sporadic form (90%), mutations in genes, such as a-synuclein, DJ1, Parkin1, and others, have been implicated in the familial pattern of PD, mainly due to their associations with oxidative stress responses and depolarization of mitochondrial membrane. However, gene alterations in the familial form of PD are ambiguous because they do not explain the selective pattern of apoptosis between STNc and VTA, both formed predominantly by dopaminergic neurons (**Figure 2**) [14, 16]. Another hypothesis associated to the oxidative stress and mitochondrial changes is related to Ca^{+2} imbalance homeostasis in dopaminergic neurons of the STNc, as well as the presence of K_{ATP} channels acting as a metabolic sensor by coupling glucose metabolism to mitochondrial membrane potential (Mit-ψ) (see **Figures 3** and **4**) [17]. In other words, understanding the mechanism of specific vulnerability, by which only dopaminergic neurons in specific areas are associated with PD, remains an impressive challenge; however, some evidences, that will be discussed here, may shed light in an intricate neurobiology of Parkinson's condition [14, 18].

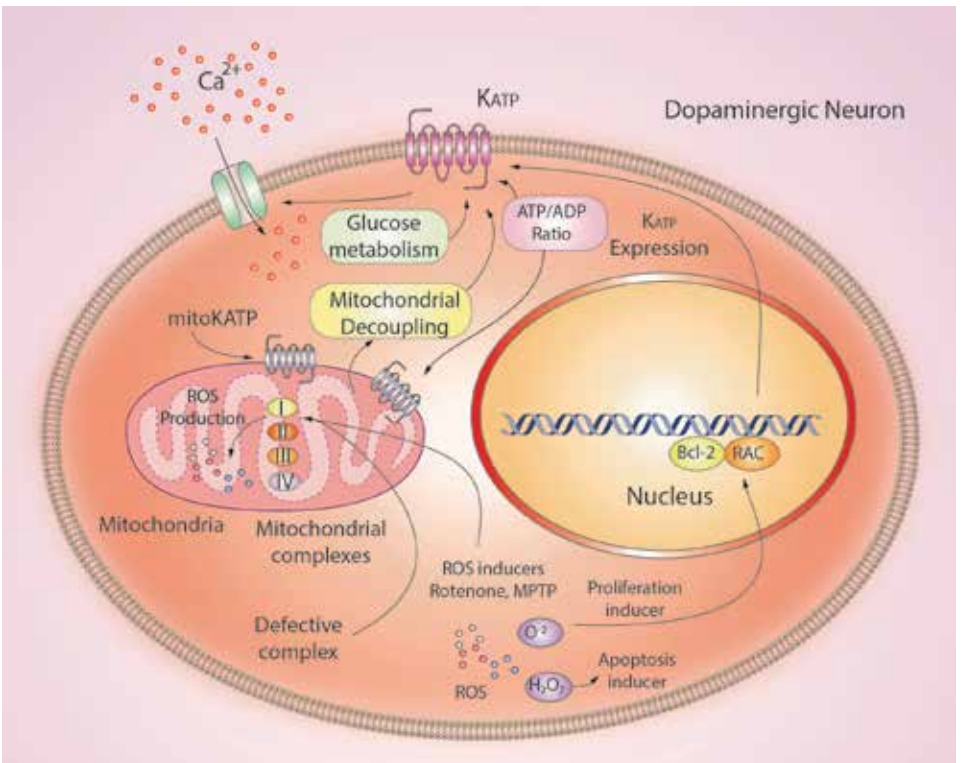

Figure 3.
K-ATP and mitochondrial functions may be a potential relationship. K-ATP sensor is subjected to regulation via several mechanisms as glucose metabolism, ATP/ADP ratio, mitochondrial decoupling, and gene expression. K-ATP may lead the neuron to depolarize via potassium and calcium fluxes. It is reported that K-ATP has other subtypes of receptors, for example, the mito-K_{ATP}. It is possible that the pathogenic production of ROS may alter the function of K-ATP with protective functions. So, it is plausible that the modulation of K-ATP receptors can be used to protect dopaminergic neurons.

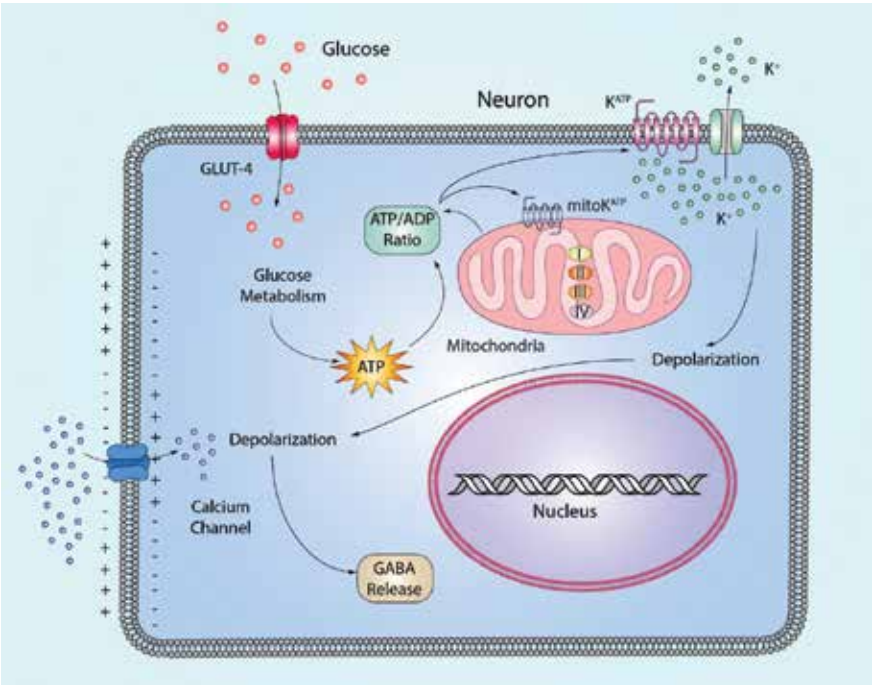

Figure 4.
Glucose and energetic metabolism may regulate the function of K-ATP channel. The change in the ATP/ADP ratio by glucose metabolism induces a response in K-ATP that blockade the potassium outward with the subsequent loss of membrane potential. It may lead to depolarization with several functions, for example, the release of GABA.

2. Substantia nigra compacta and ROS formation

The use of rotenone and MPTP, two pesticides, which act on the mitochondrial complex-I, brought mitochondrial damage induced by oxidative stress to the center of PD etiology. The uplift of reactive oxygen species (ROS), caused by a defective complex-I, such as observed in PD patients, makes mitochondria the main source of ROS in the intracellular environment (**Figure 3**) [19, 20]. Superoxide (O_2^-) and peroxide of hydrogen (H_2O_2), the two main species of ROS derived from electron transport chain (ETC) activity, seem to govern the internal state of the cell between proliferative and apoptotic. According to this model, high levels of O_2^- tend to favor cell proliferation due to increased transcription of oncogenes, such as the Rac1-Bcl2 pathway, whose overexpression increases mitochondrial respiration. On the other hand, prevailing levels of H_2O_2 promote apoptosis, and finally, very high rates of H_2O_2 promote cellular necrosis due to irreparable damage to cell physiology (**Figure 3**) [21].

The hypothesis of oxidative stress and mitochondrial changes is apparently the most relevant cause in the sporadic PD (**Figure 3**). However, they alone do not explain selective dopaminergic neuron vulnerability. The key element for this may lie in the differential expression of K_{ATP} channels (Kir6.2) between STNc neurons and ventral tegmental area (VTA) [22]. In in vitro studies, the total decoupling of the mitochondrial respiratory chain leads to the activation of K_{ATP} channels in all dopaminergic neurons. However, partial decoupling of complex-I strongly affects neurons from STNc, showing an opposite effect on K_{ATP} channels in dopaminergic neurons of VTA, whose process increases the neuronal activity, reducing ROS formation due to the closure of the K_{ATP} channels (**Figure 4**). It has been identified

that D2-autoreceptor (D2-AR) acts as an inhibitor of STNc-DA neurons in response to local high DA release [23]. All the processes have been achieved by activation of Kir6.2, an inward rectifier potassium channel coupled to G-protein [23]. Although ventral tegmental area DA neurons (VTA-DA) do not present the same response in such like condition [24], studies account for the presence of $Ca_v^{+2}1.3$ channel as the main responsible for this selectivity in STN-DA neurons, whose function would be associated with the downregulation of STN-DA neuronal cell activity in response to dangerous transient of local DA release [25].

2.1 The starting point of oxidative stress and K_{ATP} channel disposition

In PD, pathogenesis predominates the selective loss of dopaminergic neurons. These neurons are in the STNc, with projections up to the striatum zone. The neurochemistry of degeneration involves several molecular events triggered by mitochondrial dysfunction with increased oxidative stress and excitotoxicity caused by extracellular Ca^{+2} overflow. These events promote important changes in protein conformation, e.g., alpha-synuclein, responsible for Lewy's body formation, a defective protein aggregation resulting in mitophagies and apoptosis [26–28].

Dopamine is a catecholamine synthesized from the L-dihydroxyphenylalanine (L-dopa) of the amino acid tyrosine by the enzyme tyrosine hydroxylase (TH). In the next step, L-dopa undergoes decarboxylation by the aromatic amino acid decarboxylase (AADC) to generate dopamine and CO_2. TH and AADC form a complex with the vesicular monoaminergic carrier-2 (VMAT-2), facilitating the uptake of dopamine in the monoaminergic synaptic vesicles [29]. The TH, the AADC complex, and the VMAT-2 transporter facilitate the absorption of dopamine in the monoaminergic synaptic vesicle, thus avoiding the oxidation of dopamine to o-quinones by the dissociation of the hydroxyls of the catechol present in the molecule when at p. 7.4 of the cytosol [30]. In the monoaminergic vesicle, the stability of the molecule in the protonated form is conferred by an estimated pH of approximately 5 [30].

Dopamine, which is not absorbed by VMAT-2, is transported freely by the cytosol and may undergo oxidation by monoamine oxidase to give rise to dihydroxyphenylacetic acid, methylation by ortho-methyltransferase, and structure oxidation of catechol to o-quinone aminochrome [31]. 0-Quinones derived from dopamine to form aminochrome are rapidly mopped by cysteines (or other thiols present) generating forms that are oxidized to form melanotic pigments [32–34]. The action of flavenzyme FADH, such as DT-diaphorase induce the formation of hydroquinone and ROS from reduction of o-quinones derived of freely dopamine in the cytosol [35, 36]. Semiquinone is a highly reactive radical, and under aerobic conditions, it catalyzes the reduction reaction of oxygen to the superoxide that activates the redox cycle between the leucoaminochrome o-semiquinone radical and the aminochrome [37, 38].

Aminochrome leads to the formation of species with proteins of complexes I and III of the mitochondrial electron transport chain associated with reduced flavin adenine dinucleotide ($FADH_2$) [39]. It forms compounds with the isocitrate dehydrogenase, leading to mitochondrial dysfunction due to a decreased ATP production [40]. In addition, aminochrome forms adducts with alpha-synuclein protofibrils and with Parkin leading to proteasome dysfunction, with actin leading to dysfunction in axonal and cytoskeletal transport, aggregation of α-β tubulins leading to autophagy dysfunction [41, 42]. In PD models, the active metabolite of 1-metyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), MPP^+, and rotenone are mitochondrial toxins that inhibit the NADH-quinone oxidoreductase complex respiratory [37, 43, 44].

2.2 Mitochondrial K_{ATP} channels

Mitochondrial dysfunction seems to play a crucial role in PD [44–47]. Mitochondria is directly implicated in ROS generation and consequently in neuronal cell death in vulnerable population. Mitochondrial K_{ATP} channels (mito-K_{ATP}) act as a gate control linking metabolism with cell survival and neurotransmitter releasing (**Figures 2** and **4**) [48]. Kir6.2 mito-K_{ATP} channels are encoded by KCNJ11 gene family, whereas SUR1, the K_{ATP} channel sensor subunit, belongs to the class of ABCC8, a subfamily of membranes transporters [49, 50].

K_{ATP} channels are triggered by the ATP/ADP rate, opening in response to reduced levels of ATP and, closing, otherwise, linking K_{ATP} channels in a direct relationship with the neuronal sugar metabolism and the action potential [51]. In physiological conditions, in dopaminergic neurons, these channels are probably closed. On the other hand, in PD model induced by MPTP administration in mice, the ATP depletion and mitochondrial dysfunction are observed, thus triggering the opening of the mito-K_{ATP} channels (**Figure 4**) [52].

Activation of K_{ATP} channels upon damage may play a neuroprotective role by decreasing the cellular metabolic demand, reducing activation rate of the action potential, thus leading to hyperpolarization of the dopaminergic neurons and loss of its normal pacemaker activity [53].

K_{ATP} channels play an important role in signal transduction in the central nervous system (CNS). For example, these channels are implicated in rest potential of most neuronal cell controlling the duration of action potential, firing frequency, and nonspecific intervals, thus regulating pacemaker time [54]. These ionic channels stabilize the membrane potential and the mitochondrial matrix volume during the ATP decline in order to increase the firing in dopaminergic neurons, as well as activation of metabolic pathways to provide cell energy (**Figures 3** and **4**) [25].

During mitochondrial dysfunction caused by oxidative stress or in the presence of neurotoxins (MPTP or rotenone), high calcium concentration and the hyperpolarization of membrane potential may be involved in the reduction of cellular activity in adult rats [52]. However, the vulnerability of dopaminergic neurons may be related to the differential expression of K_{ATP} (Kir6.2) between STNc and VTA neurons. Acute activation of rotenone-induced K_{ATP} channels in rat brain slices in responsive dopaminergic neurons increases the expression of the K_{ATP} channel subunits, the SUR1 and Kir6.2 [55]. However, the chronic effect of ATP depletion and consequent opening of K_{ATP} channels (Kir6.2/SUR1) due to its metabolic sensitivity in the vulnerable STNc and VTA-DA neurons decrease the expression of the decoupling protein (UCP2) due to the lower degree of mitochondrial decoupling conducted by the metabolic stress in PD [25].

The opening of the K_{ATP} channels may result in the hyperpolarization of the neurotransmitters modulating the release of glutamate and g-aminobutyric acid (GABA) in the *substantia nigra reticulata* (StNr) and in the striatum, reducing glutamatergic transmission into the brain (**Figure 4**) [56]. This fact suggests the significance of oxidative stress and mitochondrial alterations as a common remarkable cause in the development of PD (**Figures 3** and **4**).

During PD development, $Ca_v1.2$ in favor of $Ca_v1.3$ is differentially expressed in brain areas, thus resulting in an increase of neuronal susceptibility to events associated with oxidative stress [1, 24]. The hypothesis of differential expression of Ca_v1 subtypes to explain neuronal selective cell death remains inconclusive, but the fact that there is a change in its prior expression throughout the brain in early stages of the disease's development reinforces our previous proposition that calcium imbalance is a fundamental requirement to understand PD pathogenesis.

3. Conclusions

In this review, we suggest that both mitochondrial K_{ATP} channel and calcium1.3-voltage-gated contribute to maintain a balance between cell proliferation and apoptosis, acting as a metabolic sensor by coupling ROS and glucose metabolism to mitochondrial membrane potential in dopaminergic neurons. Finally, in conclusion, it may lead to a new pathway of drug development and treatment of PD.

List of abbreviations

AADC	aromatic amino acid decarboxylase
ABCC8	ATP-binding cassette subfamily C member 8
ADP	adenosine diphosphate
a-syn	alpha-synuclein
ATP	adenosine triphosphate
Cav1.2	voltage-dependent calcium channel subunit alpha 1C
Cav1.3	voltage-dependent calcium channel subunit alpha 1D
CNS	central nervous system
D2-AR	dopaminergic D2-autoreceptor
DA	dopaminergic
DJ1	protein deglycase 1
PD	Parkinson's disease
ETC	electron transport chain
FADH2	Flavin adenine dinucleotide
GABA	g-aminobutyric acid
GPe	external globus pallidus
K_{ATP}	potassium channels
KCNJ11	potassium voltage-gated channel subfamily J member 11
Kir6.2	subunit ATP-sensitive K^+ channel
L-dopa	L-3,4-dihydroxyphenylalanine
Mito-K_{ATP}	mitochondrial ATP-dependent K^+ channel
mit-psi	mitochondrial membrane potential
MPP+	metabolite of 1-metyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPTP	1-metyl-4-phenyl-1,2,3,6-tetrahydropyridine
NADH	nicotinamide adenine dinucleotide
NC	nucleus accumbens
ROS	reactive oxygen species
STNc	substantia nigra compacta
STNr	substantia nigra pars reticulata
SUR1	sulfonylurea receptor
TH	tyrosine hydroxylase
UCP2	decoupling protein 2
VMAT-2	vesicular monoaminergic carrier-2
VTA	ventral tegmental area
VTA-DA	ventral tegmental area DA neurons

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Chapter 3

The Causative and Curative Roles of Brain-Derived Neurotrophic Factor in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is characterized by the activation of degenerative and inflammatory processes in brain circuits that control movement and, according to the degree of progression of the damage, can cause neuropsychological disorders such as cognitive dysfunction. Changes in gene expression profile or post-translational modifications in secretory proteins such as neurotrophic factors could define the disease progression. Brain-derived neurotrophic factor (BDNF) is relevant, because it not only participates in neuronal survival, neurotransmission, dendritic growth and cellular communication but also in disease progression. In this chapter, considering both experimental evidences and clinical reports, the authors will analyze the contribution of BDNF as one of the causes of neurodegeneration and neuroinflammation; discuss the participation of this neurotrophic factor in the development of cognitive dysfunction, and finally the scope of novel BDNF-based therapies for PD.

Keywords: neurodegeneration, regeneration, BDNF, therapy, cognitive dysfunction

1. Introduction

Parkinson's disease is the second most common neurodegenerative disease worldwide, with high annual costs of treatment. The death of dopaminergic neurons and inflammation are the main cellular processes associated with motor and cognitive dysfunctions in PD [1–4]; these events can be potentiated by the loss of the brain-derived neurotrophic factor (BDNF), a key neurotropic factor in degeneration and regeneration processes.

2. BDNF

2.1 Sources

BDNF, discovered in 1982, is a pleiotropic neurotrophin (NT). The gene encoding for *BDNF* is located on chromosome 11p14.1. Under normal conditions, this neurotrophic factor is synthesized as a non-covalently bound homodimer that contains a signal peptide next to the initiation codon, a pro-region containing an N-linked glycosylation site, and interacts with its receptor as a homodimer [5]. The *BDNF* gene, in rodents, consists of nine untranslated 5′ exons, each linked to individual promoter regions, and a 3′ coding exon (IX), which encodes the amino acid sequence of the BDNF pre-protein. Similarly, human *BDNF* gene also consists of multiple 5′ exons spliced to a single 3′ coding exon. The transcription of neurotrophins is finely regulated by several intracellular signaling pathways and by different transcription factors [6].

This NT is synthesized as an inactive precursor form, pre-pro-BDNF that can be cleaved to form a mature neurotrophin that is transported to the plasma membrane and then released in an unprocessed manner. The "pre" sequence is normally deleted when it translocates through the Golgi membrane, producing the pro-BDNF of 32 kDa. Small amounts of a truncated 28 kDa pro-BDNF can also be formed in the endoplasmic reticulum without interfering with the final levels of active, mature 14 kDa BDNF (m-BDNF). The N-terminal pro-domain of BDNF facilitates intracellular trafficking and regulated secretion. After cleavage of N-terminal region, the m-BDNF is released, although this does not exclude the release of the pro-BDNF form [6].

The BDNF shows affinity for two types of receptors. The first is a 75 kDa glycoprotein from the family of tumor necrosis factor receptors, represented by p75 NTR and P75 + sortilin receptors, and the second is a receptor from the protein tropomyosin receptor kinase (Trk) family, which involves the TrkA, TrkB and TrkC, whose main ligands are neuronal growth factor (NGF), BDNF/neurotrophins (NT-4 and NT-3), respectively. The p75 receptor binds to the pro-BDNF isoform and can induce apoptosis and bind non-neurotrophic ligands such as the glycoprotein of rabies virus, amyloid peptides and also other pro-neurotrophins; it can also generate neurite retraction and synaptic weakening and facilitate long-term depression [6–8]. The m-BDNF binds to TrkB receptors promoting cell survival, neurite extension and long-term synaptic potentiation and improves learning and memory; it also promotes synaptic plasticity, neurogenesis, formation of angiogenic tubes, regulation of neurotransmitter release and dendritic growth [5, 6, 9–11].

2.2 Physiological relevance

At the brain level, BDNF is produced in the hippocampus, amygdala, *stria terminalis*, septum, nuclei of the solitary tract and cortex [8, 12], where it regulates the survival and differentiation of various neuronal populations, including sensory neurons, cerebellar neurons and spinal motor neurons. However, it was observed that the brain is not the only source of BDNF, since its expression has been demonstrated in human immune cells (T or B cells and monocytes), adipose tissue cells, β-cells, vascular endothelial cells and in blood [13, 14]. Its presence in ovaries has also been described, where it participates in folliculogenesis [15]; in the heart [16] and in other organs, it participates in angiogenesis and immunomodulation process [17]. The presence of BDNF in other organs of the body raises the hypothesis that exogenous neurotrophic factors provide a symptomatic treatment during the patient's disease state rather than a cure for the nervous system disorders that cause the disease [18].

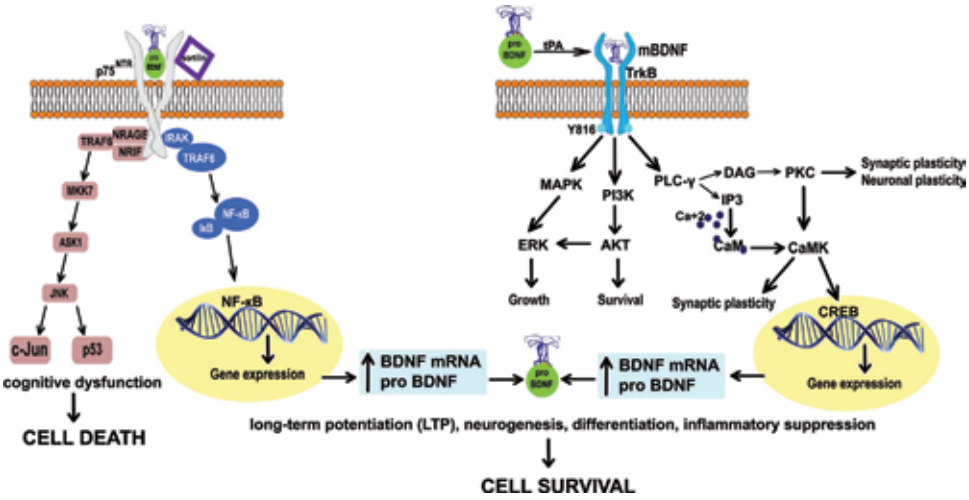

Figure 1.
Causative and curative roles of BDNF. Schematic view of cognitive dysfunction mediated by binding of pro-BDNF to p75NTR receptor leading to apoptotic cell death. Induction of BDNF gene due to the binding of pro-BDNF to p75NTR + sortilin and mBDNF to TrkB receptors leading to cell survival mediated by NF-κB and CREB, respectively. BDNF, brain-derived neurotrophic factor; mBDNF, mature BDNF; p75NTR, p75 neurotrophin receptor; NRAGE, p75NTR interacting protein; NRIF, neurotrophin receptor interacting factor; TRAF, tumor necrosis factor receptor-associated factor; MKK7, mitogen-activated protein kinase kinase 7; ASK1, apoptotic signal-regulating kinase 1; JNK, c-Jun N-terminal kinase; IRAK, interleukin-1 receptor-associated kinase; IκB, kappa light polypeptide gene enhancer in B-cell inhibitor; NF-κB, nuclear factor kappa-light chain enhancer of B cells; TrkB, tropomyosin receptor kinase B; tPA, tissue plasminogen activator; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositol 3-kinase; AKT, protein kinase B; PLC-γ, phospholipase C gamma; DAG, diacylglycerol; PKC, protein kinase C; IP3, inositol triphosphate; CaM, calmodulin; CaMK, calmodulin-dependent protein kinase; CREB, cyclic adenosine monophosphate response element-binding protein.

Alterations of BDNF expression are implicated in the development of a variety of central nervous system (CNS) diseases, including neurodegenerative disorders, such as Alzheimer's, Parkinson's, Huntington's disease and amyotrophic lateral sclerosis, and psychiatric disorders, such as depression and schizophrenia [14, 18]. However, several studies have shown that the therapeutic application of BDNF prevents neuronal degeneration after axotomy and other forms of neuronal injury [19–22]. In addition, beneficial effects of BDNF have been reported in animal models of neurodegenerative diseases. Therefore, BDNF is now considered as a potential therapeutic agent for human neurodegenerative disease, for example, motor neuron disease and PD (**Figure 1**).

3. BDNF in Parkinson's disease

The cause of PD is linked with several molecular factors related to the survival and susceptibility of the dopaminergic neurons (DN) of the *substantia nigra* (SN) [23–25]. The imbalance in the levels of this neurotrophic factor can affect the motor and cognitive performance in parkinsonian patients. It has been detected that BDNF levels decrease in serum as well as in the SN and caudal-putamen nuclei of patients with PD [26, 27].

Recently, it has been proposed that the detection of a low concentration of BDNF in serum is a biomarker of the early stages of the disease [28, 29]. The low concentration of this neurotrophic factor in serum of PD patients may be due to a low transcription of the *BDNF* gene. Howells et al. [30] reported that the surviving DN located in the SN of patients with PD contained low levels of BDNF

mRNA, suggesting that this condition contribute to the death of DN and to the development of the disease. To counteract the death of DN, Salehi and Mashayekhi [31] proposed that BDNF is produced by glial cells that increase their population as a result of an active response to neurodegeneration, since they reported an increase in BDNF levels in cerebrospinal fluid of patients with PD [31].

Currently, well-known mechanisms of microRNAs (miRNAs) play a crucial role in neurotrophin gene regulation. These miRNAs are short non-coding RNAs of ~22 nucleotides that are coupled to the RNA-induced silencing complex (RISC) and regulate the degradation of the RNAs [32]. Several miRNAs regulate BDNF expression and could be directly involved in the survival of DN. It has been reported that miR-1 represses the levels of BDNF expression through regulatory sites in the 3′-UTR sequence of the gene [33–35]. In addition, miR-1 levels have been found to be decreased in patients with PD compared with healthy individuals [36]. The decrease in miR-1 in patients with PD may be due to an activated mechanism to increase the expression of BDNF and promote the survival of the remaining DN in the SN.

In this regard, it has also been reported that BDNF is negatively regulated by the damage induced with neurotoxin in a murine model of Parkinsonism using MPP+. The MPTP neurotoxin is converted to MPP+ by the enzyme monoamine oxidase (MAO-B), expressed by astrocytes. The MPP+ is then internalized into the DN specifically by the dopamine transporter and upon reaching toxic levels in the mitochondria and inhibits the complex I of the electron transport chain [37]. Zhang et al. [38] reported that the treatment with MPP+ led to an increased expression of miR-210-3p and decreased expression of BDNF. To corroborate the results, they performed the inhibition of miR-210-3p and observed that the levels of BDNF increased and the survival of the tyrosine hydroxylase-positive DN of the SN in mice injected with MPTP was also significantly improved. The regulation of BDNF expression has become a key strategy for the rescue of damaged DN in PD.

Another factor that alters the secretion of BDNF is the single nucleotide functional polymorphism Val66Met, whose effect has been widely studied in humans [39–41]. This polymorphism consists of a substitution of valine amino acid by methionine at position 66 of the precursor protein (pro-BDNF) causing a decrease in secretion induced by depolarization [42]. The distribution of alleles has been reported in several populations, with the Val/Val allele prevailing (from 59 to 72%), followed by Val/Met (from 25 to 38%) and with a lower prevalence of the Met/Met allele (from 2 to 4%) [43–45]. The effect of polymorphism has been studied with controversial results as some groups argue that there is an advantage of the carriers of the Met/Met allele, by showing a better cognitive performance than the individuals who presented the Val/Met allele [44]; other researchers conclude that the fact of carrying at least one 66Met allele has a high prevalence of having a greater cognitive deterioration when PD is present [43].

One of the main characteristics of PD is the formation of Lewy bodies that are composed mainly of α-synuclein protein [46]. Recently, it was found that this protein interacts with the neurotrophic receptor TrkB, inhibiting its internalization and its correct distribution. This interaction blocks BDNF signaling and results in increased death of DN induced by the MPTP [47]. In addition, α-synuclein has been shown to affect the retrograde axonal transport of BDNF and confirm the inhibition of the signaling pathway in a PD model [48]. The inhibition of this neurotrophic factor makes them susceptible to the DN of the SN and contributes to the symptoms observed in PD.

4. Parkinson: clinical aspects and neurological bases

Currently, PD affects the adult population (˃65 years) and even young people [49, 50]. Although PD is multifactorial, indisputable signs of the disease include the progressive degeneration of the DN of the nigrostriatal pathway due to oxido-redox imbalance, followed by neurodegeneration, neuroinflammation, Lewy bodies' deposits and the generalized damage of the neural circuits that control movement [24, 51, 52].

The degenerative process develops mainly in the DN. In humans, the early loss of dopaminergic neurons from the SN drastically reduces the striatal dopamine concentration [53, 54]. The origin of the motor and non-motor alterations can be sporadic due to genetic deregulation. Several genetic alterations have been described in *α-synuclein*, *SNCA*, *PINK 1*, *DJ-1*, *LRRK2*, *ATP13A2*, *PLA2G6*, *FBX07*, *VPS35* and *BDNF* genes [55, 56]. Independent of the etiologic origin, patients with PD develop motor and even cognitive dysfunctions.

4.1 Motor impairment

The Parkinson's motor symptoms are bradykinesia, rigidity, inclined posture and tremor at rest. Neuroimaging studies suggest that the motor signs of the disease appear when 50–70% of the DN damage is present [57]. Tremor at rest is the symptom that is present in more than 70% of the patients with PD; these idiopathic tremors are more noticeable when the patient is not performing a specific movement [58]. Electrophysiological studies suggest that tremor at rest in PD is generated by multiple oscillatory circuits that are operating at the same frequencies (4 ± 6 Hz); this tremor is improved with the administration of levodopa, while orthostatic tremor, in PD, is characterized by rapid and specific tremors that affect the legs and trunk when standing. This tremor presents a frequency of 14 ± 18 Hz, where levodopa has no effect, which indicates that the pathophysiology of orthostatic tremor in PD might be different from the tremor at rest [59].

The bradykinesia or slowness of movement is manifested by the decrease in manual dexterity or the difficulty to get up from where they are sitting. Also during the progress of the disease, patients show postural instability with increased risk of falls as they take much faster and shorter steps, and postural instability has a poor response to dopamine treatments [58]. The symptoms of PD are progressive; however, the rate of progression in motor symptoms is variable according to the period of development of the disease in which they occur [60].

Other motor imbalance is the hypomimia, which is characterized by the decrease in facial expression or in the number of eye blinks, blurred vision, altered look, speech alteration, as well as the presence of dystonia or movement disorders, which causes involuntary contractions of the muscles, stooped posture, difficulty turning, kyphosis or scoliosis, which refer to an abnormal curvature of the spine, walking with the drag of the feet, or "freezing" or inability to move in patients with advanced stage of PD [59].

In functional magnetic resonance imaging studies (fMRI) of akinetic patients, changes have been observed during the performance of a complex sequential motor task, showing a reduced functional magnetic resonance signal in the rostral part of the supplementary motor area and in the right dorsolateral prefrontal cortex. In addition, these patients also showed a significant bilateral increase in the activation of the primary sensorimotor cortex, the premotor cortex lateral, the caudal part of the supplementary motor area, the inferior parietal cortex and the anterior cingulate cortex, and in other cortical motor areas [61]. It has been mentioned that during

the earliest pathological stage of PD, neuronal degeneration occurs in motor nuclei of the brainstem, olfactory bulbs and limbic areas; as it proceeds, it continues to the temporal and paralimbic cortices, as well as to the thalamic nuclei, until reaching associative areas such as the prefrontal lobes, and to finally involve the first order and sensory motor areas [62–64].

However, Agosta et al. [65] found that the progression of the disease in patients with moderate and severe PD shows a small cortical atrophy compared with healthy individuals; this atrophy involves the thalamus and the prefrontal cortex; they also report that the loss of gray matter did not significantly worsen in later stages of the disease, with the thalamus showing this atrophy. They also observed that a microstructural damage of the white matter (WM) occurs with the increase in the severity of the disease, involving the brainstem, cerebellum, thalamocortical, interhemispheric and limbic pathways, as well as the extra motor association tracts. They correlate the damage in WM with the degree of cognitive deficit, considering that the damage in WM probably contributes to the more severe motor and non-motor dysfunctions that occur in patients in later stages.

4.2 Cognitive dysfunction

Parkinson's disease is associated with multiple cognitive deficits and an increased risk of dementia, especially in its late stage. In addition, alterations in visuospatial, attentional, executive and memory functions may occur [66]. Epidemiological studies show that cognitive impairments are present between 24 and 62% of patients with newly diagnosed PD, and in the long term about 15% of patients remain cognitively intact [67]. The incidence of dementia is approximately 100 per 100,000 patients per year among patients with PD, suggesting that people with PD have a three to six times greater risk of developing dementia than people of the same age without PD [68]. However, the pathophysiological mechanisms involved in these cognitive deficits are not yet clear.

At present, neurotrophic factors have attracted attention from both clinical and experimental levels. BDNF is one of the key molecules in the modulation of cerebral plasticity and can induce long-term potentiation (LTP) through the activation of signal transduction routes; this LTP plays a key role in the neurophysiological basis for learning and memory [69]. In experimental animal models, it has been observed that the inhibition of BDNF signaling in knockout mice can affect spatial learning and memory; on the contrary, in the general population, it has been observed that at higher levels of BDNF in the hypothalamus there is a better cognitive function, including memory [70]. Recently, it has been detected that serum levels of BDNF decrease significantly in those diseases with cognitive deficits, such as Alzheimer's disease, mild cognitive impairment and Huntington's disease [27, 71, 72].

At the clinical level, there has been an association between serum BDNF levels and cognitive impairment. For example, one study observed the association between the decreased levels of BDNF present in cerebrospinal fluid, which contributes to early cognitive deterioration in PD, in particular to executive-attentional dysfunction [20]. On the other hand, an increase in BDNF concentrations has been detected in the same sample type of individuals with this pathology with respect to non-diseased controls [31], which could be due to a glial activation to increase the synthesis of this neurotrophin in response to brain damage [19]. Some authors have reported the association between the Val66Met BDNF polymorphism and cognitive dysfunction in patients with PD [43, 44]; subjects with Met BDNF allele show decreased cognitive flexibility when compared to homozygous carriers of the Val BDNF allele [45] (**Figure 2**).

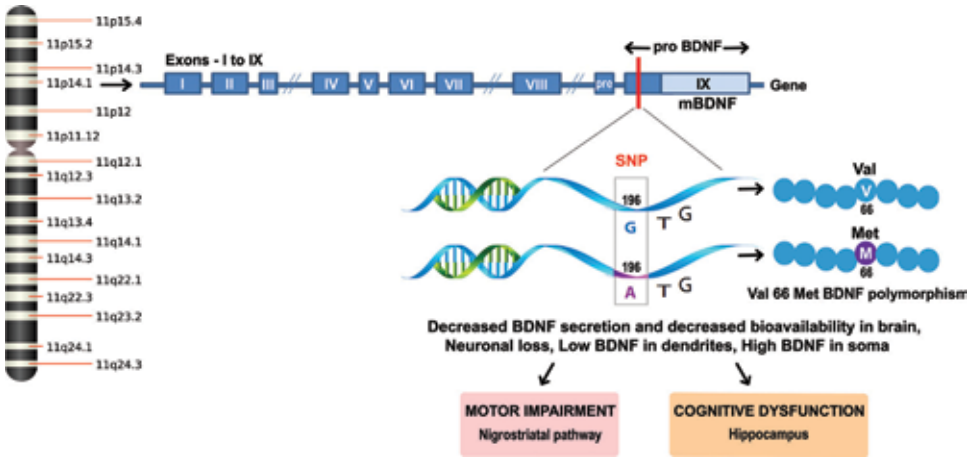

Figure 2.
Val 66 Met/G196A BDNF polymorphism in Parkinson's disease. Schematic representation showing the structure and location of BDNF gene and the location of single nucleotide polymorphism (SNP) that leads to the disease. BDNF, brain-derived neurotrophic factor.

In basic research, it has been observed that a higher concentration of hippocampal BDNF improves spatial memory in Morris's water maze [73]. The hippocampus is an important nucleus for learning and memory consolidation processes, and since BDNF plays an important role in the neuroplasticity of the hippocampus, the absence of this neurotrophin might affect the processes of learning and memory in the short and long term. Also, BDNF as well as TrKB has been shown in animal models to participate in the survival of DN in the SN [74], which is one of the main populations affected in PD. Therefore, the deficiency of BDNF, as well as its TrKB receptor, could be related to the loss of DN and the progression of the disease.

In studies of patients with dopaminergic neurodegeneration, a reduction in serum BDNF levels was observed, accompanied by a loss of striatal dopamine transporter (DAT) binding, that is, a positive correlation was found between the striatal DAT junction and BDNF levels [75]. On the other hand, there are several reports showing an increase in serum BDNF levels and also improvement in cognitive performance in PD patients, who underwent cognitive rehabilitation, when compared to a placebo group. These findings suggest that serum BDNF levels may represent a biomarker for the effects of cognitive rehabilitation in PD patients affected with mild cognitive impairment [76].

4.3 BDNF and aging in PD

Aging is another important variable that not only leads to the slow progression of PD but also hampers the medical treatment response [77]. There is aging without PD, but there is no PD without aging [78], showing decreased dopamine levels, increased sensitivity to mitochondrial dysfunction, alterations in calcium channel activity, accumulation of iron and neuromelanin, changes in protein degradation pathways [79], striatal spine retraction [80] and loss of striatal spine density [81]. With advancing age, the loss of DA neurons is fully expressed in PD genetic models in *C. elegans* [82] and human-induced pluripotent stem cells [83]; thus, aging is the key to the pathogenesis of PD [84]. In PD patients, aging leads to severe gait disturbances including musculoskeletal rigidity, axial impairment and age-related dementia [85].

In the brain, next to nigrostriatal pathway, hippocampus is highly sensitive to aging and BDNF is critically involved in the regulation of age-related hippocampal

decline [86]. In normal striatum, BDNF maintains dendritic spine density and synapse function, whereas in aged striatum, impaired BDNF signaling is common, which is further intensified in BDNF Val66Met SNP individuals [87]. With an increase in human age, BDNF mRNA levels remained same but TrkB mRNA levels decreased in hippocampus [88], indicating that BDNF-TrkB system of hippocampus is sensitive to aging [89] and deficiency of BDNF-TrkB signaling leads to the progression of PD [74]. Recent reports in aged brain suggest a diminished capacity of aged brain to transcribe, release and/or respond to BDNF [87]. As a result, treatment with TrkB agonist activates TrkB and downstream signaling cascades in BDNF-independent manner, which is neuroprotective both *in vitro* and *in vivo* [90].

5. Anxiety and depression in PD: BDNF role

At pre-clinical level, alterations in the synthesis and presence of BDNF are related to psychiatric disorders such as anxiety and depression [91, 92]. PD patients with Val66Met BDNF and G/G-BDNF-Val66Met polymorphisms are more predisposed to develop symptoms of anxiety or depression when observed at genetic level [39]. At the protein level observation, pro-BDNF is a facilitator of hippocampal long-term depression (LTD), and Val66Met pro-BDNF impairs memory function but pro-BDNF with Met completely inhibits hippocampal LTD indicating the antagonistic activities of pro-BDNF and BDNF on hippocampal LTD [93]. A *post-mortem* study on PD patients who received antidepressant drugs reported that the treatment with antidepressants can induce BDNF expression in hippocampus [94]. However, activity-dependent secretion of BDNF and understanding the mechanism of $p75^{NTR}$-pro-BDNF pathway are crucial to completely understand the hippocampal LTD modulation [93].

In this context, murine models has led to demonstrate the presence of the Val66MetBDNF polymorphism associated with anxiety-like behavior and significant increase of corticosterone, the physiological stress hormone, in serum [95]. Similar to human findings, the decreased production of BDNF in the hippocampus, amygdala and prefrontal cortex [96, 97] can be reversed with antidepressant drugs [91]. Whereas Tuon et al. evaluated the anti-depressant effect of BDNF, in a 6-hydroxydopamine (6-OHDA) murine model, by replacing the pharmacological therapy with physical exercise and observed a decrease of depressive-like behavior, which was associated with the restoration of pro-BDNF, BDNF and TrkB receptor levels both in the hippocampus and the *striatum* of rats [98].

Despite the importance of BDNF in plasticity and cellular maintenance, the serum levels of this NT have been studied [99]. Existing evidence shows that low concentration of BDNF is a risk factor to generate depression in PD patients [100].

6. Therapy using BDNF: experimental approaches and patents in animal models

In brain, BDNF not only mediates region-specific effects on synaptic function and neuronal morphology [8] but is also involved in various functions including aging [101], anxiety [102], chronic pain [103], deafness [104], depression [105] and long-term memory storage [9]. BDNF is proven to be the best therapeutic gene for treating metabolic syndrome [106], Friedreich's ataxia [107], neuropsychiatric or neurocognitive disorders [108], brain ischemia [109], schizophrenia [110], glaucoma [111], epilepsy [112], spinocerebellar ataxia typ. 6 [113], Huntington's disease

[21], multiple sclerosis [114], amyotrophic lateral sclerosis [115], spinal cord injury [116], Alzheimer's disease [22] and PD [117].

Despite encouraging and numerous researches supporting the potential therapeutic role of BDNF in non-human primate trials, no satisfactory results were found in clinical trials due to the disability to cross blood-brain barrier (BBB) and to reach degenerating neurons as such [118]. Hence, alternative methods like addition of poly ethylene glycol (PEG), either at N-terminal or at C-terminal, and vector-mediated BBB drug delivery were done to improve the BDNF distribution for use in clinical trials [119].

However, very short half-life of BDNF limits the effectiveness as a therapeutic protein, and thus, exogenous delivery methods are necessary to translate BDNF-based therapies to the clinic. In this direction, gene delivery methods through viral vectors have gained lot of attention by researchers in the beginning, but later on, it was proved that the use of viral vectors in the clinic was proven difficult due to the limited biodistribution and host immunogenicity [120]. Later on, non-viral and nanocarrier (liposome and polyplex) mediated gene delivery drew the attention as nanotechnology offers new possibilities for designing vehicles. Along with the nanotechnology, proteomics also integrated leading to the production of fusion protein vectors and mimetics (both protein and non-protein). The outline of the potential therapeutic role of BDNF in treating neurodegenerative disorders, specific focus on PD, by various researches (**Table 1**) and the patents related to BDNF (**Table 2**) are tabulated.

Animal model (toxin)	Mode of BDNF supply	Result/outcome
Mouse (MPTP) [121–123]	Intranigral	Increased cell survival
	Non-peptide mimetics of BDNF	
Rat (6-OHDA) [117, 124–127]	Intranigral transplants of human mesenchymal stem cells (hMSC) secreting the BDNF protein	Regulated neurotrophic effect and proved vehicle for the targeted neurotrophic delivery
	Intranigral injections of recombinant human BDNF in healthy rats	Chronic BDNF did not attenuate dopaminergic parameters in either striatum or SN
	Intra ventricular infusion	Adult brain parenchyma may recruit and/or generate new neurons
	Intranigral neurotensin (NTS)-polyplex nanocarrier mediated gene delivery	Neurorecovery by neuritogenesis in early stage of PD
	Intranigral recombinant adeno-associated virus (rAAV) vector-mediated gene delivery	No signs of neuroprotection
Rat (MPTP) [128]	Transplanting genetically engineered fibroblasts expressing BDNF protein	Axonal regeneration
Monkey (MPTP) [129]	Intrathecal infusion	Less neuronal loss and damage was observed in SN
Rhesus monkey [130, 131]	Stimulation of BDNF secretion by caloric restriction; physical exercise	Increased neuronal survival and locomotor activity in both SN and striatum

Table 1.
Therapeutic research works using BDNF.

Assignee/s	Inventor (date)	Title
Max-Planck Gesellschaft zur Forderung der Wissenschaften, Regeneron Pharmaceuticals Inc.	Yves-Alain Barde (1989)	Brain derived neurotrophic factor
Synergen Inc.	Frank Collins (1990)	Production of biologically active recombinant members of the NGF/BDNF family of neurotrophic proteins
Teva Pharmaceutical Industries Ltd.	Liat Hayardeny (2009)	Treatment of BDNF-related disorders using laquinimod
Center for research and advanced studies of the national polytechnic institute	Daniel Martinez-Fong (2012)	Compositions and methods for Parkinson's disease treatment by BDNF-flag gene transfer through neurotensin polyplex to nigral dopamine neurons
Curna Inc., The Scripps Research Institute	Faghini Mohammad Ali and Coito Carlos (2013)	Treatment of brain derived neurotrophic factor related diseases by inhibition of natural antisense transcript to BDNF
VDF FutureCeuticals	Zbigniew Pietrzkowski (2013)	Compositions and methods of BDNF activation
Meiji Co., Ltd.	Midori Natsume (2015)	Promoting the production for the composition of the brain-derived neurotrophic factor
Zhou Yi	Zhou Xinfu (2015)	Application of brain-derived neurotrophic factor precursor protein as target for treating affective disorders

Table 2.
Patents related to BDNF and its therapeutic role.

The experimental models of Parkinson give evidence of many recovery strategies to BDNF *in situ*, however till date exist great limitations to use these findings in novel therapies. Some pre-clinical and clinical resources have been patented (**Table 2**).

7. Clinical perspectives of BDNF-related therapy

The main objectives of experimental and clinical research include better understanding and proper diagnosis, developing new treatments and preventing them to the maximum extent. Currently, there are innumerable experimental pathology studies dedicated to solve the pathophysiology and possible treatment of PD. Based on this, clinical trials offer an excellent opportunity to help doctors and researchers to find better ways in detection, treatment or prevention in a safe way and, therefore, offer hope to people suffering from PD. Current studies include genetics, diagnostic imaging, studies that allow the identification of biomarkers of this disease, pharmacological treatment methods and various proposals for experimental therapies [132, 133]. Development and application of deep brain stimulation through implanting electrodes at specific sites to recover neuronal function is now a treatment option for some people with advanced PD when patients no longer respond to medications [134].

Having PD during aging involves rapid progression of motor impairment, altered mood and cognitive dysfunction. At the cellular level, there is a rapid loss of function and neuronal survival due to the absence of production of neurotrophic

factors such as BDNF. In the preclinical phase, some experimental approaches evaluated in animal models have partially prevented the DN degeneration and neuroinflammation. However, these approaches have great challenges; the therapies should be specific to one cell population, guarantee biosafety for human use, low cost and induce a sustained therapeutic effect.

Although BDNF was found to be promising in animal models of PD, no significant results from clinical trials are reported [135], and thus, therapeutic usage of BDNF for PD in humans is not yet reported. However, as BDNF cannot pass through the BBB, intracranial administration is must and this may be overcome by delivering BDNF bound to certain molecular carriers that can cross BBB to avoid intracranial surgery-related complications and long-term effects on behavioral disorders [136]. In this aspect, researchers from University of California have combined BDNF with mesenchymal stem cells (MSC) for treating neurodegenerative diseases, but no published scientific reports exist on preclinical and clinical trials of MSC/BDNF stem cell product [137].

8. Conclusion

Brain-derived neurotropic factor is relevant to neuronal maintenance and participates in the survival of dopaminergic neurons. The deficit of this neurotrophin is the key for the pathophysiology of PD because it limits the regeneration of motor and cognitive circuits. The absence of BDNF could promote the cognitive dysfunction in vulnerable subjects. The knowledge of the synthesis and delivery routes of this neurotrophin will allow the search for better therapies focused in patients with neurodegenerative diseases.

Acknowledgements

This work was supported by Consejo Nacional de Ciencia y Tecnologia (Catedra CONACyT # 1840) for DH-B and TC-LL, the Instituto de Neuroetologia from Universidad Veracruzana (DGI-174332015137 & CA-UV025) to MJR-H, the Instituto Mexicano del Seguro Social (FIS/IMSS/PROT/G15/1480) to LMZ-F and PRODEP (UANL-PTC-908) to AV-O. AP-O received fellowship from CONACyT for postgraduate studies in Neuroethology (# 297410).

Conflict of interest

The authors declare that there are no conflicts of interest.

Glossary

6-OHDA (6-hydroxydopamine) is an analogue of dopamine that produces high neurotoxicity into catecholaminergic neurons. The intracerebral 6-OHDA model is widely used to evaluate some Parkinson's symptoms in rodents.

Cognitive dysfunction is characterized by damage in neuronal circuits that regulate intellectual function, memory and concentration in humans.

Functional magnetic resonance imaging (fMRI) is a clinical technique to evaluate function and systems-level structure in living brain.

Gene delivery is referred as inserting or silencing foreign material into host cells for eliciting a therapeutic benefit. This can be achieved by vectors which include viral/non-viral, liposome, nanoparticles and peptides.

Levodopa (L-3, 4-dihydroxyphenylalanine) is a molecule derived from tyrosine (Y) amino acid, a catecholamine precursor. Levodopa is the drug more widely used to treat early stage of PD.

Lewy bodies are intracytoplasmic inclusions comprising mainly aggregates of α-synuclein protein.

Long-term depression (LTD) is lasting of neuronal synapses for a long time followed by a long patterned stimulus.

Long-term potentiation (LTP) is a result of increased levels of signal transmission of neurons in learning and memory processes.

MicroRNAs are short sequences of ribonucleotides. These molecules show complementarity and thus with messenger RNAs (mRNAs), thereby degrading their mRNA targets or preventing their translation into proteins.

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a pro-drug to MPP+ neurotoxin that induces loss of catecholaminergic and GABAergic neurons. The systemic administration of MPTP is referred as classic model of PD in mouse and monkeys.

Neurodegeneration means progressive loss of structure and/or function of neurons and finally leading to death.

Neuroinflammation is a highly regulated process that makes the host organism to deal and eradicate the infection by means of innate and adaptive immune systems. This includes the activation of immune cells and release of pro or anti-inflammatory cytokines, thus protecting the nervous tissue.

Neurotrophins are growth factors that regulate the survival and cell differentiation in several processes such as motor control, learning, memory and cognition.

Mitochondrial dysfunction is characterized by the loss of electron transport chain efficiency leading to reduced synthesis of adenosine-5′-triphosphate (ATP) and increased synthesis of free radicles. This is the characteristic feature of aging and chronic disorders.

Polymorphism is referred as diverse forms of a gene, formed due to the result of mutations or epigenetic changes.

Trk (tropomyosin receptor kinase) receptors correspond to membrane receptor proteins that regulate several biological processes including synaptic strength and plasticity in nervous system. Till date, TrkA, TrkB and TrkC are recognized as members of this family.

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Chapter 4

Neuroimaging in Parkinson Disease

Roohi Mohammad and Fatima Mubarak

Abstract

Over many decades, neuroimaging which included structural, functional and molecular modalities—have provided invaluable insights into the mechanisms underlying Parkinson disease (PD). These studies have shown changes in brain structure and metabolic activity. Although it is now considered to be complex, still neuroimaging modalities are recommended for routine use in clinical practice. Special sequences such as susceptibility weighted and proton density sequences are recommended for characterization. Now, the world is switching more towards the deep brain stimulation so the neuroimaging also helps in pretreatment planning and post treatment complications assessments. This chapter discusses the radiological anatomy, sequencing and imaging appearances. It will also discuss new approaches with potential applicability to clinical practice.

Keywords: MRI, PET, deep brain stimulation, Parkinson, substantia nigra

1. Introduction

Parkinson's disease (PD) is a communal neurodegenerative disorder with a prevalence of 160/100,000 in Western Europe rising to 4% of the population over 80 [1]. With an increase in average age, the management of PD is increasingly imperative and perplexing aspect of medical practice for the neurologists and general physicians. The pathogenesis of the disease has been advanced in the last decade with the identification of several gene mutations and the mechanisms of pathogenesis in sporadic cases of PD. The diagnosis of PD remains fundamentally a clinical, and it is significant to recognize the early features together with symptoms and signs suggesting other causes of Parkinsonism. There has also been a rapid expansion in the management options together with a greater awareness of non-motor complications. Guidelines for the diagnosis and management of patients with PD have been published from the National Institute for Health and Clinical Excellence (NICE) in the UK [2]. Parkinson disease can be diagnosed with Magnetic resonance imaging (MRI). Apart from good clinical diagnosis the imaging also helps in either endorsing the diagnosis or ruling out other possible differential possibilities. MRI can take a long time and it needs pre-scan screening of patients who cannot undergo this exams as there are certain contraindications which are beyond the scope of this chapter.

2. Neuroimaging in Parkinson's disease

Over the past decades, neuroimaging studies which include structural, functional and molecular modalities—have provided priceless understandings about the Parkinson disease (PD) [3]. Although PD is very complex, no neuroimaging modalities are specifically recommended for routine use in clinical practice. However, conventional MRI and dopamine transporter imaging are used as adjuvant apparatuses in the differential diagnosis between PD and other causes of Parkinsonism. Single-photon emission CT and PET are equally effective at differentiating between degenerative and nondegenerative causes of parkinsonism; MRI and PET can differentiate between PD and atypical parkinsonism, but need sophisticated enhancement methods [4]. Dopaminergic and serotonergic PET can be used to monitor PD progression, motor and nonmotor symptoms, and complications, whereas cholinergic PET is currently the most sensitive approach for assessing PD dementia. PET and other neuroimaging techniques should have a primary role in the development of protocols for new clinical trials, particularly those investigating cell therapy. Hybrid PET-MRI technology could offer a revolution in PD imaging [5].

The development of imaging which targets specific sites in the brain represents a significant advance in neurodegenerative diseases and Parkinson's disease. The major roles of imaging include: (1) the use of neuroimaging in order to improve the accuracy, timeliness, and reliability of diagnosis; (2) objective monitoring of the progression of disease; (3) the evaluation of s "disease-modifying" treatments designed to retard the progression of disease by interfering with pathways thought implicated in the ongoing neuronal loss or replace dopamine-producing cells; (4) planning and evaluation of deep brain stimulation technique in candidates of surgery [6].

2.1 Radiological anatomy

In Parkinson disease, the main part involved is extrapyramidal system. The substantia nigra is the main brainstem nucleus and other one is the nucleus. The substantia nigra is seen in axial slices at both superior and inferior colliculi and red nuclei within an axial slice at the superior colliculi (see **Figure 1**). These nuclei are situated in the anterior midbrain and mark the transition point of the tegmentum and cerebral peduncles.

Substantia nigra consists of a compact part (dark, containing melanin) called pars compacta and a reticular part (reddish, containing iron) known as pars reticulata. Most of its axons are projected diffusely to other brain areas and not arranged into tracts. Numerous axonal tracts terminate in the substantia nigra: from caudate nucleus (striatonigral fibers) from anterior cerebral cortex (corticonigral fibers) and from putamen from precentral cortex.

High resolution T2*/SWI weighted MRI is able to recognize the substantia nigra and red nuclei. They appear as hypointense on T2W, proton density and SWI sequences.

2.2 Protocol in neuroimaging

Magnetic resonance imaging (MRI) has proven to be the mainstay imaging technique in making the differential diagnosis between atypical Parkinsonism and Parkinson's disease.

Conventional T1- and T2-weighted MRI sequences are not very helpful in diagnosing idiopathic Parkinson's disease because nigral structures appear normal

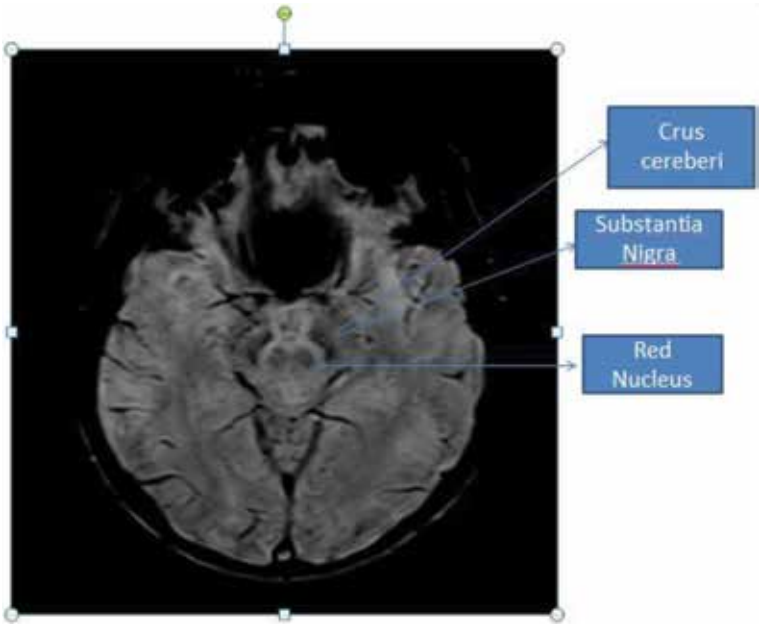

Figure 1.
MRI anatomy of deep brain stem nuclei.

in these routine sequences. Standard MRI sequences are very helpful in excluding secondary causes of Parkinsonism like structural basal ganglia lesions like granulomas, calcification, vascular lesions, Wilsons disease/ephedrine poisoning.

With the advent of newer techniques-such as neuromelanin-sensitive MRI, T2/T2* relaxometry (quantification of iron overload), proton spectroscopy, diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), magnetization transfer imaging, susceptibility-weighted imaging, perfusion-weighted imaging, and functional MRI—the role of MRI has evolved as has its role in the differential diagnosis between Parkinson's disease and atypical parkinsonism.

Conventional MRI scans with T1-weighted, T2-weighted, weighted, fluid-attenuated inversion recovery sequences and proton density-are usually normal in Parkinson's disease. In Parkinson's disease in axial T2-weighted sequences and susceptibility-weighted sequences significant thinning of the substantia nigra pars compacta diffuse cortical atrophy is noted however this imaging feature has shown high specificity, but low sensitivity and is found only in advanced stages of the disease [7].

2.3 Role of diffusion in Parkinson's disease

In patients of Parkinson's disease changes in water diffusion can be found in other regions of the brain even in its early stages, even when there is no significant cortical atrophy. It has been shown in studies that the fractional anisotropy is seen to be lower in the motor, premotor, and supplemental motor cortices of patients with Parkinson's disease than that of control patients, likely due to degeneration in the corticostriatal and thalamocortical projections in the former [8].

Susceptibility-weighted imaging (SWI) uses the differences in magnetic susceptibility of tissues. By applying a gradient-recalled echo (GRE) sequence, a SW image combines a phase image with a magnitude image under high-intensity magnetic field such as 3 T and 7 T. In healthy individuals, in posterior one third of

substantia nigra a linear or comma shaped high signal intensity called Nigrosome-1 is located it shows a distinct likeness to the split tail of sparrow in patients with Parkinson's disease, the high SWI signal in nigrosome-1 is lost and the normal 'swallow tail sign' cannot be seen.

Advanced MRI sequences in high field magnets have opened the possibility of in vivo visualization of substantia nigra (SN) and has been able to investigate pathological changes specific to PD. It thus has enabled the development of high precision tools for disease diagnosis in early stages.

Early in the course of the disease and in preclinical stages there is diminution of dopaminergic neurons in the substantia nigra (SN) pars compacta (SNpc) and noradrenergic neurons in the locus coeruleus (LC), which is characteristic of PD [9].

Depigmentation of the SN and LC is a discernible pathological feature of PD, which results due to the loss of a melanin pigment called neuromelanin.

A Japanese group in 2006 first described the use of specific MRI sequence that allowed the visualization of neuromelanin to the study of PD patients. Authors first described a high signal on specific T1-weighted images which is related to paramagnetic properties of melanin pigment and has allowed for the first time in vivo of pathologic characteristics of PD. Neuromelanin (NM)-sensitive MR imaging is a T1-weighted fast spin-echo (FSE) sequence performed on 3.0 Tesla. NM-sensitive sequences have been successful in depicting neuromelanin signals through the use of high signal-to-noise ratio (using 3.0 T magnetic fields), the prolonged T1 relaxation time of the brain and an indirect magnetization transfer effect [10].

Quantitative measurement of volumes of various regions of the brain are done by the use of advanced MR software. Voxel-based morphometry can be applied to volumetric MRI to see significant brain volume reduction in patients of Parkinson's disease at voxel level. Patients with Parkinson's disease studied with voxel-based morphometry, significant hippocampal, thalamic, and anterior cingulate atrophy can be detected of the brain [11].

MR spectroscopy has proven to be helpful in determining the levels of different metabolites in the brain parenchyma. Spectroscopy done in the affected region of brain shows a decreased N-acetyl aspartate to creatine (NAA/Cr) ratio. Evaluation of the pons, midbrain and putamen can be done for differentiating the various subtypes [12].

Magnetization transfer imaging: Different studies in literature have shown that magnetization transfer (MT) ratios are decreased in the affected areas of the brain. Therefore measurement of MT ratios in the substantia nigra, putamen and brainstem can be very helpful not in the diagnosis of PD but also to differentiate one from the other subtypes [13].

2.4 Role of NICE guidelines in Diagnosis of Parkinson's disease

Parkinson's disease is one of the most common neurodegenerative diseases, it was first described by James Parkinson in 1817, and the disease occurs due to nigral degeneration and striatal dopamine deficiency. Parkinson's disease is clinically, characterized by motor symptoms such as stiffness, bradykinesia, resting tremor, and postural instability.

Symptoms PD do not appear until approximately 50% of the nigral dopamine (DA) neurons are lost. Expert clinical opinion is the gold-standard diagnostic technique in PD. In clinicopathological studies the sensitivity for establishing a clinical diagnosis of PD by a movement disorder specialist is reported to be as high as 91.1% in [14].

According to NICE guidelines for diagnosis of Parkinson's disease:

1.2.1 Suspect Parkinson's disease in people presenting with tremor, stiffness, slowness, balance problems and/or gait disorders [2006].

1.2.2 If Parkinson's disease is suspected, refer people quickly and untreated to a specialist with expertise in the differential diagnosis of this condition [2006, amended 2017].

2.4.1 Clinical and post-mortem diagnosis

1.2.3 Diagnose Parkinson's disease clinically, based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria. [2006].

1.2.4 Encourage healthcare professionals to discuss with people with Parkinson's disease the possibility of donating tissue to a brain bank for diagnostic confirmation and research. [2006].

2.4.2 Review of diagnosis

1.2.5 Review the diagnosis of Parkinson's disease regularly, and reconsider it if atypical clinical features develop. (People diagnosed with Parkinson's disease should be seen at regular intervals of 6–12 months to review their diagnosis.) [2006] Single photon emission computed tomography.

1.2.6 Consider ^{123}I-FP-CIT single photon emission computed tomography (SPECT) for people with tremor if essential tremor cannot be clinically differentiated from Parkinsonism [2006, amended 2017].

1.2.7 ^{123}I-FP-CIT SPECT should be available to specialists with expertise in its use and interpretation. [2006].

2.4.3 Positron emission tomography

1.2.8 Do not use positron emission tomography (PET) in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials [2006, amended 2017].

2.4.4 Structural MRI

1.2.9 Do not use structural MRI to diagnose Parkinson's disease [2006, amended 2017].

1.2.10 Structural MRI may be considered in the differential diagnosis of other parkinsonian syndromes [2006].

2.4.5 Magnetic resonance volumetry

1.2.11. Do not use magnetic resonance volumetry in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials [2006, amended 2017].

2.4.6 Magnetic resonance spectroscopy

1.2.12. Do not use magnetic resonance spectroscopy in the differential diagnosis of parkinsonian syndromes [2006, amended 2017].

2.4.7 Acute levodopa and apomorphine challenge tests

1.2.13. Do not use acute levodopa and apomorphine challenge tests in the differential diagnosis of parkinsonian syndromes [2006, amended 2017].

2.4.8 Objective smell testing

1.2.14. Do not use objective smell testing in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials [2006, amended 2017].

2.5 Emerging role of neuroimaging

Structural and functional neuroimaging has become a valuable tool both in neuroscience research and in clinical settings. Different clinical and research applications of functional neuroimaging to Parkinson's disease (PD) have advanced over the past decade.

2.5.1 Hybrid imaging

Hybrid PET/MRI has made it possible to obtain structural (MRI) and functional (PET) information simultaneously. The advantage of PET/MRI as a single-investigation for the comprehensive evaluation of neurodegenerative disorders like PD is foreseeable. The role of PET/MRI, utilizing the F-18 florbetaben labeled stilbene derivative, a radiopharmaceutical that is developed to visualize beta-amyloid plaques in the brain in diagnosing patent's with Alzheimer's disease (AD) and is helpful in differentiating it from with Lewy body dementia (LBD) of Parkinson's disease has been reported [15].

2.5.2 Functional imaging-SPECT and PET

In PD the imaging pattern of striatal involvement for all tracers shows an asymmetric striatal decrease, which appears marked in side contralateral to the clinically affected side with a rostro-caudal gradient of uptake in this the posterior putamen is maximally affected [16].

2.5.3 Perfusion and metabolism imaging

Resting-state measurement of regional glucose utilization in the brain can be calculated by using F-18 Fluorodeoxyglucose (FDG) PET. The pattern that is specific for PD is known as 'Parkinson's disease related pattern' (PDRP), in which there is characteristic pallidothalamic and pontine hypermetabolism with hypometabolism seen in the prefrontal and parieto-occipital cortices. This pattern results from the underlying dopaminergic deficit in PD [17].

In patients with medically refractory tremors deep brain stimulation (DBS) of the motor thalamus and, the ventral intermedius nucleus (VIM), was first used in 1986 [18]. In Parkinson's disease, DBS of the internal globus pallidus (GPi) and the subthalamic nucleus (STN) were found to be safe and effective.

At present subthalamic nucleus (STN) is the main target nucleus for DBS in PD. Symptoms like rigidity, tremor akinesia and postural instability, that usually respond well to levodopa can be effectively treated by subthalamic nucleus (STN) DBS. Studies have shown that best outcome might be achieved by stimulation of the dorsolateral motor part of the STN. DBS should usually be performed bilaterally to relieve motor symptoms on both sides that allows for optimal reduction of medication.

In our institution we had diagnosed cases of Parkinson's disease who underwent deep brain stimulation and they responded very well and there was significant reduction in motor symptoms of the patients.

3. Insight in brain activation studies for motor functions

This is an overview of brain activation studies which describes findings that help in our understanding of the pathophysiology of motor, cognitive, and behavioral symptoms seen in Parkinson's disease PD and the underlying neuronal changes. Activation studies of PD patients have been utilized to see the basal-ganglia-thalamocortical circuit function. Several types of motor tasks have been used in conjunction with different neuroimaging techniques to study the motor circuit in PD.

Most common tests included the repetitive tasks, involving either of these two, one was repeated thumb to other finger opposition movements second was manipulation of a joystick in different directions. When normal subjects did repetitive right-hand joystick movements in different directions while they underwent [^{15}O]H_2O PET, an increase in regional cerebral blood flow (rCBF) was noted in the contralateral primary sensorimotor cortex and lentiform nucleus. Activation was also noted in the bilateral anterior cingulate gyrus, supplementary motor area (SMA), lateral premotor cortex, and dorsolateral prefrontal cortex. Opposite to that, PD patients showed a more complex activation pattern, which showed impaired rCBF changes in the lentiform nucleus, anterior cingulate gyrus, SMA, and dorsolateral prefrontal cortex. However normal activation was seen at the level of sensorimotor cortex, lateral, and parietal premotor cortex when compared with healthy controls [19].

The pattern of activation in PD varies significantly depending upon the stage of the disease, use of medication, and the type of motor task. In 1997 Samuel et al. hypothesized that nigrostriatal dopaminergic degeneration leads to hypoactivation of a mesial premotor system (SMA, anterior cingulate gyrus, and dorsolateral prefrontal cortex), frequently involved in self-paced movements.

The activation of the SMA was markedly improved when akinesia was reversed with apomorphine [19], rCBF was measured in PD patients at rest and when they performed joystick movements with the right hand in one of four freely chosen directions. All such patients were studied before and after treatment, in off state, and when "on" with apomorphine. It was seen that under resting conditions apomorphine had no effect on CBF, while significant activation of the SMA was observed while using the joystick with apomorphine.

The same group was also able to demonstrate that activation of the SMA significantly improved when akinesia was reversed with apomorphine [19]. In particular, rCBF was measured in PD patients at rest and when performing paced joystick movements with the right hand in one of four freely chosen directions. All patients were studied before treatment, in an off state, and when "on" with apomorphine. Under resting conditions apomorphine had no effect on CBF, while significant activation of the SMA was observed while using the joystick with apomorphine [20].

Studies in the past few years have suggested that chronic electrical stimulation of the primary motor cortex (MCS) may alleviate motor symptoms of PD. This new approach can be viewed as another alternative approach for PD patients who are not ideal candidates for DBS of these subthalamic nuclei (STN). A study was conducted by Strafella et al. to understand the cortical and subcortical effects of MCS. Interestingly, they found that MCS at 50 and 130 Hz did not produce significant changes in joystick motor performance or rCBF at cortical or subcortical levels. Therefore they concluded that while MCS was although a simpler and safer surgical procedure than DBS of the STN, it was not able to modify the pattern of movement related rCBF activation in PD patients [21, 22].

In conclusion, brain activation studies have been able to show the pathophysiology of PD and the neurobiological foundation of its motor, cognitive, and behavioral manifestations.

4. An overview of the current clinical evidence for morphological changes in the brain associated with symptoms (i.e. motor symptoms) and potential associated neural mechanisms

Parkinson's disease (PD) is characteristically shown to have motor symptoms including resting tremor, rigidity, and bradykinesia but cognitive and behavioral problems in PD are more common and they have a direct effect on the quality of life.

The estimated prevalence of dementia in patients with PD ranges between 24 and 31% has conservatively been estimated to range between 24 and 31%. Cognitive function in PD patients with dementia (PDD) is significantly different than that of the cortical dementia of Alzheimer's disease (AD). Patients with PDD often exhibit difficulties with executive functions, the retrieval aspects of memory, and visuospatial skills [23].

Patients with PDD often show a typical pattern of cognitive decline which shows characteristically a subcortical dementia that can be differentiated from AD in which cortical areas are affected early in the disease process and often include clear aphasia, apraxia, or agnosia. Dementia in PD is gradual in onset, and it is typically exhibited years after the onset of motor symptoms.

There is a difference between the pathophysiology of cognitive symptoms in PD and the pathophysiology of motor symptoms as well. Various factors have been implicated in the mechanism of disease process these, include dopamine depletion in the striatum and, to a lesser degree, in the prefrontal cortex. Due to disruption of dopamine levels at either site may there is resultant frontal-like deficits either directly or via downstream effects in striatal-pallidal-thalamocortical loops (CSPTC) [24].

Evidence has shown widespread cortical cholinergic dysfunction to be factor of cognitive decline in PD. Adrenergic and serotonergic deficits have also been described in PD but they have been associated with behavioral rather than cognitive function. Regional cortical Lewy body formation, have also been implicated in cognitive decline in PD.

Antiparkinsonian therapy either surgical or medical has shown heterogeneous effects on cognitive functioning. Neuroimaging and behavioral studies in PD patients as well as experimental models have associated this heterogeneity to (i) task-specific differences in regional activation responses, (ii) differences in the location/degree of dopaminergic denervation which in turn depends on the stage of disease progression, (iii) baseline genetic features such as the COMT genotype, and (iv) on individual treatment status [25].

In short, neuroimaging studies have contributed significantly to the current understanding of cognitive functioning in PD, therefore because of the high variability seen in the time course of cognitive decline with advancing disease, and in cognitive response to antiparkinsonian treatment, further research and work are warranted.

5. Conclusion

PD is now a common neurodegenerative disease. A combination of genetic and environmental factors are likely cause leading to cell dysfunction and then death. The diagnosis is essentially clinical, and there should be a high index of suspicion to exclude other causes of Parkinsonism. A large number of investigation tools together with surgical interventions are now available to treat early and late complications of PD. Increasing consideration is being given to the diagnosis and treatment in PD.

Conflict of interest

There are no conflict of interest.

Notes/Thanks/Other declarations

Nil.

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Chapter 5

Levodopa-Induced Dyskinesias and Dyskinesias-Reduced-Self-Awareness in Parkinson's Disease: A Neurocognitive Approach

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Abstract

Levodopa-induced dyskinesias are one of the most common disabling motor complications in advanced Parkinson's disease. The subjective perception of motor impairment is a clinical phenomenon that needs to be adequately analyzed. Indeed, the determination of patient dyskinesias-reduced-self-awareness (DRSA) and of its relationship to daily dysfunction is an important aspect of the debate on the gold standard for treatment. As the association with executive dysfunction is a matter of debate and we hypothesize it plays an important role in DRSA, we analyzed metacognitive abilities related to action monitoring and other factors, such as response-inhibition and "Theory of Mind," which represent a novel explanation of the phenomenon. Moreover, we investigated whether and how a dysfunction in action monitoring related to the cingulo-frontal-ventral striatal circuit would be associated with DRSA using an event-related Go-NoGo fMRI experiment. Our findings suggest the presence of executive dysfunctions in DRSA pathogenesis, with a key leading role played by the cingulo-frontal network as part of a functionally impaired response-inhibition network.

Keywords: dyskinesias, self-awareness, action monitoring, theory of mind, response-inhibition, fMRI, anterior cingulate cortex

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease with a slow but progressive evolution, which mainly involves the control of movements and balance. PD is part of a group of diseases called "movement disorders," and among these, it is the most frequent. The disease is present throughout the world and in all ethnic groups. It is found in both sexes, with a slight prevalence, perhaps, in males. The average age of onset is around 58–60 years, but about 5% of patients may present a juvenile onset between 21 and 40 years. Before the age of 20, it is extremely rare. Over the age of 60, it affects 1–2% of the population, while the percentage rises to 3–5% when the age is above 85.

The symptoms have perhaps been known for thousands of years: a first description would have been found in an Indian medicine treaty, which referred to a period of around 5000 BC. A more recent Chinese document dating back 2500 years is also known: "Huangdi Neijing" by Ti Huang [1]. However, the history of the disease is linked to the name of James Parkinson, a nineteenth-century London surgeon pharmacist, who first described most of the symptoms of the disease in a famous booklet, the "An Essay on the Shaking Palsy."

PD is characterized by cardinal motor symptoms and several non-motor features. The former include bradykinesia, rigidity, and tremor, while the latter encompass autonomic symptoms, sleep disturbances, and neuropsychological disorders (i.e., cognitive impairment and dementia, affective disorders, impulse control disorder, psychosis) (see **Table 1**). In recent years, it has been understood that mild cognitive impairment associated with Parkinson's disease (PD-MCI) is more widespread than previously thought. It is estimated that 15–53% of total patients suffer from PD-MCI, with a higher frequency among the elderly and those with advanced Parkinson's disease. In 2012, the Movement Disorders Society commissioned a taskforce to unify the diagnostic criteria for PD-MCI. PD-MCI can be classified into *single-domain* and *multiple-domain* subtypes, each of which may show impairment in amnestic or non-amnestic domain [2]. Indeed, cognitive deficits associated with PD-MCI tend to involve frontal-based dysfunctions, including executive and attention/working memory deficits [3, 4]. Importantly, PD-MCI patients are at an increased risk of developing dementia (PDD), compared with cognitively intact PD subjects [5]. Neuropsychiatric symptoms such as apathy, visual hallucinations, and rapid eye movement sleep behavior disorders are often present. Attention processes, executive, recognition memory, and visuospatial dysfunctions tend to dominate [6]. In clinical practice, it is important that PDD should be recognized and appropriately treated [7].

After a first phase of the disease characterized by a good control of motor symptoms with the dopaminergic drugs (mainly levodopa and dopamine-agonists), patients inevitably enter the "advanced phase" of PD, developing the so-called motor complications, characterized by presence of involuntary movements (dyskinesia), painful dystonia, and re-emergence of parkinsonian symptoms ("off" periods) that can appear before the next levodopa dose (wearing-off) or suddenly (sudden or unpredictable "off") (see **Table 1**). In the majority of cases, these complications occur alternately during the same day. Moreover, two opposite issues can

Cardinal motor symptoms	Motor complications	Involuntary movements	Non-motor complications
• Bradykinesia • Rigidity • Tremor	• Motor fluctuations • Loss of answer to levodopa • Suboptimal response • End of dose deterioration • Wearing off • Awakening akinesia • On-off phenomena • Freezing	• Peak dose dyskinesia • Diphasic dyskinesia • "Off" state dystonia • "On" state dystonia • Yo-yoing	• Autonomic disorders (gastrointestinal, orthostatic hypotension, sweating, urologic, sexual dysfunction) • Sleep disorders (insomnia and sleep fragmentation, excessive daytime sleepiness, restless legs syndrome, rapid eye movement behavior disorder) • Sensory disorders • Mood disorders (depression, anxiety) • Psychosis • Cognitive impairment and dementia

Table 1.
Motor and non-motor complications and classification of levodopa-induced dyskinesias in advanced Parkinson's disease.

limit the adherence of patients to medical therapies in advanced PD phase. While for some patients, the need of dividing the levodopa daily dose in 5 or 6 administrations per day is considered a limitation, other patients develop a sort of craving for dopaminergic drugs, partly due to an impulse control disorder, and partly to a reduced awareness of therapy complications such as dyskinesia [8, 9].

The subjective experience of what it is like to be a PD patient is fundamental for the treatment complaint that is put at risk in cases of poor awareness of symptoms. Indeed, PD may result in reduced self-awareness of cognitive and behavioral symptoms. Moreover, patients may have reduced awareness of motor complications and—in particular—of dyskinesias secondary to the levodopa treatment. The determination of dyskinesias-reduced-self-awareness (DRSA)—and of its relationship to functional, behavioral, and neuropsychological (dys)functions—is a key aspect of the debate on the gold standard for treatment in PD. Considering the above, in this chapter, we will discuss therapies of the advanced phase and their management from a neurological and neuropsychological point of view; the case of levodopa-induced dyskinesias; the phenomenon of dyskinesias-reduced-self-awareness in PD; the neurocognitive approach to this phenomenon; the associated neuropsychological factor and neural underpinnings as well as from our research experience.

2. Parkinson's disease: therapies of the advanced phase and role of the neuropsychological evaluation

Along with the progressive worsening of the disease and the motor complications, the patient's management could represent a difficult clinical challenge for physicians.

During the last two decades, the treatment of the PD advanced phase has radically changed with the advent of therapeutic options that include deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus internus (GPi), levodopa/carbidopa intestinal gel infusion (LCIG), and subcutaneous infusion of apomorphine [10]. These therapies demonstrated a significant and long-lasting improvement in the management of parkinsonian symptoms and motor complications but their application, in particular for DBS, needs a thorough evaluation of patients. In this scenario, the neuropsychological evaluation has acquired a leading role, due to the important implications of cognitive and affective status in the selection of the best advanced therapeutic option, and in the patient's follow-up. Both STN- and GPi-DBS proved to be effective in relieving PD cardinal symptoms and improving patients' quality of life. In fact, several studies demonstrated that DBS has a long-term efficacy in PD, yielding a 60% reduction on levodopa-related motor complications [11], a 40–60% improvement in quality of life [12], and a significant gain in quality-adjusted life years [13]. Since its breakthrough in 1987, about 150,000 patients worldwide were treated with DBS, which is now the most common and effective surgical procedure for advanced PD. However, the significant improvement obtained by patients is strictly related to the selection of the optimal candidates. Indeed, in 1999, the scientific community developed a "Core Assessment Program for Surgical Interventions in PD" (CAPSIT-PD) based on strict neuropsychological, clinical, and surgical inclusion criteria with the aim of improving the risk/benefit balance of PD patients undergoing neurosurgical procedures. According to the CAPSIT-PD criteria, it has been estimated that less than 10% of PD patients are suitable for DBS [14].

In general, the best PD surgical candidates have idiopathic Parkinson's disease (not parkinsonism); tend to be younger (below age 69, but may be older); have at least 30% improvement at the unified Parkinson's disease rating scale (UPDRS) part III after

levodopa administration; have medication-related complications, such as wearing-off of medications prior to the next dose, on-off fluctuations, and dyskinesias; and have no or mild cognitive dysfunction. The latter is one of the most controversial aspects of patient selection since many PD patients suffer from cognitive deficits also in the early phase of the disease, but are quite functional in their daily lives. Given the range of deleterious effects from PD-MCI/PDD and increased emphasis on neuropsychiatric features on patients' management, compliance to treatment and prognosis, there is a compelling need for a good neuropsychological evaluation. In particular, as part of the cognitive and mood preoperative assessment for DBS candidacy, the CAPSIT-PD committee recommended the following tests: Mattis Dementia Rating Scale (MDRS) and Montgomery and Asberg Depression Rating Scale for general screening and mood evaluation; verbal fluency (letters F, A, and S), Paced Auditory Serial Addition Test (PASAT), Odd Man Out (OMO), and Modified Brown Peterson Paradigm (MBPP) for the assessment of executive functions; Rey Auditory and Verbal Learning Test (RAVLT) and visual amnesic battery of Signoret for the assessment of explicit memory; and short version of Tower of Hanoi for the assessment of procedural memory.

Movement disorders centers that perform DBS have adapted the CAPSIT-PD protocol over time to fit the needs of their individual institutions, and in 2006, a report from the consensus on deep brain stimulation for Parkinson's disease, a project commissioned by the congress of neurological surgeons and the Movement Disorder Society, has been published to address all aspects of DBS preoperative decision-making [15].

Still, a high variability exists in the evaluation of good DBS candidates and the experience of the Movement Disorders Centers plays a major role in the patients' selection. Especially the cognitive assessment is relevant in the candidate selection, since dementia is the most frequent exclusion criterion for DBS surgery. This is due to three relevant aspects: (1) the vast majority of PD patients show some cognitive deficits, in particular, in the executive function domain; (2) dementia may be worsened by DBS; and (3) demented patients may not take advantage of the surgery-related improvement of motor symptoms. Given these premises, the clinical challenge is represented by the difficulty to know the extent of cognitive dysfunction that may affect the outcome of DBS. Moreover, while a thorough neuropsychological evaluation is mandatory within 1 year before DBS to exclude dementia, there is no consensus on the type of testing and level of performance that would exclude patients from receiving DBS. In 2007, the Movement Disorders Society established criteria for the diagnosis of PD dementia, and also proposed practical suggestions for their verification [16]. Nonetheless, it is common practice to repeat the evaluation after 6–12 months to ascertain that cognitive functions are stable when borderline cognitive deficits are outlined. Moreover, it is important to ascertain that cognitive dysfunction is not related to treatable causes such as depression or antiparkinsonian medication, especially anticholinergics. Given an accurate candidate selection, DBS surgery showed excellent motor outcome with no or few neuropsychological issues. In fact, cognitive or affective symptoms may transiently appear as postoperative side effects but only rarely they are permanent. In particular, only the verbal fluency showed a significant deterioration after DBS and exclusively in STN-DBS-treated patients. Nonetheless, patients with preexisting mild cognitive impairment (MCI) have shown a shorter latency to dementia development in comparison with patients with presurgical normal cognitive status [17].

Finally, in patients treated with STN-DBS, particular attention needs to be paid for the affective state both in the selection phase and in the postsurgical follow-up, since depression and anxiety may worsen in some patients and few cases of suicides have been reported after surgery. Therefore, current psychiatric disorders and moderate to severe depression are further contraindication for DBS.

LCIG improves PD symptoms and motor complication [18] by means of a continuous delivery of levodopa directly in the jejunum, promoting stable plasmatic concentration and augmented bioavailability [19]. Unlike DBS, no strict neuropsychological indications are needed for starting LCIG treatment. Nevertheless, the patient's cognitive status has to be carefully evaluated. In fact, due to the gastrostomy and device management, the presence of severe cognitive impairment could unbalance the risk/benefit profile toward lower efficacy and higher prevalence of complications and side effects [20]. For the same reason, the presence of a caregiver is strongly recommended in patients with mild to moderate cognitive impairment undergoing LCIG treatment. On the other hand, LCIG does not seem to accelerate cognitive deterioration, and no significant differences in the long-term cognitive decline were reported in comparison with DBS or oral medical treatment [21]. Finally, amelioration of depression, anxiety, impulse control disorder, and psychosis has also been reported [20].

Subcutaneous infusion of apomorphine is a well-established treatment for advanced PD [22]. Similar to LCIG, no strict neuropsychological criteria exist for patient's selection, and no significant cognitive worsening seems to be associated with apomorphine infusion [23]. However, due to its powerful dopamine-agonist action, apomorphine treatment can be associated with acute confusional states, hallucinations, and paranoid psychosis. On the other hand, an improvement in mood and anxiety has been reported.

In conclusion, the management of the advanced phase of PD still represents a clinical challenge. A comprehensive neuropsychological evaluation is mandatory to guide the physician in the correct choice of treatment and to follow-up patients during the progression of the disease. The neuropsychological evaluation is also useful for understanding any dysfunctions in terms of "awareness of symptomatology" that may alter the compliance to the treatment and/or put the patient at risk in the daily living.

3. Levodopa-induced dyskinesias in Parkinson's disease

Levodopa is the most effective drug treatment for Parkinson's disease. However, its long-term use is complicated by disabling motor fluctuations and involuntary movements (the so-called levodopa-induced dyskinesias, LIDs) [24]. LIDs are involuntary choreiform ("soft") movements, which disturb the execution of voluntary movements and, when they are serious, cause very important disabilities in the patient. Dyskinesias are due to a denervation hypersensitivity of striatal neurons: changes in levodopa blood levels (dopamine precursor, with very short drug half-life) trigger dyskinesias because striatal cells—which have not received dopamine from the substantia nigra for long—become hypersensitive to the molecule. Despite significant advances, the pathogenesis of LIDs remains incompletely understood. It is known that dyskinesias appear only after dopaminergic therapy and there is a time lag between the start of treatment and the emergence of LIDs. Several possible mechanisms, both peripheral and central, have been proposed. A schematic representation of the whole process leading to LID is proposed in **Figure 1**.

LIDs are clinically heterogeneous [25]. LIDs generally first appear on the side worst affected by Parkinson's disease and in legs before arms [25]. Based on their relationship with levodopa dosing, LIDs are classified as peak-dose, end of dose, diphasic, off-state, on-state, and yo-yo dyskinesias (see **Table 1**). Peak-dose dyskinesias are the consequence of the maximum levodopa concentration (linked to an increase in dopamine at the synaptic level); diphasic dyskinesias are present both in growth and in decrease of the dopamine level; and end of dose dyskinesias are due

to a reduction of dopamine at the synaptic level. In this last case (or in the case of dystonia), we are in the presence of protracted movements that cause the patient to twist the neck, arms, legs, and hands (alterations of the harmonic regulation of the muscular tone between the agonist-antagonist muscle groups). They usually occur when the levodopa levels in the blood are low/reduced rapidly, more frequently at night or in the morning, before the first dose of levodopa (see **Figure 2**).

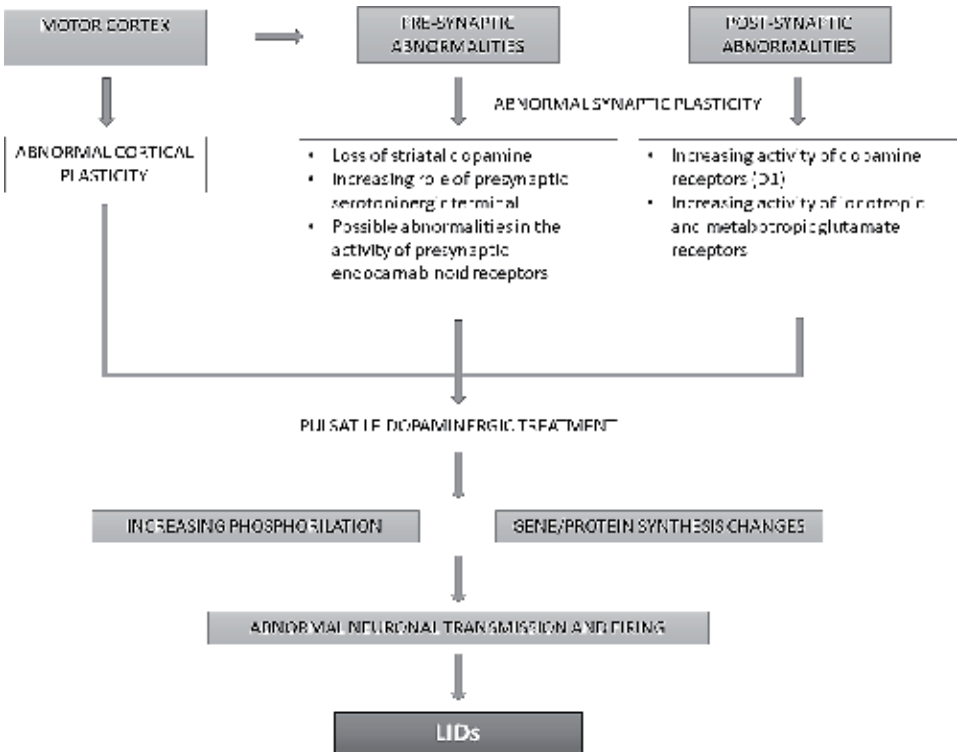

Figure 1.
Schematization of the pathophysiological processes leading to the emergence of dyskinesias.

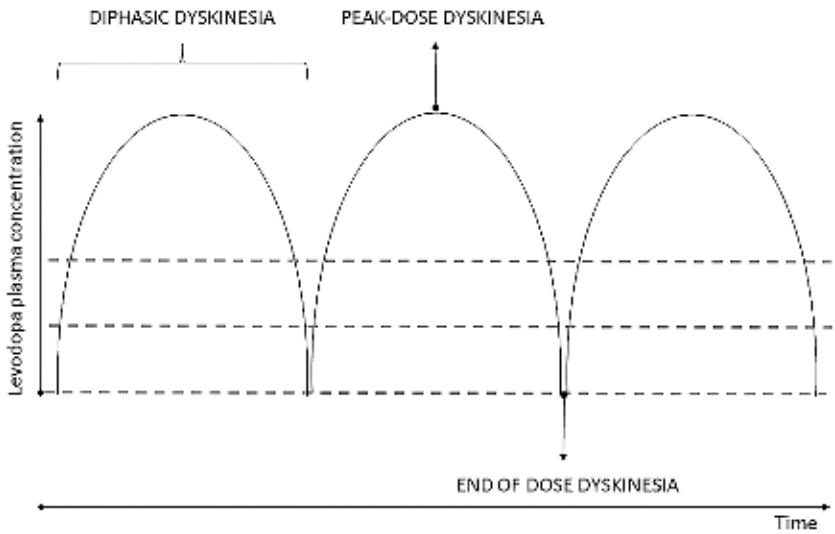

Figure 2.
Main types of dyskinesias in relation to the plasma concentration of levodopa over time.

Once levodopa-induced dyskinesias have developed in patients, they are difficult to treat [24]. LIDs negatively affect patients' quality of life and substantially augment the costs associated with their health care [26]. Prevention of onset would therefore be the best strategy [25]. Recommended interventions include: controlled-release preparations of levodopa; continuous delivery of levodopa; using catechol-O-methyl transferase (COMT) inhibitors; using dopamine receptor agonists; and neuroprotective agents [25]. In the case of overt LIDs, some treatment options may include: reduction of levodopa doses; using dopamine receptor agonists; drugs acting on NMDA receptors; drugs acting on serotonergic systems; miscellaneous agents; and neurosurgery [25].

LIDs are certainly one of the most common disabling motor complications in advanced PD. Indeed, the subjective ability to perceive motor impairment is a clinical phenomenon that needs to be adequately analyzed. Reduced awareness of illness is one of the factors associated with medication nonadherence. Moreover, unaware parkinsonian patients are of particular concern to caregivers, as they may incur unnecessary risks in order to complete their daily activities, causing a deterioration of their own and others' quality of life [27].

4. Dyskinesias-reduced-self-awareness (DRSA) in Parkinson's disease

In clinical neuropsychology, "awareness of illness" is considered as a form of self-knowledge (the so-called "self-awareness"). Its construct is complex when considering an operational semantic level [28]. This term is used to describe the ability to identify, recognize, and evaluate a deficit in sensory, perceptual, motor, affective, or cognitive functioning and to consider the impact of these disturbances on the patient's daily life [8, 29–34].

Reduced self-awareness leads to numerous negative effects, such as augmented stress and burden for primary caregivers, families, personal care and health care partner. Moreover, it worsens patient-caregiver relations, eases deflection of mood, somatoform anxiety, and poor adherence to treatment [35]. Moreover, a reduction in self-awareness has been found to be associated with a decline in help-seeking behavior and compliance with medical treatment, presumably because of a reduction in motivation [34].

The neurocognitive approach considers cognitive functions and behavior as closely linked to the function of single brain area, neural pathways, or cortical networks. This approach emphasizes how reduced self-awareness is associated to brain pathology, particularly concerning focal lesions, motivational and emotional factors, and concomitant cognitive disturbances [8, 29–33, 36]. In particular, since the frontal lobes are involved in self-awareness and monitoring of cognitive functions, reduced self-awareness could be viewed as a deficit in self-monitoring [37]. Furthermore, deficits in the internal representation of external outputs have been suggested to be a possible mechanism of decreased awareness [32, 34, 38]. Indeed, any deficit in monitoring, response inhibition, or cognitive flexibility can affect patients' self-awareness [34, 35]. In our experience, patients with neurodegenerative disorders such as Alzheimer's and Parkinson's (PD) diseases or frontotemporal dementia show reduced self-awareness due to deficits in self-monitoring [8, 9, 29–31, 39, 49].

When considering PD, it may result in reduced self-awareness of cognitive and behavioral symptoms. A form of awareness reduction for dysexecutive [40–42] and mnestic [43, 44] symptoms has been previously detected. If we consider the diagnostic spectrum ranging from complete cognition, to mild cognitive impairment (MCI), to the major neurocognitive disorder, a reduced self-awareness is

associated with the level of cognitive impairment and the simultaneous presence of mood abnormalities or executive dysfunctions [45]. In particular, reduced self-awareness has been detected in 36% of PD patients with mild dementia and 16% with MCI [45]. Moreover, more severe unawareness for cognitive impairment has been associated to depression, reduced hedonic tone, and more severe executive dysfunctions [45].

The phenomenon also manifests itself on the motor side. The determination of dyskinesias-reduced-self-awareness (DRSA)—and of its relationship to functional, behavioral, and neuropsychological (dys)functions—is a key aspect of the debate on the gold standard for treatment in PD. However, the relationship between subjective and objective evaluations of motor symptomatology in PD has so far been poorly investigated. Previous evidence has shown that parkinsonian patients have deficits in the subjective evaluation of levodopa-induced dyskinesias, with percentages ranging from 23 to 61% [39, 46–49]. Importantly, the hypothesis that dopaminergic overstimulation of mesocorticolimbic loops might be responsible for DRSA is currently suggested [8, 9, 39]; however, the role of dopaminergic treatment in the occurrence of metacognitive-executive dysfunctions is not yet fully clarified and requires more attention from the scientific community. Importantly, the kind of association between DRSA and executive dysfunction in PD patients has not been solved yet [8, 9, 49].

5. The proposal of a neurocognitive model of DRSA in Parkinson's disease

Reduced self-awareness may be considered an organically based decreased/lack of insight about neurological, cognitive, and behavioral deficits [34]. After a brain damage, sometimes patients become unable to detect the presence—or to realistically assess the severity—of sensory deficits, and motor, affective, or cognitive impairments, although, they are evident to doctors and family [34].

"Self-awareness" is a complex neuropsychological notion, defined as "the ability to consciously process information about ourselves in a manner that reflects a relatively objective view while maintaining our unique phenomenological or subjective sense of self" ([50], p. 301). Indeed, self-awareness is above all a form of self-knowledge and a higher-order cognitive function covering information about the state of the disease, its functional consequences, the way in which it affects the patient and influences his/her interaction with the environment [34].

A neurocognitive model of awareness may help in understanding the contribution of metacognitive-executive abilities related to DRSA in PD [8, 9, 34, 49]. Indeed, it is possible to interpret a reduction in disease awareness by referring to the *Cognitive Awareness Model* (CAM), which incorporates a comparator system within the central executive to detect mismatches between a personal database and experience of failures and successes [51]. When a discrepancy is found, a signal is sent out to the metacognitive awareness system, enabling a conscious experience of failure/success. If the executive system does not work properly, the comparator mechanism may not detect mismatches, and subsequently experienced failures may not produce any metacognitive output or conscious awareness, leading to an "executive unawareness" in the CAM [51]. In line with the interpretative model associating DRSA with executive dysfunction [8, 9, 34, 49], if the comparator mechanism for "attentive performance-monitoring" is compromised, then PD patients lose the ability to recognize their motor disturbances and levodopa-induced dyskinesias do not achieve conscious awareness.

6. Neuropsychological factors associated with DRSA

In their first study, Amanzio et al. [39] evaluated the presence of awareness of movement disorders in 25 PD patients. None before have analyzed the differences in DRSA by comparing the "on" and "off" states. PD patients were compared on three different scales to measure awareness of movement disorders: global awareness of movement (GAM) disorders, dyskinesia/hypo-bradykinesia rating scales. The authors found that PD patients had greater awareness and psychological suffering in the "off" than in the "on" state: patients explicitly complained about hypokinesias, mood-related symptoms, and perceived disability in their daily living [39]. Importantly, patients only showed DRSA in the "on" state and this reduced awareness was associated with executive cognitive dysfunction [39].

Since the dopaminergic overstimulation of mesocorticolimbic pathways may cause a dysfunction of prefrontal-subcortical connections and, subsequently, may negatively affect executive functions, more attention has been given to metacognitive-executive abilities related to action monitoring, that represent a novel explanation of DRSA [49]. The Wisconsin Card Sorting Test-metacognitive-version [52] turned out to be a fruitful neuropsychological tool to assess the executive functions of the prefrontal-ventral-striatal circuitry [49]. Indeed, DRSA was associated with global monitoring, monitoring resolution, and control sensitivity, suggesting that when the comparator mechanism for monitoring attentive performance is compromised at a prefrontal striatal level, patients lose the ability to recognize dyskinesias and to be aware of nonvoluntary movements [49]. These results support the interpretive efficacy of the CAM model not only in the case of major neurocognitive disorders [29–31], acquired brain injuries [33], and neuropsychiatric disorders [33], but also in the case of movement disorders.

Although dyskinesias-reduced-self-awareness in PD is related to deficit in metacognition, other factors, such as "Theory of Mind" (ToM), could operate [8]. Indeed, ToM has been a topic of interest in recent studies on unawareness of disease in neuropsychiatric disorders such as schizophrenia and bipolar disorder [33]. Not only decreased self-awareness may be considered a critical manifestation of impaired ToM abilities—in terms of meta-representation—but second-order false belief tasks and affective ToM abilities [33] seem to be of critical importance for preserved awareness of illness. For all the above, Palermo and collaborators [8] investigated whether DRSA could be influenced by cognitive and affective ToM as a contributing factor that has not yet been evaluated. Perspective-taking abilities were tested using ToM visual stories [53], while the ability to recognize the mental state of others was tested using the Reading the Mind in the Eyes task [54]. Multiple logistic regression models were used to estimate the impact of ToM disabilities on awareness evaluation [8]. DRSA was associated with the automatic and rapid processes of decoding mental states [8], which have often been ascribed to the affective ToM subcomponent [54]. Moreover, the association with executive dysfunctions has been reconfirmed [8].

7. New findings concerning the association between executive functions and the neural correlates of DRSA

We have previously demonstrated a noteworthy association between DRSA and decreased functional recruitment of the cingulo-frontal and cingulo-opercular pathways due to prolonged iatrogenic overstimulation [8, 39, 49]. This kind of association engaged in loading executive-monitoring onto the processing of task-relevant information, so as to avoid interference by goal-irrelevant stimuli.

Importantly, response-inhibition dysfunction is often observed in PD. Besides being involved in response-inhibition tasks, the anterior cingulate cortex is part of a functional system based on self-awareness and engaged across cognitive, affective, and behavioral contexts [9]. Considering the above—and since a dysfunction in action monitoring related to the cingulo-frontal-ventral striatal circuit would be associated with DRSA—it is important to evaluate whether and how ACC could be involved in the arising of DRSA in PD.

The association between blood oxygenation level-dependent response over the whole brain during an ACC-sensitive response-inhibition task and DRSA was investigated to clarify the kind of association between brain dysfunction and concomitant cognitive-behavioral disturbances [9]. The proposed paradigm is a prototypical task to measure the ability to inhibit an overpowering response [55, 56]. The task involves visual discrimination and a simple choice: to respond (GO) or not respond (NoGO) depending on the current stimulus. Response conflict arises from competition between the execution and the inhibition of a single response (response-inhibition conflict), rather than from competition between two alternative responses (response-selection conflict) [55, 56].

DRSA was associated with a reduced functional recruitment in the bilateral ACC, bilateral anterior insular cortex, and right dorsolateral prefrontal cortex ($p < 0.05$) (see **Table 2** and **Figure 3**). Moreover, DS-I scores significantly correlated with percent errors on the NoGO condition ($r = 0.491$, $p = 0.009$). Indeed, the worse the response-inhibition's performance, the worse the ability of a subject to notice and adequately assess the severity of his/her own dyskinesias [9].

Brain areas	MNI coordinates			Voxels	r-Score	p-Value
	X	*Y*	*Z*			
ACC	4	26	29	982	−0.84	0.000
ACC	−5	25	27	798	−0.81	0.000
AIC	33	22	−4	1855	−0.64	0.001
AIC	−39	27	3	1654	−0.41	0.002
DLPFC	−45	10	47	2128	−0.39	0.007

Peak activity coordinates are given in MNI space. Peak activities are significant at $p < 0.05$, FWE corrected for multiple comparisons at the voxel level. ACC: anterior cingulate cortex; AIC: anterior insular cortex; DLPFC: dorsolateral prefrontal cortex.

Table 2.
Linear correlation between the "NoGO" vs. "GO" contrast and DS-I scores (FWE $p < 0.05$).

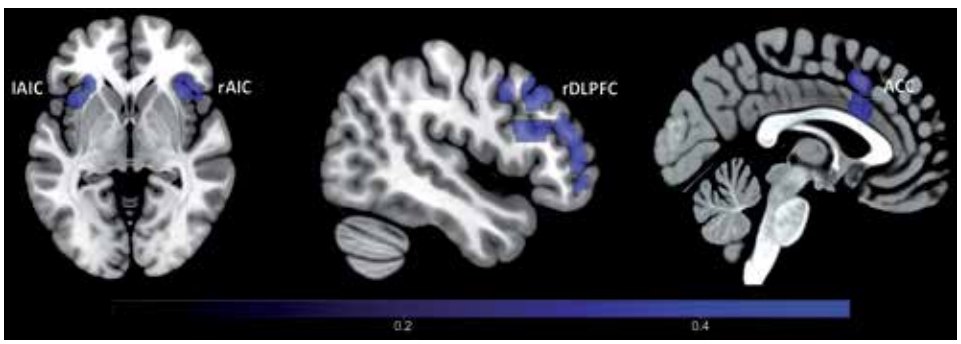

Figure 3.
Brain area negatively associated with DRSA in the NoGO/GO contrast (adapted from [9]).

8. Conclusions

Our findings show how DRSA was related with metacognitive-executive functions and the affective component of ToM, thus caused by a complex interplay between specific neuropsychological and motor factors.

Executive functions are a predictor of DRSA pathogenesis, with a key role played by ACC. Imaging biomarkers for DRSA are important to be studied, especially when the neuropsychological assessment seems to be normal. Our findings suggest that when the comparator mechanism for monitoring attentive performance is compromised at a prefrontal striatal level, patients lose the ability to recognize their motor disturbances that do not achieve conscious awareness.

It is important to consider the specific neuropsychological characteristics (including DRSA and metacognitive-executive (dys)functions) along with the neurological symptoms to define tailored interventions and adopt a personalized clinical approach avoiding increased doses of dopaminergic drugs, which would in turn enhance the risk of side effects.

Acknowledgements

We would like to thank all the members of the Center for the Study of the Movement's Disorder, directed by Professor Leonardo Lopiano (Department of Neuroscience, University of Turin, Italy). In particular, special thanks go to Professor Lopiano for his teachings, valuable scientific supervision, and expert guidance and Dr. Elisa Montanaro, Dr. Maurizio Zibetti, and Dr. Mario Rizzone for their precious support in every phase of the research.

Finally, we would like to thank Dr. Maria Consuelo Valentini, director of the Neuroradiology Unit (Azienda Ospedaliera Universitaria "Città della Salute e della Scienza di Torino") for her teachings, precious collaboration, and scientific supervision.

The authors have not received any funding from any institution, including personal relationships, interests, grants, employment, affiliations, patents, inventions, honoraria, consultancies, royalties, stock options/ownership, or expert testimony for the last 12 months.

Conflict of interest

No conflicts of interest considering all the authors.

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Edited by Sara Palermo, Mario Stanziano and Rosalba Morese

Parkinson's Disease and Beyond - A Neurocognitive Approach aims to bring together in a single publication the knowledge of diagnosis and characterization of the clinical and neuropsychological profile in Parkinson's disease. The strong impulse to research this topic has produced in recent years a large literature that documents the high level of complexity of the issue. Due to this complexity, a reasoned multidimensional analysis able to integrate expertise of different disciplines (neurology, neuropsychology, neuroradiology, and neuroscience) is necessary. This book offers an excellent synopsis of perspectives, methods, empirical evidences, and international references. It represents an extraordinary opportunity to target challenging unmet needs and to outline new horizons in Parkinson's disease research.

Published in London, UK

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ISBN 978-1-83880-870-9