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NEUROIMAGING – COGNITIVE AND CLINICAL NEUROSCIENCE

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http://dx.doi.org/10.5772/1815
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Notice

First published in Croatia, 2012 by INTECH d.o.o.
eBook (PDF) Published by IN TECH d.o.o.
Place and year of publication of eBook (PDF): Rijeka, 2019.
IntechOpen is the global imprint of IN TECH d.o.o.
Printed in Croatia

Legal deposit, Croatia: National and University Library in Zagreb

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

Neuroimaging - Cognitive and Clinical Neuroscience
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p. cm.

ISBN 978-953-51-0606-7

eBook (PDF) ISBN 978-953-51-6996-3

Meet the editor

Dr. Peter Bright was educated at the Universities of Surrey (BSc, 1991), Reading (MSc, 1993) and Cambridge (PhD, 1999). His research in the fields of memory and conceptual knowledge are well known. He has held research positions at the MRC Cognition and Brain Sciences Unit in Cambridge (1994-1995), King's College London (1998-2001), and the University of Cambridge (2001-2005). He currently holds the position of Reader at Anglia Ruskin University in Cambridge (since 2005).

Contents

Preface

The rate of technological progress is encouraging increasingly sophisticated lines of enquiry in cognitive neuroscience and shows no sign of slowing down in the foreseeable future. Nevertheless, it is unlikely that even the strongest advocates of the cognitive neuroscience approach would maintain that advances in cognitive *theory* have kept in step with methods-based developments. There are several candidate reasons for the failure of neuroimaging studies to convincingly resolve many of the most important theoretical debates in the literature. For example, a significant proportion of published functional magnetic resonance imaging (fMRI) studies are not well grounded in cognitive theory, and this represents a step away from the traditional approach in experimental psychology of methodically and systematically building on (or chipping away at) existing theoretical models using tried and tested methods. Unless the experimental study design is set up within a clearly defined theoretical framework, any inferences that are drawn are unlikely to be accepted as anything other than speculative. A second, more fundamental issue is whether neuroimaging data alone can address *how* cognitive functions operate (far more interesting to the cognitive scientist than establishing the neuroanatomical coordinates of a given function – the *where* question).

The classic neuropsychological tradition of comparing neurologically impaired and healthy populations shares some of the same challenges associated with neuroimaging research (such as incorporation of individual differences in brain structure and function, attribution of specific vs general functions to a given brain region, and the questionable assumption that the shared components operating in two tasks under comparison recruit the same neural architecture. However, a further disadvantage of functional neuroimaging relative to the neuropsychological approach is that it is a correlational method for inferring regional brain involvement in a given task – and interpretation of signal should always reflect this fact. Spatial resolution and sensitivity is improving with the commercial availability of ultra-high field human scanners, but a single voxel (the smallest unit of measurement) still corresponds to many thousands of individual neurons. Haemodynamic response to input is slow (in the order of seconds) and the relationship between this function and neural activity remains incompletely understood. Furthermore, choice of image preprocessing parameters can appear somewhat arbitrary and an obvious rationale for selection of statistical thresholds, correction for multiple corrections, etc. at the analysis stage can

likewise be lacking in some studies. Therefore, to advance our knowledge about the neural bases of cognition, rigorous methodological control, well-developed theory with testable predictions, and inferences drawn on the basis of a range of methods is likely to be required.

Triarhou (Chapter 1) provides a translation of Georg Koskinas' 1926 presentation to the Athens Medical Society in which the neuropsychiatrist described 107 cytoarchitectonically defined cortical areas (plus 60 "transition" areas) in the human brain. In comparison to Brodmann's (1909) universally recognised system (in which 44 cortical areas are defined), the von Economo and Koskinas system (published as an atlas and textbook in 1925) provided a fourfold increase in cortical specification. The author provides a compelling argument for more widespread adoption of von Economo and Koskinas' detailed criteria (commonly used in clinical neuroscience) in neuroimaging studies of human cognition.

Heterogeneity in brain structure and function across individuals is an important issue in neuroimaging research. Although attempts are made to manage such differences during stages of preprocessing and statistical analyses of datasets (as well as during the participant selection process), there can be a tendency to neglect the importance of individual differences due to the importance in the literature of identifying commonalities in the functioning of our brains. For example, it is quite common in fMRI studies to find participants who have relatively "silent" brains relative to others undertaking the same cognitive task. Age is a well recognised factor affecting brain structure and function, but the importance of cultural differences is relatively poorly understood. Goh and Huang (Chapter 2) present neuroimaging findings associated with age and cultural experience and also consider their interaction. Interestingly, research appears to suggest that culture-specific functional effects present in early adulthood are robust and remain in place despite subsequent age-related neurobiological change. Such observations also suggest that ageing effects in the brain may, in part, be contingent upon the nature of external experiences – raising clinical implications for modulating or offsetting neurocognitive changes associated with increasing age.

Danckert and Mirsattari (Chapter 3) consider the viability of fMRI studies of single neurological cases for furthering our understanding of brain-behaviour relationships. With careful attention to methodological issues, the authors present a strong argument for the single case approach (for both clinical and cognitive neuroscience purposes) in which comprehensive neuropsychological assessment and fMRI are employed and the results interpreted in the context of large-scale normative structural and functional MRI data. Chapter 4 (Martín-Loeches & Casado) provides a useful review of recent research on the neural correlates of human language and Chapter 5 (Yokoyama) considers whether (and the extent to which) brain regions responsible for core language processes can be dissociated from those responsible for more general cognitive processes associated with working memory and central executive function.

Tedeschi and Esposito (Chapter 6) present an excellent consideration of the utility of measuring resting state networks (RSNs) in clinical populations using fMRI. Some authors have questioned whether systematic neuroimaging analysis of the resting state represents an appropriate context for advancing cognitive theory. Nevertheless, this review presents a highly compelling argument for studying RSNs (particularly when combined with MRI tractography) in order to enhance understanding of pathological mechanisms in a range of neurological conditions. Kanahara et al. (Chapter 7) focus their comprehensive review on single-photon emission computed tomography (SPECT) and photon emission tomography (PET) studies of resting state blood flow and metabolism in a range of psychiatric conditions including schizophrenia, major depressive disorder, bipolar disorder and obsessive-compulsive disorder.

Sleep deprivation is associated with a wide range of neurocognitive effects, but attention and other aspects of executive function appear particularly vulnerable. Kirov and Brand (Chapter 8) review evidence for the role of sleep in the regulation of cognitive functions, with particular focus on neuroimaging investigations. The distinction between vegetative state (VS) and minimally conscious state (MCS) is clearly expressed in the clinical literature. The former refers to a state of "wakeful unawareness" in which patients are awake, can open their eyes and produce basic orienting responses, but have a total loss of conscious awareness. MCS differs to the extent that patients with this diagnosis are able to produce cognitively mediated behavioural responses. From a clinical perspective however, the distinction can be very difficult and a number of recent neuroimaging studies have provided indirect evidence that some VS patients have been able to communicate answers to orally presented questions. This rather disturbing finding that such patients may be more aware than the clinicians (or family members) may realise is of profound clinical importance given the very different prognosis and treatments indicated in the two conditions. Marino et al. (Chapter 9) review the role of neuroimaging in improving our understanding of coma, VS and MCS while recognising the continuing importance of comprehensive standardised clinical assessment.

Impulsive behavior is a major component of several neuropsychiatric disorders including schizophrenia, attention-deficit/hyperactivity disorder (ADHD), substance abuse, bipolar disorder, and borderline and antisocial personality disorders. The temporal, motor and reward related aspects of impulsiveness and decision-making are exemplified by the impulsive behaviors typically evident in ADHD and borderline personality disorder (BPD), with or without comorbidity. Archer and Bright (Chapter 10) consider the role of structural and functional neuroimaging for furthering our understanding of the cause and development of impulsivity in these conditions.

Marks and Katz (Chapter 11) carefully evaluate the potential role of MRI for establishing the nature of the relationship between exercise and the integrity (both physiological and cognitive) of the brain. The question of whether (and the extent to which) exercise can offset age-related cognitive decline is one which has attracted a

wealth of dubious "research findings" reported in the popular press, and this well argued and balanced review is a very welcome addition to the literature.

Recent research suggests that synchronization of oscillatory phases across brain regions (measured by EEG and MEG) may provide the basis for goal-directed attentional allocation and working memory functions. Kawasaki (Chapter 12) presents two EEG investigations implicating the role of frontal theta oscillations in conditions requiring active manipulation of the contents of working memory and parietal alpha oscillations in simple maintenance of working memory contents. These findings complement recent claims in the literature about the hierarchical organization (and dissociation) of cognitive control mechanisms in the human brain.

It is now recognized that bipolar disorder (BD) is associated with reductions in grey matter volume, particularly in right prefrontal, insular and anterior temporal regions. Nevertheless, in their review of neuroimaging findings, Dell'Osso et al. (Chapter 13) reveal inconsistencies in the literature (particularly on MRI). Most neuroimaging studies of structural changes in BP have small sample sizes and may therefore lack the power to detect subtle effects relative to appropriately matched controls. While some very recent meta-analyses have sought to address this problem, the current chapter serves a useful reminder that neuropsychiatric conditions typically encompass heterogeneity in symptom severity and diversity and in the ratio of organic to psychosocial factors driving their expression.

Silvetti and Verguts (Chapter 14) consider the utility of biologically driven reinforcement learning models for clarifying our understanding of attention and executive functions. The literature highlights the importance of functional relationships between anterior cingulate cortex and basal ganglia in cognitive control, but arguably the framework in which such relationships are investigated is overly constrained. The authors suggest that neural Darwinism (which, in this context, predicts that a sensory state will be considered valuable only if it subsequently leads to another valuable state) provides a broader and more appropriate context for explaining adaptive behaviour.

Principles and applications of functional near-infrared spectroscopy (fNIRS) are presented by Bourdillon and Perrey (Chapter 15), with particular focus on the measurement of cerebral oxygenation during motor performance. The size and portability of fNIRS devices provides opportunities for enhancing ecological validity of research investigations (in comparison to the restrictive conditions of fMRI), but strength of inferences which can be drawn are limited by a range of potential confounds and the lack of a standardised approach to data analysis. Nevertheless, the authors convincingly demonstrate the utility of this approach, particularly for the mapping of exercise-related brain functions.

Streri and Gentaz (Chapter 16) provide a fascinating review of intermanual and intermodal transfer in newborns. In contrast to the long held view that newborns

primarily display involuntary reflexes and reactions, evidence (based on habituation-dishabituation procedures) indicates that the haptic system is able to detect regularities and irregularities in the shape or texture of different objects – and that the tactile knowledge newborns accrue about an object held in one hand is transferred to the other hand despite the immaturity of the corpus callosum. Interestingly, cross-modal transfer is not always bidirectional. For example, newborns appear unable to apply haptic perception to recognise a visually presented shape but they can visually recognise the shape of an object they have held in their hand. In contrast, intermodal transfer for texture does appear to be bi-directional between touch and vision. The authors review behavioural studies of infants and neuroimaging data in adults in order to address the interdependencies of the visual and haptic systems from a predominantly developmental perspective.

Golaszewski et al. (Chapter 17) present a detailed overview of the somatosensory system, with particular focus on functional neuroimaging investigations. Principles and methods of somatosensory stimulation are discussed including practical considerations, clinical applications and safety issues. Chang et al. (Chapter 18) describe the process of oxidative stress caused by carbon monoxide intoxication and present nicely illustrated structural and functional neuroimaging features.

Li et al. (Chapter 19) provide a very clearly written and beautifully illustrated introduction to the measurement of effective connectivity with fMRI, in which the functional influence of one or more spatially distributed brain areas on another brain area is modelled. The authors are careful to emphasise the importance of a rigorous theoretical background, tight error control, intuitive interpretation and acknowledgement of likely commonality as well as diversity in connectivity within and across clinical and healthy populations.

Until very recently, it is probably fair to suggest that the status of EEG as a tool for exploring human cognition had diminished, due in no small part to the staggering increase in fMRI based research published in leading journals in cognitive neuroscience and related fields over the past 10-15 years. However, such a diminution is unwarranted, because both approaches continue to offer outstanding and complementary opportunities for understanding the neural bases of cognition (while also presenting significant methodological and interpretative challenges). Many of the leading journals are now encouraging manuscript submissions incorporating multiple methods, and the simultaneous employment of EEG and fMRI has had important repercussions both for progressing cognitive theory and promoting advances in method. Ibanez et al. (Chapter 20) describe the role of event related potentials (ERPs), measured with EEG, for understanding the temporal dynamics of sensory, perceptual and cognitive activity and consider the importance of this method to the study of social neuroscience.

Claims that “cognitive training” has a positive impact on structural and/or functional integrity of the brain are often raised in the media but are typically unsupported by

empirical evidence (this, of course has not prevented unscrupulous companies marketing "brain training" exercises and devices to the unwary customer). In particular, where specific studies *have* been reported in the media, they typically fail to offer evidence that results generalise beyond a straightforward practice effect on the employed tasks. Suo and Valenzuela (Chapter 21) provide a welcome review of neuroimaging outcomes associated with brain training trials by selecting only those studies published in peer reviewed publications which meet established criteria for scientific rigour. Nevertheless, readers may remain sceptical about the likelihood that the reported effects (often based on quite limited training) reflect general and robust non-specific improvements in cognitive performance (rather than simply reflecting changes associated with task-specific practice), and this review effectively communicates the heterogeneity in methods and outcomes across studies. The authors provide a number of suggestions for improving the quality and standardisation of research designs, and the strength of the inferences that can be drawn.

EEG-biofeedback (EBF) is an approach used to encourage participants to modulate CNS arousal by responding to real-time representation or feedback about their own brain activity. Diaz et al. (Chapter 22) describe the efficacy of this method for treating attention deficit hyperactivity disorder (ADHD) and insomnia. While acknowledging considerable theoretical and methodological issues, not least concerning the validity of the method as an effective form of therapy, the authors outline a number of sensible procedural guidelines that are now being followed (particularly the use of confirmatory evidence derived from other methods). Well controlled studies are appearing in the literature, and these tend to suggest promising avenues for EBF therapy in the treatment of some clinical disorders affecting CNS arousal. Central pain is a debilitating condition resulting from lesion or disease involving the central somatosensory system. In central post-stroke pain (CPSP), which occurs in approximately 10% of stroke patients, thalamic nuclei are most frequently implicated in the mechanism of central pain. On the basis of their review of psychophysical and neuroimaging findings in CPSP, Cheng et al. (Chapter 23) suggest a more complex distributed network of cortical regions is involved in the mechanism of central pain.

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Cytoarchitectonics of the Human Cerebral Cortex: The 1926 Presentation by Georg N. Koskinas (1885–1975) to the Athens Medical Society

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1. Introduction

The Greek neurologist-psychiatrist Georg N. Koskinas (1885–1975) is better known for his collaboration with Constantin von Economo (1876–1931) on the cytoarchitectonic study of the human cerebral cortex (von Economo & Koskinas, 1925, 2008). Koskinas seems to have been one of those classically unrecognised and unrewarded figures of science (Jones, 2008, 2010). Such an injustice has been remedied in part in recent years (Triarhou, 2005, 2006). The

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Kurz-Goldenstein, Primarius, Niederhart b. Linz, Irrenanstalt.

Fig. 1. The Vienna General Hospital on the left, where Koskinas worked between 1916 and 1927 under the supervision of Julius Wagner von Jauregg (1857–1940) and Ernst Sträussler (1872–1959) (author's archive). The 1926 roster of the Vienna Society for Psychiatry and Neurology on the right, showing Koskinas as a regular member (Hartmann et al., 1926)

year 2010 has marked the 125th birthday anniversary of Koskinas (1 December 1885) and the centennial of his graduation from the University of Athens (M.D., 1910).
As soon as the Atlas and Textbook of Cytoarchitectonics were published in 1925, Koskinas briefly returned to Greece and donated a set to the Athens Medical Society. On that occasion, he delivered a keynote address, which summarises the main points of his research with von Economo. That address (Koskinas, 1926) forms the main focus of this paper. There are only two other presentations known to have been made by Koskinas: one with von Economo at the Society for Psychiatry and Neurology in Vienna in February 1923 (von Economo & Koskinas, 1923), presenting an initial summary of cytoarchitectonic findings on the granularity of sensory cortical areas especially in layers II and IV; and the other with Sträussler at the 88th Meeting of the German Natural Scientists and Physicians in Innsbruck in September 1924 (Sträussler & Koskinas, 1925), reporting histopathological findings on the experimental malaria treatment of patients with general paralysis from neurosyphilis.

2. The 1926 presentation by Koskinas

The following is an exact English translation of the *Proceedings* of the Athens Medical Society, Session of Saturday, 23 January 1926, rendered from the original Greek text (Koskinas, 1926) by the author of the present chapter.

2.1 Introductory comment by Constantin Mermingas, presiding

"I am in the gratifying position of announcing an exceptional donation, made to the Society by the colleague Dr. G. Koskinas, sojourning in Athens; having temporarily come from Vienna, he brought with him a copy, as voluminous as you see, but also as valuable, of the truly monumental compilation, produced by the two Hellenic scientists in Vienna, C. Economo and G. Koskinas, who is among us today. It involves the book—text volume and atlas—*Cytoarchitektonik der Hirnrinde des erwachsenen Menschen*, about the value of which we had learnt from reviews published in foreign journals, but also convinced directly. Dr. Koskinas deserves our warm thanks, as well as our gratitude, for being willing to deliver a synopsis of that original scientific research and achievement."

2.2 Main lecture by Georg N. Koskinas, keynote speaker

"Thanks to the ardour of the honourable President of the Society, Professor Dr. Mermingas, who is meritoriously making every attempt to highlight the Society as a centre of noble emulation in scientific research and the promotion of science and at the encouragement of whom I have the honour of being a guest at the Society today. Enchanted by that, I owe acknowledgments because you are offering me the opportunity to briefly occupy you in person about the work published by Professor von Economo and myself in German, and deposited to the chair of the Society, "The Cytoarchitectonics of the Human Cerebral Cortex" *(Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen).* An attempt on my behalf to analyse that work requires much time and many auxiliary media which, simply hither passing through, I lack. That is why I wish to confine myself, such that I very briefly cover the following simply and to the extent possible.

Fig. 2. Previously unpublished photographs of Koskinas and family members. The left photograph, taken in Vienna around 1926, shows Koskinas (first from the right) with his wife Stefanie, their daughter, his sister Paraskevi and her husband. The right photograph shows Koskinas (second from the right) in the Peloponnese in the 1940s—the bridge of the Eurotas River appears in the background—with his wife and daughter (left), and the children of his sister Irene and their father (photos courtesy of Rena Kostopoulou)

2.2.1 Incentives and aim

The incomplete and largely imperfect knowledge of the histological structure of the brain constituted the main reason that led us to its detailed architectonic research, and its ultimate goal was the localisation, to the extent possible, of the various cerebral functions and the pathological changes in mental disorders, as well as the interpretation of numerous problems, such as individual mental attributes, i.e. the talent in mathematics, music, rhetoric, etc.

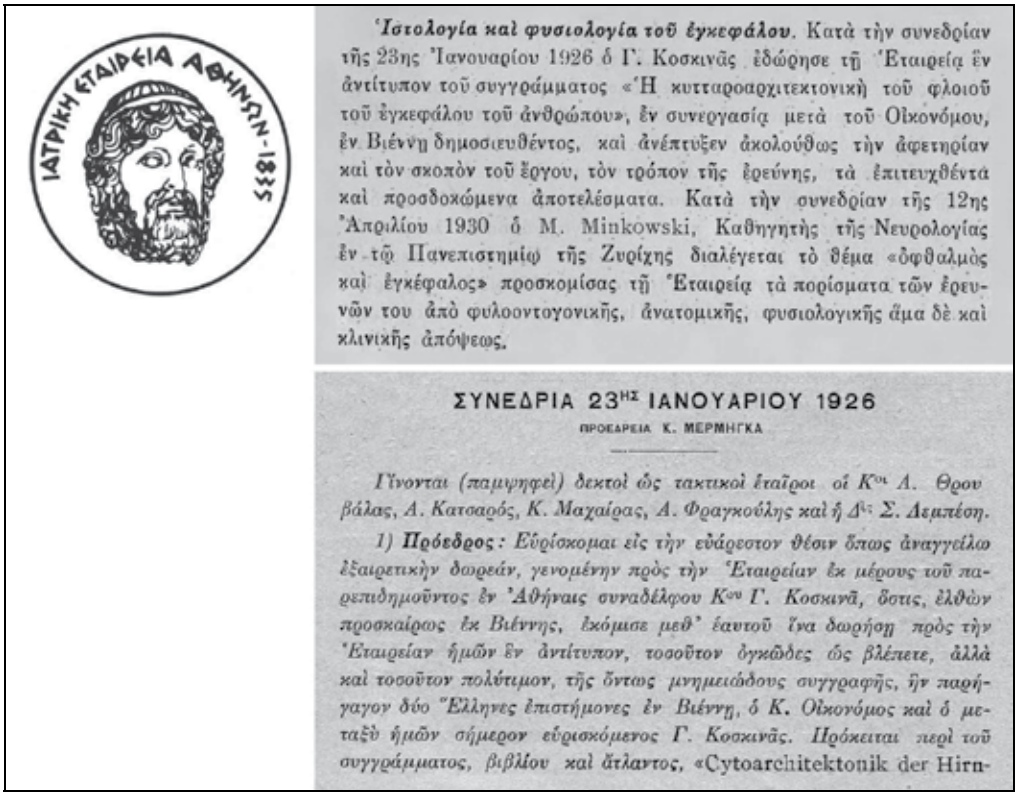
2.2.2 Methods

At the outset of our studies we came across various obstacles and difficulties deriving on one hand from the very structure of the brain and on the other from the deficiency of the hitherto available research means. That is why we were obliged to modify numerous of the known means, to incise absolutely new paths, taking advantage of any possible means towards a precise, reliable and indelible rendition of nature. We modelled an entire system of new methods of brain research from the autopsy to the definitive photographic documentation of the preparations. Thus, we were able to not only solve many of the problems, but also, and above all, to provide to anyone interested various topics for investigation, as well as the manner for exploring them.

Allow me to mention some of the employed research means.

Sectioning method. Instead of the hitherto used method of sectioning the whole brain serially perpendicular to its fronto-occipital axis (Fig. 5), whereby gyri are rarely sectioned perpendicularly, we effected the sections always perpendicular to the surface of each gyrus and in directions corresponding to their convoluted pattern (Fig. 6). We arrived at that act

by the idea that, in order to compare various parts of the brain cytoarchitectonically, sections must be oriented perpendicularly to the surface of the gyri, insofar as only then is provided precisely the breadth of both the overall cerebral cortex and of each cortical layer.



Ἱστολογία καὶ φυσιολογία τοῦ ἐγκεφάλου. Κατὰ τὴν συνεδρίαν τῆς 23ης Ἰανουαρίου 1926 ὁ Γ. Κοσκινᾶς ἐδώρησε τῇ Ἑταιρείᾳ ἓν ἀντίτυπον τοῦ συγγράμματος «Ἡ κυτταροαρχιτεκτονικὴ τοῦ φλοιοῦ τοῦ ἐγκεφάλου τοῦ ἀνθρώπου», ἐν συνεργασίᾳ μετὰ τοῦ Οἰκονόμου, ἐν Βιέννῃ δημοσιευθέντος, καὶ ἀνέπτυξεν ἀκολούθως τὴν ἀφετηρίαν καὶ τὸν σκοπὸν τοῦ ἔργου, τὸν τρόπον τῆς ἐρεύνης, τὰ ἐπιτευχθέντα καὶ προσδοκώμενα ἀποτελέσματα. Κατὰ τὴν συνεδρίαν τῆς 12ης Ἀπριλίου 1930 ὁ M. Minkowski, Καθηγητὴς τῆς Νευρολογίας ἐν τῷ Πανεπιστημίῳ τῆς Ζυρίχης διαλέγεται τὸ θέμα «ὀφθαλμὸς καὶ ἐγκέφαλος» προσκομίσας τῇ Ἑταιρείᾳ τὰ πορίσματα τῶν ἐρευνῶν του ἀπὸ φυλοοντογονικῆς, ἀνατομικῆς, φυσιολογικῆς ἅμα δὲ καὶ κλινικῆς ἀπόψεως.

ΣΥΝΕΔΡΙΑ 23ΗΣ ΙΑΝΟΥΑΡΙΟΥ 1926

ΠΡΟΕΔΡΕΙΑ Κ. ΜΕΡΜΗΓΚΑ

Γίνονται (παμψηφεὶ) δεκτοὶ ὡς τακτικοὶ ἑταῖροι οἱ Κ^οι Α. Θρου βάλας, Α. Κατσαρός, Κ. Μαχαίρας, Α. Φραγκούλης καὶ ἡ Δ^ις Σ. Δεμπέση.

*1) **Πρόεδρος**: Εὑρίσκομαι εἰς τὴν εὐάρεστον θέσιν ὅπως ἀναγγείλω ἐξαιρετικὴν δωρεάν, γενομένην πρὸς τὴν Ἑταιρείαν ἐκ μέρους τοῦ παρεπιδημοῦντος ἐν Ἀθήναις συναδέλφου Κ^ου Γ. Κοσκινᾶ, ὅστις, ἐλθὼν προσκαίρως ἐκ Βιέννης, ἐκόμισε μεθ' ἑαυτοῦ ἵνα δωρήσῃ πρὸς τὴν Ἑταιρείαν ἡμῶν ἓν ἀντίτυπον, τοσοῦτον ὀγκώδες ὡς βλέπετε, ἀλλὰ καὶ τοσοῦτον πολύτιμον, τῆς ὄντως μνημειώδους συγγραφῆς, ἣν παρήγαγον δύο Ἕλληνες ἐπιστήμονες ἐν Βιέννῃ, ὁ Κ. Οἰκονόμος καὶ ὁ μεταξὺ ἡμῶν σήμερον εὑρισκόμενος Γ. Κοσκινᾶς. Πρόκειται περὶ τοῦ συγγράμματος, βιβλίου καὶ ἄτλαντος, «Cytoarchitektonik der Hirn-*

Fig. 3. The *Proceedings* of the Athens Medical Society for the Session of 23 January 1926

Staining method. The staining of the preparations was perfected by us such that a uniform tone was achieved not only of a single section, but of all the countless series of sections into which each brain was cut for study. And that was absolutely mandatory, on one hand in order to define the gradual differences of the histological elements of the neighbouring areas of the cerebral cortex, and on the other hand to achieve a consistent photographic representation.

Specimen depiction method. The hitherto occasional histological investigations of the brain depicted things schematically and therefore subjectively. Instead of such a schematic depiction, aiming at a precise representation of the preparations with all the relationships of the countless and polymorphous cells, we used photography. Photographic documentation constitutes the most truthful testimony of the exact depiction of nature, providing truly objective images of things as they bear in natural form, size and arrangement (Fig. 7). But to succeed in the photographic method it became necessary to turn to the study of branches foreign to medicine, such as advanced optics and photochemistry. We took advantage of both of these as much as we could. Lenses, light beams, filters, photographic plates and finally the photographic paper itself were all adopted towards the accomplishment of the intended goal of the most perfect, i.e. the photographic, depiction.

Fig. 4. Constantin Mermingas (1874–1942), Professor of Surgery at the University of Athens and President of the Athens Medical Society (left), Georg N. Koskinas (1885–1975) in the centre, and Spyridon Dontas (1878–1958), Professor of Physiology and Pharmacology at the University of Athens and President of the Academy of Athens (right). © 1957 *Helios Encyclopaedical Lexicon* (signatures from the author's archive)

2.2.3 Accomplished and anticipated results

Through our work an extremely precise and detailed description was achieved of the normal histological structure of the cerebral cortex as it is depicted in the photographic plates and explained in the text. Our photographic plates in the atlas, as such, constitute an ageless, imprescriptible opus, the basis and the control of any future research on the cerebral cortex. Whatever in such research is in agreement with the plates, must be considered as normal, and whatever diverges constitutes a pathological condition. From that precise knowledge of the architectonic structure of the cerebral cortex, which we achieved, it is allowable to anticipate the solution of numerous and different questions and issues of utmost importance; from their endless number I suffice in mentioning e.g. the following.

a. *The problem of problems, i.e. the problem of the psyche.* When, as anatomists and physiologists, we speak of the psyche, we do not refer to it as a metaphysical being that finds itself a priori outside any anatomical and physiological weight, but as a moral, mental, active and historical personality which interacts with others and influences ourselves.
b. *The problem of individual mental attributes, i.e. intellectual talents,* such as rhetoric, music, mathematics, delinquency and the variations in the mental development of human phyla on the earth. By comparing e.g. the centres of music in individuals who genetically present a total lack of music perception to individuals who possess an evolved musical talent we may exactly pinpoint differences in such music centres.

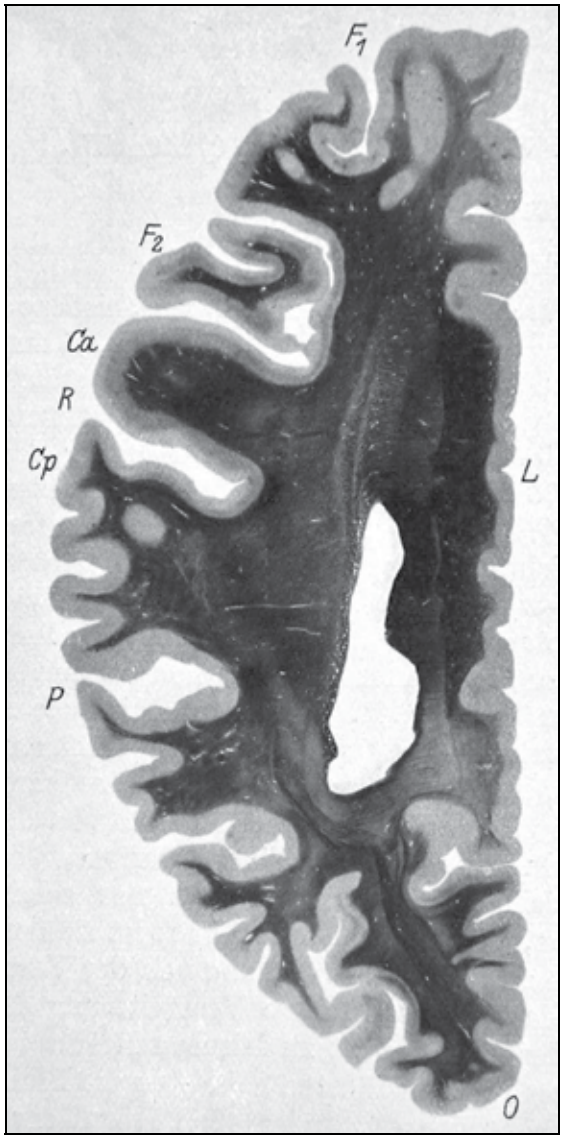


Fig. 5. Horizontal section through the left human cerebral hemisphere, depicting the sizeable regional differences in cortical thickness and the random orientation of the gyri (Koskinas, 2009). Weigert method. F_1 and F_2, superior and middle frontal gyrus; *Ca*, precentral gyrus; *R*, central sulcus; *Cp*, postcentral gyrus, *P*, parietal lobe; *O*, occipital lobe; *L*, limbic gyrus

c. *The problem of pathological lesions in numerous mental disorders* both primarily and secondarily encountered in the brain.
d. *The problem of the localisation of various centres.* The various localisations of sensation, movement, stereognosis, speech, etc., which thus far were mostly defined without an exact histological control, from now on, admittedly, can be readily and precisely defined on the basis of the cerebral cortical areas that we have designated, which from a total number of 52 known thus far we brought to 107 (Fig. 8–10). The solution of this

problem also possesses utmost sense, insofar as in that way diagnosis can be readily effected, foci can be defined with precision and brain surgery can be enhanced.

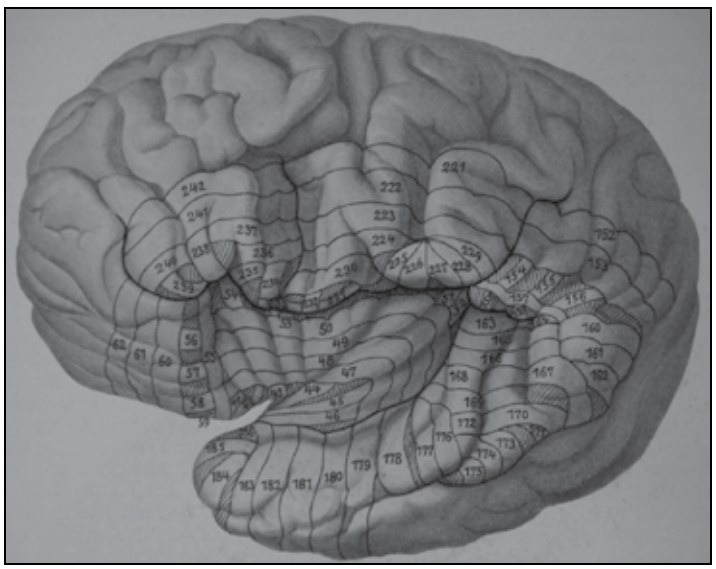


Fig. 6. Indication on the convex cerebral facies around the lateral (Sylvian) fissure of the von Economo & Koskinas (1925, 2008) method for dissecting each hemisphere into an average of 280 4mm-thick blocks perpendicular to the course of each gyrus for cytoarchitectonic study; hatched areas indicate the "cancelled" tissue

Sirs, in the phylogenetic line of living beings, nature, at times acting slowly and at times saltatorily, but always continually, produces new complex and viable animal forms. The same resourceful force that has given over the eons wings to the eagle to fly, has indirectly bestowed humans, by understanding their mind, with the capacity to construct wings themselves in order to defeat the law of gravity and to conquer the air. Nonetheless, the mind has its organic locus, its seat, its altar in the cerebral cortex. That is why one would be justified in saying that the anatomical and the physiological exploration of that noblest of organs deserves the utmost attention of science. The mind which explores and tends to subjugate everything, which tames everything and cannot be tamed, has to fall."

2.3 Response by Spyridon Dontas, annotator

"The work of Drs. Economo and Koskinas is monumental and constitutes a milestone of science, opening up new pathways towards the understanding of the brain from an anatomical, physiological and pathological viewpoint. It further forms the first comprehensive reference on the architecture of the adult human brain. And because the most precise of known methods was used, the optical, and through it a reproduction of the structure of the brain was achieved, in the natural, I reckon that this work will persevere as an everlasting possession of science. I further wish that Drs. Economo and Koskinas continue and complement their work, studying the remaining parts of the nervous system as well, to the great benefit of science."

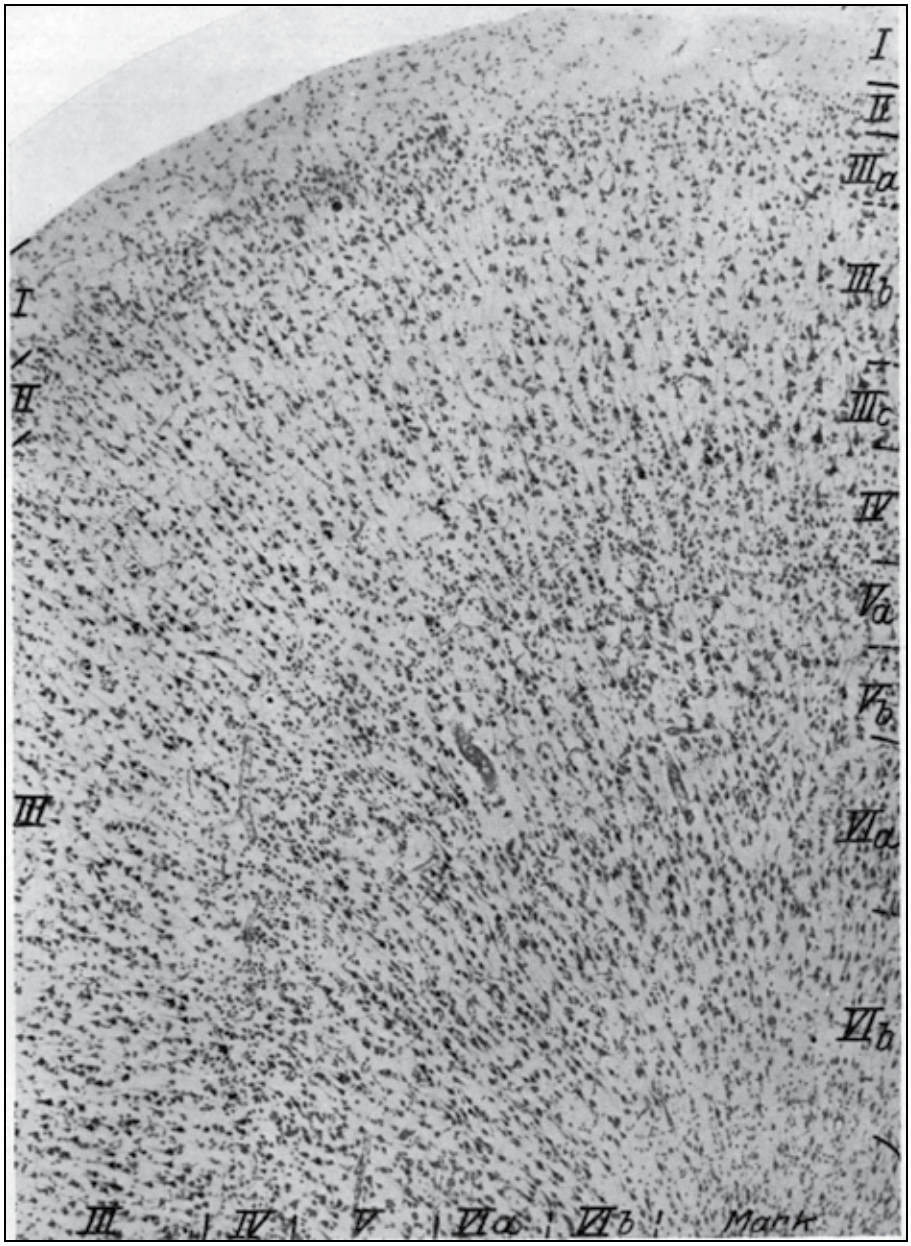


Fig. 7. Section of the dome of a gyrus from the frontal lobe of a human cerebral hemisphere, showing the normal six-layered (hexalaminar) cortex. The white matter (*Mark* in German), which is devoid of nerve cells, is seen on the lower-right hand corner. The six superimposed cortical cell layers are denoted in Latin numbers (I–VI). Photographed with a Carl Zeiss 2.0 cm Planar, a special objective lens with a considerably larger field than could be obtained with common microscopy objectives, especially valuable for large area objects under comparatively large magnifications and an evenly illuminated image free from marginal distortion. Planar micro-lenses are used without an eyepiece. ×50 (von Economo, 2009)

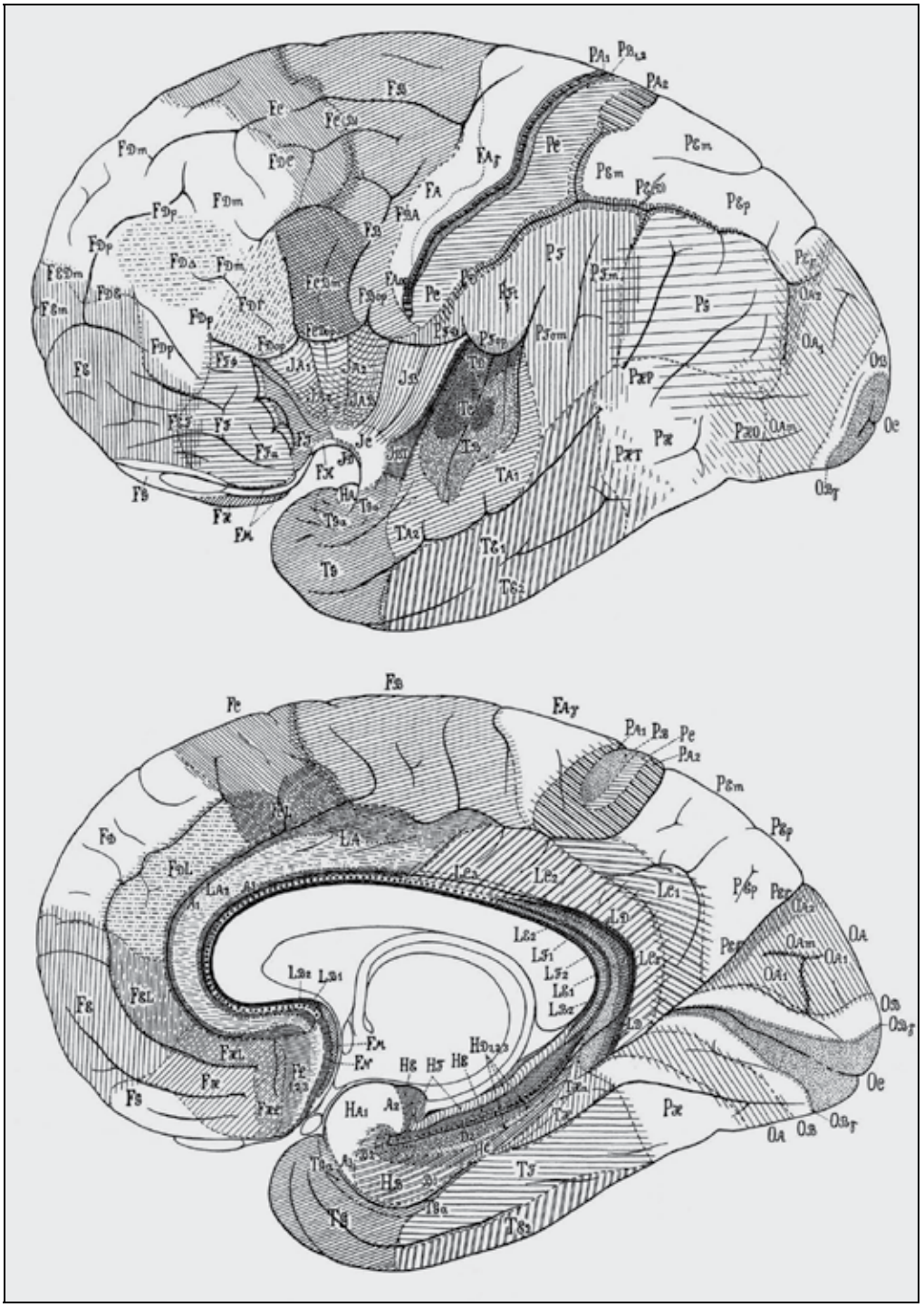


Fig. 8. The cytoarchitectonic map of von Economo and Koskinas, depicting their 107 cortical modification areas on the convex and median hemispheric facies of the human cerebrum

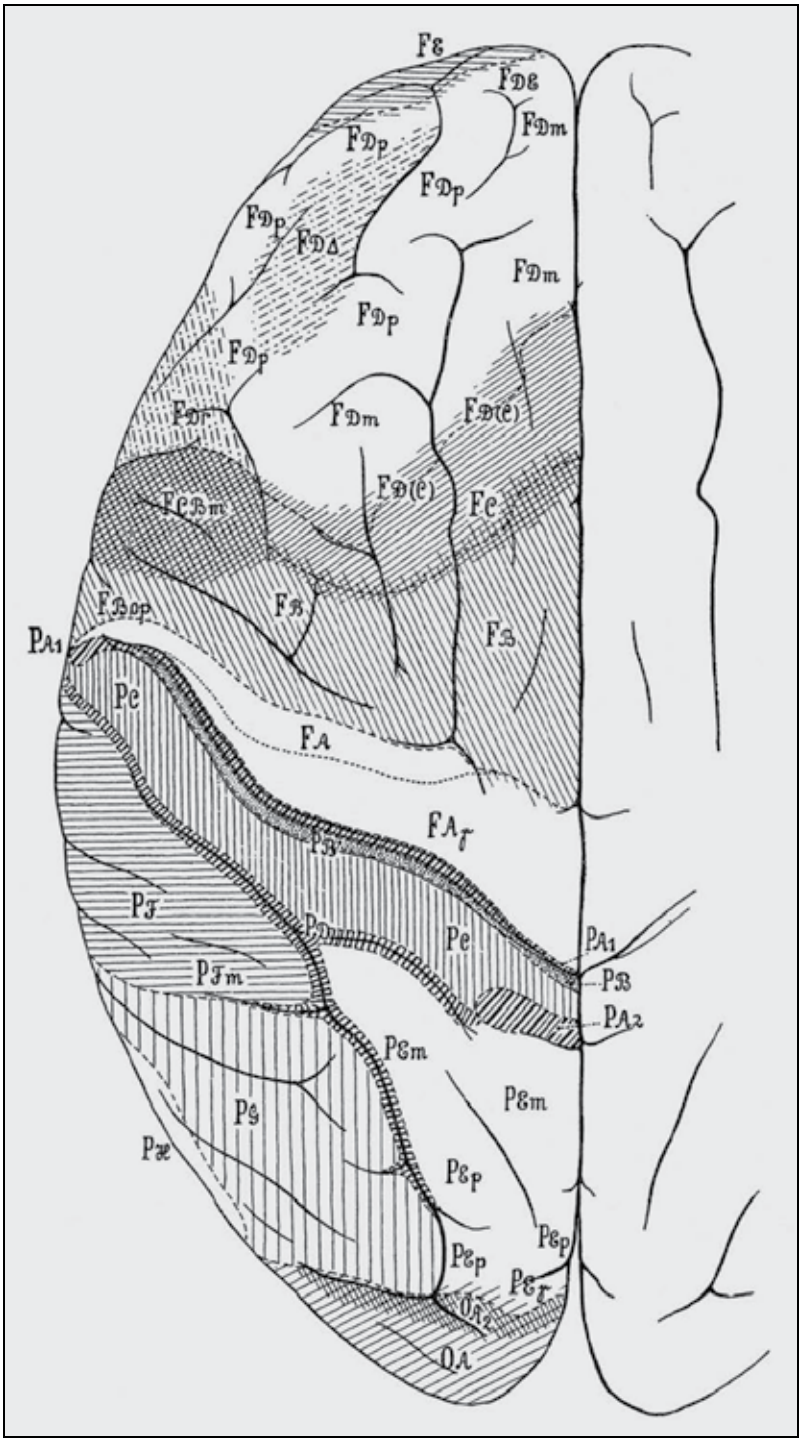


Fig. 9. The cytoarchitectonic map of von Economo and Koskinas, depicting their 107 cortical modification areas on the dorsal hemispheric surface of the human cerebrum

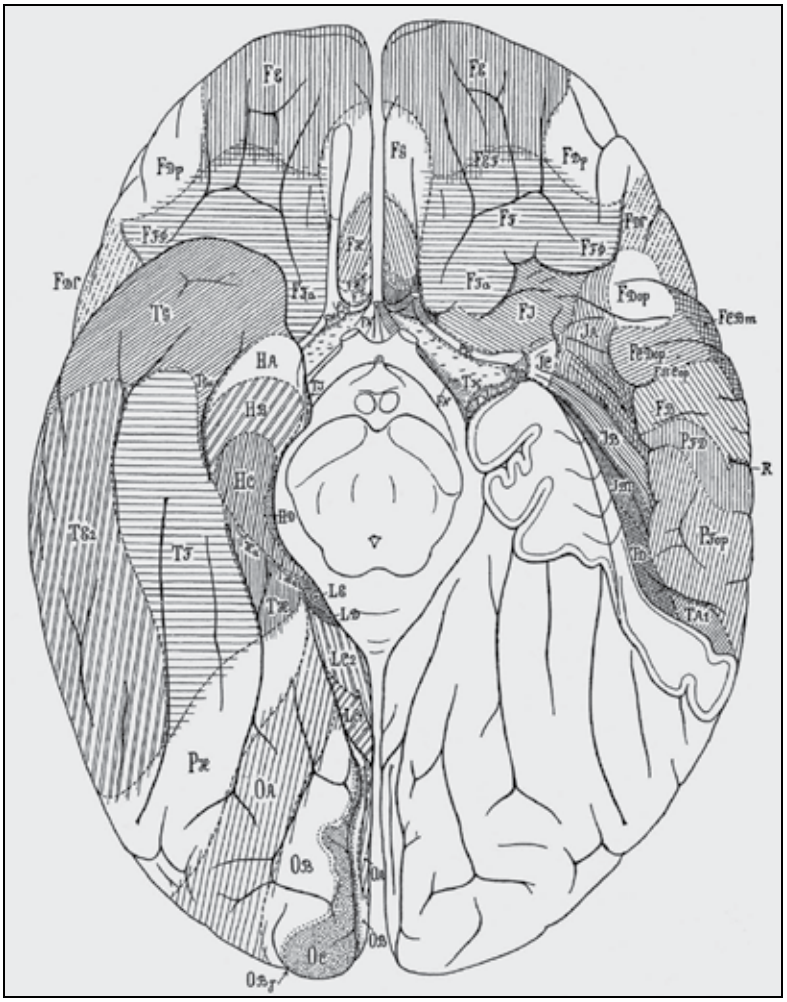


Fig. 10. The cytoarchitectonic map of von Economo and Koskinas, depicting their 107 cortical modification areas on the ventral hemispheric surface of the human cerebrum

3. Conclusion

Besides a histological mapping criterion, variations in cellular structure (cytoarchitecture) of the mammalian cerebral cortex reflect regional functional specificities linked to individual cell properties and intercellular connections. With the current interest in functional brain imaging, maps of the human cerebral cortex based on the classical cytoarchitectonic studies of Korbinian Brodmann (1868–1918) in Berlin are still in wide use (Brodmann, 1909; Garey, 2006; Olry, 2010; Olry & Haines, 2010; Zilles & Amunts, 2010). The Brodmann number system comprises 44 human cortical areas subdivided into 4 postcentral, 2 precentral, 8 frontal, 4 parietal, 3 occipital, 10 temporal, 6 cingulate, 3 retrosplenial, and 4 hippocampal.

Following in the footsteps of the Viennese psychiatrist and neuroanatomist Theodor Meynert (1833–1892), who is considered to be the founder of the cytoarchitectonics of the cerebral cortex (Meynert, 1872), von Economo and Koskinas, also working at the University

of Vienna (Triarhou, 2005, 2006), took cytoarchitectonics to a new zenith almost two decades after Brodmann's groundwork by defining 5 "supercategories" of fundamental structural types of cortex (agranular, frontal, parietal, polar, and granulous or *koniocortex*), subdivided into 54 *ground*, 76 *variant* and 107 cytoarchitectonic *modification* areas (von Economo & Koskinas, 1925, 2008), plus more than 60 additional intermediate *transition* areas (von Economo, 2009; von Economo & Horn, 1930).

Topographically, the 107 Economo-Koskinas modification areas are subdivided into 35 frontal, 13 superior limbic, 6 insular, 18 parietal, 7 occipital, 14 temporal, and 14 inferior limbic or hippocampal. Moreover, the frontal lobe is subdivided into prerolandic, anterior (prefrontal), and orbital (orbitomedial) regions; the superior limbic lobe into anterior, posterior and retrosplenial regions; the parietal lobe into postcentral (anterior parietal), superior, inferior and basal regions; and the temporal lobe into supratemporal, proper, fusiform and temporopolar regions (von Economo, 2009; von Economo & Koskinas, 2008).

The detailed cytoarchitectonic criteria of von Economo & Koskinas (1925, 2008) confer a clear advantage over Brodmann's scheme; their work represents a gigantic intellectual and technical effort (van Bogaert & Théodoridès, 1979), an attempt to bring the existing knowledge into a more orderly pattern (Zülch, 1975), and the only subdivision to be later acknowledged by von Bonin (1950) and by Bailey & von Bonin (1951). It is meaningful that basic and clinical neuroscientists adopt the Economo-Koskinas system of cytoarchitectonic areas over the commonly used Brodmann areas (see also discussion by Smith, 2010a, 2010b).

Brodmann (1909; Garey, 2006) described the comparative anatomy and cytoarchitecture of the cerebral cortex in numerous mammalian orders, from the hedgehog—with its unusually large archipallium—up to non-human primate and human brains; he introduced terms such as *homogenetic* and *heterogenetic formations* to denote two different basic cortical patterns, which, respectively, are either derived from the basic six-layer type or do not demostrate the six-layer stage. Brodmann was intrigued by the phylogenetic increase in the number of cytoarchitectonic cortical areas in primates, and was astute in pointing out the phenomenon of phylogenetic regression as well (Striedter, 2005). Vogt & Vogt (1919) laid the foundations of fiber pathway architecture; they defined the structural features of allocortex, proisocortex, and isocortex, and extensively discussed the differences between paleo-, archi-, and neocortical regions (Vogt & Vogt, 1919; Vogt, 1927; Zilles, 2006).

Combining cyto- and myeloarchitectonics, Sanides (1962, 1964) placed emphasis on the transition regions *(Gradationen)* that accompany the "streams" of neocortical regions coming from paleo- and archicortical sources (Pandya & Sanides, 1973). [Vogt & Vogt (1919) had already spoken of "areal gradations".] The idea of a "koniocortex core" and "prokoniocortex belt areas" in the temporal operculum (Pandya & Sanides, 1973) was modified by Kaas & Hackett (1998, 2000), who speak of histologically and functionally distinct "core", "belt" and "parabelt" subdivisions in the monkey auditory cortex, with specified connections.

There are three major advantages in using the system of cytoarchitectonic areas defined by von Economo and Koskinas as opposed to the maps defined by Brodmann (von Economo, 2009; Triarhou, 2007a, 2007b):

3.1 Timing of publication

Brodmann published his monograph in 1909. Von Economo began work on cytoarchitectonics in 1912, with Koskinas joining in 1919; their *Textband* and *Atlas* were published in 1925, almost two decades after Brodmann, and comprised 150 new discoveries

(Koskinas, 1931, 2009), including the description of the large, spindle-shaped bipolar cells in the inferior ganglionic layer (Vb) of the dome of the transverse insular gyrus, currently referred to as "von Economo neurons" (Watson et al., 2006)—although a more accurate term would be "von Economo-Koskinas neurons". Ngowyang (1932) appears to be the first author to refer to fusiform neurons as "von Economo cells".

3.2 Defined cytoarchitectonic fields

Brodmann defined 44 cortical areas in the human brain. Von Economo and Koskinas defined 107 areas (von Economo, 2009; von Economo & Koskinas, 2008), plus another more than 60 *transition* areas (von Economo, 2009), thus providing a greater "resolution" over the Brodmann areas for the human cerebral hemispheres by a factor of four. Brodmann correlations can be found in the *Atlas* (von Economo & Koskinas, 2008) and in a related review (Triarhou, 2007b).

3.3 Extrapolated versus real surface designations

Brodmann maps are commonly used to either designate cytoarchitectonic areas as such, or as a "shorthand system" to designate some region on the cerebral *surface* (DeMyer, 1988). Macroscopic extrapolation of Brodmann projection maps are effected on the atlas of Talairach & Tournoux (1988), rather than being based on real microscopic cytoarchitectonics. Such a specification of Brodmann areas is inappropriate and may lead to erroneous results in delineating specific cortical regions, which may in turn lead to erroneous hypotheses concerning the involvement of particular brain systems in normal and pathological situations (Uylings et al., 2005). On the other hand, the unique sectioning method of von Economo and Koskinas, whereby each gyrus is dissected into blocks *always perpendicular to the gyral surface*, be it dome, wall or sulcus floor, essentially offers a "mechanical" solution to the generalized mapmaker's problem of flattening nonconvex polyhedral surfaces (Schwartz et al., 1989), one of the commonest problems at the epicentre of cortical research.

Furthermore, microscopically defined borders usually differ from gross anatomical landmarks, cytoarchitectonics reflecting the inner organisation of cortical areas and their morphofunctional correlates (Zilles, 2006). Despite the integration of multifactorial descriptors such as chemoarchitecture, angioarchitecture, neurotransmitter, receptor and gene expression patterns, as well as white matter tracts, it is clear that the knowledge of the classical anatomy remains fundamental (Toga & Thompson, 2007). The structure of cortical layers incorporates, and reflects, the form of their constitutive cells and their functional connections; the underpinnings of neuronal connectivity at the microscopic level are paramount to interpreting any clues afforded by neuroimaging pertinent to cognition.

4. Acknowledgment

I thank the Aristotelian University Central Library for providing a copy of the *Proceedings*, as well as Ms. Rena Kostopoulou and Dr. Vassilis Kostopoulos for providing archival material of the Koskinas family.

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2

Images of the Cognitive Brain Across Age and Culture

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1. Introduction

While structural and functional characteristics of the brain are largely similar across individuals, there is also evidence that much neural heterogeneity, both structural and functional, is present between different groups of people. For example, some individuals have greater regional brain volumes and thicknesses than others, and neural activity in response to the same stimuli varies across different individuals as well. Moreover, neural structure and function are temporally dynamic, showing changes across the human lifespan. Understanding how such neural heterogeneity arises between different individuals over the human lifespan is important for uncovering factors that influence developmental trajectories from adulthood to advanced age. In this article, we consider two general sources that contribute to neural heterogeneity over the adult lifespan – age-related biological changes and culture-related differences in external experience.

Over the human lifespan, biological processes related to brain structural integrity and neurobiological function change from adulthood to advanced aging (Goh, 2011; Goh & Park, 2009a; Park & Goh, 2009; Park & Reuter-Lorenz, 2009). In brief, aging has been associated with shrinkage of gray matter volume and thickness, reductions in white matter integrity, reductions in neurogenesis, and dysregulation of neuromodulatory mechanisms such as neurotransmitter action and synaptic communication. These age-related neurobiological changes have been associated with age-related changes in cognitive processing that is generally characterized by lower performance in tests of cognitive flexibility, fidelity, and speed in older adults compared to younger adults. Functionally, aging is associated with a decrease in the selectivity of brain responses to different types of stimuli as well as an increase in engagement of frontal regions. Importantly, it has been suggested that because age-related neurobiological changes tend to level off individual differences, neural differences between older adult individuals may be reduced compared to younger adult individuals (Baltes & Lindenberger, 1997; Park & Gutchess, 2002; Park et al., 1999; Park et al., 2004; Park & Gutchess, 2006). Thus, along with lower cognitive behavioral performance, aging may also be associated with greater, albeit compromised, similarity in brain structure and function across individuals.

Over the lifespan as well, individuals undergo different life experiences such as culturally different social and cognitive environments that emphasize dissociable ways of processing information (Nisbett, 2003; Nisbett & Masuda, 2003; Nisbett et al., 2001). For example,

Western culture has been associated with an emphasis on independence and individualism as important societal values. In addition, studies have shown that these values may bias Westerners towards a more analytic cognitive processing style, reflected as greater attention to objects and the features associated with an object. In contrast, East Asian culture tends to emphasize societal interdependence and collectivism, which are reflected in a bias towards a more holistic style of cognitive processing, involving greater attention to contextual relationships between different objects. Importantly, neuroimaging studies have shown that there are neural differences between Western and East Asian samples that are associated with these culture-related differences in individualistic-collectivistic values and analytic-holistic cognitive processing biases, respectively (Goh & Park, 2009b; Han & Northoff, 2008; Park & Huang, 2010). These neuroimaging findings suggest that culture-related differences in external experience may result in dissociable neural structural and functional development over the lifespan.

A key question that arises when considering the influences of age and culture on the brain is how they interact with each other over the human lifespan (Park & Gutchess, 2002; Park et al., 1999; Park & Gutchess, 2006). Three possible cases arise with respect to this interaction between age and culture. First, culture-related neural differences across individuals may accentuate with increasing age. With increasing age, and assuming that individuals remain in the same cultural environment, individuals gain greater experience in their cultural environment. Such prolonged cultural exposure may result in more engrained psychological biases and also increasingly divergent expression of neural structural and functional development between different cultural groups. Second, culture-related neural differences, once attained, may remain at the same level throughout the lifespan. This case may arise because external cultural factors reach an asymptotic level of influence on neurocognitive processing, such that further experience does not increase the biases. This cap on the influence of external experience may be necessary to maintain a homeostatic level of neural processing important for adaptive function in the environment. For example, it would be detrimental for Westerners to become so completely attentive to objects and lose all attention to contextual information (and vice versa for East Asians) the more experience they accrue in their analytic processing style. In addition, the maintenance of cultural neural differences over the lifespan may also arise because neurobiological effects of age in reducing individual neural differences dampen the diverging effects of cultural experiences. Third, culture-related neural differences may be reduced with increasing age. It is possible that age-related neurobiological changes impact all individuals to such a degree that differences in brain structure and function across older individuals is diminished relative to younger adults. Overall, these first two cases of age by culture interactions (or lack thereof) suggest that the neurobiological effects of age do not completely diminish individual differences in brain structure and function that arise from external experience, at least those associated with cultural influences. In contrast, the third case of an attenuation of culture-related neural differences with aging would suggest that the neurobiological effects of age exert a stronger influence on brain structure and function than external experiences related to culture.

To characterize how age and culture influence brain structure and function, this article reviews recent neuroimaging studies from both these fields, and considers the evidence for the above three cases of interaction between age and culture. In the following section, we provide an overview of neuroimaging findings pertaining to cognitive aging. We show that, due to changes in neurobiological structure and function, aging is generally associated with a reduction in the distinctiveness of neurocognitive representations as well as increases in

the neural effort involved in cognitive processing perhaps to compensate for the age-related declines. Next, we provide an overview of findings pertaining to cultural differences in cognition. We cover the evidence for cultural differences in behavior and functional brain responses related to perceptual processing and attention that are consistent with an analytic-holistic dichotomy in processing styles between Westerners and East Asians. We then consider some findings in children and older adults that relate to the development of cultural biases over the lifespan. These studies are few, but they provide an initial platform for understanding how neurobiological changes with aging and culture-related external experiences interact in the brain. Finally, we evaluate some important methodological issues that limit the extent to which current data can be interpreted and applied to other samples.
Overall, the findings reviewed below will show that culture-related behavioral and neural differences are quite evident and seem to be present from a very young age during childhood. Moreover, these culture-related neural differences appear to be present even in older adulthood. Thus, the evidence suggests that aging does not disproportionately diminish the influence of experience on neural processing in the brain, at least for those sensitive to culture-related experiences.

2. Age-related functional imaging findings

There is a wealth of literature that documents age-related changes in fundamental cognitive processes across the lifespan (Park et al., 2002). The speed at which information is processed (Salthouse, 1996), the capacity of working memory (Park et al., 1996; Park et al., 2002), the ability to selectively attend to relevant information (Hasher & Zacks, 1988), and the efficiency of sentence processing (Wlotko et al., 2010) - all of these behavioral measurements of cognitive functions show age-related declines in many older adults (Figure 1). At the same time, studies have shown age-related reductions in gray matter regional brain volumes and thickness (Fjell et al., 2009; Raz et al., 2005; Raz & Rodrigue, 2006; Salat et al.,

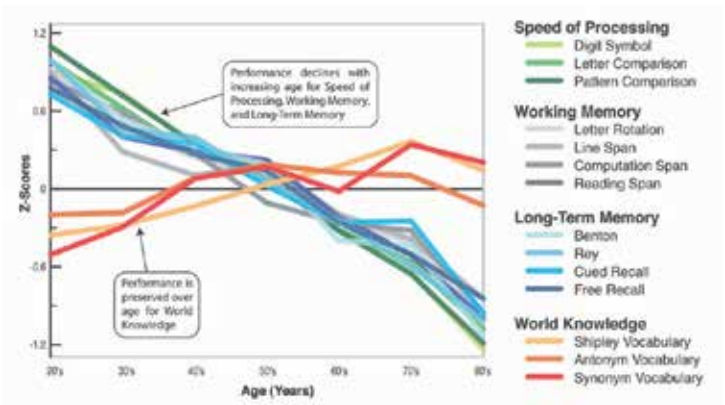

Fig. 1. Age-related cognitive changes in fluid and crystallized abilities in normal aging. Cross-sectional aging data show gradual age-related declines on the cognitive mechanisms of speed processing, working memory and long-term memory, beginning in young adulthood. But verbal-crystallized knowledge is protected from age differences. Copyright © 2002 by the American Psychological Association. Adapted with permission from Park et al. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology and Aging*, 17(2), 299-320.

2004), reductions in white matter integrity (Davis et al., 2009; Head et al., 2004; Kennedy & Raz, 2009a, 2009b), slower rates of neurogenesis and proliferation of new neuron (Kempermann & Gage, 1999; Kempermann et al., 2002; Kempermann et al., 1998), and dysregulation of neurotransmitter and synaptic action (Burke & Barnes, 2006; Burke & Barnes, 2010; Kaasinen et al., 2000; Li & Sikström, 2002), that may be underlying bases for cognitive declines observed in older adults (Goh, 2011; Goh & Park, 2009a; Greenwood, 2007; Park & Goh, 2009; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2010). However, despite such universal age-related declines in neurobiology and cognition, cognitive aging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have revealed a more mixed picture. These studies, which we now review, show that the functional brain ages in a dynamic way, declining in some respects but maintaining the ability to engage adaptive neural functions even in advanced age (Dennis & Cabeza, 2008; Park & Reuter-Lorenz, 2009).

2.1 Reduced distinctiveness of cognitive representations

Studies have shown that young adults have a high degree of functional specialization in the ventral visual cortex for different categories of visual stimuli (for review, see Grill-Spector & Malach, 2004; Grill-Spector et al., 2008; Spiridon & Kanwisher, 2002). Briefly, the ventral visual cortex is a broad region encompassing the infero-medio-temporal and occipital regions that are specialized for processing the identity of objects—the "what" pathway (Mishkin et al., 1983), with many structures within this region characterized by a high specificity of neural responses. These functionally distinct subregions that respond selectively to categories of visual input include (1) the "fusiform face area (FFA)" within the fusiform gyrus that is specialized to process faces but not other categories of stimuli (Kanwisher et al., 1997), (2) the "parahippocampal place area (PPA)" in the parahippocampal gyrus that is specialized to selectively respond to outdoor scenes, places, and houses (Epstein & Kanwisher, 1998), (3) the lateral occipital complex (LOC) that is specialized to recognize objects (Grill-Spector et al., 1998; Malach et al., 1995), and (4) the left visual word form area (VWFA) located in the fusiform gyrus that is specialized for letters and words (Polk et al., 2002). Note that these visual categories elicit responses across a network of ventral visual regions (Haxby et al., 2001; Haxby et al., 2000), but these specialized regions respond most preferentially to these respective categories.

It has been shown that, relative to young adults, there is a reduced distinctiveness of cognitive representations (i.e., dedifferentiation) in perceptual function with age. Baltes & Lindenberger (1997) and Lindenberger & Baltes (1994) examined a large lifespan sample and reported that measures of visual and auditory perception explained most of the age-related variance on measures of high-level cognition such as memory and reasoning. This suggests that whereas younger adults have a high degree of specificity across different cognitive domains, a dedifferentiation of different cognitive functions occurs with age. In addition, some studies have shown that older adults are less able than younger adults to behaviorally distinguish between stimuli that are close in perceptual resemblance (Bartlett & Leslie, 1986; Betts et al., 2007; Goh et al., 2010a; Stark et al., 2010). It has been suggested that such age-related reduction in distinctiveness of cognitive representations is due to a decrease in neural specificity and a broadening of neural tuning curves such that a given region that responds selectively in young adults will respond to a wider array of inputs in older adults (Goh et al., 2010a; Leventhal et al., 2003; Park & Reuter-Lorenz, 2009; Schmolesky et al., 2000; Wang et al., 2005; Yu et al., 2006).

Indeed, Park et al. (2004) presented pictures of faces, houses, pseudowords, chairs and scrambled controls to both older and young adults and acquired functional brain data as the participants passively viewed the stimuli. The results showed markedly less neural specificity for these categories in the aging brain in the fusiform face area (FFA) and parahippocampal place area (PPA), amongst others. Whereas the FFA showed greater response to faces and less activation to other categories (i.e., places, chairs and words) in young adults, the FFA in older adults responded to faces but also with considerable activation to other categories, reflecting an age-related reduction in selective neural responses to these different visual categories. Voss et al. (2008) replicated this neural pattern of reduced selectivity of neural responses to different visual categories in older compared to younger adults, indicating the robustness of this finding across different samples of older adults.

In initial work on exploring age-related differences in functional specialization of ventral visual cortex, Goh et al. (2004) used fMRI adaptation to isolate brain regions that were involved in processing objects from those involved in processing scenes in younger adults. The fMRI adaptation paradigm allows for the evaluation of neural selectivity and specialization based on the phenomenon that neural response to repeated stimuli is typically reduced (Grill-Spector & Malach, 2001; Henson, 2003). In Goh et al., (2004), research participants passively viewed quartets of pictures that consisted of central objects embedded within background scenes (Figure 2). The objects and scenes of the picture quartets were selectively changed allowing for the identification of distinct brain regions in young adults that were clearly sensitive to object repetition only (object-processing regions in the LOC), or background scene repetition only (scene-processing regions). In subsequent studies, Goh and colleagues applied the same experiment on older adults and compared age-related differences in functional specialization of the ventral visual cortex for objects and scenes, albeit in an East Asian sample (Chee et al., 2006; Goh et al., 2007). They found a decreased specificity in older adults for object recognition within the lateral occipital cortex, suggesting that age-related reduction in distinctiveness of cognitive representation is present even in a culturally different sample of older adults.

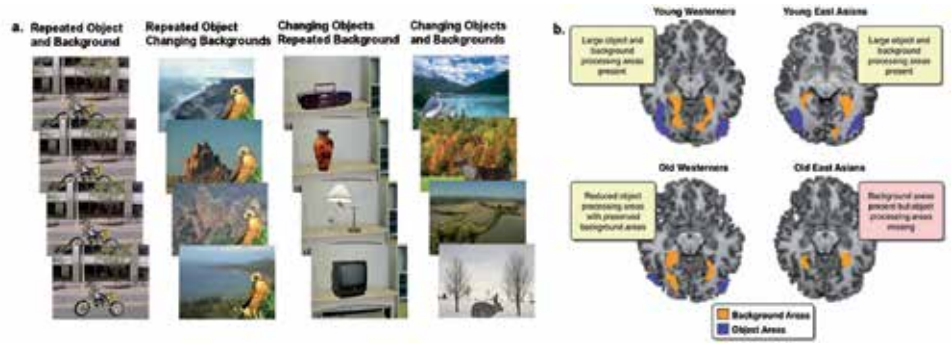

Fig. 2. Ventral visual brain regions selectively sensitive to object and background scene repetition in young and older, Westerners and East Asians, adapted from Goh et al. (2007), Age and culture modulate object processing and object-scene binding in the ventral visual area, *Cognitive, Affective & Behavioral Neuroscience*, 7(1), 44-52, copyright © 2007, with permission from Psychonomic Society Publications. a) Sample of picture quartet stimuli with selectively repeated objects and backgrounds used in that fMRI adaptation study. b) Young adults show clear object-related processing in lateral occipital regions and background-related processing in parahippocampal regions. Object processing regions are reduced in older adults with older East Asians showing disproportionately greater reduction.

Goh et al. (2010a) further demonstrated that age-related cognitive dedifferentiation is associated with reduced neural selectivity for within-category stimuli (i.e., different types of faces) as well. In this fMRI adaptation study, young and older adults were instructed to make same-different judgments to serially presented face-pairs that were Identical, Moderate (40 % difference) in similarity through morphing, or completely Different. They found that older adults showed adaptation in the fusiform face area (FFA) during the identical as well as the moderate conditions relative to the different condition (Figure 3). In contrast, young adults showed adaptation during the identical condition, but minimal adaptation to the moderate condition relative to the different condition. In addition, greater adaptation in the FFA was associated with poorer ability to discriminate faces. These findings provided clear evidence for reduced fidelity of neural representation of faces with age that was associated with poorer behavioral perceptual performance.

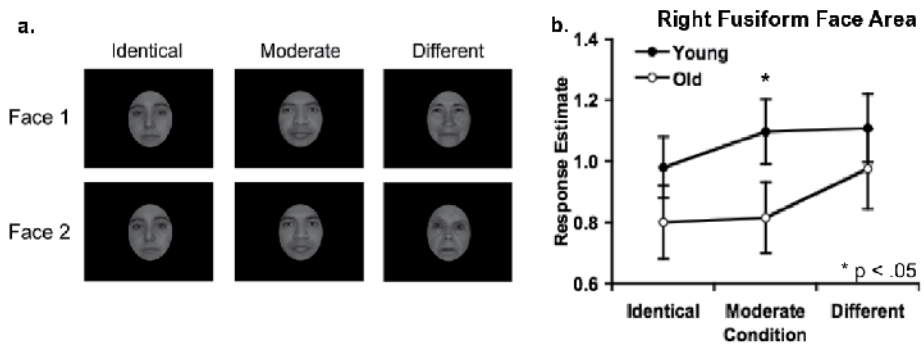

Fig. 3. Functional responses to Identical, Moderate (40% morph difference), and Different face-pairs in young and older adults, adapted from Goh et al. (2010a), Reduced neural selectivity increases fMRI adaptation with age during face discrimination, *NeuroImage*, 51(1), 336-344, copyright © 2010, with permission from Elsevier. a) Sample face-pair stimuli used in the fMRI adaptation experiment. b) Functional responses in the right fusiform face area show that younger adults treated moderately different face-pairs like they were completely different, whereas older adults treated moderately different face-pairs like they were identical.

In a different approach involving multi-voxel pattern analysis (MVPA), Carp et al. (2010) compared age differences in the distinctiveness of distributed patterns of neural activation evoked by different categories of visual images. They found that neural activation patterns within the ventral visual cortex were less distinctive among older adults, congruent with neural dedifferentiation with aging. In addition, they also showed such age-related neural dedifferentiation extend beyond the ventral visual cortex, with older adults showing decreased distinctiveness in early visual cortex, inferior parietal cortex, and prefrontal regions. Moreover, using MVPA as well, J. Park et al. (2010) investigated how well these age-related differences in neural specificity could explain individual differences in cognitive performance. They found that neural specificity significantly predicted performance on a range of fluid processing behavioral tasks (e.g., dot-comparison, digit-symbol) in older adults (~ 30% of the variance in a composite measure of fluid processing ability).

Taken together, the evidence from these different neuroimaging studies consistently demonstrate a reduced neural distinctiveness of cognitive representations with age in ventral visual cortex. Given such age-related dedifferentiation of the ventral visual cortex, which links age-related changes in behavior with brain changes, we now consider a more mixed pattern of functional responses in older adults in cognitive aging studies on the frontal regions.

2.2 Increased neural effort involved in cognitive processing

Although some studies have reported an under-recruitment of brain activity with age (e.g., Logan et al., 2002), different patterns of age-related neural over-recruitment, especially in the prefrontal cortex, have been consistently reported across several cognitive domains (Dennis & Cabeza, 2008; Grady, 2008; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008). These neural patterns are such that older adults appear to (1) exhibit increased activity in similar regions engaged by young adults, (2) reveal additional activation in regions that are not activated in young adults, and (3) elicit greater bilateral activity than the more unilateral activity observed in their young counterparts (Cabeza et al., 2002; Cabeza et al., 2004; Daselaar et al., 2003; Jimura & Braver, 2010; Morcom et al., 2003) when performing equivalently or only slightly poorer relative to young adults. Prefrontal over-recruitment is so common across such a wide range of tasks that some authors have suggested that it is a general characteristic of age-related neural change (Cabeza et al., 2004; Davis et al., 2008).

A dominant observation of age-related over-recruitment is the bilateral activation of homologous prefrontal regions in older adults on tasks where their younger counterparts show unilateral activation pattern. Specifically, whereas young adults typically engage left lateralized frontal activity for tasks that involve verbal working memory, semantic processing, and recognition memory, older adults tend to show preserved left frontal activity with additional contralateral recruitment in the homologous site of the right hemisphere that is not observed in young adults (Figure 4; Cabeza et al., 1997; de Chastelaine et al., 2011; Daselaar et al., 2003; Duverne et al., 2009; Leshikar et al., 2010; Madden et al., 1999; Reuter-Lorenz et al., 2000; Schneider-Garces et al., 2010). Similarly, older adults engage both right and left prefrontal activity during tasks in which younger adults engage only right lateralized prefrontal activity, such as in tasks associated with face processing, spatial working memory, non-verbal spatial judgment, and episodic recall (Cabeza et al., 1997; Grady et al., 1995; D. Park et al., 2010; Reuter-Lorenz et al., 2000). This additional contralateral prefrontal recruitment that results in the pattern of greater bilateral activation in older adults has been described as Hemispheric Asymmetry Reduction in OLDer adults (HAROLD; Cabeza, 2002).

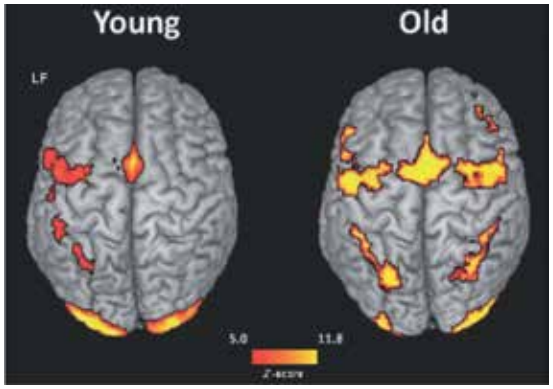

Fig. 4. Age-related over-recruitment of neural activation in verbal working memory. young adults engage unilateral frontal activity for tasks that involve verbal working memory, whereas older adults reveal preserved left frontal activity with additional contralateral recruitment in the homologous site of the right hemisphere. Adapted from Schneider-Garces et al. (2010), Span, CRUNCH, and beyond: working memory capacity and the aging brain, *Journal of Cognitive Neuroscience*, 22(4), 655-669, copyright © 2010, with permission from MIT Press.

Age-related over-recruitment of frontal regions is often interpreted as being compensatory and involved in the improvement or maintenance of performance in the face of age-related neurodegeneration (Cabeza, 2002; Davis et al., 2008; Heuninckx et al., 2008; Vallesi et al., 2011). For example, Rossi et al. (2004) reported direct evidence for the compensatory role of age-related over-recruitment in prefrontal regions by conducting a repetitive Transcranial Magnetic Stimulation (rTMS). rTMS is a technique which transiently disrupts neural function by applying repetitive magnetic stimulation to a specific area of the brain, creating a temporally artificial brain lesion. Rossi et al. (2004) showed that younger adults' memory retrieval accuracy was more affected when the rTMS was applied to the left prefrontal cortex but less affected when rTMS was applied to the right prefrontal region. In contrast, older adults' retrieval accuracy was equally affected, whether rTMS was applied to the left or right prefrontal regions, suggesting bilateral prefrontal activation has a causal link to behavioral performance in older adults. A compensatory account of age-related over-recruitment was also supported in Morcom et al. (2003) who showed that greater frontal bilaterality in older adults compared to young predicted better performance when successfully encoding subsequently remembered items.

Some studies have reported impaired behavioral performance associated with additional contralateral prefrontal recruitment, suggesting that prefrontal over-recruitment may not always be compensatory. For example, de Chastelaine et al. (2011) found that older adults' memory performance positively correlated with neural over-recruitment in the left prefrontal cortex, a region also engaged by young adults. However, the correlation was negative with respect to additional recruitment in the right prefrontal cortex of older adults, a region that was not observed in young adults, suggesting that over-recruitment in the right frontal regions in older individuals does not always contribute to memory performance (see also Duverne et al., 2009). Resolving whether age-related over-recruitment is associated with compensatory or declining function, would require studies that more effectively measure and equate differences in cognitive ability and performance across young and older adults, as well as better define what compensation means. Nevertheless, a broad number of studies are at least in agreement that there is consistent age-related over-recruitment that is generally associated with better cognitive outcomes.

In addition to being beneficial for behavioral performance, evidence also suggests that increased neural effort observed in prefrontal cortex may reflect a compensatory response to deteriorating neural systems in more posterior sites of the brain, including the medial temporal lobe (Cabeza et al., 2004; Gutchess et al., 2005; Park et al., 2003), and occipital cortex (Cabeza et al., 2004; Davis et al., 2008; Goh et al., 2010a). Park & Gutchess (2005) systematically reviewed neural activations associated with long-term memory and noted that decreased hippocampal and parahippocampal activation in medial temporal lobes are coupled with the increased frontal activation in older adults. Indeed, Gutchess et al. (2005) showed that during an incidental memory encoding task, older adults had lower activation than young adults in the left and right parahippocampus and greater activation than young adults in the middle frontal cortex. Goh et al. (2010a) also showed that increased frontal engagement was also associated lower neural selectivity in the ventral visual regions. Moreover, Cabeza et al. (2004) reported that older adults showed increased bilateral prefrontal activation and decreased occipital function compared to their young counterparts across various cognitive tasks, indicating a Posterior Anterior Shift in Aging (PASA) functional activity (Davis et al., 2008). These results suggest a neurocognitive compensatory role of prefrontal regions for age-related neural deterioration in posterior brain regions.

With this review on the pattern of age-related reductions in neural distinctiveness in cognitive representations and increases in frontal engagement, we now turn to consider the evidence for the second source of influence on brain structure and function – cultural experience.

3. Culture-related findings

In a comprehensive review of sociopolitical and historical progressions, Nisbett (2003) proposed that the value system of one's cultural environment exerts an influence on self-perceptions and even cognitive processing. That is, social and physical pressures in the cultural environment encourage certain modes of behavior and thinking and suppress others. Over time, these cultural pressures become internalized and act as a bias with which individuals process subsequent social and physical situations as well. In this article, we focus on differences between Westerners and East Asians, as there have been more studies that directly compared these two culture groups. It has been shown that whereas Western culture places more emphasis on independence and individualism, East Asian culture values interdependence and collectivism (Hofstede, 1980, 2001; Kitayama et al., 1997; Nisbett, 2003; Nisbett & Masuda, 2003; Nisbett et al., 2001; Oyserman et al., 2002; Triandis et al., 1988; Triandis, 1995). Nisbett (2003) argues that Westerners embedded in a culture of individualism tend to adopt an analytic style of cognitive processing. This style of processing can be characterized as a bias to treat stimuli items in the environment as individual and distinctive objects composed on a set of features. Likewise, East Asians are embedded in a culture of collectivism that is associated with a holistic style of cognitive processing, which is reflected as a bias to regard items in the environment as related to one another, and more tightly bound to the context.

This section considers the evidence for the existence of these culture-related differences in analytic and holistic processing styles between Westerners and East Asians and their neural correlates. While many of these studies have been previously reviewed (Goh & Park, 2009b; Han & Northoff, 2008; Nisbett & Masuda, 2003; Nisbett & Miyamoto, 2005; Nisbett et al., 2001), we highlight important and novel aspects of these findings here as they pertain to the overall question on the interaction between age and culture. As will be seen, many of these studies show culture-related differences in the way Westerners and East Asians perceive and attend to items in the visual environment. Critically, both behavioral and neuroimaging studies report findings that are remarkably consistent with the analytic and holistic biases in Westerners and East Asians, respectively.

3.1 Cultural differences in perception and attention: Behavioral foundations

3.1.1 Face stimuli

In a study that used visual aesthetics as an approach to characterizing object-context perception in Westerners and East Asians, Masuda et al. (2008a) evaluated differences in the content of portrait photographs taken by American and Japanese participants. They found that American participants took portrait photographs in which the face, the object of the portrait, occupied a larger ratio of the frame than the background. In contrast, photographs taken by Japanese participants consisted of a much larger portion of the background relative to the face. Thus, Japanese may have considered the background context as more important to the portrait than Americans did. In another study on the degree to which Americans and Japanese incorporate contextual social information, Masuda et al. (2008b) asked participants

to judge the emotion of a facial expression that was presented amidst other emotional facial expressions that were either congruent or conflicting with the target expression. The results of that study suggested that Japanese were more likely to modulate their judgment of the target face emotion based on the other faces whereas Americans were less sensitive to contextual face emotions in their behavioral responses.

Eye movements to face stimuli also show distinctions between Westerners and East Asians. In Masuda et al. (2008b) study above, eye-movements of participants were also measured as they judged the emotional content of a target face amidst other faces in the background. They found that Japanese devoted less time fixating on the target face than Americans, and thus, Japanese were looking more at the contextual faces than the Americans as well. Blais et al. (2008) recorded eye movements as Westerners and East Asians viewed single face stimuli across several different types of tasks to examine which components of the face participants tended to look at. It was found that, across all tasks, Westerners tended to fixate on the eyes and mouth of the faces whereas East Asians focused on central regions of the face, around the nose. Westerners may have attended to facial features that contain distinguishing information about the face, consistent with an analytic style of face processing. In contrast, East Asians may have treated faces more holistically and thus de-emphasized the distinctiveness of facial features. Taken together, these findings reflect the bias for a more analytic style in Westerners and a more holistic style in East Asians when processing aesthetics and social information involving face stimuli.

3.1.2 Objects and backgrounds

Culture-related differences in analytic-holistic processing is supported by evidence that shows that Westerners have a greater affinity for visuo-spatial judgments involving absolute quantities whereas East Asians are better at relative comparisons. In the Frame Line Test, participants are presented with a test stimulus consisting of a line embedded within a square box frame. The test stimulus is then removed and replaced with probe, which was an empty square frame that was either smaller or larger in size relative to the test square. During the absolute judgment task, participants were instructed to draw a line in the probe square that was of the same length as the original test line, regardless of the size of the square. During the relative judgments task, however, participants were to draw a line that was of the same length relative to the size of the square frame. Kitayama et al. (2003) found that Americans were more accurate for the absolute line drawing and Japanese were more accurate for the relative line drawing. Thus, Westerners may have attended more to the features of the line (length), in accordance with an analytic style of processing, whereas East Asians integrated the line and square frame as a whole, in according with a holistic processing style.

Differences between Westerners and East Asians have also been found in the sensitivity to changing visual elements of complex scenes. Change blindness refers to the phenomenon whereby participants take some time to detect relatively salient changes in rapidly alternating scenes (Simons & Ambinder, 2005; Simons & Levin, 1997). Boduroglu et al. (2009) found that East Asians were better at detecting color changes in the stimuli periphery than Westerners, but East Asians also showed poorer performance than Westerners when the color changes occurred in the central regions of the screen. Using the change blindness paradigm as well, Masuda & Nisbett (2006) presented Americans and Japanese with rapidly alternating pictures of scenes with objects. They found that whereas Americans were faster at detecting changes occurring in the central object, they were slower with background changes.

In contrast, Japanese were equally fast for changes occurring in both objects and backgrounds. Moreover, Americans detected more object changes whereas Japanese detected more background changes. Thus, the more analytic style of processing in Westerners was reflected as greater sensitivity to central object changes, and the more holistic processing style in East Asians manifested as greater sensitivity to the peripheral background.

Again, evidence from eye-tracking studies provides compelling evidence that Westerners and East Asians are attending in different ways to the same scene stimuli. Chua et al. (2005) recorded eye-movements while American and Chinese participants looked at naturalistic pictures that depicted a central object presented against a contextual background scene. Compared to American participants, Chinese participants made more fixations to the background and had slower onsets of the first fixation to central objects. In addition, Chinese participants generally showed a greater proportion of background relative to object fixations throughout the time course of the stimulus viewing, whereas Westerners had greater proportions of object fixations over the time course with very brief periods of increased proportions of background fixations. Goh et al. (2009c) further evaluated whether these cultural differences in eye-movements were robust to visual stimuli that captured participants' attention against their own cultural preferences, using an experimental design adapted from Goh et al. (2007). It was found that, as expected, Westerners were more sensitive to object changes than East Asians, and East Asians alternated more between the objects and backgrounds. Moreover, these cultural differences in eye-movements were relatively robust to the attention capturing manipulation of changing objects and backgrounds. Critically, Westerners' eye-movements were characterized by fewer fixations with longer dwell times whereas East Asians had fewer but shorter fixations that covered a greater area of the visual stimuli (Figure 5).

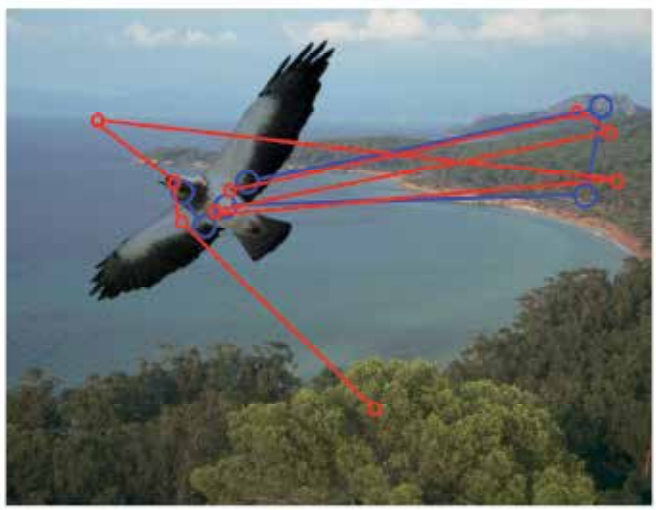

Fig. 5. A schematic of eye-movements during scene viewing in Westerners (blue) and East Asians (red). Circles represent fixations and size of circles represent fixation dwell times, with larger circles indicating longer times adapted from Goh et al. (2009c).

Some eye-tracking studies did not find cultural difference in eye-movements when Westerners and East Asians viewed scenes (Caldara et al., 2010; Miellet et al., 2010; Rayner

et al., 2009). For example, Rayner et al. (2009) found that when visual scenes depicted a bizarre or impossible circumstance (e.g. a boy with an extra leg), there were no differences in the way Westerners and East Asians fixated on the scene. It is possible that in such cases, basic universal attentional processes take precedence over cultural differences in visual attention. It is also certainly possible that these results reflect how cultural biases are amenable to change since Westerners are capable of focusing on scenes and East Asians are capable of focusing on objects (see studies on cultural priming; Chiao et al., 2010; Miyamoto et al., 2006).

Overall, these findings show that there are culture-related differences in perception and attention between Westerners and East Asians. These differences are such that Westerners have a more analytic processing style, focusing on object features, and East Asians have a more holistic processing style, focusing on contextual information. With this in mind, we now consider the neural correlates of these visual processing behavioral patterns.

3.2 Cultural differences in perception and attention: Functional brain studies

3.2.1 Face, object, and scene processing in the ventral visual cortex

As mentioned previously, one of the most consistent observations related to visual processing in the brain is that specific regions within the ventral visual cortex show heightened sensitivity to specific categories of visual stimuli. It should also be noted that greater attention to the stimulus tends to increase the selectivity of the ventral visual region involved in processing that stimulus (Murray & Wojciulik, 2004; Yi et al., 2006). The following studies show that there are culture-related differences in the way the selective regions of the ventral visual cortex respond to faces, objects, and scenes in Westerners and East Asians, and that the analytic-holistic dichotomy operates in visual perception and attentional neural processes as well.

In a simple blocked-design fMRI experiment, Goh et al. (2010b) presented Americans (Westerners) and Singaporeans (East Asians) with face and house stimuli and compared the selectivity of their fusiform regions for faces relative to houses, and lingual regions for houses relative to faces. It was found that Americans showed greater face selectivity than Singaporeans in the left fusiform region, and face selectivity in the right fusiform regions was equivalent in both groups (Figure 6). Right fusiform engagement has been associated with more holistic processing of face stimuli as a whole; however, left fusiform activity has been associated with more analytic face processing of specific facial features (Rossion et al., 2000). Thus, the finding that Americans engaged greater left fusiform responses than Singaporeans to faces, and the findings on cultural differences in behavioral and eye-movement responses to faces reviewed above, provide a compelling basis for a greater bias to attend to facial features in Westerners than East Asians, consistent with a more analytic face processing style in Westerners. In addition, Goh et al. (2010c) found that Singaporeans showed some evidence for greater house selectivity than Americans in bilateral lingual regions. Taken together with the behavioral findings again, this suggests that Singaporeans were attending more than Americans to the contextual environment, consistent with a more holistic processing style for scenes in East Asians.

With respect to objects and scenes, fMRI studies have also found that Westerners engage more object-related processing in the ventral visual regions compared to East Asians. In Gutchess et al. (2006), Westerners and East Asians performed an incidental encoding task on stimuli consisting of objects and scenes. Whereas they did not find any group differences in

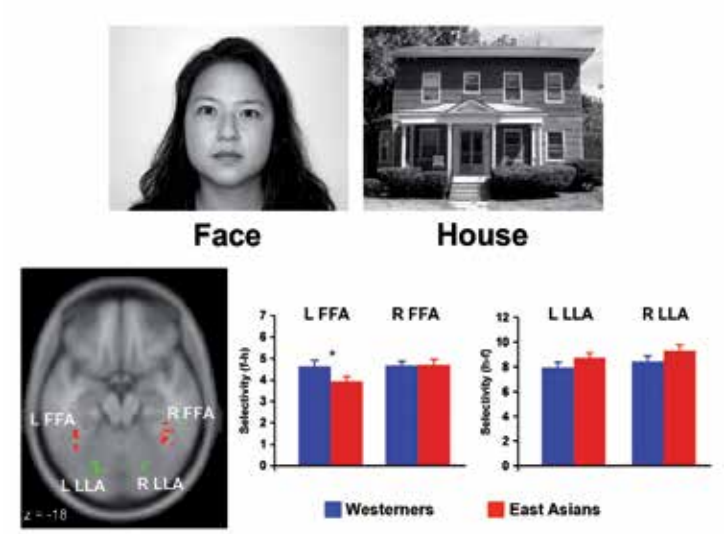

Fig. 6. Neural selectivity to face and house stimuli in the fusiform face areas (FFA) and lingual landmark areas (LLA) of Westerners and East Asians, adapted from Goh et al. (2010b), Culture differences in neural processing of faces and houses in the ventral visual cortex, *Social Cognitive and Affective Neuroscience*, 5(2-3), 227-235, with permission from Oxford University Press. Sample stimuli used in the blocked-design fMRI experiment are on top. The bottom left panel illustrates peak voxel locations of the FFA and LLA from a sample of individual participants. The bottom right panel shows greater selectivity for faces (f-h) in the left FFA in Westerners compared to East Asians (* $p < .05$), and marginally greater selectivity for houses (h-f) in bilateral LLA in East Asians compared to Westerners.

background-related processing regions, Westerners showed greater recruitment of object processing regions than East Asians in the middle temporal, supramarginal, and parietal regions. In Goh et al.'s (2007) fMRI adaptation study mentioned in the section on aging, brain imaging data from both Westerners and East Asians were also acquired to investigate cultural differences in ventral visual responses to objects and background scenes (see Figure 2). They found that although there were no group differences in scene processing regions, East Asians showed less object-related responses in the lateral occipital regions compared to Westerners. Interestingly, this culture-related difference in object processing was more evident in older adults than in younger adults, implying an age dependency, which is further discussed below.

Apart from cultural differences in the processing of objects and scenes as separate items, studies have also found evidence for cultural differences in sensitivity to the relationship between objects and scenes in the stimuli. Jenkins et al. (2010) used a similar fMRI adaptation experiment as in Goh et al. (2007), and presented participants pictures with selectively repeated objects and scenes. Critically in that study, some of the object-scene pairings were congruent (e.g. a plane in the sky) whereas some objects were incongruent with the scenes (e.g. an elephant in a kitchen), but not impossible. They found that whereas Westerners were relatively insensitive to object-scene congruity, East Asians showed greater responses to incongruent relative to congruent pairings, suggesting that they attended more to objects when the pairing with the scene was incongruent (see Goto et al., 2010, for a

similar study using event-related potentials). Taken together, these findings are consistent with the analytic-holistic dichotomy, and suggest that Westerners treat each visual element in a picture more as separate objects, whereas East Asians regard the picture elements as more tightly bound together into the whole context.

3.2.2 Visual attention processing

Using the Frame Line Test from Kitayama et al. (2003), Hedden et al. (2008) acquired fMRI data as Westerners and East Asians made absolute and relative line judgments in the scanner. They found that Westerners showed greater brain responses during relative compared to absolute line judgments in frontal and parietal regions, brain areas typically associated with attentional processing. In contrast, East Asians showed greater brain responses during absolute compared to relative judgments in the same regions (Figure 7). These findings suggest that participants required greater effort when engaging non-preferred visual processing styles, which is associated with cultural differences in attention-related responses in fronto-parietal regions. Importantly, the finding that Westerners required greater effort for relative judgments and East Asians for absolute judgments is again consistent with the analytic-holistic dichotomy in these two groups.

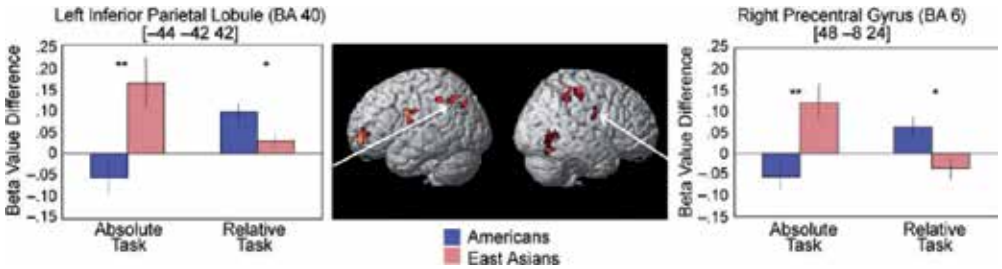

Fig. 7. Functional brain responses during the Frame Line Test in Americans and East Asians, adapted from Hedden et al. (2008), Cultural influences on neural substrates of attentional control, *Psychological Science*, 19(1), 53-81, copyright © 2008, with permission from Sage Publications. Americans showed greater responses in fronto-parietal regions during the relative compared to the absolute task. East Asians showed greater responses during the absolute compared to the relative task.

In a yet unpublished study, Goh et al. (submitted) acquired fMRI data as Westerners and East Asians made judgments on the distance between a dot and a horizontal line, relative to the length of a vertical line. In that study, while accuracy was equivalent in both groups, East Asians responded significantly faster than Westerners, suggesting that the task was easier for East Asians and harder for Westerners. In line with this interpretation, during task performance, Westerners showed greater activation of the frontal and parietal regions compared to East Asians. Importantly, they also found that Westerners showed greater suppression of responses compared to East Asians in the default-network regions that included the medial frontal and supramarginal regions. Suppression of these default-network regions has been linked to a greater need to attend to external stimuli (Anticevic et al., 2010; Benjamin et al., 2010; Greicius et al., 2003; Hayden et al., 2010; Mayer et al., 2010; Raichle et al., 2001). Thus, Westerners may have required greater attention than East Asians to perform the relative spatial judgment task, and correspondingly suppressed default-network activity more in the process.

In Goh et al. (2007), it was also suggested that the lack of object-processing responses in the lateral occipital regions in older adult East Asians was related to a reduction in attentional resources. Interestingly, Chee et al. (2006) investigated this by repeating the fMRI adaptation experiment on the same older East Asians but with the instruction to attend to the object while ignoring the scenes. Under those circumstances, the older East Asians showed a reinstatement of object-related processing in the lateral occipital region, suggesting that the lack of responses in the initial study was indeed due to attentional mechanisms. This finding suggests that under reduced attentional resources, the older East Asians maintained their focus on the background scenes but devoted less attention to objects, in line with a bias for holistic processing in East Asians.

Thus, culture-related functional brain differences are observed in perceptual regions as well as in regions involved in attention. It is possible that such chronic differential functional engagement may result in structural brain differences. And, while there are fewer studies on cultural differences in brain structure, there have been several studies on how different external experiences and expertise do bear on regional brain size and integrity.

3.3 Culture, experience, and brain structure

At present, only four studies have directly compared brain structural differences between Westerners and East Asians. Zilles et al. (2001) only examine gross brain size and shape differences and found that Japanese brains were shorter and wider, i.e. more circular in shape, compared to European brains, which were more elongated or oval. Green et al. (2007) and Kochunov et al. (2003) examined structural differences related to differences in the usage of the Chinese and English language. These latter two studies generally found that Chinese-speaking East Asians have more brain tissue than English-speaking Westerners in the left inferior frontal, middle temporal, and right superior temporal regions. The fourth study by Chee et al. (2011) examined a much larger sample of structural brain images of Americans and Singaporeans, which is critical since there is a large amount of variability in structural MRI data. Using various data analysis methods, including cortical thickness

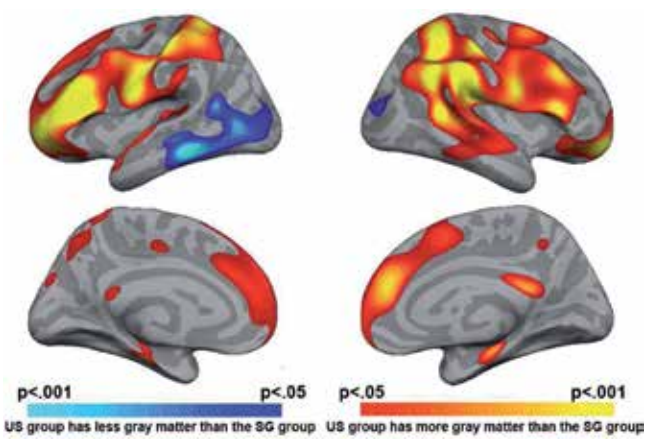

Fig. 8. Cortical thickness differences between Americans (US) and Singaporeans (SG). Adapted from Chee et al. (2011), Brain structure in young and old East Asians and Westerners: comparisons of structural volume and cortical thickness, *Journal of Cognitive Neuroscience*, 23(5), 1065-1079, copyright © 2011, with permission from MIT Press.

measures, voxel-based morphometry and pattern classification approaches, they found that Americans had thicker cortical gray matter than Singaporean in frontal, parietal, and temporal polymodal association areas, whereas Singaporeans had thicker left inferior temporal regions (Figure 8).

While more studies are required to relate these culture group differences in cortical thickness, it is clear from other non-culture studies that external experiences do have a modulatory influence on brain structure. For example, Maguire et al. (2000) showed London taxi-cab drivers have larger hippocampal volumes than control participants possibly due to the their expertise in navigating around the city streets. This finding was consistent with the important role that hippocampus has in spatial navigation as well as memory (Cohen et al., 1999). In addition, Draganski et al. (2004) showed that novices who acquired juggling skills longitudinally developed more gray matter in the middle temporal gyrus and intra-parietal sulcus, regions important for visuo-spatial coordination. It is therefore no surprise that cultural differences in functional engagement of specific brain regions would also result in the regional differences in brain structure described above, and future studies will establish more mechanistic links between cultural experience and brain structure.

4. Cultural differences across age

Having established that there are culture-related differences in brain structure and function, we now evaluate how these brain differences interact with the neural changes associated with aging described above. Studies that integrate age and culture are sparse at present. Nevertheless, the few studies that do consider this aspect of neural structure and function over the lifespan provides some initial guidance as to the nature of culture-related neural differences in older adulthood.

It is useful to first consider when culture-related neural differences start in the course of the human lifespan. As yet, we are not aware of any neuroimaging studies that have directly examined culture-related brain differences in children or adolescents. A few developmental studies, however, provide some clues as to when cultural experience may begin to have an influence on neurocognitive processes. For example, a linguistic study involving Western and East Asian infants developing in different language environments (English vs. Japanese) show language-specific perceptual biases as early as 7 months (Yoshida et al., 2010). In addition, Wang & Leichtman (2000) examined narratives of 6-year-old children and found that compared to Western children, East Asian children described stories and memories with a greater emphasis on social relationships and contextual information, characteristic of a collectivistic culture. Wang (2008) also examined autobiographical memory in Western and East Asian children as young as 3 years old. It was found that Western children tended to recall memories with greater specificity whereas East Asian children recalled memories in a more general manner, consisting of less specific details. In an fMRI study, Golarai et al. (2007) managed to examine the selectivity of the ventral visual cortex of young children, albeit just in a sample of Westerners. They showed that by 7 years of age, children had developed selective responses for faces in the FFA and scenes in the PPA to the level observed in mature adults. This imaging finding and the behavioral comparisons above suggest that the culture-related neural differences observed in young adults at approximately 20-30 years of age may begin in quite early in childhood.

With respect to culture-related differences in older adults, only one published functional neuroimaging study thus far has directly examined the interaction between age and culture.

As mentioned, Goh et al. (2007) used the fMRI adaptation paradigm to investigate ventral visual selectivity for objects and scenes in young and older, Westerners and East Asians (Figure 2). The main finding in that study was that older East Asians (aged 65 and above) showed reduced object-related processing compared to the other three groups. This finding was interpreted as an accentuation of the bias for contextual processing in older East Asians due to a reduction in attentional resources with age. In addition, Chee et al.'s (2011) structural brain study also compared young and older, Westerners and East Asians. It was found in that study that whereas the cultural differences in cortical thickness seen in younger adults was not present in older adults as a whole group, cultural differences emerged when older adults were split into high and low cognitive performance. This result suggests that in older adult individuals who show greater susceptibility to neurobiological decline with aging and thus poorer cognition, culture-related experiential influences on the brain become diminished with age. However, in older adults who remain relatively cognitively intact, cultural differences in brain structure are maintained throughout the lifespan.

Distinct from the more global effect of aging on the brain, the effect of cultural experience on the brain seems more localized and specific. That is, whereas aging is associated with a general decline in brain structure and function, culture and other experiential factors modulate neural structure and activity only in regions that are involved in a given cognitive process (e.g. the FFA for processing faces). While more studies are required to evaluate the extent and robustness of these effects, it appears that neurobiological declines associated with aging do not completely overwhelm the influence of experiential factors, at least those related to culture. Thus, the effect of culture-related experiences is likely to have an enduring impact on neural structure and function from adulthood to advanced age.

5. Methodological issues

Interpreting age-related differences in cognitive performance between age groups has proven to be a unique challenge, and exploring the effects of age and culture compounds these difficulties. Here we evaluate some important methodological issues that may limit the extent to which current data can be interpreted and applied to other samples, and suggest recommendations for future studies.

5.1 Cohort, age, and culture considerations

At all times, it should be noted that there is much heterogeneity in the cultural makeup of Westerners and East Asians and the attribution of cultural characteristics is always at the group level. In addition, while culture is defined in terms of value systems, many studies operationalize culture based on geopolitical boundaries, i.e. countries and nationalities. For example, Westerners are predominantly Americans and East Asians are typically Japanese, Chinese, or other Chinese Asian individuals (e.g., Hong Kong Chinese, Singaporean Chinese, Taiwanese Chinese, etc.). Moreover, people within these different cultural affiliations demonstrate varying degrees of individualism and collectivism. For example, Oyserman et al. (2002) documented that native Japanese are not necessarily more collectivistic relative to Caucasian Americans, and cultural differences in individualism and collectivism are not static over time between groups (Oyserman & S. W. S. Lee, 2008). Moreover, in an fMRI study involving native Japanese and Americans, Chiao et al. (2009) reported that neural activity within the ventral medial frontal regions predicted how individualistic or collectivistic a

person is across cultures, regardless of the participants' cultural affiliation. These findings suggest that although some aspects of cultural groups remain stable across time, neural representations of self in Americans and East Asians are not inherently different, but instead reflect different cultural values that are endorsed by the individual.

Given the cost of conducting imaging studies and relatively low reliability of physiological signals, it is also particularly difficult to acquire neuroimaging data from participant samples that are saturated with culture- and/or age-specific experience, yet equated on other factors such as education, cohort-specific experiences and other demographics (Manly, 2008; Park et al., 1999; Whitfield & Morgan, 2008). Thus far, a variety of approaches to explore group differences across several neuroimaging studies have been utilized to deal with these sampling issues. The majority of cross-cultural studies involve East Asian and Western participants studying at the same institution (usually undergraduate/graduate students) as well as neuroimaging data from one MRI scanner (Gutchess et al., 2006; Hedden et al., 2008; Jenkins et al., 2010). However, there are two limitations to such an approach. First, immigrant participants from another culture (e.g., Chinese students in the United States) may already have had some biasing experiences in the host culture, even if they have not been exposed to the new environment for that long. This potentially results in an underestimation of cultural differences in behavioral performance and neural activation. Second, immigrant participants are often a select group of individuals (e.g. international students) who have been qualified to study or work overseas according to their conspicuous achievement, leading to a more high-performing, homogenous sample compared to native individuals. In such cases, conclusions of cultural variation may in fact be associated with sample differences in cognitive capabilities. To reduce these sampling biases described above, it is necessary to select samples based on equivalent levels of education, similar demographics and matched cognitive abilities between groups (Park & Huang, 2010).

Cohort-related effects within a cultural group may also influence the individual's value system, self-perceptions, cognitive processing, and even neural processing, over and above the cultural environment. For instance, in China, only older adults lived through the Cultural Revolution (~1970s), which had tremendous impact on their lifestyle and thinking, whereas younger adults in China had no such experience. A similarly situation applies to the Great Depression (~1930s) for young and older adults in America, and on a worldwide level, World War II. The effects of such socio-historical events on neuropsychological differences between age and culture groups are substantial and should be considered when recruiting participants in future studies.

The careful development of hypotheses and clear predictions of differentiated patterns of activation in older and young adults across cultures is also critical (Park et al., 1999; Park & Gutchess, 2006). Because of the distal nature of culture-related effects on the brain, combined with effects of education, diet, genetics and many other variables (Chee et al., 2011), it is difficult to simply theorize and test that differences observed in neural activation are directly linked to cultural experiences and behavioral practices. As an example, both well-established knowledge from the analytic-holistic framework (Nisbett & Masuda, 2003; Nisbett et al., 2001) and empirical findings from cross-cultural eye-movement studies (Chua et al., 2005) were used to guide Goh et al. (2007) and Goh et al.'s (2010) studies on neural correlates of age and culture in ventral visual processing. Using the existing knowledge base that prescribed specific expectations about the data facilitated the interpretation of the complex patterns of neuroimaging findings from different age and cultural groups in those studies.

5.2 Measurement and instrument comparability

Prior to cross-group comparisons in studies on cognitive neuroscience of aging and culture, it is first important to evaluate whether the experiment stimuli are equally familiar to both age and culture groups. Stimuli that are less familiar or evoke specific types of processing in one group during scanning would confound patterns of neural activation due to the stimuli familiarity differences rather than cognitive processes. Indeed, studies have found culture- and age-related variations in norms associated with how individuals from these groups name pictures of everyday objects (Yoon, et al., 2004a) and categorize words (Yoon et al., 2004b). Hedden et al. (2002) also found that Chinese had better performance than Americans in numerical cognitive tests such as digit comparison (a measure of speed of processing) and backward digit span (a measure of working memory). They suggested that such group differences could be due to differences in the number system and representation in the Chinese and English languages, rather than actual cognitive differences in speed or working memory. Thus, future studies should be aware of such differences in the stimuli used to ensure comparability of cognitive processing across cultural and age groups.

In studies that involved data from two different MRI scanner machines from different sites, it is possible that differences in the blood oxygen level dependent (BOLD) signal between cultural groups could occur as a result of differing properties between hardware rather than actual neural differences between cultures (Park, 2008; Park & Gutchess, 2002). Cases in point are Goh et al. (2007) and Goh et al. (2010), who acquired imaging data from Singapore and the United States, with both sites having identical imaging hardware and software.

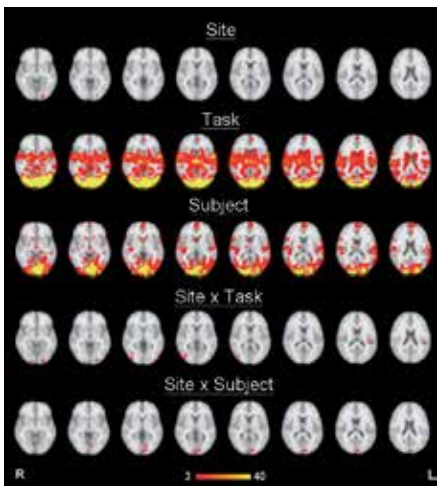

Fig. 9. Between-site comparison of functional MRI signal from Singapore and the United States equipped with identical imaging hardware and software. The same participants performed the same tasks at two magnet sites over several sessions. The statistical brain maps of a three-way Analysis of variance (ANOVA) are shown with the main effects and interactions of site, subject, and task, colored with increasing red intensities ($P < 0.001$ uncorrected). There were extensive regions showing significant main effects and interactions of subject and task, but the effects associated with magnet site were negligible. Adapted from Sutton et al. (2008), Investigation and validation of intersite fMRI studies using the same imaging hardware, *Journal of Magnetic Resonance Imaging*, 28(1), 21-28, copyright © 2008, with permission from John Wiley and Sons..

Prior to conducting these studies, the authors examined functional imaging data with a visual and motor task from four participants who were repeatedly imaged in both machines in Singapore and the United States (Sutton et al., 2008). They found that there was minimal variance in BOLD as a function of site, between-subject differences accounted for 10 times more variance than site of data collection, and task differences (motor versus visual) also accounted for a significant proportion of the variance (Figure 9). Phantom scans were also routinely acquired before testing participants in order to evaluate signal noise and stability of the two scanners as further checks that the two magnets were similarly calibrated. Given the careful evaluation of BOLD signal properties of the two different magnets, the results suggest that obtaining neuroimaging data from two geographically different sites with the identical systems used in those studies was feasible and had sufficient reliability.

6. Conclusion

In this review, we have covered imaging findings related to neurocognitive changes associated with aging and culture, and some findings pertaining to their interaction. Studies on neurocognitive aging show a general reduction in the distinctiveness of neural responses to different stimuli in the posterior brain regions that may be related to neurobiological declines. In the midst of such neurobiological declines, there is also consistent evidence showing increases in frontal responses that may be part of a compensatory response, in particular for the declines associated with posterior brain regions. In contrast to the more global effect of aging, studies on cultural differences in values, perception and attention have also shown specific and more localized differences in neural function that are consistently associated with the analytic-holistic dichotomy in Westerners and East Asians respectively. Specifically, Westerners show functional brain responses that reflect their bias for analytic processing styles that is associated with increased responses in object-processing regions probably related to greater attention to object features. In contrast, East Asians show brain responses that reflect a more holistic processing style associated with attention to contextual information in regions like the lingual landmark area. Some differences in brain structure have also been observed in these cultural groups, although a clear mechanism between cultural experience and brain structure has yet to be established. A few studies have shown that the impact of culture-related experiences on neural structure and function may be acquired at a very young age, and importantly, endures through to advanced aging with even some cases of accentuation.

In sum, the findings covered in this review suggest that there is a reliable and consistent effect of cultural experiences on neural structure and function. While more studies are required to strengthen the findings, initial studies have shown also that at least some of these culture-related effects present in young adults are maintained even in the face of neurobiological changes associated with aging. Importantly, these findings also suggest that neurobiological aging does not always lead to neurocognitive decline in a uniform manner, and that external experiences can modulate and perhaps alleviate some of the neural effects of aging in the brain.

7. Acknowledgement

We thank Dr. Wayne Chan and Dr. May Baydoun for their helpful comments. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging, USA.

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3

Neuroimaging of Single Cases: Benefits and Pitfalls

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1. Introduction

Single case studies of neurological patients has a long and storied history (Zillmer & Spiers, 2001). First used as a teaching tool (Haas, 2001), the method of thoroughly exploring the cognitive and motor functions of a unique individual patient has led to extraordinary advances in our understanding of structure-function relationships in the human brain. Single cases have led to important advances in many fields, including pioneering work on language (Broca, 1861; see also Ryalls & Lecours, 1996) and visual perception (Poppelreuter, 1917/1990; see also Humphreys & Riddoch, 1996) to more recent work on memory systems (Scoville & Milner, 1957; Milner & Penfield, 1955-1956; see Milner, 2005 for a recent review) where one patient (HM) has arguably done more to advance that field than any other single case study in history. Prior to the advent of x-rays and eventually computerised axial tomography (CT scans), the method of studying single cases was the only way to determine the location of a patient's pathology. The advent of CT scans in the 1970's obviated, to some degree, the need for detailed neuropsychological testing, at least as it was needed to determine the *location* of pathology (Banich, 2004; Lezak, et al., 2004; Kolb & Wishaw, 2009). A few decades later and the advent of functional MRI (fMRI) provides an even more powerful tool for examining the nature of structure-function relationships in humans and in non-human primates (Ogawa et al., 1992; Ford et al., 2009). Indeed, the rapid rise of fMRI studies (Fox, 1997; Raichle, 1994) has outstripped the pace of single case studies in the past few decades (Figure 1).

By 2005 the proportion of neuroimaging abstracts accepted for presentation at the Cognitive Neuroscience Society meeting was around 35% compared to only 15% for patient studies (which included group and single case methods; Chatterjee, 2005[1]).

There are a range of reasons behind the rise of functional neuroimaging studies including the ease and relatively low cost with which these studies can be carried out (Chatterjee, 2005). Although per hour imaging costs seem high to most, the cost of patient research is undoubtedly far higher both in time committed and real costs related to screening and following patients over longer periods of time (Chatterjee, 2005). In addition, each method

[1] A search of the 2011 CNS program using "fMRI", "neuroimaging" and "patients" separately showed that neuroimaging references were almost double those of references to patients.

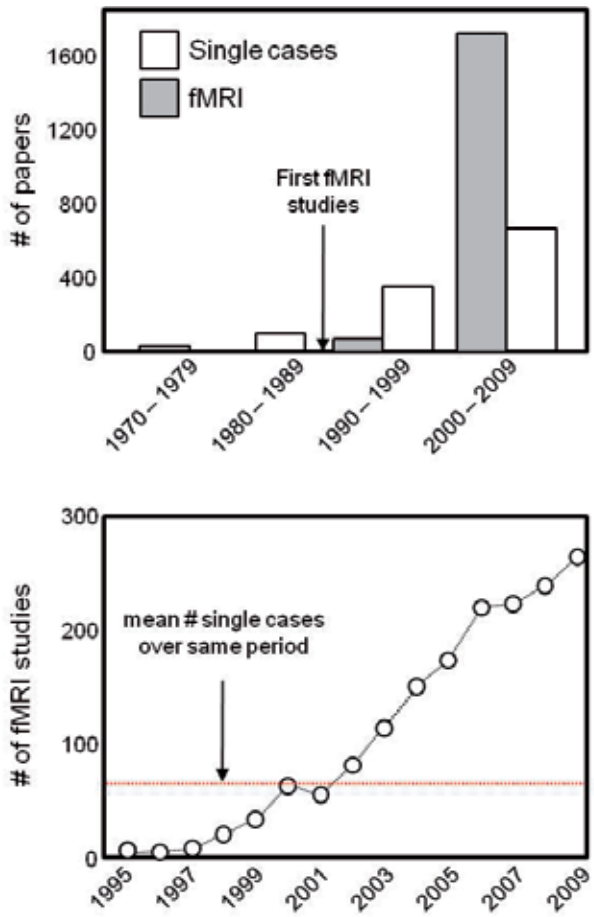

Fig. 1. Proportion of single case and fMRI studies in the past few decades. Upper panel shows the results of two Pubmed searches, the first using the term 'memory' (open bars) and the second using the conjunction search terms 'memory AND fMRI'. The first search included the following constraints: case studies published in English, dating from 1970 onwards (under the 'limits' tab of Pubmed the following criteria were selected: 'English', 'Humans', 'Case Studies', 'dates from 1970.01.01 to 2010.01.01'). The resulting abstracts were inspected to ensure that only single case studies of neurological patients were included. The second search term included the same constraints with the exception that the constraint 'case studies' was removed from the search term. Again, all abstracts were inspected to ensure that only fMRI studies examining memory processes were included.

provides distinct information. By design, human functional neuroimaging studies are necessarily correlational and as such can not address which brain regions are *necessary* for a given function but highlight only those regions or networks that are *sufficient* (Chatterjee, 2005; Friston & Price, 2003). In fact, given that the vast majority of fMRI studies present only group averaged data, it is feasible that much of what we see represents 'cognitively degenerate' neural systems - that is, typical imaging findings may highlight only one of several regions or networks each capable of subserving the same cognitive function (Friston

& Price, 2003). On the other hand, case studies of neurological patients, while capable of demonstrating which brain regions are necessary for a given function, encounter a range of distinct problems (Rorden & Karnath, 2004). Human lesions tend to be large and highly variable and in turn lead to heterogeneous behavioural symptoms. Furthermore, it is not possible to determine the effects of disconnection – the consequences not only of damage to a particular brain region but of removing that 'node' from the network of regions it once participated in (e.g., Bartolomeo, et al., 2007).

Perhaps the best way to compensate for the shortcoming of single case and neuroimaging methods is to combine the two (Friston & Price, 2003; Price et al., 2006, 1999; Chatterjee, 2005). Unfortunately, both methods demonstrate a strong within citation bias (although the bias is stronger in neuroimaging work; Chatterjee, 2005). There have been elegant studies using fMRI in groups of patients to address a wide variety of behaviours from motor control in Parkinson's disease (e.g., Nandhagopal et al., 2008), to strategy selection in social games in psychopathy (Rilling et al., 2007; see also Hoff et al., 2009 for a single case study of psychopathy) and recovery of function in neglect patients – a common disorder typically arising from right hemisphere strokes (Corbetta et al., 2005). Far fewer studies have made use of fMRI to examine single case studies. In this chapter we will first discuss some of the challenges to using fMRI as another tool for exploring single cases before giving some examples of how such an approach could be used to advance our understanding of structure-function relationships in humans.

2. Design issues relevant to single case studies in fMRI

Several technical aspects related to collecting the Blood Oxygenated Level Dependent (BOLD) response that forms the basis of fMRI data pose problems for single case studies. First, the shape of the haemodynamic response function (HRF) may vary from one experimental session to another (Aguirre et al., 1998). Within a given subject the shape of the HRF tends to be robust particularly within a single scanning session (Aguirre et al., 1998). More variability is evident within individuals when scanning runs span multiple sessions. This may be related to hardware issues in the scanner itself with some variability in measures of magnetic susceptibility from one session or day to the next (Huettel et al., 2004). Noise may also be introduced from the subject themselves with differing levels of alertness being an important factor in testing neurological patients (Lerdal et al., 2009; see also Tyvaert et al., 2008 for a study of the effects of alertness on BOLD signals). Even factors such as levels of caffeine influence the BOLD signal (Chen & Parrish, 2009). The variability of the HRF and subsequent BOLD measures when testing over multiple sessions is particularly problematic for single case designs as it constrains the number of tasks, and repetition of those tasks, one can expect to complete in a given session. Commonly, fMRI designs require multiple repetitions of the same task within a single session to achieve the appropriate statistical power to demonstrate a robust change in the BOLD signal (Huettel et al., 2004; Monti, 2011). While the same can be said of behavioural studies of single cases, such studies can often extend over days or weeks with an opportunity to replicate findings within the patient and to examine an extensive range of behaviours (e.g., Danckert et al., 2002; Branch-Coslett & Lie, 2008). Issues of fatigue in this instance can be addressed by testing the patient at the same time of day in each instance or collecting a control task as an index of fluctuations in alertness (e.g., a basic information processing task such as the Trails A test

would suffice for this purpose; e.g., Gaudino et al., 1995). In contrast, collecting fMRI data across a range of cognitive functions within one scanning session can be time prohibitive, especially in instances where repetition of each domain specific task is ideal to achieve the appropriate statistical power (Huettel et al., 2004). These limitations can in part be overcome through the choice of tasks to be implemented and the design chosen (i.e., block design vs. the various forms of event-related designs). In general, block designs lead to larger percent signal changes than do event-related designs (Bandettini & Cox, 2000) due to a loss of signal-to-noise ratio for the latter. Tasks exploring basic sensory or motor functions also tend to lead to larger BOLD signal changes than do tasks exploring more complex cognitive functions (Huettel et al., 2004).

A second issue in fMRI scanning impacting upon single case studies using this methodology relates to susceptibility artefacts (Huettel et al., 2004). Susceptibility artefacts can be readily distinguished from true BOLD signal and other artefacts such as motion, using a range of statistical techniques including independent components analysis (e.g., DeMartino et al., 2008). With abnormally developed or injured brains, however, these issues could be compounded. In particular, if one is interested in examining hemispheric differences in activation, it is important to determine that susceptibility artefacts do not impact the damaged and undamaged hemispheres differentially (e.g., Danckert et al., 2007). This can be overcome statistically by contrasting activation for similar regions across each hemisphere (Adcock et al., 2003; Danckert et al., 2007; Shulman et al., 2010). In this instance, however, it is crucial to first determine what one might expect in the healthy brain. For example, basic sensory processes may be expected to lead to symmetrical activations across the two hemispheres (e.g., motion processing and object perception; Dukelow et al., 2001; Kourtzi & Kanwisher, 2000), whereas more complex cognitive processes may be expected to lead to asymmetric activations (e.g., language processing; Price, 2000, 2010). Language functions represent a pertinent case as many individuals may be expected to have bilateral activations during language tasks (Fernandes et al., 2006; Fernandes & Smith, 2000) or even shifted language dominance to the right hemisphere (e.g., Peng & Wang, 2011; Wong et al., 2009). In this instance, fMRI with a single case suffers from the same methodological issues that behavioural studies do – without a baseline measure of performance in some cognitive domains it is difficult if not impossible to determine what has *changed* for the patient. This is particularly problematic for patients suffering from traumatic brain injury (TBI), especially at the mild end of the spectrum, in which subtle changes to executive functions, social functioning and personality are difficult to quantify (e.g., Vaishnavi et al., 2009).

Another issue to consider concerns the nature of damaged or abnormal tissue in neurological patients. More to the point, given that BOLD fMRI depends on changes in oxygenation at the level of capillaries (Huettel et al., 2004; Price et al., 1999), it is possible that damaged or abnormal tissue will also demonstrate abnormal, or at the very least altered, vascularization (Beck & Plate, 2009). Cerebral angiograms are not useful in this circumstance as only gross vascular morphology can be imaged (e.g., obvious abnormalities such as arterioveinous malformations can be detected but the consequences of such malformations for the capillary bed are more complex). This is particularly problematic when faced with null results, an issue we will explore in more detail below. Briefly, any absence of activation could, among other things, be explained due to abnormal vascularization related to the pathology in question. This could be related to abnormally developed tissue (e.g., heterotopias; Guerrini & Barba, 2010) or changes to vascularization due to insults such as stroke (Beck & Plate, 2009). Statistical approaches can in part address this issue (i.e., lowering statistical thresholds should show

some level of activity even in abnormal tissue) and comparisons with similar patients and healthy controls can also partly address these concerns (e.g., Danckert et al., 2007; Danckert & Culham, 2010). These approaches however, never fully remove the concerns surrounding null results and can be seen only as increasing the degree of confidence regarding alternate reasons for an absence of activation. This issue will be revisited with the examples to be discussed in more detail below.

One final vital issue when utilising neuroimaging techniques with neurological patients concerns task design. As already suggested, it is often best to make use of tasks that lead to well documented, robust activation patterns (e.g., tasks known to activate primary sensory and motor cortices). Given that each patient presents with a unique behavioural deficit, however, it is not always possible to stick with the robust, simple tasks. In that sense, task choice and design necessarily feeds off neuropsychological testing – in other words single case methodology. While the temptation may be to choose tasks that fully highlight the patient's particular deficits, this may not be the ideal approach (Price & Friston, 1999). If the patient is completely incapable of performing a given task, interpretation of any neural activity (should any even exist) is limited. Instead, those tasks that the patient can perform either to the same level as healthy controls or to some suboptimal level, should be preferred. In the first instance, when a patient performs to an equivalent level of controls, it is possible to explore the extent to which the same networks are invoked (e.g.,. Yucel et al., 2002). In many instances, patients will utilise alternate neural networks to achieve the same level of behavioural performance as controls (this may be especially important when investigating disorders such as schizophrenia). The difficulty with this kind of finding comes from interpreting the abnormal neural responses as either *causing* the behavioural syndrome or deficit in question or arising as a *consequence* of the syndrome/deficit (note: in this case the task used may show no deficit per se but tap into a component process known to be impaired in the patient; Price & Friston, 2006). Essentially this arises from the fact that neuroimaging data are correlational in nature and do not allow for conclusions related to the cause of changed patterns of activation. In the second instance, in which the patient performs a task at suboptimal levels, it is possible to correlate performance with the BOLD signal directly (i.e., activations related to correct vs. error trials; Price & Friston, 2006) or to address which parts of the normal neural network are necessary for the task at hand (e.g., Steeves et al., 2004). For example, Steeves and colleagues (2004) examined object processing in a visual form agnosic patient who performed at above chance levels, but well below that of healthy individuals, when asked to recognise visual representations of objects. In their study they were able to examine more precisely which components of object recognition, including colour diagnostics, form outlines and greyscaled images, were most impaired in their patient thereby enabling a more detailed exploration of the variety of processes involved in object perception (Steeves et al., 2004). In instances such as these, however, there remains the possibility that abnormal neural activation patterns arise due to either a loss of function from the damaged region or as a consequence of the fact that the damaged region is disconnected from a broader network (see Price & Friston, 2006 for a detailed review of these and related issues in single case neuroimaging).

Task choice and design are ultimately dictated by the nature of the question being asked. In many instances (including the first two patients to be discussed below) the questions asked are primarily patient focused - that is, the studies represent an attempt to determine the degree of recovery or reorganisation of function in a given patient. In this instance tasks with well-described patterns of activation in the healthy population are essential. In other

instances, the patient serves as a means to understanding normal cognitive processes by virtue of either the demonstrated behavioural deficits or alterations in neural functioning needed attain normal performance (Price & Friston, 2006). Here one can utilise behavioural performance in conjunction with imaging data (e.g., correlate BOLD with correct vs. incorrect trials) to examine changes in neural function.

In summary, single cases of unique neurological patients provides an opportunity to examine structure-function relationships, with a particular focus on which brain regions may be necessary for a given behaviour. Functional MRI provides another tool that can be used with single cases to examine a broad range of issues. In utilising fMRI with single cases it is important to consider the nature of the pathology for the particular patient, expectations regarding activation in the healthy brain (i.e., is there a demonstrated pattern of activity in healthy individuals related to the task at hand?) and the limitations of the paradigms to be employed (e.g., block designs focussing on well-documented structure-function relationships vs. event-related designs focussing on more complex behaviours). Some of these issues will be explored further below relative to particular examples of fMRI used with single cases.

3. Potential uses of fMRI in single case studies

Below we examine three distinct uses of fMRI in single case studies to illustrate some of the benefits and potential pitfalls of combining the two methodologies. These examples are by no means exhaustive, but represent a disparate range of approaches to combining fMRI and single case studies.

3.1 Examining the consequences of unusual neuropathologies

We recently examined a range of cognitive functions in two patients with epileptic disorders arising from distinct etiologies (Danckert et al., 2004; 2007). The aims for these studies were varied and so posed distinct challenges. Our first case involved a patient with a large left hemisphere porencaphalic cyst (Figure 2). The remaining left frontal tissue was also the site of seizure onset for the patient and fMRI was employed in the first instance to determine whether or not that residual tissue supported cognitive and motor functions. In this sense then, fMRI becomes an additional tool for the clinician that has the potential to aid in treatment decisions. In fact, fMRI serves another important clinical function in epilepsy research as it has recently begun to surpass traditional methods of determining language lateralisation in epilepsy patients (i.e., the WADA; Abou-Khalil & Schlaggar, 2002; Jones et al., 2011; Woermann et al., 2003). A secondary aim in this case, was to use fMRI to determine the extent to which normal structure-function relationships had been distorted in this patient. In other words, to what extent had his pathology led to a reorganisation of function? Our approach in this instance was to examine basic motor and somatosensory functions and language functions that would all be expected to activate left frontal regions (i.e., when using the right hand for the motor and somatosensory tasks; Toma & Nakai, 2002; Price, 2000). The motor and somatosensory tasks have the added benefit of being robust, simple tasks with predictable activation patterns expected in the unaffected hemisphere, thereby enabling comparisons between the intact and affected cortex. Results showed that the remaining tissue in the left frontal region of this patient did in fact support a range of cognitive and motor functions (Figure 2). Importantly, this indicated that tissue that was demonstrated to be the focus of seizure activity was also capable of supporting normal functioning.

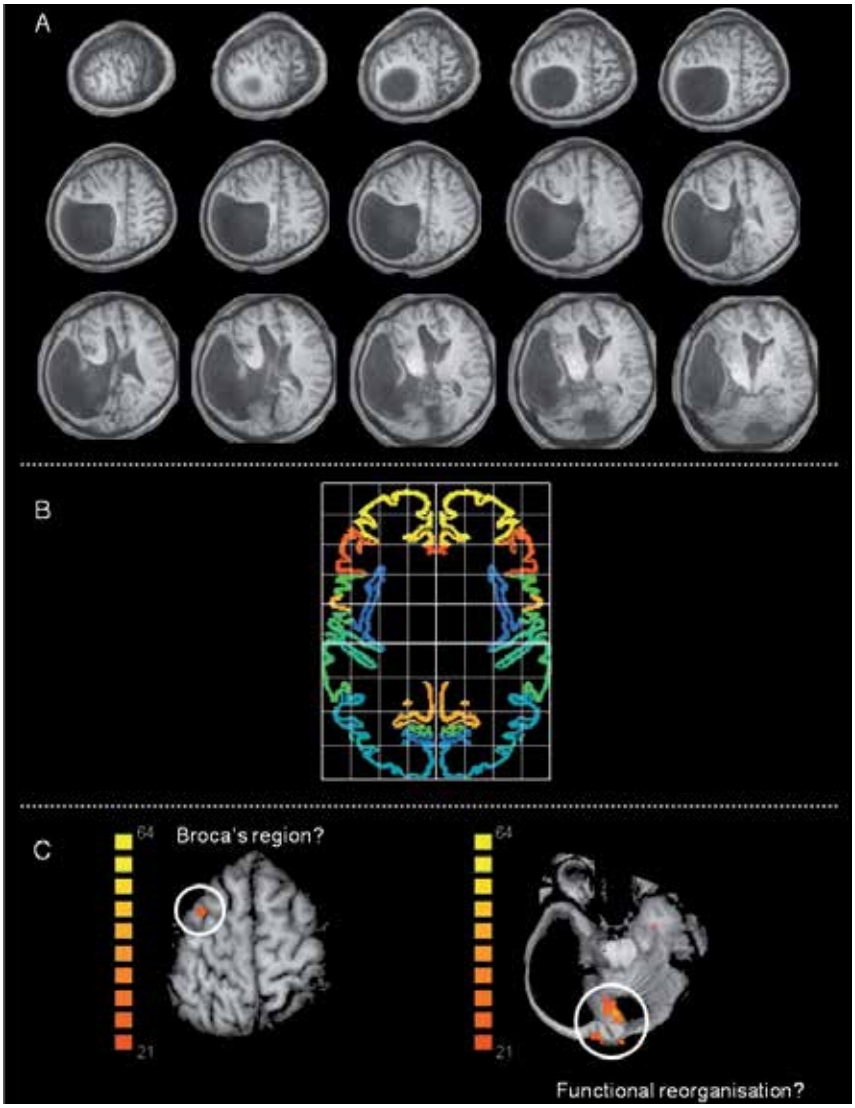

Fig. 2. Selected results from the first case study discussed. Panel A shows anatomical images showing that the patient's skull had been deformed by his porencephalic cyst making it difficult to align the patient's images to a standardised space (indicated in the Panel B using the Talairach template from BrainVoyager software). Panel C shows two data points from this patient. To the left is activity during a silent word naming task in which a left frontal region was activated. Given the distortions evident in the patient's brain and skull it is impossible to know whether this region represents Broca's area. Similarly, the data to the right shows activity in a remaining portion of occipital cortex during silent word naming. This region would not normally be activated in this task (and the undamaged hemisphere showed no occipital activity) and the patient was hemianopic suggesting that the remaining occipital cortex was unlikely to support visual functioning. Nevertheless, caution should be employed when interpreting data of this sort in terms of functional reorganisation. Data adapted from Danckert et al., 2004.

Challenges arising from the case described above that are pertinent to studies of this kind included alignment of the patient's structural scan to a standardised space and a lack of exhaustive testing, especially for unusual activations. As can be seen in Figure 2, the patient's skull had been deformed by the cyst making it difficult to find the landmarks normally used to align structural scans to a normalised space (e.g., Talairach & Tournoux, 1988; see Price & Friston, 2006 for further discussion of this issue). In instances such as this estimates of missing or distorted landmarks are required. This is relatively trivial given that the patient's data will stand alone (i.e., there is no 'group average' to worry about). Where it does pose a problem is in localising activations one would normally expect to see. For example, we found a region of frontal cortex that was active for silent word production that may have been analogous to Broca's region (Danckert et al., 2004). However, given the obvious distortion in gross morphology and without appropriate landmarks, this kind of association was at best speculative.

Perhaps more difficult to address was the fact that it was simply not possible to perform the full range of tasks we would have liked to have collected on this patient. This is likely a problem for all single case studies using fMRI for all of the reasons noted above. For our patient, silent word naming activated a small region of remaining occipital cortex. Given that the patient was hemianopic, any activation in this region is difficult to interpret without further testing. For example, visual perceptual tasks (e.g., object recognition protocols; even retinotopy; Kourtzi & Kanwisher, 2000; Sereno et al., 1995; Tootell et al., 1995) may have been informative regarding the role this remaining region of occipital cortex played in the patient's behaviour (e.g., would the patient have shown residual functions akin to blindsight, or would visual imagery evoke activity in this region even though it receives no afferent input?). Unfortunately, we had been guided in the first instance by other aspects of his presentation (e.g., some mild apraxia) and the fact that his seizures originated not in the sliver of remaining occipital tissue, but in the frontal cortex. This merely serves to highlight some of the restrictions one encounters when addressing unusual single cases in fMRI. Perhaps more important to highlight is the fact that this work was able to demonstrate that a range of functions were subserved by the compromised left hemisphere which in turn guided treatment decisions to some extent. That is, surgery to remove the remaining left frontal tissue had been considered a treatment option, with the fMRI demonstrating just how devastating this approach would have been for the patient's daily functioning.

In our second case, we examined a patient with heterotopic tissue in the anterior temporal cortex (Danckert et al., 2007). In contrast to our first patient, this patient's pathology was not the site of the origin of his seizures, which was more posterior in normally differentiated tissue. Here we wanted to know whether the heterotopic tissue supported any normal cognitive functioning. In addition, what if any, were the consequences to expected structure-function relationships in the tissue where seizures originated? Here we were able to take advantage of imaging results in healthy individuals to examine laterality effects in our patient. Using tasks that would normally activate brain regions identified as the origin of his seizures or tasks that would activate neighbouring regions (i.e., object recognition and motion processing tasks) we were able to demonstrate that our patient had asymmetrical activations where symmetrical activation patterns would have been expected (Figure 3). Taken together with results from our first case, this highlights an important finding in

epilepsy research such that tissue that supports epileptic activity is also likely to support normal function. In the current case we were able to demonstrate an asymmetry of processing such that the epileptic hemisphere showed less activity than the unaffected hemisphere (Figure 3).

The challenges in this case were more substantial than in our first case for several reasons. First, we were unable to demonstrate activation in the heterotopic tissue for any of the tasks we used (Danckert et al., 2007). This raises the spectre of null results briefly mentioned above with the obvious caveat that an absence of evidence is not evidence of absence. This issue would be particularly important if fMRI results of this kind were to be used to guide surgery. Although there was no gross distortion of the patient's brain, the heterotopic tissue also raises concerns regarding abnormal vascularization (see D'Esposito, et al., 2003 for a review of this issue). Any such abnormalities may well have been the root cause of the failure to find significant activations. In addition, task choice may well determine whether or not activation is observed. Without the right task, one would not expect to see activation in a given region. Two approaches can be utilised to address these concerns although it should be noted that what is provided here is some degree of corroborating evidence and not certainty. First, data from healthy individuals using the same tasks/protocols used in the patient can demonstrate what would normally be expected with respect to a given brain region (note, we were unable to do this for all tasks in our case). If the same task that fails to activate a brain region in the patient nevertheless leads to robust and reliable (i.e., evident in all subjects) activity in healthy individuals, one can have more confidence that the patient`s pathology has disrupted normal function.

A second approach to dealing with null results involves lowering the threshold for significant activation to determine whether changes in the BOLD response will be evident with less stringent statistical approaches (Figure 3; Danckert et al., 2007; Danckert & Culham, 2010). In our case, even at the lowest statistical thresholds there was no evidence of activity within the heterotopic tissue. Even instances where lowering the statistical threshold does show changes in BOLD signal that were not evident at more conventional thresholds can be informative (Danckert & Culham, 2010). Changes in BOLD signal seen at lower statistical thresholds that fail to modulate with task manipulations (i.e., no difference between BOLD in the task vs. baseline conditions) should be considered meaningless (Danckert & Culham, 2010).

In both cases described above, careful neuropsychological testing was also carried out to compliment the imaging findings. Where possible, such clinical and/or experimental testing is vital as it can cover more ground than imaging alone. In our first case, neuropsychological results (i.e., mild apraxia) directed us towards tasks that would examine basic and more complex (i.e., praxic) motor skills. Similarly, our second case exhibited some mild object naming deficits on neuropsychological testing that guided our choice of tasks (i.e., both language and object naming tasks were used; Danckert et al., 2007). Not only do neuropsychological findings of this kind help guide the choice of tasks for imaging, they can corroborate certain imaging findings. For example, our patient with heterotopic tissue showed asymmetric activation of the lateral occipital complex when naming objects, which could be interpreted in the context of both his pathology (i.e., LOC was proximal to the region of cortex deemed to be the origin of his seizures) and his neuropsychological profile (i.e., mild naming deficits).

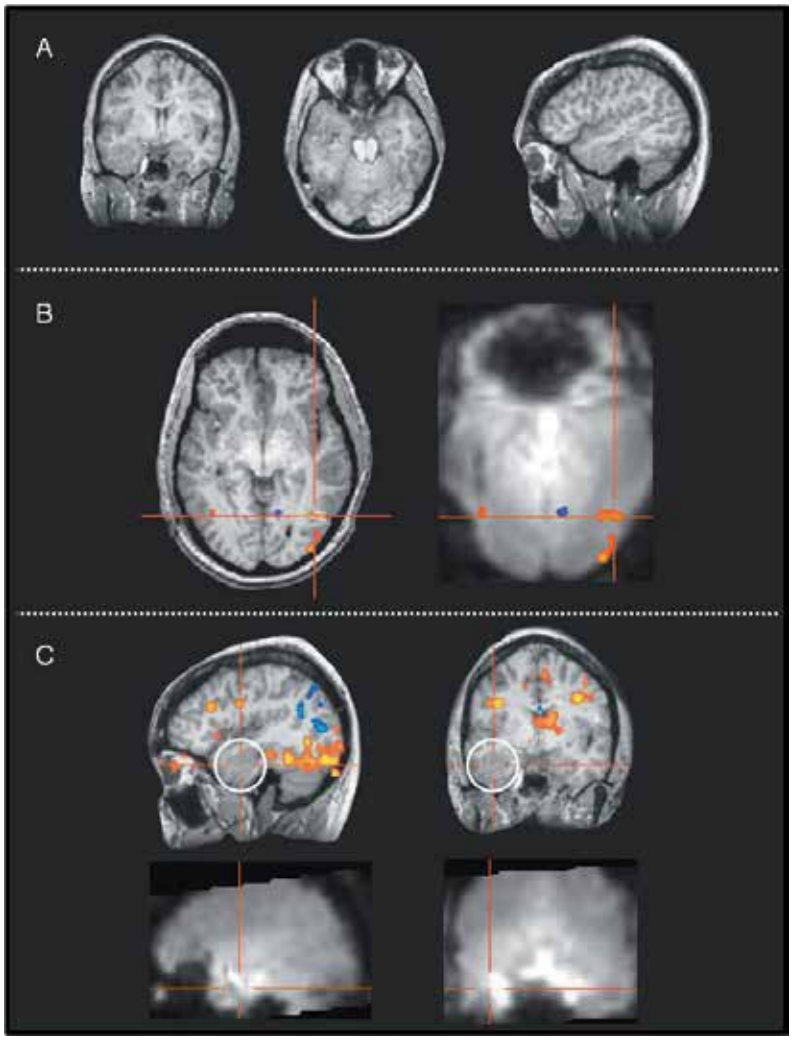

Fig. 3. Selected results from the second case study discussed. Panel A shows anatomical images highlighting the region of heterotopic tissue in the left anterior temporal cortex. Panel B shows activity in response to expanding and contracting concentric circles in area MT bilaterally. Both area and peak BOLD signal were weaker in the damaged hemisphere. Importantly, the raw fMRI data shows no drop-off in signal-to-noise ratio in the damaged hemisphere. Panel C shows activity (both raw and overlaid data) from an object naming task in which the statistical thresholds have been lowered to determine whether heterotopic tissue supported activity. This shows that a failure to detect activity in this region was not due to a lack of statistical power. Nevertheless, caution should be exercised in this instance as other explanations (e.g., abnormal vascularization) can not be ruled out. Data adapted from Danckert et al., 2007.

In both instances discussed above tasks were chosen that would lead to robust, predictable activations with a limited number of experimental runs to maximise the range of behaviours that could addressed within a single scanning session. This allowed us to explore issues of

symmetry, reorganisation of function and the association between epileptiform activity and function across a reasonably large range of tasks. In other instances, the *range* of tasks to be explored is less relevant as specific hypotheses regarding particular functions allow the focus to be narrowed. For instance, recent investigations into memory functioning in an epilepsy patient who underwent resective surgery of anterior temporal cortex, focused only on specific component processes of memory – namely, familiarity vs. recollection, to determine the role played in each process by the region surgically removed (Bowles et al., 2007). Another instance in which the fMRI approach to single cases can be more narrowly focussed – that of blindsight – is discussed in more detail below.

3.2 Residual visual pathways in blindsight

Patients presenting with visual field defects, such as hemianopias, arising from lesions of primary occipital cortex (area V1) can nevertheless respond to blind field stimuli at better than chance levels (Pöppel et al., 1973; Weiskrantz et al., 1974). The term 'blindsight' was first coined by Weiskrantz and colleagues (1974) to refer to these residual visual abilities. Initial demonstrations of above chance responding to blind field stimuli showed that some patients were surprisingly accurate when reaching to, or making a saccade to target locations that had been briefly flashed in their 'blind' field (Weiskrantz et al., 1974; Zihl & Werth, 1984). Note, that the patients were "guessing" at these locations as they had no conscious experience of the targets themselves. Research on blindsight has demonstrated a myriad of residual abilities including motion discrimination, colour and form interference effects, wavelength discrimination and even semantic priming (Danckert et al., 1998; Magnussen & Mathiesen, 1989; Marcel, 1998; Morland et al., 1999; Stoerig & Cowey, 1989).

The demonstration of a broad range of residual abilities in blindsight patients indicates that secondary visual pathways carry information to extrastriate cortex in the absence of input from V1 (Cowey, 2004; Danckert & Goodale, 2000; Danckert & Rossetti, 2005; Stoerig & Cowey, 1997; Weiskrantz et al., 1974). The most prominent of these pathways spared following damage to V1 connects the superior colliculus directly to the pulvinar nucleus of the thalamus, which in turn has direct connections with extrastriate visual cortex (Cowey, 2004; Stoerig & Cowey, 1997; see Sincich et al., 2004 for demonstration of another pathway in the monkey from koniocellular layers of the LGN directly to motion-selective regions of extrastriate cortex).

One key issue in blindsight research involves demonstrating conclusively that the residual visual functions demonstrated are not in fact explained by factors not related to secondary visual pathways. Light scattering from blind to sighted portions of the retina (intraocular scatter) or from blind to sighted portions of the visual field (extraocular scatter) represent a major challenge to blindsight research (Campion et al., 1983). Masking off regions of the blind field and modifying the physical properties of the target stimuli can address these issues to some extent (King et al., 1996; Danckert et al., 2003; Danckert & Culham, 2010). A second challenge can be addressed through both anatomical and functional MRI. Some have suggested that blindsight does not rely on residual pathways bypassing V1, but instead reflects subthreshold activation in residual 'islands' of cortex within V1 (Campion et al., 1983; Fendrich et al., 1992; Gazzaniga et al., 1994). Anatomical scans in this case can conclusively address whether such islands even exist in a given patient. Functional scans have suggested that, in at least one blindsight patient, despite evidence of anatomical sparing of V1, there was no evidence that the spared region supported any functions (Stoerig et al., 1998). Although this work suffers from the absence of evidence argument

discussed above, activation in the undamaged hemisphere can act as a 'control' site for the patient. In other words, if stimuli presented to the sighted field leads to robust activation in the undamaged hemisphere one can be reasonably confident that the task, equipment and statistics are not responsible for a lack of activation when the same stimuli are presented to the blind field (Stoerig et al., 1998). Furthermore, the fact that extrastriate regions *did* show activity in this patient goes a long way towards dismissing the hypothesis that residual visual capacities are in fact reliant on spared islands of cortex in V1.

Functional neuroimaging can also provide insights into the neural structures and potentially the pathways connecting those structures, that would support the range of blindsight phenomena observed. One of the more robust activation paradigms in fMRI makes use of simple flickering checkerboard stimuli to highlight retinotopic maps in striate and extrastriate cortex (e.g., Tootell et al., 1998). For example, various neuroimaging techniques, including fMRI, positron emission tomography (PET) and visual evoked potentials, have been used in the most extensively tested blindsight patient, GY, to demonstrate that, although V1 has been almost completely destroyed in this patient's left hemisphere, spared processing occurs in the visual motion complex, MT+/V5 (Barbur et al., 1993; ffytche et al., 1996; Zeki & ffytche, 1998; Bridge et al., 2008; Goebel, Muckli et al., 2001), in dorsal extrastriate cortex (Baseler et al., 1999; Goebel, et al., 2001), and even in the amygdala, colliculus and prefrontal cortex within the damaged hemisphere in response to blind field stimuli (Morris et al., 2001; Sahraie et al., 1997). Finally, diffusion tensor imaging has the potential to illuminate the white matter pathways that until recently were merely hypothesised to support the range of blindsight phenomena discussed (Leh et al., 2006).

We recently used fMRI to determine the veracity of an unusual case of responding to blind field stimuli (Danckert & Culham, 2010). Our patient had surgery to remove V1 as treatment for medication resistant epilepsy. The patient presented with unusual responses to blind field stimuli in that she consistently localised targets presented in the periphery of her blind field to locations closer to the midline of her field defect and vice versa (Figure 4).

We used fMRI to determine whether we would see residual activation in MT to blind field motion stimuli – a phenomenon evident in other blindsight patients (Magnussen & Mathiesen, 1989). We were also able to contrast our patient's performance with that of GY on similar tasks. Results showed there was no residual activation in the extrastriate cortex of the damaged hemisphere in response to blind field motion stimuli in our patient (Danckert & Culham, 2010). Again, this result suffers from the 'absence of evidence' argument. Here we were able to show reliable activity to blind field motion stimuli in GY`s damaged hemisphere and were then able to show that this activity was evident in only one experimental run (Figure 4). That is, responses to blind field stimuli were reliable and robust in patient GY with only minimal exposure. The same could not be said of our patient who showed no reliable activity on any single experimental run even at lowered statistical thresholds (Figure 4). Just as in our case of heterotopic tissue discussed above (Figure 3), this kind of evidence provides additional support to the notion that the absence of activity is not simply due to a lack of statistical power. In contrast to that patient, lowering statistical thresholds in this case did show some level of signal in the voxels of the damaged hemisphere that would be expected to support blindsight motion processing (Figure 4). In this case, however, we were able to show that the 'activity' in these voxels did not show any reliable modulation with the experimental paradigm (Figure 4). Again, caution is still needed with respect to evidence of this kind as it does not rule out other potential explanations for the lack of activation.

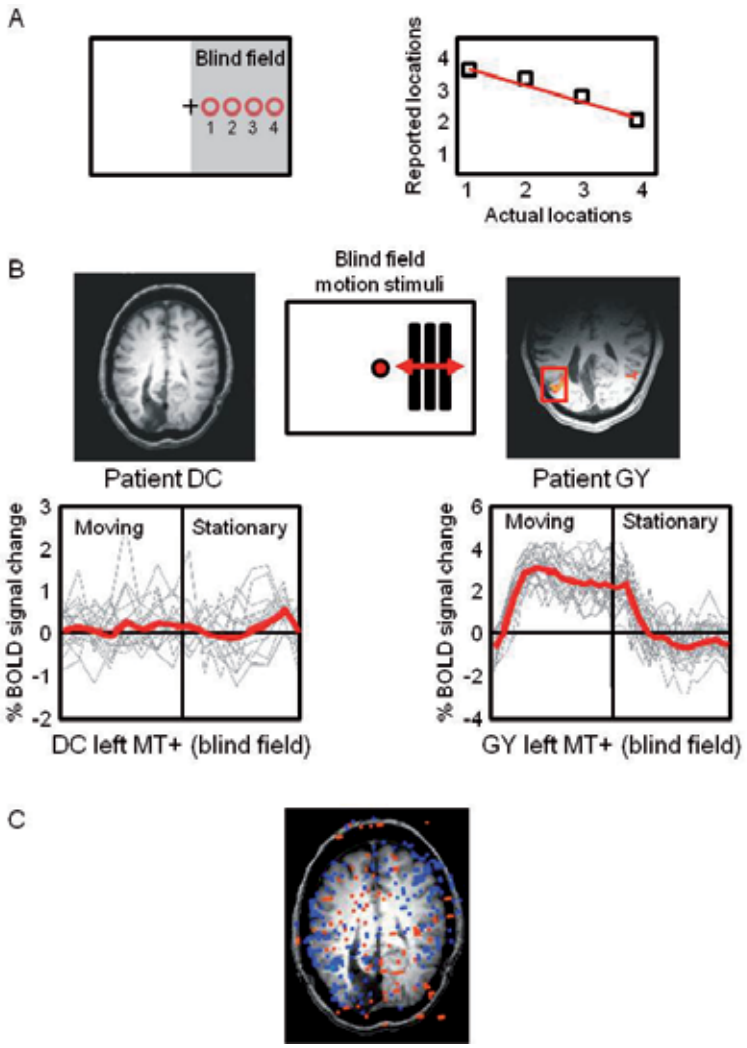

Fig. 4. Panel A shows behavioural data from a hemianopic patient (DC) who showed unusual residual behaviour. To the left is the stimulus setup in which targets could be flashed to either her sighted or blind fields (only blind field targets are shown). When asked to guess blind field target locations DC consistently mislocalised targets - that is, she consistently guessed that targets presented at location 1 in her blind field had instead appeared at location 4 and vice versa. Panel B shows fMRI data from DC and GY, a well tested blindsight patient, when motion stimuli were presented to their blind fields. For GY (to the right) blind field motion stimuli reliably activated MT bilaterally despite a lack of awareness of the stimuli (the red line below represents mean activation across a number of runs for the region highlighted on the anatomical scan show above). This response was evident even in single experimental runs (indicated by the grey lines in the event-related average). In contrast, DC showed no reliable activation to blind field motion stimuli. Panel C shows activity for DC when statistical thresholds were lowered which failed to show any reliable activation suggesting that statistical power was not responsible for the lack of activity to blind field stimuli. Data adapted from Danckert & Culham, 2010

The approaches to examining residual vision in hemianopic patients discussed above highlight many of the issues facing single case studies with fMRI. In most instances robust paradigms (e.g., retinotopy, motion processing) with known activation patterns localised to specific brain regions in the healthy brain (Sereno et al., 1995) were utilised. This enables the testing of specific and directed hypotheses concerning what one would expect to see in the patient. In contrast to the cases of epilepsy discussed above, these cases did not require an extensive range of behaviours to be tested (or accompanying neuropsychological profiling) and instead could focus on particular aspects of residual visual processing in more detail. Finally, utilising fMRI in single cases of residual vision (suspected or demonstrated) can inform not only the neural pathways necessary for supporting residual vision but also the neural signatures of conscious experience. For example, it is possible to contrast activations to stimuli that the patient does report some degree of awareness of with those instances in which they responded to stimuli without any conscious perceptual experience. The final use of fMRI in single cases to be discussed below – synaesthesia – has similar potential to inform our understanding of the neural correlates of consciousness.

3.3 Synaesthesia and the neural bases of consciousness

Synaesthesia represents an unusual perceptual phenomenon in which the subject perceives multiple percepts in response to a single sensory stimulus (Rich & Mattingley, 2002, Ward & Mattingley, 2006). Perhaps the most common synaesthetic experience is grapheme-colour associations in which a digit presented in black ink is perceived by the synaesthete to have an additional, consistent colour associated with it (e.g., 7 is always red; Rich & Mattingley, 2002, Ward & Mattingley, 2006; Ramachandran & Hubbard, 2001; Dixon et al., 2000). The study of this unusual phenomenon has the potential to offer new insights into two key issues in cognitive neuroscience: first, how are different perceptual characteristics bound to the same object? That is, colour-grapheme synaesthesia may represent an unusual form of binding in the absence of an external percept (Robertson, 2003). Second, given that synaesthetes experience conscious percepts in the absence of external stimuli, they present an interesting avenue for exploring the neural bases of consciousness and in particular, in discriminating between preconscious and conscious processes (i.e., a synaesthetic experience is by definition not preconscious; Gray 2003; Gray et al., 2006). Functional neuroimaging represents another tool through which these and other questions related to synaesthesia (e.g., is attention necessary for a synaesthetic experience?) can be addressed (Rich et al., 2005).

A key issue in synaesthesia research is the idiosyncratic nature of the individual's experience (see Hochel & Milán, 2008 and Ward & Mattingley, 2006 for review). The authenticity of the particular experience must first be verified through behavioural testing. In essence then, functional imaging approaches to synaesthesia largely *require* single case methodology. That is, given the idiosyncratic experiences of individual synaesthetes, any imaging study will need to tailor tasks to the individual's experience making group comparisons problematic (although see van Leeuwen et al., 2010). A key issue highlighted by fMRI in synaesthetes is the need for appropriate control tasks and participants. For example, Blakemore and colleagues (2005) tested a synaesthete who experienced touch sensations when observing others being touched. They first demonstrated that the synaesthete and controls showed similar patterns of activity for somatosensory stimuli of the self before examining the potential differences in activation when observing others being touched. In the latter case the intention was to determine whether the synaesthete would

show differential activation to the observation of touch in the form of either *increased* activity in regions also shown to be active in controls or *additional* regions not normally activated. Results showed that the synaesthete demonstrated both kinds of activation patterns, with higher activation relative to controls in somatosensory cortex when observing others being touched and additional regions of activity in the anterior insular cortex bilaterally.

One problem with interpreting activations in synaesthetes (or indeed in neurological patients) not evident in controls is that it remains possible that statistical power or other analysis variables may have led to the failure to see those same regions in controls (Friston & Price, 2003). Essentially, additional activations seen in the synaesthete may be evidence of a cognitively degenerate system. That is, there may be more than one brain region or network capable of performing a given cognitive task with only a subset of those regions evident in the analysis of the control group (Friston & Price, 2003; Price & Friston, 2006). One approach to address this concern is to match the synaesthete (or patient, as in the blindsight example above) with a control subject with similar behavioural competencies or idiosyncracies (or similar deficits in the case of neurological patients). Elias and colleagues (2003) did this by contrasting a grapheme-colour synaesthete with a cross-stitch expert. Cross-stitching involves consistent, overlearned associations between colours and numbers. Both the synaesthete and the cross-stitch expert showed Stroop-like interference effects for incongruently coloured numbers (i.e., for the synaesthete this means presenting a number in a colour inconsistent with her perceptual experience, whereas for the cross-stitch expert this meant presenting a number is an incorrectly associated colour with respect to the standards used in cross-stitching). Despite similar behavioural effects, the synaesthete showed distinct neural activations (Elias et al., 2003). The power of this design is that the two individuals (who were also contrasted with a healthy control group) demonstrated comparable behaviours. Some would argue that this is an essential component of using fMRI to explore neurological cases (Price & Friston, 2006) although it is far more challenging to find tasks that patients and controls perform at a similar level. Regardless, the advantage is that with identical behavioural performance, differences in neural activation are less ambiguous. In the example discussed above, the cross-stitch expert represents an 'over-trained' normal control individual, whereas the synaesthete, by virtue of the distinct neural activations observed, clearly invokes different neural patterns to support her unique perceptual experience. Without such a control participant (and beyond the most commonly experienced form of synaesthesia it is hard to see how one would obtain such controls; Smilek et al., 2007) additional activations evident in synaesthesia are difficult to interpret.

As already mentioned in the other examples presented in this chapter, choosing tasks with well documented activation patterns in the healthy brain represents an important component of the approach to investigating the neural basis of synaesthesia. For example, retinotopic mapping demonstrates the borders of visual areas in the healthy brain including those regions most responsive to colour – areas V4 and V8 (Sereno, et al., 1995; Tootell, et al., 1998). Sperling and colleagues (2006) tested four grapheme-colour synaethetes using retinotopic mapping to first delineate areas V4/V8. Subsequent tests then presented graphemes that did and did not have associated syneasthetic colour experiences (idiosyncratic to the individual synaesthete) in regions corresponding to the retinotopically mapped V4/V8. For the synaesthetes, graphemes with associated colours led to higher activity in V4/V8 than did graphemes with no colour association (Sperling et al., 2006). In contrast, van Leeuwen and colleagues (2010) used another fMRI technique – MR adaptation, in which repeated presentation of a stimulus leads to reduced BOLD signal – to demonstrate

that adaptation occurred not in colour responsive cortex but in the left superior parietal lobule. This result was taken to suggest that synaesthetic experiences depend on feedback from higher cortical regions. Nevertheless, in both instances conclusions regarding the neural basis of syneasthetic experiences benefited from the use of robust paradigms with well documented activation patterns.

Perhaps the primary concern in fMRI with syneasthetes involves the interpretation of additional activations not seen in the healthy brain (Price & Friston, 2003). Closely matched controls, robust tasks with predictable activation patterns and closely matching BOLD signal with behaviour (e.g., dissociating BOLD signal to graphemes that do vs. do not lead to syneasthetic percepts) represent important considerations that can at least partly assist with interpretations of additional activations.

4. Conclusion

Neuroimaging techniques, including functional MRI, are necessarily correlational in nature. From neuroimaging then, we can make conclusions regarding which regions are *sufficient* for a particular function (Friston & Price, 2003; Price & Friston, 2006). In addition, activity may reflect one or many regions/systems capable of subserving the function under consideration (i.e., cognitive degeneracy; Friston & Price, 2003). In contrast, single case studies of neurological patients can demonstrate which brain regions are *necessary* for a given behaviour. The combination of the two methodologies has the potential to provide insights into brain-behaviour relationships that each technique alone can not address, with both clinical and basic science implications. Issues concerning changes to vascularisation as a consequence of neural insult or abnormal neural development, altered signal-to-noise ratios in those regions and consistency of the haemodynamic response function across sessions all represent challenges to implementing single case fMRI studies. In addition, task choice and design involve a number of important considerations: can the patient perform the task? Can performance be correlated with changes in BOLD signal (e.g., differences related to errors vs. correct trials, conscious vs. unconscious percepts, etc.)? Are there precedents in the healthy population (i.e., does the task lead to robust, reliable patterns of activation)? Contrasting activation with similar patients (e.g., Danckert & Culham, 2010) also represents an important strategy with the potential to bolster interpretations of either additional activations or a lack of activation. Nevertheless, the absence of activations in expected regions represents a significant challenge in applying fMRI to single case methods. One approach might be to conduct large scale normative fMRI studies or meta-analyses to provide robust expectations regarding patterns of activation for a range of behaviours that could then be applied to single case studies with either a basic or clinical focus (see Vigneau et al., 2006 for an example of this with respect to language tasks). Given appropriate consideration, the combination of fMRI and single case methodologies has the potential to lead to insights into a wide range of important issues in clinical and cognitive neuroscience.

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4

Functional and Structural Magnetic Resonance Imaging of Human Language: A Review

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1. Introduction

In this review we outline the range of functional processes involved in language comprehension and their anatomical underpinnings, including recent data on neural connectivity specifically wired for language, using magnetic resonance imaging (MRI) as main tool. A review of this type certainly implies such a large number of references that, for the sake of concision, we have selected the most outstanding and representative studies and reviews. Our interests in identifying possible cues for the evolutionary origins of language partially guided this selection; this review is actually intended as a contribution to better understand human language.

To start with, a description of language and its components appears necessary. In this regard, we will follow the proposal by Ray Jackendoff (2002), who provides one of the most comprehensive and valuable current accounts from the linguistics. Jackendoff proposes at least three structural layers in language, all of them working simultaneously in the processing of every utterance. These layers consist of a *phonological structure*, a *syntactic structure*, and a *semantic/conceptual structure*. Additionally, a number of processes -or subprocesses- coexist within each of these three structures, all of them again working simultaneously.

The phonological structure, which roughly refers to the "sounds" of language, is probably the most complex one, containing the largest number of subprocesses. The auditory-verbal nature of human language may not be alien to this complexity. The phonological structure is actually subdivided into a *prosodic* one -referring to the different intonations along the course of a general envelope covering an entire utterance- and more partial processes referring to *syllabic*, *segmental*, and *morpho-phonological* structures. These latter three structures refer to what most people would call "phonology" as such, and roughly cover the sounds of single syllables, larger word segments, and complete words, respectively.

Syntax refers to the structure of a sentence; that is, the way in which the different words or morphemes constituting a sentence are organized -most often hierarchically-, determining their mutual relationships and dependencies. The hierarchical structure achieved by syntax establishes what the main information is and its relationships with other, secondary items of information; that is, the concrete state of affairs described in an utterance in which the meaning of individual words and morphemes combine. This structure appears "desemantized", i.e., it can be entirely independent of the individual

meanings of its constituents, as in the classical example by Chomsky: "*Colorless green ideas sleep furiously*".

The semantic/conceptual structure of a linguistic utterance is probably the most central one. Indeed, the main aim of processing any linguistic message, regardless of its syntactic structure and transmission modality, is the realization of this semantic structure. This basically consists on the "meaning" of any whole sentence, that is, what it specifically means, or the idea in the mind of the speaker that she wants to elicit in the mind of the hearer. Although this information largely relies on syntax and phonology, the semantic/conceptual structure is completely independent of them –the same idea can actually be transmitted using the two other structures in many ways-. Although single words or morphemes in isolation convey semantic/conceptual information, the combination of these individual meanings by means of syntax, which in turn is achieved by means of phonology, gives place to a different, very specific meaning or semantic structure describing a concrete and detailed situation. It is not clear, however, to which extent the semantic/conceptual structure belongs to language as such, or whether it is a general process, common to other input options such as the non-linguistic interactions between the individual and her environment. In this regard, several authors still distinguish between semantic aspects specific of language and general semantic aspects common to any domain, and this distinction is particularly applicable at the level of the meaning of single words or morphemes. However, the distinction between semantics for language and general semantics appears difficult to embrace from the neural perspective, as we will see. Whatever the case, the semantic structure taps into reality, "*space* structure", i.e., the events in the real world a linguistic message refers to.

Semantics also applies to a layer not explicitly highlighted in Jackendoff's proposal but playing a significant role in language comprehension: the *discourse* level. This level refers to the situation in which two or more sentences are comprehended together, i.e., it is the semantic analysis beyond sentences. Indeed, many of the phenomena involved at this level are even less language-specific than those at the other layers or structures. In a discourse, although the hearer is attempting to get the whole comprehension of a longer message, the final picture does not depend for the most part on what is actually heard or read but, rather, on inferences and logical relationships between the ideas transmitted linguistically. These relationships are indeed extra information added by the hearer and based on her previous knowledge of the world. Although this might not be "language" as such, language would be useless if this level is not achieved.

All the processes described so far, i.e., the phonological, prosodic, syntactic, semantic, and discourse structures, may participate in sequential order –actually following this same order - or occur largely in parallel -mostly before the first 250 ms after stimulus onset (Pulvermüller et al., 2009b)-. In the literature, these two opposing views still remain. Whatever the case, the high degree of specialization and efficiency of the human brain for speech processing at all these levels is granted by most authors.

The fact that language can be transmitted using other than the auditory/verbal modality, as in the sign languages of deaf people, or, more frequently, in written form, also deserves some consideration. Consequently, a few lines in this review will be devoted to written language. Overall, most authors would agree that the linguistic machinery in the brain is largely common to any modality, with notable exceptions appearing only when specific peripheral mechanisms are engaged during the emission or decoding of a given message.

2. The sounds of language

Phonology has been less extensively studied using neuroimaging techniques than any other aspect of language. The perspective that phonology may not be as crucial in defining human language when compared to non-human forms of communication as other aspects of language, such as semantics or, particularly, syntax (Hauser et al., 2002), has probably biased the interests of the authors apart from this structure. However, human language is primarily an auditory-verbal process which, in turn, implies cerebral specializations at this level. On one hand, phonological aspects seem to be processed into specialized brain areas located within and around primary auditory ones (Brodmann Areas –BA- 41/42, Heschl's gyrus). In this regard, there is evidence of the use of extensive regions within the superior temporal gyrus largely specialized for these functions. These regions are mostly bilateral, though some degree of left-lateralization also emerges. Accordingly, a very first step in the processing of phonological information seems to be localized very dorsally in the temporal lobe, in Heschl's gyrus, where phonology would be already distinguished from non-linguistic sounds (Price, 2000). Thereafter, an antero-lateral functional gradient starting in Heschl's gyrus and progressing toward the temporal pole seems involved in further integrating heard sounds, identifying and distinguishing concrete phonological sounds such as familiar vowels against single formants (Leff et al., 2009). Additional data complete this picture by adding more ventral -middle temporal gyrus- and posterior areas of the left temporal lobe as involved as well in these functions (Specht et al., 2009).

An additional specialization for auditory language processing refers to whole words. This is known as "word-form" analysis, which means that, rather than the processing of single phonemes or longer auditory segments, what is processed and identified at this level is the overall specific sound of an entire word; a holistic analysis. There seem to be specialized cortical regions for the integration of phonological sounds into these larger and unitary sound chains, these regions corresponding to auditory association areas in the left hemisphere. A possible candidate for this process seems to be Wernicke's area. Its location next to primary auditory areas would favor such specialization. Wernicke's area is normally located in the posterior part of BA 22 within the superior temporal gyrus and sulcus (Wise et al., 2001). There are other alternatives for the location of Wernicke's area, however. Some of them spread the posterior part of BA 22 to also cover parts of BA 39 and 40 in the parietal lobe (Mesulam, 1998), whereas others locate Wernicke's area at the unimodal auditory association areas in the superior temporal gyrus just anterior to the primary auditory cortex (Démonet et al., 1992) –then covering portions that have been already mentioned here as participating in lower-level phonological analyses-. Indeed, irrespective of whether these more anterior regions can be considered or not as belonging to Wernicke's area, they have actually been claimed as the precise location for the "auditory word form area" (Cohen et al., 2004). Interestingly, however, it has been also claimed that there are no such specific cortical sites devoted to auditory word-form processing (Price et al., 2003; these authors also claim against a "visual word-form area" -see below-).

In any event, the systemic nature of the brain becomes already patent even at these very primary stages of language comprehension. In other words, the perception of speech sounds would not be limited to the temporal auditory and surrounding cortical areas, but is also significantly involving frontal cortical regions and subcortical nuclei normally implied in production (i.e., motor) processes. Accordingly, in addition to the superior temporal cortex, the most posterior portions of the left inferior frontal regions -comprising parts of Broca's

area-, the left basal ganglia, and even the (right) cerebellum, seem to play a crucial role in identifying the phonemes and sounds used during speech processing (Bozic et al., 2010). Although specific roles for these neural circuits have still to be elucidated, their involvement has been proposed as a mechanism to better process speech sounds regardless of large variability in the input, a way to internally produce those sounds as if the hearer herself were the emitter (Lieberman, 2000). Kotz and Schwartze (2010) stress that these regions, particularly the basal ganglia and the cerebellum, process timing variables crucial for speech. Overal, this is an example of the conjoint action of perceptual and motor brain systems in cognitive processing, as supported by direct evidences as the mirror neurons (Rizzolatti & Craighero, 2004).

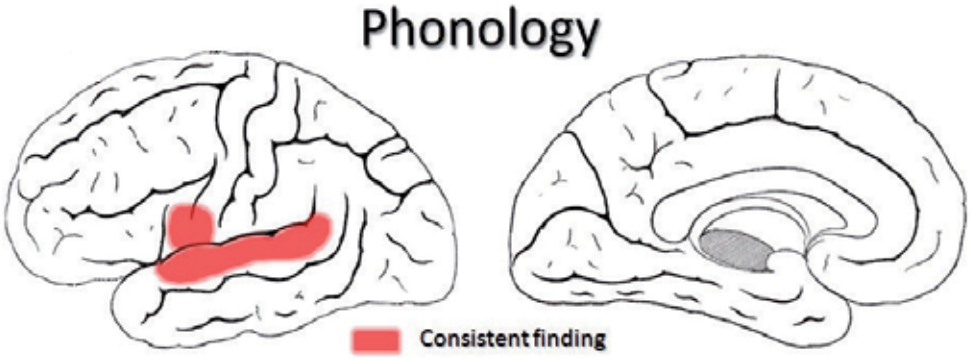

Fig. 1. Approximate locations of the phonological system

If, overall, phonology has been scarcely studied by means of MRI, the case is still worse specifically for prosody, even if this type of auditory information may be as relevant as to determining the syntactic structure of a linguistic message (Snedeker, 2008). There is evidence of the involvement of right fronto-lateral cortical areas (fronto-opercular portions in the right inferior frontal gyrus) and the right superior temporal regions in main analyses of prosody, as has been found when comparing normal speech and pseudo-speech (i.e., speech with normal prosodic intonations but devoid of known words) with degraded speech (e.g., Meyer et al., 2004). Even though, the role of the counterparts regions in the left hemisphere for the processing of prosodic information cannot be obliterated. A common circuit for language, music, and song perception comprising mid and superior temporal gyri as well as inferior and middle frontal gyri, all bilaterally, has been described (Schön et al., 2010). It is true, nonetheless, that the main implication of either hemisphere appears a function of the phonological vs. melodical nature of the input material (corresponding to left vs. right side, respectively).

3. The pictures of language

As mentioned, language can also be visual (as well as gestural), even if this is not originally the "natural" modality for human language. The human brain exhibits a high degree of flexibility and adaptability, yielding high levels of efficacy in tasks to which it is most probably not genetically prepared; reading is an outstanding example in this regard. For a long time, the place in the brain for the "visual word-from area" has been the target of strong debates, even its existence has been put into doubt (Price et al., 2003). The angular

gyrus was originally proposed as playing this role by the very first (historical) neurolinguistic models, and indeed it has appeared as such occasionally in recent functional MRI (fMRI) studies (e.g., Bookheimer et al., 1995). However, the fact that this activation is not consistent, while this region seems better characterized as semantic, has encouraged researchers to look elsewhere. A number of studies locate this functional region into Wernicke's area. But this activation is common to both visual and auditory words (Price et al., 2003) and, indeed, the most plausible functional characterization of Wernicke's area as auditory associative is difficult to conform to a visual word-form area. Some portions of the occipito-temporal cortex appear as better candidates for this function. Specifically, the most outstanding in this regard is located within the fusiform gyrus and surrounding areas -such as the lingual gyrus- in the basal temporal cortex (Dehaene et al., 2002). Interestingly, these areas would be genetically prepared for the processing of faces and objects, these functions emerging as a result of natural selection. However, by virtue of education, a portion of these regions could turn into specifically devoted to the processing of letters and visual word-forms (Dehaene, 2009).

4. The structure of language

Common to any input modality there are processes involved in understanding linguistic messages that appear of the highest interest. Syntactic processes may be among the most outstanding of these factors. As outlined above, syntax permits to determine the hierarchical structure of a sentence composed by a sequence of words (word-forms and their meanings). Studies in this regard have usually approached brain areas involved in syntactic processing using either of two procedures. On the one hand, the comparison between syntactically incorrect and correct material would enhance the activity of brain areas specialized in detecting grammatical errors. As an example, the activation during a sentence like "*the cake was eat*" is compared with its corresponding correct version. On the other hand, comparing grammatically complex sentences with simpler sentences would imply activations in areas particularly handling the complexity of syntactic structures and, hence, areas presumably involved in the hierarchical organization of the sentences. Complexity is usually increased either by embedding material within (e.g.) a main clause, rendering what is called a "recursive" structure, or by changing canonical order (usually, SVO: subject-verb-object) to a non-canonical one, as in the case of passive sentences. Examples of these situations imply comparing "*the child that my mother saw was small*" or "*the cake is being eaten by the children*", respectively, with their corresponding simpler versions (i.e., "*my mother saw a child; the child was small*", and "*the children are eating a cake*"). The case of complexity poses a problem on whether it is actually syntax what is being measured or, instead, working or short-term memory activations necessary to hold information active until the corresponding structural assignments are completed. However, it is also possible to accept that the brain areas specifically involved in working memory for syntactic structures in fact pertain to syntax processing properly, as it can be assumed that working memory for syntax implies the transient activation of circuits actually devoted to syntactic processing (e.g., Fuster, 1999; MacDonald & Christiansen, 2002).

Overall, both types of approaches to the study of human syntax have been comparable, yielding largely similar results. As one of the most consistent findings, the left inferior frontal gyrus (IFG), emerges as a central place involved in syntactic errors detection, grammatical complexity processing, and verbal working memory (e.g., Bornkessel-

Schlesewsky et al., 2009; Friederici et al., 2006; Friederici et al., 2009; Koelsch et al., 2009; Meltzer et al., 2010; Newman et al., 2009; Raettig et al., 2010; Rogalsky et al., 2008). Accordingly, the left IFG can be viewed as a main hub in the brain networks supporting syntax.

Nonetheless, IFG is a relatively extensive area, whereas syntactic rules and processes comprise a number of apparently different operations. In this regard, it seems that there are differential demands within specific portions of the left IFG as a function of the task in course. It is difficult, however, to condense the results from the different studies due to systematic inconsistencies in the criteria employed to describe their main results. In terms of Brodmann's cytoarchitectonic areas, IFG occupies, approximately -and starting from a more posterior position next to the precentral sulcus towards a more anterior one, in the left hemisphere- the most inferior portion of BA6, the whole of BA 44, the inferior half of BA 45, and BA 47 (Gray, 1918/2000; Brodmann, 1909/1994). At the same time, the IFG can be anatomically subdivided, following the same spatial sequential order as before, into the *pars opercularis*, the *pars triangularis* and the *pars orbitalis* (Gray, 1998/2000). Whereas both the anatomical and the cytoarchitectonic divisions do not match largely, some studies adopt one system but not the other, and vice versa. Several studies refine their findings by focusing on Broca's area, which certainly pertains to the left IFG. However, this is not solving the problem since there are also historical inconsistencies about what exactly are the boundaries of Broca's area. In this regard, Broca's area corresponds to BA 44 for a number of authors; for several others, BA 44, 45, and 47 should be included; for a number of other authors, the areas involved are just BA 44 and 45 (e.g., Uylings et al., 1999). Finally, in an attempt to refine anatomical exactitude when describing main results, several studies use Talairach or MNI 3D coordinates (Price, 2010). This highly precise system nonetheless obliterates the fact that fMRI is not as precise as to use these millimetrical coordinates, particularly considering the number of processing stages needed for normalization and statistical processing of the data. In addition, results in 3D coordinates usually refer to the centroid of an activated region regardless of its total size or whether its limits overlap with or surpass the anatomical or cytoarchitectonical subdivisions. In the following, we will try to minimize as far as possible these current limitations when describing the main results reported in the literature, carefully inspecting and contrasting the data reported by the different authors.

According to some reports, the most ventral part of the *pars opercularis*, roughly –but not solely- coinciding with BA 44, appears involved in verbal (syntactical) working memory (Friederici et al., 2006; Price, 2010; Rogalsky et al., 2008). In line with this might also be interpreted different results for this area as those by Bornkessel-Schlesewsky et al. (2009) for the processing of word-order variations in sentences, or Christensen (2010) and Rodd et al. (2010) for garden-path and ambiguous sentences -in which the structure must be reanalyzed and reconstructed, or several candidate structures must be kept active during sentence processing-. This ventral part of the *pars opercularis* has further been subdivided into two depending on whether the portions belong to BA 44 or to BA 6; the former would be involved in phrase structure grammar, the latter in finite state grammar (Friedrici et al., 2006). The first type of grammar refers to the use of embedded sentences, therefore demanding more working memory than the latter, simpler (linear) structures with no nesting. Detecting grammatical errors also tap on BA 44 (e.g., Heim et al., 2010), a result consistent with a role of this area in syntactic working memory to the extent that the detection of errors also increases processing demands. Overall, all these data are in line with a syntactic working memory interpretation as a main role of BA 44 (or the anterior ventral

pars opercularis). However, if we approach working memory in the sense mentioned above – i.e., that it consists of the transient activation of circuits devoted to accomplish specific operations- then BA 44 might be better seen as containing core circuits for syntactic processing determining the hierarchical syntactic structure of a sentence. This would harmonize with the variety of different syntactic operations that have been seen to tap on this area, as outlined above. In sum, BA 44 seems a central place for syntax in the brain.

The dorsal portion of the *pars opercularis* (overlapping with the most superior part of BA 44 and a portion of BA 9) appears also involved in the processing of syntactic complexity, even when working memory is factored out (Makuuchi et al., 2009). In this regard, however, it has also been claimed that this cortical region is involved in hierarchical ordering of sequences of events regardless of whether they are linguistic or not, as it has been seen to sequence (e.g.) colored shapes or nonlinguistic visual symbols (Bahlmann et al., 2009; Tettamenti et al., 2009). Its language-specificity, therefore, appears challenged. As we will see below, this is also the case for most, if not all of the areas involved in language.

This is in fact the case of BA 44 or the ventral portion of the *pars opercularis* described earlier. Tactile imagery (Yoo et al., 2003), word and face encoding (Leube et al., 2001), object manipulation (Binkofki et al. 1999), smelling familiar odors (Ciumas et al., 2008), or music enjoyment (Koelsch et al., 2006), among several others, are tasks in which BA 44 has been seen importantly involved. Moreover, and within the frame of language, even the role of BA 44 as exclusive for syntax processing does not appear to be proved. In this regard, semantic and articulatory (phonological) processes have been seen to tap also on this area (see our previous section for phonology and the next one for semantics). Possibly, these data might be understood if we assume the proposal of a functional gradient along the whole left IFG, in which -using Brodmann's areas as reference, and from left to right- BA 47 and 45 would appear mainly involved in semantic unification, BA 45 and 44 in syntactic unification, and BA 44 and ventral BA 6 in phonological unification (Hagoort, 2007). Unification is, in the end, the main defining purpose of syntactic operations: unify or "put together", according to the hierarchical structure of the sentence, the different constituents of a sentence. As the posterior part of BA 44 has been seen involved in articulation/phonology and the anterior part in semantics, it might appear that BA 44 is relevant for both phonology and semantics; or, rather, for something in between, maybe what we properly call "syntax". It might also be the case –we are here certainly speculating- that what we call syntax is indeed an abstraction that actually relies on both phonology and semantics. As can be seen, studying language with fMRI gives rise to core questions on the very nature of human language.

In this regard, the role of BA 45, roughly coinciding with the *pars triangularis* of the IFG, might also appear ambiguous. As has been just-mentioned, it seems involved in analyzing the semantic structure of the sentence. Several studies comparing sentences containing semantic anomalies with their correct counterparts (Kuperberg et al., 2008), or sentences with and without semantic ambiguities (Davis et al., 2007), consistently report activations in BA 45. But this area also appears particularly involved in analyzing embedded structures (Shetreet et al., 2009), which can be considered as a more genuine syntactic process. In line with this, BA 45 has also been seen to support the syntactic constituent structure of the sentence, in a study in which syntactic and semantic structures were disentangled (Pallier et al., 2011). In this latter study, the activation of BA 45 in *pars triangularis* spread also to IFG *pars orbitalis*, therefore including BA 47. However, it is a consistent finding the role of BA 47 in semantic processing (e.g., Binder et al., 2009; see also our section below). In sum, and as an eclectic solution, it might be possible that the most posterior part of BA 45 is relatively

more syntactic in nature, conforming a somehow unitary system together with part of BA 44; the anterior part, in turn, would be more semantic, working together with BA 47. Overall, the above-mentioned functional gradient within the left IFG might actually be more gradual than the labels currently available to describe it (i.e., semantic, syntactic, and articulatory/phonological), which might also explain why the ventral portion of BA 6, most consistently described as an articulatory/phonological area (it actually belongs to the premotor cortex) has also been seen occasionally involved in detecting syntactic errors or analyzing syntactically ambiguous sentences (Christensen, 2010; Friederici et al., 2006). The picture can be yet more complicated when considering that even language processing at the discourse level consistently recruits large portions of the IFG, as we will see below.

Additionally, a number of studies also support the involvement of other regions apart from the IFG in syntactic processing. One of the most consistent findings in this regard is the existence of a fronto-temporal network supporting syntactic processing. Whereas the frontal pole of this network implies the left IFG, especially in and around BA 44, the temporal portion is mainly comprising the left superior temporal gyrus (STG) and superior temporal sulcus (STS), most likely excluding primary auditory areas (i.e., BA 41 and 42), and roughly corresponding to BA 22 (Christensen, 2010; Rodd et al., 2010). Interestingly, these activations may plainly include Wernicke's area (Shetreet et al., 2009), which is mainly involved in the processing of language sounds (see our previous section in this regard). In several studies, large (anterior and posterior) portions of BA 22 appear relevant in syntactic processes (Friederici, 2002; Rodd et al., 2010). In other occasions, however, it is only a small portion of BA 22 what is involved, such as the posterior portion of the STS (Pallier et al., 2011). Upper portions of the middle temporal gyrus (MTG), comprising part of BA 21, have been also reported to participate in syntactic processing (Christensen, 2010; Friederici et al., 2006; Shetreet et al., 2009). Interestingly, although the main findings are located within the left hemisphere, occasional activations in corresponding areas of the right hemisphere are also reported. Several studies also report activations in the ventral portion of the supramarginal gyrus (SMG, part of BA 40), together with the *planum temporale*, a posterior portion of BA 22 (Raettig et al., 2010), although these regions appear more consistently as rather semantic, particularly the SMG (Binder et al, 2009).

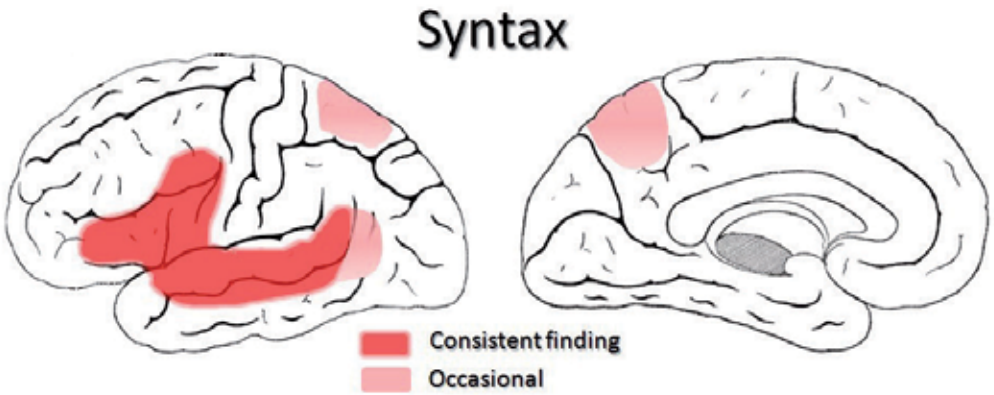

Fig. 2. Approximate locations of the syntactic system

Finally, still other brain regions have been seen also involved in syntactic processing, though less consistently. Among these, we can mention the precuneus (in the medial

parietal lobe), small portions of BA 37 (next to BA 22), superior parietal cortex (BA 7), as well as the lentiform and the caudate nuclei (e.g., Chistensen, 2010; Friederici et al., 2006; Shetreet el al., 2009).

5. The meaning of language (I)

Linguistic messages normally tell something about the world and its components (objects, persons, places, and so forth). As such, a linguistic message includes words (word-forms with their individual semantic contents or meanings) that are combined, usually through syntax, rendering a concrete description of their relationships intended to mirror a real situation or an idea. Within the brain, indeed, extensive regions of the cerebral cortex appear devoted to semantic information processing. This seemingly provides a clue on the relationships between language and other cognitive processes. But it also poses some doubts on the boundaries between what can be labeled as "linguistic" and "non-linguistic". It is also the case that "semantic" might appear as a rather vague and imprecise term, covering a large number of otherwise different processes or operations. In fact, terms as "pragmatic", "conceptual", as well as several others, often appear next to "semantic" as equivalent or corresponding to a somehow unitary system.

Actually, the meaning of words, one of the main features that the term semantic can refer to, can be just about anything in the world. In other words, human languages have words –and, then, meanings- for absolutely all (or almost all) things known so far in the world, be they real, imagined, or with a large amount of ambiguity and abstraction (e.g., Pinker, 2007). In this regard, some authors even think that the so-called "syntactic words" (i.e., complements, determiners, suffixes, and so many words or particles with a specific syntactic function) have also a meaning to be considered as plainly pertaining to the same semantic system of the brain as any other type of content word, such as nouns or verbs. In this line, it could be the case that syntactic regions reviewed above might be part of the "semantic" system, but only the part preferentially dealing with abstract structural hierarchical relationships between a number of items, be they words or whatever. Indeed, it is a plausible scenario that syntax words emerged initially as any other, less functional words during the evolution of human language (Heine & Kuteva, 2007).

This said, it should not be surprising that semantic areas have been proposed to occupy most of the cerebral cortex. Providentially, Binder et al. (2009) have recently published an extensive review of functional neuroimaging studies of semantic processing, in which not only strict inclusion criteria were applied but also advanced statistical analyses for determining the probability of a given region as belonging to the semantic system. The studies included in that review used words as stimuli, so that we can be certain that the areas suggested as supporting the semantic system are indeed areas activated by language. This note is important because, as we will see, the areas constituting the semantic system are actually and for the most part classically considered as heteromodal association areas of the neocortex, located both in frontal and posterior regions. They are therefore common to a large amount of non-linguistic processes involved in either perception or action. Additionally, areas of the limbic system involved in emotional processing are also part of the semantic system.

According to the review by Binder et al. (2009), the semantic system in the brain can be subdivided into three main widespread locations. A first one includes large portions of the posterior multimodal and heteromodal cortex, namely the angular gyrus (AG, in BA 39), the

SMG, and the MTG, including part of the temporal pole (comprising small parts of BA 38 and 29). Also in the posterior parts of the brain other areas highly involved in semantics are basal temporal areas, particularly within the fusiform and parahippocampal gyri (comprising portions of BA 20 and 37; mainly high-order visual regions, as we saw for reading). A second location of the semantic system comprises portions of the heteromodal frontal cortex, namely the upper and –especially- medial portions of BA 8 and part of BA 9. Interestingly, BA 8 contains the supplementary motor area (SMA) and has been seen involved in a variety of tasks, including motor learning and imagery (Malouin et al., 2003; Matsumura et al., 2004), executive functions and planning (Kübler et al., 2006), and even speech motor programming (de Waele et al., 2001). On the other hand, BA 9 is also involved in executive functions (e.g. Kübler et al., 2006) and, as we will see below, in discourse processing. Another frontal heteromodal association area included in the second locus of the semantic system is BA 47 in the IFG, an area that was already mentioned in our previous section on syntactic processing, its most probable function being related to semantic/pragmatic unification. Finally, the third group of areas supporting the semantic system according to Binder et al. (2009) includes the posterior cingulate/precuneus region and the ventromedial prefrontal cortex. Whereas the former has been seen to be associated with emotional processing (Maddock, 1999), it has also been related to visuospatial memory and imagery (Burgess, 2008; Epstein et al., 2007), among several other functions, including –occasionally, as we saw- syntax. Indeed, the role of this area seems rather polyvalent; later on, we will see that it is implicated in the semantic analysis of whole sentences and longer language emissions (discourses). The ventromedial prefrontal cortex, roughly corresponding to BA 11 and other BAs (such as portions of the most ventral parts of BA 10, 24, 25, and 32), comprising the rostral part of the anterior-ventral cingulate, is linked to motivation, emotion, and decision making involving reward (e.g., Ernst et al., 2004), among several other functions such as olfaction (Royet et al., 1999).

It must be remarked that all the regions outlined so far in Binder et al. (2009) as constituting the semantic system are mainly and preferentially in the left hemisphere, in consonance with the fact that they were circuits activated by words. This in turn harmonizes with the left-lateralization of other linguistic functions, such as syntax and phonetics. Overall, it seems that the semantic system activated by words largely overlaps with the system used by our brain to understand and process, as well as to interact with, the external world. In fact, this is what language crucially conveys in the very end. We have seen that words can activate association areas involved in action planning, perception, and emotions, and certainly the meaning of words ultimately refers to any of these things, or to a combination of them. However, it is also possible that the view of the semantic system sketched by Binder et al. (2009) is to some extent a restrictive one. Indeed, interactions with the external (or internal) reality imply not only heteromodal association areas, but also more primary areas. Actually, the brain areas directly supporting body movements or first stages in the perceptual processing might also be part of our semantic system. This is the idea endorsed by Pulvermüler and colleages (e.g., Pulvermüler, 2010; Pulvermüller, & Fadiga, 2010). An overview of fMRI evidences in this regard by these authors (e.g., Boulenger et al., 2009), as well as by other groups (e.g., Martin & Chao, 2001; Tomasino et al., 2007) can be summarized as supporting that words referring to concepts in which movements or actions are crucial (e.g., tools, as well as many verbs), activate cortical areas specifically devoted to directly perform those movements or actions. When the words refer to arm movements (e.g., "catch"), leg movements (e.g., "run"), or face movements (as any facial expression, like

"smile"), they activate corresponding areas for these actions within the primary motor cortex (BA 4), also largely respecting its somatotopic organization. The same is the case for words referring to specific stimulus features, or in which these features are crucial in their definition. Words such as "ellipse" or "red", or words belonging to semantic categories in which visual features prevail (like "animals"), activate visual areas specifically related to the processing of those perceptual features. Binder and colleagues, in their 2009 review, mention this type of findings, but consider them as secondary, less conspicuous and consistent than the other regions substantiating their proposal. It is possible, nonetheless, that the participation of these primary regions in the semantic system of the brain is less systematic namely because they refer to very specific actions or perceptions, so that only the linguistic material referring to these very concrete body features would activate them. This would not be the case, however, of the heteromodal and multimodal association areas, the main areas according to Binder et al. (2009) review, which by definition would be activated by any stimulus of any modality. This depiction is supported in Pulvermüller et al. (2009a).

By considering the semantic system as composed by both heteromodal and multimodal association areas as well as by primary or secondary areas of the perceptual and motor systems extends the size of the semantic system and is a very plausible scenario. Under this perspective, the semantic system would be substantiated by the cortical circuits involved in all of our interactions with the world; the semantic system would be equivalent to our whole "world knowledge" system. Part of this knowledge is concrete, but also part of it refers to abstractions and relations performed in the heteromodal and multimodal association areas. The involvement of limbic regions in the semantic system also fits with this line of reasoning, since emotions are also an important part of our world knowledge. Indeed, this depiction harmonizes well with recent theories of "embodied language" (e.g., de Vega et al., 2008), according to which language directly and straightforwardly makes use of the brain areas involved in performing or processing what is described in an utterance. Embodied language theories contrast with traditional proposals for a more "abstract" code created by language (or from which language emerges, in case of production) that can in turn be converted into the mental representation of specific perceptions and actions. Both views could complement each other, however, if both abstract and "body" codes working simultaneously and in cooperation are accepted. The former would be related to heteromodal and multimodal association areas, the latter to more primary or secondary areas. Indeed, not all that can be uttered can be visualized or executed externally. We can also add that there is a noticeable overlap between the most abstract and heteromodal portions of the semantic system -i.e., the proposed by Binder et al. (2009)- and part of the so-called "human default system", a rather bilateral network of activations in the human brain appearing when the subject is involved in mental tasks other than those linked to externally present stimuli or tasks. The fact that the human default system is involved in such a variety of mental operations as autobiographical memory, envisioning the future, theory of mind, or moral decision making, among many others (for a good review, see Buckner et al., 2008), suggests that this system can eventually apply to circumstances that can be visualized or externally performed. If we apply the same reasoning as we did above for the semantic system, the parallelisms between both systems are more apparent, as situations supported by the human default system should also involve the occasional recruitment of more primary or secondary perceptual or motor cortical areas in order to imagine specific perceptions and actions. This is a very plausible scenario (see, e.g., Kosslyn & Thompson, 2003 for fMRI evidence of primary visual areas activated in visual imagery).

The main purpose of language comprehension is nevertheless not the understanding of single words within a given utterance, but rather the specific relationships between those words. Helping to determine these relationships is the main role of syntax, which in turn contributes to elucidate the semantic structure of the sentence. The latter is a semantic frame representing the actual relationships between the different entities (objects, persons, places, and so on) mentioned in a sentence. Brain activations related to these combinatorial or propositional semantic processes are normally obtained in experiments in which grammatically correct but semantically incongruent sentences are compared with semantically congruent or plausible sentences. As an example, compare "*She spreads the warm bread with shoes*" and the same sentence ending with "*butter*" instead. In other occasions, the activations produced by normal sentences have been compared with the activations produced by sentences composed of pseudowords, or "jabberwocky" sentences, in which a syntactic structure can still be determined but -given that pseudowords have no semantic content as they are not real words-, no semantic structure can theoretically be extracted. As an example, here is a portion of the poem by Lewis Carroll that gave birth to the name of this type of paradigm: "*Twas brillig, and the slithy toves / Did gyre and gimble in the wabe; / All mimsy were the borogoves, /And the mome raths outgrabe*". Overall, the activations observed with these experimental paradigms tap on several places within the "more general" or heteromodal semantic system for words commented so far. Two of these places locate within the parieto-temporal junction and the temporal pole (Mashal et al., 2009; Obleser & Kotz, 2010; Pallier et al., 2011), that is, two portions within the posterior heteromodal association areas of the system used for words. Another portion of the semantic brain system for words that seems also importantly involved in the combination of semantic information is the posterior cingulate/precuneus (Mashal et al., 2009; Whitney et al., 2009). Finally, an area within the IFG belonging to the frontal heteromodal association areas of the semantic system -BA 47, eventually spreading to BA 45-, has also been seen implied in combinatorial semantic operations (reviewed in Hagoort, 2007). As can be seen, most of these loci have been implied in the processing of the semantic content of words; a few of them (BA 45, posterior cingulate/precuneus) have been occasionally observed in syntactic operations as well (particularly BA 45; see above). Interestingly, several of these regions also play a relevant role in discourse processing, as we will see in the next section.

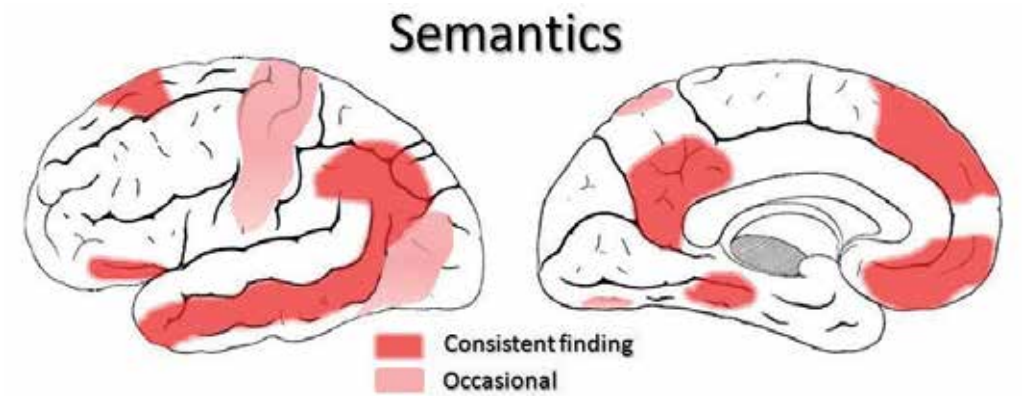

Fig. 3. Approximate locations of the semantic system

6. The meaning of language (II)

Human language normally extends beyond sentences, most often consisting of longer messages usually known as discourses, narratives, stories, or –simply- texts. The global or unitary comprehension of a group of sentences would involve even more associative areas than simpler levels, namely because additional processes, known to demand higher levels of association, play a relevant role in discourse comprehension. Among these additional processes, the most outstanding appear to be the achievement of *inferences* and *pragmatic interpretations*, obtained by using world-knowledge and discourse context constantly in interaction. Finally, according to the so-called "situational models" (Zwaan, 2004), it is also assumed that reading or hearing long linguistic messages or discourses conveys, when feasible, the recreation of the situation depicted in the text, normally by simulating or recreating the events described in the story. Results from the fMRI studies reported so far in this topic seem to support this overall depiction.

Experiments studying text comprehension have been very varied in their designs and procedures. In principle, whenever we have two or more sentences, the same processes presumably involved in text comprehension should be already in play, as linking two sentences would be sufficient to activate inferential and interpretive processes. Accordingly, if two sentences, as "*The telephone was ringing*" and "*My brother wanted to tell me the news*", are uttered consecutively, one understands that the second is an idea related to the first sentence; in this case, that it is my brother who was calling, and that the reason for his call was that my brother wanted to tell me something of interest. Without these inferences, performed easily and automatically and based on our world-knowledge, the two sentences would be just two senseless isolated emissions. A good example of the study of the coherence we normally achieve during text comprehension is extracted from Ferstl and von Cramon (2001), where coherence was compared with cohesion, that is, the linkage of two sentences by means of a cohesive element as "*therefore*" in the following pair of sentences: "*Mary's exam was about to start. Therefore, her palms were sweaty*". These two sentences are cohesive, due to the presence of a linking element, as well as coherent, since our world-knowledge tells us that sweaty palms are a possible consequence of being nervous, the latter being a normal consequence of an examination situation. In fact, both sentences are coherent even without the cohesive element. Now read the following pair of sentences: "*Mary's exam was about to start. Therefore, the pizza arrived*". Even with the cohesive element, these two sentences are not coherent; our knowledge of the world cannot help us to infer a possible logical link between these two utterances.

In other occasions, discourse processing has been studied using loosely structured passages rendered coherent only by providing a title or an illustration. As a good example, consider a portion of a classical ambiguous paragraph from Bransford and Johnson (1972): "*A newspaper is better than a magazine. The seashore is a better place than the street. At first it is better to run than to walk but walking is fine after a while. You may have to try several times, it takes skill but it's easy to learn. Even young children can enjoy it. Once successful there are very few complications. Birds seldom get too close. […]*". This paragraph is noticeably better understood -and remembered- when preceded by the title: "*Making and flying a kite*". Comparing the processing of this type of paragraphs preceded by the title and the same paragraphs without the title would yield, for the former, the activation of brain areas supplying global coherence and, for the latter, the attempts to attain it (Martín-Loeches et al., 2008).

Two recent reviews by Evelyn C. Ferstl and colleagues (Ferstl, 2010; Ferstl et al., 2008) -the first one using similar statistical methods as in Binder et al. (2009) for the semantic system-

provide an unbeatable account of the topic. Overall, and interestingly, the main results suggest that most of the areas supporting discourse comprehension overlap with the semantic system activated by words (see above), also comprising regions used as well for other more basic linguistic processes. There also exist brain regions specific for discourse processing, a remarkable finding that will be discussed later in detail.

The reviews by Ferstl et al. (2008) and Ferstl (2010) outline a number of results that could –in our view- be grouped into four principal regions. One of the most consistent findings appears to involve the anterior temporal lobes, bilaterally, particularly the temporal poles. As mentioned, this is part of the semantic system for words proposed by Binder et al., (2009), and we have seen it is also involved when sentences have to be interpreted semantically. Nonetheless, a remarkable particularity is that in discourse processing both anterior temporal poles, bilaterally, are involved whereas semantics for words was rather left-lateralized. Another distinctiveness is that the area of the anterior temporal poles involved in discourse processing is larger than the portion used for words, the former spreading ventrally and dorsally covering the whole temporal poles. Accordingly, the anterior temporal lobes, and especially the temporal poles, seem crucial for understanding the meaning of words, sentences, and paragraphs, seemingly constituting a main hub of the semantic system used in language processing. Fertl et al. (2008) propose that a main role for this area in *propositionalization*, the process required for combining words into semantically based content units. Together with the temporal poles, discourses seem also to consistently activate other region that is also crucial for word and sentence semantics: the parieto-temporal junction. This is yet a portion of the posterior heteromodal association cortex already clustered with the temporal poles when we reviewed sentence semantics.

A second group of results would comprise the left IFG and STS/STG, spreading to part of the MTG. Ferstl et al. (2008) suggest that at least part of this "fronto-temporal network", substantiate language perception, integration, and interpretation. On the other hand, these activations are not present in a number of studies, being therefore less consistent than other areas contributing to discourse processing. As we have seen earlier, the left IFG seems to exhibit a functional gradient in language processing where syntax appears to be central but phonological and semantic processes are also importantly present; additionally, the role of the STG in syntax analysis is also a consistent finding, but again phonological processes are also observed in this region. Accordingly, even if activated during discourse processing, the role of these perisylvian areas might be not so specific of longer texts. However, this issue may still need further clarification. Recent studies of very slow brain blood flow fluctuations (around 0.1 Hz) have shown that regions in the posterior part of the left superior temporal sulcus/gyrus are consistently correlated at these frequencies with left IFG, particularly within BA 44 or the *pars opercularis* (Lohman et al., 2010). This type of fluctuations might thus reflect processes clearly beyond sentences, in the range of discourse or very large language emissions. The role of these very slow fluctuations for overall language comprehension is still unknown, but the fact that this fronto-temporal network participates, to a larger or a lesser degree, in apparently all the language processes studied so far (even if mainly in phonological and syntactic) emerges as a revealing cue to better understand human language and its possible evolutionary origins.

A third group of findings outlined in Ferstl et al. (2008) and Ferstl (2010) reviews relates to mid-parietal areas, namely the posterior cingulate/precuneus. Acccordingly, apart from participating in syntactic analysis (though very occasionally) and semantics of words and sentences, this region appears of relevance for discourse processing. Indeed, this is a very consistent finding.

The fourth and last region involved in discourse processing comprises the fronto-medial prefrontal cortex (dorso-medial and ventromedial prefrontal cortex), including large portions of the medial side of BAs 8, 9, 10, and 11. To some degree, all of these areas have been mentioned before as mainly implied in the semantic analysis of words. Even though, this grouping here is somewhat different. The main divergence is that the system comprising these areas for discourse processing complements with substantial additions of neural tissue. One addition is the involvement of the entire BA 10, including not only the medial parts, but also the lateral parts -even spreading to BA 46-, which was not the case in word semantics. The other addition conveys the whole anterior cingulate gyrus (in semantics for words, only a very small ventral anterior portion of this gyrus appeared involved). The involvement of these additional portions in discourse processing may convey important consequences. First, BA 10 is the largest cytoarchitectonic area in the human brain, having increased its size substantially during human evolution, as is the case for its connections (Semendeferi et al., 2001). Second, most of these connections seem to affect the anterior cingulate particularly (Allman et al., 2002), which is another milestone in human brain evolution. In fact, the anterior cingulate is so peculiar in the human brain that it is the main structure containing a special type of neurons, the spindle or Von Economo cells. Only the great apes within the primate order posses this type of neurons presumably related with complex social behaviour, humans exhibiting a disproportionate larger number of them (Allman et al., 2011). Third, BA 10 has recently revealed as the single region showing a significant effect unique to *g*, the psychometric construct of *general intelligence* (Gläscher et al., 2010). Consequently, although this is a group of areas directly involved in language processing, its language-specificity does not appear evident.

The same appears to be the case of the posterior cingulate/precuneus region, the third group of findings involved in discourse processing. The concrete role of the posterior cingulate/precuneus has yet to be elucidated. This region participates in many linguistic processes, but also in a number of other non-linguistic operations. As mentioned earlier, it appears a certainly polyvalent region, involved in emotion, memory, and imagery; it also belongs to the human default system, and it is one of the very few regions connected reciprocally with most other cortical regions. Indeed, this part of the brain is one of the main hubs of the "human core system", the anatomical counterpart of the human default system (Chudek et al., 2008). On the other hand, the anterior medial regions also involved in discourse processing are again largely overlapping with corresponding portions of the human default system. This outstanding overlap between brain systems for word semantics and, particularly, discourse processing and the human default system has been already raised by Binder et al. (2009) and Speer et al. (2009). Ferstl et al. (2008) and Ferstl (2010) focused on the similarities of the discourse-processing system and the system supporting theory of mind. However, considering that the circuits for theory of mind and the human default system have been seen to be largely equivalent (e.g. Buckner et al., 2008), Ferstl and colleagues' suggestion could surely be reworded to imply the default system. Overall, the human default system appears to be such a general and abstract-coded system that it can apply to a considerable number of situations and circunstances, including word semantics and discourse processing in language. Eventually, the recruitment of more primary and secondary perceptual or motor areas would also be necessary in order to visualize or imagine specific perceptions, actions, or any type of situations outlined in a text.

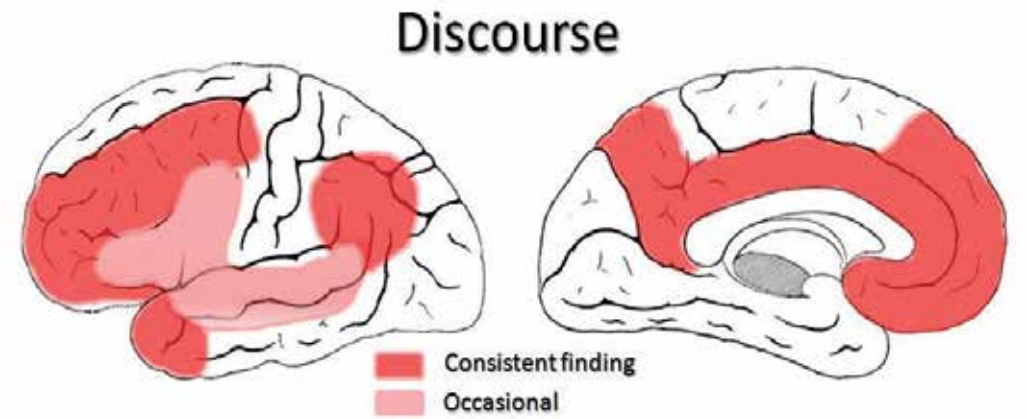

Fig. 4. Approximate locations of the system to process discourse

7. All together

Recent developments in brain imaging techniques include brain *tractography* with MRI, which has been promptly used to study human language. Brain tactography can be achieved through *diffusion tensor* and *diffusion spectrum* techniques. The main difference between the two of them depends on the deterministic vs. probabilistic approaches used to analyze the movement of water molecules within the main tracts substantiating cortico-cortical connections (de Schotten et al., 2011). It must be noted here, however, that the novelty and the relative scarcity of studies approaching language with this technique may explain certain inconsistencies between studies (for an extensive review, see Friederici, 2009).

Although it is well known after Karl Wernicke, the relevance for human language of the *arquate fasciculus* (AF) connecting Broca's and Wernicke's areas appears largely strengthened by tractographic techniques. The data also stress the relevance for language processing of other fascicles connecting anterior and posterior brain areas. A detailed description of all these connections is also emerging.

One of the first studies applying tractography to approach language was developed by Catani et al. (2005). These authors reported a direct strong connection between Broca's and Wernicke's areas through the FA, but given the fact that the areas actually connected covered a wider territory than the classical Broca's and Wernicke's areas (though, as shown earlier, the precise limits for these two areas may vary depending on the author), Catani and colleagues suggested to call them Broca's and Wernicke's *territories*, respectively. Their results also revealed the existence of two additional but indirect pathways connecting Broca's and Wernicke's territories. One would run laterally, consisting of an anterior segment connecting Broca's territory and the inferior parietal cortex. The other would be a posterior segment connecting the inferior parietal cortex with Wernicke's territory. Given the apparent relevance of these two indirect segments, and the fact that the inferior parietal cortex appears the main meeting point for these indirect connections, Catani et al. (2005) suggested to call this region the *Geschwind's territory*, in the memory of Norman Geschwind, who already proposed a relevant role of the inferior parietal cortex in language. This region largely overlaps with semantic areas involved in word and discourse processing, as we have seen.

The AF seems to have evolved substantially in the human brain from tiny tracts connecting the IFG with the posterior part of BA 22 and the inferior parietal regions, already present in the macaque brain. These connections appear more robust and abundant in the chimpanzee, thereafter reaching the plainest robustness of the human brain (Rilling et al., 2008). Actually, one of the main differences between the human and the chimpanzee brains in this regard is the notable expansion of the posterior ramifications of the AF, which spread not only to involve Wernicke's area and surrounding parietal regions, but also posterior portions of the MTG. The development of these connections, occurring particularly and noticeably within the left hemisphere, seem to have played a critical role in the evolution of human language.

Interestingly, two other tracts connecting anterior and posterior regions seem relevant in language processing. One is the superior longitudinal fasciculus (SLF), connecting Broca's area (particularly, BA 44) with the posterior temporal lobe, namely in the STG and the MTG and also involving portions of BA 40. As this tract runs parallel to the AF, several authors (e.g., Rilling et al., 2008) consider both as representing together a functional unit called the *dorsal stream*. The other connection is more primitive; part of it is actually the most developed fronto-temporal connection in the macaque brain and conveys the ventral portion of the extreme capsule and the uncinate fasciculus. Through these connections, the IFG is connected with the anterior and posterior STG (Frey et al., 2008; Rilling et al., 2008), and it is indeed possible that at least part of this *ventral stream* is preferentially used in simpler grammar such as finite-state, relatively accessible to other non-human primates (Friederici et al., 2006).

Finally, there are evidences for an additional number of connections importantly involved in language, most of them located locally within the IFG and the STG (Friederici, 2009).

8. Conclusions

The moment arrives to summarize and interpret the major milestones that could be elucidated from the preceding exposition. In the following, we will also express a number of reflections on human language using brain function as a main perspective.

A first and relatively robust conclusion that can be extracted so far is that the human brain contains at least two major "centers of gravity", or main hubs in the networks devoted to language processing. These foci are, on the one hand, the left inferior frontal gyrus (IFG) and, on the other, the left superior temporal gyrus (STG), the latter probably spreading to the superior temporal sulcus (STS) and posterior portions of the middle temporal gyrus (MTG) as well as to some parts of the inferior parietal cortex. Both foci are highly and densely interconnected by means of several tracts, the most outstanding one being the arquate fasciculus (AF). Most of the primary functions and processes involving these foci are seemingly phonological/articulatory and syntactic in nature. These two main hubs are located in perisylvian areas and appear critical for human language. Actually, the main loci of the cerebral lesions yielding core symptoms highly specific of language are the perisylvian areas; the most conspicuous aphasias are usually the consequence of lesions affecting either these regions or the AF (e.g., LaPointe, 2011).

If the depiction in the preceding paragraph can be taken as relatively robust, the same is not the case when we attempt to subdivide each hub (IFG and STG). An approximate

depiction seems that as we move from more posterior/dorsal regions to more anterior/ventral in the left IFG, a gradient of activations can be found to be specifically involved (in this order) in phonology/articulation, syntax, and semantics. A similar gradient could be found in the STG when moving from the primary auditory association areas in or around Hesch's gyrus, spreading widely to both anterior and posterior regions in the STG, probably covering also parts of the inferior parietal cortex. In the latter case, the gradient seems to cover, following this order, phonology/articulation and syntax. If we want to expand these functions to semantic processes, then STS and at least several portions of the MTG should be included.

From there, the system spreads to notably many other brain regions, comprising, posteriorly, large portions of the whole temporal lobes, including the temporal poles and part of the basal regions, as well as significant portions of the parietal cortex. Frontally, the system spreads to more anterior regions, including large extensions of the prefrontal cortex; among them, an area showing the most substantial increase in size in humans when compared to other primates and importantly involved in general intelligence. Significant medial regions, both in the prefrontal cortex and in the parietal cortex, are also included in this system. This *extended language network* (using an expression coined by Ferstl et al., 2008) largely overlaps with the *human default system*, a bilateral network in the human brain active when we are involved in "internal" mental tasks. If the linguistic message implies the visualization or representation of a given situation, then the corresponding primary or secondary areas of the neocortex can be activated, either motor or perceptual.

The system can therefore be viewed as a continuous flux of information spreading from perisylvian areas toward multiple, distant areas. In turn, it also seems that the limits between linguistic and non-linguistic processes within this system appear blurred. An overall rule seems to be that the closer we move toward the sylvian fissure, the more specifically linguistic the process is. But even in this case (as we have seen), these regions are not exclusively linguistic.

Finally, that the flux of information spreads from perisylvian areas toward extensive regions of the cerebral cortex (actually, nearly all portions of the cortex appear susceptible of being involved) does not necessarily mean that this spreading strictly follows a temporal (sequential) order. Actually, brain networks continuously fire at different frequencies (e.g., Buzsáki, 2006), and it is plausible that information fluxes continuously in a reciprocal way and almost simultaneously between perysilvian and more distant areas. This would be a possible underlying mechanism explaining the large number of mutual influences from one structural layer of language (phonology, syntax, and semantics) to each other, as reported in the literature (e.g., Pulvermüller et al., 2009b). Indeed, considering that there are about 10.000 connections per neuron in the cerebral cortex, firing up to 1.000 times per second and therefore performing a comparable number of calculations (Previc, 2009), a parallel or at least cascade mode of operation of the whole (extended) language network emerges as a very plausible picture. On the other hand, the centrality of auditory/verbal (i.e., phonological/articulatory) information in human language would be consistent with the position of the two main hubs involved in language processing and the direction of the information flux spreading from them as primary receptors of language information to widespread areas, even if the overall processes largely unfold in parallel.

9. Acknowledgements

The authors are funded by grant PSI2010-19619 from Ministerio de Ciencia e Innovacion, Spain (MICINN).

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5

Neuro-Anatomical Overlap Between Language and Memory Functions in the Human Brain

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1. Introduction

In the nineteenth century, two studies in aphasiology comprise a turning point for research of brain-language relationships: Broca, 1861 and Wernicke, 1874. Based on these two studies, it was claimed that Broca's area (i.e., the pars triangularis and pars opercularis of the left inferior frontal gyrus) and Wernicke's area (i.e., the posterior part of the left superior/middle temporal gyrus, but in some situations including a part of the inferior parietal lobule) were involved in language production and comprehension, respectively (Geschwind, 1970). Recently, due to the development of functional brain imaging techniques (e.g., PET and fMRI), normal brains have been measured to examine the neuro-cognitive architecture of language processing. In particular, both Broca's and Wernicke's areas have been shown to be responsible for several language functions, such as single word processing and sentence processing (Fig. 1).

However, these two important regions are also activated for working memory-related processes, at least, including executive functions and short term memory processes of linguistic information, and the processes of storage and access to long term memory of linguistic information. This memory system could be assumed essential for language comprehension. For example, in order to comprehend a word, we have to first identify a series of sounds or letters as a certain word and to access its semantic information from long term memory. For sentence comprehension, we have to tentatively memorize several words comprising the sentence to compute the syntactic and semantic structure of the sentence. For example, it is clear that if we do not tentatively memorize words comprising the sentence, we cannot comprehend the sentence, since we have to compute the syntactic/semantic information of the sentence by using these words. Hence, in order to understand a language expression, we need the involvement of both the short and long term memory systems. In previous studies, there were essentially two types of standpoints regarding the involvement of the memory system in language comprehension. The first is that of the „specialist", who assumes that the syntactic processing system of the language processing system exists in our brain and is independent from other congnitive functions. The second is that of the „generalist", who assumes that the syntactic processing system has neural substrates in common with other cognitive functions, mainly the working memory system.

In this chapter, recent neuroimaging studies of the neuro-cognitive architecture of single word and sentence processing will be briefly reviewed and the relationships between language and memory in the human brain will be discussed in the context of functional neuroimaging evidence.

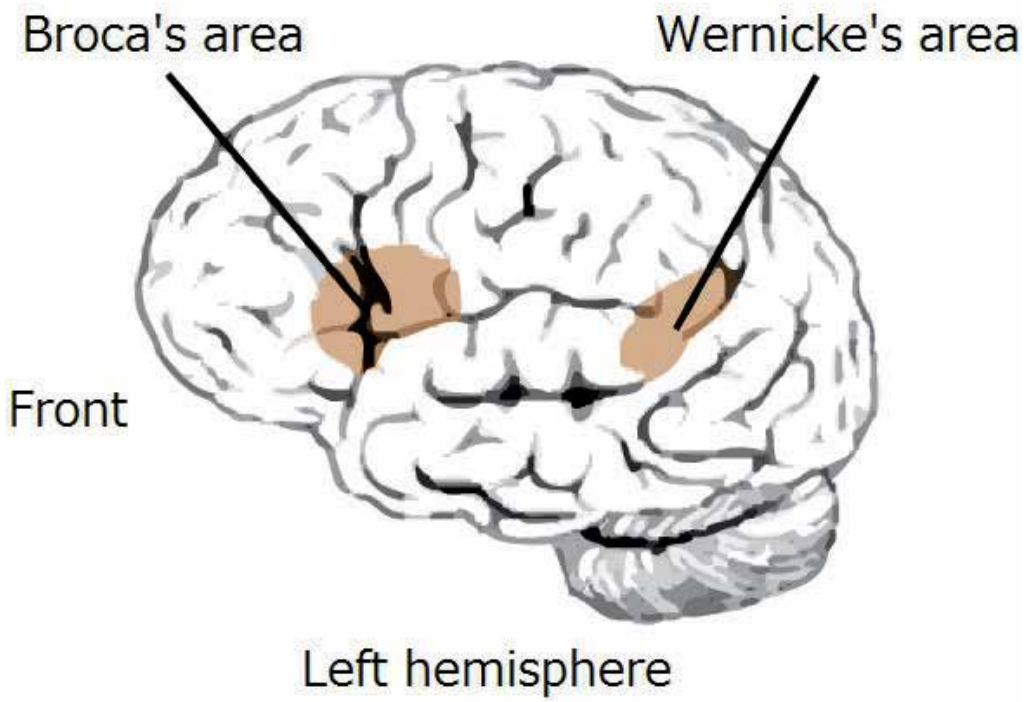


Fig. 1. Broca's area and Wernicke's area.

2. Neural basis of language comprehension

2.1 Neural basis of single word processing

There is a wealth of evidence that auditory and visual word processing have at least partly independent neural bases, particularly in the early stages of stimulus processing. While these two processes have been reported to utilize different brain regions in the early stages of processing (i.e., modality-related processes and the processing of non-linguistic to linguistic information translation), a common word recognition system exists in the late stages of processing (i.e., phonological processing and semantic processing) (e.g., Chee et al., 1999; Booth et al., 2003). Chee et al. study used semantic concreteness judgment task, non-semantic syllable counting control task for auditory stimuli, and case size judgement control task for visual stimuli, while Booth et al. study used semantic relation judgment task and rhyming control task. Both studies reported that the left inferior frontal and middle temporal gyri were commonly activated for both auditory and visual word processing. In contrast, while visual word processing activated visual-related areas including the occipital lobe, the ventral part of inferior temporal gyrus, and the fusiform gyrus, auditory word processing activated auditory-related areas including the superior temporal gyri.

2.2 Phonological working memory involvement in single-word processing

It is known that phonological working memory is essential for processing words. It is assumed that the anterior part of the left inferior frontal gyrus (i.e., the pars triangularis of

the inferior frontal gyrus/Brodomann area 45) and the left inferior parietal region (i.e., the supramarginal gyrus) comprise the verbal working memory circuit (for a recent meta-analysis see Vigneau et al., 2006). The former area is thought to be involved in articulatory rehearsal and the latter in phonological storage (e.g., Poldrack et al., 1999; Warburton et al., 1996; McGuire et al., 1996; Paulesu et al., 2000; Jessen et al., 1999; Zattore et al., 1996; Price et al., 1996). These two areas have often been reported to be active during single word processing (e.g., Hautzel et al., 2002; Jonides et al., 1998; Rypma et al., 1999; Cohen et al., 1997). The neuroimaging results are compatible with the working memory theory proposed by Baddeley, since the correlation between the sub-functions and locations of the involved brain regions reported in these neuroimaging studies is in line with the assumption of this model (e.g., Baddeley, 2003).

2.3 Lexico-semantic processing

The left inferior frontal region, the left lateral and ventral middle/inferior temporal regions, and the left inferior parietal region are activated during semantic processing tasks. It is still unclear whether the left inferior frontal region is actived by single word semantic processing per se. Demb et al. (1995) have reported that brain activity in this region is greater for more difficult semantic processing tasks than for corresponding less difficult semantic processing tasks. Similarly, the left inferior frontal region was modulated by the frequency of words (Fiebach et al., 2002). It is common knowledge that low frequency words are more difficult to process than high frequency ones. Hence, in single word semantic processing, there exists the possibility that modulation of the left inferior frontal region by word frequency is explained by access to lexico-semantic information stored in long term memory. In contrast, it has been claimed that only the orbital part of the left inferior frontal gyrus is associated with the processing of semantic information retrieval. Several meta-analysis results in particular have supported this claim (Fiez, 1997; Bookheimer, 2002; Binder et al., 2009). A meta-analysis (Vigneau et al., 2006) has also supported the report that the left parietal lobe contributes to semantic processing regardless of the difference between pictures and words (Vandenberghe et al., 1996).

While the temporal lobe plays a role in storing long term memory, the role of the left posterior part of superior/middle temporal gyri is still unclear. As evidence, most neuroimaging studies using comparisons between real word and pseudoword comprehension have reported that this region is more active for real word comprehension than for pseudoword comprehension (e.g., Pugh et al., 1996; Price et al., 1997; Friederici et al., 2000; Booth et al., 2002; Fiebach et al., 2002; Perani et al., 1999; Yokoyama et al., 2006b, and others). In contrast, Fiebach et al. (2002) showed that the left inferior frontal region is modulated by word frequency while the left posterior part of the middle temporal gyrus is not. Hence, at least the role of the left posterior part of the middle (and/or superior) temporal gyrus differs from that of the left inferior frontal region in lexico-semantic processing.

It has been made clear that the left inferior temporal region contributes to semantic processing. The inferior temporal region is commonly known to be involved in the storage or the long term memory of word information. Lesion studies have reported that damage to the temporal lobe cause category-related deficits (Kapur et al., 1994; Gitelman et al., 2001; Lambon Ralph et al., 2007; Noppeney et al., 2007; Warrington, 1975; Hodges et al., 1992, 1995; Mummery et al., 2000). Patients with anterior temporal damage show more difficulty processing the concept of living things than that of artifacts, while patients with posterior

temporal and parietal damage show the opposite pattern (Warrington & Shallice, 1984; Warrington & McCarthy, 1987; Forde & Humphreys, 1999; Gainotti, 2000; Lambon Ralph et al., 2007; Warrington & McCarthy, 1987, 1994; Hillis & Caramazza, 1991). Functional brain imaging studies have replicated such results from lesion studies (Cappa et al., 1998; Moore & Price, 1999; Perani et al., 1999; Grossman et al., 2002; Kable et al., 2002; Tyler et al., 2003; Davis et al., 2004; Kable et al., 2005).

2.4 The role of sensorimotor areas on language comprehension

It has recently been reported that sensorimotor areas are active during language comprehension. Even in language or picture comprehension without sensorimotor input, sensorimotor areas are active (Pulvermuller, 1999; Malach et al., 2002; Gainotti, 2004; Kable et al., 2002; Grossmann et al., 2002; Hauk et al., 2004; Pulvermuller et al., 2005; Tettamanti et al., 2005; Kemmerer et al., 2008; Desai et al., 2009; Hwang et al., 2009). Hauk et al. (2004) reported that the silent reading of action words related to face, arm, and leg movements activates the motor areas related to the movement of the tongue, fingers, and feet. Such sensorimotor activation has also been found during sentence listening stimuli describing hand movements and visual events (Desai et al., 2010). According to sensorimotor theories, sensorimotor areas play a role in category-related long term memory through the encoding process of sensorimotor experiences (e.g., Martin, 2007). Hence, it has been assumed that concepts are wholly or partially organized by sensorimotor experience (Barsalou et al., 2003; Gallese & Lakoff, 2005; Pulvermmuller, 1999).

2.5 Grammatical category

Regarding grammatical category, the neural dissociation between nouns and verbs in the brain has been investigated by neuroimaging techniques. However, there exists some discrepancy at this time. In lesion studies, it has been reported that nouns and verbs are distinctly processed in the human brain (e.g., Bates et al., 1991; Miceli et al., 1988; Shapiro & Caramazza, 2003). In contrast, in neuroimaging studies, while several studies reported that different brain activations exist between noun and verb processing (Perani et al., 1999; Tyler et al., 2004; Yokoyama et al., 2006b), others find no difference between them (Tyler et al., 2001; Li et al., 2004). Based on the reported findings, several possibilities are proposed at this time. One possibility is that a cross-linguistic difference influences such discrepancy as the reported neuroimaging studies used different languages as stimuli (Yokoyama et al., 2006b). Still, despite the discrepancy among languages, the reported brain activations were located in the left inferior frontal gyrus and posterior superior/middle temporal gyrus. Hence, at least the word information related to grammatical category information, such as nouns and verbs, and is consistent with the hypothesis that long term memory of word information is stored in the temporal lobe.

2.6 Morphological processing of words

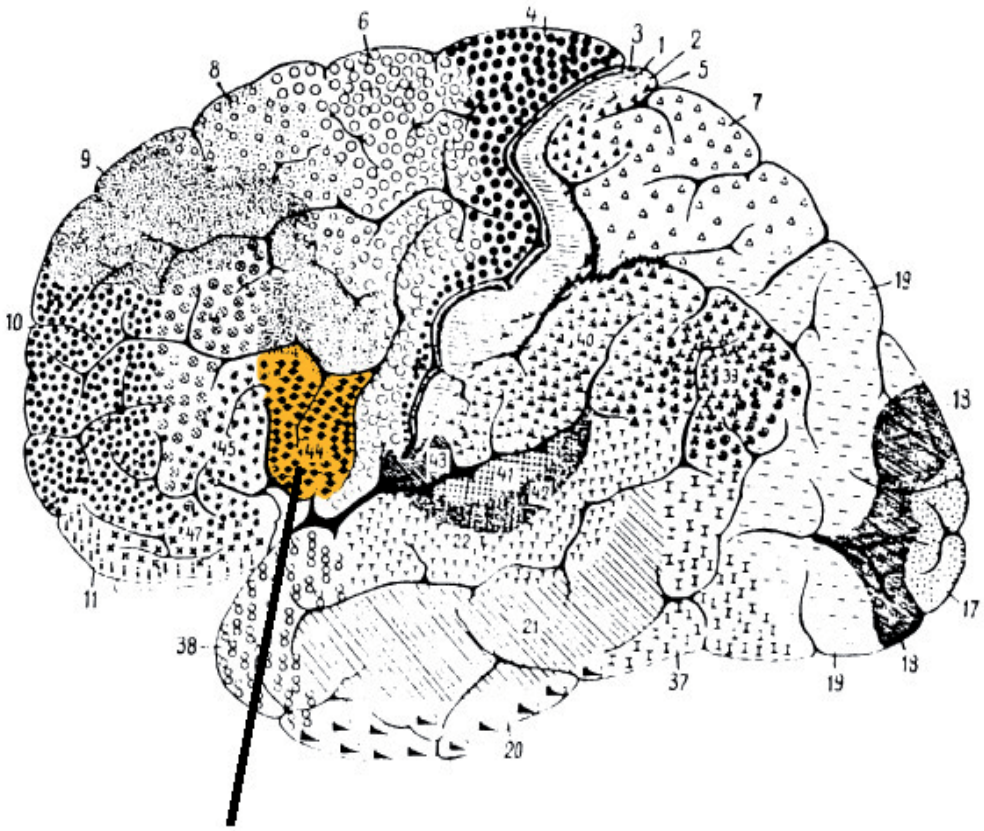
Regarding the morphological processing of words, one plausible hypothesis exists, namely that of „rule and memory“ (Pinker, 1999; Ullman, 2001; 2004). However, actual neuroimaging results have not completely support this hypothesis. In this hypothesis, while rule-based morphological processing of words (e.g., “-ed” past tense form) would be processed as a procedural memory circuit in the left inferior frontal region and basal ganglia, words with irregular morphological changes would be stored in an independent

form in the temporal lobe (Ullman, 2001; 2004). Since rule-based computation is reflected by task difficulty or task performance, this hypothesis is consistent with the above results in neuroimaging studies reporting that the left inferior frontal gyrus is related to task performance or working memory load. Also, since the temporal lobe plays a role in the storage of word information, this hypothesis is fully in line with the results of neuroimaging studies on the long term memory of semantic information, as described in section 2.3.
Additionally, Yokoyama et al. (2006b) showed partially supportive evidence that the left inferior frontal gyrus (and also the left premotor area) are active during the morphological processing of verbs. Yokoyama et al. (2009a) further showed that the developmental change of brain activity in L2 verb acquisition is observed, not in the temporal region which would be related to semantic memory, but in the inferior frontal gyrus which would be related to procedural memory. These results are in line with the above hypothesis. Also, fMRI results reported in Beretta et al. (2003) support the rule and memory hypothesis but show no clear dissociation in the brain activation between rule processing and memory processing of words. Hence, while supportive evidence at this time has been reported in several previous neuroimaging studies, it remains unclear whether the rule and computation hypothesis is correct or not.

2.7 Neural basis of sentence processing

One of the main issues regarding sentence processing in cognitive neuroscience is whether lexico-semantic and syntactic processing are dissociable or not in the human brain (e.g., Firederici et al., 2003). In particular, it is controversial what role Broca's area and the inferior frontal gyrus play in sentence processing. Some researchers have reported that the neural basis for the syntactic computation system overlaps that of workload related to working memory (e.g., Just et al., 1996), workload related to task performance (Love et al., 2006), the phonological working memory system (Rogalsky et al., 2009), the cognitive control system for resolving competition etc. (January et al., 2008; Yokoyama et al., 2009b), or other interpretation (e.g., Bornkessel et al., 2005). These overlapped brain regions basically include the left inferior frontal gyrus (Broca's area) and the posterior part of the left superior/middle temporal gyrus (Wernicke's area). The pars opercularis (Brodomann area 44) and pars triangularis (Brodomann area 45) of the inferior frontal gyrus, which are corresponding to Broca's area (Fig. 2), were commonly activated for lexico-semantic and syntactic processing in the most recent meta-analysis study (Vigneau et al., 2006).
In contrast, other studies have reported that the neural basis for syntactic processing of sentence comprehension is independent from other cognitive systems. Yet to claim such dissociation, we have to pay careful attention to other confounding factors and interpretations. For example, since the left dorsal prefrontal cortex, or middle frontal gyrus, was active for sentence comprehension independent of phonological short term memory load, this region is specific to sentence comprehension (Hashimoto & Sakai, 2002). However in Baddeley's working memory theory, the working memory system has a modality-free executive processing system and modality-dependent short term memory systems. To claim that the observed brain activation is independent from the working memory system, it is necessary to compare brain activities, not only between sentence comprehension and short term memory process, but also between sentence comprehension and the executive process. Indeed, in neuroimaging studies of executive process, the left dorsal prefrontal cortex was active (e.g., Eldreth et al., 2007). This region was close to the brain region observed in

Hashimoto and Sakai (2002). Contrastively, the left posterior part of the temporal region was specifically active for sentence reading independent of phonological short term memory (Cutting et al., 2006). However, it is unfortunate that only the sentence comprehension condition included verbs in this study and the phonological short term memory condition did not. The comprehension of verbs has been reported to activate the left posterior superior/middle temporal gyrus (Perani et al., 1999; Yokoyama et al., 2006b). Therefore, the comprehension of verbs would cause brain activation in the left posterior temporal region in the sentence comprehension condition in Cutting et al. (2006). Makuuchi et al. (2009) has reported that the pars opercularis of the inferior frontal gyrus is specifically active for syntactic computation regardless of syntactic difficulty. This study did not directly consider the executive process in working memory, similar to Hashimoto and Sakai (2002). Hence future studies are necessary to at least consider each aspect of the working memory system in order to propose that the neural substrate for sentence comprehension or its syntactic computation is independent from other cognitive processes, including the working memory system.



The pars opercularis of the inferior frontal gyrus

= Brodmann area 44

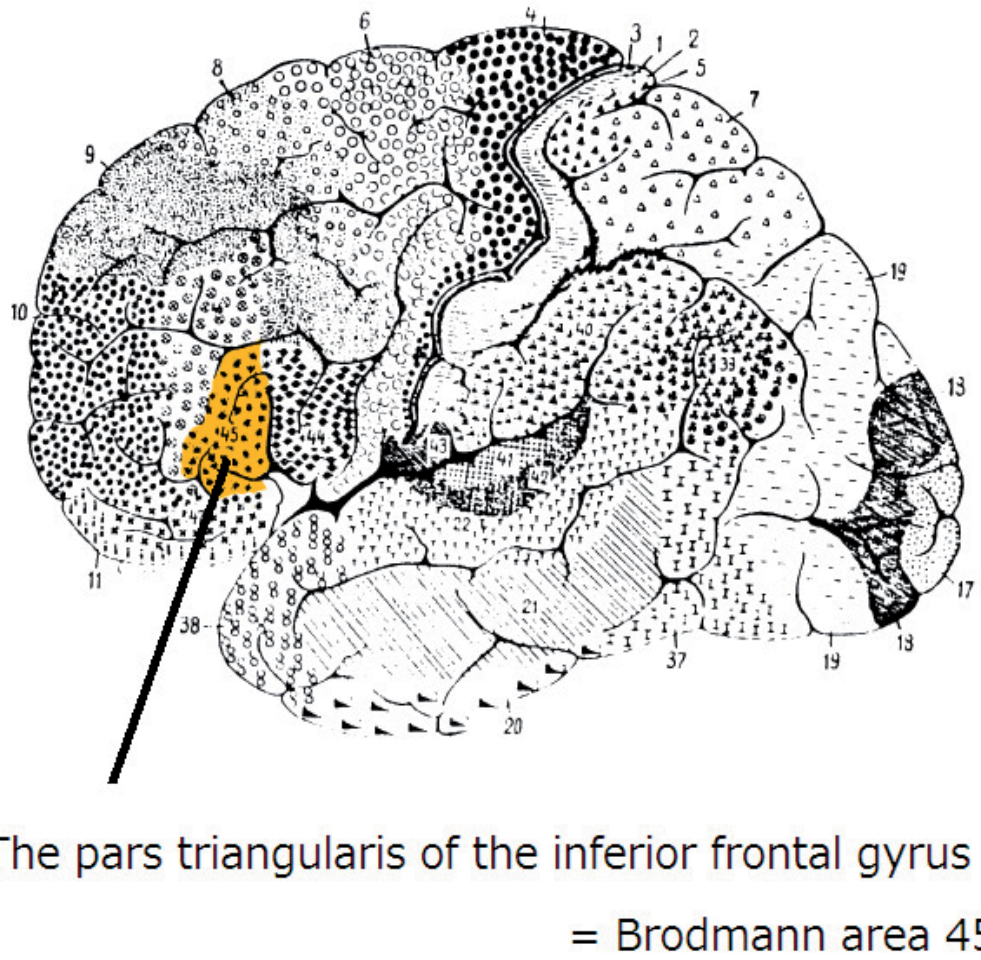


Fig. 2. The pars opercularis (Brodomann area 44) and pars triangularis (Brodomann area 45) of the inferior frontal gyrus.

Furthermore, in such previous neuroimaging studies, experimental stimuli using sentences with highly complex syntactic structures tended to be used to manipulate working memory load in the experimental design. In our daily lives we would not often use such complex sentences with long embedded clauses or relative clauses. Since such complex sentences are thought to be incomprehensible without intentional monitoring, additional intentional cognitive control or monitoring processes would affect brain activation compared to cases using simple sentences. It is necessary to test whether a hypothesis built using such complex sentences can be applicable to cases using simplex sentences or not.

3. Regional overlap between language comprehension and memory system

According to the above review, most sub-processes for language comprehension can be observed in the frontal, temporal, and parietal lobes (Fig. 3).

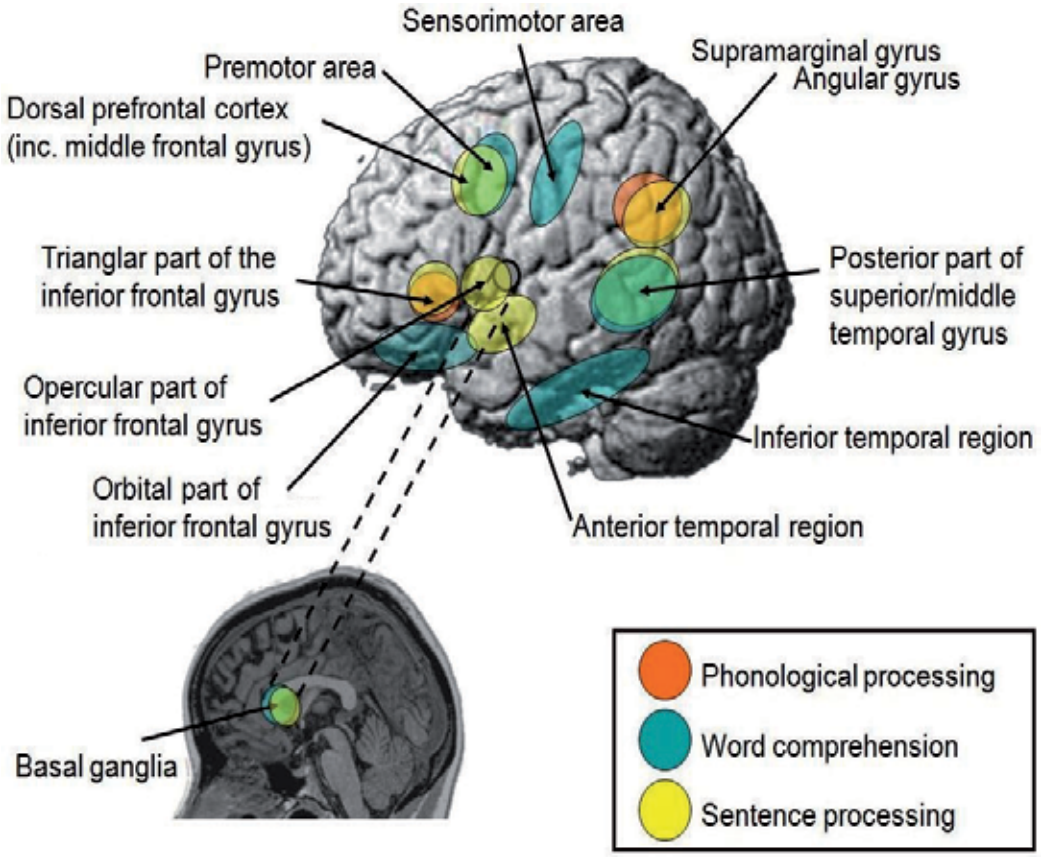


Fig. 3. Brain mapping of language function.

While different processing systems are utilized in the early stages of the language process (i.e., modality-related processes (i.e., visual and auditory input) and the processing of non-linguistic to linguistic information translation), a common word recognition system exists in the late stages of the process (i.e., phonological processing, semantic processing, and sentence processing). Findings suggest that the inferior frontal and inferior parietal regions are associated with working memory load and/or phonological processing to perform experimental tasks for single word processing. The left inferior frontal region is malso suggested to be associated with intended acts, planning, and/or cognitive control to resolve competition, which have common processes with other cognitive functions (Owen et al., 2005; January et al., 2008; Yokoyama et al., 2009b). Thought to be involved in the semantic processing of words are the orbito-frontal and parietal "retrieval" system, and the temporal "storage" system (i.e., long term memory). Also, sensorimotor areas have been shown to be activated during word and sentence comprehension tasks. Their activation may be due to sensorimotor experiences which induce the storage of long term memories in the sensorimotor areas. While sentence comprehension activates the left inferior frontal and dorsal prefrontal cortex, these activations are thought to be based on phonological working memory and executive functions. Taken together, language comprehension would be supported by the neural substrates of the working memory and

long term memory systems, as well as other cognitive function systems (e.g., intended act, planning, and cognitive control).

While the above mentioned results reported in previous studies at least indicate that a common neural substrate supports language comprehension and memory-related processes which are functionally similar, observation of the overlapped activation between other cognitive processes might not necessarily indicate a functional overlapping of these processes. Even if both language comprehension and memory processes utilize the same brain region, the roles of the brain region are thought to be different between them. Hence, the simple subtraction analysis used in previous neuroimaging studies may not be enough to resolve this issue and functional and/or effective connectivity analysis methods might be useful or necessary in future studies. Such methods would be able to test whether a commonly activated area is connected with different regions between different conditions. If this is the case, it would mean that both language comprehension and other cognitive processes utilize common neural substrates, though the roles of the commonly activated brain regions would be different between them.

4. Conclusion

Through a review of the literature we find that, since the neural basis of language comprehension overlaps that of other cognitive systems, mainly the memory system regionwise, most previous neuroimaging studies support the „generalist" view. However, it is to be noted that the overlaps of the neural substrate may not indicate a functional overlap since there exists a possibility that, while a brain region is commonly activated for both processes, the brain region plays different roles between them. In future studies, to clarify which brain region or cognitive process is common for language comprehension and other cognitive systems, and which is different between them, it will be necessary to develop a new experimental paradigm and also a new data analysis method, such as the functional/effective connectivity and multi-voxel pattern analysis. These methods should then be applied to language comprehension studies. Additionally, it will be necessary to consider the relationship between language and memory functions in language acquisition (i.e., Yokoyama et al., 2006a; 2009a), since, at this time, findings in neuroimaging studies regarding this issue are very few. Examination of whether or not and how semantic memory is related to the acquisition of lexico-semantic information, as well as whether or not and how procedural memory is responsible for proficienct gramatical processes such as morphological processing and sentence structure computation, might also be necessary.

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6

Neuronal Networks Observed with Resting State Functional Magnetic Resonance Imaging in Clinical Populations

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1. Introduction

Functional Magnetic resonance imaging (fMRI, (Ogawa et al., 1990)) in the absence of experimental tasks and behavioral responses, performed with the patient in a relaxed "resting" state (rs-fMRI), takes advantage of the neural origin of spontaneous blood-oxygen-level-dependent (BOLD) signal fluctuations (Biswal et al., 1995) to represent the rate and timing of activity synchronization across the entire brain (Damoiseaux et al., 2006; Mantini et al., 2007; van de Ven et al., 2004).

Independent component analysis (ICA) (Hyvarinen et al., 2001), when applied to whole-brain rs-fMRI, allows extracting from each individual patient data set a series of activation images describing the BOLD signal temporal correlations within and between functionally connected brain regions, forming highly reproducible neural networks called resting state networks (RSN) (Damoiseaux et al., 2006; Mantini et al., 2007). Particularly, ICA transforms individual patient rs-fMRI data sets into series of RSN maps, allowing for a voxel-based population analysis of whole-brain functional connectivity without the need to specify "a priori" the regions of interest constituting the layout of the neural network (McKeown et al., 1998; van de Ven et al., 2004).

In normal volunteers there are at least six RSNs consistently found whose neurological significance has been established according to the functional specialization and anatomical connectivity of the constituent regions (Greicius et al., 2009; van den Heuvel et al., 2009) as well as to the possible association with neuro-electrical rhythms (Mantini et al., 2007). Altogether the functional connectivity of these RSNs represents a basic physiological condition of the human resting brain (Gusnard & Raichle, 2001).

While the number, role, meaning and potential of RSNs in representing and interpreting the functional architecture of the human brain is still debated and sometimes controversial (Morcom & Fletcher, 2007), a number of voxel-based population rs-fMRI studies have uncovered significant differences between normal and clinical populations in various neurological disorders, and a particular attention has been given to cognitive decline as a

primary or secondary aspect of neurodegeneration (Bonavita et al., 2011; Cherkassky et al., 2006; Greicius et al., 2007; Greicius et al., 2004; Mohammadi et al., 2009; Nakamura et al., 2009; Rocca et al., 2010; Rombouts et al., 2005; Roosendaal et al., 2010; Sorg et al., 2007; Sorg et al., 2009; Tedeschi et al., 2010).

In this chapter we will review the physiological and technical background of resting state neural networks and the ICA methodology currently used for observing and analyzing RSNs in normal and clinical populations. The main physiological RSNs will be illustrated and discussed with special emphasis to those exhibiting functional abnormalities in neurological disorders. In addition, two clinical applications will be presented, where this methodology showed pathological changes in amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) patients in comparison to normal subjects.

2. Physiology and anatomy of the resting-state networks

In a functional connectivity study, the active human brain is conveniently represented in terms of independent functional networks of mutually interacting regions (Friston et al., 1996). Anatomically, these regions can be either distant from each other or result from a fine segregation of bigger into smaller neuronal assemblies. Functionally, two imaging voxels or regions exhibiting neural signals highly correlated in time (synchronized) are conceptually part of the same network.

When measuring the brain with fMRI over prolonged intervals of time (e. g. from two to ten minutes), it is possible to detect throughout the brain characteristic spontaneous fluctuations in the BOLD signal which occur at relatively low frequencies (<0.1 Hz) and are not of technical (artifactual) origin (Biswal et al., 1995; Damoiseaux et al., 2006; Mantini et al., 2007; Smith et al., 1999; van de Ven et al., 2004). When assessing the functional connectivity of these fluctuations across regions, a series of networks can be built, that clearly resemble the same functional networks activated during the performance of active tasks, even if the participant is not performing any specific task and is simply instructed to remain still, with eyes closed and without thinking to anything specific. In other words, under simple resting conditions, the brain is engaged in spontaneous activity which is not attributable to specific inputs or to the generation of specific output, but is intrinsically originated.

A possible link between functional connectivity and spontaneous synchrony of brain signals was already proposed in early electroencephalography (EEG) studies (French & Beaumont, 1984), suggesting that long-range EEG coherencies across cortical regions and between hemispheres could be originated from a relatively small number of interacting regions and processes (see, also, e.g., (Koenig et al., 2005; Locatelli et al., 1998)). Even if EEG and fMRI signals have very different spatial and temporal scales, it has been later demonstrated that a tight correspondence exists between the spatial distribution of low-frequency BOLD signal fluctuations and the main EEG rhythms, for at least six reproducible RSNs (Mantini et al., 2007), in line with the idea that the two modalities share a common neurophysiological origin, represented by the local field potential (LFP) (Logothetis & Pfeuffer, 2004). More specifically, it has been hypothesized that the low-frequency BOLD signal fluctuations are themselves due to low-frequency LFPs or to low frequency modulations of high-frequency LFPs (Raichle, 2010).

The most frequently and consistently reported RSNs, which are also correlated with EEG rhythms, include the default-mode network (DMN), functionally connecting the posterior and anterior cingulate cortex (PCC and ACC) and, bilaterally, the inferior parietal lobules

(Greicius et al., 2003; Raichle et al., 2001); the visual network (VIS) involving bilaterally the retinotopic occipital cortex up to the temporal-occipital junctions and middle temporal gyri (Lowe et al., 1998; Wang et al., 2008); the fronto-parietal network (FPN) including, bilaterally, the intra-parietal cortex and the superior-lateral frontal cortex (Corbetta & Shulman, 2002); the sensori-motor network (SMN) involving, bilaterally, the pre- and post-central gyri, the medial frontal gyrus, the primary and supplementary motor and the primary and secondary sensory areas (Biswal et al., 1995); the auditory network (AUD), involving, bilaterally, the superior and middle temporal cortex (Seifritz et al., 2002) and the self-referential network (SRN) involving the ventro-medial prefrontal cortex and the perigenual anterior cingulate cortex (D'Argembeau et al., 2007). The brain maps of these six typical RSNs in a normal population are exemplarily shown in figure 1 using different colors for the different networks.

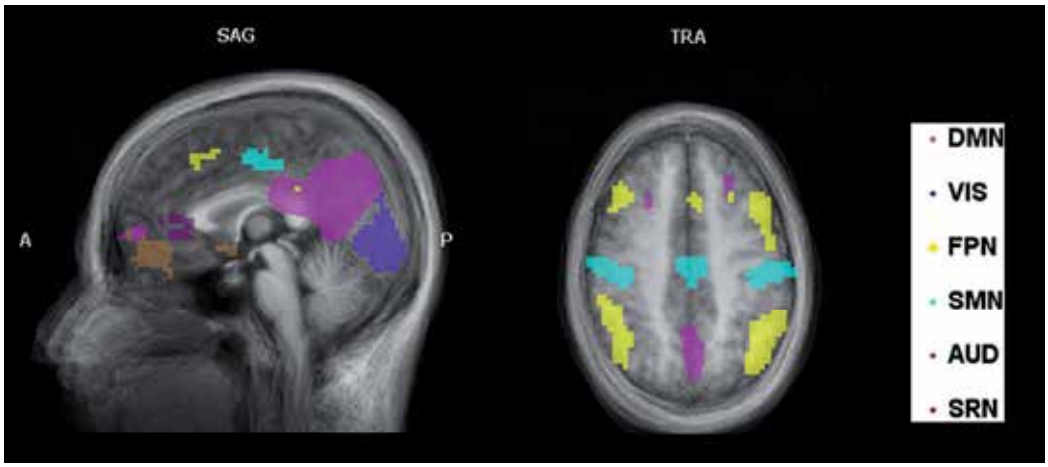

Fig. 1. Typical RSN maps. Visual network (VIS), default-mode network (DMN), fronto-parietal network (FPN), sensori-motor network (SMN), auditory network (AUD) self-referential (SRN) network.

As anticipated (and exemplified in figure 1), all the RSNs consist of anatomically separated, but functionally connected regions, sharing and supporting the same sensitive, motor or cognitive functions (Cordes et al., 2000). The RSNs reported in the normative literature have generally resulted to be quite consistent across studies, despite some differences in data acquisition and analysis techniques that partially account for the variability observed in the number and lay out of the networks. For instance, the DMN has been sometimes distinguished into two separate subnetworks, the anterior and posterior DMN (see, e. g., (Damoiseaux et al., 2008)), and the FPN as two lateralized networks (right and left FPNs, RFPN and LFPN) (see, e. g., (Damoiseaux et al., 2006; Tedeschi et al., 2010)). The auditory and visual networks have been presented in terms of a one single network (see, e. g., (Mantini et al., 2007)), two (see, e. g., (Damoiseaux et al., 2006)) or even three (see, e. g., (Rocca et al., 2011)) subnetworks.

Understanding the functional correlate of a given RSN under normal physiological conditions is crucial to correctly address any possible link between altered rs-fMRI patterns and behavioral and clinical variables. However, it should also be recognized that cytoarchitectonically distinct brain regions are kept functionally connected by white matter

connections that directly (monosynaptically) or indirectly (multisynaptically) make the ongoing communication physically possible (Greicius et al., 2009; van den Heuvel et al., 2009). Thereby, it is equally important to clarify whether the observed RSN functional connectivity is mediated by direct or indirect structural connections, e. g. by combining rs-fMRI with diffusion tensor imaging (DTI), an MRI technique that allows the study of white matter fiber bundles.

By far, the most studied RSN in the clinical and research neuroimaging community is the DMN (Greicius et al., 2003; Raichle et al., 2001). This network has attracted considerable interest in the neuroscience community for its possible role as the baseline cognitive state of a subject and its link to memory and executive functions in normal and pathological conditions. In fact, the DMN normally includes the ACC and PCC regions, known to be involved in attention-related processes (Badgaiyan & Posner, 1998) and often detectable as transiently or consistently deactivated during many different types of cognitive tasks (McKiernan et al., 2003). For this reason, Raichle et al. (2001), who first targeted this type of brain activity with positron emission tomography (PET) imaging, have introduced the concept of "default-mode" activity and attempted to differentiate a "cognitive" baseline state from a "general" resting state in human brain. Thereafter (Greicius et al., 2003) the DMN has been often conceptualized as a "stand-alone" function or system to be analyzed with data models specifically oriented to functional connectivity (Bullmore et al., 1996). Within the DMN, the PCC node, one of the most intensively interconnected regions in the whole brain (Cavanna & Trimble, 2006; Hagmann et al., 2008), seems to mediate all the intrinsic functional connectivity of the brain (Fransson & Marrelec, 2008). Indeed, the PCC plays an essential role in all types of introspective mental activity, ranging from immediate suppressing of distracting thoughts to avoid mistakes (Li et al., 2007; Weissman et al., 2006) up to modulating rethinking about the past to imagine the future and awareness (Buckner et al., 2008).

The VIS network involves regions in the striate, peri-striate and extra-striate visual cortex, which are normally activated by a visual task. This network extends from the lingual and fusiform gyri (i. e. V1 to V4) up to the occipito- and middle temporal regions (i. e. MT/V5), even if, in some reports, regions belonging to the primary and secondary visual system are shown to belong to separate visual RSNs (see, e. g., (Rocca et al., 2011)).

The fronto-parietal (or "executive-attention") network (FPN), sometimes found to be lateralized (i.e., right and left FPN), is also relevant for cognition. Particularly, the FPNs seem to be central for cognitive processing as they involve regions such as the dorsal frontal and parietal cortices potentially overlapping with the dorsal attention network which is known to mediate executive control processing (Corbetta & Shulman, 2002).

The SMN includes regions in the precentral and postcentral gyrus and in the supplementary motor area, all regions that both anatomically and functionally correspond well to motor and sensory areas, e. g. activated during a finger tapping task (Biswal et al., 1995).

The AUD network involves regions in the auditory cortex, which are normally activated by an auditory task. This network extends from the Heschl's gyrus to the superior temporal gyrus and the insula and has been also reported as one or two RSNs (see, e. g., (Damoiseaux et al., 2006)).

3. Methodology for the analysis of the resting-state networks

RSN can be observed using several functional connectivity analysis tools. A straightforward approach entails extracting the extracting the time-course of the BOLD signal from a pre-

defined region-of-interest (ROI) and subsequently searching all regions whose time-course significantly correlates with the ROI time-course. This method produces RSN maps that are extremely simple to interpret (Fox & Raichle, 2007; Greicius et al., 2003), but has the important drawback that the resulting functional connectivity maps will depend on the location, extension and order of the "seed" regions chosen, and on how these are defined in advance of the analysis. By contrast, "component-based" statistical techniques (Andersen et al., 1999; Friston et al., 1993), that do not require a-priori assumptions on the regions involved, enable the observation of multiple neural networks from whole-brain resting state data sets, thereby avoiding the possibility of bias.

ICA (Hyvarinen et al., 2001) has been successfully applied to neuroimaging data of diverse imaging modalities for generating convenient representations of activated brain networks in single subjects and groups. Particularly, in fMRI, ICA is commonly applied in its spatial variant (Calhoun et al., 2001b; McKeown et al., 1998) where each statistically independent component process corresponds to a spatial map distributed over all voxels of the imaging slab. Besides separating many types of structured dynamic artefacts from fMRI time series (see, e. g., (De Martino et al., 2007)), spatial ICA can provide a meaningful representation of function-related BOLD signals and unravel the whole-brain distributed functional connectivity under different experimental and clinical conditions. Particularly, spatial ICA is commonly applied in rs-fMRI to model the spontaneous low-frequency BOLD signals in terms of whole-brain distributed maps (Mantini et al., 2007).

When exploring fMRI data with spatial ICA, it is always necessary to decide how many ICA components to extract and, among these, select those components that can be consistently and reliably associated with functional connectivity networks of interest for a given application. The number of components is basically a "free choice" parameter (Calhoun et al., 2009), typically ranging between 20 and 60, even if potential changes in the layout of certain ICA generated RSN maps, such as splitting of a network into multiple networks, may result from the extraction of substantially more components than the minimum needed for a stable decomposition (Abou-Elseoud et al., 2010; Kiviniemi et al., 2009).

After fMRI data preparation and preprocessing, a group statistical analysis is typically required to summarize RSN functional connectivity in one or more populations of interest and to search for possible regional differences between populations within selected RSNs.

In many cases, population-level studies based on ICA use a two-level approach, first running single-subject ICA and then combining the components into a second-level group (random effects) analysis; in order to match components between subjects clustering and spatial correlation techniques are used (Esposito et al., 2005; Schopf et al., 2011; Wang & Peterson, 2008). This strategy provides maximal power to model subject-level structured noise (Cole et al., 2010) and has the important advantage of capturing unique spatial and temporal features of the subjects' data set even if the signal to noise ratio (SNR) is substantially lower in some subjects compared to other subjects. The disadvantage of this approach is that the components that are matched across subjects are not necessarily extracted in the same way for each subject of a group (Erhardt et al., 2010).

As an alternative to clustering, temporal (Calhoun et al., 2001a; Varoquaux et al., 2010) and spatial (Svensen et al., 2002) concatenation as well as "tensorial" (Beckmann & Smith, 2005; Guo & Pagnoni, 2008) data aggregation schemes have been previously examined to perform only one ICA decomposition, thereby circumventing the problem of a "first-level" component matching. The most used aggregate group ICA approaches (Calhoun et al.,

2001a; Zuo et al., 2010) are based on temporal concatenation and assume "common" ICA maps for all subjects in the first level analysis. A population analysis is then performed retrospectively determining the individual ICA components from the group ICA components. Thereby, all these methods implicitly assume that a given component is really present with exactly the same layout in all the subjects.

4. Resting state networks in clinical populations

The observational study of RSN functional connectivity in normal and clinical populations allows generating a comprehensive picture of brain functions and dysfunctions by the sole analysis of resting state fMRI activity, i. e. without relying on an active performance or engagement of the patient. This aspect is particularly attractive when studying uncooperative populations, but is generally suited to all cases where behaviors and performances are pathologically impaired. For this reason many research groups have studied RSN functional connectivity in different neurological and psychiatry disorders, detected differences between patients and controls and correlated these measures to clinical variables.

The largest numbers of studies and the most consistent results have been obtained for disorders like Alzheimer disease (AD) (Greicius et al., 2004; Petrella et al., 2011; Rombouts et al., 2005; Sorg et al., 2007; Supekar et al., 2008; Wang et al., 2007; Wang et al., 2006; Zhang et al., 2010; Zhang et al., 2009) and schizophrenia (Bates et al., 2009; Bluhm et al., 2007; Foucher et al., 2005; Greicius, 2008; Hoptman et al., 2010; Jang et al., 2011; Lagioia et al., 2010; Lynall et al., 2010; Mannell et al., ; Ongur et al., 2010; Repovs et al., 2011; Rotarska-Jagiela et al., 2010; Shen et al., ; Skudlarski et al., ; van den Heuvel & Hulshoff Pol, ; Woodward et al., 2011; Zhou et al., 2008). In this chapter, we present two examples of clinical RSN study, applied to ALS and MS.

4.1 Resting state networks in Amyotrophic Lateral Sclerosis

ALS is a chronic progressive disease that predominantly affects the motor system (Turner et al., 2009b), but neurodegeneration may also extend beyond motor areas (Geser et al., 2008; Geser et al., 2009; Murphy et al., 2007; Turner et al., 2009a). In fact, ALS patients often exhibit variable degrees of cognitive impairment with rather typical involvement of frontal executive functions (Grossman et al., 2008; Murphy et al., 2007). Thereby, studying the SMN, but also the DMN and the FPN, is crucially important to elucidate both motor and extra-motor involvement in ALS, to examine the possible interaction between physiologically sensitive and disease modified rs-fMRI parameters and to compare these functional measures with the clinical and MRI structural aspects of the neurodegenerative process.

The fact that rs-fMRI allows exploring whole-brain functional connectivity in all these RSNs with minimal bias towards a specific motor or cognitive function is particularly attractive for studying ALS patients, whose degree of cooperation normally introduces substantial variability in their performances.

The rs-FMRI fluctuations within the SMN network are reduced or even suppressed in ALS patients compared to age- and sex-matched normal controls (Mohammadi et al., 2009; Tedeschi et al., 2010). For instance, comparing the SMN maps on a voxel by voxel basis has shown statistically significant group differences bilaterally in the primary motor cortex (PMC) (figure 2).

ALS has long been characterized as a neurodegenerative disorder affecting the motor system, therefore, the observation that the coherent RS-fMRI fluctuations within the SMN

are strongly reduced can be easily linked to most existing animal models of ALS explaining motor neuron degeneration both at the cellular and molecular levels (Dal Canto et al., 1995; Wong et al., 1995; Wils et al., 2010).

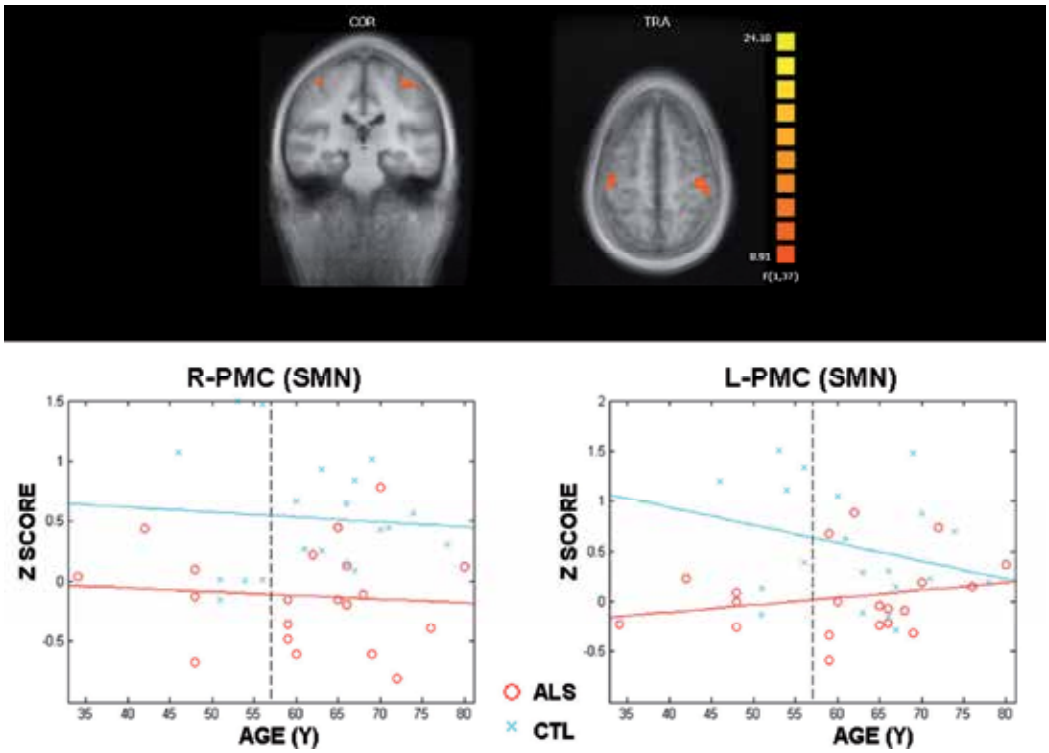

Fig. 2. ALS disease effects in the SMN. Upper panel: F-map of statistically significant disease effects within the SMN network (P=0.05, cluster-level corrected) overlaid on the average Talairach-transformed T1 image (coronal and axial cuts). Lower panel: Scatter plots of the regional ICA z-scores vs age in the R-PMC (left) and in the L-PMC (right). PMC = primary motor cortex. ALS = amyotrophic lateral sclerosis patients. CTL = control subjects.

The RFPN network is also partially suppressed in ALS patients. Figure 3 shows the localization of two regions within this network, in the superior frontal gyrus (SFG) and in the supra-marginal gyrus (SMG), where the network-specific RS-fMRI fluctuations resulted suppressed in ALS compared to controls. These effects in a cognitive executive network like the RFPN likely reflect a rather typical frontal cortex dysfunction observed in ALS patients (Abrahams et al., 1996; Hatazawa et al., 1988; Rule et al., 2010; Vercelletto et al., 1999).
Observing RSNs in ALS patients over an extended range of age has highlighted the possible interaction between aging and neurodegeneration (Tedeschi et al., 2010). Previous work has reported a significant effect of aging on DMN regions in the normal population (Esposito et al., 2008; Grady et al., 2006; Greicius et al., 2004; Koch et al., 2009; Persson et al., 2007). In ALS patients, the DMN network has shown an age-by-disease interaction effect in the PCC (figure 4), with the strength of the RS-fMRI fluctuations relatively increased rather than reduced with increasing age (and disease duration). In addition, there was also a group-by-age interaction effect in RFPN, and more precisely the middle frontal gyrus (MFG) (figure

4), further reflecting a possible attempt of the ALS brain to compensate the motor neuron degeneration by reorganizing the functional connectivity in cognitive networks within unaffected (or less affected) domains.

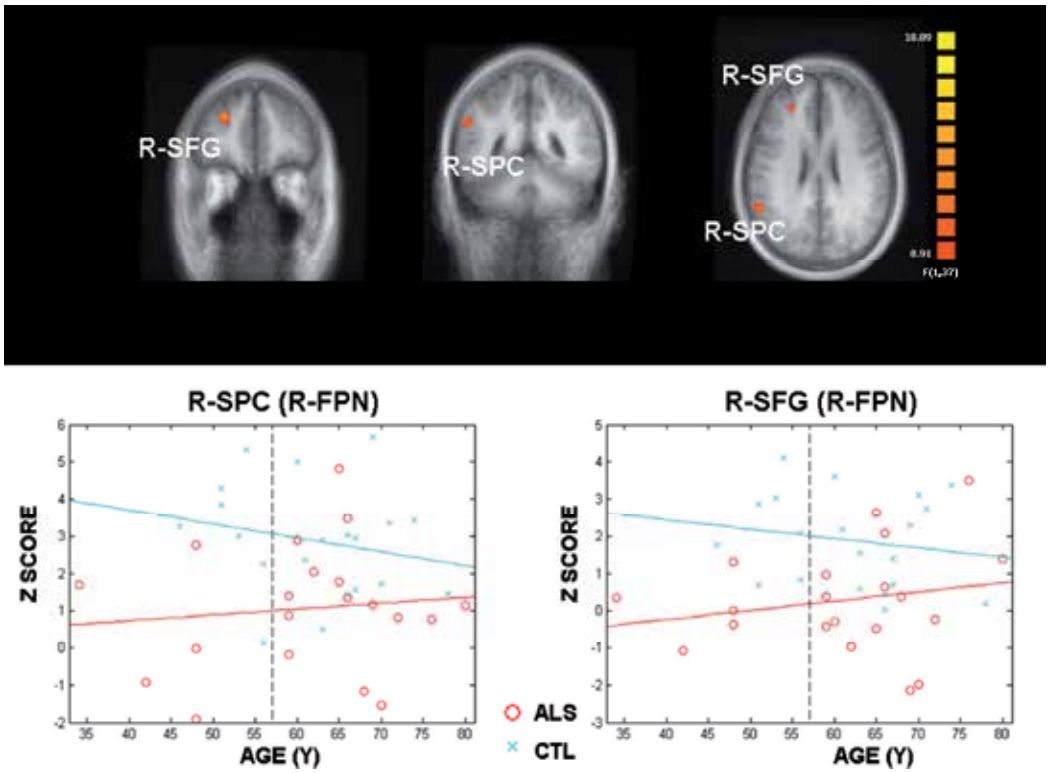

Fig. 3. ALS disease effects in the RFPN network. Upper panel: F-map of statistically significant disease effects within the R-FPN network (P=0.05, cluster-level corrected) overlaid on the average Talairach-transformed T1 image (two right sagittal cuts and one axial cut). Lower panel: Scatter plot of the regional ICA z-scores vs age in the SMG (left) and in the SFG (right). SMG = supramarginal gyrus. SFG = superior frontal gyrus. ALS = amyotrophic lateral sclerosis patients. CTL = control subjects.

This age compensatory effect on the functional connectivity can also be linked to biological processes of neuronal aging and degeneration. In fact, a few studies based on animal and cellular models of ALS pathophysiology (see, e. g., (Madeo et al., 2009)) have linked neurodegeneration and aging to specific strategies of neuroprotection by which the cell damage is contrasted with adaptive mechanisms against the physiological stress implied by aging. Thereby, these interaction patterns might represent the functional expression of the interaction between a widespread brain neurodegeneration and a physiological mechanism activated by aging. Particularly, the observed positive correlation between aging and spontaneous functional connectivity might be the result of a specific change in the default system to counteract the physiologically driven decline with age, given that ALS patients continuously alert the default system for performing any task potentially requested and made possible by the residual motor capabilities.

4.2 Default-mode network dysfunction in Multiple Sclerosis

Cognitive impairment is frequently observed in MS pathology (Benedict et al., 2006; Rao et al., 1991) and fMRI activation studies in MS patients with cognitive impairment have suggested that cerebral reorganisation (Filippi & Rocca, 2004; Mainero et al., 2004) and recruitment of non impaired cortical regions may occur as a compensatory mechanism to limit the cognitive consequences of tissue damage (Filippi & Rocca, 2004; Wishart et al., 2004).

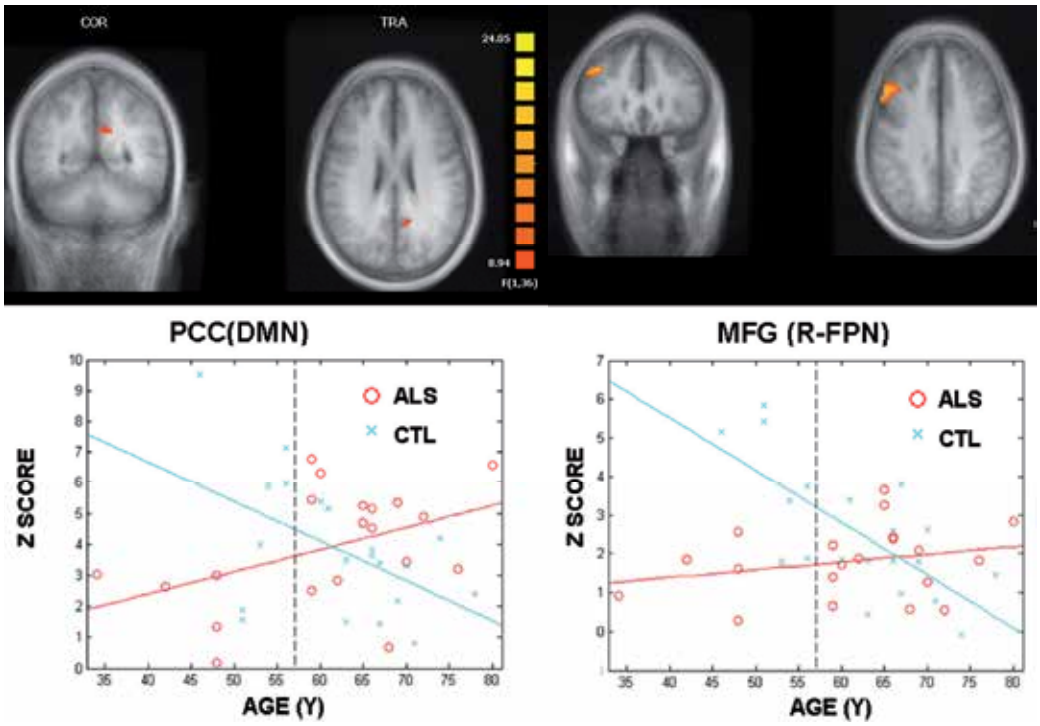

Fig. 4. ALS disease-by-age interaction in the DMN (left panel) and RFPN (right panel). Upper panels: F-map of disease by age interaction effects (P=0.05, cluster-level corrected) overlaid on the average Talairach-transformed T1 image (coronal and axial cuts). Lower panels: Regional ICA z-scores vs age in the PCC (left) and in the MFG (right).

Thereby, rs-fMRI is an attractive way to explore the spatio-temporal distribution of the spontaneous coherent fluctuations of BOLD signals within and between different regions throughout the entire human brain in different functional domains.

RS-FMRI studies have reported DMN alterations in both relapsing-remitting (RR) and progressive MS patients, when comparing MS patient groups with age and sex-matched healthy controls (Bonavita et al., 2011; Rocca et al., 2010).

The DMN connectivity distribution in RR MS patients may deviate from the control group both in the anterior node (in the ACC), that is substantially suppressed in the RR MS patient groups, and in the posterior nodes (in the PCC and, bilaterally, in the IPC), where a more distributed spatial re-organization seems to occur. Figure 5 shows a DMN comparisons map between a group of RR MS patients and a control group which clearly indicates that rs-fMRI coherent fluctuations within the DMN are reduced in RR MS patients close to the midline, both in the ACC and in the PCC, but also that, RR MS patients exhibit spots of more

coherent fluctuations far from the midline, at the periphery of the PCC and toward the parieto-occipital regions of the DMN.

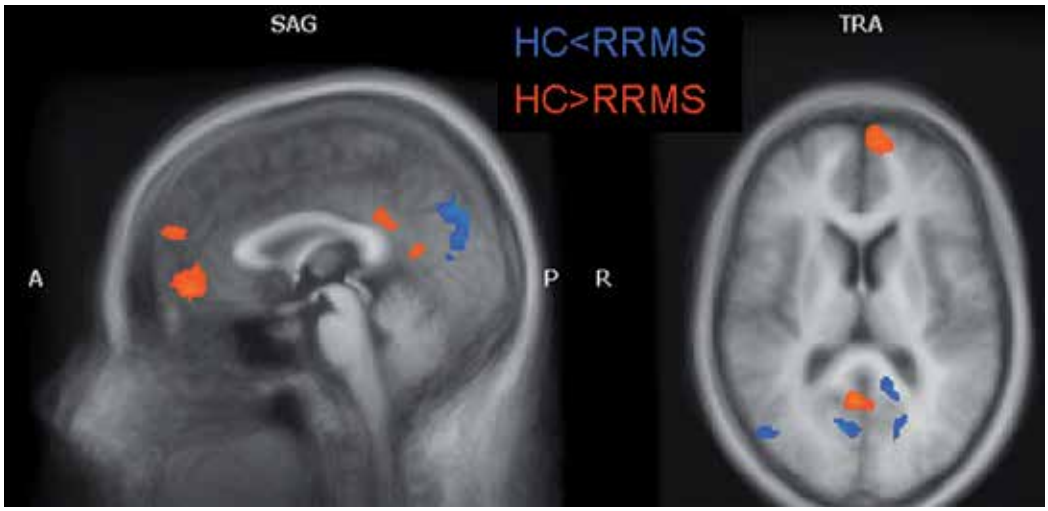

Fig. 5. Comparison between a group of RR MS patients and healthy controls (HCs). The clusters of significant differential activity are overlaid on two orthogonal slices of the averaged normalized anatomy.

A better display of the differences in the DMN functional connectivity distribution between the RR-MS and control groups is visible in figure 6, where all clusters with statistically significant differential effects are reconstructed as 3D volumes with separate colours in relation to the sign of the differences.

The comparison between RR-MS patients and normal controls becomes certainly more interesting if cognitive impaired (CI) and cognitive preserved (CP) subgroups are separately compared. Figure 7 shows this comparison and the 3D maps suggest that, while the suppression of the ACC node is a common aspect to both CI and CP RR MS patients, the re-organization of the functional connectivity in the posterior DMN can be different depending on the cognitive impairment of RR MS patients.

In summary, RR MS patients, regardless of their cognitive status exhibit a weaker DMN connectivity at the level of the ACC and the central/midline region of the PCC, together with an expanded connectivity at the level of the peripheral portions of the PCC and bilateral IPC. However, distribution changes in the posterior DMN appear with different lay outs in CI and CP patients and may thus be associated with the cognitive status of RRMS patients.

As for the other MS forms, progressive MS patients also exhibit reduced DMN connectivity, but mainly in the anterior part of the DMN (Rocca et al., 2011), where as clinically isolated syndrome (CIS) suggestive of MS seem to have increased DMN connectivity in the PCC node when compared to RR MS patients (Roosendaal et al., 2010), thus suggesting that the possible compensatory mechanism observed in the posterior DMN might be visible quite early in the disease course.

With respect to the selective involvement of the ACC in MS, one should consider that the ACC has extensive associative connections with other areas (Paus, 2001). Thereby, if cortico-cortical functional connectivity reduction is the result of axonal transection by white matter lesions, then highly connected (and distant) regions like ACC should be more vulnerable than regions

with relatively fewer connections. Actually, there is evidence from histopathological studies that the cingulate gyrus shows a higher prevalence of cortical demyelinated lesions than other areas (Bo et al., 2003; Kutzelnigg & Lassmann, 2006) and therefore it is likely that these regions are intrinsically more vulnerable and more directly involved by the disease.

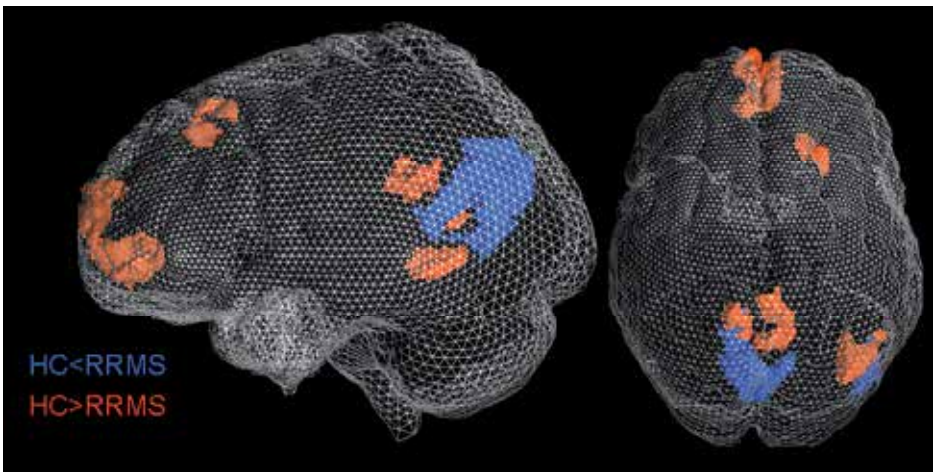

Fig. 6. Comparison between a group of RR MS patients and healthy controls (HCs). The clusters of significant differential activity are displayed as reconstructed as 3D volumes.

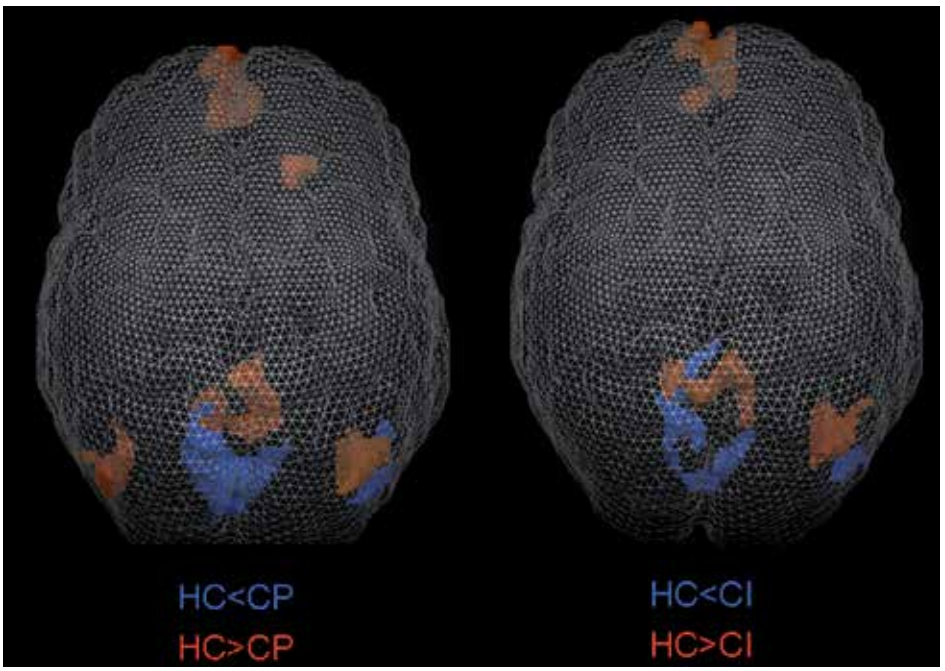

Fig. 7. Comparison between the separate groups of cognitive preserved (CP) (left) and cognitive impaired (CI) (right) RR MS patients and healthy controls (HC). The clusters of significant activity are displayed reconstructed as 3D volumes.

Van den Heuvel et al. (van den Heuvel et al., 2008) have investigated the structural connection of the DMN by combining diffusion tensor imaging and rs-fMRI data and found that the microstructural organization of the interconnecting cingulum tract, as measured by fractional anisotropy, is directly associated with the level of functional connectivity of the DMN, in particular the cingulum tract is confirmed to interconnect the PCC to the ACC of the DMN. This direct anatomical connection reflects a vast number of axonal connections between the posterior node/PCC and anterior node/ACC, responsible for the facilitation of neuronal communication between these regions. The cingulum tract is a thin white matter association bundle that is located just above and all along the corpus callosum, therefore it is expected to be frequently involved by WM lesions of MS. Thereby, if white matter MS plaques significantly contribute in determining the disconnection phenomena observed between the PCC and the ACC with the net functional loss of the ACC in the DMN of RRMS subjects, it is likely that DMN distribution changes in the posterior node represent a compensatory mechanism to sustain cognitive performances.

5. Conclusion

The present chapter has highlighted the importance of observing RSN in clinical populations in relation to both physiological and pathological factors and the potential impact of rs-fMRI as a non-invasive technique to explore whole-brain functional connectivity in neurological diseases for which the biological mechanisms are not completely understood. Particularly, since rs-fMRI does not require patient interaction, it will be possible to apply the present functional neuroimaging methodology to patients at highly advanced stages of the disease and eventually allow for longitudinal investigations.
Besides potentially shedding light on the pathological mechanisms occurring in certain neurological disorders, the clinical applications may also favor a better understanding of RSN functional connectivity in the context of brain neurophysiology, especially when the rs-fMRI patterns are carefully examined in relation to physiological and anatomical factors and to the possible interaction between these and the temporal course of a disease.

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7

Resting State Blood Flow and Glucose Metabolism in Psychiatric Disorders

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1. Introduction

Over the last 20 years, SPECT and PET, along with CT and MRI have been the main methodologies used in studies investigating psychiatric disorders. The structural alterations in patients' brains found by CT and MRI are usually quite subtle, while those found by the nuclear imaging modalities (PET and SPECT) are more pronounced. Partly for this reason, the latter methods have led to discoveries in a wide range of psychiatric disorders. In the 90s, region of interest (ROI) method provided only sketchy results due to the low spatial resolution of the nuclear imaging, but rapid progression in analytic and statistical methods in the 2000s had led to more detailed and accurate determinations of the differences in regional cerebral blood flow (rCBF) and glucose metabolic ratios (rGMR) between patients and comparison subjects. On the other hand, whereas an improved understanding of the etiology of psychiatric disorders has led to significant progress in multiple research areas, SPECT and PET studies measuring only the rCBF/rGMR distribution at rest have come to face some limitations for elucidation of the disease pathophysiology. Accordingly, at resting studies using SPECT/PET have tended to focus on certain kinds of clinical information, such as symptomatology and treatment. This review summarizes the history of at rest SPECT and PET studies, and provides a comprehensive survey in psychiatric disorders including schizophrenia, major depressive disorder, bipolar disorder and obsessive-compulsive disorder.

2. Schizophrenia

Functional neuroimaging has been used to elucidate patterns of increased or decreased activity within the brains of schizophrenic and normal subjects during rest and various assigned tasks, revealing that the affected parts of the central nervous system are not contained within a single brain region, but rather lie within neural networks over several brain regions. Numerous structural brain researches studies employing CT and MRI have demonstrated significant volume reductions in key brain regions such as the lateral prefrontal cortex, anterior cingulate cortex (ACC), superior temporal cortex, hippocampus/parahippocampus, striatum and thalamus in patients with schizophrenia relative to normal subjects (Shenton et al., 2001). In support of these structural alterations, functional neuroimaging studies have produced representations of abnormalities in and across these regions. Taking these results together, a variety of symptoms, including

hallucination/delusion and negative symptoms, have been attributed not to abnormalities in a single brain region but to abnormalities in a distributed network of spatially distinct regions. Furthermore, functional neuroimaging studies have demonstrated that antipsychotics have substantial effects on brain functions, and have helped to elucidate the differences in action mechanisms among them.

2.1 Hypofrontality and negative symptoms in schizophrenia

Ingvar and Franzen (1974) reported that patients with chronic schizophrenia showed significant reduction in the rCBF ratio of the frontal to occipital region compared to normal subjects and subjects with first-episode schizophrenia measured with ^{133}Xe. This was the first study to report an abnormality in rCBF in schizophrenia. Following this work, several other studies examined the resting state blood flow and metabolism (Buchsbaum et al., 1982; Wolkin et al., 1985; Tamminga et al., 1992; Sachdev et al., 1997) and repeatedly reported significant decreases in patients with schizophrenia relative to normal participants. On the other hand, there have been studies showing no difference in this parameter between patients and normal controls (Gur et al., 1995; Sabri et al., 1997, Scottish Schizophrenia Research Group, 1998), or even an increase in rCBF/rGMR in patients compared to normal controls (Cleghorn et al., 1989; Ebmeier et al., 1993).

Early studies on this issue have presented very disparate results with respect to not only the presence or absence of hypoperfusion/hypomtabolism, but also, in cases in which it was present, the degree, relevant regions and correlation with symptoms of hypoperfusion/hypometabolism. The reason for these differences is presumed to be the large number of confounding factors, such as disease heterogeneity, treatment with antipsychotics, imcompleteness of results derived from the ROI method, measured value of absolute or relative data, different reference regions for relative data, measurement conditions under varied physiological states, and so on. Therefore, additional explorations with a more sophisticated study design for the drug-naïve subjects group, the same scanning conditions and reliable analytic methods are needed to reach a definitive conclusion on this issue.

As for the effects of antipsychotic medications, several studies on drug-naïve patients with first-episode schizophrenia demonstrated a significant reduction in blood flow and metabolism in the frontal cortex relative to age-matched normal controls under a resting condition (Buchsbaum et al., 1992a; Steinberg et al., 1995; Vita et al., 1995; Erkwoh et al., 1997) and task-related activation (Andreasen et al., 1992, 1997; Ashton et al., 2000) and suggested that the abnormal reduction in the prefrontal region occurs from a very early stage of the disease. With respect to the problem of analytic methods, ROI methods have been a mainstream from the 80s to late 90s, but voxel-wise methods representative of Statistic Parametric Mapping (SPM) have prevailed from the mid-90s and are the standard modality at present. This voxel-wise methods have successfully addressed two important problems in brain analyses: individual structural differences between the brains of participants and examiners' arbitress on target brain regions depending on *a priori* hypothesis. Numerical researches based on these methods have demonstrated a significant reduction in particularly the lateral, medial and orbital phases of the prefrontal cortex relative to normal controls (Andreasen et al., 1997; Ashton et al., 2000; Kim et al., 2000; Potkin et al., 2002; Lehrer et al., 2005; Molina et al., 2005a, 2005b, 2009), and these findings have shown that areas with hypoperfusion and hypometabolism were pervasive and further

accompanied by other areas with hyperperfusion/hypermetabolism within the frontal cortex (Andreasen et al., 1997; Kim et al., 2000). The measurement conditions used under rest or the performance of a given task should also be taken into consideration. Whereas most of the studies with SPECT have been conducted under a resting state, many studies using FDG-PET have performed the comparison under a cognitive task such as continuous performance task (CPT) or California verbal learning task (CVLT). This is because of the possibility that a spontaneous fluctuation of mental state under a resting condition during scanning could result in varied distribution of rGMR in the participant group as a whole. Indeed, several PET studies using CPT (Potkin et al., 2002; Molina et al., 2005a, 2005b, 2009) or a visual attention task (Lehrer et al., 2005) showed a significant reduction of rGMR in the prefrontal cortex in patients compared to normal controls, very similar to the results obtained in almost all studies under a resting state. Then, reduction of rCBF/rGMR in the prefrontal cortex in patients relative to normal controls under a static state during the performance of cognitive tasks and under a resting state collectively indicates hypofrontality.

Although earlier studies have dealt this issue with dichotomous problem; presence or absence of hypofrontality, afterward, improvements in research design and analytic methods provide more detailed information such as distributed patterns within the frontal lobe within patients' brains or the degree of difference of the finding between patients and controls. In this context, in some meta-analysis studies (Davidson and Heinrichs, 2003; Hill et al., 2004), the finding of hypofrontality has been supported and thus established as a more convictive finding in the disease.

The hypoperfusion and hypometabolism in the frontal lobe have been presumed to be closely linked with negative symptoms and cognitive impairments in schizophrenia. These notions were demonstrated by the negative relationship between negative symptoms and blood flow/metabolism (Liddle et al., 1992; Wolkin et al., 1992; Ebmeier et al., 1993; Schröder et al., 1996; Andreasen et al., 1997; Erkwoh et al., 1997; Sabri et al., 1997; Ashton et al., 2000) and the significant reductions of blood flow/metabolism in the patients group with profound negative symptoms (Potkin et al., 2002; Gonul et al., 2003a), although several negative studies have existed (Vita et al., 1995; Min et al., 1999). On the other hand, whereas the cognitive dysfunctions that have recently received so much attention are closely related with negative symptoms, the reports exploring the relationship between the impairments and at rest blood flow/metabolism are very restricted (Penadés et al., 2002; Molina et al., 2009). A hypodopaminergic state in the prefrontal cortex is presumed to underlie the negative symptoms and cognitive impairments (Lynch, 1992; Remington et al., 2011) and thus, in this context, it is noted that hypofrontality strongly suggests an important part of core pathophysiology in schizophrenia.

2.2 rCBF/rGMR patterns in key regions other than the frontal lobe

As for brain regions other than the frontal lobe, a number of previous studies have demonstrated substantial variations between the patients with schizophrenia and normal controls, with some reports observing increases in various activities and other reports documenting decreases, and thus no convincing consensus has been reached.

Both the lateral and medial phases in the temporal cortex have been closely related with positive symptoms, particularly hallucination and delusion. Based on accumulating evidence from fMRI studies, for example, the primary auditory cortex located in the

superior temporal cortex has been demonstrated to be closely related to auditory hallucination (Dierks et al., 1999; Lennox et al., 2000). Indeed, the first-episode and drug-naïve patients with auditory hallucinations presented higher (Horga et al., 2011) and lower metabolism (Cleghorn et al., 1992; Vita et al., 1995) compared with normal controls. Further, activity in this region was reported to be negatively associated with disorganization as a form of thought disorders (Ebmeier et al., 1993; Erkwoh et al., 1997; Sabri et al., 1997). The hippocampal and/or parahippocampal gyrus are also related with hallucination/delusion and disorganization. PET studies have shown an increase (Gur et al., 1995; Molina et al., 2005b) and decrease (Tamminga et al., 1992; Kim et al., 2000; Horga et al., 2011) in rCBF/rGMR of the regions in schizophrenia compared with normal controls, and positive (Liddle et al., 1992) and negative correlations (Schröder et al., 1996) between metabolism in the regions and hallucinations. Although these reports have very conflicting results and do not reach a definitive conclusion, they do suggest that both the lateral and medial parts of the temporal lobe are closely related with the positive symptoms.

The findings of activity within other key brain regions in schizophrenia have been very controversial. As for the striatum, several reports on drug-naïve patients have shown a significant reduction relative to normal controls (Buchsbaum et al., 1987, 1992a; Shihabuddin et al., 1998), suggesting a relation with putative neurological soft signs in the very early stage (Dazzan et al., 2004). The thalamus has a function of filtering all sensory signals from input to the cortex, and is known to play a primary role in the etiology of schizophrenia- namely, dysfunction in the correct perception of information from the external world. The activity in the thalamus has been alternatively reported to increase (Andreasen et al., 1997; Jacobsen et al., 1997; Kim et al., 2000; Clark et al., 2001) or decrease (Vita et al., 1995; Hazlett et al., 1999, 2004; Buchsbaum et al., 1996; Lehrer et al., 2005). Moreover, increases of rCBF/rGMR in the cerebellum (Andreasen et al., 1997; Kim et al., 2000; Desco et al., 2003) and the subcortical regions (Buchsbaum et al., 1998, 2007a; Desco et al., 2003) have been observed. As described above, attempts to clarify the pathophysiology of schizophrenia have focused on brain regions from the frontal and temporal cortex to the subcortical regions including the striatum, thalamus, hippocampus and cerebellum. It appears that the approach of elucidating the pathophysiology requires an integrative interpretation based on the putative aberrant networks and their correlation with symptoms. Taken together, these findings suggest that resting blood flow and metabolism studies contribute to the elucidation of the disease pathophysiology by macroscopic investigation over the whole brain and microscopic investigation focusing on key regions.

2.3 Impacts of antipsychotics on blood flow and metabolism

Antipsychotics have some significant effects on brain blood flow and metabolism, and are presumed to be closely related to the potency of neuroleptics. All antipsychotics commonly induce dopamine (DA) D2 receptor antagonistic actions, resulting in the most direct action for improvement of delusions and hallucinations. Traditionally, typical antipsychotics such as haloperidol, an almost pure DA D2 blocker, had been widely used. But more recently, atypical antipsychotics have become the mainstay in the clinical practice. These atypical antipsychotics can reduce the extra-pyramidal symptoms and improve the negative symptoms and cognitive impairments by an antagonistic action on the 5-HT 2A receptors. Functional neuroimaging studies have provided important insights about the differences in pharmacological action and treatment effect among a diverse range of antipsychotics, and the subsequent functional changes in the central nervous system.

A number of previous studies have shown that typical neuroleptics such as haloperidol reduce blood flow and metabolism in the frontal lobe. These effects were repeatedly replicated in studies of both acute (Bartlett et al., 1998; Lahti et al., 2005) and chronic administration (Bartlett et al., 1991; Buchsbaum et al., 1992b; Miller et al., 1997, 2001; Lahti et al., 2003). Further, whereas haloperidol was reported to be related with hypoperfusion and hypometabolism in the hippocampus in terms of amelioration of positive symptoms (Lahti et al., 2003), increases of rCBF/rGMR in the motor cortex induced by haloperidol were presumed to be related with extra-pyramidal symptoms (Molina et al., 2003; Buchsbaum et al., 2007), and the decrease in activity in the occipital cortex following haloperidol treatment might be related with sedative effects (Bartlett et al., 1991; Desco et al., 2003; Lahti et al., 2003).

An increase in rCBF/rGMR in the basal ganglia in patients with schizophrenia by neuroleptics, in particular haloperidol, is the most consistent finding among numerous reports on antipsychotics. This has been replicated very well in the acute effect (Lahti et al., 2005) as well as the chronic effect (Buchsbaum et al., 1987, 1992a, 2007a; Miller et al., 1997, 2001; Scottish Schizophrenia Research Group, 1998; Corson et al., 2002; Desco et al., 2003; Lahti et al., 2003). The increase of blood flow and metabolism in this area is presumed to be due to increases of activity in the post synapses through upregulation of DA D2 receptors induced by a potent blocking action of the receptor by haloperidol (Miller et al., 1997; Corson et al., 2002). This notion is in line with the increase of volume in this area following haloperidol treatment in structural MRI studies (Shenton et al., 2001).

Studies on the effects of atypical antipsychotics on brain perfusion/metabolism have become to be examined based on more detailed neuronal substrates than studies on typical antipsychotics by appearance of voxel wise analysis. Although risperidone has less effect on the reduction of blood flow in the frontal lobe than haloperidol (Miller et al., 2001), the drug induces a significant reduction in the prefrontal cortex relative to baseline (Berman et al., 1996; Liddle et al., 2000; Ngan et al., 2002; Molina et al., 2008). In the basal ganglia, the degree of increase in blood flow/metabolism by risperidone is likely smaller than that by haloperidol (Liddle et al., 2000; Miller et al., 2001). Liddle et al. (2000) demonstrated that treatment with risperidone for 6 weeks showed a significant positive relation between decrease in the hippocampus and decrease in reality distortion, suggesting that the hippocampus is an important target area of risperidone.

Olanzapine is likely that its effect of blood flow/metabolism in the frontal lobe is lesser than that by risperidone (Gonul et al., 2003b; Molina et al., 2005c; Buchsbaum et al., 2007b).

Clozapine, the gold standard among the atypical neuroleptics, has a pharmacological profile with weaker blockade of DA D2 receptors and broader actions for multiple receptors than other atypical antipsychotics, and these characteristics are presumed to be related to its superior clinical efficacy relative to other neuroleptics. Interestingly, several previous studies have reported that clozapine induced a significant reduction in blood flow/metabolism in the prefrontal cortex (Potkin et al., 1994, 2003; Cohen et al., 1997; Lahti et al., 2003; Molina et al., 2005d, 2008). On the other hand, increases in several parts of the prefrontal cortex, including the ACC (Lahti et al., 2003) and decreases in the hippocampus (Lahti et al., 2003; Potkin et al., 2003) have been shown by some studies, supporting the drug's clinical actions such as ameliorations of delusions/hallucinations and cognitive impairments. Indeed, responders to clozapine exhibited more prominent changes in blood flow/metabolism above mentioned rather than non-responders (Potkin et al., 2003; Molina

et al., 2008). These complex patterns induced by clozapine have been suggested to be strongly related to the drug's superior clinical characteristics.

2.4 Conclusion

Functional neuroimaging studies performed in schizophrenic subjects under a resting state have made progress in the accumulation of findings on hypoperfusion/hypometabolism in the frontal lobe. It is noted that the hypofrontality is closely related with negative symptoms. On the other hand, the brain regions relevant to positive symptoms are still clearly unknown. The studies performed thus far have well explored the effects of various antipsychotics on the brain blood flow and metabolism, but neuroleptic-induced reductions in blood flow/metabolism in the prefrontal cortex have been obscure in terms of their relationship with the improvement of positive symptoms or secondary negative symptoms. By contrast, alteration in the limbic regions or the medial phase of the temporal cortex, such as the hippocampus, has been shown to be related with positive symptoms, and functional neuroimaging studies have contributed to detection of the origin of positive symptoms.

3. Major Depressive Disorder

Functional neuroimaging studies measuring at-rest brain perfusion and metabolism in patients with major depressive disorder (MDD) have demonstrated that the etiology of the disease is closely linked with multiple components of the frontal lobe, temporal lobe, parietal lobe, limbic/paralimbic regions, and basal ganglia. Recent knowledge on affection and perception acquired from multiple human and animal research fields strongly support the findings that have been observed within depressive patients' brains in neuroimaging studies. Although a number of functional neuroimaging studies for MDD have been conducted to date, the results were varied widely among the studies. However, a sequence of inconsistent findings on MDD has demonstrated that depressive patient groups consist of highly heterogeneous subtypes, and that the etiology of depression contains multiple symptoms.

Studies on the effects of antidepressants on brain perfusion and metabolism have reported the relatively consistent finding that abnormal activity in the key brain regions relevant to depression could be normalized by successful treatment. However, no reliable markers on response prediction have been available to date in the imaging studies. On the other hand, studies of electroconvulsive therapy (ECT), an established treatment modality for refractory depression, have suggested that its effective mechanism is involved in the inhibitory process within subjects' brains that occurred immediately following the ECT course.

3.1 Abnormalities in multiple prefrontal cortex and limbic regions in MDD

Earlier functional neuroimaging studies on depression have reported significant reduction in rCBF/rGMR in the frontal lobe or prefrontal cortex in patients with depression relative to normal subjects (Baxter et al., 1989; Martinot et al., 1990; Bench et al., 1992). However, several subsequent studies with the voxel based analyses have failed to confirm this finding (Skaf et al., 2002; Videbach et al., 2002; Bonne et al., 2003). Great progression made in research on human and animal emotion and perception has elucidated that the frontal lobe and limbic/paralimbic systems are tightly involved in affective and perceptive controls, including mood, attention, decision-making, anxiety, behaviors dependent on

reward/punishment, and so on. It is, therefore, very reasonable that hypoactivity in the frontal lobe is observed in subjects with depression relative to normal subjects. Inconsistent results among the previous studies mentioned above, suggest great heterogeneity of patients with the disease. Therefore, a number of confounding factors, such as age, sex, brain organic condition (ischemia and atrophy), pharmacotherapy (drug class, dose and duration), and disease stage (acute or remit), could easily affect brain activity, leading to a varied distribution of rCBF/rGMR in the patient group as a whole.

Studies with careful sample selection, in which subjects who were, for example, in a drug-naïve state or in withdrawal from antidepressants for several weeks, were careful selected in order to reduce the heterogeneity have reported significant hypoperfusion and hypometabolism in the dorsolateral prefrontal cortex in subjects with depression relative to normal controls (Kimbrell et al., 2002; Gonul et al., 2004). The reduction in activity in this region was the most consistent finding among those in the frontal lobe as a whole. Additionally, rCBF and rGMR in the dorsolateral prefrontal cortex were negatively correlated with the severity of depression (Baxter et al., 1989; Martinot et al., 1990; Hurwitz et al., 1990; Bonne et al., 1996; Kimbrell et al., 2002; Gonul et al., 2004). Subanalyses of each symptom have shown the degree of psycho-motor retardation and the activity in the prefrontal cortex to be negative correlated (Bench et al., 1993; Dolan et al., 1993; Videbach et al., 2002). Although increased activities in the ventrolateral prefrontal cortex and OFC have been suggested by a sequence of studies by Drevets (Drevets et al., 1992, 1997; Drevets, 1999, 2000), other studies did not sufficiently examine these areas. With respect to the medial prefrontal cortex and ACC, although most studies with relatively large ROIs in this area, observed hypoperfusion and hypometabolism (Hurwitz et al., 1990; Bench et al., 1992, 1993; Bonne et al., 1996; Mayberg et al., 1997; Videbach et al., 2002; Gonul et al., 2004), several detailed studies on these regions demonstrated decreased activities in the dorsal medial prefrontal and dorsal ACC (Kimbrell et al., 2002; Fitzgerald et al., 2008) and increased activities in the rostral ACC (Drevets, 1999; Konarski et al., 2007). In particular, the latter region was suggested that the greater perfusion and metabolism was, the better clinical response to antidepressant treatment was predicted (Mayberg et al., 1997).

As for the limbic region, increases in rCBF/rGMR in the amygdala (Drevets et al., 1992; Abercrombie et al., 1998; Videbach et al., 2002) and caudate (Gonul et al., 2004; Périco et al., 2005) were observed in patients with depression relative to normal subjects. The subgenual ACC, a component within the paralimbic system, was hypoactive in patients with unipolar depression (Drevets et al., 1997; Skaf et al., 2002; Fitzgerald et al., 2008), but also in patients with bipolar depression (Drevets et al., 1997). The caudate was also reported to show hypometabolism (Baxter et al., 1985; Drevets et al., 1992). These reductions in activity in anatomically small areas, such as the subgenual ACC and caudate, might be due to the partial volume effects (Krishnan et al., 1992; Drevets, 2000). The ventrolateral prefrontal cortex, including the subgenual ACC, has closely reciprocal connectivities with the amygdala, hypotharamus and brain stem, and disturbances of these networks could lead to the hypersensitivity to failure, pathological guilt and exaggeration of self-esteem shown in patients with MDD.

3.2 Change of rCBF/rGMR induced by antidepressants and ECT

Antidepressant agents are shown to be effective for 50-60% patients with MDD (Hirschfeld et al., 2002), and only 20-35% of patients reach remission (Mann, 2005). While diverse classes

of antidepressants are available in clinical practice at present, studies on the effect of specific antidepressants on brain perfusion or metabolism and the studies on the relationship between clinical improvement and the brain activity induced by antidepressants have been very restricted, and, further, the few such studies that exist usually have very small sample sizes. According to previous studies on these issues, aberrant regions at baseline prior to initial treatment in subjects with MDD appear to be normalized, particularly in responders to the agent. However, it is very uncertain whether the abnormalities can be recovered to a level similar to that in normal subjects (Baxter et al., 1985, 1989; Tutus et al., 1998; Ishizaki et al., 2008) or remain to a certain degree (Hurwitz et al., 1990; Martinoti et al., 1990). The discrepancies among these studies might be due to differences in class, dose of antidepressant, diverse treatment durations, different definitions of effectiveness or recovery of symptoms, or small sample sizes. Several selective serotonin reuptake inhibitors (SSRIs; paroxetine and citalopram) and serotonin and noradrenaline reuptake inhibitors (SNRIs; venlafaxine) in some well-designed studies have been examined most extensively in terms of their effects on brain perfusion/metabolism in patients with MDD. However, although several key regions, such as the frontal, temporal, parietal, and limbic regions and the basal ganglia, have been widely found to be relevant areas affected by the depressants studied, consistent findings on the combination of the relevant areas or their change directions have been very scarce. With respect to the prediction of the response to antidepressants, the greater the perfusion in the ACC (Mayberg et al., 1997), rectul gyrus (Buchsbaum et al., 1997), and lateral prefrontal cortex (Joe et al., 2006; Brockmann et al., 2009) prior to treatment was, the better the expected response. On the other hand, a decrease in rCBF/rGMR prior to treatment in the ACC (Brody et al., 1999; Konarski et al., 2009), lateral prefrontal cortex (Navarro et al., 2004) and hippocampus/basal ganglia/thalamus (Milak et al., 2009) led to a good treatment response. Therefore, the studies on this issue to date have failed to confirm conclusions.

ECT is usually indicated the patients with MDD who have been treatment-resistant to antidepressants. While this modality provides a relatively high rate of response for these patients, the understanding of its mechanism of action remains very poor. During seizures induced by ECT, evident reductions in rCBF/rGMR occurred over large brain areas (Takano et al., 2007). Afterwards, hypoperfusion and hypometabolism, to a lesser degree than during the seizure, in several brain regions, including the prefrontal region, have continued for a maximum of several months. This findings is presumed to be related to clinical responsiveness (Prohovnik et al., 1986; Rosenberg et al., 1988; Guze et al., 1991). However, some studies have demonstrated significant increases in rCBF in several brains (Bonne et al., 1996; Kohn et al., 2007). These discrepancies might be due to several confounding factors, such as procedural-related factors including anesthetics and electrode replacements, or to varying durations between the termination of the ECT course and imaging scanning.

3.3 Conclusion

The etiology of depression is strongly suggested to be related to the frontal lobe and limbic/paralimbic regions. However, the highly heterogeneity of patients with depression could lead to inconsistent results observed among studies. In addition, assessing the results in anatomically small areas or components with obscure boundaries, such as the subgenual ACC, amygdala, and OFC, is very difficult, and this serious problem in the interpretations of these regions stems from the effects of volume reduction in these regions in patients with

depression relative to normal. With respect to antidepressants and ECT, their mechanisms have been under examination.

4. Bipolar Disorder

Bipolar Disorder is characterized by distinctive affective labile episodes of manic/hypomanic state and/or depressive state. Concurrently, cognitive dysfunctions such as impairments of attention, working memory and executive function usually accompany the disease. Based on recent careful clinical observations, lifetime prevalence, including all bipolar II disorder, subthreshold bipolar disorder and drug-induced manic/hypomanic episode, is up to 5% (Merikangas et al., 2007). About 60% of patients with bipolar disorder are misdiagnosed as having MDD, and further, one-third of patients experience any psychiatric symptoms for more than 10 years before a correct diagnosis is made (Hirschfeld et al., 2003). Therefore, understanding the pathophysiology of bipolar disorder is very important for exact diagnosis and effective treatment. In neuroimaging studies on bipolar disorder, however, there have been a number of difficulties with the research, such as difficulty in recruiting patients with mania into the study and with safely scanning them, and the large heterogeneity within such patient groups in terms of affective state and disease subtype. Therefore, neuroimaging studies conducted to date have tended to have small sample sizes. Also, almost all studies on bipolar disorder have employed depressive patient groups combining cases of bipolar and unipolar depression, and the data acquired to date in manic and euthymic patients have been relatively restricted compared to the findings in depressive patients. In this context, resting state rCBF/rGMR studies on bipolar disorder have appeared to be inconsistent (Stoll et al., 2000; Strakowski et al., 2000). Still, recent resting state studies are providing a cortical-anterior subcortical dysfunction model of the disease pathology through several kinds of examination, including studies on mania and comparative studies between bipolar and unipolar depression (Keener and Phillips, 2007; Pan et al., 2009).

4.1 Bipolar mania

There have been few studies on manic patients, and those that have been performed have been largely biased by very small sample size, patients with manic level that can cooperate with study, and continuous pharmacotherapy consisting of a mixture of mood stabilizers, antidepressants and antipsychotics. In these studies, rCBF/rGMR reduction in the prefrontal cortice, particularly the ventral prefrontal cortex and increase in the subcortical areas compared to normal controls have been relatively consistent, providing cortical-subcortical or cortical–limbic/paralimbic regions impairment as a disease model in bipolar disorder. Decrease in brain perfusion/metabolism in the frontal cortex has been reported in the lateral prefrontal cortex at rest (al-Mousawi et al., 1996; Bhardwaj et al., 2010; Brooks III et al., 2010) and during cognitive tasks (Blumberg et al., 1999; Rubinsztein et al., 2001) and in the orbitofrontal cortex at rest (Blumberg et al., 1999) and during cognitive tasks (Blumberg et al., 1999; Rubinsztein et al., 2001). On the other hand, increases of rCBF/rGMR have been reported in the dorsal ACC (Rubinsztein et al., 2001), caudal ACC (Blumberg et al., 2000) and ventral/subgenual ACC (Drevets et al., 1997; Blumberg et al., 2000; Brooks III et al., 2010) and the head of the caudate (Blumberg et al., 2000; Brooks III et al., 2010). Goodwin et al. (1997) reported that in patients with relapsed manic episodes following withdrawal of

lithium, increase of rCBF in the ACC was positively correlated with manic symptoms. These findings lead to and partly support the anatomical-functional hypothesis that while the orbitofrontal and lateral prefrontal impairments are related with affective/impulsive dysregulation and cognitive dysfunction, respectively, compensatory functional hyperactivity reflects the findings of increase in the ACC and limbic/paralimbic regions observed in resting-state studies (Keener and Phillips, 2007; Pan et al., 2009).

4.2 Bipolar depression

Although there have been more reports on bipolar depression than on mania, the findings from this body of work are rather confusing. This may be due, at least in part, to the design of these studies. That is, earlier studies have frequently used a disease group combining cases of unipolar and bipolar depression, and when they have compared bipolar depression with other conditions, they have alternatively used normal healthy subjects, patients with unipolar depression and subjects with mania/euthymia as the comparison group. Moreover, the different studies have different target regions (ACC, subgenual prefrontal cortex and amygdala). With respect to the cortex, although few reports demonstrated any regions with hyperperfusion and hypermetabolism in bipolar depression relative to normal controls, areas with hypoperfusion/hypometabolosm in the patients compared to normal controls spread very broader in the lateral prefrontal (Baxter et al., 1985, 1989; Ketter et al., 2001; Brooks III et al., 2009a), medial prefrontal (Baxter et al., 1985; Bauer et al., 2005; Brooks III et al., 2009a), subgenual ACC (Drevets et al., 1997; Brooks III et al., 2009a), temporal lobe (Baxter et al., 1985; Ketter et al., 2001; Bhardwaj et al., 2010), occipital lobe (Baxter et al., 1985; Ketter et al., 2001) and parietal lobe (Baxter et al., 1985; Ketter et al., 2001). On the other hand, hyperperfusion/hypermetabolism have also been observed in the subcortical or limbic/paralimbic areas, including the amygdala (Ketter et al., 2001; Drevets et al., 2002; Bauer et al., 2005; Mah et al., 2007), subgenual ACC (Drevets et al., 1997; Bauer et al., 2005; Mah et al., 2007), ventral striatum (Bauer et al., 2005), caudate nucleus (Ketter et al., 2001; Mah et al., 2007), and putamen (Ketter et al., 2001; Mah et al., 2007), nucleus accumbens (Ketter et al., 2001; Mah et al., 2007), thalamus (Ketter et al., 2001; Bauer et al., 2005) and cerebellum (Bauer et al., 2005).

There have been a few reports comparing patients with bipolar depression and bipolar mania within the same study. Examination of the subgenual ACC (Brodmann area 25) by Drevets et al. (1997) demonstrated clear distinction of increased activity when mania and decreased activity when depression, and growing attention has been paid to this area as a mood-state marker in bipolar disorder. However, some subsequent studies showed higher metabolism in the depressive state (Bauer et al., 2005; Mah et al., 2007), indicating a failure to conform. The inconsistency among studies on small anatomical area such as the subgenual ACC may be related to shortcomings in the characteristics of nuclear imaging, such as insufficient spatial resolution of the scanner or inaccurate normalization to the standard brain (Drevets et al., 2002).

4.3 Euthymia

Although manic state and depressive state represent clinically extreme and opposite symptoms, neuroimaging findings on the two states are relatively similar. Thus, a cortical-subcortical model raises some questions as to whether this model means trait marker in the

disease, or whether reliable mood-state markers in the disease exist. In this context, studies on euthymia will be more and more important for addressing these issues.
Some studies on patients with euthymic state compared to normal controls have reported a decrease of rCBF/rGMR in the lateral prefrontal (Culha et al., 2008; Brooks Ⅲ et al., 2009b) and ACC (Culha et al., 2008) at rest, and the lateral prefrontal (Krüger et al., 2003) and OFC (Blumberg et al., 1999; Krüger et al., 2003) during cognitive tasks or symptom-provocation. On the other hand, regions with increased perfusion/metabolism were observed in the subcortical areas such as the amygdala (Brooks Ⅲ et al., 2009b) and parahippocampus (Brooks Ⅲ et al., 2009b) at rest. Krüger et al (2003, 2006) in symptom-provocation studies demonstrated that although increased rCBF in the subgenual ACC seen in normal controls was deficit in euthymic patients, increased perfusion in the dorsal ACC was observed only in the patients. Though there have been very few studies conducted on euthymia, patients with euthymia appear to show a decrease of rCBF/rGMR in the prefrontal cortex and an increase in rCBF/rGMR in the subcortical areas, according to previous reports. These notions are comparable to recent clinical observations that patients in a euthymic state show significant cognitive impairments identical to the distinctive pathological states of mania and depression (Kessing, 1998; Elshahawi et al., 2011), and they are in preparatory stage to relapse fragile to stress (Swann, 2010), but not asymptomatic state not meeting manic and depression.

4.4 Conclusion

Functional neuroimaging studies on bipolar disorder have demonstrated hypoactivity in the cortex, particularly the ventral prefrontal cortex, and concurrent hyperactivity in the subcortical or limbic/paralimbic regions. To data, however, this knowledge has not reflected the clinical bipolarity of mania and depression and thus remains a trait marker. Furthermore, these findings cannot be distinguished from those of other psychiatric disorders, including unipolar depression. Studies with more sophisticated designed and larger sample size will be needed in the future.

5. Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) has a lifetime prevalence of 2-3% (Weissman et al., 1994). OCD is characterized by persistent and recurrent thoughts that invade conscious awareness against a patient's will (obsessions) and is further usually accompanied by ego-dystonic, ritualistic behaviors that the patient is obliged to perform in order to prevent overwhelming anxiety (compulsions). Patients with OCD form a more homogeneous group than those with other psychiatric disorders, and this perhaps accounts for the fact that previous functional neuroimaging studies have provided relatively consistent findings on aberrant brain regions in this disorder, which include the OFC, ACC, caudate nuclei, thalamus and so on. That is, the etiology of OCD has been presumed to follow a cortico-subcortical model. Functional neuroimaging techniques have contributed substantially to the exploration of these areas relevant to the disorder. Furthermore, recent reports on treatment intervention for OCD have strongly suggested that selective serotonin reuptake inhibitors (SSRI) and cognitive behavior therapy (CBT), both established treatment approaches, raise some effects on patients' brain blood flow and metabolism, and further normalize aberrant regional perfusion and metabolism within these networks in treatment responders.

5.1 Dysfunction of the orbitofrontal-subcortical circuit in OCD

The basal ganglia is a candidate abnormal area in OCD to which great attention was initially paid. The reason for this is a high rate of patients with obsessive symptoms were found to have certain diseases, such as Von Economo encephalitis (Schilder, 1938), Sydenham's chorea (Swedo et al., 1989) and Tourette's syndrome (Nee et al., 1980), which have presumed to be impaired in the basal ganglia. Afterwards, functional neuroimaging studies on OCD have focused on the striatum, in particular caudate nucleus as aberrant region within patients' brains and concurrently have successively detected some abnormal brain areas such as the OFC, ACC and thalamus in patients with OCD, when compare them with normal healthy subjects. In this context, researchers have proposed a dysfunction of cortico-striatum-thalamus-cortical network as an etiological model of OCD (Modell et al., 1989; Baxter et al., 1996; Saxena et al., 1998).

It has been classically recognized that the cortico-subcortical network consists of direct and indirect pathways. The thalamus in the network has a gating function which filters all stimuli from the outer world and receives two main inputs from the striatum. The one is the direct pathway where signals from the striatum input to the thalamus via the globus pallidus internal/substantial nigra and the other is the indirect pathway where signals from the striatum input to the globus pallidus internal/substantial nigra through the globus pallidus external or subthalamic nucleus, and are further sent to the thalamus. Afterwards, feedback signals from the thalamus are sent to the cortex. These pathways consist of neurotransmissions combined with excitatory signals by glutamate and inhibitory signals by GABA. The direct pathway inputting to the thalamus disinhibits the thalamus (reinforcement of positive feedback) and the indirect pathway inhibits the thalamus (negative feedback), thereby helping to maintain the balance of the system (Alexander and Crutcher, 1990). In patients with OCD, it is presumed that this circuit represents an imbalance of hyperactivity. In the dysfunctional network, impairment in the striatum leads to an insufficient gating function of the thalamus, resulting in cortical hyperactivities. In this context, the direct pathway in the patients with OCD predominates over the indirect pathway. In terms of symptom-relations, the striatum is essentially involved in unconscious acquisition of the initial process of action or behavior, and hypermobilization of the impaired striatum could lead to compulsive symptoms in the manner of ritual behaviors, in order to normalize the undesirable thoughts or anxieties occurring via the dysfunctional thalamus. On the other hand, these invasive thoughts and excess anxieties would relate with hyperactivity in the OFC and ACC, respectively.

Previous functional neuroimaging studies in subjects at rest or undergoing symptom-provocation have implicated an increase in rCBF/rGMR in the OFC (Baxter et al., 1987, 1988; Benkelfat et al., 1990; Horwitz et al., 1991; Rubin et al., 1992, 1995; McGuire et al., 1994; Alptekin et al., 2001), ACC (Swedo et al., 1989; Horwitz et al., 1991; Perani et al., 1995), caudate nucleus (Baxter et al., 1987, 1988; Diler et al., 2004; Saxena et al., 2004), putamen (Benkelfat et al., 1990; Perani et al., 1995) and thalamus (McGuire et al., 1994; Perani et al., 1995; Alptekin et al., 2001; Saxena et al., 2001, 2004), strongly suggesting hyperactivities in the cortico-subcortical loop in patients with OCD. However, other studies have demonstrated inverse results, i.e., decreases in the OFC (Crespo-Faccoro et al., 1999; Busatto et al., 2000), ACC (Busatto et al., 2000), caudate nucleus (Rubin et al., 1992, 1995; Edmonstone et al., 1994; Lucey et al., 1995, 1997), putamen (Edmonstone et al.,

1994) and thalamus (Martinot et al., 1990; Lucey et al., 1995). These discrepancies were presumed to be due to varied treatment duration of serotonin reuptake inhibitors (SRIs) (Rubin et al., 1995), or to childhood- or adult-onset of the disease (Geller et al., 1995), presence or absence of comorbidity disorders such as MDD or tic disorder (Crespo-Faccoro et al., 1999; Hoehn-Saric et al., 2001) and the measurement of different parameters (brain blood flow or metabolism). Interestingly, whereas SPECT studies tended to indicate a decrease in rCBF, FDG-PET studies tended to show an increase in rGMR in the key regions in the disease, suggesting a possibility of uncoupling between brain blood flow and glucose utilization (Whiteside et al., 2004). At the very least, these regions are closely involved in the pathophysiology of OCD.
Studies on the relation between the symptom severity and the degree of abnormality in these areas have presented very varied results and failed to provide consistent findings.

5.2 Change following intervention by SRIs and cognitive-behavior therapy

Previous studies have replicated well that aberrant findings of rCBF/rGMR relevant to OCD-related regions could be normalized by pharmacological intervention of SRIs. Treatment of clomipramine, a tricyclic antidepressant, over several months could normalize regional blood flow or metabolism in the OFC and/or caudate nucleus from significant increase level prior to intervention compared to normal controls (Benkelfat et al., 1990; Swedo et al., 1992; Rubin et al., 1995). Also, intervention by two SSRIs, paroxetine and fluoxetine, provided similar results to clomipramine; increased rCBF/rGMR in the OFC and/or caudate nucleus at baseline were reduced significantly following treatment with paroxetine (Saxena et al., 1999, 2002; Hansen et al., 2002; Diler et al., 2004) and increased rCBF/rGMR in the ACC/caudate nucleus/thalamus at baseline decreased significantly after fluoxetine treatment (Hoehn-Saric et al., 1991; Baxter et al., 1992). Furthermore, in most of these studies, responders in clinical symptoms to pharmacological intervention tended to show a significant decrease relative to baseline, whereas non-responders showed no change by the treatment (Benkelfat et al., 1990; Baxter et al., 1992; Swedo et al., 1992; Saxena et al., 1999; Hoehn-Saric et al., 2001; Diler et al., 2004; Ho Pian et al., 2005). With respect to response prediction, several studies have found that the lower the brain blood flow or metabolism in relevant regions prior to treatment was, the greater was the reduction in OCD symptoms (Benkelfat et al., 1990; Saxena et al., 1999). In addition, there were significant correlations between decrease of metabolism at baseline in the OFC or caudate nucleus and improvement of OCD symptoms (Benkelfat et al., 1990; Swedo et al., 1992; Baxter et al., 1992). However, studies on significant response predictors have been very restricted and reliable parameters on response prediction have never been explored to date.
CBT, interestingly, also appears to normalize increased rCBF/rGMR in some relevant areas, including the caudate nucleus (Baxter et al., 1992; Schwartz et al., 1996; Nakatani et al., 2003) and thalamus (Saxena et al., 2009). Additionally, responders to CBT exhibited greater reduction in the caudate nucleus from baseline to CBT intervention than did non-responders (Schwartz et al., 1996). Although there have been few studies up to now on the alteration of brain function before and after CBT, growing notions on the effects of CBT on brain functions within subjects would address some important issues on whether the functional brain change induced by SRIs is a direct consequence of their pharmacological actions, or a state consequence occurring regardless of treatment approaches.

5.3 Depression as a comorbidity with OCD

Although most studies have been directed to the patients with OCD without MDD, in clinical practice OCD patients frequently have major depression as a comorbidity; approximately one-third of OCD patients also have MDD (Rasmussen and Eisen, 1992; Weismann et al., 1994), whereas 22-38% of patients with MDD have obsessive-compulsive symptoms (Kendell and DiScipio, 1970). Thus, notions acquired from studies performed on pure OCD patients without depression might deviate from the actual pathophysiology of OCD. Further, since SRIs and CBT are commonly effective for improvement of both OCD and MDD, exploration of the neuronal substrates shared by the two diseases might provide very valuable information for understanding the etiology.

Saxena et al. (1999) demonstrated that patients with concurrent OCD and MDD showed a significant reduction in metabolism in the hippocampus similar to that of patients with MDD alone. Furthermore, treatment with paroxetine for patients with concurrent OCD and MDD induced a reduction of rGMR in the ventral lateral prefrontal cortex, which was similar to the findings in patients with MDD alone, but did not show a decrease in the OFC and caudate nucleus like that seen in the patients with OCD alone (Saxena et al., 2002). These findings suggested that patients with concurrent OCD and MDD had the pathophysiology of MDD, and thus may constitute a distinctive subtype within OCD, such that both the etiologies of OCD and MDD should be considered carefully when devising a treatment strategy.

5.4 Conclusion

Functional neuroimaging studies on OCD have provided much more consistent findings than structural MRI studies. That is, in patients with OCD, some important regions in the cortical and subcortical areas present with hyperactivity and are normalized by pharmacotherapy. Since improvements by SRIs and CBT occur in only about half of patients (responders), further neuroimaging studies controlled by treatment intervention are strongly needed.

6. References

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8

The Memory, Cognitive and Psychological Functions of Sleep: Update from Electroencephalographic and Neuroimaging Studies

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1. Introduction

Sleep is a universal biological feature in almost all, if not in all species, and represents a global state of immobility with greatly reduced responsiveness to environmental stimuli, which can be distinguished from coma or anaesthesia by its rapid reversibility (Cirelli & Tononi, 2008). It is by no means a dormant state. When it is prevented, the body tries to recover the lost amount. The existence of sleep rebound after deprivation reveals that sleep is not simply a period of reduced activity or alertness regulated by circadian or ultradian rhythms (Dinges et al., 2005). Notably, in most vertebrates and all mammal species, including man, sleep displays a specific architecture roughly described as a cyclic occurrence of rapid eye movement (REM) sleep and non-REM sleep. Further, dramatic changes in brain electrophysiology, neurochemistry and functional anatomy biologically distinguish the different sleep stages from one another (Hobson & Pace-Schott, 2002; Pace-Schott & Hobson, 2002). Also, human and animal neurophysiologic studies have shown that the magnitude of changes in brain metabolism and neuronal activity in many discrete brain structures during certain sleep stages exceeds that during most of the waking periods (Gottesmenn, 1999; Maquet et al., 1996; Nofzinger et al., 1997; Steriade & Timofeev, 2003).
Although the precise functions of sleep are still beyond comprehensive understanding (Cirelli & Tononi, 2008), many studies point to the critical role of sleep for physiological functioning and adaptation. Its vital importance is well documented by the fact that its deprivation in rodents and flies can cause death more quickly relative to food deprivation (Rechtschaffen, 1998). Thus, sleep is shown to serve many energetic and metabolic, immune, thermoregulatory, cardiovascular, and respiratory functions, all responsible for normal brain and body homeostasis (Siegel, 2009; Tononi & Cirelli, 2006). Notably, along with these functions, sleep is shown to play a key role for important cognitive and psychological processes, among which learning and memory have been most intensively studied (Diekelmann & Born, 2010; Rasch & Born, 2007; Stickgold, 2005; Walker, 2008; Walker & Stickgold, 2006; 2010). Accordingly, an extensive body of research has revealed a cruicial

role for sleep in human cognitive abilities (Mander et al., 2008; Schabus et al., 2006; 2008; Yoo et al., 2007b), heuristic creativity and insightfulness (Cai et al., 2009; Stickgold et al., 1999; 2001; Wagner et al., 2004; Yordanova et al., 2008; 2009; 2010), constructive thinking and decision making (Durrant et al., 2011; Venkatraman et al., 2011), and emotional regulation (Walker, 2009; Walker & van der Helm, 2009). The latter engages consolidation of emotional memory (Nishida et al., 2009; Wagner et al., 2001; 2006; Walker, 2009) and emotional processing (Gujar et al., 2011a; 2011b; Yoo et al., 2007a). Collectively, these various associations suggest that sleep provides unique conditions for off-line memory consolidation, reconsolidation and information reprocessing to take place. However, it is still not precisely known whether these mechanisms are distinctly different from the restoring and energetic functions of sleep, whether the two types of functions are coupled, or whether the latter simply facilitate the cognitive functions of sleep.

Many electroencephalographic (EEG) and neuroimaging studies including functional magnetic resonance imaging (fMRI) have found that the structural and functional organization of the neural substrate undergoes changes during sleep in relation to human cognition. The entity of neural mechanisms underpinning cognitive and psychological functions of the brain is generally recognized as brain plasticity, i.e., as the capability of the neural substrate to reorganize over time as a result of previous experiences. In this chapter, studies demonstrating that sleep affects cognition by neural plasticity mechanisms in humans will be updated and overviewed to provide a converging framework for better understanding the role of sleep for memory, cognitive abilities and psychological functioning. Since mechanisms of brain plasticity are closely related to sleep physiology, architecture and neurobiological regulation, the reader will be first introduced to neurobiology of sleep.

2. Neurobiology of sleep

2.1 Sleep architecture and physiology

The heterogeneous nature of sleep can be seen in human and in most animal polysomnographic (PSG) records, which traditionally use electrophysiological techniques including electroencephalography (EEG), electromyography (EMG) and electro-oculography (EOG) to characterize sleep at system levels. In humans, overnight sleep is characterized by a cyclic occurrence of non-REM sleep and REM sleep. Non-REM sleep includes lighter sleep stages 1 and 2 and stages 3 and 4 of the deeper slow wave sleep (SWS) (Rechtschaffen & Kales, 1968). Whereas SWS dominates the first half of the night, REM sleep and stage 2 of non-REM sleep dominate the second half. This ultradian dynamics reflects the circadian regulation of sleep that is distinguishable from its homeostatic regulation seen after sleep deprivation or prolonged wakefulness (Borbély 1982; Borbély & Ackermann, 1999). Normally, sleep onset begins with a brief period of stage 1 of non-REM sleep, which is subsequently followed by sleep deepening marked by appearance of stage 2 of non-REM sleep and a further progressive transition to stages 3 and 4 of SWS. The latter is followed by a relatively short transient of stage 2 of non-REM sleep, after which a period of REM sleep appears. This progression of sleep stages, and in particular, the non-REM sleep - REM sleep alternation forms one sleep cycle with approximately 90 min duration. About 5 or more such sleep cycles are usually observed in the normal human overnight sleep (Broughton, 1987; Rechschaffen & Kales, 1968; Sinton & McCarley, 2000).

2.2 Electrophysiological signatures of sleep stages

The distinct sleep stages of either human overnight sleep or human daily naps can be determined by their specific "macroscopic" electrophysiological signatures, which are described by Rechschaffen & Kales (1968) and are commonly used for human sleep stages scoring. Unlike the desynchronized mode of EEG activity during wakefulness, the electrophysiological signatures of different sleep stages are more complex, which reflects a more heterogeneous nature of sleep than that of wake (Hobson & Pace-Schott, 2002). Basically, wakefulness is divided into active wake, characterized by desynchronized low-voltage fast EEG activity including beta (~ 15-30 Hz) and gamma (> 30 Hz) rhythms as well as by theta (~ 5 Hz) EEG activity with frontal-midline location, and quiet wake, characterized by posterior alpha (~ 10 Hz) and central sigma (~ 12-14 Hz) EEG rhythms that replace the desynchronized EEG mode of the active wake (Niedermeyer, 1993). The electrophysiological signatures of both active and quiet are show in Figure 1.

Sleep initiation is described as a replacement of waking EEG by theta or slower rhythms paralleled by an appearance of very slow circular eye movements, and both electrophysiological features form stage 1 of non-REM sleep (Broughton, 1987; Sinton & McCarley, 2000). Stage 2 of non-REM sleep is defined by presence of the classical EEG sleep spindles oscillating at ~ 12-15 Hz with central-parietal location, slower sleep spindles oscillating at ~ 9-13 Hz with frontal location and sporadic biphasic slow waves known as K-complexes (Anderer et al., 2001; De Gennaro & Ferrara, 2003). Sleep spindles are present also in the deeper SWS stages, but in less pronounced and discrete forms, among which spindle activity in the frequency range of ~ 8-12 Hz with frontal location is recognized to dominate SWS (Cantero et al., 2002; Salih et al., 2009). K-complexes are regarded as precursors of EEG components of the SWS (Amzica & Steriade, 1997; De Gennaro & Ferrara, 2003). These "macroscopic" human electrophysiological signatures of distinct sleep-wake stages are shown in Figure 1.

SWS is hallmarked by synchronous high-voltage (> 75 μV) EEG delta (~ 1-4 Hz) waves and slow (< 1 Hz) oscillations (SO) (Achrermann & Borbely, 1997; Crunelli & Hughes, 2010; Steriade et al., 1993), both recognized as slow wave activity (SWA) (Fig. 1). SO are also shown to occur in stage 2 of non-REM sleep (Crunelli & Hughes, 2010; Nir et al., 2011), and the SO during both stage 2 of non-REM sleep and SWS are shown to group and synchronize sleep spindles and delta waves (Mölle et al., 2002; Mölle et al., 2004; Steriade, 2001). Whereas sleep spindles originate form interactions between thalamo-cortical circuits involving γ-aminobutyric (GABA)-ergic thalamic neurons and glutamate-ergic cortical neurons (De Gennaro & Ferrara, 2003; Steriade, 2006), SO are shown to have a neocortical origin (Achrermann & Borbely, 1997; Nir et al., 2011; Steriade et al., 1993), although they are also proposed to emerge form the thalamus (Crunelli & Hughes, 2010). Another important EEG signature of SWS seen not only in animals but also in human intracranial EEG recordings, is reflected by hippocampal sharp-wave/ripple (SWR) bursts. Hippocampal sharp waves generated in the hippocampal CA3 region are fast depolarizing events, on which high-frequency oscillations (~ 80-200 Hz) originating from an interaction between inhibitory interneurons and pyramidal cells in CA1 (so-called ripples) are superimposed (Buzsáki, 2006; Csicsvari et al., 1999). Notably, SO have been shown to group also SWR in rodents (Battaglia et al., 2004; Sirota et al., 2003), and a temporal phase-coupling between SO, sleep spindles and SWR has been demonstrated in human depth EEG records during SWS (Clemens et al., 2007; 2011; Nir et al., 2011). The complex relationship between these sleep signatures is regarded as reflecting brain plasticity mechanisms at a system level, which is

important for the memory consolidation and reconsolidation during SWS (Diekelmann & Born, 2010).

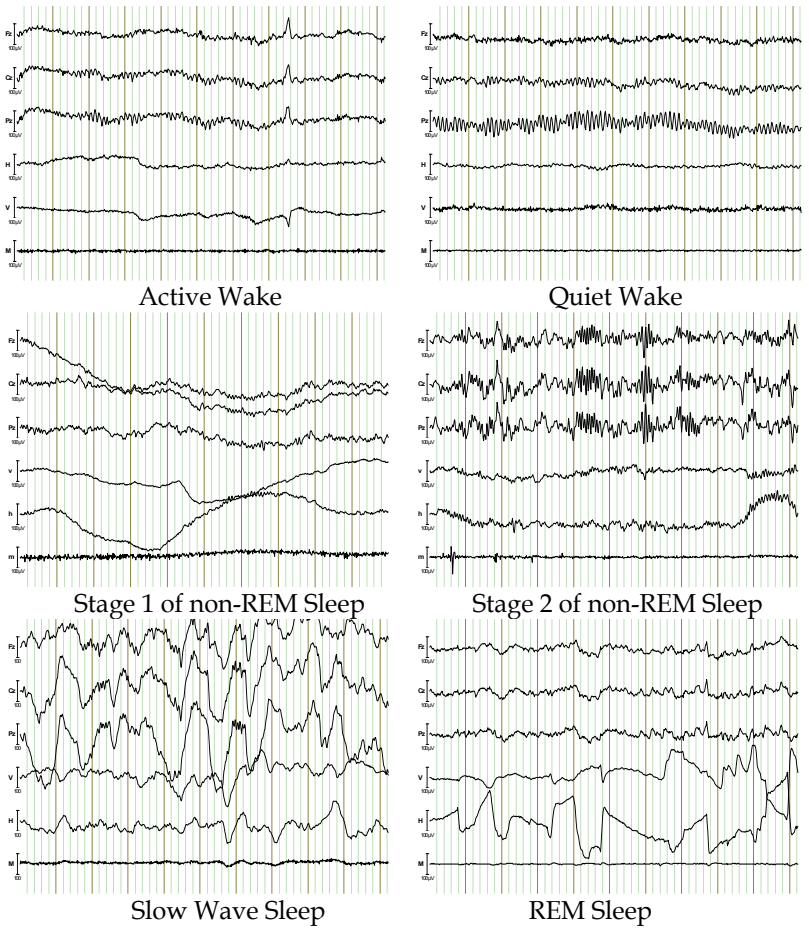

Fig. 1. Electrophysiological signatures of distinct sleep-wake stages: EEG recorded from Fz, Cz and Pz, vertical (v) and horizontal (h) eye movements, and electromyogram (m). Calibration marks are set-up at 100 μV, time (horizontal) marks are 1 s.

Unlike non-REM sleep electrophysiology, REM sleep EEG signatures (Fig. 1) include low-voltage desynchronized wake-like EEG activity comprising theta and fast (beta and gamma) rhythms accompanied by a swift occurrence of rapid eye movements (REM) upon lack of muscle tone (Aserinsky & Kleitman, 1953; Cantero et al., 2003; Clemens et al., 2009). Hippocampal theta rhythm is a prominent REM sleep EEG signature in rodents (Gottesmann, 1999; Kirov & Moyanova, 2002) and felines (Hobson & Pace Schott, 2002), while in human hippocampus and neocortex it is less coherent (Cantero et al., 2003). Further, REM sleep is hallmarked by ponto-geniculo-occipital (PGO) waves. PGO waves are driven by intense bursts of synchronized activity that propagate from the pontine brainstem mainly to the lateral geniculate nucleus and visual cortex (Callaway et al., 1987; Hobson & Pace-Schott, 2002; Pace-Schott & Hobson, 2002). They occur in temporal association with

REM in rats and felines (Callaway et al., 1987; Stickgold et al, 2001), as well as in humans (Lim et al, 2007; Miyauchi et al., 2009), and are suggested to reflect both dream mental states of REM sleep and cognitive processing during this sleep stage (Stickgold et al., 2001). REM sleep signatures are shown to reflect mechanisms of brain plasticity at synaptic and genetic levels (Ribeiro et al., 1999; 2002), which may promote not only REM sleep specific processes, but also a further transformation of consolidated memories (Walker & Stickgold, 2010).

2.3 Mechanisms of sleep regulation

The regulation of sleep is active in its own rights, and is closely related to sleep's physiology and functions (Hobson, 2005; Pace-Schott & Hobson, 2002). The respective neurobiological mechanisms are represented by complex reciprocal interactions between different neuronal populations and their chemical modulators and transmitters in distinct functional states across sleep-wake cycle leading to distinct functional states (Gottesmann, 1999; Hobson et al., 1975; Hobson & Peace-Schott, 2002; Peace-Schott & Hobson, 2002). Two major brain regions are mostly considered in sleep regulation, especially when functions of sleep are concerned (Pace-Schott & Hobson, 2002). The first engages neuronal populations located in the diencephalon, in particular, the hypothalamus, mostly involved in the circadian regulation of sleep. The second brain region engages brainstem or meso-pontine and basal forebrain nuclei spread in the reticular ascending system (RAS) and projecting noradrenaline (NA), serotonin (5-Hydroxytryptamine, 5-HT) and acetylcholine (Ach) neuromodulatory signals to upper brain structures including the basal ganglia and amygdala, thalamus, hippocampus, and cortex. These mechanisms are essential for the ultradian alternating expression of non-REM sleep-REM sleep periods (Gottesmann, 1999; Hobson et al., 1975; Pace-Schott & Hobson, 2002). Briefly, during wake, brainstem/meso-pontine NA, 5-HT, Ach, and hypothalamic histamine (HIS) neurons projecting to upper brain structures and cortex, are all active, thus sustaining functional brain states optimal to the environmental requirements (Gottesmann, 1999; Hobson & Pace-Schott, 2002; Pace-Schott & Hobson, 2002). As sleep deepens from stages 1 and 2 to SWS, all these neuromodulators progressively decrease their activities, with their lowest levels observed during SWS. This leads to strongly diminished or lacking RAS neuromodulation of upper brain structures and cortex, which in turn, is responsible for the appearance of non-REM sleep EEG signals represented by sleep spindles, K-complexes and SWA, all originating from thalamo-cortical and cortico-cortical interplay (McCormick & Bal, 1997; Pace-Schott & Hobson, 2002; Steriade & Timofeev, 2003). In REM sleep, all NA, 5-HT and HIS neurons cease their firing. In contrast, Ach excessive over-activity emerges projecting to the cortex and all sub-cortical structures, which produces the electrophysiological signatures of REM sleep (Gottesmann, 1999; Pace-Schott & Hobson, 2002).

2.4 Neuroimaging of sleep and wake

Several neuroimaging studies using either fMRI or positron-emission tomography (PET) have investigated the pattern of brain activation across wake, non-REM and REM sleep. These studies have demonstrated that anterior cingulate cortex, right and left amygdaloid complexes, pons, parahippocampal cortex, and extrastriate visual cortex are more active during REM sleep compared with wake and non-REM sleep, whereas the activation of other brain areas including right and left dorsolateral prefrontal cortices, right and left parietal cortices and precuneus, posterior cingulate cortex, and primary visual cortex, is suppressed in REM sleep compared with wake. All these brain regions have been shown to be the most

suppressed during non-REM sleep (Broun et al., 1997; 1998; Maquet et al., 1996; Miyauchi et al., 2009; Nofzinger et al., 1997). Yet, other brain structures are shown to specifically increase their activation in relation to distinct non-REM sleep stages and their EEG signatures. For example, blood oxygen level-dependent (BOLD) signal from the thalamus is strongest during spindle activity in stage 2 of non-REM sleep (Schabus et al., 2007), whereas during SO in SWS, brain functional activation is strong in the medial temporal cortex, the parahippocampal cortex, and neocortical areas (Dang-Vu et al., 2005; 2008; Maquet et al., 1997).

2.5 Mental characteristics of the sleep-wake stages

Notably, from a cognitive point of view, the mental characteristics of sleep-wake stages well correspond to their brain activation patterns found in neuroimaging studies (Fosse et al., 2001; 2004; Hobson & Pace-Schott, 2002; Hobson et al., 2000; Stickgold et al., 2001). Thus, wake is characterized by strongest and most logic thoughts in the presence of sensory input, executive control and goal-directed behavior. Sleep onset is hallmarked by the so called hypnagogic hallucinations, and as sleep deepens from stage 2 of non-REM sleep to SWS, thinking becomes more and more scares, and almost absent during SWS. Yet, there are logic thoughts mostly associated with previous wake experiences (Fosse et al., 2004; Hobson, 2005; Hobson et al., 2000; Stickgold et al., 2001). During REM sleep, mental activity is likely hallucinatory, and is behaviorally expressed in vivid, bizarre and elusive dreams (Fosse et al., 2004; Hobson et al., 2000; Stickgold et al., 2001). Also, REM sleep mentality is characterized by a most salient emotional tone upon lack of sensory input (Hobson et al., 2000) and executive control, as evidenced by the neuroimaging data (suppression of the dorsolateral prefrontal cortex, e.g., Maquet et al., 1996).

3. Sleep and memory

Likewise the heterogeneous structure of sleep, memory categories believed to exist in human brain are distinctly different. Roughly, they can be divided into declarative and non-declarative or procedural memory, and the same categorization holds true for the processes of learning (Dienes & Perner 1999). Declarative memory is considered to comprise consciously accessible memories of fact-based information (i.e., knowing "what"). Several subcategories of the declarative system exist, including episodic memory (autobiographical memory for events of one's past) and semantic memory (memory for general knowledge, not tied to specific events, but rather tied to its verbal components) (Tulving 1985). Current neural models of declarative memory formation emphasize the critical importance of structures in the medial temporal lobe, especially the hippocampus, and thus, declarative memory is also known as hippocampus-dependent memory (Eichenbaum, 2000). In contrast, procedural or implicit memory is regarded as non-conscious, comprising memory of knowing "how", such as learning of actions, habits, and skills, as well as implicit learning (Dienes & Perner 1999). Procedural memory formation appears to be less dependent on medial temporal lobe structures, and to include sensori-motor cortices, basal ganglia and cerebellum (Forkstam & Petersson 2005).

3.1 Overview of human EEG data

Since the discovery of SO (< 1 Hz) in cats (Steriade et al., 1993) and (~ 0.7-0.8 Hz) in humans (Achrermann & Borbely, 1997), this hallmark of human non-REM sleep, and SWS in

particular, has been proposed as an essential mechanism underlying the consolidation of hippocampus-dependent memories (Buzsáki, 1989; Marshall & Born, 2007; Mölle et al., 2004; Steriade, 2001). In human SWS, "up" and "down" EEG states of SO are shown be dissimilarly associated with a number of electrophysiological events. Specifically, the "up" state of the SO is marked by increased occurrence of delta slow waves and sleep spindles, whereas during the 'down" state of SO, delta slow wave and sleep spindle activities markedly decrease (Mölle et al., 2002; 2004). Thus, human SO are demonstrated to group both slow waves and spindles. Further, a rapid increase of the underlying neuronal activity (depolarizing state) and a rapid decrease in it (hyperpolarizing state) have recently been shown to characterize human SO "up" and "down" wave forms, respectively (Nir et al., 2011). Finally, human studies have demonstrated time and phase coupling between SO, slow waves, sleep spindles, and hippocampal SWR bursts (Clemens et al., 2007; 2011; Nir et al., 2011). Collectively, these findings strongly indicate that non-REM sleep/SWS SO represent an EEG mechanism involved in plastic changes sub-serving the hippocampus-dependent memory consolidation.

Indeed, SO have been shown to be strongly associated with both procedural (Huber et al., 2004) and declarative (Mölle et al., 2004) memory consolidation taking place in human non-REM sleep/SWS. Later, to verify the specific role for SO in hippocampus-dependent memory consolidation, a series of studies, in which brain rhythms have been modulated using trans-cranial direct current stimulation (tDCS), has been conducted in humans. This method is now recognized as a reliable tool for modulating both the internally generated brain rhythms and the activity of underlying neuronal populations, depolarized under anodal tDCS and hyperpolarized under cathodal tDCS, respectively (Fröhlich & McCormick, 2010; Reis et al., 2008).

Initially, weak (not perceived by subjects) anodal tDCS oscillating at 0.75 Hz (slow oscillation stimulation, SOS) has been delivered during the transition from stage 2 of non-REM sleep to SWS after declarative and procedural learning before sleep. Compared with a sham condition, stimulation has selectively produced a gain in only declarative memory after sleep. Importantly, it has also produced a substantial increase in SO (~ 0.75 Hz) and frontal slow alpha spindle (8-12 Hz) activity, possibly by entraining these sleep EEG rhythms (Marshall et al., 2006). These findings have provided strong evidence for the role of SO and/or frontal slow spindle activity for the hippocampus-dependent memory consolidation. However, they have not addressed the question of whether SOS itself or whether endogenous SO boosted by the SOS have resulted in improvement of the consolidation of declarative memory found. This question was addressed in two later studies. In these studies, weak anodal tDCS oscillating at frequencies not common for the respective functional brain states was applied. In particular, SOS oscillating at 0.75 Hz was applied during quiet or resting wake retention period after learning declarative and procedural tasks. SOS did not affect either declarative or procedural memory consolidation, nor did it affect working memory and mood at retest. However, in contrast to its EEG effects during non-REM sleep (Marshall et al., 2006), it produced only a local (at the frontal sites of stimulation) increase in EEG power in SO (0.4-1.2 Hz) frequency band, accompanied by a widespread and strong increase in theta (4-8 Hz) EEG power. Further, when delivered in active wake state during encoding of a verbal learning memory task, the 0.75 Hz SOS produced virtually the same EEG effects as during quite wake (local increase in SO and widespread increase in theta power), but it significantly improved encoding of declarative verbal information (Kirov et al., 2009). Recently, tDCS oscillating at 5 Hz (wake and/or REM

sleep EEG rhythm, theta stimulation) was applied in the first non-REM sleep cycle of overnight sleep, during the transition from stage 2 of non-REM sleep to SWS, after subjects have learned tasks of both declarative and procedural memory before sleep. Notably, theta stimulation disrupted the normal progression of SWS, SO (0.5-1 Hz) and SWA (1-4 Hz) EEG power in the course of the stimulation. Also, it significantly decreased slow spindle activity (8-12 Hz) only frontally. These EEG changes were associated with a strong impairment of only declarative memory consolidation at recall after sleep (Marshall et al., 2011). Collectively, these findings strongly indicate that SO, SWA and frontal slow spindle activity reflect specific EEG mechanisms of hippocampus-dependent memory consolidation, which do not act beyond non-REM sleep/SWS. Moreover, they provide one of the strongest evidence for the assumption that during active wake, encoding of memory is reflected by theta EEG oscillations, which possibly reflect a transfer of information from the cortex to the hippocampus (Sederberg et al., 2003). Essentially, they strongly support the notion that memories encoded during wake undergo off-line consolidation during non-REM sleep/SWS by mechanisms involving an interplay between the hippocampus and the cortex, as reflected by the SO and frontal slow alpha activity (Buzsáki, 2006; Mölle et al., 2002; 2004; Marshall et al., 2006). Another recent investigation clearly showed strong and positive correlations between SO and sleep spindle EEG activities during the earliest portion of overnight non-REM sleep/SWS and rates of off-line improvement of both declarative and non-declarative memories (Wilhelm et al., 2011). These sleep EEG rhythms correlated positively with gain of improvement of only memories that were expected to be of further relevance, and not with memories that were not, with the latter memories being not found affected by sleep. Notably, this study demonstrates that SO and sleep spindles during non-REM sleep/SWS, are important EEG patterns not only for memory consolidation but also for memory reprocessing or reconsolidation (Wilhelm et al., 2011).

Some of the observations in the studies of Marshall et al. (2006; 2011) and Wilhelm et al. (2011) deserve further mentioning. These studies clearly show associations of non-REM sleep/SWS EEG signatures with either memory consolidation or reconsolidation in the first non-REM sleep cycle (Marshall et al., 2006; 2011) and even before the occurrence of the first SWS period (Wilhelm et al., 2011). A more recent study demonstrates that during the first half of overnight sleep, SO and SWA represent a global electric brain event that can be reliably recorded from hippocampus, medial temporal lobe and neocortex, whereas during the second half, both SO and SWA are expressed rather like a local phenomenon without strong phase and time coupling (Nir et al., 2011). Thus, regarding the studies using oscillating tDCS during sleep (Marshall et al., 2006; 2011) together with these of Wilhelm et al. (2011) and Nir et al. (2011), it can be concluded that SO, frontal slow alpha activity and sleep spindles, all represent important sleep EEG signatures reflecting processes of hippocampus-dependent memory consolidation and reconsolidation, which processes take place in the earliest part of non-REM sleep.

Similarly, classical sleep spindles, the major EEG signature of stage 2 of non-REM sleep, have been proposed to reflect mechanisms of brain plasticity that take place during non-REM sleep (Sejnowski & Destexhe, 2000; Steriade, 2001). Many human studies have demonstrated that either number, density, or EEG power spectral activity of spindles during stage 2 of non-REM sleep have been significantly involved in both declarative (Clemens et al., 2005; Gais et al., 2002) and procedural (Clemens et al., 2006; Fogel & Smith, 2006; Fogel et al., 2007b; Nishida & Walker, 2007; Shabus et al., 2004; Tucker & Fishbein, 2009) memory consolidation. Moreover, Nishida & Walker attempted to distinguish between use-

dependent and experience depended sleep processes. They subtracted sleep spindle EEG activity measured at a "non-learning hemisphere (left)" from that measured at a "learning hemisphere (right)" and were able to demonstrate strong positive correlations with offline memory improvement that were not evident for either hemisphere alone (Nishida & Walker, 2007). Thus, classical sleep spindles appear to represent an EEG pattern reliably associated with memory processes.

3.2 Overview of human neuroimaging data

Notably, the first human neuroimaging study almost entirely confirm previous rodent findings, which have shown that sleep-dependent memory consolidation relies on reactivation of the so-called hippocampus place cells during SWS in response to spatial or maze navigating tasks (Wilson & McNaughton, 1994). Thus, Peigneux et al. (2004) using a combination of PET and sleep EEG (PSG) methods, showed for the first time such a reactivation of hippocampal and neocortical regions in humans. At encoding during wakefulness, subjects were trained (or not) to learn and find their way inside a complex three-dimensional virtual town. Compared with the non-trained group, subjects who learned the task at encoding during wake displayed an increase in their regional cerebral blood flow (rCBF) in a bilateral pattern of neural activation, including the right and left hippocampus, the right and left parahippocampal gyri, superior parietal lobules, right and left precuneus, lingual and posterior cingulate gyri, middle and superior occipital cingulate gyri, and the anterior lobes of cerebellum. In the trained group, rCBF was consequently measured during stage 2 of non-REM sleep, SWS and REM sleep. The neural pattern of activity found at training sessions during wakefulness was reactivated only during SWS. This pattern of reactivation during SWS strongly correlated with the level of improvement on the task at recall after sleep (Peigneux et al., 2004). Three years later, Rasch et al. (2007) also used a combination of fMRI and PSG methods to investigate specifically the role for SWS in declarative memory consolidation. The authors first established a robust association between declarative learning (card place location) stimuli and a smell, olfactory stimulus (the smell of a rose). Subjects learned object locations in a two-dimensional (2D) object location memory task in the evening before sleep. During the first two periods of subsequent SWS, the odor cue was presented again (in an alternating 30 s on/30 s off mode). In a control condition, odorless vehicle was delivered. At retrieval testing after sleep, memory of card locations was distinctly enhanced when the odor was presented during SWS as compared to presentation of vehicle alone. Re-exposure to odor during SWS improved retention of memory in a hippocampus-dependent manner: bilateral reactivation of the hippocampus and medial prefrontal lobe, as measured by BOLD signal (Rasch et al., 2007). Further, an fMRI study demonstrated that compared with total sleep deprivation, post-learning sleep enhances hippocampal responses during recall of word pairs (declarative memory) 48 h after learning, thus indicating intra-hippocampal memory processing during sleep (Gais et al., 2007).. At the same time, it was shown that sleep induced a memory-related functional connectivity between the hippocampus and the medial prefrontal cortex. Six months after learning, recalling the same declarative memories reactivated the medial prefrontal cortex even more strongly than they did during encoding before sleep, thus showing that sleep leads to long lasting changes in representation of memories at a system (hippocampal-cortical) level. Although this study does not show

reactivation of the hippocampus and medial prefrontal cortex during sleep, basing on previous findings, the authors assume an important role of hippocampal-cortical connectivity for sleep-dependent declarative memory consolidation (Gais et al., 2007). The last convincing evidence concerning the role for SWS in memory formation comes from a recent fMRI study where the effect of declarative memory reconsolidation on declarative memory consolidation during SWS and wake was investigated (Diekelmenn et al., 2011). By using an experimental protocol similar to that previously applied by Rasch et al. (2007), the authors aimed at reactivating memories in humans by presenting associated odor cues either during SWS or during wake. During wake, reactivation of memories was followed by an interference task to probe memory stability, and as expected (Brown & Robertson, 2007; Robertson, 2009), this reactivation resulted in destabilized memories. In contrast, reactivation during SWS immediately stabilized memories, thereby directly increasing their resistance to interference. Importantly, BOLD signal revealed quite different patterns of reactivation during SWS and wake. The reactivation during SWS was mainly seen in the hippocampus and posterior cortical regions, whereas reactivation during wake was primarily found in the prefrontal cortical areas, thus showing that reactivation of memory serves distinct functions depending on brain state: wake versus SWS (Diekelmann et al., 2011). It is to be noted that similar differences between effects of oscillating trans-cranial direct current stimulation on both EEG activity and memory processes was also shown during wake when compared to SWS, although these differences distinguished specifically verbal memory encoding from declarative memory consolidation (Kirov et al., 2009; Marshall et al., 2006; 2011).

To our knowledge, only one neuroimaging study was able to provide convincing evidence for reactivation of brain regions during REM sleep in association with sleep-dependent consolidation of procedural memory (Maquet et al., 2000). In this study, three groups of subjects learned a serial reaction time task (SRTT) during wakefulness. To verify which brain regions are activated by SRTT, one group was scanned by using of PET either during training or during the subsequent rest wake period, and was not further examined. Subjects from a second group were trained on the task during two sessions in the afternoon, and then scanned during the night after training, both during wake and during various sleep stages. This group was retested at recall after sleep to verify that sleep-dependent learning had occurred. A third group was scanned at the same time points as the second group was, however, under absence of learning (no learning condition). Sleep architecture in the latter two groups was assessed by a routine PSG, and rCBF was measured across both three groups and all time points. Interestingly, although the third group improved implicit learning component of SRTT at recall after sleep, no any changes in sleep architecture between the learning and the non-learning conditions were found. However, as measured by the rCBF, a specific pattern of brain activation found in the first group during and after learning was reactivated only in the second group, and only during REM sleep. This pattern engaged a set of brain regions located in occipital and premotor cortices (Maquet et al., 2000). A later PET study by the same group (Laureys et al., 2001) confirmed that specific brain reactivation occurs during REM sleep in relation to procedural memory consolidation (Maquet et al., 2000). The authors showed that the left premotor cortex is functionally more correlated with the left posterior parietal cortex and bilateral pre-supplementary motor area during REM sleep in subjects previously trained to a reaction time task relative to untrained

subjects. The increase in functional connectivity during post-training REM sleep additionally suggests that the reactivated brain areas participate in an optimization of a network that subtends subject's visuo-motor response (Laureys et al., 2001).
Altogether, the above neuroimaging findings show that the mechanisms of memory processing during early night non-REM sleep/SWS are distinctly different from those that take place in REM sleep. The former include complex interactions between hippocampus and cortex, thus reflecting brain plasticity mechanisms at system and neural levels. The latter include local patterns of brain reactivation, which are proposed to reflect brain plasticity mechanisms at synaptic and genetic levels.

4. Sleep and cognitive functions

The strongest evidence for the important role that sleep plays in a variety of cognitive functions comes from many observations of effects of sleep loss and sleep deprivation on cognition (Killgore, 2010; Walker, 2008). The exclusively important role of sleep for cognitive functions has been best demonstrated in a study showing that even one night of total sleep deprivation results in inability to learn facts, i.e. deficient encoding of episodic memories (Yoo et al., 2007b). The neuroimaging correlates of this impaired learning ability will be presented below in the respective section.

4.1 Overview of human EEG data

Sleep spindles, the major hallmark of stage 2 of non-REM sleep, have been for long proposed to be associated with human individual cognitive abilities or intelligence. For example, Bódizs et al. (2005) found that both grouping of fast sleep spindles by cortical slow oscillation over the left frontopolar derivation (Fp1) and fast sleep spindle density over the right frontal area (Fp2, F4) during stage 2 of non-REM sleep, correlated positively with general mental ability. Further, a robust positive correlations were found between slow (< 13 Hz) and fast (> 13 Hz) spindle activity in stage 2 of non-REM sleep and both individual cognitive abilities and implicit/explicit memory-related abilities (Schabus et al., 2006). Later, Fogel et al. (2007a) showed first that number of spindles in stage 2 of non-REM sleep remains relatively stable within individuals from night to night. Second, the authors demonstrated that the number of spindles and EEG power of sigma (slow spindle) activity were positively correlated with performance intelligence quotient (PIQ), but not with verbal IQ. Also, perceptual/analytical skills measured by the PIQ accounted for most of the interindividual differences in spindles. Interestingly, in the same study, a relationship between rapid eye movements in REM sleep and VIQ in individuals with higher IQ scores was also demonstrated (Fogel et al., 2007a). However, Tucker & Fishbein (2009) demonstrated that while subject's intelligence correlated positively with pre-sleep acquisition and post-sleep retest performance on both procedural and declarative tasks, it did not correlate with over-stage 2 of non-REM sleep spindle events. These findings suggest that intelligence may not be a powerful modulator of sleep's effect on memory performance (Tucker & Fishbein, 2009).
One major question arising from the above described findings is whether sleep contributes to human intelligence in a state dependent manner (i.e., by providing neurobiological conditions for memory consolidation and reconsolidation), whether sleep is associated with intelligence in a trait dependent manner (i.e., strictly individual sleep characteristics are

related to individual intelligence), or whether sleep and human intelligence are related in both ways (Geiger et al., 2011; Fogel & Smith, 2011). It has been previously proposed that sleep serves human intelligence by complex interactions between its unique physiological and mental states, and individual sleep patterns and cognitive traits (Kirov, 2007). One study has addressed this question providing some evidence that stage 2 of non-REM sleep spindle increase after learning is related to elaborate encoding before sleep, whereas individual's general learning ability is well reflected by inter-individual (trait-like) differences in absolute sleep spindle activity (Schabus et al., 2008). However,, the precise mechanisms involved in the complex association between sleep and intelligence remain so far poorly understood (Kirov, 2007). As will be seen in the paragraph below, the role for sleep in human heuristic creativity and insightful behavior can further illuminate this issue.

Importantly, it has been consistently shown that sleep provides unique conditions for development of human heuristic creativity (Cai et al., 2009; Stickgold et al., 1999; Walker et al., 2002), among which the insightful behavior, as a higher form of human intelligence, is of major importance (Wagner et al., 2004; Yordanova et al., 2008; 2009; 2010; in press). Human insight refers to discovering of regularities that are out of awareness. Notably, it has been demonstrated that as twice as many subjects who had slept after initial learning of a number reduction task (NRT) gained insight into a hidden regularity relative to subjects who had been sleep deprived (Wagner et al., 2004). However, Wagner and co-authors (2004) have not objectively assessed sleep architecture by PSG. Thus, it has remained unclear how and through which mechanisms sleep promotes insight. This question was addressed in a series of later studies using the so-called split night design (Plihal & Born, 1997; 1999). The first study investigating sleep's role for insight by the split night design demonstrated that implicit knowledge acquired at encoding of NRT before sleep was transformed into insight throughout the early night sleep rich in SWS, thus pointing a role for SWS in insight (Yordanova et al., 2008). Further, the same study demonstrated that implicit learning of NRT acquired at encoding (during awakening before the second half of night) was not further transformed but was preserved by the late night sleep rich in REM sleep, thus indicating that REM sleep stabilizes implicit learning (Yordanova et al., 2008). In two later studies, Yordanova and co-authors demonstrated that SWS contributes to gaining insight in a state dependent instead of a trait-dependent manner. First, they revealed a topographic re-distribution of slow cortical potentials (SPs) indicating that a spatial reorganization occurred only after early sleep rich in SWS, but not after late sleep, and only for predictable responses on NRT. This SPs reorganization correlated with the amount of SWS (Yordanova et al., 2009). Second, they showed that only after SWS a pattern of brain activation shown as a precondition for insight (increased alpha and beta EEG desynchronization at the right hemisphere and a lack of such at the left) occurred (Yordanova et al., 2010). Finally, these authors were able to extract a specific for SWS EEG rhythm, slow (8-12 Hz) alpha activity at the right hemisphere, which was associated with transformation of implicit knowledge into insight on the NRT, and which was distinctly different form use-dependent (SWA and 12-15 Hz spindle activity) found at the left hemisphere in response to task performance (Yordanova et al., in press). Collectively, these findings strongly indicate that sleep promotes insight, as a higher form of human intelligence, in a state dependent rather than in a trait dependent way.

Finally, a recent study questioned which sleep mechanisms may play a role for abstraction of an implicit probabilistic structure in sequential stimuli using a statistical learning

paradigm, and searched for a predictive relationship between the type of sleep obtained and subsequent performance improvements (abstraction). Participants who consolidated over either a night of sleep or a nap improved significantly more than those who consolidated over an equivalent period of daytime wakefulness. Importantly, PSG revealed a significant correlation between the level of improvement or abstraction and the amount of SWS obtained (Durrant et al., 2011).

4.2 Overview of human neuroimaging data

The existing so far neuroimaging data concerning sleep and cognition do not reveal patterns of brain reactivation during sleep. Instead, they reveal altered brain activities associated with impaired cognitive processes in response to sleep deprivation. One of the most important findings is presented in the study of Yoo et al. (2007b). In this study, two groups of subjects were randomly assigned to either a sleep deprivation (SD) or a sleep control (SC) group. All subjects underwent an episodic memory encoding session during fMRI scanning, in which they viewed a series of picture slides and were retested two days later (after two recovery nights of sleep) for a recognition test session (without fMRI). Compared with SC group, SD subjects displayed much worse recognition at retest after two days, though they had two nights recovery sleep. This finding clearly shows that sleep deprivation impairs learning. The fMRI scans at learning/encoding demonstrated a significant impairment of activation in the hippocampal complex in the SD relative to SC group, a region known to be of critical importance for learning of new information (Yoo et al., 2007b). Another study showed that compared with normal sleep, SD produced impairment of spatial attention that correlated with a reduced activation in the posterior cingulate cortex, as measured by fMRI (Mander et al., 2008). Similarly, it is shown that SD produces lapses of attention manifested as delayed behavioral responses to salient stimuli. To identify changes in task-related brain activation associated with lapses after SD, fMRI scans during a visual selective attention task were conducted. It was demonstrated that SD-related lapses in attention corresponded to (1) reduced ability of frontal and parietal control regions to raise activation in response to lapses, (2) dramatically reduced visual sensory cortex activation and (3) reduced thalamic activation during lapses (Chee et al., 2008). Another fMRI study by the same group tested the hypothesis of whether SD impairs short-term memory due to reduced storage capacity or whether it affects processes contributing to appropriate information encoding. Scans were conducted during performing a short-term memory visual task and during presenting varying visual array sizes without engaging memory. Whereas the magnitude of intraparietal sulcus activation and memory capacity after normal sleep were highly correlated, SD elicited a diminished pattern of activation on both tasks, indicating that deficits in both visual processing and visual attention account for loss of short-term memory capacity (Chee & Chuah, 2007). Further, an fMRI study showed that SD abolishes selective attention in association with a decreased BOLD signal found within fronto-parietal cognitive control areas (the left intraparietal sulcus and the left inferior frontal lobe) and parahippocampal place area (PPA) during a selective attention task performance. Additionally, SD resulted in a significant decrement in functional connectivity between the PPA and the two cognitive control fronto-parietal areas (Lim et al., 2010). Interestingly, a single night of SD was shown to produce a strategy shift during risky decision making such that healthy human volunteers moved from defending against losses to seeking increased gains. An fMRI assessment revealed that this change in economic preferences was correlated

with the magnitude of an SD-driven increase in ventromedial prefrontal activation as well as by an SD-driven decrease in anterior insula activation during decision making (Venkatraman et al., 2011).

Regarding the above described neuroimaging findings together, it can be concluded that sleep is of critical importance for almost all, if not for all types of cognitive processes, including decision making. However, which mechanisms are responsible for substantial deficits of the many cognitive functions seen after sleep deprivation is still elusive.

5. Sleep and psychological functions

Herein, we will review existing data about sleep's role in functions different from the above described memory and cognitive ones. These include consolidation of affect, emotional regulation and dreaming mental states. As will be shown, the mechanisms, trough which sleep serves these psychological processes are distinctly different from those involved in its memory and cognitive functions. It is to be emphasized, however, that mostly REM sleep has been so far consistently and reliably associated with these human psychological processes. REM sleep characteristics are implicated for both normal psychological processes and psychopathology. Thus, REM sleep and its mental content incorporated in the co-occurring dreaming production have been proposed to aid resolution of personal emotional, affective and social conflicts (Cartwright et al., 2006; McNamara et al., 2001; 2005; 2010). Notably, REM sleep mechanisms and mental signatures have also been proposed to be involved in the pathogenesis of a number of psychopathological conditions, including posttraumatic stress disorder, anxiety, depression, schizophrenia, etc. (Benca et al., 1992; Gottesmann, 2010; Kirov & Brand, in press; Wagner et al., 2006; Walker, 2009; Walker & van der Helm, 2009). These observations are conceptualized in the so-called continuity hypothesis, according to which cognitive and emotional experiences generated, developed and used during wakefulness do continue to evolve during dreaming in REM sleep (Dumhoff & Hall, 1996; Pesant & Zadra, 2006). A recent study tested this hypothesis in both congenitally paraplegic and deaf-mute persons and matched controls. Surprisingly, perceptual representations, even of modalities not experienced during wakefulness, were quite common in dream reports not only in the control persons but also in the handicapped subjects (Voss et al., 2011). These interesting results give support to a protoconsciousness theory of REM sleep dreaming state that was recently forwarded by Hobson (2009). The REM sleep-dream protoconsciousness hypothesis proposes that development and maintenance of waking consciousness and other high-order brain functions (secondary consciousness) depends on brain activation during REM sleep (primary consciousness, i.e., simple awareness that includes perception and emotion in sleep), thus implicating for phylogenic aspects of dreaming. Accordingly, the neurobiology of REM sleep and co-occurring dreaming mentality reflect more basic (i.e., threaten, feeding, sexual, etc.) features not only in humans but also in lower species (Hobson, 2009). Interestingly, this view seems to have much in common with a previously proposed hypothesis about the psychological functions of REM sleep as an interactive genetic programming brain state (Jouvet, 1998). These two views (Hobson, 2009; Jouvet, 1998) predict that human experience during wakefulness is given more basic biological characteristics during REM sleep, which may have important adaptation roles. Also, they well fit with a more recent opinion about the memory functions of REM sleep, according to which memories consolidated during SWS undergo further transformation during REM sleep in terms of placing them in a more general and individually specific context (Walker & Stickgold, 2010).

5.1 Overview of human EEG data

Notably, human REM sleep has been so far shown to consolidate declarative (episodic or semantic) memory only when items have emotional salient components, and only when these emotional components have negative valence (Wagner et al., 2001; 2006; Nishida et al., 2009). Recently, REM sleep was shown to be very important for recalibration of the sensitivity of human brain to specific emotions (Gujar et al., 2011a).

Data concerning human sleep EEG findings about the role of REM sleep in psychological functioning are still scarce. One study investigated the effect REM sleep portion of a daily nap on episodic memory consolidation. No memorizing effects on emotionally neutral fact-based information were found. However, when episodic items were associated with negative emotional components, REM sleep strongly consolidated them. Moreover, the improvement strongly and positively correlated with all, REM sleep latency, amount of REM sleep, and importantly, with the theta (4-8 Hz) REM sleep EEG signature (Nishida et al., 2009). A more recent study tested whether boosting REM sleep EEG signatures could produce overnight improvement of memory consolidation. In this study, REM sleep EEG was potentiated by delivering theta (5 Hz) anodal trans-cranial direct current stimulation during REM sleep periods in the second half of night. The stimulation did enhanced gamma (25-45 Hz) EEG activity during REM sleep, but it did not improve either declarative or procedural memory consolidation at morning recalls. Instead, this increase in gamma EEG during REM sleep resulted in a worsened mood, as assessed by positive and negative affect scale, in the morning after sleep, accompanied by worsening on working memory, as assessed by a word fluency test (Marshall et al., 2011). Collectively, these studies demonstrate that specific REM sleep EEG rhythms are involved in affective behavior.

Interestingly, a recent study demonstrated the EEG signatures of dream recall from both REM sleep (theta, 5-7 Hz EEG activity) and stage 2 of non-REM sleep (alpha, 8-12 Hz EEG activity) (Marzano et al., 2011). These findings document different modes of mentality in REM sleep versus non-REM sleep. Furthermore, they suggest that the neurophysiological mechanisms underlying encoding and recall of episodic memories may remain the same across different states of consciousness.

5.2 Overview of human neuroimaging data

The existing so far human neuroimaging studies about the role for sleep in emotional regulation demonstrate deteriorated patterns of brain activation after total sleep deprivation (SD). By using fMRI, it has been shown that a disconnection between medial prefrontal cortex and amygdala following SD has been associated with improper response to negative emotional stimuli (Yoo et al., 2007a). Further, Sterpenich et al. (2007) showed that a successful recollection of emotional stimuli elicited larger BOLD responses in the hippocampus and various cortical areas, including the medial prefrontal cortex, in a sleep control (SC) group than in a sleep deprived (SD) group. In contrast, the recollection of negative items elicited larger responses in the amygdala and in occipital areas in the SD relative to the SC group (Sterpenich et al., 2007). A later fMRI study examined the effect of a single night SD on consolidation of aversive emotional stimuli and corresponding patterns of brain activation at retest that took place six months after encoding. At retest 6 months later, the recollection of subjects allowed to sleep, compared with SD subjects, was associated with significantly larger fMRI responses in the ventral medial prefrontal cortex (vMPFC) and precuneus, areas involved in memory retrieval, and in the extended amygdala and occipital cortex, areas involved in emotion modulation at encoding. These results

suggest that sleep during the first postencoding night profoundly influences long-term systems-level consolidation of emotional memory and modifies the functional segregation and integration associated with recollection of affective memories in the long term (Sterpenich et al., 2009). Finally, using fMRI, it was recently demonstrated that SD amplifies reactivity throughout human mesolimbic reward brain networks in response to pleasure-evoking stimuli. In addition, this amplified reactivity was associated with enhanced connectivity in the early primary visual processing pathways and extended limbic regions, yet with a reduction in coupling with medial frontal and orbitofrontal regions. These neural changes were accompanied by a biased increase in the number of emotional stimuli judged as pleasant in the sleep-deprived group, the extent of which exclusively correlated with activity in mesolimbic regions (Gujar et al., 2011b). These results may offer a neural foundation on which to consider interactions between sleep loss and emotional reactivity in a variety of mood disorders (Gujar et al., 2011b).

Collectively, the above findings demonstrate sleep-related mechanisms of emotional regulation and consolidation of affective memories that partially differ from those shown to be involved in emotionally neutral memory consolidation and in the cognitive functions of sleep. The emotional "fingerprint" seems to involve mostly connections between prefrontal cortices and amygdala. However, it still remains to be revealed which sleep portions or sleep stages might have contributed to the impaired brain activation patterns after SD responsible for the behavioral results.

6. Conclusions

It is undeniable that highly specific sleep EEG rhythms and patterns of brain activation *actively* serve the memory, cognitive and psychological functions of sleep. The corresponding mechanisms involve brain plasticity at system, neural, synaptic, and genetic levels, and are closely related to the neurobiology of sleep. However, these mechanisms are *distinctly different* for certain memory, cognitive and psychological categories that sleep promotes, being *dissimilarly associated* with distinct sleep portions and sleep stages. Thus, both declarative and procedural memory consolidation and reconsolidation occur in earliest part of non-REM sleep/SWS by mechanisms of brain plasticity at system and neural levels, engaged in hippocampus-cortical relationships. Those, occurring during REM sleep appear more complex. Their pattern of brain activation engages a large set of areas, and possibly involves brain plasticity mechanisms at synaptic and genetic levels. The emotional 'fingerprint" of memory consolidation seems to be presented by connections between amygdala and cortical areas.

Further, the mechanisms involved in other cognitive functions of sleep appear different from those involved specifically in its memorizing effects. Also, it seems that sleep contributes to cognitive processes in a state dependent rather than in a trait dependent manner, but a complex interaction between both also can be suggested. Thus, since some of the EEG data imply a trait dependent role for sleep in cognitive abilities, most of the neuroimaging data indicate a state dependent role. However, these conclusions need further experimental evidence.

Importantly, different types of sleep mentality incorporated in different forms of dreaming production suggest a role for dreams in memory and cognitive processes. Data from such studies may open new perspectives of research and may provide new views about cognitive functions of sleep.

Finally, it can be concluded that the mechanisms underpinning memory, cognitive and psychological functions of sleep substantially contribute to human intelligence. Further investigation of the relationship between sleep and intelligence is clearly warranted.

7. Acknowledgment

We apologize to those whose work was not cited because of space limitations. We thank Drs. J. Yordanova and V. Kolev for their support.

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Neuroimaging and Outcome Assessment in Vegetative and Minimally Conscious State

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1. Introduction

Consciousness is a multifaceted concept that has two dimensions: arousal, or wakefulness (i.e., level of consciousness), and awareness (i.e., content of consciousness) (Laureys et al., 2004). An accurate and reliable assessment of the arousal and awareness of consciousness in patients with severe brain damage is of greatest importance for the differential diagnosis of low levels consciousness patients and for outcome evaluation. Following coma, some patients permanently lose all brainstem function (brain death), some progress to "wakeful unawareness" (vegetative state - VS), whereas others recover typically and progress through different stages before fully or partly recovering consciousness (minimally conscious state - MCS). Patients in VS can open their eyes and exhibit basic orienting responses, but show no conscious, purposeful activity. Reflex and other movements are seen, mediated by brainstem, spinal cord, and brainstem-diencephalic arousal systems (Laureys et al., 2004). VS can occur after patients emerge from an acute catastrophic brain insult causing coma, or can also be seen in degenerative or congenital nervous system disorders. The two common findings are necrosis of the cerebral cortex, thalamus and brainstem (usually after anoxic injury) and diffuse axonal injury (usually after trauma), although other pathological findings can be seen in degenerative and other disorders (Laureys, 2008). The MCS patients do not meet diagnostic criteria for coma or VS because they demonstrate some inconsistent but clear evidence of consciousness (Laureys et al., 2008; Giacino et al., 2002). In the MCS, there is variable impaired function of the cerebral cortex, diencephalons and upper brainstem. This allows occasional conscious behaviours to occur, unlike in VS or coma. Patients may enter the MCS as they emerge from coma or VS, or they can become minimally conscious as a result of acute injury or chronic degenerative diseases. Recent studies suggest a number of potential clinical and rehabilitative applications of magnetic resonance (MR) techniques. Although bedside clinical examination remains the criterion standard for establishing diagnosis, MR may provide an adjunctive diagnostic role when behavioural findings are very limited or ambiguous. The future of diagnostic and prognostic assessment of patients with disorders of consciousness (DOC) envisions a battery of neurobehavioral and neuroimaging techniques (such as structural and functional MR imaging (MRI and

fMRI), MR spectroscopy (MRS), diffusion tensor imaging (DTI), fiber tracking, positron emission tomography (PET)) that serve as complementary clinical tools that may help differentiate the effects of underarousal, sensory impairment, motor dysfunction, and cognitive disturbance in the search for potential causes of behavioural unresponsiveness.

2. Magnetic Resonance and Magnetization Transfer Imaging

The morphological MRI acquisitions usually include non-contrast-enhanced sagittal T1, axial diffusion, axial fluid attenuated inversion recovery (FLAIR), axial T2-SE, coronal T2 sequences and a 3D T1-weighted volume acquisition. FLAIR and T2-SE sequences permit to detect brain edema, contusion, hematoma, herniation, subarachnoid hemorrhage, or hydrocephalus. T2 sequences are useful in detecting hemorrhagic diffuse axonal injuries (DAI). The total number of lesions detected by FLAIR and T2 are shown to be inversely correlated with Glasgow Outcome Scale (GOS) of traumatic coma patients; while the 3D T1 sequence provides an opportunity to evaluate the brain atrophy during the follow up of these patients. A lot of studies performed on traumatic coma patients with conventional MRI showed that lesions of the pons, midbrain, and basal ganglia were predictive of poor outcome especially when they are bilateral. Despite their encouraging results, these studies fail to explain why some patients in VS or with long-term marked cognitive impairments have no or minimal lesions on conventional MRI examination. This raises the question of the lack of specificity and insufficient sensitivity of conventional MR sequences which fail to reveal lesions such as ischemic axonal injuries. Therefore, it is clear that morphological and conventional MRI alone cannot be considered as a reliable tool to assess consciousness disorders severity or to predict their evolution and outcome (Tshibanda et al., 2009). Several studies investigated patients in VS and in MCS using non-conventional, quantitative and volumetric MR techniques, useful to provide information about the anatomical patterns, the prognosis and the outcome of these patients. Ammermann et al. (2007) have used volumetric analysis of MRI to determine the pattern of lesions in 12 patients with a severe neurological impairment after acute ischemic injury. At the time of scanning, the patients were either in VS or in an early remising state, that is MCS. Lesions were classified as having been present in the gray and/or white matter in four different brain regions (frontal, parietal, temporal, occipital). An additional separate evaluation was performed for the basal ganglia, thalamus, hippocampus, cerebellum, and brainstem. The total clinical follow-up period of all patients from the time of the causative event lasted for at least 5 months. The clinical outcomes were reported according to the Rancho Los Amigos Cognitive Scale (RLACS) as a universal guide to assess a patient's level of functioning. The final RLACS levels were correlated to the MRI lesion size with a Spearman correlation. All patients demonstrated extensive white matter lesions, with the largest lesions observed in the frontal and occipital lobe. A preferential involvement of the white matter located in the periventricular area and in the subcortical regions below the motor and internal temporal cortices was found, in addition to the classifically described lesions of the striatum, motor and occipital cortices. Lesion magnitude showed an association with the severity of the outcome as quantitatively assessed by RLACS. With respect to gray matter lesions, the vulnerability pattern observed included frontal and occipital and in some cases parietal cortical areas, moreover in most cases the thalamus. Additionally, almost all of patients showed lesions of the hippocampus or lesions to the basal ganglia. An association between the extent of the MRI defined lesions located within the white matter and the clinical

outcomes of the patients was found. All patients in the most unfavorable class III clinical outcome group (i.e. persistent VS) exhibited white matter lesions exceeding 2/3 of the volume of at least one lobe, most frequently the occipital lobe.

Moreover, Juengling et al. (2005) investigated 5 patients in persistent VS due to prolonged cerebral hypoxia of non-traumatic origin, using combined Voxel-Based Morphometry (VBM) of 3D MRI and FDG-PET analysis. In the analysis of the regional distribution of gray matter atrophy, VBM revealed multiple areas of significantly decreased gray matter density at $p<.001$, corrected for multiple comparisons. Those were localized in multiple cortical areas, in particular including inferior parietal lobe, superior and medial frontal lobe, paracentral lobule, superior and medial temporal lobe, the cingulum, and the fusiform gyrus. Thalamic changes were limited to small voxel clusters in dorso-medial areas. These structural atrophic changes were compared with the local distribution of functional loss as assessed by regional hypometabolism in the FDG-PET group analysis. At the threshold pb0.001 (corrected for multiple comparisons), PET showed a widespread pattern of hypometabolic areas. In particular, the parietal and frontotemporal cortices, the cuneus/precuneus, the cingulum, the frontal medial and precentral gyrus, and the transverse temporal gyrus were involved, additionally the bilateral thalamus (mainly dorso-medial subnucleus). All changes were, similar to the VBM results, nearly symmetrical. Improved understanding of this complex lesion pattern gained by in vivo group analyses like here might help to provide deeper insights into the general pathoanatomy of patients in the persistent VS.

Using high-resolution T1-weighted magnetic resonance images and a novel approach to shape analysis applied SIENAX software, Fernandez-Espejo et al. (2010) investigated thalamic global and regional changes in a sample of patients in a VS or an MCS. They found that total thalamic volume was significantly lower in patients than in healthy volunteers. Shape analysis revealed significant bilateral regional atrophy in the dorso-medial body in patients compared to controls; this atrophy was more widespread in VS than in MCS patients. Lower thalamic volume was significantly correlated with worsening of Disability Rating Scale (DRS) scores. Shape analysis suggested that the dorso-medial nucleus and the internal medullar lamina were the main regions responsible for this correlation. These findings suggest that MCS and VS patients present different patterns of regional thalamic abnormalities. In particular, VS patients showed a more widespread pattern of atrophy than controls, producing differences in global thalamic volume. MCS patients did not show volumetric differences compared to controls, and regionally they showed a less pronounced inward collapse in both the dorsal and ventral areas, with the anterior-ventral body significantly spared. Neuropathological studies have demonstrated that thalamic damage is less common in MCS than in VS patients (Jennett et al., 2001).

Another quantitative RM technique is the Magnetization Transfer Imaging (MTI). The MTI relies on the principle that protons bound in structures exhibit T1 relaxation coupling with protons in the aqueous phase. When an off-resonance saturation pulse is applied, it selectively saturates those protons that are bound in macromolecules. These protons subsequently exchange longitudinal magnetization with free water protons, leading to a reduction in the detected signal intensity (Sinson et al., 2001). The MTI may provide a quantitative index of the structural integrity of tissue and might be useful to study the outcome of patients with low levels of consciousness.

However, further studies, on larger groups of patients, need to be performed to confirm the usefulness of quantitative MRI in the assessment of the eventual neurological prognosis and outcome of these challenging patients.

3. Functional Magnetic Resonance Imaging and Positron Emission Tomography

At present a diagnosis of VS or MCS is made using prognostic markers from the patient's clinical history supported by detailed neurological and behavioral assessment by a multidisciplinary team over several weeks. However, the behavioral assessment of these patients predominately relies upon the subjective interpretation of observed spontaneous and volitional behavior. A diagnosis of VS is supported if the patient demonstrates no evidence of awareness of self or environment, no evidence of sustained, reproducible, purposeful or voluntary behavioral response to visual, auditory, tactile or noxious stimuli and critically no evidence of language comprehension or expression (MSTF, 1994). In contrast the patient in MCS demonstrates partial preservation of awareness of self and environment, responding intermittently, but reproducibly, to verbal command and therefore demonstrating some degree of basic language comprehension (Giacino et al., 2002).

PET and recently fMRI, by measurement of cerebral metabolism and brain activations in response to sensory stimuli, can provide important MR indices on the presence and location of any residual brain function.

PET is the most sensitive method to image trace amounts of molecules in vivo. Therefore this technique is used to measure in man or in the living animal biochemical and physiological processes in any organ with three dimensional resolution. The last 25 years have seen a rapid and still ongoing development in the production of positron emitters, radiochemical labeling techniques, tomograph technology and image reconstruction algorithms. Because of the possibility to see and measure quantitatively physiological disorders in an early stage, before permanent morphological damage has occurred, which will only then be visible in x-ray or magnetic resonance computer tomography, PET is finally finding its way from a sophisticated research tool into routine clinical diagnosis.

Resting cerebral metabolism derived from quantitative glucose uptake provides an indirect assessment of neuronal activity against which brain states may be compared quantitatively (Levy et al., 1987). All previous quantitative [^{18}F] fluorodeoxyglucose–positron emission tomograph (FDG-PET) investigations of VS have correlated the condition with a global reduction of brain metabolic activity: Laureys et al. (1999) have assessed regional cerebral glucose metabolism (rCMRGlu) and effective cortical connectivity in four patients in VS by means of statistical parametric mapping and FDG-PET. Results showed a common pattern of impaired rCMRGlu in the prefrontal, premotor, and parietotemporal association areas and posterior cingulate cortex/precuneus in VS. In a next step, they demonstrated that in VS patients various prefrontal and premotor areas have in common that they were less tightly connected with the posterior cingulate cortex than in normal controls. Schiff et al. (2005) have described the first evidence of reciprocal clinical–pathological correlation with regional differences of quantitative cerebral metabolism. They studied five patients in VS with different behavioral features employing FDG-PET, MRI and magnetoencephalographic (MEG) responses to sensory stimulation. Each patient's brain expressed a unique metabolic pattern. The specific patterns of preserved metabolic activity identified in these patients reflect novel evidence of the modular nature of individual functional networks that underlie conscious brain function. In three of the five patients, co-registered PET/MRI correlate islands of relatively preserved brain metabolism with isolated fragments of behavior. Two patients had suffered anoxic injuries and demonstrated marked decreases in overall cerebral

metabolism. Two other patients with non-anoxic, multifocal brain injuries demonstrated several isolated brain regions with relatively higher metabolic rates. A single patient who suffered severe injury to the tegmental mesencephalon and paramedian thalamus showed widely preserved cortical metabolism. The variations in cerebral metabolism in chronic VS patients indicate that some cerebral regions can retain partial function in catastrophically injured brains.

fMRI is based on the increase in blood flow to the local vasculature that accompanies neural activity in the brain. This result in a corresponding local reduction in deoxyhemoglobin because the increase in blood flow occurs without an increase of similar magnitude in oxygen extraction (Roy & Sherrington, 1890; Fox & Raichle, 1985). Since deoxyhemoglobin is paramagnetic, it alters the T2 weighted magnetic resonance image signal (Ogawa et al, 1990). Thus, deoxyhemoglobin is sometimes referred to as an endogenous contrast enhancing agent, and serves as the source of the signal for fMRI. Using an appropriate imaging sequence, human cortical functions can be observed without the use of exogenous contrast enhancing agents on a clinical strength (1.5 T) scanner (Bandettini et al., 1992, 1993; Schneider et al, 1993).

Functional activity of the brain determined from the magnetic resonance signal has confirmed known anatomically distinct processing areas in the visual cortex (Schneider, et al, 1993), the motor cortex, and Broca's area of speech and language-related activities (Hinke et al., 1993; Kim et al., 1995). Further, a rapidly emerging body of literature documents corresponding findings between fMRI and conventional electrophysiological techniques to localize specific functions of the human brain (Atlas et al., 1996; Detre, et al, 1995; George, et al, 1995). Consequently, the number of medical and research centers with fMRI capabilities and investigational programs continues to escalate.

Several fMRI studies in the VS have confirmed the findings of previous PET studies. Di et al. (2007) used fMRI to evaluate differences between seven VS and four MCS patients in brain activation occurring in response to the presentation of the patient's own name, spoken by familiar voice (SON-FV). They prospectively studied residual cerebral activation to SON-FV in seven patients with VS and four with MCS. Two patients with VS failed to show any significant cerebral activation. Three patients with VS showed SON-FV induced activation within the primary auditory cortex. Only two of the VS patients, and all four MCS patients, showed activation not only in the primary auditory cortex but also in hierarchically higher-order associative temporal areas.

Three months after fMRI examination, these two VS patients had progressed to the MCS. This study showed that fMRI measurement might be a useful tool for pre-clinically distinguishing MCS-like cognitive processing in some patients behavioural classified as vegetative. Schiff et al. (2005) have tested the hypothesis that MCS patients retain active cerebral networks that underlie cognitive function. fMRI was employed to investigate cortical responses in two male adults with severe brain injuries resulting to MCS and in seven healthy volunteers. Three passive stimulation tasks were performed: tactile stimulation, auditory narratives of familiar events presented by a familiar person, and the same auditory passages without language-related content. Results have showed a residual brain activity of cortical systems involved in a potential cognitive and sensory function despite their inability to follow simple instructions or communicate reliably.

In conclusion, results of these studies we analyzed confirm the idea that PET and fMRI activation profiles may constitute useful adjunctive diagnostic methods when behavioral

findings are very limited or ambiguous, helping in differential diagnosis, prognostic assessment and identification of pathophysiological mechanism.

4. Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is an emerging technique that complements traditional MRI and may be able to provide erstwhile unavailable information about the pathological substrates of DOC. DTI is a modified MRI technique that is sensitive to microscopic, three-dimensional water motion within tissue. In cerebrospinal fluid, water motion is isotropic, i.e., roughly equivalent in all directions. In white matter, however, water diffuses in a highly directional or anisotropic manner. Due to the structure and insulation characteristics of myelinated fibers, water in these white matter bundles is largely restricted to diffusion along the axis of the bundle. DTI can thus be used to calculate two basic properties: the overall amount of diffusion and the anisotropy (Douaud et al., 2007; Benson et al., 2007; Kraus et al., 2007; Ringman et al., 2007; O'Sullivan et al., 2004). It is only very recently that DTI has been used to evaluate white matter integrity in patients with DOC. For example, Voss et al. (2006) described two patients with traumatic brain injury: one who had remained MCS for 6 years and one who had recovered expressive language after 19 years diagnosed as MCS. In both cases, widespread changes in white matter integrity were observed. Interestingly, however, the increased anisotropy and directionality in the bilateral medial parieto-occipital regions that was observed in the second patient reduced to normal values in a follow-up scan performed 18 months later. This coincided with increased metabolic activity, leading the authors to interpret these observations as evidence of axonal regrowth in this region. Although this is certainly a landmark finding in two high spectrum MCS patients, it remains to be seen whether DTI has any diagnostic or prognostic utility in a broader group of patients with disorders of consciousness. To this end, Tollard et al. (2009) and Perlbarg et al. (2009) have recently demonstrated that DTI measures in sub-acute severe traumatic brain injury may be a relevant biomarker for predicting the recovery of consciousness at 1 year. However, VS and MCS patients were classified in the same outcome category and potential differences between these two groups were not investigated. Although, in this context DTI has been generally used to address specific clinical problems, the study of white matter integrity in behaviorally defined states has a more basic relevance to understanding the relationship between brain and behavior in both health and disease. For example, in healthy volunteers, DTI techniques have been used recently to examine how structural changes underpin the behavioral changes that are related to learning a complex skill (Scholz et al., 2009). In a very recent study (Espejo et al., 2011), the integrity of white and grey matter regions was assessed in a group of 25 VS and MCS patients in vivo. In accordance with previous post-mortem work (Jennett et al., 2001; Adams et al., 1999) significant changes were observed in the integrity of the tissue in subcortical, thalamic and brainstem regions in the patients when compared to healthy volunteers. The precise location of this damage was not different between the MCS and VS sub-groups, which, again, accords well with previous post-mortem studies. However, an analysis of the MD values within two of these regions of interest (subcortical white matter and thalami), revealed significant differences between the patients meeting the clinical (behavioral) criteria defining VS and those who met the criteria defining MCS. Specifically, the VS patient group exhibited a decrease in the peak height of

the histograms derived from the subcortical white matter and the thalami and an increase in the peak width of the thalamic histogram.
In addition, DTI may be a valuable biomarker for the severity of tissue injury and a predictor for outcome. It reveals changes in the WM that are correlated with both acute GCS and Rankin scores at discharge (Huisman et al., 2004). Significant early reduction of anisotropy was observed in WM structures, in particular in the internal capsule and the corpus callosum, which are the sites most commonly involved by DAI (Arfanakis et al., 2002). Moreover, several regions recovered normal values of anisotropy 1 month after the injury (Arfanakis et al., 2002). Xu et al. (2007) found significant differences in the corpus callosum, internal and external capsule, superior and inferior longitudinal fascicles, and the fornix in TBI patients. They showed that FA and ADC measurements offered superior sensitivity compared to conventional MRI diagnosis of DAI. Salmond et al. (2006) reported increased diffusivity in TBI patients at least 6 months after their injury in the cerebellum, frontal, insula, cingulate, parietal, temporal, and occipital lobes. The anisotropy seems to be reduced both in the major WM tracts such as the corpus callosum and the internal and external capsule, and the associative fibers underlying the cortex. DTI has a number of advantages as an imaging biomarker of brain injury: first, it can be used to evaluate brain trauma in an unconscious or sedated patient; second, it could permit the evaluation of responses to treatment even when the clinical scores are inadequate for assessing the patient; third, quantitative DTI measurements are unlikely to be tainted by adverse central nervous system (CNS) effects of hypnotic drugs, unlike clinical scores; and fourth, DTI may be an important alternative marker, as low initial Glasgow Come Scale scores are of limited value in predicting the prognosis (Huisman et al., 2004). Finally, Perlbarg et al. (2009) showed significant FA differences between favorable and unfavorable 1-year outcome groups around four FA tracks: in inferior longitudinal fasciculus, posterior limb of the internal capsule, cerebral peduncle, and posterior corpus callosum.

5. Magnetic Resonance Spectroscopy

Proton MRS (^{1}H-MRS) is a non-invasive imaging technique that enables in vivo quantification of certain neurochemical compounds. Using the same equipment utilized for the conventional MRI, single-voxel ^{1}H-MRS and multi-voxel Imaging (^{1}H-MRSI) or Chemical Shift Imaging (CSI) provide metabolic information on brain damage that may not be visible with the conventional structural imaging methods. Then ^{1}H-MRS, added to traditional MRI, offers the possibility to study the brain activity combining information on structure and function.
Classically, the exploration of DOC is performed on 1,5 or 3 Tesla MR scanners and at intermediate or long echo time (TE) (135-288 ms). Long TE ^{1}H-MRS detects the signal arising from four metabolites: N-acetyl-aspartate containing compounds (NAA), choline-containing compounds (Cho), creatine + phosphocreatine (Cre) and lactate (Lac). Short TE ^{1}H-MRS identifies peaks from mobile lipids, Lac, alanine, NAA, Glutamate/Glutamine (Glx), γ-aminobutyric acid, Cre, Cho, myo-inositol, and scyllo-inositol (Figure 1).
NAA, which resonates at 2.02 parts per million (ppm), represents the largest proton metabolic concentration in the human brain after water. Indeed the concentration of NAA reaches on the order of 10 µmol/g. NAA is widely interpreted as a neuronal marker and implicated in several neuronal processes, mitochondrial functioning and osmoregulation.

NAA synthesis occurs in mitochondria and requires acetyl-CoA and L-aspartic acid as substrates. NAA has been proposed to serve as a mitochondrial shuttle of acetyl-CoA used for fatty acid synthesis. Its peak decreases when there is neuron suffering or loss. The Cho peak (3.2 ppm) represents a combination of several choline-containing compounds, including free Cho, phosphorylcholine and glycerophosphorylcholine, and to a small extent acetylcholine. Free Cho acts as a precursor to acetylcholine, while glycerophosphorylcholine is a product of breakdown of membrane phosphatidylcholine and acts as an osmoregulator. Its peak increases when there is greater membrane turnover, cell proliferation or inflammatory process. The peak of Cre at 3.03 ppm represents total creatine and phosphocreatine supplies phosphate for conversion of ADP to ATP in creatine kinase reaction. Indeed these metabolites buffer the energy use and energy storage of cells. The level of total Cre mainly remains constant in many neuronal diseases. Thus, total Cre is often used as an internal reference (i.e., a denominator in metabolite signal ratio). The Lac (1.3 ppm) is an end product of anaerobic glycolysis, thus increase in Lac concentrations often serves as an index of altered oxidative metabolism, i.e., in ischemia, hypoxia, and cancer. Increases of Lac in the brain are often accompanied by decreased intracellular pH and high-energy phosphates. The proposed role of Lac is a source of energy for neurons and the transport of Lac plays an essential role in the concept of metabolic coupling between neurons and glia. Glutamate (Glu) is the highest excitatory neurotransmitter in concentration in the CNS. Its peak increases when neuronal and astrocytic activation impairs mitochondrial function and energy utilization. Indeed this process impairs Glu transport and its following enhancement is associated to cellular toxicity.

^{1}H-MRS has been used for at least 15 years in the exploration of patients with altered consciousness, both to investigate the mechanisms of vigilance and to predict the possibilities of regaining consciousness.

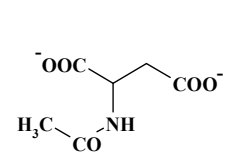
Predicting outcome of patients with DOC is an integral part of clinical care, facilitating medical decision making and therapeutic intervention. Current neurological and neurophysiological methods do not enable prediction of outcome of these patients in early stages. Although conventional neuroimaging can provide important information for acute clinical management, its prognostic value is limited, particularly at early stage of injury resolution, owing to its poor sensitivity.

Several studies present in literature have demonstrated the value of ^{1}H-MRS as an accurate tool to predict patient's clinical outcome. Indeed many investigators have shown that correlation exists between metabolite changes and outcome of patients with DOC.

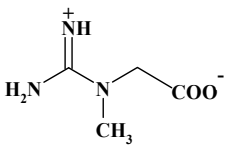
Previous studies using single-voxel technique have shown in brain-injured subjects a significant correlation between unfavorable outcome and reduction of marker NAA in occipitoparietal white and gray matter (WM and GM) (Brooks et al., 2000; Friedman et al., 1999; Ross et al., 1998; Yoon et al., 2005), frontal WM (Garnett et al., 2000), parietal WM (Shutter et al., 2004), brainstem (Carpentier et al., 2006), splenium of the corpus callosum (Sinson et al., 2001; Cecil et al., 1998), and thalamus (Uzan et al., 2003), increase in choline a marker for cell membrane disruption in frontal WM (Garnett et al., 2000) and occipitoparietal WM and GM (Brooks et al., 2000; Cecil et al., 1998; Ross et al., 1998; Yoon et al., 2005), and increase in Glx in occipital GM and parietal WM (Shutter et al., 2004).

In particular, NAA levels seem to discriminate patients who recovered from coma from those who died or remained in persistent VS (Ricci et al., 1997). Uzan et al. (2003) carried out a thalamic proton MRS in patients in VS resulting from severe TBI. They found that

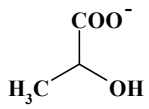
NAA/Cr ratios were able to differentiate patients in VS who recovered awareness from those who remained in persistent VS. However, this alteration was not found in the thalamus of patients in VS resulting from mild TBI (Kirov et al., 2007).



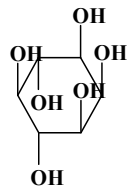
N-Acetylaspartate (NAA)



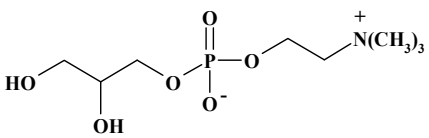
Creatine (Cre)

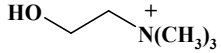


Lactate (Lac)

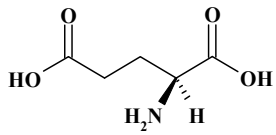


Myo-inositol (mI)





Choline - containing compounds (Cho)



Glutamate

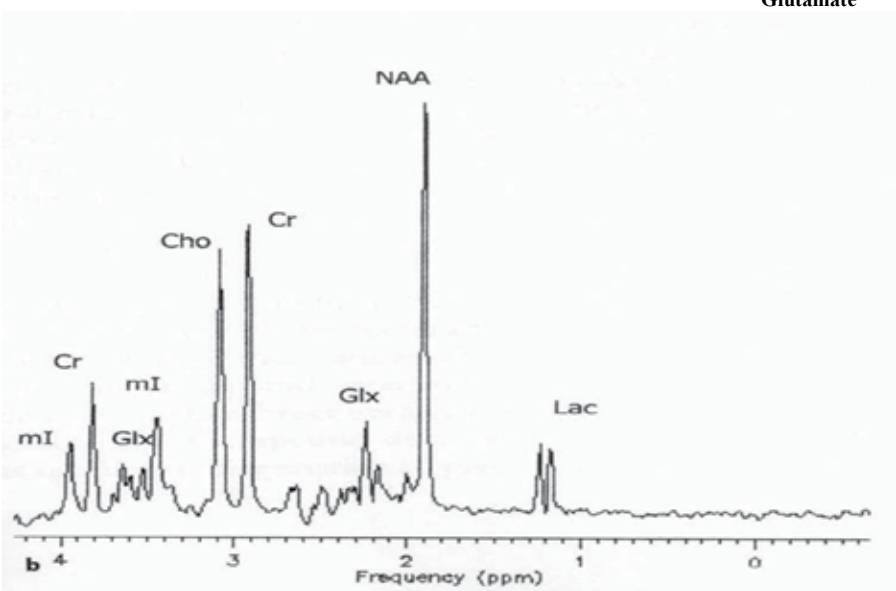


Fig. 1. Chemical structure and spectrum of main cerebral metabolites detected by ^{1}H-MRS.

In some studies has been shown that the combination of imaging techniques may be useful to predict the long-term neurological outcome. A ^{1}H-MRS study in the pons allowed separating of patients who recovered from patients with severe neurological impairment, death or in VS. In addition, ^{1}H-MRS metabolic alterations were not correlated with anatomical MRI lesions, suggesting that these two techniques are strongly complementarity (Carpentier et al., 2006). Tollard et al. (2009) reported the first study on patients with TBI based on a combined quantitative analysis of ^{1}H-MRS and DTI. This combined analysis was

97% specific for predicting an unfavorable outcome after 1 year, compared with 85% for DTI and 75% for ^{1}H-MRS. Similarly, sensitivity was better with the combined analysis (86%) than with either DTI (79%) or MRS (75%).
To study metabolite changes from a wider area of the brain, with the advantage of identifying more anatomical and functional details, a few investigators have used ^{1}H-MRSI (Holshouser et al., 2006; Marino et al. 2007; Shutter et al., 2006; Signoretti et al., 2002, 2008). This technique has an advantage over single-voxel ^{1}H-MRS because generates individual spectra from multiple voxels at the same time. Also ^{1}H-MRSI studies have highlighted close correlation between metabolite alterations and potential recovery.
Neurometabolite concentrations obtained soon after injury may be useful for predicting individual outcome. The decrease of NAA and the increase of Lac, seen by Marino et al. (2007) early after brain injury, were correlated with GOS score. Then these ^{1}H-MRS data may be, at this stage, a reliable index of injury severity and disease outcome.
However it is need to note that ^{1}H-MRS studies in patients with DOC are heterogeneous in terms of patient nature, injury types, time from cerebral damage, voxel location, methods and timing outcome assessment. In addition, in many studies the metabolite concentrations were expressed in terms of semiquantitative ratios. The assumption that the concentration of Cr as reference metabolite remains constant may be incorrect, especially in acute conditions. It is therefore advisable to obtain concentration expressed in standard units by applying absolute quantification. Some studies have expressed metabolite concentrations in term of absolute quantification (Brook et al., 2000; Friedman et al., 1999; Marino et al. 2007; Ross et al., 2000; Shutter et al., 2004).
Data reported so far demonstrate that MRS measure have the potential to provide new and important biological brain markers able to predict clinical outcome, helping in the therapeutic interventions, clinical and rehabilitative management of these patients, as well as to assist with family education.

6. Neurophysiological techniques

The neurophysiological approach to patients with DOC allows the recording of electrical activities of both CNS and Peripheral Nervous System (PNS) and provides a functional assessment, which can be integrated with data obtained mainly from morphological neuroimaging techniques (CT and MRI). The combined use of various neurophysiological examinations, such as Electroencephalogram (EEG), Evoked Related Potentials (ERPs), Transcranial Magnetic Stimulation (TMS), Deep Brain Stimulation (DBS), EEG in association with fMRI, contributes to the topographic and functional diagnosis of the various anatomical structures of the injured CNS and the PNS. The electrophysiological signals recorded from electrodes placed on the surface of the scalp reflect spatially the average post-synaptic potential originated by large neuronal populations. Experimental evidence and clinical observations suggest functional correlations among the neural mechanisms of sensory information, cognitive performance, sleep-wake cycle, alertness and electrophysiological signals generated by neuronal activity. A greater amount of patients can be assessed with electrophysiological techniques, including those who may not have access to a MRI due to geographic, financial, or physical (i.e., metal plates or pins) impairment.
The electroencephalogram in patients in VS has shown a spectrum of abnormalities with changes during the wake-sleep cycle. Patterns have included delta and theta activity and

spindle and alpha-like rhythms, but they are more diffusely distributed than in the typical posterior regions and are not reactive to sound, pain, and light stimuli (Chokroverty, 1975; Huges, 1978). During sleep, fewer muscle twitches are observed, but a REM sleep remains (Oksenberg et al., 2001). In most patients, the transition from wakefulness to sleep is accompanied by some desynchronization of the background activity. Very-low-voltage EEG activity is all that can be detected in some patients. In others, persistent alpha activity is the most remarkable feature. In around 10% of patients with VS, the EEG is nearly normal late in the course of disease but without evidence of vision-induced alpha blocking (Danze et al., 1989). There have been occasional reports of isoelectric EEGs in patients in a VS, although it has not been confirmed (Higashi et al., 1977; Mizrahi et al., 1985). Typical epileptiform activity is unusual in patients in VS, as seizure activity is (The Multi-Society Task Force on PVS, 1994). Clinical recovery from the vegetative state may be paralleled by diminished delta and theta activity and reappearance of reactive alpha rhythm. Indeed, Babiloni (2009) has observed that occipital source power in the alpha band (8-13 Hz) of resting EEG, when calculated with low-resolution electromagnetic tomography (LORETA), is correlated with recovery outcome at 3-month follow-up in a group of VS patients; those who made a behavioural recovery had higher resting alpha band power than those who did not make a significant recovery.

The EEG in MCS shows diffuse slowing brain activity, mainly of the theta band, and in most cases responsive to external stimuli. However, there are insufficient data as well as the typical pattern of MCS concerns. Evoked potentials have been studied in patients in a VS and showed normal brainstem auditory responses but abnormal somatosensory responses: prolonged conduction time or absence of scalp potentials. ERPs are more useful than EEG in the differential diagnosis between VS and MCS. ERPs studies focusing on the assessment of conscious awareness have frequently examined four specific components: the N100, the mismatch negativity (MMN), the P300, and the N400 (Connoly & D'Arcy, 2000).

In a recent work, the authors focused on the prediction of consciousness recovery in patients with post-traumatic VS. They used a classical two-stimulus oddball task to elicit the P300 using the patient's own name as deviant and a pure tone as standard stimulus (''subject's own name" paradigm). There is evidence that the amplitude of the P300 wave increases when more salient stimuli are used, such as the own first name instead of visual or auditory deviants. The authors found that P300 is a strong predictor of future recovery of consciousness in VS. This finding is in line with several studies that have confirmed the utility of P300 evoked by deviant tones to predict awakening and favourable outcome from coma and VS (Cavinato et al., 2009). In another study Cavinato et al., (2011) continue to using the "subject's own name" paradigm, but add a pure tone and an "other first name" paradigm. The authors instructed their patients to count the occurrence of deviant stimuli to better differentiate between patients in VS and MCS. The study indicates that in 6 out of 11 patients fulfilling the behavioral criteria for VS a reliable P300 component could be observed in all two conditions. These findings corroborate earlier reports showing that 38% of patients in VS generate a P300 wave. The patients in MCS exhibit significantly longer P300 latencies for the "subject's own name" and the "other first name" paradigms than patients in VS. The increase of P300 latencies for more complex and salient paradigms in MCS but not in VS might help in the difficult differential diagnosis of MCS vs. VS.

The TMS, for high temporal resolution, was proposed as an additional functional imaging technique for the study of cognitive function. To date only some studies have assessed VS and MCS patients with TMS. Moosavi et al. (1999) applied TMS to the hand and leg motor

area in 19 patients, few months after severe anoxic brain injury. Eleven patients were in VS, while eight patients were in MCS. The VS patient group differed from the MCS patient group in having a higher threshold, longer duration, and greater irregularity in the form of the response, while the threshold, form, and latency of motor evoked potentials (MEPs) from the MCS group were similar to healthy control subjects. In another study, TMS is used to monitor recovery. The authors examined MEPs from upper and lower limbs in 27 patients in the subacute period and then at 6 and 12 months post – ictus. During the study period, the authors observed an overall trend toward an increase and decrease of latency of MEPs. MEPs from upper and lower limbs progressively normalized in all patients, and at one year after trauma, only 12% of patients had mild abnormalities in MEP responses (Mazzini et al., 1999).
TMS elicited MEP responses in the majority of severely brain damage patients, and a trend toward an increase of amplitude and decrease of latency of MEPs could be observed during the recovery period.
DBS works on reactivating the cortex, aiming to produce a functional recovery. In study of Yamamoto et al. (2010) patients in VS were treated with DBS. Eight of the patients recovered from VS and were able to obey verbal commands at 13 and 10 months in the case of head trauma and a year and a half in the case of vascular disease after comatose brain injury, and no patients without DBS recovered from VS spontaneously within 24 months after brain injury.
In the last years the interest in using of neurophysiological investigations (EEG and EPs) in association with fMRI, has grown: the combination of these different neuroimaging techniques allows study of different components of the brain's activity (e.g., neurovascular coupling, electromagnetic activity) with both a high temporal and spatial resolution (Gosseries et al., 2008).
Clinical neurophysiology procedures are useful as easily performed, non invasive and repeatable at the bed side. These methods provide irreplaceable data about the degree of neuronal dysfunctions and their evolution, and gave also information to assess the outcome.

7. Cognitive recovery

A diagnosis of VS is made if a patient demonstrates no evidence of awareness of self or environment. No evidence of sustained, reproducible, purposeful or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli and critically no evidence of language comprehension or expression. In contrast, the patient in a MCS demonstrates partial preservation of awareness of self and environment, responding intermittently, but reproducibly, to verbal command and therefore demonstrating some degree of basic language comprehension (Coleman et al., 2007).
VS and MCS patients may permanently remain in their clinical condition, or may partly or fully recover consciousness through different stages (Laureys et al., 2004). In this view, it's very important evaluate the residual cognitive across the time. In fact, it allows to make a differential diagnosis between VS and MCS, to monitoring functional changes of the patients, in order to customize the treatment, and, at least, to have a baseline evaluation of the patients in case of consciousness recovery. Nevertheless, the assessment of residual brain functions and the degree of recovery of these patients remain, still today, an opened issue in the medical field. To date, there have been no detailed studies of these patients evaluating cognitive changes and recovery over time through a specific neuropsychological battery (Neumann & Kotchoubey, 2004). This might suggest a new and possible way to further investigate the potential outcome of these challenging patients.

In this paragraph we try to identify some markers of consciousness with prognostic value, based on literature review. As it has been clearly established in clinical practice, significant spontaneous recovery frequently occurs during the subacute period (Wilson et al., 2002; Giacino & Trott 2004). Two factors can facilitate cognitive recovery of these patients: young age and immediate medical assistance after the injury.

Literature findings demonstrated that no clinical tools strongly predicted good outcome. In contrast, complementary examinations such as electrophysiological and functional neuroimaging studies objectively measure residual brain functions and are indicative of recovery of consciousness.

Several studies explore the prognostic validity of behavioural assessment scales (i.e. GOS, Coma Recovery Scale, Wessex Head Injury Matrix, Western Neuro Sensory Stimulation Profile, DRS, Functional Independence Measure), electrophysiological measures (ERPs), and functional neuroimaging (PET, fMRI), to predict outcome in patients with low levels of consciousness. Particular progress towards addressing this objective has been made using brain imaging techniques such as PET and fMRI. Schiff et al. (2002) suggested that rather than a complete loss of cortical function some patients retain "island" of preserved cognitive functions. PET and fMRI studies suggest that a higher-level associative cortical activation seems to predict recovery of consciousness with a 93% specificity and 69% sensitivity (Di et al., 2008). PET work has identified preserved responses to a variety of sensory stimuli, including photographs of familiar people, noxious, tactile (Laureys et al. 2000; Owen et al., 2002; Boly et al., 2004) in some vegetative and minimally conscious patients. Some studies underline the importance of the cognitive ERPs in the assessment of residual functions in comatose, VS, or MCS patients. As a general rule, early ERPs (such as the absence of cortical response on somatosensory evoked-potentials) predict bad outcome, while cognitive ERPs are indicative of recovery of consciousness (Vanhaudenhuyse et al., 2007). Moreover, auditory cognitive ERPs are useful to investigate residual cognitive functions, such as echoic memory (Mismatch Negativity), acoustical and semantic discrimination (P300), and incongruent language detection (N400). In VS patients, cognitive potential are more frequently obtained when using stimuli that are more ecologic or have an emotional content (such as the patients' own name) than when using classical sine tones.

Electrophysiological and functional neuroimaging studies may provide useful and objective information to the outcome and possibly cognition of patients with low levels of consciousness (Di et al., 2007). To date, there have been no detailed studies of these patients combining and correlating specific neuropsychological tools and functional imaging, in order to evaluate the cognitive changes and recovery over time (Bekinschtein et al, 2005). In spite of the important findings, functional neuroimaging cannot, and should not replace, clinical and behavioural evaluation as the criterion standard for assessment of patients with DOC. It offers an objective method of differentiating brain activity measured at rest and during external stimulation, but further studies are needed to assess the temporal evolution of individual patients' somatosensory and cognitive processing (Giacino et al., 2006). Despite converging agreement about the definition of persistent vegetative state, recent reports have raised concerns about the accuracy of diagnosis in some patients, and the extent to which, in a selection of cases, residual cognitive functions may remain undetected. Objective assessment of residual cognitive function can be extremely difficult as motor responses may be minimal, inconsistent, and difficult to document in many patients, or may be undetectable in others because no cognitive output is possible (Owen et al., 2002). There are no standards of care to guide the selection of rehabilitation assessment and treatment

procedures for patients with DOC (Neumann & Kotchoubey, 2004). Cognition abilities with theory of mind tasks, decision-making tasks, social performance tests and expanded cognitive assessment, to further characterize post-traumatic or hypoxic-ischemic brain damaged vegetative patients after recovery remain under evaluation at this time. The cognitive recovery in patients with DOC is a continual process rather than a step-by-step phenomenon and confirms that a good recovery assessment should include objective measures of behavioural, cognitive and functional domains, and neurophysiological data to support diagnosis. Survivors from a coma frequently suffer from long-lasting disability, which is mainly related to cognitive deficits. Such deficits include slowed information processing, deficits of learning and memory, of attention, of working memory, and of executive functions, associated with behavioral and personality modifications (Azouvi et al., 2009). An accurate cognitive assessment during the very first phase of the convalescence, when it is possible, is the first step for the management and the implementation of an individual and effective treatment.

Appropriate management requires an experienced inter-disciplinary as opposed to multidisciplinary team working style, whose skill repertoire equips them to recognize often-subtle improvements in cognitive function and act to maximize individual patient's quality of life. The current paucity of service provision for this vulnerable group of patients is highlighted. In fact, predicting the chances of recovery of consciousness and communication in patients who survive their coma, but transit in a VS or MCS remains a major challenge for their medical caregivers. Very few studies have examined the slow neuronal changes underlying functional recovery of consciousness from severe chronic brain damage.

8. Prognosis and rehabilitation

Determining the accurate prognosis of VS and MCS is a critical step in counseling families and determining appropriate treatment. Previous studies of prognosis in VS were limited by several factors: 1) because there were no accepted diagnostic criteria for MCS prior to 2002, some patients in MCS in those studies may have been diagnosed with VS; 2) it is more accurate to determine prognosis by the etiology of brain damage than merely by categorization in a clinical syndrome; and 3) retrospective experiential analysis of outcomes, such us that by the Multi-Society Task Force, committed the fallacy of the self-fulfilling prophecy because they included patients in their survival data who died primarily because their life-sustaining therapy was discontinued (Bernat et al., 2010). Nevertheless, the prognostic guidelines published in 1994 by Multi-Society Task Force on PVS have been generally accepted, showing a very low probability of recovering awareness once VS has been present for a year following TBI or for 3 months following hypoxic-ischemic neuronal injury (Bernat et al., 2009).Two recently published studies of prognosis in VS add useful data. Luautè and colleagues (Luautè et al., 2010), confirmed the prognostic guidelines of the Multi- Society Task Force in all the patients in VS. They studied and showed that age greater than 39 years and absence of the middle-latency auditory evoked potentials were independent early predictors of poor outcome irrespective of pathogenesis. Estraneo and colleagues (Estraneo et al., 2010), found that 88% of patients in VS in their serious conformed to the Multi- Society Task Force prognostic guidelines but 12% made late recoveries of awareness but only to the point of severe disability with MCS, most of whom had TBI. Because of varying pathophysiologies, prognostic indicators for MCS as a group have been difficult to establish whereas prognostic indicators in individual pathophysiologic subsets of

MCS (e.g. patients in MCS from TBI) have been more reliable (Bernat et al.,2010). The appropriate level of treatment of patients with chronic DOC depends on their diagnosis, prognosis and prior stated treatment values and preferences. Specialized neurorehabilitation units are the optimal treatment for patients with chronic DOC , at least until they are no longer improving. Patients have better functional out comes when treated by skilled personnel who have been trained in neurorehabilitation. The difference between patients in VS and patients in MCS in their response to stimulatory treatment is noteworthy: patients in VS rarely improve as a consequence of stimulation but patients in MCS may improve to some extent. Treatment modalities that have been studied include environmental and sensory stimuli such as sounds, smells, touch, images and music. Pharmacologic stimuli include treatment with stimulants, levodopa, and dopamine agonists (by stimulating intact dopaminergic thalamic neurons), and selective serotonin reuptake inhibitor antidepressants. Electrical stimuli include deep brain stimulation of medical thalamic nuclei. Each of these modalities has been reported to improve functional responsiveness in some patients in MCS though there are few controlled studies. These therapies are also widely tried in patients in VS but a meta-analysis of their outcomes showed no consistent benefits (Bernat, 2006).

9. Sensory stimulation procedure

The use of unimodal and multimodal sensory stimulation for the treatment of comatose patient, both in the acute and prolonged states, has been advocated (Johnson et al., 1988). The rationale behind the use of these techniques is that all aspects of the patient must be treated; it is insufficient to attend to the maintenance of bodily well being alone. Sensory stimulation should at the least not have any ill-effects on the patient and could enhance the processes of recovery. S.L. Wilson et al. (1991) have observed patients diagnosed as being in prolonged coma, routinely treated according to a sensory stimulation protocol. They reported an evaluation of the efficacy of this procedure using the comparison of behavioral measures taken immediately prior and post-stimulation. Sensory stimulation treatment appears to be widely used with patients who are in VS arising from traumatic causes, but the term has to be regarded as generic rather than specific since sensory stimulation procedures appear to differ widely in content (Wilson et al., 1993). A number of studies have been published evaluating the effects of these treatment; some have methodological flaws, but the major difficulty in evaluating any treatment with this group of patients is getting sufficient subjects, so most of the published studies use relatively small numbers. Ideally, a large-scale matched control study would be looked for, which examined rate of recovery and long-term outcome. If sensory stimulation is rejected on the basis of lack of empirical evidence, then logically many other treatments used with medical settings should also be rejected. In real life, however, where definitive empirical evidence is not yet available, then clinicians can reasonably make decisions on treatment by combining clinical experience with inferences from scientific knowledge concerning related populations. For example, stimulation treatments which involve the use of some constant background stimulation within the patient's environment, such as TV or radio, have been justifiably criticized. As Wood points out, it is likely to be damaged within the brain that mediate selective attention are highly likely to be damaged within these patients; therefore it is unlikely they are going to be able to differentiate between stimuli in a situation where they are being bombarded with sensory input. In addition, habituation may exacerbate the problem.

10. Neuroimaging of self-consciousness and recovery

A recent meta-analysis by Northoff et al. (2006) of 27 PET and fMRI studies comparing hemodynamic brain responses obtained during active paradigms comparing processing of stimuli related to the self with those of non-self-referential stimuli identified activation in cortical midline structures in all studies and occurring across all functional domains (e.g. verbal, spatial, emotional, and facial). Cluster and factor analyses indicated functional specialization into ventral, dorsal, and posterior cortical midline areas. The latter encompasses the posterior cingulate cortex and adjacent precuneus and is considered to be involved in self-integration – that is linkage of self-referential stimuli to the personal context (Northoff et al., 2004). Neuroimaging studies during tasks involving self-processing (i.e. self-reflection, self-perspective and free thoughts) have also reported the activation of the medial prefrontal areas. Gusnard, Akbudak, Shulman , and Raichle (2001) for example showed medial frontal activation when subjects had to make two judgments in response to pleasant *vs* unpleasant pictures (i.e. self-referential) as compared to indoors *vs* outdoors pictures (i.e. not self-referential). The same area was also shown to be engaged when subjects had to make self-referential judgments about trait adjectives (i.e. self-referential processing) as compared to when they had to make case judgments (Kelley et al., 2002) and when subjects responded to statements requiring knowledge of, and reflection on, their own abilities, traits and attitudes , i.e. self-reflective thought (Johnson et al., 2002). Taking a self–perspective (i.e. being the agent of an history) also activated medial prefrontal/anterior cingulate cortices (Vogeley et al., 2001). Finally, activation of the mesiofrontal areas was describes in studies dealing with the conscious resting state, i.e. free thought (Mazoyer et al., 2001), a brain state which "instantiates functions that are integral to the self". The recovery of consciousness of one VS patient has previously been linked to an increase in the functional connectivity within fronto-parietal network, (Laureys et al, 1999) encompassing the areas known to be most active in resting–state conditions (Gusnard et al., 2001). A growing body of evidence from Positron emission tomography (PET) and fMRI studies of healthy volunteers in a variety of altered states of consciousness has emphasized the role of this "default-mode" network in the genesis of awareness. In keeping with this, functional impairments to this network have been observed during sleepwalking, absence of seizures, deep sleep and anesthesia (Bassetti et al., 2000). fMRI has also proved its utility in identifying a number of cognitive functions which may be preserved in DOC patients, the results of which have, in some cases, proved prognostic of positive outcomes (Owen et al., 2008). In one such fMRI study investigating language processing. Coleman et. al found evidence of speech processing in three out of seven behaviorally non-communicative VS patients (Coleman et al., 2007). Six months after the scan, each of these patients had made a marked behavioral recovery relative to those patients who did not demonstrate comparable activations. Similar findings have also been reported for the neural responses observed when patients hear their own name (Di et al., 2007). Multimodal imaging approach can provide a powerful tool for assessing the mechanisms involved in the recovery of consciousness in DOC patients. Further longitudinal studies with large cohorts will prove useful in assessing its full value in predicting outcome. Such insights may then provide guidance for decisions relating to rehabilitation programs by those orientating these towards the effective stimulation of those functions that appear preserved, in order to maintain their integrity.

11. Conclusions

Patients with severe brain damage who are unable to communicate present several ethical concerns. Foremost is the concern that diagnostic and prognostic accuracy is certain, as treatment decisions typically include the possibility of withdrawal of life-support. Although imaging techniques have the potential to improve both diagnostic and prognostic accuracy, careful and repeated neurological assessment by a trained examiner remains best practice. Accurate clinical assessments of patients in these conditions must be obtained before they undergo neuroimaging. Moreover, in reports of neuroimaging studies, all relevant clinical details must be available for comparisons between studies.

Ethical concerns are commonly raised about the participation of patients with severe brain damage in neuroimaging studies. By definition, unconscious or minimally conscious patients cannot give informed consent to participate in clinical research and written approval must typically be obtained from family or legal representatives depending on governmental and hospital guidelines. Nonetheless, researchers studying these patients have been refused grants, ethics committee approval, and research publication; these decisions tend to be made on the basis that studies of patients who cannot provide consent are unethical. We prefer an ethical framework that balances access to research with medical advances alongside protection for defenseless patients. Severe brain damage represents an immense social and economic problem that warrants further research. Unconscious, minimally conscious, and locked-in patients deserve special procedural protections. However, it is important to stress that they are also at risk of being denied therapy that may be life-saving if clinical research cannot be done on these patient groups.

Patients who are in coma, VS, MCS, or locked-in syndrome present unique problems for diagnosis, prognosis, treatment, and everyday management. At the patient's bedside, assessment of cognitive function is difficult because voluntary movements may be very small, inconsistent, and easily exhausted. Functional neuroimaging will never replace the clinical assessment of patients with altered states of consciousness. Nevertheless, using population norms it can provide an objective measure of the regional distribution of cerebral activity at rest and under various conditions of stimulation. The quantification of brain activity differentiates patients who sometimes only differ by a brief and small movement of a finger. In our opinion, PET, MRS and fMRI will increase substantially our understanding of patients with severe brain damage.

12. References

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10

Functional and Structural MRI Studies on Impulsiveness: Attention-Deficit/Hyperactive Disorder and Borderline Personality Disorders

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1. Introduction

Impulsive behavior is characterized a tendency to initiate behavior without sufficient/adequate consideration of consequences. It typically refers to ill-conceived, premature or inappropriate behavior that may be self-destructive or harmful to other individuals (Chamberlain and Sahakian, 2007). Pathological impulsiveness is associated with impaired performance on neuropsychological tests of attention and executive function and with neuroimaging evidence for structural and/or functional correlates, particular in frontal lobe regions (Congdon and Canli, 2005; Crews and Boettiger, 2009; Rubia et al., 2007). Impulsive behavior is a major component of several neuropsychiatric disorders, including schizophrenia, ADHD, substance abuse, bipolar disorder, and borderline and antisocial personality disorders. The notion of impulsiveness incorporates a multidimensional construct consisting of a range of inter-related factors including novelty-seeking and reckless behavior, lack of planning ability and self-control whereby mechanistic relations evolve from its role in initiating action (Barratt and Patton, 1983; Moeller et al., 2001). The construct incorporates motor impulsiveness, inability to tolerate delays, lack of planning and an incapacity for self-control.

Impulsiveness, with or without aggressiveness, has been associated with a range of personality disorders and other psychopathologies (Haden and Shiva, 2008; Krishnan-Sarin et al., 2007; Palomo et al., 2007a; Reynolds, 2006; Shiva et al., 2009), with impulse control difficulties often of primary diagnostic importance (e.g., Pfefferbaum & Wood, 1994; Quirk and McCormick, 1998). A variety of linear regression analyses based upon several self-report questionnaire studies including a range of cognitive-emotional personal attributes have indicated that impulsiveness is predicted by negative affect, amotivation and depressiveness and counterpredicted by positive affect and internal locus of control in healthy volunteers (Palomo et al., 2008a, b; but see also Miller et al., 2009). Cyders et al. have discussed the influence of positive urgency, acting rashly under extreme positive affect, and negative urgency as central risk factors for impulsive and maladaptive behavior (see also Cyders and Smith, 2008a, b; Cyders et al., 2009, 2010; Zapolsky et al., 2009).

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The inability to formulate decisions and plan actions presents a critical component of impulsiveness expressed in male offenders classified as both non-psychopathic and psychopathic (Dolan et al., 2001), euthymic and depressed bipolar patients, depressed unipolar patients and healthy controls (Peluso et al., 2007) and male forensic psychiatric in-patients facing severe criminal charges (Haden and Shiva, 2008). In a large-scale study of pathological gamblers, Ma Alvarez-Moya et al. (2010) identified four subtypes: Type I, (disorganized and emotionally unstable) showed schizotypic traits, high levels of impulsiveness, substance and alcohol abuse, and early age of onset, as well as other psychopathological disturbances;Type II (schizoid) showed high harm avoidance, social aloofness, and alcohol abuse; Type III (reward sensitive) showed high levels of sensation-seeking and impulsiveness but did not express psychopathological impairments; Type IV (high functioning)demonstrated a globally-adaptive personality profile, low levels of substance and alcohol abuse or smoking, without psychopathological disturbances but rather good general functioning. Thus, even among a broad population of pathological gamblers there exists a wide spectrum of cognitive and executive variability that requires the pathophysiological analysis of structure and function that magnetic resonance imaging may provide.

Individuals whose behavior is associated with high levels of impulsiveness frequently show general impairments over a wide range of neurocognitive tasks including tests of executive functioning (Dolan and Park, 2002; Keilp et al., 2005; Rogers, 2003), cognitive tasks demanding response control (Harrison et al., 2009; Potter and Newhouse, 2004) and cognitive flexibility [verbal fluency] (Barratt et al., 1997; Vieregge et al., 1997). The control of choice and decision-making processes seems to be modulated primarily by the eventual consequences of affective and cognitive appraisal with reinforcement/avoidance of actions directed by the underlying neural circuits (Beck et al., 2009; Frank and Claus, 2006; Koenigs and Tranel, 2007; Rustichini, 2005). Functional neuroimaging studies have implicated brain regions involved both in reinforcement and response inhibition. For example, financial rewards evoke differential patterns of recruitment in striatal and orbitofrontal cortex, as reflected in fMRI studies (Elliott and Deakin, 2005; Elliott et al., 2003). Other brain regions have been implicated in the different expressions of impulsiveness, including the inferior frontal gyrus, anterior cingulate cortex, regions of the prefrontal cortex (i.e. ventrolateral and dorsolateral), amygdala and the basal ganglia, insula and hippocampus (Love et al., 2009; Lee et al., 2009; Park et al., 2010). Gender effects have also been reported. For example, Lejuez et al. (2007) found that among 152 individuals in a residential substance-use treatment program, female subjects (37% of the sample) expressed greater use of crack/cocaine (current and lifetime heaviest) and were significantly more likely to show crack/cocaine dependence than their male counterparts. The female subjects expressed greater impulsiveness and higher levels of negative emotionality than their male counterparts, and were more likely to have suffered abuse during childhood. Impulsiveness presented a risk factor in the relationship between gender and crack/cocaine dependence and was also predictive of the quantity of drugs consumed and the duration of the dependency. These authors found no gender differences for any other forms of substance abuse (alcohol, cannabis or hallucinogens). Dysfunctional response to reinforcing stimuli, whether appetitive or aversive, appears to be a critical factor in the psychopathy of substance use and impulsiveness-related personality disorders (Petry, 2002).

Research indicates that in selecting among competing available behaviours immediate rewards are typically favoured over delayed rewards, such that with increasing delays the valuation of a future reward is reduced (known as *temporal discounting*; Ainslie, 1975).

Recent functional neuroimaging studies have explored the neural basis of temporal discounting, indicating that different (but overlapping) distributed networks are engaged as a function of the delay between decision and reward. Making choices between payoffs available at different points in time reliably engages a decision-making circuit that includes medial and/or dorsolateral prefrontal cortex (mPFC; dlPFC), posterior cingulate cortex (PCC), and ventral striatum (VS). However, evidence for specific functional roles in the decision making process across this distributed network is limited. Theoretical claims include the possibility that one or more of these regions: (1) is sensitive to the value of rewards discounted by a function of delay ('subjective value'); (2) is differentially sensitive to the availability of an immediate reward; and (3) is implicated in general/nonspecific impulsive and/or planned decision-making. Using event-related fMRI, Ballard and Knutson (2009) showed that although activation of the nucleus accumbens, mesial prefrontal cortex, and posterior cingulate cortex was correlated positively with future reward magnitude, the activation of the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortical (PCC) region was correlated negatively with future reward delay (see also Sripada et al., 2011). They found individuals expressing greater impulsiveness displayed diminished nucleus accumbens activation to the magnitude of future rewards and greater deactivations to delays of future rewards in the mesial prefrontal cortical, DLPFC, and PCC. Their observations imply that whereas the mesolimbic dopamine projection regions show greater sensitivity to the magnitude of future rewards, lateral cortical regions show greater (negative) sensitivity to the delay of future rewards, potentially reconciling different neural accounts of temporal discounting.

Motor impulsivity occurs when individuals act 'on the spur of the moment', inadequately inhibiting inappropriate response tendencies. Go/No go task performance (a measure of the ability to inhibit a prepotent response tendency) is typically impaired in neuropsychiatric patient groups for whom impulsivity is a common feature (Durston et al., 2003, 2006; Rubia et al., 1999) whereas in healthy controls the relationship between Go/No go performance and impulsiveness is not straightforward (Helmers et al., 1995; Keilp et al., 2005). In children with attention deficit hyperactivity disorder (ADHD), fMRI studies of Go/No go task performance have shown reduced activation in the ventrolateral prefrontal cortex (VLPFC), anterior cingulate cortex, mesial prefrontal cortex and/or caudate region in comparison to age-matched normally developing controls (Casey et al., 1997; Plitzka et al., 2006; Tamm et al., 2004). Activation of the VLPFC (particularly right hemisphere) is linked to response inhibition (Aron et al., 2004). The right VLPFC and DLPFC are implicated in the relationship between response inhibition and impulsivity (Asahi et al., 2004; Horn et al., 2003; Passamonti et al., 2006). Using fMRI, Goya-Maldonado et al. (2010) examined the relationship between trait impulsivity (BIS-11) and brain activation during motor response inhibition in an uncued Go/No go task. They obtained a significant positive correlation between motor impulsivity and bilateral activation of the VLPFC, suggesting that individuals expressing high levels of motor impulsivity show stronger recruitment of the VLPFC in order to maintain task performance. In an fMRI study examining neural activation during a food specific Go/No go task in adolescent girls, Batterink et al. (2010) required subjects to inhibit prepotent responses to appetizing foods. It was found that body mass index correlated with response inhibition at both behavioural and neural levels: greater weight was positively correlated with impulsiveness and negatively correlated with activation in frontal regions associated with inhibitory control (including superior and middle frontal gyrus, VLPFC, mPFC, and orbitofrontal cortex). It should be noted also that

bulimia nervosa is associated with response inhibition deficits and higher impulsiveness (BIS-11) scores (Kemps and Wilsdon, 2010).

Comorbid aspects of clinical impulsiveness remain an issue in the pathophysiology of neuropsychiatric disorders (Palomo et al. 2007b). Both ADHD and pediatric bipolar disorder (PBD) are characterized by inattention, impulsiveness, lack of behavioural inhibition and deficits in cognitive flexibility and sustained attention (Galanter and Leibenluft, 2008; Pavuluri et al., 2006), the latter generally associated with emotional dysregulation, elated mood, irritability, increased energy and disinhibition (Pavuluri et al., 2007, 2008; Pavuluri and Passarotti, 2008). Children with PBD were found to show less activation in the VLPFC in a response inhibition stop-signal task (Leibenluft et al., 2007). In a color-naming Stroop task, PBD patients demonstrated elevated activation in the putamen and thalamus compared with healthy controls (Blumberg et al., 2003). A recent fMRI study of response inhibition in PBD patients, ADHD patients and healthy controls implicated (in the context of similarly impaired behavioral performance in both patient groups) a more focal role for VLPFC and anterior cingulate involvement in PBD (as indicated by *reduced* activation in these regions). The inhibitory impairment in ADHD was associated with more extensive prefrontal and temporal involvement. A distributed network of brain regions, within which the prefrontal cortex is of particular importance, is therefore likely to drive observed response inhibition impairments observed both in PBD and ADHD patients.

A central aspect of adaptive, as opposed to maladaptive, risky decision-making requires monitoring the value of behavioural options, possibly mediated through a 'teaching signal' expressed as a reward prediction error (PE) in the striatum. The involvement of higher level cognitive control associated with PFC might be necessary for mobilization of executive processes. Park et al. (2010) employed fMRI and a reinforcement learning task to investigate the neural mechanisms underlying maladaptive behavior in human male alcohol-dependent patients. They observed that in these patients the expression of striatal PEs was intact. Nevertheless, an abnormal functional connectivity between striatum and DLPFC predicted impairments in learning and in the magnitude of alcohol craving shown by the patients. Their findings confirm the structural abnormalities in the DLPFC that are associated with substance abuse. It is evident that frontostriatal connectivity exerts a pivotal role in the adaptive updating of action values and that impaired behavioural regulation in alcoholism may be associated with deficient interactive functionality of this system.

Definitions of impulsiveness vary from considerations of lack of persistence, patience and resistence to delayed rewards, boredom-thresholds, risk-taking behaviors and sensation-seeking behaviors to impaired understanding of the future implications of a given behavior (Barratt, 1994; Buss and Plomin, 1975; Eysenck, 1993; Logue, 1995). The intimate role of faulty timing behavior/time estimation as a non-specific factor in impulsiveness has been established in laboratory settings (cf. Evenden and Ko, 2005; Rivalan et al., 2007), with particular relevance in ADHD (Barkley et al., 1997, 2001; Meaux and Chelonis, 2003; Sonuga-Barke et al., 1992; Toplak et al., 2006). In healthy adults, the frontal cortex, basal ganglia and cerebellum are linked generally to timing functions with long or short delay intervals (Ivry and Spencer, 2004; Meck and Benson, 2002; Wiener et al., 2010). Various aspects of time processing have been addressed in individuals afflicted with ADHD, whether children/adolescents (McInerney and Kerns, 2003; Radonovitch, 2004; Smith et al., 2008) or adults (Gilden and Marusich, 2009; Marx et al., 2019; Seri et al., 2002).

Developmental trajectories of impulsive behavior bear essential outcome-expectancies for eventual disorder pathophysiology (cf. Grall-Bronnec et al., 2010). Valko et al. (2010) studied

the developmental trajectory of the time-processing deficit that has been postulated as a neuropsychological candidate endophenotype for ADHD in 33 children and 22 adults with ADHD. They found that the children and adults displayed different patterns of deficit in the discrimination of brief intervals (600 – 1,500 msecs) in Go/No go and continuous performance tasks and concluded that time-processing deficits, though expressing different age-related forms, were present in adulthood. It is likely that the manifestation of the time-processing deficit in adult ADHDs may be more closely related to the fundamental processes of arousal and/or time perception with a peripheral role of executive function and response inhibition.

Recent research on the role of excessive alcohol consumption in the development of impulsive behaviors indicates that premorbid/baseline levels of impulsivity can predict the likelihood of increased impulsive behaviours following heavy drinking (White at al., 2011). This longitudinal study of boys assessed annually for 10 years until age 18 and again in their mid twenties indicated that a "moderate" (rather than "high" or "low") level of premorbid impulsiveness was the greatest risk factor for eliciting increased impulsive behaviors following heavy drinking. Basal levels of positive affect, a characteristic invariably counter-predictive for impulsiveness, appear related to outcomes of risk perception (drinking, getting into fights) in adolescents and young adults (Haase and Silbereisen, 2010). The notion of disturbed functional connectivity (see above) in frontal-striatal circuits bears consideration. Konrad et al. (2010) observed reduced fractional anisotropy (FA) and elevated mean diffusion bilaterally in orbitomedial prefrontal and right anterior cingulate cortex using voxel-based analyses in adult patients with ADHD compared with healthy controls. Impulsiveness was associated with FA in right orbitofrontal fibre tracts whereas attention was associated with DTI parameters in the right superior longitudinal fasciculus.

Rubia et al. (2009b) have argued that impulsive behavior is distinguished on the basis of a timing disturbance, with suboptimal recruitment of prefrontal, cingulate, striatal and cerebellar regions during temporal processing. They present the case that impulsiveness in ADHD is a dysfunction in temporal processing that may be reversed by acute treatment with a dopamine (DA) reuptake inhibitor. Valera et al. (2010) used fMRI to study paced and unpaced finger-tapping in a sample of 20 unmedicated adult ADHD patients and 19 healthy controls, matched for age, gender and IQ. They found that the ADHD adults expressed greater 'clock' (paced/unpaced tapping variation linked to a central clock rather than motor implementation) rather than motor variability that was consistent with a central timing locus for the atypical movements. Relative to healthy controls, the ADHD patients demonstrated reduced activity in several regions associated with sensorimotor timing, i.e. prefrontal and precentral gyri, basal ganglia, cerebellum, inferior parietal lobule, superior temporal gyri and insula. They concluded that (i) the ADHD abnormalities persisted into adulthood, and (ii) these abnormalities arose from the atypical functioning of corticocerebellar and corticostriatal timing circuits (see also Coull and Nobre, 2008; Smith et al., 2008; Terry et al., 2009).

A plethora of neuropsychological evidence indicates that abnormalities in executive functioning, particularly with regard to behavioural inhibition, are dysfunctional in in ADHD (Barkley, 1997; Chamberlain et al., 2010; Lambek et al., 2011; Mattison and Mayes, 2012). Arendts et al. (2010) have presented evidence of visual cortex abnormalities in adults with ADHD, using voxel-based morphometry of high resolution MRI scans, that may be related to impairments in early-stage, "subexecutive" attentional mechanisms. Accordingly, a neurocognitive model of ADHD presents the disorder as executive dysfunction

originating from disturbances in the fronto-dorsal striatal circuit and associated dopaminergic branches (e.g. the mesocortical pathway). Nevertheless, a motivation-based account of altered reward processing, consisting of fronto-ventral striatal reward circuits and those meso-limbic branches that terminate in the ventral striatum and nucleus accumbens, implicates the avoidance of delay due to disturbances in the reward centres (Dalen et al., 2004; Sonuga-Barke, 2002, 2003; Sonuga-Barke et al., 2003). Sonuga-Barke et al. (2008) have argued that while executive dysfunction and delay aversion are implicated in ADHD neither is necessary for ADHD nor specific to the disorder. Several studies focused on the neural basis of individual differences in reward sensitivity have implicated the ventral striatum as a core component of the human reward system (Sescousse et al., 2010).

Adaptive, planned decision-making involves the selection of a particular behavior from several available options on the basis of a valuation of potential costs and benefits. Neuroimaging studies of delay and effort discounting suggest that there may be distinct valuation subsystems involved in the assessment of different types of costs (Prevost et al., 2010). The ventral striatum and the ventromedial prefrontal cortex represent the increasing subjective value of delayed rewards, whereas a distinct network comprised of the anterior cingulate cortex and the anterior insula, represent the decreasing value of an effortful option. Hahn et al. (2010) have shown that dopamine transporter variation (i.e., differences in DA availability affecting synaptic plasticity within the ventral striatum) moderates the association between ventral striatum-reactivity and trait reward sensitivity. In order to analyse further the contribution of reward processes, Carmona et al. (2009) applied a manual region-of-interest approach to assay for ventral striatum volumetric (MRIcro) alterations in 42 ADHD children/adolescents (age range: 6-18 years) compared to 42 healthy controls matched for age, gender and handedness. ADHD children/adolescents displayed marked reductions in both right and left ventro-striatal volume. Furthermore, the volume of the right ventral striatum was correlated negatively with the hyperactivity/impulsivity rating given by the mothers of the ADHD children/adolescents. Reduced volume of the ventral striatum is also associated with cognitive decline in the elderly (de Jong et al., 2012; see also Sripada et al., 2011).

The notion that ADHD symptoms are linked to altered reinforcement sensitivity has gathered momentum (cf. Luman et al., 2010). In an fMRI study comparing neural activity within the striatum in ADHD adolescent individuals and healthy controls, Scheres et al. (2007) observed reduced ventral striatal activation during reward anticipation in the ADHD group. Consistent with other studies, ventral striatal activation was negatively correlated with parent-rated hyperactive/impulsive symptoms across the entire sample. Both frontal-striatal and fronto-cerebellar circuits, necessary for the prediction of occurrence and timing of behaviourally-relevant are also implicated in expectancy violations. For example, Durston et al. (2007) have found fMRI evidence that individuals with ADHD have diminished cerebellar activity in response to violations of stimulus timing and diminished ventral prefrontal and anterior cingulate activity to violations in stimulus timing and identity (relative to healthy age matched controls).

The dysfunctional processing of reward, in combination with a limited capacity to tolerate delay in reward, may offer an important feature of ADHD. Reinforcement Sensitivity Theory, as a conceptual notion, involves three basic brain systems: the Behavioral Approach System and the Behavioral Inhibition System (both of which activate in response to stimulus signalling events), and the fight-fright-freeze system (which responds to actual aversive stimuli; Gray, 1982; Gray and McNaughton, 2000). Gray's impulsivity notion, reflecting trait

reward sensitivity, deals with the extent to which environmental stimuli activate the Behavioral Approach System (Gray, 1991). Higher Behavioral Approach System activation due to increased trait reward sensitivity is implicated in 'disinhibitory' disorders, including ADHD and alcoholism (Franken et al., 2006; Mitchell and Nelson-Gray, 2006; Sher and Trull, 1994). Using fMRI in an appetitive task, Beaver et al. (2006) showed that the tendency to pursue Behavioral Approach System rewards was linked to a fronto-striatal-amygdala-midbrain network activation whereas Barros-Loscertales et al. (2006) describe a negative correlation between dorsal striatum/prefrontal cortex volumes and trait reward sensitivity using voxel-based morphometry. Hahn et al. (2009) studied the relationship, in 20 healthy subjects, between impulsiveness, according to Gray's notions, and event-related fMRI BOLD-response to reward anticipation in brain regions associated with reward processing. Higher trait reward sensitivity was related to cues for potential reward. Thus, the anticipation of reward during a monetary incentive delay task elicited activation in key components of the human reward circuitry, including the ventral striatum, orbitofrontal cortex and amygdala. Plichta et al. (2009) examined brain activation, with fMRI, in 14 adults with ADHD and 12 healthy controls in a task which required choosing between two monetary reward options based on immediate versus delayed reward conditions. For both immediate and delayed rewards, ADHD patients showed hyporesponsiveness of the ventral-striatum reward system compared with healthy controls. In the ADHD individuals, delayed rewards also elicited hyperresponsiveness in the dorsal caudate nucleus and the amygdala: in both structures neural activity correlated significantly with self-rated ADHD symptom severity. The authors concluded that hyperactivation, incremental along the ventral-dorsal caudate nucleus extension and amygdala, substantiates the delay aversion hypothesis. The spectre of temporal discounting (see above), in one form or another, emerges as a plausible mediating factor in the expression, both neural and functional, of impulsiveness in ADHD (see also, Rogers et al., 1999).

Given the cross-national prevalence of 3.4 % for adult ADHD (Fayyad et al., 2007), the potential and current problems associated with the disorder pose a bleak clinical reality. Functional imaging studies of children and adolescents with ADHD have implicated dysfunction of the VLPFC and DLPFC, anterior cingulate, insula, amygdala, hippocampus and ventral striatum (e.g. Amico et al., 2011; Kobel et al., 2010; Rogers et al., 1999; Sasayama et al., 2010; Sheridan et al., 2010); in adult ADHD similar regions are implicated (e.g. Depue et al., 2010a, b; Dillo et al., 2010; Schneider et al., 2010). For example, Schneider et al. (2010) observed (during a continuous performance Go/Nogo test) reduced activity in the caudate nuclei, anterior cingulate cortex and parietal cortical structures in ADHD, together with increased activity in the insular cortex, and that this was associated with the symptoms of impulsiveness and inattention. This widespread regional dysfunction was linked to symptom-profile severity in adults with a history of childhood ADHD, whether or not they qualified for a full ADHD diagnosis in adulthood. Such findings illustrate an important role for MRI in the characterization of neurodevelopmental trajectories (see also, Giedd and Rapoport, 2010; Wilens and Spencer, 2010).

Structural MRI studies indicate broad pathological heterogeneity in ADHD (e.g., Filipek et al., 1997; Mostofsky et al., 2002; Overmeyer et al., 2001; Semrud-Clikeman et al., 2006). Qiu et al. (2009) have published evidence that ADHD in boys may be associated with reduced basal ganglia volumes compared with boys with normal development. Large deformation diffeomorphic metric mapping (LDDMM) indicated that the two groups differed markedly with regard to basal ganglia morphology: bilateral volumetric compression was observed in

the caudate head and body and anterior putamen, as well as in the left anterior globus pallidus and right ventral putamen. Coversely, volumetric expansion was observed in the posterior putamen. The authors concluded that the observed deviations from normal brain development involved multiple frontal-subcortical control loops that included circuits with premotor, oculomotor and prefrontal cortex regions. The relevance of developmental trajectories in impulsive disorders was illustrated further by Christakou et al. (2010) who demonstrated that age-related reductions in choice impulsivity were associated with changes in activation in the VLPFC, ACC, ventral striatum, insula, inferior temporal gyrus and posterior parietal cortex. They indicate that the maturational pattern of functional connectivity incorporates activation-coupling between the VLPFC and DLPFC, and the parietal and insular cortices during selection between delayed options, and between the ventromedial PFC and the ventral striatum. Maturational mechanisms within limbic frontostriatal circuitry form the basis of post-pubertal reductions in impulsive choice with age increments linked to activation coherence in networks modulating inter-temporal decision-making (Christakou et al., 2010).

Borderline Personality Disorder (BPD), the most common personality disorder clinically, is characterized by severe and persistent emotional, cognitive, behavioural and interpersonal impairments (American Psychiatry Association, 2000); a pervasive pattern of instability in affect regulation, impulse control, interpersonal relationships, and self-image are linked to the clinical signs of emotional dysregulation, impulsive aggression, repeated self-injury, and chronic suicidal tendencies (Lieb et al., 2004). Some patients are able to sustain a certain level of social and occupational functioning, while others experience a very high level of emotional distress (cf. Jordanova and Rossin, 2010). There is often rapid fluctuation from periods of confidence to despair. Early-life stress exerts damaging effects on brain development (Archer, 2010a, b; Archer et al., 2010b) and neuroimaging studies (e.g. Koenigsberg et al., 2009) have yielded important insight into the role of the hypothalamic-pituitary-adrenal (HPA) axis in BPD (see Wingenfeld et al., 2010 for review).

Patients with BPD have shown volumetric reductions of the hippocampal and (in some cases) amygdala regions in structural MRI studies (Brambilla et al., 2004; Driessen et al., 2000; Schmahl et al., 2003), with or without comorbid aggression or depression (Zetzsche et al., 2006, 2007). Krull et al. (2010) reviewed the multi-dimensional aspect of BPD from phenotypic, genetic, and endophenotypic perspectives. One major feature is the comorbid expression of the disorder with posttraumatic stress disorder which occurs in 50%-70% of patient populations (Zanarini et al., 1998b; Zimmermann and Mattia, 1999) with marked hippocampal volume reductions (Bremner et al., 1997, 2003; Stein et al., 1997; Zlotnick et al., 2003). Both BPD and PTSD share etiologic factors, e. g., trauma, symptom profiles (such as hyperarousal or dissociation states), and neurobiological factors (such as aberrant patterns of neural activation in prefrontal cortex and limbic regions; Schmahl and Bremner, 2006). Amygdala-deactivation has been indicated in BPD patients comorbid for PTSD but not those without PTSD (Kraus et al., 2009). Schmahl et al. (2009) compared a group of BPD with PTSD (n = 10) and a group of BPD without PTSD (n = 15) with 25 healthy female controls applying T1- and T2-weighted MRIs for manual tracing and 3-dimensional reconstruction of the hippocampus and amygdala. They found that the hippocampal volumes of BPD patients with PTSD were lower than those of the healthy female controls concomitant with significant correlations between impulsiveness and hippocampal volumes in these patients. These results and similar observations underlie the necessity of comorbidity considerations in BPD (Bahorik and Eack, 2010; Joshi et al., 2012; Rösch et al., 2010).

BPD and antisocial personality disorders (ASPD) present common characteristics such as high levels of impulsiveness (Becker et al., 2005; Paris, 1997) and marked comorbidity (Chabrol and Leichsenring, 2006; Zanarini et al., 1998). Nevertheless, Völlm et al. (2004) have provided fMRI evidence that ASPD and BPD patients recruit different brain regions when successfully inhibiting pre-potent responses. Employing a Go/No Go task, they found that for healthy controls the main focus of activation during response inhibition was in the prefrontal cortex, in particular the right dorsolateral and the left orbitofrontal cortex. For ASPD and BDP patients, the active regions expressed a more bilateral and extended pattern of activation across the medial, superior and inferior frontal gyri extending to the anterior cingulate cortex. Völlm et al. (2009) studied the effects of positive (financial reward) and negative (financial loss) outcomes on blood-oxygen-level dependence (BOLD) responses in Cluster B (ASPD and BPD) patients (n = 8) and healthy controls (n = 14). They observed that: (i) there was an absence of prefrontal responses and reduced BOLD signal in the subcortical reward system of the patient group but not the control group, and (ii) for the patient group, but not control group, impulsiveness scores were correlated negatively with prefrontal responses during both reward and loss. The authors concluded that the response system to reward/loss in Cluster B was dysfunctional.

One prevailing notion is that emotional instability in BPD stems from an interaction of emotional vulnerability and an invalidating environment mediated hypersensitivity and hyperreactivity to emotional stimuli together with delayed return to baseline arousal level (Linehan, 1993; Linehan et al., 1999; Reeves et al., 2010). Niedtfeld et al. (2010) have found that both negative and neutral picture-presentations can lead to stronger activation of the amygdala, insula, and anterior cingulate cortex in patients with BPD compared with healthy controls. Structurally, a significant 24% reduction of the left orbitofrontal and a 26% reduction of the right anterior cingulate cortex in BPD in comparison to controls has been observed (Tebartz van Elst et al., 2003). Other studies show volumetric reductions of the hippocampus, orbitofrontal cortex and amygdala in BPD (Domes et al., 2009; Lis et al., 2007) and ,, enhanced emotional-cue related activation in the amygdala (Donegan et al., 2003; Minzenberg et al., 2007), and middle and inferior temporal regions (Guitart-Masip et al., 2009) known to be involved in the processing of facial features carrying emotional content. Dyck et al. (2009) suggest that a selective deficit of BPD patients in rapid and direct discrimination of negative and neutral emotional expressions may in large part underlie their difficulties in social interactions.

In BPD, fronto-limbic neural dysfunction has been implicated in the expressions of emotional dysregulation and impulsivity. Using structural MRI and impulsiveness instrument, Takahashi et al (2009), examined the insular cortex volume and its relationship to clinical characteristics in a first-presentation teenage BPD sample of 20 BPD (5 male participants) and 20 healthy controls (5 male participants). They found no association between the insular volume and parasuicidal episodes, trauma exposure, or comorbid Axis I disorders; nevertheless, the BPD participants with a history of violent episodes during the previous 6 months showed a smaller insular volume bilaterally compared with those without such episodes. In addition, the right anterior insular volume in the BPD participants correlated negatively with the impulsiveness score. The potential relationship between the insular cortex volume and impulsiveness expression seems specific to BPD. Whittle et al. (2009) investigated anterior cingulate cortex volume in a first-presentation teenage BPD population with minimal exposure to treatment. Fifteen female BPD patients and 15 healthy female control participants underwent MRI scanning. Anterior cingulate cortex volumes

were estimated with a method that accounts for inter-individual variation in sulcal morphology with measurements between the two groups compared. ANOVA revealed a decrease in volume of the left anterior cingulate cortex in BPD patients compared with control participants that correlated with parasuicidal behavior and impulsivity. Anterior cingulate cortex volumetric asymmetry correlated also with fear of abandonment symptoms, implying that these volumetric abnormalities early in the course of BPD may relate to the clinical correlates of the disorder. Krause et al. (2010) explored the neural correlates of script-driven imagery of self-injurious behavior in female BPD patients and healthy controls. When imagining the reactions to a situation triggering self-injurious behavior, BPD patients showed significantly less activation in the orbitofrontal cortex but increased activity in the DLPFC. Imagining the self-injurious act itself was associated with a decrease in the mid-cingulate in the patient group. Together, these structural and functional neuroimaging findings suggest that frontal, insular, mid- and anterior cingulate regions and medial temporal lobe structures may be critically involved in the impaired regulation of impulse and affect observed in BPD (e.g., Soloff et al., 2008).

In conclusion, the notions of aberrant reward learning, dysregulated response inhibition and pathological hypersensitivity to temporal delays in reinforcement form the essential behavioural endophenotype of impulsiveness that is witnessed in ADHD and BPD, as well as in compulsive gambling, addictive disorders and dopamine dysregulation syndrome. Developmental trajectories of impulsive behaviors and the damaging effects of early-life trauma on brain development bear essential outcome-expectancies for eventual understanding of etiopathogenesis. Structural and functional resonance imaging has served to provide a point of convergence for the resolution of neurobehavioural, epigenetic and neurodevelopmental factors.

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11

MRI Techniques to Evaluate Exercise Impact on the Aging Human Brain

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1. Introduction

The aging human brain undergoes a variety of structural and metabolic changes, often coinciding with, or leading to, cognitive decline (Bullitt et al., 2009). Over the past decade, investigators have been searching for better methods to detect, treat, and prevent cognitive decline. This has lead to the development of a plethora of pharmaceutical approaches with limited success. Identifying non-pharmaceutical approaches for the prevention/treatment of cognitive decline is paramount. Because of its non-invasiveness, neuroimaging is fast becoming a preferred technology for evaluating brain structure and function. In addition, exercise is being recognized as a potential adjunct modality for preventing or reducing structural decline in the brain and perhaps attenuating corresponding cognitive decline. These two methodologies can work in tandem: first, for identification of subtle changes in the brain not detectable via standard cognitive testing and second, for application of appropriate exercise regimes shown to be associated with healthy brain aging. Taken together, disruptions in cognitive function may be delayed, or even halted, but only if intervention occurs "soon enough". The obvious questions to answer are: 1) What is "soon enough"? 2) What type of neuroimaging might be "best"? and, 3) What kind of exercise? Simple questions with no simple answers. This chapter will begin with common, often overlooked issues regarding the use of exercise as a research modality and then progress to incorporating exercise into neuroimaging studies.

1.1 Sedentary and unhealthy

A sedentary lifestyle, low aerobic fitness and obesity are associated with both cardiovascular and cerebrovascular diseases (Burns et al. 2008). Research over the last decade has shown that 6 months of aerobic exercise may reduce or prevent brain volume atrophy in the prefrontal brain region related to executive function and memory in the aged (Burns et al., 2008; Colcombe et al., 2006; Erickson et al.,2009). It has also been suggested that aerobic fitness and obesity may selectively impact brain regions as well as different hemispheres (Cronk et al., 2009; Gustafson et al., 2004, 2008; Marks et al., 2007, 2010; Raji et al., 2009; Soreca et al., 2009; Ward et al., 2005). For instance, greater aerobic fitness has been moderately associated with greater cerebral white matter integrity in the anterior and middle cingulum regions on the left side of the brain whereas a higher body mass index and higher abdominal girth have been significantly associated with lower cerebral white matter integrity in the posterior cingulum region on the right side of the brain (Marks et al., 2010).

This of course has implications beyond executive dysfunction; disruption of cerebral white matter integrity in the middle-posterior cingulum regions could impact motor movement, learning, and reading comprehension. Early transcranial doppler studies concluded that aerobic exercise may be beneficial for maintenance of cerebral blood flow (Marks et al., 2000; Orlandi and Murri, 1996). A decade later, cerebral blood vessel morphology studies suggested physically active older adults have younger-looking cerebral vasculature (Bullitt et al., 2009, 2010).

However, the retention and improvement of human brain plasticity via exercise is still not well understood. Despite animal studies demonstrating that exercise may promote neurogenesis, and human studies demonstrating a maintenance/increase in brain volume with exercise (Cotman et al., 2007; Ferris et al., 2007; van Praag et al., 1999), there is little information demonstrating the mechanism(s) for such changes. Furthermore, much of the evidence is equivocal as to whether these brain adaptations, presumably due to physical exercise, equates to improved cognitive function (Colcombe et al., 2003; Etnier and Nowell, 2006; Heyn et al., 2004; Kharti et al., 2001).

These aforementioned discrepancies may be due, at least in part, to the state of flux with research in this area. Numerous neuroimaging techniques are being used and the technology itself is rapidly changing. Cognitive tests commonly used for those with known cognitive deficits may not be sensitive enough to detect subtle cognitive changes in presumed healthy community dwelling elderly. Furthermore, researchers are using a variety of exercise paradigms, some of which are not reproducible due to lack of reporting standard exercise prescription procedures. Other factors such as age, gender, training status, and diet, known to be potential confounders in exercise and aging studies, are often overlooked. Finally, there is confusion in which term to use to simply identify the exercise paradigm itself. All of these factors make comparisons across studies difficult and the ability to draw definitive conclusions impossible (American College of Sports Medicine, 2010; Leasure and Jones, 2008; Lommatzsch et al., 2005).

Therefore, the aims of this chapter are threefold: 1) Clarify the use of exercise, physical activity and related terms as profiling variables versus intervention modalities, 2) Review neuroimaging techniques currently being used to study the impact of exercise and physical activity on the aging human brain structure, and 3) Highlight the pros and cons for use of such methods with exercise paradigms.

2. Is it physical activity, exercise, or fitness?

Physical activity is associated with changes in brain structure. Regular exercise improves brain function. High aerobic fitness mediates cerebral white matter integrity. Do all these statements mean the same thing, or are there subtle differences in interpretation rendering the results difficult to compare?

2.1 Defining “exercise”

The terms “physical activity”, “exercise”, and “fitness” are often used interchangeably. But as with any discipline, these terms have distinct connotations and therefore should not be use as mere synonyms. To add to the terminology confusion, a myriad of additional phrases are incorporated in an attempt to better clarify the exercise paradigm. Typical terms include, but are not limited to: aerobic fitness, health fitness, physical fitness, calisthenics, circuit training, core training, resistance training, stretching and toning, strength training, and

weight lifting. Thus, physical activity or exercise could mean participating in a marathon or dance class, lifting a 10 kg medicine ball, raking leaves, meditating while performing yoga, or simply walking around a shopping mall.

2.2 Working definitions

Exercise scientists and physical educators continually find themselves clarifying the words that describe their work and this debate has raged for decades. For instance, the term *physical activity* is classically defined as any bodily movement that results in muscular contractions and increases energy expenditure above that which is used during rest (USDHHS/NHLBI, 2008). In contrast, the term *exercise* is defined as "*the regular or repeated use of a faculty or bodily orga*n" (Meriam Webster Free Dictionary, 2011). Thus, the term physical activity is often used due to its broader utility, but the term exercise should be used whenever the researcher's intent is to demonstrate the impact of *repeated exposure* to a *specific type* of physical activity. Therefore, exercise can be considered a structured sub-category of physical activity, with specific dosing parameters that result in health maintenance and/or improvement (Caspersen et al., 1985). The term *fitness,* in biological terms, simply means the ability of an organism to survive and reproduce. This generic term is most often used to connote one's health status and is expanded as needed (i.e., health fitness, physical fitness, aerobic fitness, brain fitness). The American College of Sports Medicine (1990) suggested the following definition be used for *physical fitness*: "fitness is the ability to perform moderate to vigorous levels of physical activity without undue fatigue and the capability of maintaining such ability throughout life." Obviously, this exercise science-based definition can be applied to the neurological system as well, suggesting that *brain fitness* can be defined as *the ability to perform daily cognitive tasks without undue mental fatigue or memory impairment and the capability to maintain cognitive abilities throughout life.*

3. Acute versus chronic exercise participation

Distinctions need to be made between the *acute* versus *chronic* impact of exercise on a physiological system, in this case, the brain. While it is important to know the short-term impact exercise has on physiological systems from a biological or safe participation standpoint, the establishment of long-term health benefits attributed to exercise exposures must account for the chronic adaptations due to historical (i.e., long-term) participation in an exercise regime. It is well-established that exercise is an acute stressor, thereby resulting in (relatively) immediate elevations in blood flow, heart rate, oxygen uptake, respiration, and increased circulation/uptake of most hormones and many metabolic substrates. However, the question remains, do any of these acute exercise responses, when experienced multiple times throughout the week, over several months to many years (i.e., chronic exposure), impact the brain in such a way as to become neuro-protective and prevent or attenuate neurological degeneration and cognitive decline commonly attributed to unsuccessful brain aging?

3.1 Cross-sectional or outcome study?

Evaluating the brain at one point in time with a selection of a population is a cross-sectional study. One is able to infer relationships between brain structure/function and a host of variables, ranging from cognitive test scores to health fitness ratings. This is an excellent starting point and is where most of the exercise neurobiology literature is currently focused,

likely due to time, facility limitations, and monetary constraints. However, care must be taken when reporting the results from cross-sectional studies. Regardless of the strength of the associations, results should not be reported in such a way as to infer causation. Cross-sectional research has pointed the way towards the need for more controlled, randomized longitudinal outcome studies which can take the significant associations one step further and determine causation of an intervention. While acute outcome studies are able to state how exercise stresses the brain on an immediate basis, only longitudinal outcome studies will be able to recommend more definitive exercise dosing guidelines for maintaining and/or improving brain health over a lifetime. Even then, the recommendations will likely be for specific populations, a specific gender, or specific types of physical activity. It will take several years to arrive at the more global health fitness recommendations now common in the cardiovascular literature. There is plenty of work ahead for innovative exercise-focused neuroscientists.

4. Media releases

The biggest blunder that has been occurring with the current brain studies is the pseudo-science reporting in the popular press. When public dollars are funding the research, it is important to get the science results out to the public in a media format that is understandable for the layman. However, the information is often unwittingly misrepresented by the media, resulting in conflicting reports when different modalities/populations are investigated, or worse, the media report leaves the impression that brain researchers are somehow privy to reading someone's mind. In the exercise neuroscience field, media interviews with researchers who are not trained in the exercise sciences or knowledgeable in the exercise design of a study has resulted in less than accurate interpretations of the study's purpose, strengths and/or weaknesses. This can have a dampening effect on future exercise neuroscience studies and may lessen the scientific integrity of the research itself. Thus it is critical that researchers understand the basics of the modality being used – in this case, exercise is the modality.

5. The exercise dose-response

To be comparable across studies and to better determine the most efficacious exercise plan for promoting successful brain aging, researchers and clinicians need to attend to the multi-faceted nature of the exercise prescription, or dosing, components. These components can be manipulated in a variety of ways so as to not only meet the research needs but also ensure that the participants will stick with the program. While not everyone is going to love to exercise, the exercise program should be designed to accommodate one's abilities, interests, and health status. Note that the exercise prescription is individualized not as a function of age or gender per se, but rather, it is individualized as a function of personal interests and health-fitness limitations. For research, the trick is to create a general exercise prescription for an entire group while maintaining an individualistic approach, to ensure the safety of each participant, prevent drop-outs, yet still be efficacious for the research goal. That is the "art" of an exercise prescription.

5.1 Components of an exercise prescription

When exercise is being used as a research tool, neurobiology researchers should consider the **FITT + P** paradigm (frequency, intensity, time, type, progression) of an exercise prescription

recommended by the American College of Sports Medicine (ACSM, 2009). Precisely identifying each of these components within an exercise neurobiology study makes comparison across studies, replication of results, and advancement of the exercise science of neurobiology much more accurate. Furthermore, it makes providing global recommendations to the public easy. Vaguely described exercise protocols are one of the major pitfalls encountered in the neurobiological literature utilizing exercise as a treatment modality. Often the research outcomes are either un-interpretable or non-generalizable. Manipulation of any one of the five components in the FITT + P paradigm can alter the intervention outcome significantly, and varying more than one component within a study must be done carefully. Ultimately the goal is to determine what type(s) of exercise recommendation(s) will best facilitate brain health maintenance. Reproducibility of the exercise prescription is paramount so that the findings can be applied across various physical activities and different populations.

5.1.1 Frequency ("F") of exercise

How "often" one exercises is a critical component of the exercise dose-response. It depends not only upon the health status of the individual, but also the type (or modality) of exercise. To improve cardiovascular health (or aerobic fitness), metabolic and lipid profiles, and body composition, 3 days per week is the recommended minimum number of times one should exercise (ACSM, 2009). However, if a person is at either extreme of the physical fitness continuum, (i.e., extremely deconditioned/inactive versus highly fit/active), then multiple daily sessions of very short duration (i.e. time) or nearly daily sessions of moderately long sessions may be instituted. Hence, there is a distinct relationship between frequency of exercise and duration of exercise. Simply put, the amount of time (in minutes) one should expend in a given exercise session is partially determined by how frequently one is exercising on a daily or weekly basis. Furthermore, the 3-days-per week minimum recommendation only applies to aerobic conditioning. Strength conditioning should be performed 2-3 days per week with the goal to alternate muscle groups being trained, and flexibility training recommendations is a minimum of 2 days weekly. Fitting all three of these exercise components (aerobics, strength, flexibility) into one exercise session can cause an exercise session to require at least one hour of time. Therefore, it is common to break up the exercise program into "aerobic" training days and "strength/flexibility" training days, resulting in exercising almost daily.

5.1.2 Intensity ("I") of exercise

How "hard" one exercises has many physiological parameters to consider including heart rate response, perception of effort, and workloads on various types of equipment. All of these factors contribute to the "intensity" of the exercise prescription and are manipulated according to the desired outcomes (Nieman, 2010).

5.1.2.1 Heart rate

If aerobic conditioning is desired, then the recommendation is for one to exercise within a ""stimulus zone". This zone is based upon one's health status and a percentage of one's age-predicted maximum heart rate (220 - age). For the average individual, a "moderate" intensity stimulus zone is recommended. As can be seen in *Table 1*, a moderate heart rate stimulus zone would be 64 – 76% of one's maximal predicted heart rate. So if one is 50 years old, the predicted maximal heart would be 170, and the heart rate training stimulus zone would be 109 to 129 bpm.

Intensity	%HRR	%Max HR (bpm)	RPE Range	% 1-RM
Moderate	40-59	64-76	12-14	40-69
Hard /Vigorous	60-84	77-93	14-15	50-69

Source: Modified from: Nieman, D. *Exercise Testing and Prescription, A Health Related Approach.* 7th Edition, New York: McGraw Hill Publishers, 2011, pp 180, Table 6.3, Classification of Physical Activity Intensity

Table 1. Intensity scales equating verbal descriptions to percent heart rate reserve (%HRR), percent heart rate max (%HRmax), rating of perceived exertion (RPE) based on the Borg 6-20 scale, and percent of a one-repetition maximum (%1-RM) strength test.

A slightly more complex, but more accurate way to prescribe aerobic exercise intensity is by using the Karvonen formula, a mathematical formula using percentage of one's heart rate reserve (maximal heart rate – resting heart rate). This requires knowing one's maximal heart rate (or estimating it as shown above), knowing one's resting heart rate (being able to take one's pulse rate at rest) and using the percentages listed in *Table 1*. Because this calculation more closely represents oxygen consumption requirements, the percentages shown in the table are slightly lower than the ones used with the age-predicted heart rate max method just described. Thus, the formula for determining a moderate-intensity heart rate stimulus zone using the Karvonen Method is as follows:

[(Maximal Heart Rate – Resting Heart Rage) * 40%] + Resting Heart Rate

[(Maximal Heart Rate – Resting Heart Rage) * 59%] + Resting Heart Rate

Thus, if our 50-year old person had a resting pulse rate of 75 bpm, using the Karvonen method to determine his exercise stimulus zone, his heart rate training stimulus zone would be 113 to 131 bpm.

5.1.2.2 Perception of effort

Sometimes heart rate responses are modified by medications or the exercise participant simply cannot take his/her pulse rate. In that case, exercise can be prescribed based on one's perception of the exercise intensity. This is called "rating of perceived exertion", or RPE. The most common RPE scale used is Borg's 6-20 scale, which at moderate intensity exercise, correlates well with the heart rate response. For instance if a person rates his level of exertion to be between 12-14, the heart rate is generally within 120-140 beats per minute. It does take about 3 practice sessions for the user to become familiar and comfortable with this scale in order to get the most accurate RPE scores **(**Borg, 1985). For a more complete understanding of using perceived exertion, an excellent applied book is "*Perceived Exertion for Practioners*" (R.J. Robertson, 2004, Human Kinetics Publishers).

5.1.2.3 Workload

When utilizing equipment for exercise training, the intensity of training will in part be mediated by the workload setting employed. For instance, if a moderate intensity is desired for lifting weights on a machine, a percentage of what a person is able to lift maximally one time (% 1-RM) maybe used. As seen in *Table 1*, to strength train at a moderate intensity, approximately 40-69% of a 1-RM will be recommended. That means, if the maximum weight one is able to lift is 100 pounds, then the training weight stack should be between 40 and 69 pounds (or, 45 kg max = 18 to 31 kg). If using a treadmill, the exerciser would need

instructions as to how to set the speed and percent grade; if using a cycle ergometer, the exerciser would need to know how to set the resistance and at what speed to pedal. Sometimes this is determined by an entry exercise test and the settings are based upon a percentage of their max test results; other times it is arbitrarily determined and governed simply by determining a "comfortable" pace in order to attain a desired heart rate or RPE range. Using the latter method will enable the researcher to permit the exerciser to exercise on a greater variety of equipment, thereby helping to reduce exercise boredom and dropping out of a study. However, a word of caution: if the goal of the research is to determine the impact of a certain TYPE of exercise on the brain over a certain period of time, then the researcher must give explicit instructions as to which equipment use is permissible for exercise research participation. Sometimes, giving a research volunteer too many choices can truly confound interpretation of the research results. Thus, while that new exercise club down the road may be convenient and affordable for the study, the researcher must determine how precisely the exercise prescription must be adhered to and consider the consequences if a subject veers off course.

5.1.3 Time ("T"), or duration, of exercise

The first "T" of the FITT + P paradigm is Time. How "long" one exercises, or how much time is required to achieve a desired fitness benefit, depends upon one's health status and/or fitness goals, and as stated above, the frequency of exercise. If one is very deconditioned, then multiple sessions of brief duration may be recommended. These brief durations may be as little as 5 minutes. It is common for those with a fragile health status or simply deconditioned due to inactivity (but otherwise considered healthy) to be given an intermittent exercise prescription consisting of 5 minutes of physical activity interspersed with an equal amount of rest, with that dose repeated twice more in succession so that an equivalent of 15 minutes can be accrued. As one successfully adapts to the exercise stimulus, the rest sessions will be reduced so that eventually the previously deconditioned person can exercise for 15 continuous minutes. Once a baseline level of aerobic endurance is attained, then strength conditioning can be safely and effectively added to the exercise program. As indicated above, an exercise session focusing only on aerobic conditioning can require 15 to 30+ minutes. A strength conditioning program may also require 30+ minutes if the entire body is to be trained in one session. Flexibility training can be a stand-alone program or be incorporated into the regular exercise program as part of a warm-up and/or cool-down routine. Thus, flexibility training can take as little as 5 minutes or as long as 30 minutes, depending upon the nature of the training.

While any one component of an exercise program may eventually take about 30+ minutes, it is standard to also incorporate a brief 5-10 minute warm–up before entering the "stimulus zone" and a 5-10 minute cool-down after completing the "stimulus zone" work-out. The warm-up is usually a lighter version of the stimulus and is to ensure the body is prepared to be stressed, whereas the cool-down is usually a relaxing set of stretches to enable the body to return to the pre-exercise non-stressed state. Therefore, at least 30 minutes needs to be allotted for the first week of a beginning exercise session (5 minute warm-up, ~20 minute stimulus, 5 minute cool-down), and more time thereafter as one's exercise prescription is upgraded, or progressed through several weeks of a research study.

Another aspect of "time" is the actual timing of the exercise – that is, time of day. While this does not impact the dose-response of exercise per se, it does impact the effectiveness of the

exercise plan if the time of day allotted to exercise is not compatible with the exerciser's lifestyle. For instance, if exercise is to take place under supervised conditions at a facility, the hours must be agreeable with the exercise's life – are there times available before or after one's work day, or at lunch? If recruiting a person with child care responsibilities, are there childcare services? Are weekend hours available? Other concerns are parking, commuting time, or easy bus/rail access. Will the research study pay for on-site childcare or parking?

5.1.4 TYPE ("T") of exercise

The other "T" component of the FITT + P paradigm is the TYPE of exercise (or activity) needed to achieve the stated research goals. The exercise prescription type is subdivided into three broad categories: aerobic endurance (or fitness), muscular strength/endurance, and flexibility. Of course each of these broad activity categories has numerous subtypes, thus it is crucial to specifically describe the type of activity one is to engage in. For instance, an aerobic activity is any activity that a person can complete continuously for 15 minutes or more that utilizes a large portion of the body's musculature in a rhythmic fashion. This includes common individual activities such as walking, running, swimming and cycling but it can also include games, sports and various types of dance. Muscular strength/endurance training also has many sub-types. It can consist of the traditional lifting of weights (aka weight training) or it can be termed resistance training or core training and involve not only dumbbells, free weights, or machines, but also medicine balls, resistance bands and tubing, kettle balls and one's own weight (e.g. push-ups, sit-ups). Other types of musculoskeletal training can include balance training, plyometric training, neuromuscular facilitation training, yoga, and tai chi. Flexibility training can involve static, ballistic, or dynamic stretching. Often times, strength and conditioning programs are simply called "stretching and toning", which really provides no concrete idea of the type of training actually provided. Thus, with all these options available to the researcher, creating a reproducible exercise program to investigate a particular health parameter becomes an art form. Obviously it is not possible to investigate every aspect of exercise within one study, so the researcher must narrow his/her focus to a select few options and describe them well-enough for the reader to be able to replicate. Ultimately, with enough well-designed neurobiology exercise studies, general recommendations for cerebral health will be able to be created, similar to those that now exist for cardiovascular health.

5.1.5 Progression ("P") of exercise

There are a variety of ways to "progress" an exercise prescription so that it remains challenging yet doable for the participant and prevents boredom or staleness. The progression of exercise is increased over the ensuing weeks at a percentage that is both safe and effective for that particular individual. The eventual goal is for one to attain a minimum of 30 or more minutes of continuous exercise on most days of the week (Haskell et al., 2007). One rule of thumb has been to increase any given exercise dose by as little as 2% or as much as 30% weekly or every other week. Another practice is to increase the duration of exercise by approximately 5 to 10 minutes every week, which might translate to a 15% increase in time week to week. If there is little room for adding additional time to an exercise session, then an extra day of training can be added on. If neither time nor frequency is an option to increase, then intensity becomes the progression target. When a person's perception of effort decreases along with lower heart rate responses with any given exercise stimulus, it is time to increase the exercise intensity. The goal is to make sure a slight overload is placed upon

the physiological systems so that the body can continually respond and successfully adapt to the overload. Unsuccessful adaption to an overload will result in undue fatigue, unnecessary muscle soreness, and if extreme, illness and/or injury.

Perhaps the most important concept to understand is the complex interaction between intensity, frequency and duration of the exercise prescription and how manipulation of any one of these variable impacts the exercise progression and adaption. The way to avoid unsuccessful overloading is to increase only one exercise prescription component in any given exercise session. For example, if the frequency of exercise training is scheduled to be increased from 3 days a week to 4 days a week, then the duration (total time) and intensity of the exercise session should remain the same as the previous training session. If on the other hand, the intensity of exercise needs to be increased, then the duration of the exercise session should either remain the same or be decreased slightly to accommodate for the increased effort required. On the following day, the duration can be returned to its previous level as long as the "new" exercise intensity remains the same. *Figure 1* outlines the basic components of the exercise prescription and can serve as a quick-reference exercise dosing

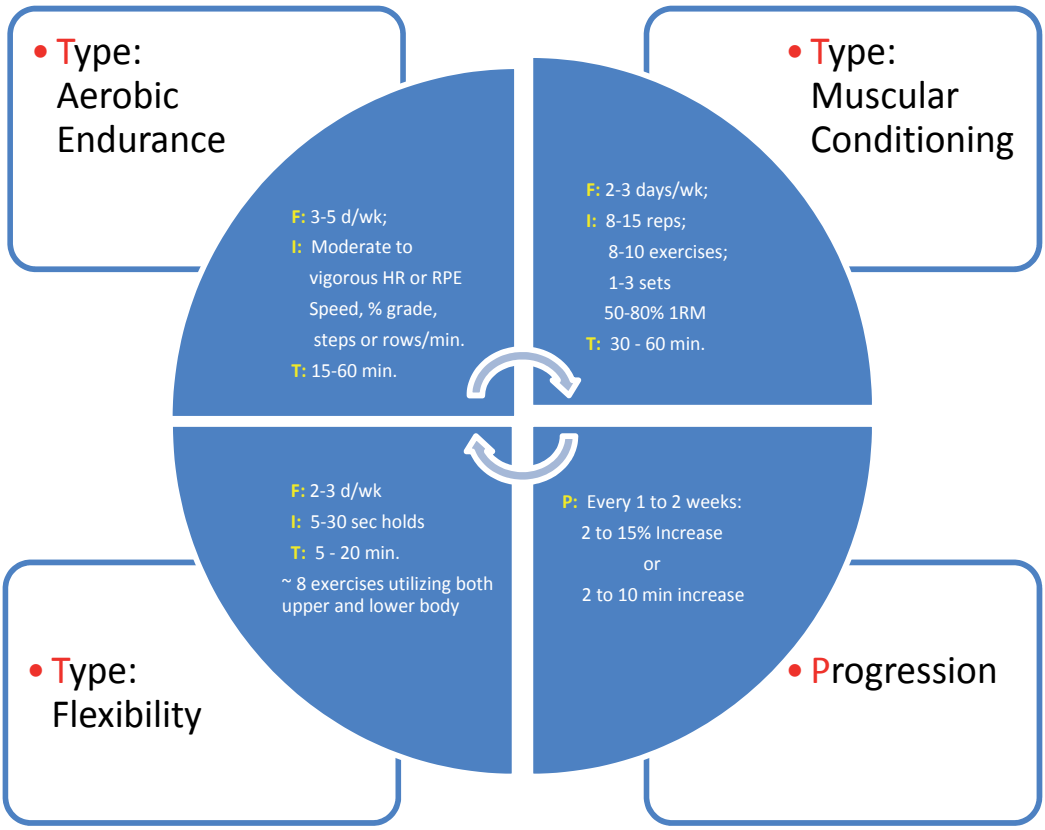

Fig. 1. Exercise prescription components featuring the FITT + P paradigm. Less active, unfit individuals would have exercise dosing at the lower ranges where as more active, higher fit individuals would have exercise dosing at the higher ranges. HR = heart rate; RPE = rating of perceived exertion.

guide. More complete exercise prescription information is available in the ACSM's Guidelines for Exercise Testing and Prescription book (2009), updated every four years. The best advice for researchers using exercise as a research treatment arm, or clinicians using exercise as a therapeutic agent is to make sure one or more ACSM-certified exercise physiologists are a part of your team.

6. Structural neuroimaging and exercise impact

What type of neuroimaging is best when trying to determine how exercise impacts the [aging] brain? That depends on the question(s) one needs to answer. If the goal is to determine the long-term impact of exercise on brain structure, then structural MRIs are appropriate. Structural imaging can track changes over time due to a stimulus such as exercise. Structural imaging can involve gray and white matter volume determination ("quantity"), cerebral white matter integrity ("quality") using diffusion tensor imaging (DTI), or both. It can also involve investigating the cerebral blood vessels utilizing magnetic resonance angiography (MRA).

6.1 Voxel-wise or ROI approach?

The MRI analysis can take a voxel-wise approach if the researchers have no particular hypotheses regarding expected areas of impact, or the MRI analysis can take a regions of interest (ROI) approach if there are research-driven hypothesis regarding expected areas of impact from physiological knowledge. There are pros and cons to both methods. It is argued that the voxel-wise approach is less biased, less time consuming, and therefore less costly. The ROI approach is argued to be driven by scientific knowledge of the physiology, more targeted and less "look-see" exploratory type research. While the ROI approach can be more costly due to the labor-intensive outlining of the specific ROI, and costly if ROI mapping is being done by more than one investigator for reliability purposes, if automated ROI templates are available, the cost and time decrease substantially. Unfortunately, not all ROI have templates. The "con" to template mapping is that a small degree of accuracy is sacrificed due to assuming a "standard shape" for a brain region when in fact there is no true standard shape (Scheibel, 2009). Thanks to the NIH Neuroscience Roadmap Initiative, there are a variety of free resources, including software mapping templates, available on the internet to download. One such site is called *MIDAS* and offers brain images as well as toolkits: http://www.insight-journal.org/midas/gallery/?flash=true

6.2 How long does it take for exercise to alter brain structure?

While rate of decline in brain mass with aging is highly individualized, it is often stated that the "normal" brain gradually decreases in size 10-15% with aging, and this shrinkage becomes particularly evident in octogenarians (Scheibel, 2004). The average rate of brain atrophy is between 0.9 to 1.5% per year after age 52, with the steepest rate of decline occurring in the frontal region with concomitant cognitive decline (Dennis & Cabeza, 2008). While it is not currently known precisely how much time is needed to facilitate structural changes (i.e., improvements) in the brain due to exercise, it is reasonable to hypothesize that relatively short-term structural change may be possible. In two separate studies demonstrating brain plasticity, as little as 1.5 to 3 months of cognitive training resulted in cortical changes in younger populations (Driemeyer et al., 2008; Haier et al., 2009). As for exercise, six months of aerobic exercise using moderate intensity walking 3 days per week

for an hour each session not only prevented brain volume atrophy but resulted in brain volume improvement in older adults (Colcombe et al., 2006). Using voxel-based morphology, improvements in brain volume were noted in both the gray and white matter regions associated with executive function, long term memory, and general intelligence (i.e., the prefrontal and temporal cortices). These improvements were cautiously reported in terms of brain atrophy risk reduction in comparison to a stretching/toning control group such that a 16% improvement in aerobic fitness resulted in a 27 to 42% risk reduction of brain atrophy. The greatest risk reduction was in the anterior cingulate cortex. The stretching/toning group experienced a non-significant 5% increase in aerobic fitness but no volumetric information was reported for them. Although it is not known if the 5% improvement in aerobic fitness also resulted in some volumetric improvement, it might be surmised that embarking upon a moderate-intensity aerobic exercise program which produces at least a 1% increase in aerobic fitness may attenuate aging-related brain atrophy. This was one of the first longitudinal outcome studies reporting the impact of aerobic versus musculoskeletal-type exercise on the aging brain.

Currently, little neuroimaging information is available on other modes or durations of exercise training; nor is there information regarding how quickly the human brain structure detrains. But if the brain/cerebrovasculature mirrors the heart/cardiovasculature in exercise adaptations, then like the cardiovascular system, the cerebrovascular system may lose that 11% gain in as little as 3 weeks of no training (Coyle et al., 1984). Thus, the protective effect against brain atrophy may be lost in one short month if one is unable to exercise sufficiently. An intriguing question remains, can cognitive brain training (e.g. suduko, puzzles, playing chess, Wii-games) supplant physical activity during periods of physical inactivity in order to maintain brain structure and function?

6.3 Exercise neuroimaging study shortcomings

Being a pioneer in exercise and aging neuroscience research also means there will likely be design flaws in the research. For instance, in Colcombe et al's study (2006), the age range was wide, 60 to 79 years with a mean age of 66 years. The study age range spanned two decades with three standard aging cohorts: the older end of middle-aged (45-64 years old), the young-old (65-74 years old), and the younger end of old (75-84 years old). No mention was made regarding how many subjects fell within each of these age cohorts, therefore it is not known if these age cohorts responded differently to the exercise programs. With no variance measure or age range provided *per group* on any variable, it is difficult to assume the study did not have a few inadvertent biases. A potential younger-age bias may have pre-existed in the aerobic treatment group (the treatment group was on average 1.4 years younger). The stretching/toning control group had a slightly higher percentage of females (4% more), creating a potential gender bias. Further, the actual pre-aerobic fitness distribution per grouping was unclear. Although the mean aerobic fitness (VO_2) values were not significantly different between groups (~ 23 ml/kg/min), the pre-intervention VO_2 values ranged from 12.9 to 49.9 ml/kg/min. Thus there were some older individuals with pre-intervention VO_2 values who would be considered highly fit and therefore have less room for improvement from any type of intervention. It is not known if an attempt was made to balance the placement of these higher-fit individuals into the two groups since the methods claim group assignment was totally randomized. Furthermore, it was reported that the aerobic group was previously sedentary, however older adults with VO_2's exceeding 40 ml/kg/min are not likely habitually sedentary. Individually, the between group differences highlighted here are small and were

reported to be non-significant, but considered collectively, these small biases could contribute to confounding the interpretation of the results.

Sociological studies have shown that women outlive men by 4 to 10 years, thereby partially explaining why there are usually more women in research studies involving older adults. Although women tend to live about a decade longer than men, they also experience an accelerated pace of physiological decline between their seventh and eighth decade of life. Older men tend to weigh more, be more physically active and have a higher degree of aerobic fitness than older women of the same age (Spriduso et al. 2005) and women's brain volumes are smaller than men (Allen et al., 2003). Thus care must be taken when studying variables with inherent age or gender differences. Colcombe et al. (2006) made no mention of controlling for age or gender in the statistical analyses of their data in order to determine if improvements attributed to aerobic fitness change was independent of age or gender influences. It is well known that both age and gender can impact brain volumes and cognition independently (Madden et al, 2009). Failure to control for these variables can lead to potentially erroneous conclusions. For example, Marks et al. (2010) initially noted moderate positive relationships in the anterior cingulum segment between cerebral white matter integrity and aerobic fitness as measured by diffusion tensor imaging (DTI). However, upon controlling for both age and gender, only the middle and posterior cingulum segments remained significantly related to aerobic fitness. Similarly, this pattern of reduced significance was repeated in a voxel-wise brain analysis on the same data (Liu et al. 2009). Thus it is critical to control for factors that are known to impact the brain and/or aerobic fitness parameters. Lastly, neither the exercise test protocol nor the "stretching and toning" prescription was ever fully described by Colcombe et al. (2006). This lack of information makes it difficult to determine the validity of the aerobic fitness and strength training outcomes, and it is even more difficult to impart health recommendations with confidence. Hence the encouraging conclusions regarding aerobic fitness and brain improvement from this study by Colcombe et al. (2006) must be viewed with cautious optimism. There are currently a few new NIH-funded exercise trials involving both healthy and diseased older adults in progress (http://projectreporter.nih.gov/reporter.cfm), with intervention timelines and exercise protocols seemingly mirroring Colcombe et al. 's initial study (2006) . Hopefully, these newer studies will not only control for potential confounding variables but also provide sufficient exercise testing and training details to render their studies replicable.

6.4 Magnetic resonance angiography and exercise impact

Magnetic resonance angiography (MRA) in conjunction with DTI is helpful in determining the status of one's cerebral blood vessels. Using a process known as arterial spin labeling (ASL), the quality and quantity of the cerebral blood flow can be determined with or without perfusion. It is believed that the progressive reduction in cerebral blood flow attributed to the aging process may be caused by a reduced metabolic demand due to a reduction in neurotransmitter synthesis (Orlandi & Murri, 1996) and/or underlying microvascular disease (Bullitt et al., 2010). The consequential neural atrophy results in smaller cerebral arteries, increased intracranial resistance and slower arteriole vasomotor reactivity (Orlandi & Murri, 1996). Even though studies suggested aging may be associated with smaller cerebral vessels, Bullitt et al. (2010) reported that vessel diameter reductions may be compensated for by an increase in vessel number and that both larger and smaller vessels were impacted. In a sub-study comparing active versus inactive older adults, Bullitt et al. (2009) reported significantly lower vessel tortuosity along with a higher number of

smaller vessels. In a separate conference paper, although cerebral blood flow velocity did not change, Rahman et al. (2008) reported less variance in the cerebral blood flow velocity in those with higher physical activity levels. To examine both the cerebral vasculature as well as cerebral blood flow, arterial-spin labeling (ASL) would be required. For either the blood oxygen level-dependent effect (BOLD) or ASL methods, intravenously (IV) injected contrast agents will produce more distinct images. However decent (but not great) images can be obtained without the IV injections. Not using invasive procedures is certainly more appealing to the volunteer subject and helps to contain the imaging costs as well.

7. Functional neuroimaging and exercise

If one is interested in determining which regions of the brain are being activated /oxygenated during an exercise or cognitve task, a functional MRI (fMRI) using the BOLD response would be needed. For exercise studies, the obvious hurdle to overcome is movement as most movement causes disruption in the scanning process and poor images are created. Whereas cognitive psychology has forged numerous research pathways using fMRI with BOLD contrasts to determine regions of activation in the brain during various cognitive tasks, this has not been the case with exercise training interventions. Clearly there is a need for this type of research if one desires to investigate changes in cerebral blood flow or neural hormonal factors due to an exercise stimulus from either an acute exercise bout or in response to a chronic adaptation. The stumbling block to overcome is the exercise test itself. Most exercise studies use upright testing protocols on equipment that are large and bulky with both metal and electronic parts. All of this precludes testing within the scanning room due to the magnetic field. Furthermore, by the time the subject could be transferred from the exercise apparatus to the scanning bed, critical time would be lost such that the exercise impact on the cerebrovascular system would likely be missed in all but the most deconditioned subjects.

7.1 MRI-friendly leg cycle ergometer

Therefore, up to this point, the more feasible methodology for cerebral blood flow investigations with exercise have been with using transcranial dopplers (TCD) and/or electroencephalography (EEG). Although these methods also have difficulty with accurate measures during movement, they are in comparison, lower in cost and easier to administer than an fMRI study. However, for approximately $75,000 (US$), the Lode MRI-compatible recumbent leg cycle ergometry system can now be purchased from ELECTRAMED Corporation, located in Flint, Michigan, http://www.electramed.com/MRI%20ERGOMETER%20CARDIOLOGY%20_Details.htm. This would enable the researcher to conduct exercise tests while the subject remains in the MRI unit. Also available are MRI-compatible electrocardiography and blood pressure measurement units, thereby solving the equipment issue. Unfortunately, this particular equipment model is only compatible with a 1.5 T MRI scanner and only with select manufacturers. Given that most research is now being done on 3.0 T or 4.0 T scanners, this ergometer may not be useable for many research protocols. The final issue left to resolve is an acceptable exercise protocol that would be taxing enough yet involve minimal movement from the torso up during scanning sequences. One potential resolution would be to develop an intermittent exercise test protocol so that exercise bouts would take place during the imaging sequence changes, akin to an event-related design. Since stimuli in an event-related design are presented as isolated events of short duration, a brief

cycling set that progressed in intensity with each event presentation could be incorporated (Carter and Sheih, 2010). Obviously, much pilot work would need to be done to determine the exact power outputs required to elicit measureable BOLD signals.

7.2 Exercise mental imagery

If actual physical exercise testing is not possible, there is still one other avenue to determine cerebral activation during an exercise task: mental imagery. For example, a sport psychology study investigated motor imagery of the golf swing to determine brain region activation. Using the sensori-motor homunculus map as a guide, Ross et al. (2003) compared the amount of fMRI BOLD response in brain regions related to the golf swing between novice versus expert golfers. It was determined that the greater the golf handicap, the greater the region of activation (greater than 2%) in specific somatatropic regions of interest relevant to golf. The powerpoint presentation can be downloaded from the internet with a search engine. A very recent BOLD fMRI study (Cremers et al., 2011) investigated mental imagery consisting of subjects envisioning themselves either walking, standing, or lying down (block design). Their imagined walking (speed = 2.3 ± 0.4 m/s) was associated with activation in the right dorsolateral prefrontal cortex, posterior parietal lobule, and the left cerebellar hemisphere. Therefore, it might be interesting to conduct an imagery intervention study to determine the acute response to an imagined exercise stress test as well as an imagined chronic response to a long-term exercise intervention. Studies of this nature have not yet been reported.

8. Testing pearls and pitfalls

Neuroimaging studies are expensive. Exercise testing and training are expensive. Recruitment drop-outs are expensive. And botched tests are expensive. They are expensive in terms of time, money and patience. Neuroimaging and exercise testing aged individuals bring a unique set of challenges to intervention research. There are the standard safety issues to consider when using a neuroimaging technique or conducting a physical exercise test; but the less obvious issues of comfort and trust sometimes slip by unasked, until it is too late and the subject has dropped out of the study. Therefore, when screening an older individual for an imaging and/or an exercise study, the following question must be asked: can the volunteer complete the testing protocol accurately and in relative comfort? The researcher must ascertain that the older volunteer can hear, see, follow directions, and adhere to the instructions. Volunteers must be able to complete enough of the exercise protocol to get valid physiological baseline data and/or remain motionless and pain free in the MRI scanner anywhere from 15 to 120 minutes. The brief breaks afforded between imaging sequences when a subject is free to move slightly may be insufficient. Arthritis, nasal-sinus drainage, and circulatory issues have thwarted many research MRI scans. For a first-time MRI scan, volunteers may back out at the last minute due to unanticipated fright (hence a simulator is an invaluable resource) or the irrational worry that the MRI will read their minds (thanks to outlandish media stories). Thus, the researcher must design protocols with both the science and the targeted subject population in mind.

8.1 Exercise testing versus physical activity recalls

Actual measurement of aerobic fitness, as opposed to estimating it in some fashion, is usually preferable. There are a variety of reference books available detailing exercise protocols for various health and fitness statuses. The researcher who wants to include

exercise in the research design should obtain the ACSM Guidelines for Exercise Testing and Training (2009). A good textbook is Nieman's (2010) exercise prescription textbook used for training undergraduates in exercise science. However, there are times when it is inconvenient, illogical, or cost-prohibitive to conduct a fitness test. For those times when actual exercise testing is ruled out, there is a rather good non-exercise aerobic fitness estimation equation that is quite easy to use, providing one is trained in obtaining a valid physical activity recall. While it can be difficult to get accurate physical activity recalls beyond a few weeks, a seasoned investigator in physical activity recall questionnaires can elicit excellent responses, even recalls spanning several years.

One physical activity recall formula for estimating aerobic fitness has been in the literature since 1990. It was gathering dust until recently when we used it for a retrospective analysis exploring the role aerobic fitness might have on cerebral white matter integrity on both younger and older adults (Marks et al., 2007). Ever since that publication, we have been getting inquiries about the formula and how to use it. The formula was developed and tested at the Cooper Aerobic Institute in Texas on over 2,000 U.S. Air Force personnel ranging in age from 18 to 70 years. The subject population included males and females, fit and unfit, healthy and unhealthy. The estimated aerobic fitness value (VO_2) has a standard error of about 5 ml/kg/min. This formula is very good for cross-sectional, population-based studies when the purpose is to simply categorize one's fitness level. However, the error range is a bit too high and the fitness categorizing a bit too vague for pre-post research designs where VO_2 change is a critical factor. For that, VO_2 does need to actually be measured. Although the formula tends to underestimate the highly fit and over-estimate the very low fit, all subjects are still able to be categorized accurately into a fitness level (e.g., low fit, average fit, high fit). The estimation formula and its accompanying physical activity rating scale (PARS) are contained in *Table 2* and T*able 3* below:

VO_2 max ≈ 56.363 – (0.381 * age) + (1.951 * PARS) – (0.754 * BMI) + (gender * 10.987)
where: *Gender*: 0 = women; 1 = men
BMI = body mass index = weight (kg) / (height in meters^2)
PARS = physical activity rating scale from 0 to 7 (see Table 3)

Table 2. Estimated Aerobic Fitness (VO_2 max) (Jackson et al., 1990).

9. Limitations and suggestions

The good news is, lines of inquiry utilizing neuroimaging are still rather novel and as such, there is much to study. The bad news is, these lines of inquiry utilizing neuroimaging are still rather novel and there is much to learn, so omissions and/or mistakes in research design are to be expected. Investigating how exercise impacts the brain is akin to the first studies investigating how exercise impacted the heart and its related vasculature several decades ago.

A limitation in several structural imaging studies (e.g., Marks et al. 2010; Bullitt et al. 2009; Colcombe et al., 2006) was lack of cognitive function testing – it is unknown if the improved brain structures found in the more active subjects would have translated into better cognitive function. Adding cognitive testing with magnetic resonance imaging (MRI) may help detect subtle changes that the standard cognitive test batteries if used alone, cannot. If the MRI is able to detect changes, independent of the cognitive tests, a therapeutic program could be implemented at an earlier stage of decline and perhaps be more effective in reducing further impairment.

Directions: Query the participant regarding his/her extent of physical activity using the activity descriptors below as well as established metabolic tables for physical activity.

A. No regular participation in programmed recreational sport or physical activity:
0 = avoid walking or exertion (always use elevator, drive whenever possible instead of walking.)
1 = pleasure slow walking, routinely use stairs, occasionally heavy breathing or perspiration

B. Regular participation modest/moderate physical activity (e.g. golf, horseback riding, calisthenics, gymnastics, table tennis, bowling, weight lifting, yard work etc):
2 = 10 to 60 minutes per week
3 = over one hour per week

C. Regular participation in heavy physical exercise (e.g. jogging, running, swimming, cycling, rowing, skipping rope, running in place, tennis, basketball, or handball etc.):
4 = run less than 1 mile per week or spend less than 30 minutes per week in comparable heavy physical activity
5 = run 1 to 5 miles per week or spend 30 to 60 minutes per week in comparable heavy physical activity
6 = run 5 to 10 miles per week or spend 1 to 3 hours per week in comparable heavy physical activity
7 = run over 10 miles per week or spend over 3 hours per week in comparable heavy physical activity

Table 3. Physical Activity Rating Scale (PARS; Baumgartner and Jackson, 1995).

There are also scanner issues to deal with when a study design goes from a single acute scan to repeated scans over several months or years. Your scanner must be intra-reliable (i.e, a measure today will yield relatively the same results tomorrow). It is well known among neuroimaging technicians that scanners "drift" over time, therefore it is important to keep track of the drift so you can be sure changes that are seen months from the initial scan are corrected for the drift. Along these same lines, in order to get larger sample sizes, multiple sites may be needed. Therefore all the scanners used must be determined to be inter-reliable. This is generally accomplished with phantom testing.

It is equally important to account for individual brain plasticity - the investigator must understand the normal brain changes over time independent of any treatment so that intervention changes seen can be distinguished from random occurrence or normal aging.

Lastly, dehydration is an issue that only recently has begun to be accounted for in neuroimaging research studies. Care must be taken to ensure the research volunteers are euhydrated, otherwise, the question that may arise when a brain volume increase is reported: Is the increase in brain volume "true"? Or is it due to dehydration known to plague not only the elderly but also exercisers who exercise in a hot environment and may not have hydrated sufficiently? A simple way to account for hydration status is to obtain a urine sample and test it for urine specific gravity using either a dip stick (aka chem. strip) or a small handheld refractometer. A non-smelly light straw-colored urine would suggest the person was adequately hydrated. If a more precise objective measure is needed, the urine specific gravity reading should be between 1.010 to 1.020 (Armstrong et al., 1998).

10. Conclusions

Aerobic fitness not only facilitates improved oxygen delivery and utilization in the cardio-cerebral vascular systems, improved oxidative capacity has been shown to up-regulate expression of important neuronal growth factors such as insulin-like growth factor I (IGF-I), brain-derived neurotrophic factor (BDNF) and related protein precursors in animal models (Ding et al., 2006; van Praag et al., 2005). Furthermore, aerobic fitness may mediate improved cerebral white matter integrity via the intricate adaptations that take place on the neural-humoral level during exercise (Marks et al., 2010). Therefore, exercise outcome studies trials need to include not only structural imaging detailed in this paper, but also hormonal measurements and perfusion imaging.

In summary, the research questions that remain to be answered are: What is a sufficient exercise dose for the brain? How much, or how little, exercise is really needed to maintain brain structure and cognitive function? Will any type of physical activity do? Will the resultant health recommendations for the brain be complementary to the current guidelines for cardiovascular health?

To move the future of brain training research forward, we must continue to revisit the past ground-breaking cardiovascular research studies and modify them for the brain. Ancient physicians and philosophers like Hippocrates and Cicero espoused the benefits of exercising both the body and the mind, and here we are, 2,000 years later, scientifically documenting the neurobiological benefits of exercise. Several investigators have been using a few standard cardiovascular disease risk reduction guidelines with success in maintaining brain volume in older adults, but so many more exercise options remain to be explored. Hopefully it will not take another 50 years to firmly establish exercise guidelines for maintaining and enhancing brain health with exercise.

11. Acknowledgment

The University of North Carolina at Chapel Hill's Libraries provided support for open access publication.

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12

Human Oscillatory EEG Activities Representing Working Memory Capacity

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1. Introduction

We can flexibly process and make decisions regarding multiple types of information in daily situations such as driving and cooking. However, human error is increased in complex or combined tasks (relative to simple tasks) because our information processing capacity is limited. This limited cognitive function is associated with working memory (WM), which is proposed to be a higher-level human ability to memorize, maintain, and manipulate mental representations in the mind for a short time (Baddeley, 1986). Most theorists think that WM function includes active manipulation as well as passive short-term maintenance. An often-used metaphor for working memory is "the blackboard of the mind." For example, imagine that you are rearranging the furniture in your room. You can move around the furniture in your mind, that is, transform the imagination any number of times. To guide behavior and make decisions about what to do next, WM temporarily selects and retains task-relevant information such as recently processed sensory input, retrieved information from long-term memory, or mentally manipulated images. Thus, WM is directly linked to any and all other brain functions, including perception, movement, emotion, and problem solving.

Baddeley & Hitch (1974) proposed a basic psychological model in which WM is divided into separate components, the "storage system" and the "central executive". The "storage system" consists of 2 temporary storage buffers for visual information (visuospatial sketch pad, i.e., visual working memory) and auditory-verbal information (phonological loop, i.e., verbal working memory) and an episodic buffer for long-term memory, whereas the "central executive" controls the allocations of attention, selects relevant information, and manipulates information held in the storage systems (Baddeley, 1986; Baddeley & Hitch, 1974; Phillips, 1974; Baddeley, 2000). Extensive experimental evidence from behavioral performance of normal subjects, lesion studies, and neuroimaging studies supports this view. For example, performance in dual tasks requiring 2 separate perceptual domains (i.e., a visual and a verbal task, or a mental processing task and a maintenance task) is nearly as efficient as performance of individual tasks (for a review, Cowan, 2001; Della Sala & Logie, 1993). These findings indicate that the visual and verbal WM are separated.

Both visual and verbal WM have 3 phases: encoding, which imports the relevant information in memory; maintenance, which stores the encoded information; and retrieval (or rehearsal), which briefly uses the information for a task. To investigate the neural substrate for WM, previous electrophysiological studies in nonhuman primates and human

neuroimaging studies have shown sustained neural activity over the retention interval in distributed brain regions including frontal, parietal, occipital, and temporal areas during maintenance of relevant information (e.g., Chafee & Godman-Rakic, 1998). If these brain regions are actually involved in maintaining mental representations, their activities are thought to be correlated with WM capacity. In fact, brain activity has been reported to increase with increasing number of objects to be remembered and saturated below the limited WM capacity (Todd & Marois, 2004; Vogel & Machizawa, 2004). Frontal regions also represent the limitation of executive functions, since activity there is increased during engagement in dual tasks (Marois & Ivanoff, 2005). These results suggest that frontal regions are associated with executive functions and posterior regions are involved in maintenance of mental representations. Thus, although much is known concerning the brain areas involved in various WM functions, understanding how these brain areas temporally communicate is more difficult.

To address this issue, measuring electrophysiological (EEG) data during WM tasks and analyzing the synchronizations in local areas and between different areas has proved particularly useful (Varela et al., 2001). Our previous EEG studies used mental calculation as the auditory WM task and mental spatial manipulation as the visual WM task (Kawasaki et al., 2010). The EEG results clearly demonstrated that the frontal theta (4–6 Hz) activity increased during the manipulation periods on both WM tasks, and the parietal and temporal alpha activities were enhanced only during the maintenance periods on the auditory and visual WM task, respectively. Phase synchronization analysis revealed significant theta synchronizations between the frontal and parietal regions for visual WM and between the frontal and temporal regions for auditory WM. These results indicated that long-range theta synchronizations could connect the different brain regions to manipulate task-relevant representations. Interestingly, the concurrent theta and alpha phases were significantly synchronized in task-relevant storage areas, which suggests the presence of gating mechanisms to extract stored information. Theta and alpha activities thus play an important role in several WM functions; however little is known regarding how these oscillations represent WM limitations.

This chapter describes investigations into the neural dynamics of EEG oscillatory activities that underlie the capacity limitations for executive functions and storage buffers in WM, particularly for visual infomation. To advance understanding of the detailed brain networks involved, the use and interpretation of EEG time-frequency analyses such as wavelet analysis and the role of each EEG oscillatory activity in WM functions is discussed, and 2 experiments are described. Visual storage systems were investigated using delayed-matching-to-sample tasks with visual stimuli, and a dual WM task with visual and auditory representations was used to identify the bottleneck of the central executive function. These EEG findings may contribute to understanding the causes of human error.

2. Capacity limitations of working memory

To investigate the limitation of visual WM (VWM) storage capacity, previous behavioral and neuroimaging studies used a change detection paradigm, namely, delayed matching to sample (DMS) tasks with a visual stimulus. In this paradim, multiple visual items are presented (sample display) and participants are required to memorize and retain these items

over retention intervals. The number of items within the sample display is manipulated. Following the retention interval, one probe item (test display) or multiple probe items (whole display) are presented at one location within the sample array, and participants are then required to judge whether a change has occurred or not. These 2 tests have shown different performance scores, since VWM storage capacity is vulnerable to visual interference created during the encoding period (Wheeler & Treisman, 2002). Therefore, many behavioral and neuroimaging studies have applied the single-probe test. To avoid the possibility of using verbal strategies, most studies involving the DMS task used very short exposure duration for the sample display (about 150 ms), and require participants to engage in phonological tasks simltaneously, e.g., repeating a word during the sample display and retention intervals (Baddeley, Lewis & Vallar, 1984).

Many previous studies have proposed a VWM capacity of 3 or 4 items (Luck & Vogel, 1997) because the accuracy rates for many DMS tasks systematically decrease as the number of items increases beyond 3 or 4. More recently, one study demonstrated that VWM capacity decreases as object complexity increases, and proposed that VWM capacity varies by the type of features (Alvarez & Cavanagh, 2004). The authors used complex items, Chinese characters, which are thought to be a combination of simple shapes. Although the issue retains some controversy, many studies have demonstrated consensus on the existence of large individual differences in VWM capacity.

To estimate the capacity of VWM in terms of objects stored in DMS tasks, Cowan (2001) has proposed a model that takes both hit rates (accurately detecting a change) and correct rejection rates (accurately reporting no change when none occurred) into account. The model estimates hit rates and correct rejection rates with the following equations:

$$H = \frac{K}{N} + \frac{(N-K)}{N} \times g \tag{1}$$

$$CR = \frac{K}{N} + \frac{(N-K)}{N} \times (1-g) \tag{2}$$

where K denotes the estimated number of items stored in VWM, N is the total number of items presented in the sample display, H is the probability of a hit rate, CR is the probability of a correct rejection rate, and g is the guessing rate for coincidentally giving a correct answer. The theory assumes that when one of the items within the VWM capacity (K/N; Fig. 1 purple area) changed, subjects could detect whether the change occurred. In contrast, they could not detect whether a change occurred in objects exceeding the capacity (($N - K)/N$; Fig. 1 green area).

However, in some cases subjects happened to answer correctly on some portion of the trials (g) under an alternative forced-choice paradigm or, in another portion of the trials ($1 - g$), coincidently report correctly that no change occurred in the no-change trial, although they could not detect this. This guessing rate could not be estimated from the performance of the DMS tasks. Thus, given the hit rates and correct rejection rates for a particular set size, these equations (1) and (2) can be solved for the set size:

$$K = N \times (H + CR - 1) \tag{3}$$

The Cowan's *K* value is obtained from the set size of each sample display as each subject's VWM capacity for a given material.

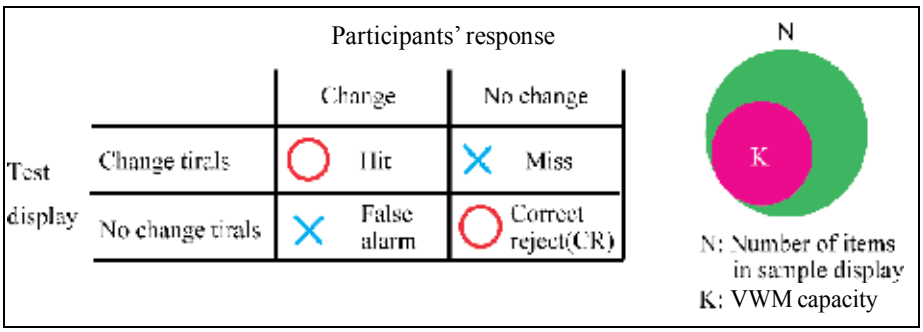

Fig. 1. Combination of participants' response and trial type (change or not) in change detection paradigm (left) and a model of Cowan's formula (right).

Unlike VWM, the WM capacity for executive functions has been evaluated using dual WM tasks. Although no interference exists between independent storage components such as visual and verbal storage, simultaneously processing more than 2 information sources that require mental manipulation and reactions is thought to be difficult. Previous studies have revealed a psychological refractory period, in which a second task elicits a longer reaction time when the interval between the first and second tasks (i.e., stimulus onset asynchrony; SOA) is short (Marois & Ivanoff, 2005). That is to say, if the 2 tasks seem to be processed simultaneously, the performance is degraded. This phenomenon is known to be a bottleneck of the central executive function.

3. Neural substrates for working memory

Over many years, numerous researchers have attempted to localize and characterize the neural implementation of VWM and dissociate its functions. Lesion studies have reported that damage to the prefrontal cortex (PFC) in monkeys impairs performance on DMS tasks with a short delay, but not on visual discrimination tasks that do not require maintenance of information (Goldman-Rakic, 1987). Likewise, electrophysiological recording studies of nonhuman primates have revealed sustained neuronal firing in the PFC during the retention interval of DMS tasks, and interpreted the activity as maintaining the previously presented representations (Fuster & Alexander, 1971; Kubota & Niki, 1971). Therefore, the PFC was believed to be the neural substrate for VWM over a longer period. Since then, numerous physiological studies have shown neurons specifically active during the delay period in a vast network of brain regions including the PFC (e.g., Funahashi, Bruce, & Goldman-Rakic, 1989), the posterior parietal cortex (e.g., Chafee & Godman-Rakic, 1998), and visual processing cortices (Bisley & Pasternak, 2000; Miyashita & Chang, 1988).

Consistent with this interpretation, human neuroimaging studies have also revealed that the blood flow in these regions continually increased during the retention interval (Courtney et al., 1997, 1998; Postle & D'Esposito, 1999). Although considerable evidence supports the sustained delay-period activity, DMS tasks include many requirements (e.g., preparation of actions) in addition to maintenance. Therefore, recent fMRI studies have assumed that the blood oxygen level-dependent (BOLD) signal captures a population of neuronal activity that

may reflect the representation of multiple items to be maintained, and have indeed shown that a subset of the distributed network demonstrated delay-period activity sensitive to the number of items in the sample display (Diwadkar et al., 2000; Glahn et al., 2002; Jha & McCarthey 2000; Linden et al., 2003). The VWM load-sensitive network includes the frontal, parietal, and visual cortices. Notably, some studies have revealed that activity in the posterior parietal cortex is correlated with the number of items to be remembered (Cowan's *K* value) and indicated that this area actually stored the representations (Kawasaki et al., 2008; Todd & Marois, 2004, 2005; Vogel & Machizawa, 2004; Xu & Chun, 2006).

In contrast to the posterior parietal and visual cortices, anterior regions including the frontal cortex have also been associated with executive processes such as attentional selection and manipulation of information (Curtis & D'Esposito, 2003). For instance, in studies using a spatial WM task that requires participants to memorize the spatial locations of simultaneous or sequentially presented items and, after a delay, select one relevant location, the prefrontal cortex has been reported to show transient activity during the selection period and no sustained activity during the retention interval (Rowe et al., 2000). Furthermore, the frontal cortex is particularly sensitive to the number of listed items to be maintained in VWM in the n-back task, which requires participants to maintain a series of items and their order, select a relevant item from VWM, and compare it with the earlier item (Smith & Jonides, 1999). Moreover, the frontal cortex is proposed to serve in maintaining task-specific goals (Miller & Cohen, 2001; Passingham & Sakai, 2004) and assist in maintaining high loads and/or long retention intervals (Braver et al., 1997; Linden et al., 2003).

Although, thus far, many neuroimaging studies have identified the neural substrate for the storage systems and central executive of WM, they have not dealt with how these brain areas temporally communicate. To address this issue, some studies have investigated the dynamic relationships governing brain activity by focusing on electroencephalograph (EEG) oscillations, which are closely related to synchronization of a large number of neurons underlying a particular function (Varela et al., 2001). Previous human scalp-recorded EEG studies have revealed modulated theta (about 4–8 Hz) and alpha (about 9–12 Hz) rhythms in distributed brain regions and phase synchronization between them during various WM tasks (Jensen & Tesche, 2002; Kawasaki & Watanabe, 2007; Klimesch et al., 2008; Mizuhara et al., 2004; Sauseng et al., 2005). Frontal theta activity in particular has been associated with the mental manipulation of WM, because these oscillations were enhanced in tasks such as mental calculation and image transfomation (Kawasaki et al., 2010). In contrast, posterior alpha activities are thought to be involved in the WM storage systems, because these oscillations are mainly observed in the retention intervals of many WM tasks. However, whether these oscillatory activities are increased or decreased during each WM period remains controversial. Furthermore, little is known regarding how these oscillations represent WM limitations; therefore, their detailed mechanisms have not yet been identified.

To clarify the functional role of the theta and alpha oscillations in WM, the study described in the following 2 sections used EEG data measured during DMS and dual WM tasks to demonstrate 2 types of EEG activity that were correlated with the WM capacities for visual storage and central executive systems.

4. EEG oscillations for visual storage capacity

This section describes the investigation of EEG oscillatory activity correlated with VWM capacity, which aimed to identify the roles of different oscillations in the VWM storage

systems (e.g., maintenance of high or low VWM demands). EEG data was measured during the DMS task.

4.1 Delayed matching to sample task

Fourteen healthy, right-handed volunteers (10 male and 4 female; mean age = 25.6 ± 4.2 years, range 21–38 years) with normal or corrected-to-normal visual acuity, normal hearing acuity, and normal motor performance took part in the delayed matching to sample tasks. All participants gave written informed consent, which was approved by the Ethical Committee of the RIKEN (in accordance with the Declaration of Helsinki), before the experiments were performed.

Participants faced a computer screen and were asked to memorize the colors of 3 or 6 colored disks (size, 1° × 1°; color, white, red, green, blue, yellow, magenta, cyan, or orange) that were distributed at random locations within an invisible 3 × 3 cell matrix in a black rectangle (size, 10° × 10°) for 0.2 s (Fig. 2, sample display). After a 2-s retention interval, one disk was presented at one location within the sample array (test display), and participants were asked to judge whether its color matched the disk at the same location in the sample display via a button press while the fixation point was red for 2 s. In one trial, the color of the probe disk matched the sample disk, and in a second trial, the color of the probe disk did not match. After the judgment, a feedback stimulus indicating whether the answer was correct (O) or incorrect (X) was presented. The duration of the inter-trial interval (ITI) was 2 s. Each participant completed 4 separate sessions which consisted of 48 trials. A behavioral training session before the EEG-measurement sessions was provided for all participants.

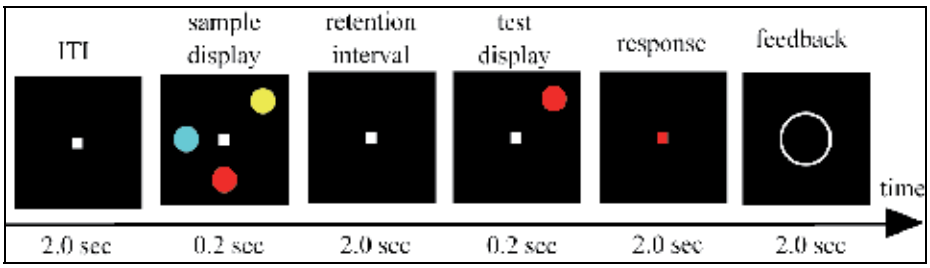

Fig. 2. Task procedure for 1 trial of the delayed-matching-to-sample task.

4.2 EEG measurements and analyses

An EEG was continuously recorded using 60 scalp electrodes embedded in an electrode cap in accordance with the extended version of the International 10/20 System of Electrode Placement. The sampling rate was 500 Hz. Reference electrodes were placed on the right and left earlobes. Artifacts due to eye blinks and movements were detected by electro-oculogram (EOG) electrodes placed above and below the left eye to monitor eye blinks and vertical eye movements, and electrodes placed 1 cm from the right and left eyes to monitor horizontal eye movements. Trials in which the amplitude of any electrode of an EEG epoch exceeded plus or minus 100 μV were rejected from the offline analysis. These EEG data were amplified using NeuroScan equipment (Compumedics NeuroScan Corp., Charlotte, NC) and filtered with a band-pass range from 0.1 Hz to 50 Hz.

We analyzed the EEG data for the correct trials. These epochs were subjected to infomax independent component analysis (ICA) with the use of EEGLAB (Delorme & Makeig, 2004;

Institute for Neural Computation, University of California, San Diego, CA) running under Matlab (Mathworks, Natick, MA). ICA components that were significantly correlated with vertical or horizontal EOGs were regarded as components related to eye movement or other artifacts and were reduced or eliminated from the data. The ICA-corrected data were recalculated using regressions on the remaining components.

To accurately evaluate cortical activity under the scalp EEG electrodes without error due to volume conduction, we used a current source density analysis at each electrode position. The spherical Laplace operator was applied to the voltage distribution on the surface of the scalp using the following parameters: the order of the spline, m = 4, and the maximum degree of the Legendre polynomial, n = 50, with a precision of 10^{-5} (Perrin et al., 1989).

Time-frequency (TF) amplitudes and phases were calculated by wavelet transforms based on Morlet's wavelets, having a Gaussian shape in the time domain (SD σ_t) and frequency domain (SD σ_f) around a center frequency (f) (Tallon-Baudry et al., 1997). The TF amplitude $E(t, f)$ for each time point of each trial was the squared norm of the result of the convolution of the original EEG signal $s(t)$ with the complex Morlet's wavelet function $w(t, f)$:

$$w(t,f) = (\sigma_t\sqrt{\pi})^{-1/2}\exp(-t^2 / 2\sigma_t^2)\exp(i2\pi ft) \tag{4}$$

$$E(t,f) = \left|w(t,f) \otimes s(t)\right|^2 \tag{5}$$

where $\sigma_f = 1/(2\pi\sigma_t)$. The wavelet used was characterized by a constant ratio ($f/\sigma_f = 7$), with f ranging from 1 Hz to 40 Hz in 0.5-Hz steps. The TF amplitude was averaged across single trials for events and conditions. The event-related TF amplitude was calculated by subtracting the baseline data measure in the ITI for each frequency band. For all statistical analyses, a nonparametric Wilcoxon signed-rank test was used across the events or conditions because the distributions of the TF amplitude populations were far from Gaussian.

4.3 Results

Accuracy rates (percent correct) for lower numbers of presented objects were higher than those for larger numbers of presented objects (3 objects: 90.2 ± 2.0%; 6 objects: 72.6 ± 2.8%). A one-factor analysis of variance (ANOVA) revealed a main effect of the number of objects ($F_{1, 26}$ = 24.3, P < 0.01) and the accuracy rates demonstrated a significant difference (Wilcoxon signed-rank test; Z = 3.71, P < 0.01).

The VWM capacity was estimated by Cowan's K formula (see Section 2; 3 objects: K = 2.41 ± 0.12; 6 objects: K = 2.71 ± 0.33). A one-factor ANOVA revealed no main effect of the number of objects ($F_{1, 26}$ = 0.64, P = 0.43), and no significant difference between K-values was detected between 3 and 6 objects (Z = 1.18, P = 0.24). These results suggested that the VWM capacity in our experiments was limited to approximately 2.7 objects.

Brain activity was evaluated using the averaged time-frequency amplitudes of the EEG data obtained during the DMS task. The EEG results demonstrated that parietal alpha amplitudes (about 12 Hz) sustainably and significantly increased during the retention intervals (POz electrode: Z = 2.11, P < 0.04), whereas enhancement of the frontal theta delay-period amplitudes (about 6 Hz) was not observed (Fz electrode: Z = 0.18, P = 0.85). Frontal theta activity during maintenance of 6 objects was significantly higher than that for maintenance of 3 obejcts (3 objects: -0.28 ± 0.21 μV; 6 objects: 0.55 ± 0.40 μV; Z = 2.12, P < 0.04). In contrast, parietal alpha activity demonstrated an opposing pattern (3 objects: 2.06 ±

0.66 μV; 6 objects: 0.45 ± 0.45 μV; $Z = 1.97$, $P < 0.05$). Interestingly, frontal theta activity was significantly and positively correlated with the VWM capacity of the individual (Fz electrode: $r(14) = 0.39$, $P < 0.05$), whereas the parietal alpha activity was negatively correlated with the VWM capacity (Poz electrode: $r(14) = -0.44$, $P < 0.05$).

4.4 Discussion

The observed VWM capacity was about 3 objects, which is consistent with many previous findings using simple visual features (Luck & Vogel, 1997). In relation to the behavioral results, the EEG results revealed that the frontal theta and parietal alpha amplitudes were sustainably enhanced during the retention interval of the DMS task. Interestingly, frontal theta activity demonstrated a positive correlation with individual WM capacity, whereas parietal alpha activity demonstrated a negative correlation.

In addition to confirming previous reports that these oscillations are involved in VWM (; Klimesch et al., 2008; Jensen & Tesch, 2002; Jensen et al., 2002), the present study was able to dissociate their functions. Frontal theta activities have been associated with central executive functions including mental manipulation and calculation tasks (Kawasaki et al., 2010) and in supporting VWM storage during high-VWM loads and demands (Curtis & D'Esposito, 2003; Kawasaki & Watanabe, 2007; Sakai et al., 2002). Parietal alpha activity has been proposed to reflect simple WM storage. Indeed, many neuroimaging studies using the DMS task with simple visual features (e.g., color) have shown that parietal activity was correlated with VWM capacity and decreased beyond the limit of VWM capacity, unlike increased frontal activity (Linden et al., 2003; Rypma et al., 2002). These results suggeted that parietal alpha activity may be involved essentially only in the maintenance of limited visual information, whereas the frontal theta activity seems to assist in VWM storage under high VWM demand, as if instead of the suppressed alpha activity.

5. EEG oscillations for central executive

This section describes the investigation of EEG oscillatory activities that represent the WM limitations for executive functions by comparing dual and single WM tasks. The dual tasks required 2 separate perceptual domains: mental manipulation with visual stimuli and the mental calculations with auditory stimuli.

5.1 Dual WM task for visual and auditory representations

Fourteen healthy volunteers (10 male and 4 female; mean age = 27.92 ± 6.76 years, range 21–41 years; 13 right-handed) with normal or corrected-to-normal visual acuity, normal hearing acuity, and normal motor performance took part in the single visual and dual WM tasks. All participants gave written informed consent, which was approved by the Ethical Committee of the RIKEN (in accordance with the Declaration of Helsinki), before the experiments were performed.

For the single VWM task, at the beginning of each trial, 5 × 5 gridded squares and a red circle included within one of those squares were presented on the computer screen as the visual stimulus for 1 s (Fig. 3A). The participants were required to memorize and then maintain the position of the red circle for 2 s after the visual stimulus disappeared. Awhite arrow designating a direction (up, down, right, or left) to which the participants should move the red circle in their minds was then presented at the center of screen for 1 s. The participants manipulated the mental representations for 2 s. Like the auditory working

memory condition, the participants were required to repeat the mental manipulation 4 times, and then determine whether the position of the red circle which they mentally moved matched a probe visual stimulus (test display). In half of the trials, the probe stimulus matched the mental representation. In the remaining trials, the wrong probe was presented by changing only the fourth direction of movement from the initial position. The participants were asked to indicate via button press whether the probe stimulus was correct or not while the fixation point was red for 2 s. The duration of the ITI was 2 s. The size of the red circle and gridded squares was $1^o \times 1^o$ and $5^o \times 5^o$ ($1^o \times 1^o$ per square), respectively.

For the dual WM task, the participants were asked to complete an auditory WM task simultaneously to the visual tast (Fig. 3B). When the visual stimuli described above were presented on the computer screen, a word indicating a one-digit number was simultaneously presented as the auditory stimulus through the headphones of both ears for 1 s (sample display). The auditory WM task requried the participants to memorize and maintain the presented number with rehearsal in their minds and, after a 2-s retention interval, to update the number by adding the another presented one-digit number for 2 s. After this a total of 4 incidences of auditory and visual manipulation, auditory and visual stimuli were simultaneously presented again, and participants were required to judge whether or not they were identical to the manipulated mental representation for both auditory and visual tasks (test display). In half of the trials, both the auditory and visual probe stimulus matched the mental representations. In the remaining trials, the incorrect probe for either the auditory or visual stimulus was presented, similar to the single VWM condition. The button press, duration of the inter-trial interval, and creation of the stimuli were identical to the single WM condition.

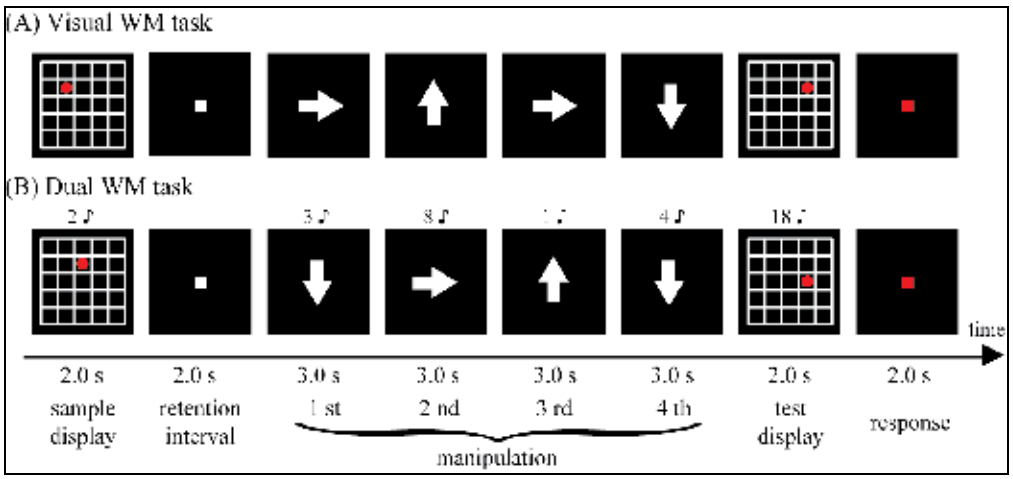

Fig. 3. Task procedure for one trial of the single visual WM (A) and dual WM (B) tasks.

5.2 EEG measurements and analyses

The same methods were used as described in Section 4.2.

5.3 Results

All participants performed all the WM tasks with high accuracy rates (mean accuracy rate (± s.d.), 97.3 ± 4.7% and 91.1 ± 7.1% for visual and dual WM conditions, respectively).

Significant differences in performance were detected between the single and dual WM conditons (Wilcoxon signed-rank test; $Z = 2.87$, $P < 0.01$), suggesting the presence of dual-task interference, that is, degraded performance of 2 simultaneous tasks relative to a single task (e.g., psychological refractory period) (Logan & Gordon, 2001; Pashler, 1994).

Time-frequency analyses of the recorded EEG data revealed enhanced theta amplitudes (4–6 Hz) of the 4 manipulation periods relative to those of the ITI in the frontal and parietal regions in both the single visual and dual WM conditions (single WM: AF3 electrode, $Z = 3.53$, $P < 0.01$; Pz electrode, $Z = 2.04$, $P < 0.05$; dual WM: AF3 electrode, $Z = 3.71$, $P < 0.01$; Pz electrode, $Z = 3.01$, $P < 0.01$). The increased frontal theta amplitudes during the dual WM conditions were significantly higher than those during the single VWM condition (AF3, $Z = 2.24$, $P < 0.03$), whereas this difference was not observed in the parietal theta activities (Pz, $Z = 0.68$, $P = 0.49$).

In addition to the theta amplitudes, alpha amplitudes (9–12 Hz) were increased only in the parietal regions during manipulation periods in the single visual WM condition (single WM: AF3, $Z = 1.15$, $P = 0.25$, Pz, $Z = 2.19$, $P < 0.05$; dual WM: AF3 electrode, $Z = 1.11$, $P < 0.27$; Pz electrode, $Z = 2.39$, $P < 0.02$). Parietal alpha amplitudes demonstrated no significant difference between the single and dual WM conditions (Pz, $Z = 1.78$, $P = 0.08$). Moreover, enhanced parietal alpha activity was observed during the retention intervals as well as the manipulation periods (Pz, $Z = 0.49$, $P = 0.62$).

5.4 Discussion

The EEG results concerning oscillatory amplitudes demonstrated the bottlenecks of central executive function in WM. In our recent study using single visual and auditory WM tasks, the frontal theta activity was mainly observed during the manipulation period and not the maintenance periods, whereas posterior alpha activity was enhanced both in the manipulation and maintenance periods (Kawasaki et al., 2010). Building upon those previous findings, the present study demonstrated that frontal theta activity further increased in the dual WM task in comparison to the single VWM task, whereas parietal alpha activity did not differ between the single and dual WM tasks. In this study, the dual WM task required a large amount of mental manipulation compared to the single WM task. However, the amount of visual representations to be remembered for the dual WM task was almost same that required for the single VWM task. Therefore, these results indicate that the bottlenecks for central executive function are represented by frontal theta activity, which is supported by the earlier evidence that the frontal cortex is associated with active manipulation, and the posterior regions are involved in simple maintenance (Curtis & D'Esposito, 2003; Postle et al., 1999; Rowe et al., 2000; Smith & Jonides, 1999; Wager & Smith, 2003). These results suggest that concurrent frontal theta and alpha activity is associated with the hierarchical control structures of the multiple operations involved in dual WM tasks.

6. Conclusion

Using data from 2 EEG experiments, this study has demonstrated the brain oscillations that are related to WM capacities for visual storage and central executive function. Frontal theta and parietal alpha activities represented the storage limitations under conditions of high and low WM demands, respectively. Moreover, frontal theta activity was also related to bottlenecks in central executive function, which is necessary to perform dual WM tasks. In addition to confirming previous findings concerning regional dissociations between WM

functions, the present study further suggests important roles for these brain oscillations, which reflect different local synchronizations within specific cell assemblies, in the WM process: theta for manipulation and alpha for maintenance.

7. Acknowledgment

This research was supported by Grant-in-Aid for Scientific Research on Innovative Areas (21120005 & 22118510) and Grant-in-Aid for Young Scientists (B) (23700328). We would like to thank Yoko Yamaguchi for her help in discussions for this study, Eri Miyauchi for her support of our data analyses, and Yuta Kakimoto, Ken'ichi Sawai, and Saoko Ikuno for their support of our data acquisition.

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13

Neuroimaging Data in Bipolar Disorder: An Updated View

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1. Introduction

BD is a prevalent mood disorder, often comorbid with other medical and psychiatric conditions and frequently misdiagnosed (Altamura et al., 2011a). Intense emotional states that occur in BD comprise manic, hypomanic, mixed or depressive episodes. According to the Diagnostic and Statistical Manual of Mental Disorders, IVth edition, text revision (DSM-IV–TR; American Psychiatric Association, 2000), BD spectrum ranges from cyclothymia to Bipolar I, Bipolar II Disorder and Not Otherwise Specified (NOS) forms. BD can also be conceptualized as a gradual change in mood scale, which ranges from severe depression to severe mania with an intermediate euthymic state or balanced mood.

Dysthymia is a chronic state of mild low mood occurring for a minimum of two years. At the other end of the scale there is hypomania and severe mania. An alternative and broader dimensional approach conceptualizes BD as a continuum, between unipolar depression, schizoaffective disorder (which is considered by some authors a subcategory of BD) and schizophrenia. This theory may be supported from a clinical point of view by the fact that, sometimes, during severe manic, mixed or depressive episodes, bipolar patients experience psychotic symptoms, such as hallucinations or delusions. It is also supported by the presence of morphometric alterations of frequent observation among major psychoses, such as enlarged ventricles and white matter volume reductions in the left and temporoparietal regions (Czobor et al., 2007).

In BD, symptomatic states are frequently associated with poor working functioning and social impairment. Bipolar patients, moreover, have higher suicide rates than the general population and among the highest of psychiatric patients. In a recent study on factors predicting suicide in BD, white race, family history of suicide, and previous cocaine abuse were considered predictive of suicidal behaviour (Cassidy, 2011). Usually BD develops in early adulthood/late teens, with an age of onset ranging from 15 to 50 years (Cassano et al., 2006).

International treatment guidelines for BD recommend the use of mood stabilizers - either in monotherapy or in association - as the gold standard in both acute and long-term therapy. The concept of stabilization, in fact, has been stressed as the ultimate objective of the treatment of BD, given the chronic and recurrent nature of the illness, which accounts for its significant levels of impairment and disability (Altamura et al., 2011b). Beyond the

aforementioned core mood symptoms and clinical features of BD, over the last decade, neurocognitive dysfunction has been stressed as another nuclear dimension of BD and, possibly, a marker of its underlying pathophysiology (Lewandowski et al., 2010). There is accumulating evidence that individuals with BD have neurocognitive impairment that persists even during euthymia: the degree of impairment is more severe in patients with depressive symptoms, with functions associated with processing speed and attentional control being particularly implicated (Chaves et al., 2011; Van der Werf-Eldering et al., 2010). In addition, in older euthimic adults with BD, resting-state corticolimbic dysregulation was related to sustained attention deficits and inhibitory control, which could reflect the cumulative impact of repeated affective episodes upon cerebral metabolism and neurocognitive performance (Brooks et al., 2011). Cognitive impairment in BD is influenced by the severity of illness (Yates et al., 2010).

In addition, neuropsychological and imaging studies in BD suggested the presence of cognitive deficits and subtle magnetic resonance imaging (MRI) changes in limbic areas that may persist over euthymia. However, other studies are inconsistent with this claim. For example, a recent study did not identify any difference between BD patients and controls in levels of cognition over a two-year period, indicating that BD doesn't have a significant adverse impact on cognition (Delaloye et al., 2011).

Neuroimaging has recently gained an important role both in clinical practice and research of psychiatric disorders, including BD. Structural imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have contributed to a deeper understanding of the structural changes in the brain in the context of psychiatric disorders. Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Functional Magnetic Resonance Imaging (fMRI) and Diffusion Tensor Imaging (DTI) are techniques which measure changes in response to cognitive demand and/or connectivity between brain regions. As such, these approaches provide an opportunity for investigating the neural bases of behavioural and cognitive impairment in psychiatric populations, including BD.

2. Structural neuroimaging

2.1 Computed Tomography (CT)

In the last two decades, the first important data about neuroanatomic abnormalities in BD were obtained by means of CT. More recently, the widespread use of MRI has brought several advantages over CT, particularly in terms of higher resolution of images of subcortical regions (Steffens, 1998). Although a typical pattern of abnormality has not been identified yet (Supprian, 2004), several brain structures were found to be affected in patients with BD according to imaging studies.

CT provides excellent imaging data and rapid image acquisition at relatively low cost, it is widely available and more easily tolerated by patients, remaining the imaging modality of first choice in many clinical situations (Dougherty et al., 2004).

CT consists of a series of slices or tomograms. Its measurements are performed at the periphery of the body. The image of each slice is acquired by means of an X-ray source and detectors positioned at 180 degrees on the other side of the body. By spinning the source and the detectors on one plane of the head, data are collected from multiple angles. A computer then processes X-ray attenuation measured from different points and uses specific algorithms to create a structural image within the plane. Ionic and non-ionic intravenous

contrasts can be used to improve the visualization of certain normal or abnormal structures (Dougherty et al., 2004).
The measurement of total brain volume and ventricular volumes has been the aim of the first investigations using CT in psychiatric disorders. In this perspective, less consistent results have been found for affective disorders compared to schizophrenia and dementia (Beyer et al., 2002). The limited number of controlled CT studies focused on bipolar patients, in fact, showed heterogeneous findings. These include increased lateral ventricle size compared to controls (Andreasen et al., 1990; Nasrallah et al., 1982; Pearlson et al., 1984) or, in contrast, non significant differences between patients and controls (Dewan et al., 1988; Schlegel et al., 1987; Young et al., 1999). A larger third ventricle has been reported as well (Dewan et al., 1988; Schlegel et al., 1987). Studies on cortical alterations in BD revealed that there was no significant difference between patients and controls with respect to the level of cortical atrophy (Iacono et al., 1988; Rieder et al., 1983; Schlegel et al., 1987). However, a positive correlation between increased cortical sulcal widening and age of onset/age of first manic episode has been observed in bipolar patients in a subsequent study (Young et al., 1999). Volumetric changes in the cerebellum have been also reported, including higher rates of atrophy in bipolar patients (Nasrallah et al., 1982), even though the research of these abnormalities is limited.
In synthesis, some studies using CT in bipolar patients found an increased lateral ventricles size. In addition, cortical atrophy (which was not statistically different from controls), atrophy in the cerebellum as well as a larger third ventricle have also been reported.

2.2 Magnetic Resonance Imaging (MRI)

MRI takes advantage of the magnetic properties of the atomic constituents of the tissues in order to create an image of the different parts of the body. Every MRI scanner has a static magnet; its strength usually ranges from 1.5 to 3 Tesla. A steady magnetic field is generated as an electric current passes through the coils. In order to have a nuclear magnetic resonance signal, only atomic nuclei with unpaired protons and/or neutrons can be used. Medical MRI uses essentially hydrogen (^1H) as it is widely diffused in the human body and it has only one proton in its nucleus. Each proton has its own magnetic field or dipole moment, induced by the rotation around its axis. When an externally magnetic field is applied, protons' magnetic dipoles tend to align and to oscillate around the longitudinal axis of the applied field (this phenomenon is called precession) (Dougherty et al., 2004).
An horizontal radio frequency (RF) pulse is applied perpendicularly to the longitudinal axis of the external magnetic field with the aim to create a transverse component to the magnetization vector. This induces the generation of an electric current which is transduced into an MRI image. T1 is the "longitudinal" relaxation time and it indicates the time required to regain longitudinal magnetization following RF pulse. T2 is the "transverse" relaxation time that measures how long the resonating protons precess "in phase" following a 90° RF pulse. Due to the T1 and T2 relaxation properties in MRI, differentiation between various tissues in the body is possible (Jezzard et al., 2001).
Despite intensive research, to date no pathognomonic structural MRI finding has been correlated with affective disorders in general and to BD in particular. There are many heterogeneous data (Table 1) revealing a variety of structural alterations in bipolar patients (Dougherty et al., 2004). It must be considered, moreover, that some of these differences may be referred to the effects of medications (Van der Schot, 2009). For instance, chronic lithium treatment may prevent volume loss in treated patients because of its neuroprotective action

(Manji et al., 2000). Furthermore, genetic and/or environmental factors involved in BD may influence some brain abnormalities. In this perspective, decreases in white matter have been associated with the genetic risk of developing BD, whereas important environmental correlations have been found in relation to cortical gray matter volume (Van der Schot, 2009).
Brain abnormalities reported by fMRI studies in patients with BD include changes in cortical volumes, cerebral white matter, cortical and prefrontal gray matter. Enlargement of the ventricles, dimensional modifications of the amygdala, nuclei of the basal ganglia, corpus callosum and cerebellum have also been detected.
Main findings on lobar volumes concern frontal, temporal and insular cortex. Results on frontal lobes are quite discordant. In fact, they were found to be smaller (Coffman et al., 1990; Schlaepfer et al., 1994) or of the same size as controls (Strakowski et al., 1999). With respect to temporal lobes, no differences (Johnstone et al. 1989), bilateral reduction of volume (Altshuler et al., 1991) or loss of normal symmetry were found. Even in terms of loss of symmetry of the temporal lobes findings were sometimes discordant. In fact, a study reported a larger right temporal lobe than the left one in male bipolar patients (Swayze et al., 1992) and another study observed a larger left temporal lobe (Harvey et al., 1994). Voxel-based morphometric (VBM) MRI studies showed an increased gray matter in the insular cortex (Lochhead et al., 2004) or non significant differences in this region (McDonald et al., 2005; Nugent et al., 2006; Scherk et al., 2008a). An inverse correlation has been observed between the volume of the anterior insular cortex and the lifetime number of depressive episodes (Takahashy, 2010).
Bipolar patients, in particular those with late onset, were found to have a higher incidence of subcortical hypertensities (Dupont et al., 1990; Figiel et al., 1991; McDonald et al., 1991; Norris et al., 1997; Soares & Mann, 1997; Stoll et al., 2000; Swayze et al.,1990; Videbech, 1997). On the other hand, another study (Botteron & Figiel, 1997) identified an increased rate of white matter hyperintensity in relatively young individuals.
Lateral ventricular enlargement has been observed in BD and associated with multiple episodes of mania (Strakowski et al., 2002). A larger third ventricle was reported in elderly depressive patients and in cases of first manic episode (Strakowski et al., 1993). Likewise, correlations have been found between third ventricle volume and psychotic symptoms, advanced age, late onset of the disease, male gender and positive dexamethasone suppression test (Benabarre et al., 2002).
Studies on alterations of the amygdala in bipolar patients reported heterogeneous results, showing normal (Swayze et al., 1992), smaller (Pearlson et al., 1997) or larger volumes (Altshuler et al., 1998). More recent studies documented an increased volume in the right amygdala (Bremner et al., 2000), in bilateral amygdala in first episode subjects (Frodl et al., 2002) and loss of normal symmetry (Mervaala et al., 2000). The heterogeneity of the adult studies may be referred to the different age of subjects. It is still unclear, however, the positive correlation between increased amygdala volume and age (Usher, 2010).
A greater caudate volume as well as asymmetries among the structures of the basal ganglia were found in male bipolar patients (Aylward et al., 1994). Another study focused on the caudate volume in manic subjects in their first episode, reporting no significant differences vs healthy controls (Strakowski et al., 1999). The alterations may be attributed to a secondary effect of neuroleptic drugs (Benabarre et al., 2002). Studies examining alterations of the corpus callosum found volume reduction in bipolar patients, correlated with greater global neuropsychological dysfunction (Coffman et al., 1990). Finally, significant reduction of the cerebellar posterior vermis area was reported in patients with BD (DelBello et al., 1999).

Central nervous system structure involved	Main MRI alterations in BD
Frontal lobes	Reduced or unchanged volume
Temporal lobes	Reduced or unchanged volume Loss of the symmetry
Insular cortex	Increased gray matter or no changes
Subcortical areas	Increased hyperintensities
Lateral ventricles	Increased (association with number of episodes of mania)
Third ventricle	Increased
Amygdala	Larger, smaller or unchanged volume Loss of normal symmetry
Caudate nucleus	Increased or unchanged volume
Corpus callosum	Reduced volume
Cerebellar posterior vermis	Reduced

Table 1. Main MRI findings in BD.

2.3 Magnetic Resonance Spectroscopy

Magnetic Resonance Spectroscopy (MRS) is an MRI complement and serves as a non-invasive tool for tissue characterization. While MRI uses the signal from hydrogen protons to create a visual representation of the tissues, proton MRS (^{1}H- MRS) uses this information to determine the concentration of brain metabolites such as N-acetyl aspartate, choline, creatine and lactate in the examined tissue (Gujar et al., 2005).

MRS has been principally used for the diagnosis of some metabolic disorders, especially those of the central nervous system. MRS has not an optimal specificity, but in association with MRI and clinical data can be very helpful. Indeed, the main purpose of this technique is to obtain biochemical information from any part of the body in a non invasive way, i.e. not by means of radioactive tracers or electromagnetic radiation (Dougherty et al., 2004).

In psychiatry, MRS can be employed to assess the activity of different neurotransmitters, membrane and second messenger metabolism. The uniqueness of MRS is to provide an overview of the biochemical pathology of BD. Studies using proton MRS (^{1}H- MRS) reported increased glutamate and GLX (glutamate, GABA and glutamine) levels in the dorsolateral prefrontal cortex, frontal lobes, basal ganglia and gray matter of medication-free bipolar subjects and in patients with acute mania (Yildiz-Yesiloglu & Ankerst, 2006). Abnormal levels of N-acetyl aspartate, choline and myo-inositol have also been reported (Scherk et al., 2008b). N-acetyl aspartate seems to be reduced in the prefrontal cortex and hippocampus in bipolar individuals. Choline levels were found to be increased in the striatum and anterior cingulate cortex and can be normalized or decreased after treatment with antidepressants and lithium (Moore et al., 2000). Myo-inositol levels were increased in individuals with mania and euthymia and, on the contrary, reduced in bipolar depression.

Studies using phosphorus MRS (^{31}P- MRS) have found phase-specific alterations of phospholipid membranes, high energy phosphates and intracellular brain pH in BD. In particular, a number of investigations reported a reduced intracellular cerebral pH in bipolar subjects which has been associated with the increased levels of lactate observed in some ^{1}H- MRS studies. Both conditions are indicative of a shift from oxidative phosphorylation to glycolysis. There is also a ^{31}P- MRS based-report of decreased levels of phosphocreatine and of phosphomonoesters in BD (Kato et al., 1995).
Stork and Renshaw proposed a cohesive model that puts together the majority of MRS findings. They hypothesized that the impaired oxidative phopshorilation, the decreased cellular energy and the altered membrane metabolism could be due to an underlying altered mitochondrial metabolism in BD (Stork & Renshaw, 2005).
Main MRS findings in BD are synthetized in Table 2.

Technique		**Main alterations**
^{1}H- MRS	N- acetyl aspartate	Reduced levels
	Choline	Increased levels
	Glutamate, GABA and Glutamine	Increased levels
	Myo-inositol	Increased levels in mania and euthymia and reduced levels in bipolar depression
	Lactate	Increased levels
^{31}P- MRS	Phosphocreatine	Reduced levels
	Phosphomonoesters	Reduced levels
	Intracellular brain pH	Reduced levels

Table 2. Main MRS findings in BD.

3. Functional neuroimaging

The major limitation of structural neuroimaging techniques is that they are suitable for studying diseases associated with morphologic alterations, such as neurologic conditions. For this reason, they are only partially useful in psychiatric disorders which are characterized by behavioral abnormalities due to neurochemical impairment. In this perspective, PET (Abraham & Feng, 2011) and fMRI represent the gold standard for brain imaging aimed to assess cognitive performance (Glower, 2011). Electroencefalography, Event-Related Potentials and Magnetoencephalography are less specific and, therefore, mostly used to exclude neurological conditions in clinical practice or for research purposes (Cohen & Cuffin, 1983). Medication, drug or alcohol abuse and genetic/epigenetic influence represent major confounding factors (Nakama et al., 2011; Schulte et al., 2010). On the other side, following the biopsychosocial model for psychiatric disorders, functional neuroimaging could help understanding the complex interaction between environmental stressors, genetic risk and precipitating events in the plasticity of neural circuitry and consequently in clinical symptoms.

Functional neuroimaging attempts to explain psychiatric disorders by means of degenerative or developmental model of illness and/or in terms of hypometabolism.
In fact, elevated activity of the hippocampus or of the ventral prefrontal cortex as well as dorsolateral prefrontal cortex hypofunction are recurrent themes in literature (Savitz & Drevets, 2009).

3.1 Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT)

PET imaging is a direct measure of a radioactive decay due to cerebral metabolism of a radioactive substance or radionuclide. Different body tissues are characterized by different consumption rates of radionuclides (Ter-Pogossian et al., 1975; Vyas et al., 2011). Radionuclides used in clinical practice are usually major compounds of biologic molecules (18-Fluorine in the form of 18-Fluorodeoxyglucose or FDG for measuring glucose metabolism, 15-Oxygen for measuring blood flow, 11-Carbon or 13-Nitrogen common in diagnostic PET procedures). The nuclide is introduced in the patient and the radioactive decay is measured (Phelps et al., 1975): in particular, the positron emitted by nuclides has a collision with electrons producing a gamma photon which is measured by the PET camera (Roncali & Cherry, 2011). PET can measure both blood flow and glucose metabolism, often used as surrogate measures of neuronal synaptic activity. A first line comparison is between the neuroligand uptake in target regions and reference area while a more complex analysis can compare blood flow or glucose uptake in the same subject in different states, i.e. while resting or during a cognitive performance. Both ways provide useful data for research and clinical analysis; anyway, a major limitation is the use of a radioactive nuclide. Specifically, targeted PET radioligands are used to investigate neurotransmitter systems (Weisel, 1989). Cerebral PET has its major use in neurological disease: excluding primary or secondary oncologic lesions, evaluation of dementia, confirming epilepsy or assessing the state in cerebrovascular disease (Cavalcanti et al., 2011; Mazzuca et al., 2011; Person et al., 2010; Quigley et al., 2010; Salas and Gonzales, 2011).
SPECT works capturing orbiting electrons without a positron-electron collision, but by means of an emission of a single photon by the SPECT nuclide. Main nuclides used in SPECT are 123-Iodine, 33-Technetium or 133-Xenon. Single photons are selected with the use of multiple collimators.
PET and SPECT studies in depressive disorders have shown that blood rate and flow are increased both in BD and in unipolar depression in the frontal lobes during depressive episodes. However, they are increased during mania in the dorsal cingulate cortex, striatal regions, and the nucleus accumbens, as well as in limbic structures of the temporal lobes and reduced in dorsolateral prefrontal cortex, possibly reflecting its loss of modulatory control over limbic structures (Gonul et al., 2009).
With respect to neurotransmitters, serotonin (5-HT) transporter was found to have an increased density in the thalamus (Laje et al., 2010), dorsal cingulate cortex, medial prefrontal cortex and insula of depressed BD patients. 5-HT has been implicated in mania as well: in particular, individuals with current mania had significantly lower 5-HT2 receptor binding potential in frontal, temporal, parietal and occipital cortical regions, with more prominent changes in the right cortical regions compared to controls (Yatham et al., 2010, 2002a, 2002b). With regards to 5-HT1A receptor, bipolar depressed patients were found to show higher 5-HT1A in raphe nuclei and forebrain (Sullivan et al., 2009). An interesting use of PET consists of assessing the role of serotonin in major depressive episodes comparing

BD vs unipolar depression. In fact, both unipolar and bipolar depression were associated with elevated 5-HT transporter binding in the insula, thalamus and striatum, but showed distinct abnormalities in the brainstem (Cannon et al., 2007).
With respect to dopamine, D1 receptor binding potentials were found to be reduced in frontal cortex, even though striatal D2 receptor density was normal in all phases of non-psychotic BD (Bauer, 2003; Suhara et al., 1992).
In synthesis, PET and SPECT studies have shown in BD a loss of modulatory control of the cortex over limbic structures, reflected by specific phase-dependent modifications of blood rate and flow. Alterations of neurotransmitters involved in the pathogenesis of BD have also been reported, particularly with respect to serotonin transporter, serotonin receptor density and dopamine receptor density.

3.2 Functional Magnetic Resonance Imaging (fMRI)

FMRI is the most used technique in brain mapping and in psychiatric research due to its non-invasive technology, wide availability, high spatial and temporal resolution and the lack of ionizing radiation that allows the clinician to repeat functional exams over time as well as in different phases of illness. FMRI, in fact, is suitable for studying bipolar patients' performances on the same cognitive tasks during depressed, manic or euthymic phases. It can also compare brain activity during symptom exacerbation as well as over periods of remission.
One limit of fMRI is that it gives limited information on subcortical structures. Spatial resolution remains anyway highly relevant for the study of psychiatric diseases, given the clear correlation between cortical dysfunction and many psychiatric symptoms. Another limit consists of the increased variance of the results obtained with this technique in psychiatric patients (Dougherty et al., 2004).
FMRI measures changes in blood flow in areas of the central nervous system (Konarsky et al., 2007). The hemodynamic response reflects neural activity in the brain or spinal cord as neurons have no reserve for oxygen or glucose and they need to rapidly increase blood flow when necessary. A Blood-oxygen-level dependent (BOLD) signal is measured by fMRI. From a physiological perspective, hemoglobin is diamagnetic when oxygenated (oxyhemoglobin) and paramagnetic when deoxygenated (deoxyhemoglobin) producing different signals that are higher when coming from activated areas. Actually, an increase in cerebral blood flow produces changes in oxygen consumption resulting in increased BOLD signals (Bandettini, 2003).
Studies with fMRI in bipolar patients showed various alterations of the activity in different regions of the cortico-limbic pathways responsible for emotional regulation: amygdala, thalamus, striatum, portions of the prefrontal cortex and anterior cingulated cortex. Studies, however, were limited by the small samples size and by the possible interference of the medication. The increased activation of amygdala, striatum and thalamus were the most constant findings among the different studies (Cerullo et al., 2009).
Increased amygdala and subcortical activity to emotional stimuli, in particular negative stimuli, as well as reduced activity of the prefrontal cortical regions during cognitive performances are common to all phases of BD, suggesting that they may be trait features of the disease (Phillips & Vieta, 2007). Other additional frontal and temporal regions were found to be activated, maybe as a compensatory mechanism (Townsed et al., 2010).
FMRI studies in bipolar patients also suggest the presence of phase-dependent abnormalities. In fact, bipolar depression is associated with attenuated bilateral orbitofrontal

or elevated left orbitofrontal activity. Right dorsolateral prefrontal cortical activity was found to be reduced, while the increased left prefrontal activity seems to be a state marker of bipolar depression (Altshuler et al., 2008).
The few studies with fMRI on manic patients report an increased activity of the amygdala, insular cortex and subcortical areas in response to negative emotional stimuli. Ventral striatal activity was found to be elevated at rest and during motor tasks. On the other hand, ventral prefrontal activity was found to be attenuated during cognitive performances (Altshuler et al., 2005; Elliott et al., 2004). In addition, bilateral orbitofrontal attenuation has been reported in mania and may represent a trait feature of the disorder as it is also present during bipolar depression (Altshuler et al., 2008).

BD Phase	Central nervous system structures involved	Main fMRI alterations
Bipolar depression	Orbitofrontal cortex	Activity reduced bilaterally or increased on the left
	Prefrontal cortex	Reduced right activity; Increased left activity
Mania	Amygdala Insula Subcortical areas	Increased activity in response to negative stimuli
	Ventral prefrontal cortex	Reduced activity during cognitive performances
	Orbitofrontal cortex	Reduced activity bilaterally
Euthymia	Ventral prefrontal cortex Anterior cingulate gyrus	Reduced activity during attentional tasks
	Dorsolateral prefrontal cortex	Increased (i.e. during attentional tasks) or reduced activity (i.e. in response to fearful stimuli, during working memory tasks)
	Subcortical areas	Increased activity during performance or working memory tasks
	Amygdala	Increased activity in response to fearful stimuli
	Striatum	Increased activity in response to fearful stimuli; Significantly increased activity in response to reward stimuli

Table 3. Main fMRI findings in BD.

Findings on euthymic bipolar patients are more consistent and have pointed out reduced activity in dorsal, ventral prefrontal cortical regions and dorsal regions of the anterior cingulate gyrus during performance of attentional tasks. Dorsolateral prefrontal cortical activity was found to be, on the contrary, increased. Other studies have reported reduced dorsolateral prefrontal cortex activity in euthymic individuals during working memory and verbal encoding tasks (Deckersbach et al, 2006; Monks et al., 2004). Increases in activity

within subcortical regions associated with emotion processing rather than working memory or attention have also been detected in remitted, euthymic individuals with BD during performance of a continuous performance task (Strakowski et al., 2004) and working memory task (Adler et al., 2004). Other studies investigated the response of the activity of these structures to fearful expressions in remitted bipolar patients. Results showed an increased activity in the amygdala and in the striatum and, on the other hand, a reduction of the dorsolateral prefrontal cortex activity (Phillips & Vieta, 2007). Of note, striatal activity in response to potentially rewarding stimuli was found to be significantly elevated. Other emotional stimuli led to decreased dorsolateral prefrontal cortical activity. These two patterns may underlie mood instabilities in euthymic patients, especially in those with comorbidities (Hassel et al., 2008).

In synthesis, fMRI findings in bipolar patients are heterogeneous: they may be present in all phases of BD and/or can be phase-dependent. Among the formers, the most significant data include an increased activity of the amygdala and of the subcortical areas to negative stimuli and a reduced activity of the prefrontal cortex during cognitive tasks. Bipolar depression has been associated with modifications of the activity of the orbitofrontal and prefrontal cortex. In mania, specific alterations include an increased activity of the striatum at rest and during motor tasks and a reduction of the prefrontal cortex activity during cognitive performances. There are several studies on euthymic patients showing modifications of the activity of the prefrontal cortex during attentional or working memory tasks. Structures implicated in the emotional processing seem to be involved as well: in fact, modifications of the activity of the amygdala, striatum and dorsolateral prefrontal cortex in response to different emotional stimuli have been reported.

3.3 Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) is an MRI application developed in order to investigate white matter connections between regions of interest. These connections provide information on functional activity between areas of the central nervous system. DTI is particularly useful to detect white matter lesions or dysfunction (Versace et al., 2008).

There are few studies with DTI in BD, most of them based on the promising results from MRI research showing microstructural alterations in white matter in various neocortical areas and in the corpus callosum. In particular, fractional anisotropy, the most sensitive DTI marker which reflects fiber density, axonal diameter and myelination in white matter, was found to be decreased significantly in the ventral part of the corpus callosum in patients with BD (Heller et al., 2011). Other interesting results coming from DTI revealed that gray matter concentration was reduced in BD in the right anterior insula, head of the caudate nucleus, nucleus accumbens, ventral putamen and frontal orbital cortex. Other studies pointed out that BD patients showed abnormalities within white matter tracts connecting the frontal cortex with the temporal and parietal cortices and the fronto-subcortical circuits (Lin et al., 2011). White matter abnormalities seem to persist by the time of remission even after the first manic episodes (Chan et al., 2010), suggesting that disruption of white matter cortical-subcortical networks as well as projection, associative and commissural tracts may be a hallmark of the illness (Heng et al., 2010) involving prefrontal and frontal regions, associative and commissural fibres.

Some recent studies reported that certain variants of BD may be due to an increased functional or effective connectivity between orbitofrontal and temporal pole structures in the dominant hemisphere. The orbitofrontal cortex codifies the value of different stimuli,

allowing goal and sub-goal structuring. Moreover, it is involved in reward prediction. On the other hand, the temporal pole seems to be activated in basic semantic processes with person-emotion linkages associated with narrative. BD patients have a deficit of performance on visuospatial and constructional praxis which suggests an atypical localization of cognitive functions. This atypical localization and the hyperconnectivity between specific regions could be responsible for the enhanced creativity and writing ability observed in BD probands (McCrea, 2008).

Recently, abnormalities in perigenual anterior cingulate cortex-amygdala functional connectivity during emotional processing have been found in BD (Wang et al., 2009). Similar findings have been reported even in children and adolescents with BD, concluding that in these subjects significant white matter tract alterations were present in regions involved in emotional, behavioural and cognitive regulation. In addition, these results suggest that alterations in white matter are present early in the course of disease in familial BD (Barnea-Goraly et al., 2009; Kavafaris et al., 2009). An impaired fiber density in anterior corona radiata (as detected with a decreased fractional anisotropy) was detected in BD in pediatric age and in Attention Deficit and Hyperactivity Disorder suggesting a possible link between the two disorders (Pavuluri et al., 2008).

DTI studies can allow to detect a possible overlap between BD and schizophrenia. In fact, reduced integrity of the anterior limb of the internal capsule, uncinate fasciculus and anterior thalamic radiation regions is common to both schizophrenia and BD suggesting an overlap in white matter pathology, possibly relating to risk factors common to both disorders (Sussman et al., 2008).

Concerning antidepressants and mood stabilizers, these compounds seem to have neuroprotective effects and are not likely to explain white matter abnormalities, even though minor effects cannot be excluded (Bruno et al., 2008). Anyway, microstructural abnormality in the white matter has been associated with a low remission rate of major depression.

In synthesis, DTI provides information on functional connectivity between regions of the central nervous system. DTI studies on bipolar probands showed a reduced gray matter in areas such as putamen, caudate nucleus, nucleus acumbens, insula and orbitofrontal cortex. As concerns white matter, connections between orbitofrontal cortex, temporal, parietal corteces and the frontosubcortical circuits were found to be altered during mania and also over euthymia, as possible traits of BD. DTI findings have interesting implications on the association between BD and creativity. The hyperconnectivity between specific regions and the atypical localization of cognitive functions seem to be correlated to the enhanced creativity and writing ability of BD subjects. On the other hand, the atypical localization of cognitive functions could underlie the visuoconstructional praxis deficit present in BD.

4. Conclusions

Since the introduction of CT, researchers focused their efforts in elucidating the connection between psychiatric diseases and the presence of structural cerebral alterations through neuroimaging. CT pioneered this research without providing, however, a complete answer. Actually, a growing body of evidence has been accumulated in literature as newer techniques such as MRI and functional imaging (i.e., SPECT, PET, fMRI) have been introduced revealing much about the biological underpinnings of neuropsychiatric disorders. Neuroimaging research in BD has already produced several data documenting the involvement of different cortical and subcortical regions in different phases of the

illness. In particular, published studies explored structural and functional abnormalities present in BD and tried to establish specific correlations with outcome (Moore et al., 2001; Wingo et al., 2009, Bearden, 2010) as well as difficult-to-treat conditions such as treatment resistant forms (Regenold et al., 2008).

The possibility to study cognitive function in BD through fMRI represents another major acquisition of neuroimaging in psychiatric research. The attainment of this goal can be facilitated by identifying biomarkers reflecting pathophysiologic processes in BD, namely impaired emotion regulation, impaired attention, and distractibility, which persist during depression and remission and are not common to unipolar depression (Phillips & Vieta, 2007).

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14

Reinforcement Learning, High-Level Cognition, and the Human Brain

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1. Introduction

Reinforcement learning (RL) has a rich history tracing throughout the history of psychology. Already in the late 19th century Edward Thorndike proposed that if a stimulus is followed by a successful response, the stimulus-response bond will be strengthened. Consequently, the response will be emitted with greater likelihood upon later presentation of that same stimulus. This proposal already contains the two key principles of RL. The first principle concerns *associative learning*, the learning of associations between stimuli and responses. This theme was developed by John Watson. Building on the work of Ivan Pavlov, John Watson investigated the laws of classical conditioning, in particular, how a stimulus and a response become associated after repeated pairing. In the classical "Little Albert" experiment, Watson and Rayner (1920) repeatedly presented a rabbit together with a loud sound to the kid (little Albert); the rabbit initially evoked a neutral response, the loud sound initially evoked a fear response. After a while, also presentation of the rabbit alone evoked a fear response in the subject. In this same paper, the authors proposed that this principle of learning by association more generally is responsible for shaping (human) behavior. According to psychology handbooks John Watson hereby laid the foundation for behaviorism. The second principle is that *reinforcement* is key for human learning. Actions that are successful for the organism, will be strengthened and therefore repeated by the organism. This aspect was developed into a systematic research program by the second founder of behaviorism, Burrhus Skinner (e.g., Skinner, 1938).

The importance of RL for explaining human behavior started to be debated from the late 1940s. Scientific criticism toward RL arrived from two main fronts. The first was internal, deriving from experimental findings and theoretical considerations within psychology itself. The second derived from external developments, in particular, advancements in information theory and control theory. These criticisms led to a disinterest for RL lasting several decades. However, in recent years, RL has been revived, leading to a remarkable interdiscplinary confluence between computer science, neurophysiology, and cognitive neuroscience. In the current chapter, we describe the relevant mid-20th century criticisms and developments, and how these were considered and integrated in current versions of RL. In particular we focus on how RL can be used as a model for understanding high-level cognition. Finally, we link RL to the broader framework of neural Darwinism.

2. Internal criticisms to RL

During the 40s, more and more data were piling up demonstrating the insufficiency of behaviorism to account for human and animal behavior. For example, Tolman and colleagues showed that animals can and do learn even without obtaining reinforcement (Tolman, 1948). They performed a series of experiments on maze learning in rats. It was shown that animals left free to familiarize themselves with the maze before the reinforcement experimental session, were afterwards able to find the food in the maze much more efficiently than completely naive animals. To explain these findings Tolman introduced the concept of the "cognitive map", i.e. an internal representation of the maze that the rats used to find reinforcers more efficiently. Because of this and other demonstrations that animals hold some kind of internal representation of the environment (memory), Tolman formed part of what became known as "the cognitive revolution".

During the same period, but in the field of psychobiology, Donald Hebb wrote *The Organization of Behaviour* (1949), a seminal work in which for the first time a neurobiological theory of learning was proposed. Hebb suggested that the synaptic connection between two neurons improves its efficacy after repeated simultaneous activity of them. This law, properly called "Hebbian rule" and describing what was called "Hebbian Learning", provided the first neural hypothesis on the basis of memory, thus opening the "black box", which behaviorists considered not scientifically investigable. The depth of Hebb's intuition can be better understood if we consider that the Hebbian rule has been experimentally proven almost twenty years after its formulation, with the discover of synaptic long term potentiation (LTP) in the rabbit hippocampus (Lømo, 1966).

Another strong criticism came from psycholinguistics. In a famous review study, Noam Chomsky (1959) argued that the RL paradigm was not suitable to explain the generative feature of natural language (i.e. the possibility to express a quasi-infinite variety of verbal expressions). In the same work, Chomsky also provided a survey on research in animal behavior (e.g., imprinting) that seemed to be in striking contrast with key behaviorist tenets. Finally, and most importantly from the theoretical point of view, Chomsky showed that Skinner himself was obliged to introduce hypotheses about internal variables (e.g., internal self-reinforcements), in order to explain human verbal behavior.

3. External developments

An important role in the demise of RL derived from advances in information theory and control theory in engineering. This happened during the 1940-50s with the publication of several seminal works like those of Shannon (1948), Turing (1936) and Wiener (1948). Their importance consisted in showing that it was possible to formulate rigorous mathematical theories and models to study information processing. In control theory (Wiener, 1948), for instance, the term "control" referred to the auto-correction of internal parameters of a system based on a feedback signal indicating the error between the wished (or the expected) value of an internal parameter and its real value, typically provided by the environment. This general theory of control (called cybernetics) (literally from ancient Greek: "the art of piloting"), did not refer to a particular system: instead, it provided mathematical models to study control phenomena occurring *inside* any system, being animal or artificial or even social. A similar story holds for information theory (Shannon, 1948), which provided the concept of "information", a measure that did not refer to any directly measurable physical variable, but instead to the *internal* "surprise" of any system receiving an external signal.

These new disciplines showed that it was possible, and indeed a proficient and powerful approach, to investigate the internal functioning of systems (including biological organisms), by mathematical modelling of their hidden machinery that was not directly investigable. In this way, the philosophical-methodological assumption of behaviorism, according to which the scientific approach should be limited to strictly empirical investigation, was shown to be unnecessary for scientific progress.

4. Precursors to the return of RL

Because of these developments, behaviorism, and with it RL, was discredited for several decades. Instead an alternative paradigm became dominant, according to which the human mind could be construed as a computer that manipulates abstract symbols (e.g., Neisser, 1967; Atkinson and Shiffrin, 1968). However, in recent years the RL framework became influential again. At least two developments in the second part of the 20th century prepared a renewed interest for RL. The first originated in human learning theory; the second from a new discipline called connectionist psychology, which proposed itself as an alternative to the then canonical symbol-manipulation paradigm for the study of cognition.

4.1 Human learning theory and the Rescorla-Wagner model

Important phenomena observed in the behavioral lab could not be accounted for with the standard behaviorist conceptualization (Rescorla and Wagner, 1972). For example, blocking (Kamin, 1969) refers to the fact that an organism only learns about the contingency between two events to the extent that one of the events is unexpected. To account for blocking, Rescorla and Wagner added a crucial ingredient to an associative learning framework, namely prediction error. Prediction error refers to the difference between an external feedback signal indicating the correct response or stimulus on the one hand, and the response or stimulus predicted by the organism on the other. Here it is worth noting the influence (and indeed similarity) of the cybernetic concept of feedback on the formulation of the concept of prediction error. Rescorla and Wagner proposed a formal model which learned by updating associations between events (e.g., stimulus and response) using prediction error (Rescorla and Wagner, 1972). This model formed the basis for many human learning theories (e.g., Kruschke, 2008; Pearce and Hall, 1980; Van Hamme and Wasserman, 1994), and can be represented by the following equations:

$$\delta_t = \lambda_t - V_t \tag{1}$$

$$V_{t+1} = V_t + \alpha\delta_t \tag{2}$$

where δ is the prediction error, V is the prediction of the organism, and λ is the actual outcome from the environment. Equation 2 shows how the new expectations are updated by the prediction error from time point t to $t + 1$; α is a learning rate parameter modulating the prediction error.

4.2 The connectionist approach

A second development preparing the cultural ground for reviving the field of RL was connectionist psychology. Here, the study of psychological phenomena was grounded on the construction of artificial neural networks, i.e. models simulating both the nervous

system and cognitive processes, providing what was called a sub-symbolic explanation of cognition. This new field was inspired by the fast developing neurosciences; in particular, the scientists developing this new branch not only did not adhere to the dogma that theorizing should remain at the behavioral level, but they also attempted to bridge the explanatory gap between the biological level of neurons and synapses on the one hand, and the psychological level of language and other forms of high-level cognition on the other.
An important step was taken by McClelland, Rumelhart and colleagues (Rumelhart and McClelland, 1986). Models similar to theirs had been developed by other researchers before (Grossberg, 1973) but Rumelhart and McClelland developed a series of applications that made these connectionist models almost instantly influential. At the core of these models is again the Rescorla-Wagner idea that learning consists of updating associations based on prediction errors. However, the authors proposed a generalized learning rule (backpropagation), which allowed learning also for so-called "hidden units", that is, neurons that do not receive external feedback. In backpropagation, such neurons use as a prediction error a linear combination of prediction errors of other neurons that do receive external feedback. This development made the learning rule many orders more powerful than that of Rescorla and Wagner. With the more powerful learning rule, the connectionists were able to investigate linguistic phenomena such as past tense formation (Rumelhart and McClelland, 1987), naming aloud (Seidenberg and McClelland, 1989), and sentence comprehension (St. John and McClelland, 1990).

4.3 The new RL approach

With these important historical precedents, RL learning became influential again during the early 1990s partly because of its important contributions to Machine Learning, a branch of Artificial Intelligence. One of the main protagonists of this revival was Richard Sutton, who developed another generalization of the Rescorla-Wagner rule, called temporal-difference (TD) learning (Sutton, 1988). The original Rescorla-Wagner rule had a *spatial* limitation in the sense that not all neurons received feedback, and this problem was solved by backpropagation. Similarly, the Rescorla-Wagner rule also has a *temporal* limitation in the sense that feedback is not always available to the model – only when there is explicit supervisory feedback. The TD learning algorithm solved this latter problem, because it allowed learning by not only comparing a prediction with external feedback (which may or may not be available, depending on an appropriate teacher's availability), but additionally by comparing a prediction with an earlier prediction (which is always available). In this case the learning signal is the TD error (here denoted as δ^{TD}), in which both the comparisons between previous prediction and external feedback and previous prediction and current prediction play a role. The TD error signal can be written as follows:

$$\delta_{t+1}^{TD} = \lambda_{t+1} + \gamma V_{t+1} - V_t \tag{3}$$

where λ is the external feedback already defined in Equation (1) and γ is a discount factor. The symbol V was used before to denote the organism's prediction; in RL applications, it refers specifically to reward prediction. This rule is more powerful than the Rescorla-Wagner rule: For example, Tesauro (1989) demonstrated that a neural network equipped with TD learning can learn to play backgammon at a worldmaster level.

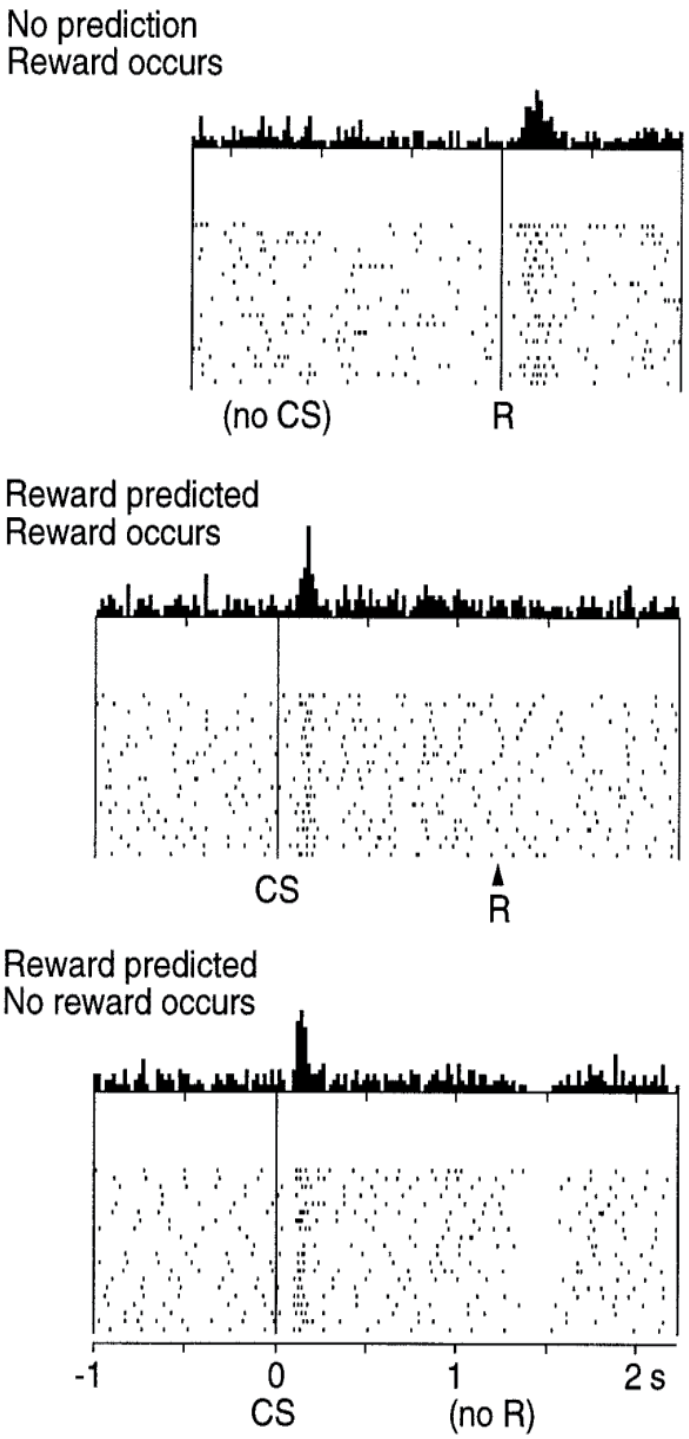

Fig. 1. Shifting of dopaminergic activity from reward to predictor of reward (CS). Reprinted with permission from Schultz et al. (1997).

A few years later, the RL paradigm received the decisive boost to come back to the attention of the broad scientific community. This derived from its official entrance into the domain of neurophysiology. In particular, with single-unit recording Wolfram Schulz and colleagues discovered dopaminergic neurons in the brainstem ventral tegmental area (VTA) and substantia nigra (SN) of macaque monkeys that exhibited a prediction error signature. In a classical conditioning experiment, Schultz et al. (1993) presented a conditioned stimulus (CS, e.g. a light), followed by an unconditioned stimulus (US, e.g. a drop of juice) some seconds later. Initially, dopaminergic neurons respond to the US only. After some trials, the dopaminergic neurons respond to the CS, but no longer to the US (Figure 1). This backward shift in time is exactly what was predicted by TD learning (Montague et al., 1996). Hence, this strongly suggested that the mammalian nervous system implements a RL (in particular, TD) algorithm to learn associations between stimuli.

5. RL in high-level cognition: Conceptual and empirical advances

Ever since the seminal findings of Schultz et al. (1993), the marriage between neuroscience and RL never stopped providing benefits for the study of learning and the nervous system. We here discuss a few highlights from the recent literature.

One conceptual development of RL consisted in the discovery that besides reward value, other value dimensions can be estimated and used to discount reward value (e.g., effort, Kennerley et al., 2006, or delay, Rudebeck et al., 2006). More generally, not only value but also upcoming states of the world can be estimated (Sutton and Barto, 1998). This allows the organism to make more far-sighted actions than with immediate values estimates only. Further, RL models have been proposed with the same computational power as the benchmark backpropagation algorithm (O'Reilly & Frank, 2004; Roelfsema and Van Ooyen, 2005), providing a biologically plausible alternative to backpropagation.

At the empirical level, clever experimental paradigms in combination with modern imaging technology allowed demonstrating the validity of RL models for human cognition. Using fMRI, Seymour et al. (2004) identified a TD signal in the human brain, similar to what was found by Schultz and colleagues in the monkey brain. Seymour et al. used a cued pain learning paradigm, in which a first CS (CS1) predicted (statistically) a second CS (CS2), which then (deterministically) predicted the upcoming pain level. In the striatum (ventral putamen), they observed a pain prediction error signal which responded to CS1 onset, and to CS2 if it differed from CS1 (i.e., was unpredicted based on CS1). Similar paradigms were used using appetitive learning (O'Doherty et al., 2003). The TD learning framework has also been applied extensively to EEG data, in particular the error-related negativity, for example in the work of Holroyd and Coles (2002). These authors successfully compared the performance of a TD learning-based computational model with the dynamics of the error-related negativity (ERN) from human volunteers. The model was aimed to clarify the roles of anterior cingulate cortex (ACC) and the ventral striatal structures in an instrumental conditioning paradigm. The authors proposed that the ventral striatum implements TD learning in order to estimate the value of external stimuli in terms of expected reward, while the ACC functions as a filter of several possible motor responses. In their proposal, the ACC would select the motor plans that are expected to be the most effective to achieve future rewards, based on the reward predictions computed by the ventral striatum. In this model, the ERN would be the result of ACC activity following the suppression of dopaminergic input from the ventral striatum. In a series of EEG experiments, Holroyd and Coles showed

that their model was indeed able to predict several effects linked to the ERN, for example the fact that this EEG component appears only when there is a violation of the reward prediction.

Another example comes from the study of Parkinson's disease, a neurological disorder whose pathological basis consists of the degeneration of the dopaminergic neurons in the substantia nigra pars compacta, source of the main brainstem input to basal ganglia. Parkinson patients are impaired in learning from positive outcomes (reward), while performance is preserved for learning based on negative outcomes (punishment) (Frank et al., 2004). A neural model was proposed representing the interactions between basal ganglia, cortex and substantia nigra (Frank, 2005). In this model, the basal ganglia consists of two neural populations; "Go" neurons fire when an action planned in cortex is allowed to be implemented, whereas "No Go" neurons suppress the action planned in the cortex. Both Go and No Go populations learn by dopaminergic (i.e., reinforcement-related) bursts and dips coming from the substantia nigra. One of the advantages of the model consists in explaining several symptoms of Parkinson's disease. For instance, with reduced dopaminergic input (simulation of the substantia nigra degeneration), the basal ganglia are impaired at learning in Go neural populations, and hence impaired specifically in learning by rewards, just like human Parkinson patients. In addition, the model successfully predicts that this distinction between Go versus No Go learning holds true in high-level cognition as well (Frank et al., 2004).

Finally, it is worth describing briefly the work of Gläscher et al. (2010), which showed, by a combined computational and fMRI study, that the human brain also implements RL-like algorithms for creating abstract models of the environment. This study resembled the historical experiment of Tolman (1948). Volunteers were at first exposed to a simplified artificial environment, in which each single state was represented by an abstract figure (a fractal) (Figure 2). The subjects were asked to "navigate" inside this environment by performing binary choices (left or right). Each choice was followed by a transition to one of two possible states, each with some probability. In the first part of the experiment, subjects freely navigated in this environment, resembling Tolman's latent learning phase. In the second part, subjects received a monetary reward in some of the final states. In this way they had to exploit the latent learning acquired during the first part of the experiment to maximize reward, again as in Tolman's paradigm. Through a model-based analysis of the fMRI signal from both experimental phases, the authors localized the brain regions involved in both the latent learning (leading to a cognitive map or model of the environment) and the subsequent model-driven RL. While the RL-related areas were those typically found in the literature (ventral striatum and dopaminergic system), the areas involved in the formation of cognitive maps were the dorsolateral prefrontal cortex and intraparietal sulci.

The merit of this work consisted not only in the localization of two separate circuits for RL and environment-model (cognitive map) learning, but also in the demonstration that the two processes can be based on very similar computational mechanisms. One is the already described "prediction error" (Equation (1)), the other the "state prediction error". The latter is formally similar to the prediction error (comparison between predictions and real outcomes), but it deals with environmental state transitions. The mathematical form of the state prediction error (δ^{SPE}) is the following (note the similarity with Equation (1)):

$$\delta_t^{SPE} = 1 - T_t(s, a, s') \tag{4}$$

where the value 1 corresponds to the probability of being in the current state (s'; with probability 1), and $T(s,a,s')$ is the expected probability of transition from previous state s (the previous state) to the current state given (chosen) action a. The expectation T is updated by means of the state prediction error:

$$T_{t+1}(s,a,s') = T_t(s,a,s') + \alpha\delta_t^{\mathrm{SPE}} \tag{5}$$

In conclusion, this work showed that prediction error and state prediction error are similar computations but calculated in different brain circuits. This suggested a neurophysiological and computational basis of Tolman's discoveries sixty years before.

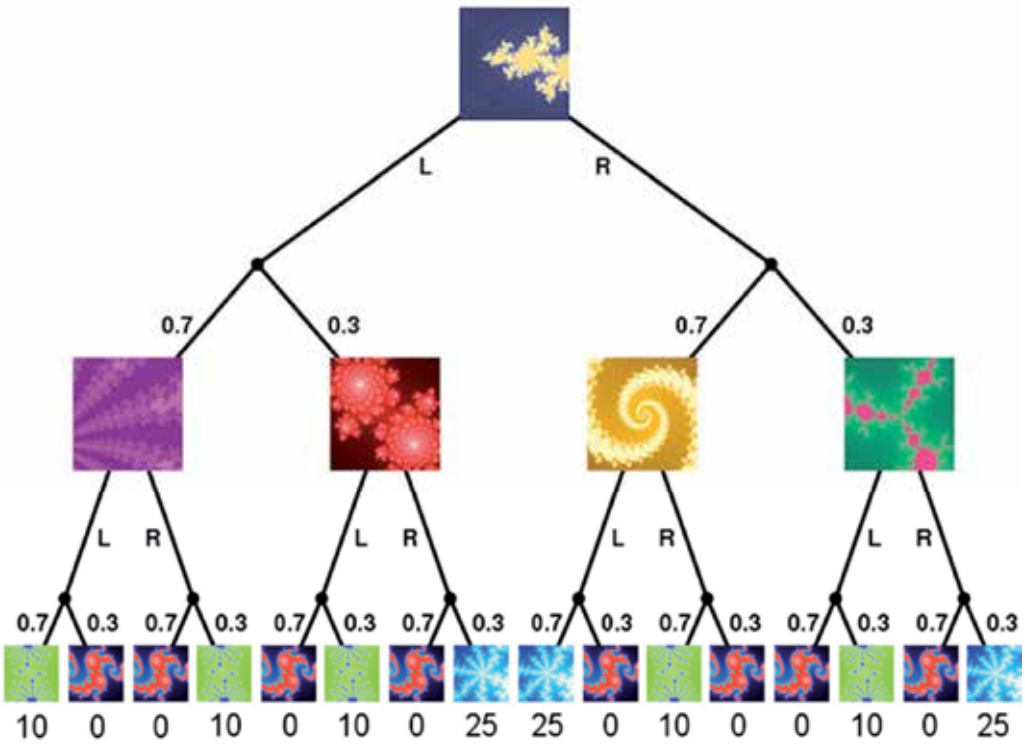

Fig. 2. Formal structure of state space in Gläscher et al.'s experiment. Reprinted with permission from Gläscher et al. (2010).

6. A case study: RL, cognitive control, and anterior cingulate cortex

One of the remaining mysteries of the human mind is executive functioning or cognitive control – the rapid modulation of behavior when called for by unexpected circumstances. In the symbol-manipulation paradigm, executive functioning was proposed to originate from a central executive endowed with two or more "slave systems" (typically the visuospatial sketch pad and the phonologic loop; Baddeley and Hitch, 1974). Detailed models have been developed of the slave systems (Burgess and Hitch, 1999), and in general great progress has been made in understanding them. However, the role of the central executive has remained

poorly understood. To tackle this issue, researchers have tried recasting executive functioning in neural models. We will describe these models and demonstrate how the union of RL and connectionist models provides steps toward understanding the neural basis of cognitive control.

6.1 Associative models of cognitive control

Working within the connectionist framework, Cohen et al. (1990) proposed a model of the Stroop task, a widely used index of cognitive control. In this task, subjects are shown a color word in a given ink color, with the color and word either congruent (e.g., the word RED written in red), or incongruent (e.g., the word RED written in green). The subject's task is to name the ink color. Because word reading is automatic in literate adults, cognitive control is required to override the automatic tendency to read the word. Although subjects can do this, a congruency cost is typically observed, with incongruent trials slower than congruent ones. The Stroop task is widely used in clinical contexts to assess executive functioning, and differentiates between healthy subjects and various patient groups suffering from impairments in cognitive control (e.g., ADHD, Willcutt et al., 2005; Parkinson's disease, Bonnin et al., 2010). In the Cohen et al. model, a distinction is made between an input layer for the relevant dimension and an input layer for the irrelevant dimension, each projecting to a response layer. Crucially, Cohen et al. added task demand units which bias responding toward the relevant dimension (input layer). This brings top-down modulation in an associative model framework.

Botvinick et al. (2001) further developed the model of Cohen et al. They argued that the earlier model did not specify when cognitive control is required. In particular, cognitive control is required only on incongruent trials (e.g., RED written in green), not on congruent ones. For this purpose, they introduced the notion of response conflict, measuring the extent to which responses are simultaneously active. They proposed the conflict monitoring model, according to which response conflict is calculated in anterior cingulate cortex (ACC). Conceptually, this was an advance over the previous model, because not only top-down modulation but also the trial-by-trial cognitive control could be captured in an associative learning framework. In addition, it has been highly influential and allowed accounting for many data. For example, using fMRI Botvinick et al. (1999) demonstrated that human ACC was more active on incongruent trials following a congruent trial than on incongruent trials following an incongruent trial. This finding contradicted the popular notion that ACC activity reflects executive control itself (because the subject should be more "controlled" after an incongruent trial), but was in line with the conflict monitoring model because there should be more conflict after a congruent trial. Note that this model is also a control model in the cybernetic sense mentioned before: It detects when something goes wrong, and when so, it leads to adaptation in the system.

Verguts and Notebaert (2008, 2009) further developed this line of work. They started from the fact that the conflict monitoring model specifies when control should be exerted, but not where (see also Blais et al., 2007). To confront this issue, the authors proposed a neural model in which the implementation of cognitive control was based on an error signal modulating the Hebbian learning between active model neurons. This error signal was, like in Gläscher et al.'s work, borrowed from the RL domain. The new measure, which could be called "conflict prediction error", was computed by comparing the actual amount of conflict, evoked by a stimulus, with the expected mean amount of conflict. This model successfully predicted that cognitive control should not extend across different task input dimensions

(Notebaert and Verguts, 2008) or even across task effectors (Braem et al., in press). Consistent with the model, it was recently demonstrated that ACC responds to item-specific congruencies, not block-level congruencies (Blais and Bunge, 2011).

6.2 New evidence on ACC function: Insights from RL-based neural modelling

Besides conflict monitoring, several other functions have been attributed to the ACC. In humans, evidence using EEG and fMRI pointed toward a role in error processing (Gehring et al., 1993), error likelihood (Brown and Braver, 2005), or volatility (Behrens et al., 2007). Moreover, in the single-cell literature, no direct evidence has been found for conflict monitoring (Cole et al., 2009), while, on the other hand, there is strong evidence for reinforcement processing (Rushworth and Behrens, 2008). More specifically, single-cell recording studies revealed the presence in ACC of three different types of neural units. One population codes for reward expectation, discharging as a function of the expected reward following the presentation of an external cue or the planning of an action. A second population codes for positive prediction error (i.e. when the outcome was better than predicted). Finally, another population codes for negative prediction errors (i.e. when the outcome was worse than predicted). We recently attempted to integrate these different levels of data and theories from the point of view of the RL framework. The model we proposed (Silvetti et al., 2011), the Reward Value Prediction Model (RVPM) demonstrated that all these findings can be understood from the same computational machinery which calculates values and deviations between observed reinforcement and expected values in an RL framework. The global function of the ACC however, remained similar to that in the conflict monitoring model and later versions of it: it is to detect if something is unexpected, and if so, to take action and adapt the cognitive system.

The evolution sketched here, from abstract cybernetic control models to the RVPM, represents a general trend in RL, in which computational, cognitive, and neuroscience concepts are increasingly integrated. Despite this success, not all features of RL have received appropriate attention in the literature. In the final section, we look at an aspect of RL that has been underrepresented.

7. RL and neural Darwinism

Despite the variety in levels of abstraction and purpose of the different models that we described, most of them implement what is sometimes called a triple-factor learning rule (Ashby et al., 2007; Arbuthnott et al., 2000). This means that three factors are multiplied for the purpose of changes in model weights: the first two factors are activation of input and output neurons, constituting the Hebbian component. The third factor is a RL-like signal, which provides some evaluation of the current situation (is it rewarding, unexpected, etc; henceforth, value signal). The value signal indicates the valence of an environmental state or of an internal state of the individual. It can be both encoded by dopaminergic signals (Holroyd & Coles, 2001) or by noradrenergic signals (e.g., Gläscher et al., 2010; Verguts & Notebaert, 2009).

This general scheme of Hebbian learning modulated by value provides an instantiation of the theory of Neural Darwinism (ND; Edelman, 1978). ND is a large scale theory on brain processes with roots in evolutionary theory and immunology. The basic idea of ND consists in the analogy between the Darwinian process of natural selection of individual organisms, and the selection of the most appropriate neural connections between a large population of

them. The general learning rule described above implements such a scheme. Because of the Hebbian component (input and output cells active together), individual synapses (which connect input and output neurons) are selected; and because of the value signal, the most appropriate synapses are chosen.

Just like in Darwinism applied to natural evolution, one key ingredient of ND is variation (called degeneracy by Edelman, 1978), or exploration when the unit of variation is not the individual synapse but rather responses (Aston-Jones & Cohen, 2001). From this variation, a selection can be made, based on an appropriate value signal. Computationally, Dehaene et al. (1987) demonstrated that temporal sequence learning can be achieved by such a variation-and-selection process. In neuroimaging, Daw et al. (2006) demonstrated that frontopolar cortex was used when subjects were in an exploration (rather than exploitation) phase of learning. Besides a few exceptions, however, variation and selection remain poorly studied. Given that it is a key component of RL, we suggest that its further exploration will learn us much more about high-level cognition and its implementation in the human brain.

8. Acknowledgements

MS and TV were supported by BOF/GOA Grant BOF08/GOA/011.

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15

What Does Cerebral Oxygenation Tell Us About Central Motor Output?

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1. Introduction

Since the fifth Century Athens, when Hippocrates identified the brain as the source of thought and understanding, humanity has been preoccupied with its functions. Anatomical descriptions have been brought to modernity by Andreas Vesalius in the sixteenth century (Vesalius, 1543) while underlying mechanisms have awaited the discovery of "bio-electricity" by Luigi Galvani in the eighteenth century to emerge (Galvani, 1791). In the nineteenth century, famous physicians such as Paul Broca or Carl Wernicke have demonstrated the role of the brain in cognitive tasks, studying patients with neurological disorders (Broca, 2004; Wernicke, 1894). From the late twentieth century to present day, neuroimaging techniques have allowed explorations in healthy subjects providing very precise locations of brain regions involved in cognitive and motor functions.

For the advancement of theory it is essential to acknowledge the strengths and limitations of available neuroimaging techniques so that converging evidence on the basis of multiple modes of investigation can be brought to bear on current controversies in the literature. Electroencephalography (EEG) was chronologically the first technique to open the way to the study of brain functions in exercising subjects (Swartz and Goldensohn, 1998). While one of the most direct methods to non-invasively measure the electrical signal arising from the synchronous firing of neurons, spatial resolution and lack of information from areas deeper than the cortex are its main limitations. Magnetoencephalography (MEG) is also a direct measure of the electrical activity of neurons and has a better spatial resolution as compared with EEG. However, the lack of detection in deep brain structures and the threshold detection (at least 50,000 neurons active simultaneously are needed) make MEG main disadvantages (Shibasaki, 2008). Functional imaging such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) overcome the EEG and MEG limitations as they can detect neuronal activity as deep in the brain as experimenters desire (Cui et al., 2011; Villringer, 1997). However, the measure is indirect as it relies on blood supply for fMRI or on radioactive tracers for PET and SPECT (Jantzen et al., 2008; Tashiro et al., 2008). Additionally, except for EEG, the experimental environments of the earlier described techniques are very restricting with regards to physical exercise. Subjects and experimenters are limited to sit or laid positions and to breathe, eye, wrist and ankle movements. Actually, *in vivo* determination of brain functions in humans requires flexible, accessible and rapid monitoring techniques (Kikukawa et al., 2008; Perrey, 2008;

Rasmussen et al., 2007). Near infrared spectroscopy (NIRS) is perhaps the technique which best gathers these qualities; which may account for the increasing popularity of NIRS among research teams in recent years.

2. Near infrared spectroscopy in humans

As suggested by its name, the NIRS technique relies on red and infrared light diffusion through the living tissues. Physically, NIRS systems consist of numerous probes designed to be attached directly on the skin, over the area(s) to explore. Either optical fibres or regular electrical wires link the probes to a dedicated hardware, which in turn feeds a computer with experimental data. Probes are made of light transmitters and light receivers; the light power emission, the receiver gain and the interoptode distance can be adapted to match with the characteristics and depth of the areas under investigation. However, those three parameters necessarily come as inputs for the NIRS dedicated software which drives the record session.

2.1 Principles of physics underlying the NIRS technique

Back in the eighteenth century, the brilliant French scientist Pierre Bouguer (1698-1758) is probably the true father of photometry (Bouguer, 1729). The goal of his publication entitled "*Essais sur la gradation de la lumière*" in 1729 was to quantify how much light is lost when travelling through a given atmospheric layer. To achieve his work, he empirically characterizes materials with an optical density (OD) as follows:

$$OD = \log\left(\frac{I_0}{I}\right) \tag{1}$$

where I_0 is the intensity of the incident light and I the intensity of the transmitted light. More than one hundred years later, the German scientist August Beer (1825-1863), based on Jean-Henri Lambert's (1728-1777) and Pierre Bouguer's works, published "*Einleitung in die höhere Optik*" (1853), where he defined transmittance of light rather than its loss when travelling through a tissue (Beer, 1853). What is now known as the Beer-Lambert's law is a different version of Bouguer's idea (eq.1). The Beer-Lambert's law (eq.2) states that there is a logarithmic dependence between the transmission of light (T) and the product of the absorption coefficient of the substance the light travelled through (α) and the distance travelled by the light (also called path length, l).

$$T = 10^{\alpha l} \tag{2}$$

In turn, the absorption coefficient α depends on the product of the extinction coefficients (ε) and the concentration (c) of the absorbers in the material. In liquids, the Beer-Lambert's law is often written as follows:

$$T = 10^{\varepsilon cl} \tag{3}$$

Equations 1 and 3 imply that there is a linear relationship between Bouguer's optical density and the concentration of species in the material explored:

$$OD = \varepsilon cl \tag{4}$$

From equation 4 (illustrated by fig.1), the main idea of NIRS is to compute the concentration of species (c) by measuring the OD according to Bouguer's definition (eq.1) and, inserting the a priori known extinction coefficients for species and the path length of light (eq. 4).

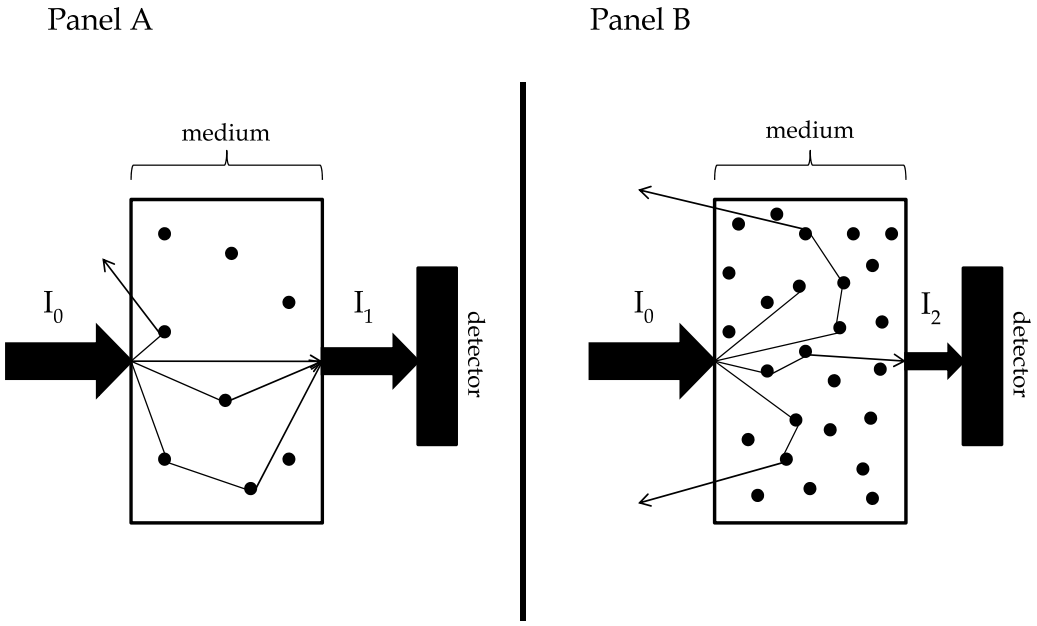

Fig. 1. Illustration of the Beer-Lambert's law. In panel A, the medium has a low OD (transmitted light I_1 is close to incident light I_0); the concentration of absorbing species is low. In panel B, OD is higher (larger difference between I_2 and I_0 than between I_1 and I_0), so is the concentration of absorbing species.

2.2 Application of NIRS to living tissues

At least six conditions have to be fulfilled in order for the Beer-Lambert's law to be valid:

- the absorbers must act independently from each others;
- the absorbing medium must be homogeneous in the interaction volume;
- the absorbing medium must not scatter the radiation;
- the incident radiation must consist of parallel rays, each travelling the same length in the medium;
- the incident radiation must be monochromatic;
- the incident radiation must not influence the atoms in the medium.

Living tissues, especially in humans, are doubtlessly among the most structured and complex in the universe. Their characteristics do not match with the Beer-Lambert's law prerequisites on numerous points. Therefore, the modified Beer-Lambert's law has to be applied in NIRS. As stated in the fifth point of the prerequisites, the incident light must be monochromatic (i.e. only one wavelength λ). In human tissues, lots of chemical species absorb light and account for its loss when travelling. However, there is a range of wavelengths at which light travel is much facilitated. Intuitively, when, in a dark environment, one looks at a flashlight through his finger or his hand, red is invariably the dominant colour. The physical explanation is that the red light travel through the human tissues is easier than for any other wavelengths. Implicitly, in the red portion of the visible

light, there are a limited number of chemical species which are responsible for the majority of light absorption and diffusion. These species are known to give its colour to the tissue and have been judiciously named chromophores. In human tissues, it is well known that haemoglobin is responsible for the colour given to tissues; in physics, haemoglobin is the chromophore whose concentration can be measured using Bouguer's idea.

2.2.1 The chromophores

Haemoglobin is a metalloprotein which transports 98% of the oxygen in most vertebrates' blood. When oxygen binds to the iron complex, it causes the iron ion to move back, and changes the optical properties of the molecule. At the human scale the phenomenon is perceptible and results in the long standing view that the red blood is filled-up with oxygen while the blue one has lost the majority of its initial quantity of oxygen. In physics, it can be considered that there are two distinct chromophores: oxygenated haemoglobin (O_2Hb) and deoxygenated haemoglobin (HHb). Therefore, according to Bouguer's idea one can compute the concentration of oxy and deoxyhaemoglobin in a tissue by measuring the changes in OD (eq. 4). However, the OD in human tissues is not strictly dependant on haemoglobin. In an imaginary case where there would be no haemoglobin in the explored area, the tissue would still absorb light. Consequently, eq.4 should be rewritten as:

$$OD_{(\lambda)} = \varepsilon_{(\lambda)} . c \ .l + ODr_{(\lambda)} \tag{5}$$

where ODr is the y-intercept of the linear relation and denotes the OD of the living tissue when there is no haemoglobin. λ denotes the chosen wavelength for the monochromatic light.

2.2.2 Two wavelengths

The Beer-Lambert's law states that the measured optical density is the sum of the absorbance of the two chromophores. Eq. 5 becomes eq. 6 with the two chromophores appearing:

$$OD_{(\lambda)} = \varepsilon_{O2Hb(\lambda)} . c_{O2Hb} \ .l + \ \varepsilon_{HHb(\lambda)} . c_{HHb} \ .l + ODr_{(\lambda)} \tag{6}$$

There are two unknowns in eq. 6 (ie. c_{O2Hb} and c_{HHb}). Thus, two equations are needed to solve the system. The two equations are provided by firing at two different wavelengths λ_1 and λ_2.

$$\begin{cases} OD_{(\lambda l)} = \varepsilon_{O2Hb(\lambda 1)} \ . c_{O2Hb} \ .l + \varepsilon_{HHb(\lambda 1)} \ . c_{HHb} \ .l + ODr_{(\lambda l)} \\ OD_{(\lambda 2)} = \varepsilon_{O2Hb(\lambda 2)} \ . \ c_{O2Hb} \ . \ l + \varepsilon_{HHb(\lambda 2)} \ . \ c_{HHb} \ . \ l + ODr_{(\lambda 2)} \end{cases} \tag{7}$$

The main idea is that one needs as many wavelengths as there are chromophores in the investigated area. Only one equation is exposed further down this line for clarity purpose. Note that NIRS systems perform every computation to solve the systems of equations.

2.2.3 Application of the modified Beer-Lambert's law

Since physiologists use NIRS to compute the haemoglobin concentration, the modified Beer-Lambert's law is then written:

$$c = \frac{(OD_{(\lambda)} - ODr_{(\lambda)})}{\varepsilon_{(\lambda)} . l} \tag{8}$$

In eq. 8, OD is measured using Bouguer's idea (eq.1), ε is known from the physicists who are able to measure it (fig.2), ODr and l are unknown but necessary to the computation of c.

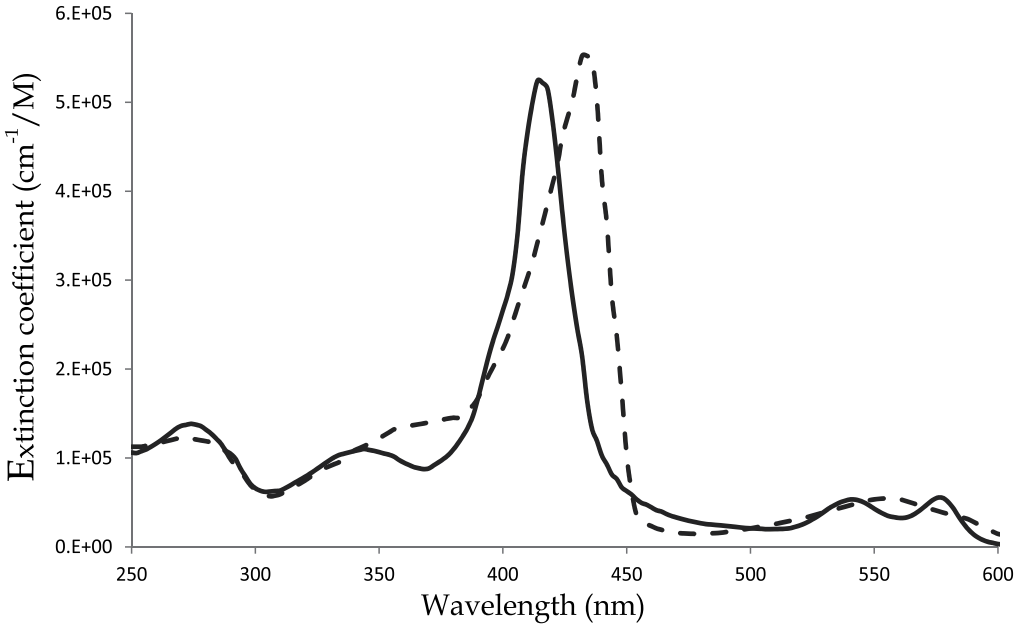

Fig. 2. Molar extinction coefficient for haemoglobin in water. O_2Hb: plain line; HHb: dashed line; x axis: wavelength (λ) in nm; y axis: extinction coefficient (ε) in cm^{-1}/M. Data compiled by Scott Prahl (Prahl, 2008).

ODr is not expected to change radically in a short lap of time. In other words, it is considered constant between two light impulsions a few tenths of seconds away. Therefore, considering two light impulsions at t_0 and t_1, it is possible to write:

$$c_{t0} - c_{t1} = \frac{(OD_{(\lambda)t0} - ODr_{(\lambda)})}{\varepsilon_{(\lambda)} \cdot l} - \frac{(OD_{(\lambda)t1} - ODr_{(\lambda)})}{\varepsilon_{(\lambda)} \cdot l} \tag{9}$$

which simplifies into

$$c_{t0} - c_{t1} = \frac{(OD_{(\lambda)t0} - OD_{(\lambda)t1})}{\varepsilon_{(\lambda)} \cdot l} \tag{10}$$

Eq. 10 states that the concentration variations depend on the measured OD variations. The advantage of the subtraction in eq. 9 is to get rid of the unknown ODr. However, the absolute concentration of the chromophore becomes unknown as only a concentration difference (or variation) can be computed.

The last unknown parameter missing to compute the concentration variation is l, the path length of light between the transmitter and the receptor (fig. 3). Its measure is almost impossible due to the numerous interactions between the matter and the light in living tissues (Ijichi et al., 2005). Three methods are available to approach the path length:

- the differential path length factor (DPF)
- the time of flight
- the Monte Carlo simulation

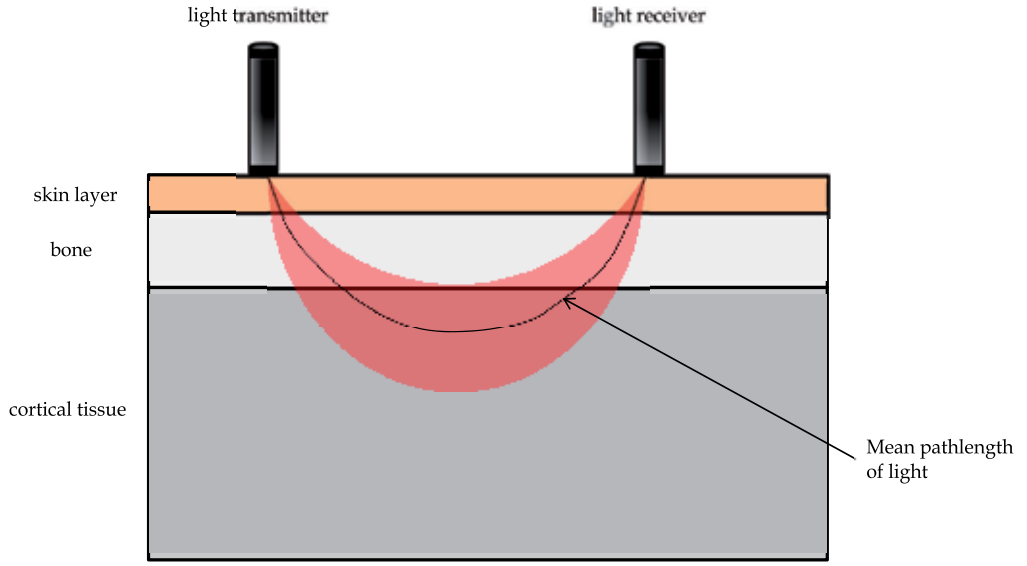

Fig. 3. Schematic representation of NIRS applied to human cerebral tissues. The mean path length of light represents the l.DPF in eq.11. Roughly, the maximum depth of the mean path length of light is believed to be half of the emitter to receiver distance.

The DPF method is doubtlessly the easiest to use but also the less precise and less satisfactory. Regrettably it is the most common method nowadays. In this method, l is considered the most direct way between the light transmitter and receptor, DPF is multiplied to l to lengthen the global path length, eq. 10 is then written:

$$\Delta c = \frac{\Delta OD_{(\lambda)}}{\varepsilon_{(\lambda)} . l . DPF} \tag{11}$$

DPF is arbitrarily set from abacus found in the literature. Only a few studies give the DPF, often as a function of age (Duncan et al., 1995; Essenpreis et al., 1993a; Essenpreis et al., 1993b; Firbank et al., 1993; Ijichi et al., 2005; Kohl et al., 1998a; Kohl et al., 1998b; Nolte et al., 1998; Pringle et al., 1999; Ultman and Piantadosi, 1991; van der Zee et al., 1992; Zhao et al., 2002). Another way to approach the path length of light is to measure the time of flight between the light transmitter and the receptor. The speed of light in the vacuum is used to compute the path length. This method is more precise than the DPF method but costly financially and in terms of load of computation. Billion of photons are detected by the receptor at each light impulsion. One of the advantages is the possibility to select the photons to study; the first detected photons have a priori a shorter path length, which means that they did not go deep into the tissues (Ferrante et al., 2009). The latest photons, which have a longer path length, went a priori deeper into the tissues and carry more information. Finally, the Monte Carlo simulation is a statistical method representing the distribution of energy in the explored volume. It is a way to assume the random path length

of photons between the light transmitter and the receptor (Hiraoka et al., 1993; Simpson et al., 1998; Zhang et al., 2007a, b). This is the most precise method nowadays, usable with regular measurement devices but costly in terms of computation. The Monte Carlo method might be performed after the monitoring session as computers may not be powerful enough to ensure simultaneously proper recording of the data and Monte Carlo analysis (Avrillier et al., 1998a; Avrillier et al., 1998b). Roughly, for all methods the maximum depth of the mean path length of light is believed to be half of the emitter to receiver distance.

3. Signal characteristics and interpretations

NIRS data consist of oxy and deoxyhaemoglobin time series (Fig. 4 and Fig. 5), with sampling rate usually ranging from 2 to 20Hz, and occasionally above. Usual measurement sites exclude locations where large arteries or veins would be reachable by the NIRS light as experimenters are rather interested in tissue data. In the tissues, the light crosses three types of blood vessels:

- arterioles (diameter below 100µm, average 20-30µm)
- capillaries (average diameter 5-10µm)
- venules (average diameter 8-30µm)

NIRS signal is believed to originate in its major part from the venous compartment (approx. 70%); however, vasomotion makes the part of each segment variable (Bourdillon et al., 2009; Peltonen et al., 2009). Briefly, capillaries form an extensive network which connects the arterial and venous sides of the vascular system. The blood flow through a given capillary bed strongly depends on the vascular tone of the parent arteriole and the pre-capillary sphincters. Both adjust the local blood flow to meet the physiological demands. Despite the smooth muscles of the arterioles and sphincters are connected to the sympathetic nervous system, the vascular tone is largely dependent on the local factors (Segal, 2005). Concerning the motor areas of the brain, it is generally assumed that, when activated, the neurons increase their firing rates to generate the motor command and thus increase their metabolic demands (Villringer, 1997). One of the consequences is to increase the local blood flow; this

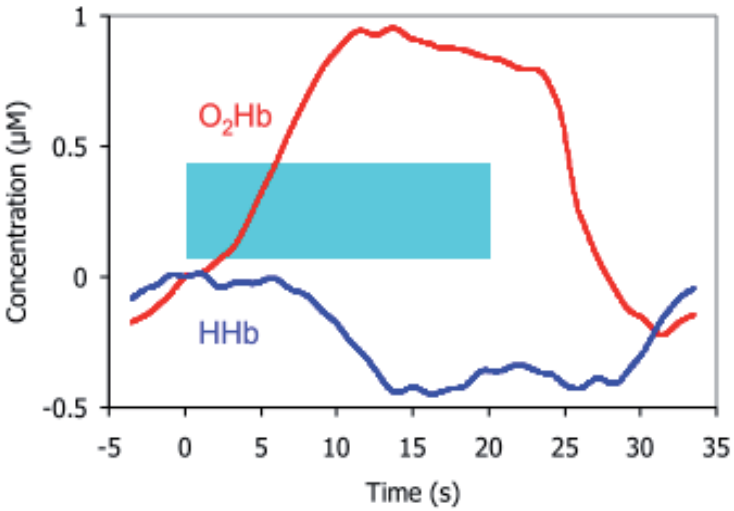

Fig. 4. Example of a NIRS signal pattern over the motor cortex during a 20 seconds lasting handgrip task (Wolf et al., 2007).

phenomenon can be detected by NIRS. It is obvious that the NIRS measurements are indirect with regards to neuronal activity and rely on the assumption that the latter is coupled to blood supply. Moreover, NIRS measures the concentrations of oxy and deoxyhaemoglobin (the sum of both, Hbtot, giving a proxy of local blood volume), not the blood flow nor the oxygen consumption. Fig. 4 shows a typical NIRS record during a simple motor task (handgrip).

3.1 Patterns

Empirically, activation pattern in the motor cortex is identified as an increase in oxyhaemoglobin concomitant to a decrease in deoxyhaemoglobin (Fig. 4). The reasons which give the activation pattern such a shape are not fully elucidated (Dai et al., 2001; Harada et al., 2006; Matsuura et al., 2011). However, it is commonly thought that the vasodilation caused by the increase in metabolic demand from the firing neurons overcomes the needs in oxygen; which results in an apparent increase in tissue oxygenation as measured by NIRS (Franceschini and Boas, 2004; Gervain et al., 2011; Leff et al., 2011; Rooks et al., 2010; Shibasaki, 2008; Shibuya and Tachi, 2006). The amplitudes of changes in oxy and deoxyhaemoglobin within the motor cortex areas have been shown to be dependent on the force production: the stronger the push, the higher the oxyhaemoglobin (Shibuya and Tachi, 2006; Smith et al., 2003). However, at low levels of force, there might be no detection by the NIRS systems (at least 10% of maximal voluntary contraction needed); while at high levels (about 50% of maximal voluntary contraction and above) there might be no plateau but only a peak in oxyhaemoglobin (Ekkekakis, 2009). This type of activation pattern is valid only for steady systemic variables (ie. globally non moving body). The NIRS signal, as it comes from the circulatory system, is strongly dependent on the cardio-respiratory parameters. Modifications in cardiac output, autonomic nervous system balance, hormonal response,

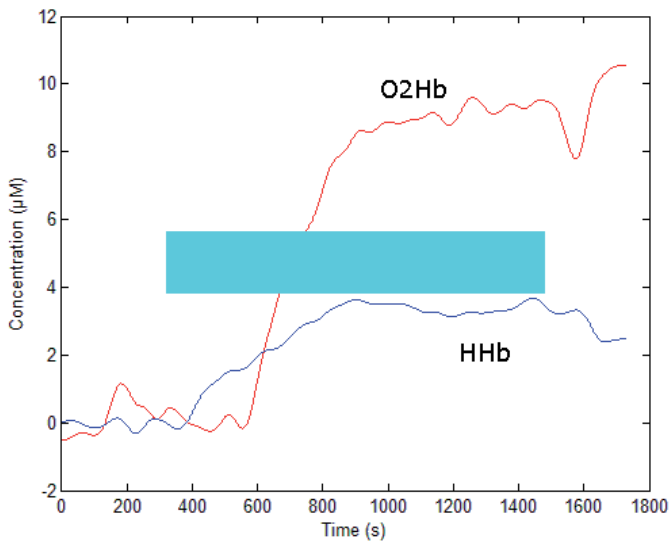

Fig. 5. Example of a NIRS signal pattern over the motor cortex during a high intensity whole body cycling exercise at a constant work rate from baseline level (warm up) at 600 s. Personal data.

blood concentration in oxygen or carbon dioxide, baroreflexes and neural feedbacks from metabo and mecano receptors in the skeletal muscle potentially affect the vascular tone and thus the NIRS signal. Consequently, in subjects exercising at high metabolic rates (elevated oxygen consumption), with hyperventilation, hyper/hypocapnia and high cardiac output, the NIRS signal is rather dependant on systemic variables than on motor command (Pereira et al., 2007; Rasmussen et al., 2007). Fig. 5 shows a typical NIRS response from the motor cortex of a subject exercising on a cycloergometer above the ventilatory threshold for 20 minutes (Rooks et al., 2010; Rupp and Perrey, 2008). The amplitudes of the variations are way larger as compared with fig. 4 and the "activation pattern" is altered as there is no apparent decrease in deoxyhaemoglobin. In any case, the interpretation of the NIRS signals has to be modulated following the experimental design and the systemic conditions (Gervain et al., 2011; Rooks et al., 2010).

3.2 Delay

As shown in fig. 4 or fig. 5, there is a delay between the stimulus, the neural responses and the hemodynamic modifications as detected by the NIRS systems (Cui et al., 2010b; Yasui et al., 2010). If the NIRS signal depends on the motor command, the delay has been shown to range between 2 and 5 seconds (Fig. 4). In the case of fig. 5 the NIRS signal is rather dependant on systemic parameters (i.e. ventilation) and the delay ranges between 1 and 4 minutes. Such variations in delays are due to the facts that the NIRS records of cerebral hemodynamic parameters depend whether on the motor command or on systemic parameters, following the experimental design. To date, the time course analysis of NIRS signals has yet to be established, notably with regards to the transition periods and the experimental designs.

3.3 NIRS computed indicators

The only parameters measured by NIRS are the optical densities at two (or more) wavelengths as stated in the part 2.2.2 of this article. O_2Hb and HHb are directly computed variables; the computer usually performs calculations during data acquisition. Afterwards, experimenters are using to computing other parameters from O_2Hb and HHb to present NIRS data. Among the most often found parameters in the literature there are: the difference between O_2Hb and HHb (usually abbreviated $O_2Hbdiff$ or Hbdiff); the tissue or capillary saturation (usually abbreviated StO_2 or ScO_2) and the tissue oxygenation index (TOI). TOI, StO_2 and ScO_2 are given by the simple formula:

$$TOI = \frac{O_2Hb}{O_2Hb + HHb} \tag{12}$$

These indicators are thought to summarize O_2Hb and HHb signals and reflect tissue oxygenation. However, physical exercise results in a large heterogeneous increase in cerebral oxygenation (Rooks et al., 2010). It seems that the primary factor influencing this increase is the intensity of exercise, followed by the training status of the subjects, age, health status (i.e., patients vs. healthy subjects) and methodology.

3.4 Pre-processing

In most studies, NIRS data is pre-processed in order to improve the signal quality (Boas et al., 2004). The first step typically aims at removing noise (Gervain et al., 2011). The noise

comes from the devices as well as from physiological parameters not a priori linked to the stimulation (eg. Exercise) and are thus undesirable (Nolte et al., 1998). This kind of noise is considered high frequency with regards to the frequencies of interest (Cui et al., 2010a). Low-pass filters are used to remove heart rate, blood pressure variations, breath, swallowing etc. Usually, the cut-off frequency ranges between 0.1 and 1Hz. Detrending is performed using a high-pass filter when NIRS signals slowly drift throughout the experimental session. High-pass filters usually range between 0.01 and 0.05Hz. However experimenters must care as the frequencies of interest could be part of this range. Finally, experimenters have several tools to choose from to remove movement artefacts. If possible set a marker during the experimental session when the subject moved his head is a good start. Retrospectively, the eye of the physiologist is the first tool which can be used. However, its somehow objective behaviour and its inability to treat large amounts of data make its main limits. Abrupt changes in the signals can be detected and corrected by algorithms (Lloyd-Fox et al., 2010; Wilcox et al., 2008). However, the thresholds must be defined carefully in order to preserve the changes that supposedly belong to the awaited hemodynamic response (Gervain et al., 2011).

3.5 Data analysis

Since NIRS is a relatively new technique for brain investigations, there is no standardised method to analyse data. Up to date, the only invariant is that different experimental designs require different analysis techniques.

In block-designed studies, experimenters are used to analysing time series by averaging multiple trials of the same condition. Mean variations and mean time courses are then obtained for each condition. The critical points of such techniques are the determination of the relevant windows of the time series and the baseline which it is compared to. Once determined, student t-test and analyses of variance are the most often used statistical methods.

More complex, three main freeware packages are downloadable and provide analysis methods derived from the BOLD signal of fMRI: HomER (Huppert et al., 2009), fOSA (Koh et al., 2007) and NIRS-SPM (Ye et al., 2009). The general linear model (GLM) and the statistical parametric mapping (SPM) offer the possibility to create three dimensional pictures of the brain, where activated/inhibited cortex areas are colour encoded (Friston et al., 1999; Plichta et al., 2007; Schroeter et al., 2004; Zarahn et al., 1997). In most studies, the NIRS records are performed off the MRI scan. Then, the input of the three dimensional coordinates of the optodes/channels is crucial for the reconstitution of the pictures. In the case of a co-record of NIRS and fMRI techniques, the coordinates of the NIRS optodes can be precisely assigned; else, skull measurements and probe placement are made either by reference to the 10-20 EEG system or by kinematic acquisition using such devices as optotrack or fastrack.

3.6 Dos and don'ts

Doubtlessly, the toughest part of the NIRS based studies, is to draw physiological and cognitive conclusions from the data. Multi-channel setups cover wide cortical zones and result in several time series and three dimensional coloured images in which probability to give statistically significant results is high. The question experimenters inevitably face is "What do those results mean?". A typical NIRS channel includes a great number of capillary

beds, corresponding to a greater number of neurons (estimated around 300,000 to 500,000) from various depths in the cortex (Gervain et al., 2011). The pool of capillary beds enlighten by a channel is believed to belong to a given cortex area, which supposedly has a single function. This makes a huge simplification if compared to the brain complexity and its capacity of integration, not to mention the neuro-vascular coupling assumption (see part 4.1.)! Moreover, probe placement is based on the skull anatomy as no direct access to the brain is allowed by NIRS (except in the case of fMRI co-recording) giving a probability to fire over multiple cortex areas or even over a wrong area. Additionally, the proportion of excitatory and inhibitory neurons in the volume aimed by NIRS is unknown yet potentially affects the results.

3.7 Confounding factors

At this stage of the article, the most impeding factors have been brought to discussion. However, some factors, not directly linked to the NIRS concepts nor to brain characteristics must be debated. Before entering the tissue of interest, light travels through the skin and the fat layers (as well as the hair and skull layers in case of brain investigations, Fig. 3). The skin colour (and hair colour) has been shown to influence light absorption (Pringle et al., 1999). Intuitively, human eyes perceive various skin colours because skin absorbs and reflects light depending on its properties. The same (or the opposite) happens in the near infrared portion of the spectrum. Light skins are believed to absorb light more than dark skins, while Asian originated skins are the less absorbent. NIRS gain or laser power must then be modulated to fit with the skin properties of a given subject; which can be performed automatically by the NIRS hardware before starting the data acquisition.

Skin blood flow is one of the main confounding factors as the haemoglobin molecules present in the capillary beds located in the skin are the first (and last) exposed to NIRS light (Tew et al., 2010). In exercising subjects, blood flow is increasing in proportion to the intensity of exercise, for well-known thermoregulation reasons. However, skin is not believed to consume more oxygen at high intensity as compared with low intensity exercises. This means that skin blood flow overcomes by far the local metabolic demands; which necessarily biases the NIRS measurements.

The fat and bone layers are probably easier to take into account as they can be integrated in the automatic gain setup which occurs in most modern NIRS devices, before data acquisition.

Finally, gender has been shown to influence NIRS responses to various stimuli, notably motor, cognitive tasks and emotions (Marumo et al., 2009; Yang et al., 2009).

4. Measuring the brain activities related to the motor stimulation using NIRS

4.1 Physiological processes associated with brain activity

Physiological events associated with brain activity can be subdivided into intracellular events, events occurring at the cell membranes and those that are mediated by neurovascular coupling and occur within the vascular space. Increased brain activity is correlated not only with oxygen consumption but also with glucose consumption. The brain has only negligible stores of glucose and therefore relies both on the circulating glucose and on the active transport system which moves glucose across the blood-brain barrier. Increased activity in brain cells is associated with an increase in glucose consumption and

thus the intracellular glucose concentration might fall in the early activation period (Villringer and Dirnagl, 1995). This transient drop in glucose is accompanied by a transient rise in local lactate concentration (Villringer and Dirnagl, 1995). Magistretti and Pellerin (Magistretti and Pellerin, 1999a, b) have provided new insights on the role of astrocytes in coupling neuronal activity with energy metabolism. They propose an initial glycolytic processing which occurs in astrocytes during activation, resulting in a transient lactate overproduction; followed by a recoupling phase during which lactate is oxidised by neurons. In addition to the events taking place intracellularly, local brain activity induces a local arteriolar vasodilation (Villringer and Dirnagl, 1995). Although small arteries and arterioles probably contain less than 5% of the blood volume in the brain parenchyma, they control most of the resistance and therefore blood flow at a local level. As a consequence of local vasodilation the local cerebral blood volume as well as the blood flow increase. This relationship between neuronal activity and vascular response is termed "neurovascular coupling". In other words, the changes in Hbtot most probably reflect the match between oxygen supply and oxygen demand, whereas changes in O_2Hb reflect the alterations in cerebral blood flow, an overshoot in cerebral oxygenation during brain activation. Several NIRS studies conducted in the past fifteen years have demonstrated that activation- induced changes in brain activity can be assessed non-invasively during the performance of various whole-body motor activities (Maki et al., 1995; Obrig et al., 1996).

4.2 Brain activity and motor performance

The NIRS is applicable under a variety of conditions ranging from bedside monitoring in intensive care to documenting the effects of maximal whole body exercise in the physiology laboratory. To date, several studies have used NIRS to examine alterations in cerebral oxygenation during dynamic exercise, and have found an increase in cerebral oxygenation with medium and high-intensity exercise (Bhambhani et al., 2007; Shibuya et al., 2004a; Subudhi et al., 2007; Suzuki et al., 2004).

While a rather detailed understanding of brain activity during hand movement has been developed (Dettmers et al., 1995), less is known about the functional anatomy of motor control for leg or foot movements. Due to its advantages compared to other neuroimaging techniques, NIRS technique allows recording of cerebral activity during ordinary gait (Fig. 6). For instance, Miyai et al. (2001) were able to compare cerebral activities evoked during gait, alternating foot movements, arm swing and motor imagery of gait. Gait-related responses along the central sulcus were medial and caudal to activity associated with arm swing, in agreement with the known somatotopic organisation of the motor cortex (Perec, 1974). Crucially, these authors showed that walking increased cerebral activity bilaterally in the medial primary sensori-motor cortices and the supplementary motor area, and to a greater extent than the alternation of foot movements. Unfortunately, the spatial distribution and intensity of these responses were not statistically compared. In a different NIRS study, Suzuki et al. (2004) examined the effect of various walking speeds on cerebral activity. They demonstrated that cerebral activity in the prefrontal cortex and premotor cortex tended to increase as the locomotion speed increased, whereas cerebral activity in the medial sensori-motor cortex was not influenced by the locomotion speed. In summary, NIRS is particularly useful for studying the cortical bases of locomotion control. Unfortunately, given the limited depth penetration of the infrared light (a few centimetres from the skull surface), the NIRS

technique can only assess the responses of the most superficial portions of the cerebral cortex.

Neuroimaging studies have reported a proportional relationship between cortical signals and exerted joint force in humans, indicating that brain signals are positively correlated to voluntary efforts, as a high level of effort is required for exerting greater muscle force (Liu et al., 2007; Liu et al., 2003). Recently several authors have proposed combining neuroimaging techniques with the classical twitch interpolation to investigate the central aspects of fatigue after and during ongoing exercise. Most studies on central fatigue have investigated isometric contractions of isolated muscle groups. Post et al. (2009) showed, during a sustained high force contraction, that the hemodynamic response (BOLD signal) in the most important motor (output) areas increased (primary sensorimotor cortex, supplementary motor area, premotor area), whereas the voluntary activation (accessed via the twitch-interpolation technique) of the index finger muscle during a unilateral task decreased with time. This finding suggests that although the central nervous system (CNS) increased its input to the motor areas, these increases did not overcome fatigue-related changes in the voluntary drive to the motor units. During a progressive maximal cycling exercise, Rupp and Perrey (2008) showed a decrease in prefrontal cortical oxygenation before motor performance failure, which may be compatible with the notion of a role for the prefrontal cortex in the reduction of motor output by the cessation of exercise. However, this finding was not associated with a decrease in voluntary activation, but measured 6 min post-exercise. Support for the role of a failure of the CNS to excite the motor neurons adequately (i.e., central fatigue) in fatigue during challenging exercises has been provided by the finding that voluntary activation of skeletal muscles is reduced after fatiguing exercise.

This suboptimal muscle activation has also been functionally observed via lowered surface electromyographic (EMG) activity on several occasions during fatiguing exercises (Mendez-Villanueva et al., 2007). However, what triggers these acute changes in the CNS behaviour remains to be determined. Central fatigue may be elicited by low brain oxygenation, i.e., by insufficient O_2 delivery and/or low pressure gradient to drive the diffusion of O_2 from the capillaries to the mitochondria. Direct and indirect evidences support the contention that inadequate cerebral oxygenation depresses cortical neuron excitability, although the mechanisms remain debated (for review see Nybo and Rasmussen, 2007). The non-invasive technique of NIRS offers real-time measurement of oxygenation and hemodynamic responses in tissues, and thus, constitutes a relevant tool to enhance our current knowledge of central (CNS) and peripheral (muscle) determinants of whole-body exercise performance. Some studies have reported that muscle deoxygenation occurs during repeated cycling tests (Racinais et al., 2007). However, exercises of this nature appear to induce a fairly constant level of deoxygenation in prime mover muscles across repetitions, and therefore authors have suggested that muscle O_2 uptake was well preserved and was not likely to represent a limiting factor. Data on cerebral oxygenation changes during fatiguing tests are currently presented in the literature. Based on studies conducted during constant workload exercise, incremental test to maximal effort (Rupp and Perrey, 2008), and supramaximal exercise (Shibuya et al., 2004b), the deoxygenation of the cerebral cortex has, in general, been incriminated in the cessation of exercise, or at least in the reduction of exercise intensity. This finding, however, is confounded by the availability of O_2 (Subudhi et al., 2007). Although an association exists between cerebral oxygenation and performance in various

exercises, no studies have yet determined if a critical level of cerebral deoxygenation impairs whole body exercise. Shibuya and colleagues Shibuya et al. (2004a) reported a progressive cerebral deoxygenation during intermittent exercises. Specifically, these authors observed a reduction in $\Delta[O_2Hb]$ and $\Delta[Hbtot]$, while $\Delta[HHb]$ increased, over the course of seven, 30s cycling exercises performed at an intensity corresponding to 150% $\dot{V}O_2max$ and interspersed with 15s of rest. It was concluded that fatigue, resulting from such intermittent supramaximal exercises, was related to a decrease in the cerebral oxygenation level.

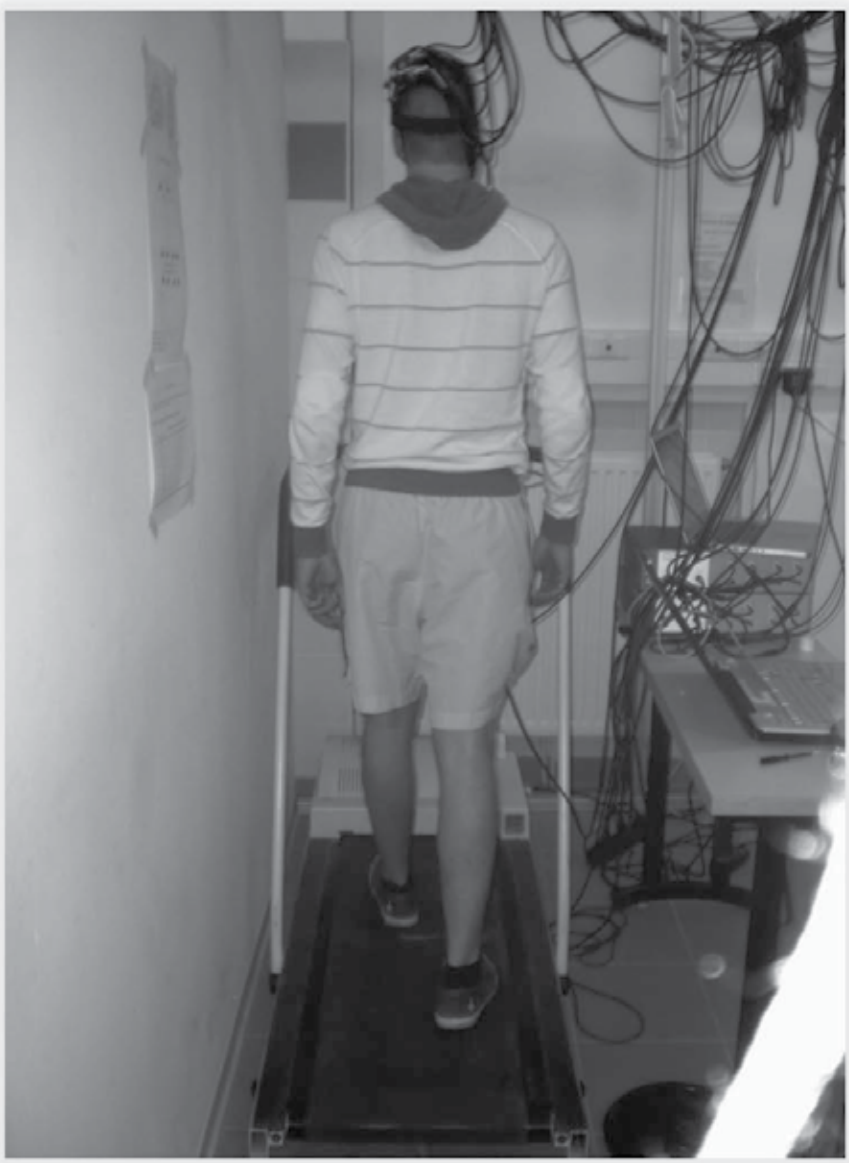

Fig. 6. Example of a NIRS setting while the subject is walking on a treadmill.

To date based on recent evidences; we may propose that reductions in cerebral oxygenation during exhaustive intensities are caused by decreased cerebral blood flow coupled with increased cerebral oxygen uptake (Gonzalez-Alonso et al., 2004). It has also been proposed that this change in flow and metabolism at high intensities is sensed or controlled by a 'central governor' so that during oxygen availability reduction, peak exercise performance is reduced to prevent the development of ischemia in vital organs including the brain (Noakes et al., 2005). In this way, an increase in Hbtot and a decrease in cerebral oxygenation represent potential metabolic indicators, signalling either directly or indirectly to sub-cortical and cortical motor areas of the brain to reduce muscle unit recruitment and thus protect the brain and peripheral organs.

5. Conclusion

NIRS utilises light to measure cortical haemoglobin concentration changes associated with neural activity. This technique is more tolerant compared with other comparable techniques, regarding the subjects' movements, thus allowing a wider range of experimental tasks in the range of dynamic exercises. However, it has some shortcomings that need to be addressed. In this chapter, we showed how technical obstacles could be overcome, how NIRS contributes to the mapping of exercise-related brain functions, and further promotes the understanding of human movement and motor performance. In this context, we propose NIRS as a potential mediator between physiology and neuroscience. Beside these advances in technique and analysis of the data, we believe that users should consider the methodology's strengths and weakness when designing a NIRS study.

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Intermanual and Intermodal Transfer in Human Newborns: Neonatal Behavioral Evidence and Neurocognitive Approach

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1. Introduction

Until recently, newborns had typically been described as displaying mainly involuntary reactions and clumsy arm movements. However, in recent years investigation of exploratory perception of objects has emerged as key area research. Newborns' hands have often been described as closed or exhibiting either grasping or avoidance reactions which are inappropriate behaviors for holding an object and gathering and processing information (Katz, 1925; Roland and Mortensen 1987; Twitchell, 1965). However, besides possessing manual brief reactions (reflex), newborns are also able to handle small objects and to perceive their properties. To reveal this tactile ability, researchers have applied a habituation-dishabituation procedure to the tactile modality, just as in the visual modality (Streri & Pêcheux, 1986a). This procedure, which is controlled by the infant, is effective in revealing the early perceptual capacities of young babies (cf. Streri, 1993). It unfolds in two phases. The first phase, habituation, includes a series of trials in which the infants receive a small object in one hand. A trial begins when the infant holds the object and ends when the infant drops it or after a maximum duration defined by the experimenter. This process is repeated several times. As a consequence, the habituation process entails several grasps of determined duration (usually between 1 sec to 60 sec of holding). Trials continue until the habituation criterion is met. The newborn is judged to have been habituated when the duration of holding on any two consecutive trials, from the third onwards, totals a third (or a quarter, depending on age) or less of the total duration of the first two trials. Total holding time is taken as an indicator of the duration of familiarization. The mean number of trials taken to reach habituation ranges from four to twelve, and often varies with shape complexity. The decrease in holding times is considered to reveal the infants' ability to perceive and form a memory of the shape and subsequently recognize it. Then, in the dishabituation phase, a novel object is put in the infant's hand. If an increase in holding time of the novel object is observed, it is inferred that the baby is reacting to novelty, having noticed the difference between novel and familiar objects. That these processes reveal a form of mental representation of stimuli is now well established (cf. Pascalis & De Haan, 2003; Rovee-Collier & Barr, 2001).

Using this experimental procedure, Streri, Lhote, and Dutilleul (2000) showed that full-term newborns (the youngest was 16 hours old) were able to detect differences in the contours of

two small objects (a smoothly curved cylinder versus a sharply angled prism) with both right and left hands. After habituation with one of the two objects placed in the right or left hand, the newborns reacted to novelty when a new object (the prism or cylinder) was put in their hand. This was the first evidence of habituation and reaction to novelty observed with the left as well as the right hand in human newborns. Thus, newborns are able to discriminate between curvilinear and rectilinear contours in small objects. However, this behavior does not show that babies have a clear representation of what they are holding in their hand. Because young infants are unable to perform the integration and synthesis of information in working memory required for haptic exploration, their shape perception is probably partial or limited to the detection of clues such as points, curves, presence or absence of a hole, etc. The information gathered is provided by the enclosure of the object (cf. Lederman & Klatzky, 1987), which seems to be an effective exploratory procedure for these limited purposes. To understand the emergence of these manual abilities in full-term newborns, it is important to recall the early maturation of touch (first among the senses to begin functioning) in the foetal period (from a cephalo-caudal point of view). Tactile receptors can be found in the epithelium of the mouth and the dermis of the peri-oral area as early as 8-9 gestational weeks. Meissner and Pacini corpuscles develop soon after. Tactile receptors are found on the face, the palms and the soles of the feet by 11 weeks. By the 15th week they are found on the trunk and proximal zones of arms and legs, and on the whole skin by the 20th week (Humphrey, 1964). Taken together, these data suggest that this ability to perceive various shapes with both hands observed in full-term newborns may be a "core ability" already present in the foetus. To investigate this hypothesis, the study of this manual ability in preterm babies is relevant and may reveal continuity in sensory functioning between foetal and neonatal periods, by determining whether preterm babies are able to extract information with their hands.

The current World Health Organization definition of premature is a baby born before 37 weeks of gestation, counting from the first day of the last menstrual period, where 40 weeks of gestation is the normal term. Moreover, the viability of foetuses is between 22 and 24 weeks of gestation, depending on the country. Studies about preterm babies and touch have generally focused on pain and developmental concerns (Sizun & Browne, 2005). They have shown that neonates' pain responses are influenced by the number of painful procedures previously experienced by the infant (Johnston & Stevens, 1996). Bartocci, Bergqvist, Lagercrantz and Anand (2006) showed that tactile and painful stimuli specifically activate somatosensory cortical areas. This result indicates that central integration of tactile information occurs in preterm newborns at 28-36 weeks of gestation. A link between hand movements and somatosensory cortical activation has also been shown in preterm newborns at 29-31 weeks of gestation (Milh *et al*., 2007). Recently, Lejeune, Audéoud, Marcus, Streri, Debillon and Gentaz (2010) investigated the ability of preterm babies' hands to discriminate between various shapes. Twenty-four preterm babies underwent a habituation phase followed by a test phase. The entire observation is performed in such a way the newborns cannot see their hands and the held object. In the test phase, twelve babies (experimental group) were tested with a novel object whereas twelve babies (control group) were tested with a familiar object (the one presented during the habituation phase). The shapes used were similar to those used by Streri *et al* (2000): a cylinder and a prism with identical object/hand surface ratio. These objects were smaller than those used by Streri *et al*. (2000) because preterm babies' hands are smaller than those of full term babies. The

results revealed that when an object is placed in a preterm newborn's hand, holding time decreases trial by trial until the habituation criterion is reached. In the test phase, the experimental group held the novel object significantly longer compared to the preceding two habituation trials, in contrast to the control group in which this was not the case. These results suggest that preterm babies react differentially to a novel shape. These findings are in accordance with the early maturation of touch.

Taken together, these results show that preterm and full-term babies are able to memorize the shape of an object with each hand. These abilities reflect the very early existence of some internal representation of a stimulus. However, what is the nature of this internal representation? If it has some level of abstraction, newborns should be able to transfer object information from one hand to the other (low level of abstraction) or from one hand to the visual modality (high level of abstraction). Thus, the first goal of this chapter was to show that full-term and preterm newborns are capable of transferring shape and texture information from one hand to the other. The second goal was to show that full-term newborns are capable of transferring information between touch and vision in some, but not all, conditions. These limits or failures may be explained by neuroimaging evidence in adults.

2. Intermanual perception of object shape in human newborns

One reason for interest in intermanual transfer is its potential value in assessing communication between the two hemispheres and cerebral plasticity during cognitive development. Sann and Streri (2008a) investigated the inter-manual transfer of shape in twenty-four 2-day-old full-term newborns. After tactual habituation to a shape (prism or cylinder) in one hand, full-term newborns held the familiar shape longer in the opposite hand, and not the novel shape as usually expected in such procedure (Soroka, Corter, & Abramovitch, 1979). But in the same study, infants also exhibited inter-manual transfer of texture (smooth or granular), with a preference for the novel texture in the opposite hand. According to Sann and Streri (2008a), these discrepancies in performance between object properties indicate that the property of shape requires a more abstract and elaborate representation relative to texture. However, given the design of the study, it is not possible to draw definite conclusions about the type of shape information that was transferred: the entire shape of the object, edge information (round vs. angled), or other contrasts or differences. Regardless, these results provided evidence of intermanual transfer of shape in full-term newborns, confirming the hypothesis that the development of the corpus callosum at this stage is sufficient to permit some transfer of shape information between the two hands. Indeed, an fMRI study has demonstrated the essential contribution of posterior corpus callosum to the inter-hemispheric transfer of tactile information (Fabri et al., 2001, 2005).

Considering that the corpus callosum is less mature in preterm infants than full-term infants (Anderson, Laurent, Woodward, & Inder, 2006) and that very preterm birth (before 33 GW) may be associated with perinatal brain injury including the corpus callosum (Kontis et al., 2009), Lejeune et al. (in press) explored whether preterm infants are capable of inter-manual transfer of shape after the age of 33 GW. Using a classic tactile habituation-dishabituation procedure the authors predicted that after successive presentations of the same object, each preterm infant would show a decrease in holding time regardless of the hand tested or

object shape. Second, the hypothesis of discrimination in intermanual transfer would be confirmed by differential treatment of novel and familiar objects in the opposite hand, as demonstrated previously in full-term newborns (Sann & Streri, 2008a). Thus, discrimination would be considered to have occurred when mean holding time for novel and familiar objects in the opposite hand differed significantly. Firstly, the results confirmed the occurrence of haptic manual habituation for each hand and for each shape in preterm infants between 33 and 34+6 GW. The second and main result was that, after habituation to the shape of an object in one hand, preterm infants held the novel object longer in the opposite hand. These results revealed intermanual transfer of shape in preterm infants between 33 and 34+6 GW for the first time. Fabri et al. (2005) showed the essential contribution of posterior corpus callosum to the inter-hemispheric transfer of tactile information: its development thus seems to be sufficient to permit the transfer of some shape information between hands in preterm infants between 33 and 34+6 GW. However, preterm infants' holding time in the opposite hand increased with both novel and familiar objects, although this increase was significantly greater for the novel object than for the familiar one. While the increase in holding time was expected for the novel object, confirming the presence of discrimination, the increase in holding time for the familiar object was more surprising. This second result relates to the influence of changing hands on manual discrimination. This pattern of results could be due to two factors, one peripheral and one central. At a peripheral level, the tactile receptors were not the same as those stimulated during habituation and the information collected by the opposite hand had to be sent to the central nervous system by another pathway. In addition, given that the infant participants had underdeveloped muscle tone, the increase in holding time could also be caused by muscle fatigue in the habituated hand, compared to the unfatigued contralateral hand. Any form of tactile stimulation of the contralateral hand would induce some degree of recovery from habituation. At a central level, comparing objects information collected from the two hands may require more time than during an intramanual discrimination. This increase in holding time could reflect the time required to transfer information between the two hemispheres via the corpus callosum.

Finally, the direction of preference (preference for novelty) differed from that observed in 2-day-old full-term newborns with a similar procedure. Lejeune et al. (in press) propose two interpretations for this difference. First, because it is impossible to determine what type of shape information was transferred (entire shape, edge information or other contrasts or differences), one possible interpretation could be that full-term and preterm infants extract different types of shape information, leading to this discrepancy of preference. A second interpretation could be that experience prevails over maturation. Preterm infants were tested at a lower post-conceptional age (34+3 GW) than full-term newborns (40+2 GW) but at a higher postnatal age (30 days *vs.* 2 days). Consequently, the results could be explained by a greater tactile experience *ex utero* than for the full-term newborns. However, 2-month-old full-term infants have also been found to demonstrate a familiar preference (Streri, Lemoine, & Devouche, 2008) even though their postnatal age was higher than that of our preterm infants. A second factor that could explain this second discrepancy is the type of tactile experience which, combined with the length of experience, might influence the direction of preference. Preterm infants in their incubators receive a great deal of repetitive and stereotyped tactile stimulations (daily care, feeding, medical examinations, etc.). Hospitalized infants experience up to 14 painful procedures per day and up to 53 different

procedures during their first 15 days of life (Simons et al., 2003). Furthermore, Gimenez et al. (2008) showed that the maturation of brain tissue may be accelerated by factors associated with preterm birth, perhaps through the direct effects of the extrauterine environment. These particular tactile experiences could enhance the development of the intermanual transfer of information in preterm infants, even among younger infants who are at least 9 days old. In this case, according to the hypothesis proposed by Sann and Streri (2008a), preterm infants could have a more elaborate representation of shape than full-term newborns, leading to a preference for the novel shape in the opposite hand. However, these interpretations remain entirely speculative and post-hoc and require further investigation. More generally, the explanation of direction of preference is still debated in the infant studies literature, and seems to depend on several factors (e.g., Kerzerho, Streri, Gentaz, 2009; cf. Pascalis & De Haan, 2003). A preference indicates the presence of discrimination, whatever its direction, and suggests that the development of the corpus callosum is sufficient to permit some transfer of shape information between the two hands in preterm infants from 33 GW.

In conclusion, these results show that intermanual transfer of shape information is present at 33 GW in preterm infants. The occurrence of these intermanual abilities in full-term and preterm newborns suggests that some internal representation of a stimulus already has some level of abstraction. A second set of findings in favor of the existence of a higher-level internal representation stems from cross-modal studies on vision and touch in newborns.

3. Cross-modal transfer between touch and vision

In cognitive psychology, amodal perception is usually considered to be present at birth (see Streri, in press; Streri & Gentaz, 2009) as suggested by E. J. Gibson (1969). Beyond the details provided by individual sensory modalities, newborns are able to perceive a multimodal object as unified. However, the links between the haptic and the visual modalities are not fully established and will not be it until about the age of 15 years. Because newborns cannot engage in bimodal visual-haptic exploration of an object, a cross-modal transfer paradigm can be used to uncover the nature of these links and thereby evaluate young infants' ability to match the same object property captured by two modalities. However, cross-modal transfer tasks involve two successive phases (familiarization with an object in one modality and recognition test in a second modality). These tasks require cognitive processes (manual and visual information-processing capacities, memory load, etc.) that can weaken the links between sensory modalities and reveal failures in the establishment of amodal perception. Here we present a series of studies that illustrate these constraints.

3.1 Initial evidence in newborns

Newborns' visual abilities are weak. Nevertheless, numerous studies have revealed that babies can perceive speaking faces, photographs, objects, pictures, discriminate between large numbers, etc. (Coulon, Guellai and Streri, 2011; Féron, Gentaz, and Streri 2006; Guellai and Streri, 2011; Izard, Sann, Spelke and Streri, 2009; Meary, Kitromilides, Mazens, Graff and Gentaz, 2007; cf. Kellman and Arteberry, 1988, for a review). As discussed above, various studies have provided evidence that newborns are able to detect differences between shapes and textures with their hands (Streri et al. 2000; Molina and Jouen, 1998). All of these findings show that the prerequisites in both modalities are present to obtain cross-modal transfer between these senses.

Streri and Gentaz (2003; see also Streri and Gentaz, 2004) conducted an experiment on crossmodal transfer of shape information from the right hand to the eyes in 24 human newborns (mean age: 62 hours). They used an intersensory paired-preference procedure that included two phases: a haptic familiarization phase in which newborns were given an object to explore manually without seeing it, followed by a visual test phase in which infants were shown the familiar object paired with a novel one. Tactile objects were a small cylinder (10 mm in diameter) and a small prism (10 mm triangle base). Because the vision of newborns is immature and their visual acuity is weak, visual objects were the same 3D shapes, but much larger (45mm triangle base and 100mm in length for the prism and 30mm in diameter and 100mm in length for the cylinder). An experimental group (12 newborns) underwent the two phases successively (haptic then visual) whereas a baseline group (12 newborns) underwent only the visual test phase with the same objects as the experimental group but without haptic familiarization. Comparison of looking times between the two groups provided evidence of crossmodal recognition, with shapes explored by the hands of the experimental group recognized by the eyes. The newborns in the experimental group looked at the novel object for longer than the familiar one. In contrast, the newborns in the baseline group looked equally at both objects. Moreover, infants in the experimental group made more gaze shifts toward the novel object than the familiar object. In the baseline group this was not the case. Thus, this recognition in the experimental group stems from the haptic habituation phase. These results suggest that newborns recognized the familiar object through a visual comparison process as well as a comparison between the haptic and visual modalities. Moreover, the discrepancy between the sizes of the visual and tactile objects was apparently not relevant for crossmodal recognition. Shape alone seems to have been considered by newborns.

3.2 Limits of cross-modal shape transfer

Sann and Streri (2007) tested transfer from eyes to hand and from hand to eyes in order to ascertain whether this would demonstrate a complete primitive 'unity of the senses.' After haptic habituation to an object (cylinder or prism), the infants were shown the familiar and the novel shape in alternation. After visual habituation with either the cylinder or the prism, the familiar and the novel shape were put in the infant's right hand. The tactile objects were presented sequentially in an alternating manner. Again, visual recognition was observed following haptic habituation, but the reverse was not the case: no haptic recognition was found following visual habituation. Evidence of a visual recognition of shape also depended on the hand stimulated during the familiarization phase. No evidence of crossmodal recognition was found when the left hand was stimulated (Streri and Gentaz, 2004). Thus, cross-modal transfer seems not to be a general property of the newborn human; instead it is specific to certain parts of the body.

To understand this lack of bi-directional crossmodal transfer we must examine the differences between the ways that the two modalities process object shape. Vision processes shapes in a global manner, whereas touch processes information sequentially. Moreover, infants do not use efficient tactile exploratory procedures such as "*contour following*" to establish good representations of shapes (Lederman and Klatzky,, 1987). Earlier research performed on 2-month-old infants and using a bi-directional crossmodal shape transfer task (Streri 1987) revealed that two-month-old infants visually recognize an object that they have previously held, but do not manifest tactile recognition of an already-seen object. A

plausible explanation of these results on lack of bi-directional crossmodal transfer is that, as in newborns, the levels of representation attained through each modality are not sufficiently equivalent to exchange information between sensory modalities. This hypothesis seems to be validated by the fact that if a two-month-old baby is presented with degraded visual stimulation (a bi-dimensional sketch of an 3D object) in which volumetric and textural aspects are missing, leading to a blurred percept, tactile recognition is possible, which is not the case with a visual volumetric object (Streri and Molina 1993). This result means that the infant's hand cannot sufficiently explore the held object to obtain a clear representation of this object.

A number of studies have also revealed that over the course of development, the links between the haptic and the visual modalities are fragile, often not bi-directional, and representation of objects is never complete: this holds not only in infancy (Rose and Orlian 1991; Streri 2007; Streri and Pêcheux 1986), but in children (Gori *et al.* 2008) and adults (Kawashima *et al.* 2002). For example, in a behavioral and PET study on human adults, Kawashima *et al.* found that the human brain mechanisms underlying crossmodal discrimination of object size follow two different pathways depending on the temporal order in which the stimuli are presented. They found crossmodal information transfer to be less accurate with VT transfer than with TV transfer. In addition, more brain areas were activated during VT than during TV. Crossmodal transfer of information is rarely reversible, and is generally asymmetrical even when it is bi-directional. However, in adults, these asymmetries can be due to experience, learning and maturation and the characteristics of these asymmetries cannot be used directly to explain the brains of newborns. To better understand results from newborns and two-month-olds, a comparison with another property (texture) in bi-directional cross-modal transfer tasks was carried out.

3.3 Shape vs. texture

The comparison between shape and texture, amodal properties, should allow testing the hypothesis of amodal perception in newborns and to shed light on the processes involved in information-gathering by both sensory modalities. However, shape is best processed by vision, whereas texture is thought to be best detected by touch (see Bushnell and Boudreau 1998; Klatzky *et al.* 1987). According to Guest and Spence (2003), texture is "more ecologically suited" to touch than to vision. In many studies on shape (a macrogeometric property), transfer from haptics to vision has been found to be easier than transfer from vision to haptics in both children and adults (Connolly and Jones 1970; Jones and Connoly 1970; Juurmaa and Lehtinen-Railo 1988; Newham and MacKenzie 1993; cf. Hatwell 1994). In contrast, when the transfer concerns texture (a microgeometric property), for which touch is as efficient as (if not better than) vision, this asymmetry does not appear.

Sann and Streri (2007) undertook a comparison between shape and texture in bi-directional crossmodal transfer tasks. They sought to examine how information is gathered and processed by the visual and tactile modalities and, as a consequence, to shed light on the perceptual mechanisms of newborns. If the perceptual mechanisms involved in gathering information on object properties are equivalent in both modalities at birth, then reverse crossmodal transfer would be expected. In contrast, if the perceptual mechanisms differ in the two modalities, then non-reversible transfer should be found. Thirty-two newborns participated in two experiments (16 in crossmodal transfer from vision to touch, and 16 in the reverse transfer). The stimuli were one smooth cylinder and one granular cylinder (a

cylinder with pearls stuck on it). The results revealed crossmodal recognition of texture in both directions.

The findings suggest that for the property of texture, exchanges between the sensory modalities are bi-directional. Complete cross-modal transfer occurs with texture but not shape. However, this is true if only the object is volumetric and not flat, because newborns do not use the *"lateral motion"* exploratory procedure to detect differences between the textures of flat objects (Sann and Streri, 2008b). Cross-modal transfer between hands also reveals differences between shape and texture properties, and suggests that establishing representations of object shape is difficult for newborns. How should these results be explained? Human infants are particularly immature at birth, and brain maturation is protracted until adulthood. Almost no neuroimaging data is available because non-invasive techniques are difficult to apply in healthy infants. For example, newborns and young infants are often asleep (however, see Fransson et al., 2010 for a review on the functional architecture of the infant brain). Adult neuroimaging data, in contrast, offer some insights on how the brain processes cross-modal tasks.

3.4 Neuroimaging data

On the basis of these findings, two main questions emerge: First, why is bi-directional intermodal transfer observed for texture and not for shape? Second, how is haptic input translated into a visual format in newborns, i.e. by an organism that has never both seen and felt a 3D object?

On the basis of animal and human studies, Hsiao (2008) claimed that 3D shape processing involves the integration of both proprioceptive and cutaneous inputs from the hand. As the hand explores objects, different combinations of neurons are activated, and object recognition occurs as these 3D spatial views of the object are integrated. Cutaneous inputs related to 2D stimulus form and texture properties do not need such integration and may be processed differently than 3D shape in cortex. Cutaneous inputs stemming from the form and texture of 2D stimuli are processed in area 3b of SI cortex, whereas the sensitivity of neurons in area 2 to cutaneous inputs depends on hand conformation and its changes. Moreover, according to Hsiao (1998), the mechanisms underlying the early stages of 2D form processing are similar for vision and touch. Newborns' exploration of objects is very weak, and they may not be able to establish the 3D representations needed to perform tactile recognition after visual exploration of the object. Since texture and 2D form are similar in vision and touch, this data could explain why in 2-month-olds intermodal transfer from visual 2D object to haptic 3D objects is found, but not transfer from visual 3D objects to haptic 3D objects. Similarly, this data could explain the bi-directional transfer of texture between touch and vision observed in newborns.

Moreover, neuroimaging data from human adults suggests a functional separation in the cortical processing of micro- and macrogeometric cues (Roland et al. 1988). In this study, adults had to discriminate the length, shape, and roughness of objects with their right hand. Discrimination of object roughness activated lateral parietal opercular cortex significantly more than length or shape discrimination. Shape and length discrimination activated the anterior part of the intraparietal sulcus (IPA) more than roughness discrimination. More recently, Merabet *et al.* (2004) confirmed the existence of this functional separation and suggested that occipital (visual) cortex is functionally involved in tactile tasks requiring fine spatial judgments in normally sighted individuals. More specifically, a transient disruption

of visual cortical areas using rTMS (repetitive Transcranial Magnetic Stimulation) did not hinder texture judgments, but impaired subjects' ability to judge the distance between dots in a raised dot pattern. Conversely, transient disruption of somatosensory cortex impaired texture judgments, while interdot distance judgments remained intact. In short, detection of shape and texture properties requires different exploratory procedures, and takes place in two different pathways in adult brains.

A second important question is that of how haptic input is translated into a visual format given that the sensory impressions are so different and that newborns have no experience with tactile and visual object inputs. To date, there is substantial neuroimaging evidence from adults showing that vision and touch are intimately connected, although views on this interconnectedness vary (see Amedi *et al., 2001*; Sathian, 2005 for reviews). Cerebral cortical areas that were previously considered as exclusively visual, notably lateral occipital complex (LOC), are activated during haptic perception of shape (Lacey *et al.,* 2007). Crucially, LOC is activated in tactile recognition without mediation by visual recognition. Allen and Humphreys (2009) tested a patient with visual agnosia due to bilateral lesions of the ventral occipito-temporal cortex that had spared dorsal LOC. This patient's visual object recognition was impaired, but his tactile recognition was preserved. As a consequence, activation of dorsal LOC by tactile input can work directly through tactile inputs, and visual experience is unnecessary for LOC regions to be active in tactile object recognition. It seems plausible that visual imagery does not exist in newborns because they have little or no experience of the visual world of objects. It is possible that the LOC is activated in newborns brains when they explore an object haptically, and that the visual recognition of felt shape in cross-modal transfer tasks is not due to any visual imagery.

4. Conclusions

We recognize, understand, and interact with objects through both vision and touch (cf. Hatwell, Streri and Gentaz, 2003; Gentaz, 2009). In infancy, despite the various discrepancies between the haptic and visual modalities—such as asynchrony in the maturation and development of the different senses, distal vs. proximal inputs, and the contrast between the parallel character of vision and the sequential nature of the haptic modality—both systems detect regularities and irregularities when they are in contact with different objects, from birth onward. Conceivably, these two sensory systems may encode object properties such as shape and texture in similar ways. Behavioral evidence in newborns has revealed the involvement of different levels of abstraction in different types of transfer. Intermanual transfer of shape and texture seems to be bi-directional from birth. When newborns hold an object in one hand, left or right, its shape and texture are recognized by the other hand despite the immaturity of the corpus callosum. The maturity of the haptic sense is sufficient for gathering and processing information in a way that makes symmetrical correspondences between hands possible. This intermanual transfer may involve a low level of abstraction, because it does not require a change of representational format, since the steps involved, habituation and recognition, occur entirely within one modality—despite the fact that the transmission runs through the corpus callosum, which is immature at birth. Cross-modal transfers between vision and touch require a change of format and seem to be more difficult for newborns because of the higher level of abstraction involved.

Studies on crossmodal transfer tasks have revealed some links between the haptic and visual modalities at birth. Newborns are able to visually recognize a held object (Streri and

Gentaz 2003). This neonatal ability is independent of learning or the influence of the environment. However, by means of bi-directional crossmodal transfer tasks, Streri and colleagues have provided evidence on the perceptual mechanisms present at birth that constrain or limit the exchange of information between the sensory modalities. Newborns visually recognize the shape of a felt object, but are unable to recognize the shape of a seen object with their hands (Sann and Streri 2007). The link is obtained from the simplest information gathered, i.e. tactile information. Moreover, it is observed only with the newborn's right hand and not with the left (Streri and Gentaz 2004). A third striking result is that crossmodal transfer depends on object properties, being bidirectional with texture but not with shape (Sann and Streri 2007)—although this finding holds if, and only if, the felt textured object is volumetric, and not flat (Sann and Streri 2008b). For shape, just as for texture, the newborn's exploratory procedures are limited to the grasping reflex, which makes effective exploration of object properties impossible. All of these findings suggest that at birth, the links between the senses are specific to individual modalities and are not yet or entirely a general property of the brain.

Asymmetries in cross-modal transfer tasks continue to be found throughout the course of development. Several studies have also revealed that the links between the haptic and visual modalities are fragile, often not bi-directional, and representation of objects is never complete: this holds not only in infancy (Rose and Orlian 1991; Streri 2007; Streri and Pêcheux 1986b), but in children (Gori *et al.* 2008) and adults (Kawashima *et al.* 2002). Crossmodal transfer of information is rarely reversible, and is generally asymmetrical even when it is bi-directional (see Hatwell, Gentaz and Streri, 2003 for a review). The links between sensory modalities for object shape over the course of development appear to be flexible rather than immutable.

Why does cross-modal integration of spatial information develop in an asymmetrical manner? Several explanations may be offered. Sensory systems are not mature at birth, but become increasingly refined as children develop. Sometimes seen objects are observed to be well-recognized by touch, and more often, felt objects are well-recognized by vision. One possibility is that the sensory systems involved in spatial perception need to be continuously recalibrated during development, to take into account physical growth, such as changes in digit length (which affect haptic judgments), interocular separation, and eyeball length (affecting visual judgments). However, from birth, the links between the senses are more often effective when they begin with the hands rather than the eyes. Animal and adult neuroimaging studies also highlight asymmetries in cross-modal transfer tasks. Another suggestion would be that the links from eyes to hands are more effective for reaching and grasping objects than for cross-modal recognition. When we see an object, usually we take in information for some other purpose: e.g., transporting it to the mouth or somewhere else. In infancy, the hands are used as instruments to transport objects to the eyes or mouth, and the acquisition of this new ability develops to the detriment of the hands' perceptual function. Sensorimotor coordination triggered by the sight of an object is present from birth even though this ability mainly starts to be effective at about 4/5 months, at the beginning of prehension-vision. This ability may be better understood as the counterpart of cross-modal transfer from touch to vision. In both cases, perception and action are strongly linked. It is therefore important to note that sensory integration problems have often been observed in developmental disorders such as autism, dyslexia, and attention deficit disorder: understanding how incoming sensory information is transformed into outgoing motor commands is crucial for the diagnosis of such disorders (see Stein et al., 2009).

5. Acknowledgement

This work was supported by CNRS and by grants from the Agence Nationale de la Recherche (A.N.R.) and from the Institut Universitaire de France (I.U.F.).

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Somatosensory Stimulation in Functional Neuroimaging: A Review

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1. Introduction

Functional brain imaging of the somatosensory system has evolved over the past two decades and it has become an important tool in the preoperative planning in neurosurgery, in the monitoring in neurorehabilitation and for the understanding of motor recovery after brain damage for the planning and optimization of neurorehabilitation strategies.
Mapping of movement related cortical areas and areas that are related to body sensation was initially performed during neurosurgical procedures using direct cortical stimulation (Penfield, 1937). Several functional brain mapping techniques have subsequently evolved (Toga and Mazziotta, 2002). The era of functional brain imaging began in the 1980s with the implementation of the Positron Emission Tomography (PET) which provided a measure of the regional cerebral blood flow. Since the 1990s functional brain imaging is dominated by the rise of functional magnetic resonance imaging (fMRI) based on the blood oxygenation level dependant (BOLD) effect that was discovered 1990 by Ogawa et al. (Ogawa et al., 1990;Ogawa et al., 1992). Subsequently continuous evolution and progress of fMRI as well as its increasing popularity and spreading clinical use as a highly sensitive diagnostic neuroimaging instrument suitable for the assessment of a large variety of neurological and neurosurgical indications made fMRI to the leading functional neuroimaging modality. In this chapter we review somatosensory stimulation in PET and fMRI during the past decades, their advantages and disadvantages, optimal stimulation protocols as well as corresponding brain maps of different approaches of somatosensory stimulation in functional brain imaging and their clinical and neurophysilogical applications.

2. Positron Emission Tomography

In the 1980s, Positron Emission Tomography (PET) was used for the first time to detect focal neuronal activation within the primary somatosensory cortex of humans induced by

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cutaneous vibratory stimulation with a vibration frequency of 50 Hz and an amplitude of 1 mm (Fox et al., 1987). $H_2{}^{15}O$ labeled water was used as a blood flow tracer. The cutaneous surfaces of lips, fingers, and toes were tested. Intense and highly focal distinct responses within the primary somatosensory cortex with a medial-to-lateral homunculus were seen in each subject. The study demonstrated that eliciting regional cerebral blood flow responses within the somatosensory cortex by cutaneous vibration provides a safe, rapid, and reproducible tool for locating and assessing its functional status and for the localization of the central sulcus that is crucial in preoperative neurosurgical planning. The study has established normative values for future applications of the vibration paradigm in functional brain imaging.

In 1990, Tempel and Perlmutter compared the regional cerebral blood flow responses to vibrotactile stimulation in patients with predominantly unilateral idiopathic focal dystonia and normal subjects using $H_2{}^{15}O$ PET (Tempel and Perlmutter, 1990). The somatosensory stimulation led to consistently localized and robust peak response in the primary sensorimotor cortex, contralateral to hand vibration in normal subjects. The sensorimotor response in dystonic patients was also consistently localized to the same area, but significantly reduced in magnitude when vibrating the affected as well as the unaffected hand. Furthermore, vibration induced a dystonic cramp in the stimulated arm and hand in some patients, but in no normal subjects. This abnormal sensorimotor response had important implications for the understanding of the pathophysiology of idiopathic dystonia.

Two years later, Tempel and Perlmutter performed another significant $H_2{}^{15}O$ PET study with vibration-induced regional cerebral blood flow responses in healthy young and elder subjects in order to investigate whether vibration-induced regional cerebral blood flow responses change with increasing age (Tempel and Perlmutter, 1992). Left and right hand vibration led to consistent responses within the contralateral primary sensorimotor cortex and the supplementary motor area with no changes in the physiologically aging brain.

In the same year, Seitz and Roland were able to demonstrate with a vibratory stimulus to the right hand palm of healthy volunteers and $H_2{}^{15}O$ PET that activation of some cerebral structures is accompanied by deactivations of corresponding other structures elsewhere in the brain (Seitz and Roland, 1992). Increases in the regional cerebral blood flow were localized in the left primary somatosensory area, the left secondary somatosensory area, the left retroinsular field, the left anterior parietal cortex, the left primary motor area, and the left supplementary motor area. The decreases occurred bilaterally within the superior parietal cortex, paralimbic association areas, and the left globus pallidus. The mean global cerebral blood flow did not change compared with rest. The decreases in cerebral oxidative metabolism were interpreted as regional depressions of synaptic activity.

In an $H_2{}^{15}O$ PET study by Drevets et al., changes in the human primary and secondary somatosensory cortices during the period when somatosensory stimuli were expected were investigated (Drevets et al., 1995): In anticipation of either focal or innocuous touching, or localized, painful shocks, the blood flow decreased in the parts of the primary somatosensory cortex located outside the representation of the skin locus of the expected stimulus. Specifically, attending to an impending stimulus to the fingers produced a significant decrease in blood flow in the somatosensory zones for the face, whereas attending to stimulation of the toe produced decreases in the zones for the fingers and face. Decreases were more prominent in the side ipsilateral to the location of the expected stimulus. No significant changes in the blood flow occurred in the region of the cortex representing the skin locus of the expected stimulation. These results were concurrent with a

model of spatial attention in which potential signal enhancement may rely on generalized suppression of background activity.

In the same year, Ibanez et al. demonstrated in a PET study that there is no evidence that the primary motor and supplementary motor area are involved in the generation of the P22 and N30 components of somatosensory evoked potentials (SSEPs) caused by electrical stimulation of the median nerve at the wrist (Ibanez et al., 1995). PET was performed in normal subjects to study the cerebral areas activated by median nerve electrical stimulation at frequencies of up to 20 Hz. Stimulation evoked a single focus of activation in the primary somatosensory area. An increase of the regional cerebral blood flow in this area was linearly correlated with stimulus frequencies of up to 4 Hz and then reached a plateau. The supplementary motor area was not significantly activated by stimulation at any of the frequencies tested. In contrast to the primary somatosensory area, the supplementary motor area showed no trend toward a correlation between the regional cerebral blood flow changes and the stimulus repetition rate. These results suggested that a contribution of the primary motor cortex and the supplementary motor area to the generation of the P22 and N30 components of SSEPs is unlikely.

$H_2{}^{15}O$ PET studies with different application forms and intensities of innocuous and noxious thermal stimuli were performed by Casey et al (Casey et al., 1994;Casey et al., 1996) to identify the forebrain and brain stem structures that are active during the perception of acute heat pain in humans. Healthy subjects received repetitive noxious (50°C) and innocuous (40°C) heat pulses with duration of five seconds to the forearm and each subject rated the subjective intensity of each stimulation series. Significant regional cerebral blood flow with a maximum at 50°C stimuli was found in the thalamus, the cingulate cortex, the secondary and primary somatosensory cortex, the insula, the medial dorsal midbrain and the cerebellar vermis. In the second study noxious and innocuous heat and cold thermal stimuli to the non-dominant arm of healthy subjects were applied.

A detailed analysis of somatosensory representations within the parietal postcentral gyral and the lateral sulcal-opercular cortex in a $H_2{}^{15}O$ PET study was performed by Burton et al. (Burton et al., 1997). To investigate the issue of possible multiple activation foci in these regions and possible differences due to stimulating skin directly or through an imposed tool, changes in the regional cerebral blood flow during passive tactile stimulation of one or two fingertips were studied. Restrained fingers were rubbed with embossed gratings using a rotating drum stimulator. For different scans, gratings touched the skin directly for optimal stimulation of cutaneous receptors (skin mode stimulation) or indirectly by using an imposed guitar plectrum snugly fitted to the same fingers (tool mode stimulation). The latter was expected to better stimulate deep receptors better. The subjects were asked to estimate the roughness after each scan. Direct skin contact activated statistically validated foci in both hemispheres, on the contralateral side these foci occurred in the anterior and posterior limbs of the postcentral gyrus and on the ipsilateral side only in the posterior limb. Tool mode stimulation activated one contralateral focus that was in the posterior limb of the postcentral gyrus. These results suggested at least two maps for distal fingertips in the primary somatosensory area with the anterior and posterior foci corresponding, respectively, to activations in the Brodmann area 3b and the junction between the Brodmann areas 1 and 2. In the contralateral secondary somatosensory area, skin mode stimulation activated a peak that was anterior and medial to a focus associated with tool mode stimulation. The magnitude of the PET counts contralateral to stimulation was higher in the anterior primary and secondary somatosensory regions during initial scans, but reversed to

more activation in the posterior primary somatosensory region during later scans. These short-term practice effects suggested changes in neural activity with stimulus novelty.

Another method for selectively activating the cortical projections of deep receptors for proprioceptive perception in a study with $H_2{}^{15}O$ PET was presented by Mima et al. (Mima et al., 1999). Functional brain maps during active and passive finger movements driven by a servo-motor were compared. The authors were able to selectively activate proprioception with a minimal contribution from the epicritic sensation with a newly developed device. Proprioception was represented only within the contralateral primary and secondary somatosensory areas, whereas active movements were cortically represented within the contralateral primary sensorimotor cortex, the premotor cortex, the supplementary motor area, the bilateral secondary somatosensory areas, the basal ganglia and the ipsilateral cerebellum. In this study, differential brain maps for cortical representations of different components of the sensorimotor system were displayed for the first time in the field of functional neuroimaging.

Xu et al. elucidated the functional localization and somatotopic organization of pain perception in the human cerebral cortex with PET during selective painful stimulation. Response to painful stimuli to the hand and foot were elicited using a special CO_2 laser, which selectively activates nociceptive receptors (Xu et al., 1997). Multiple brain areas, including the bilateral secondary somatosensory areas and both insulas, the frontal lobe, and thalamus contralateral to the stimulus side were found to be involved in the response to painful stimulation. While the data indicate that the bilateral secondary somatosensory area plays an important role in pain perception, they also indicate that there is no pain-related somatotopic organization in the human secondary somatosensory cortex or insula. Pain processing during three levels of noxious stimulation that produced differential patterns of central activity was investigated by Derbyshire et al. (Derbyshire et al., 1997).

Bittar et al. investigated presurgical mapping of the primary somatosensory cortex compared with intraoperative cortical stimulation with $H_2{}^{15}O$ PET (Bittar et al., 1999a;Bittar et al., 1999b). PET scanning with vibrotactile stimulation of the face, the hands or the feet to localize the primary somatosensory area before surgical resection of the mass lesions or epileptogenic foci affecting the central area was performed in patients with brain tumor. With the aid of image-guided surgical systems, the location of significant activation foci on the PET scanning were compared with those of positive intraoperative cortical stimulation performed at craniotomy. In 95%, the PET activation foci were spatially concordant with the intraoperative cortical stimulation. Intraoperative cortical stimulation was positive in 40% of the stimulation sites where the PET did not result in statistically significant activation. According to these results, it was concluded that PET is an accurate method for mapping the primary somatosensory area prior to surgery.

Boecker et al. investigated the functional anatomy of somatosensory processing in two clinical conditions characterized by basal ganglia dysfunction in Parkinson's and Huntington's disease (Boecker et al., 1999) in a $H_2{}^{15}O$ PET study. Continuous unilateral high-frequency vibratory stimulation was applied to the immobilized metacarpal joint of the index finger. In the control subjects, the activation pattern was lateralized to the side opposite to the stimulus presentation, including the primary and secondary somatosensory areas, as well as subcortical (globus pallidus, ventrolateral thalamus) regions. Inter-group comparisons of the vibration-induced changes of the regional cerebral blood flow between patients and control subjects revealed differences in central somatosensory processing. In Parkinson's disease, decreased activation was found in the contralateral sensorimotor cortex,

the lateral premotor cortex, the contralateral secondary somatosensory area, the contralateral posterior cingulate cortex, the bilateral prefrontal cortex (Brodmann area 10) and in the contralateral basal ganglia. In Huntington's disease, decreased activation was detected contralateral in the secondary somatosensory area, the parietal Brodmann areas 39 and 40, the lingual gyrus, the bilateral prefrontal cortex (Brodmann areas 8, 9, 10 and 44), the primary somatosensory area, and the contralateral basal ganglia. In both clinical diseases, relative enhanced activation of the ipsilateral somatosensory cortical areas, notably the caudal primary and secondary somatosensory regions as well as the insular cortex, could also be detected. The data show that Parkinson's and Huntington's disease, beyond well-established deficits in the central motor control, are characterized by abnormal cortical and subcortical activation on passive somatosensory stimulation. Furthermore, the finding that the activation increases in the ipsilateral somatosensory cortical areas may be interpreted as an indication of either altered central focusing and gating of the somatosensory impulses, or enhanced compensatory recruitment of the somatosensory areas.

A ^{18}F-fluorodeoxyglucose PET study with somatosensory stimulation in patients suffering from spinal cord injuries was performed by Roelcke et al. (Roelcke et al., 1997a) to assess the effect of a transverse spinal cord lesion on cerebral energy metabolism in view of sensorimotor reorganisation. PET was used to study resting cerebral glucose metabolism in patients with complete paraplegia or tetraplegia after spinal cord injury compared with healthy subjects. The global absolute glucose metabolism rate was lower in the spinal cord injury patients than in the healthy subjects. A relatively increased glucose metabolism was discovered particularly in the supplementary motor area, the anterior cingulate, and the putamen. A relatively reduced glucose metabolism was found in patients with spinal cord injury was found in the midbrain, the cerebellar hemispheres, and the temporal cortex. It was concluded that cerebral deafferentation due to reduction or loss of sensorimotor function results in the low level of an absolute global glucose metabolism rate found in patients with spinal cord injury. Relatively increased glucose metabolism in brain regions involved in attention and initiation of movement may be related to secondary disinhibition of these regions.

PET studies using noxious electrical stimuli to the median nerve were also performed on patients in persistent vegetative state (actually referred to as unresponsive wakefulness syndrome) to assess cortical pain processing (Kassubek et al., 2003;Laureys et al., 2002). Even though cortical metabolism (in FDG-PET) was decreased up to 40% of normal values, both studies showed reliable activations in residual parts of the pain processing networks in $H_2{}^{15}O$ PET. Compared to age-matched controls, noxious stimuli activated the primary somatosensory cortex, contralateral thalamus and midbrain, but failed to activate higher-order associative cortices (secondary somatosensory, bilateral posterior parietal, premotor, polysensory superior temporal and prefrontal cortices). These findings help to understand cortical processing after severe brain injury, however, but they can neither prove nor disprove awareness of pain or any other stimulus in this patient group.

3. Functional Magnetic Resonance Imaging

Somatosensory stimuli were applied in many functional magnetic resonance imaging (fMRI) studies. Especially light stimulation using air puffs (Stippich et al., 1999b) or other tactile stimuli (Hodge et al., 1998;Moore et al., 2000;Rausch et al., 1998;Servos et al., 1998), scratching of the hand palm (Hoeller et al., 2002), vibration (Gelnar et al., 1998b;Golaszewski

et al., 2002;Golaszewski et al., 2006;Golaszewski et al., 2002;Hodge et al., 1998), electrical stimulation (Arthurs et al., 2000;Backes et al., 2000;Korvenoja et al., 1999;Krause et al., 2001;Kurth et al., 1998;Takanashi et al., 2001), noxious stimuli (Apkarian et al., 2000;Peyron et al., 2000), and proprioception induced by passive joint movement (Rausch et al., 1998) were used. Usually, the primary somatosensory cortex in the postcentral gyrus and the secondary somatosensory cortex in the parietal operculum, insula, and more posterior ventral parietal areas are activated. A clear somatotopic organization in the primary somatosensory cortex could be demonstrated, whereas this somatotopic organization could not be clearly shown in the secondary somatosensory area (Disbrow et al., 2000;Gelnar et al., 1998b;Hodge et al., 1998;Krause et al., 2001;Kurth et al., 1998;Servos et al., 1998). An evident somatotopy also in the secondary somatosensory area was demonstrated in a study by Gelnar et al. (Gelnar et al., 1998c). A vibratory stimulus was applied to an individual digit tip (digit 1, 2, or 5) on the right hand of healthy adults which led to a BOLD response in cortical regions located on the upper bank of the Sylvian fissure, the insula, and the posterior parietal cortices. Multiple digit representations were observed in the primary somatosensory cortex, corresponding to the four anatomic subdivisions areas 3a, 3b, 1, and 2. There was no simple medial to lateral somatotopic representation in individual fMRI maps but a clear spatial distance between digit 1 and digit 5 was seen on the cortex in both the primary and secondary somatosensory regions. Ruben et al. was able to demonstrate a somatotopic organization of the secondary somatosensory area with electrical stimulation of the right hallux, the index and the fifth finger (Ruben et al., 2001). They were not able to observe separate representations of digit 2 and 5 in the secondary somatosensory area, but a somatotopic representation between the fingers and the hallux could be detected bilaterally within the secondary somatosensory region. Kurth et al. demonstrated a somatotopy in the primary somatosensory cortex by using electrical finger stimulation (Kurth et al., 2000). Functional MRI detected separate representations for all five fingers in the primary somatosensory cortex. Responses were located in the posterior wall of the deep central sulcus (corresponding to Brodmann area 3b), and the anterior (Brodmann area 1) or the posterior crown of the postcentral gyrus (Brodmann area 2) with rare activations in Brodmann area 3a and 4. In Brodmann area 3b, a regular somatotopic mediolateral digit arrangement for fingers 5 to 1 with a mean Euclidean distance of 16 mm between fingers 1 and 5 was found. In contrast, Brodmann area 1 and 2 showed a greater number of adjacent activation foci with a significantly greater overlap and partly even reversed ordering of the neighboring fingers. This paradigm can be used to localize the central sulcus preoperatively (Kurth et al., 1998) and it is applicable even in patients with severe hemiparesis without severe hemianesthesia.

In many studies investigating the primary somatosensory cortex, only a contralateral BOLD response could be elicited, whereas the secondary somatosensory areas were activated bilaterally (Backes et al., 2000;Disbrow et al., 2001;Korvenoja et al., 1999). It is still uncertain, what stimulus leads to the most robust BOLD response within the somatosensory cortex. There is evidence that pain stimuli are less reliable than vibrotactile or electrical stimuli for evoking primary somatosensory activation (Backes et al., 2000;Disbrow et al., 2001;Korvenoja et al., 1999;Peyron et al., 2000). Activation magnitude in the primary somatosensory cortex depends on the intensity of stimulation (Arthurs et al., 2000;Krause et al., 2001), the size of the stimulated body surface (Apkarian et al., 2000;Peyron et al., 2000), and the rate of stimulation (Apkarian et al., 2000;Peyron et al., 2000;Takanashi et al., 2001). Nelson et al. demonstrated an increasing stimulus-response relationship between the

amplitude of vibrotactile stimuli delivered to the volar surface of the right index finger and BOLD activity in the primary somatosensory area that persisted during an attention-demanding tactile tracking task (Nelson et al., 2004). The secondary somatosensory cortex did not show any clear relationship with the vibration amplitude, but was more often activated during the attention demanding tracking task compared with passive vibration. Responses in secondary areas seem to be less influenced by these variables, but are probably more dependant of the level of attention directed to the stimulus (Apkarian et al., 2000;Backes et al., 2000;Peyron et al., 2000;Takanashi et al., 2001) and on whether stimulation is delivered uni- or bilaterally (Apkarian et al., 2000;Backes et al., 2000;Disbrow et al., 2001;Peyron et al., 2000;Takanashi et al., 2001). Regarding attentional phenomena interfering with somatosensory processing, tactile processing while varying the focus of attention was studied. Activations were contrasted between attend and ignore conditions, both of which employed identical stimulation characteristics and an active task. Random effects analysis revealed significant attention effects in the primary somatosensory area. The blood oxygenation level-dependent response was greater for attended than for ignored stimuli. Modulations were also found in the secondary somatosensory cortex and the middle temporal gyrus. These findings suggest that the stimulus processing at the level of the primary representations in the primary somatosensory area is modulated by attention (Sterr et al., 2007).

Somatosensory stimulation has the advantage of not requiring movement which may cause artifacts. With somatosensory stimulation (repetitive brushing of the hand palm) in brain tumor patients, a lower incidence of severe movement artifacts was found compared to an active motor paradigm (finger-to-thumb-tapping), however, the motor paradigm elicited a significantly higher percentage of signal increases. (Apkarian et al., 2000;Backes et al., 2000;Disbrow et al., 2001;Hoeller et al., 2002;Peyron et al., 2000;Takanashi et al., 2001). Several fMRI studies discovered a similar functional localisation comparing somatosensory stimulation and active motor paradigms (Golaszewski et al., 2002;Golaszewski et al., 2006;Golaszewski et al., 2002;Lee et al., 1998). Lee et al. (1998) demonstrated in an fMRI study similar results with active and passive activation tasks by comparing palm-finger brushing with sponge-squeezing and active finger movements according to their functional localisation. The sensorimotor and somatosensory BOLD responses were located to a large extent in the postcentral gyrus, and their spatial locations were not significantly different. Golaszewski et al. showed largely similar functional maps by active finger-to-thumb tapping and vibration of the hand palm (Golaszewski et al., 2002a;Golaszewski et al., 2002b). In patients who are physically unable to perform active finger-to-thumb-tapping, hand-squeezing or fist clenching as sensorimotor activation tasks the vibration of the hand palm can be regarded as a proper paradigm in presurgical fMRI mapping of the sensorimotor hand area.

In an fMRI study with a piezoelectric vibration device Francis et al. found a frequency dependence of the primary and secondary somatosensory area (Francis et al., 2000). With both frequencies applied to the index finger during the same scanning session, an increase in the vibration frequency from 30 to 80 Hz showed a significant increase of the BOLD response within the secondary somatosensory area and the posterior insula, while the number of pixels activated in the primary somatosensory area declined.

Moreover, functional imaging studies are important for the monitoring of rehabilitation and the understanding of motor recovery after cortical strokes (Cramer et al., 2000). Functional MRI was used to compare sensory and motor maps obtained in normal controls with

functional maps from two patients with good recovery six months after a cortical stroke. Cortical map reorganization along the detected infarct rim might be an important contributor to recovery of motor and sensory function after stroke. Moreover, functional imaging studies with somatosensory stimulation are also important for the monitoring of the rehabilitation after extremity transplantations (Piza, 2000). A close relationship between the intensity of phantom limb pain in amputees and the amount of reorganization of the somatosensory cortex was reported in fMRI studies (Flor et al., 2001;Hamzei et al., 2001;Koppelstaetter et al., 2007).

Functional MRI was also used to investigate brain activations underlying menthol-induced cold allodynia (Seifert and Maihöfner, 2007). Healthy volunteers were investigated using a block-design fMRI approach. Brain activity was measured during application of innocuous cold stimuli (5°C above cold pain threshold) and noxious cold stimuli (5°C below cold pain threshold) to the skin of the forearm using a peltier-driven thermostimulator. The stimuli were adjusted to the individual cold pain threshold. Cold allodynia was induced by topical menthol and cortical activations were measured during previously innocuous cold stimulation (5°C) that was at this situation perceived as painful. On a numeric rating scale for pain (0-10) innocuous cold, cold pain and cold allodynia were rated. Sensory and affective components of allodynia and cold pain were equal in the McGill pain questionnaire (Roelcke et al., 1997b). All tested conditions (innocuous cold, noxious cold and cold allodynia) led to significant activations of the bilateral insular cortices, the bilateral frontal cortices and the anterior cingulate cortex. When compared with innocuous cold, noxious cold led to significantly more activations of the posterior insula and to less activations of the ipsilateral insular cortex.

Significantly increased activations in bilateral dorsolateral prefrontal cortices and brainstem (ipsilateral parabrachial nucleus) were found during cold allodynia when compared with equally intense cold pain conditions. Cold allodynia led to significantly more activations of the bilateral anterior insula, whereas the activation of the contralateral posterior insula was equal. It was concluded that cold allodynia activates a network similar to that of normal cold pain, but additionally recruits bilateral dorsolateral prefrontal cortex and the midbrain, suggesting that these brain areas are involved in central nociceptive sensitization processes.

In the authors' facility, somatosensory stimulation is also used in the clinical routine to assess patients with chronic disorders of consciousness (unresponsive wakefulness syndrome, minimally conscious state) in fMRI (unpublished data). In a series of 22 consecutive patients with chronic disorders of consciousness, seven patients showed reliable response in typical brain areas using a pneumatic activation device (Figure 3, 4, 6). The above-mentioned somatosensory assessment combined with cognitive testing in functional neuroimaging is routinely acquired in patients with chronic disorders of consciousness for the planning of neurorehabilitation and estimation of prognosis.

4. Current devices for somatosensory stimulation

Next to the classical electrical nerve stimulation, vibrotactile stimulation has become very common in functional brain imaging. Vibrotactile stimulation has several advantages over electrical stimulation. First, the stimuli are not painful and therefore a certain stimulus can be presented over a long time period. This is often necessary to obtain a stable cortical

response. Second, by selecting the site and frequency of the stimulus, the different receptor types (cutaneous mechanoreceptors, proprioceptors, thermo receptors) can be specifically excited and their functional integration at the cortical level can be studied. Third, the stimulus response underlies adaptation which can be used to analyze the somatosensory information processing, its influence to cortical structures, and the modulation by other brain regions (Giabbiconi et al., 2007). On the other hand, a cortical response may be affected adversely by somatosensory adaptation phenomena. This has to be considered when designing a specific stimulation protocol.

In clinical routine, the vibrotactile sense is assessed by brushing on a certain body region (Frey hair) or by using a tuning fork. These manual stimulations were used in the earlier studies of somatotopic mapping (Polonara et al., 1999). However, for more complex stimulation designs, it is more convenient to use quantitative testing equipment. Within the past ten years, various prototypes of stimulation devices have been tested for somatotopic mapping. Among these devices, pneumatically driven air bags were introduced (Gelnar et al., 1998b;Golaszewski et al., 2002a;Stippich et al., 1999b), as well as piezodisks (Harrington et al., 2000b;Maldjian et al., 1999b), cable driven rotating masses (Golaszewski et al., 2002b) and even coil designs using the static magnetic field of an MR scanner (Graham et al., 2001). As most of these devices were used in fMRI-paradigms, the interactions between MRI and the certain stimulation device must be considered. In this chapter, we first focus on the MR compatibility and the MR safety and subsequently give an overview on the different types of devices.

4.1 MR compatibility and MR safety

According to the safety guidelines by General Electric (GE) Medical Systems (GE-Medical Systems, 1997), a device is considered to be MR save, if it can be demonstrated that it does not lead to an increased safety risk towards the patient and the staff, when the device is introduced or used in the MR scanner room. For a certain device to be labeled MR compatible, it has to be demonstrated that it performs in its intended function without performance degradation. For the MR compatibility, effects on the devices and effects on the imaging have to be differentiated (Chinzei et al., 1999). These devices are influenced by induced static magnetization as well as torque and translational forces (see Figure 1). Both effects influence the performance of devices containing ferromagnetic materials. Standard springs made of metal do not function as expected. According to the guidelines mentioned above, devices containing ferromagnetic materials should be operated behind the 20-mT line. In this zone, the effects on the devices are irrelevant. However, the risk that such a device is pulled towards the scanner bore (projectile effect) still is high. For safety reasons, not permanently fixed electromagnetic devices should be operated only behind the 5-mT line. The imaging quality is degraded by field inhomogenities and RF (radio frequency) emission (see Figure 1). Static field inhomogenities come from the ferromagnetic materials contained in the devices, but in most cases the image quality can be restored after shimming the magnet. RF is typically produced by pulsed electronics and the digital hardware emitted by the cables of the device. As MRI is highly sensitive to RF noise, such devices have to be operated outside the MR scanner room. On the other hand, small amplitude electromagnetic fields up to some hundred Hz, as produced by some vibrotactile stimulation devices, only showed minor effects on imaging.

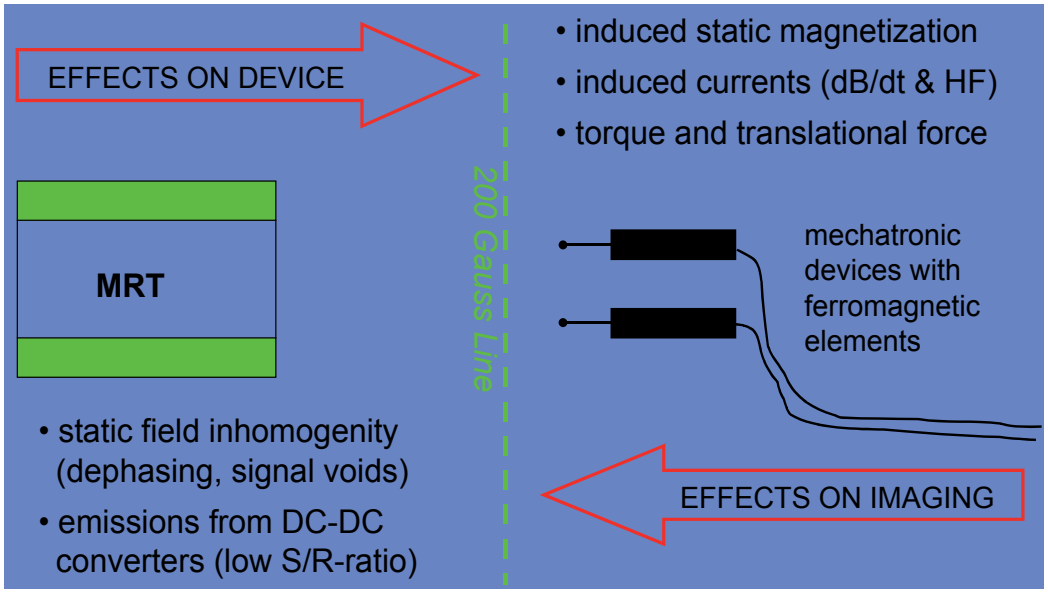

Fig. 1. Overview on MR-compatibility (GE Medical Systems. MR safety and MR compatibility. http://www.ge.com/medical/mr/iomri/safety.htm; 1997).

4.2 Principles and technical designs

For somatosensory mapping, well-controlled and reproducible stimuli are required. Principally, this can be achieved by using pneumatic, piezoceramic and electromechanical devices. Concerning MR compatibility and safety, pneumatic devices are the best choice. The hardware of a pneumatic stimulation device typically consists of a pressure source, a valve for converting the air stream into the desired pressure oscillations and a vibrotactile display to deliver the stimuli to the skin surface. As vibrotactile probe, a latex balloon, a pickup with an integrated rubber membrane (Briggs et al., 2004), or an injector element to produce air puffs was described (Huang and Sereno, 2007). The pressure oscillations are transmitted to the vibrotactile display via long plastic tubes so that all other components of the device can be operated outside of the MR scanner room. However, pneumatic systems have the disadvantage of limited vibration frequencies. Due to the mechanical damping of the pressure oscillations in the plastic tubes the stimulus frequency is limited to about 30 Hz. Higher stimulation frequencies can be achieved by using nonmagnetic valves, suited for operation inside the MR scanner room. Multi-channel stimulation designs are feasible with multiple valves and pickups (Wienbruch et al., 2006). Pneumatic devices have shown to cause somatosensory brain activation, but failed to additionally activate motor cortical areas in somatosensory paradigms.

Piezoceramic devices provide a wide range of frequencies, but only have small displacement amplitudes, which limits their application to the skin receptors. Stimulation frequencies up to 1000 Hz can be obtained. The vibration amplitude achieved by these devices is limited to some hundred μm and even for this relative high operation voltages (up to 200 Volts) are necessary. Because these devices are nonmagnetic, they can be operated inside the MR scanner room. Basically, bar- and disk-like actuators as well as piezomotors are available. The bar- and the disk-like actuators directly convert the

electrical signal into bending motions (Piezomechanik Gmbh, 2002). For stimulation applications, these devices can either be held between the fingertips (Harrington et al., 2000b) or touched by the fingertips (Maldjian et al., 1999b). Functional MRI with piezoceramic vibrators showed brain activation within the somatosensory cortex but not within motor cortical areas (Harrington et al., 2000a). It is important to avoid loops in the cables, because this may lead to currents from the RF- and gradient coils. These may cause heat and even fire hazard. There is less data with piezomotors. Basically, piezomotors are well suited for construction of MR compatible robotic stimulation devices, for example to induce passive limb motions. For their operation, high driving frequencies (> 40 kHz) are necessary, therefore effects on the MR imaging have to be considered, when using such devices (Chinzei et al., 1999).

Electromagnetic stimulation devices may be classified into three groups depending on the vicinity to the MR scanner at their operation. In the first group, there is common standard equipment containing motors or actuators with pulsed electronics. Such equipment causes RF-emission and therefore has to be operated outside the shielded area of the MR scanner room. For vibrotactile stimulation long cables are needed to transmit the stimulus from the outside to the subject. Cable driven rotating eccentric masses are an example for such type of stimulation device. A frequency range between 1–130 Hz and displacement amplitudes up to 4 mm can be reached. In an fMRI study implementing this technique, BOLD responses within the somatosensory as well as the motor cortical areas could be demonstrated (Golaszewski et al., 2002b). The second group consists of non-switched moving magnet, and moving coil devices, which can be operated inside the scanner behind the 20-mT line (Golaszewski et al., 2006;Gallasch et al., 2006). With this technique, the parameters of a stimulus (amplitude, frequency, waveform) can be selected within a wide range, which is advantageous for basic investigations. On the other hand, these devices also need some mechanics for translating the stimulus to the subject under investigation. When these mechanic parts are made of metallic materials, the device will also influence the imaging and itself be influenced by the magnetic field. In the third group of somatosensory stimulation, the devices comprise coil actuators utilizing the static magnetic field of the MR scanner. By applying currents to a coil, Lorenz forces generate vibration (Graham et al., 2001), as well as load and movement (Riener et al., 2005). This type of actuator-stimulator is suited for the operation inside the MR scanner, but it is important to be careful in order to prevent heating of the coils due to induced currents.

4.3 Device for stimulation of the foot sole

A recently developed stimulator for the foot sole is described here as an example for an electromechanical device to be operated inside the scanner room (Gallasch et al., 2006). It consists of two moving magnet actuators rigidly connected on a platform by two non-magnetic adjustable stands (see Figure 2). To preserve MR compatibility (operation behind the 20-mT line) the foot sole is contacted via long indentors (30 cm). Further, to avoid effects on imaging, the actuators are powered by non-pulsed servo amplifiers. All other components containing pulsed electronics (digital controller and PC) are operated outside the MR scanner room. For stimulation of slowly and rapid adapting mechanoreceptors a mixed open and closed loop control scheme was implemented. Slowly adapting receptors respond to nearly static loading (0 - 1 Hz). This is achieved by

an open loop programming of the contact force (0- 20 N). Rapid adapting receptors respond to vibration, which is achieved by the closed loop control scheme. With the implemented controller arbitrary vibration waveforms within the frequency band of 20 to 100 Hz can be generated. A computer is used for stimulus synthesis, sequencing of the stimuli and synchronization with the MR scans. The first MRI studies with this device show that specially designed electromagnetic devices are well suited for somatotopic mapping.

Fig. 2. Example of an electromagnetic vibrotactile stimulation system (Gallasch et al., 2006).

4.4 Perspectives

Recently, various types of stimulation devices were evaluated for somatotopic mapping. Although substantial physiological results have been obtained with some of these devices, this technology still needs to be improved. Clinicians expect equipment for quantitative sensory testing, which is safe and simple to use. Other systems will be needed for stimulation of the entire spectrum of somatosensory fibers. These are the large diameter A-beta fibers mediating touch and vibration, the smaller A-delta fibers mediating cool sensation and the first signs of pain, and the small diameter C-fibers mediating sensation of heat and pain. We therefore suggest a bimodal stimulation system to deliver with both vibrotactile and temperature stimuli. For the sole of the foot, such a system may have an arrangement as shown in Figure 2 with additional Peltier elements on the tip of the indentors, however with pneumatic actuators instead of the electromagnetic ones. For hand and fingers wearable stimulation devices are prospective, e.g. pneumatic finger or toe cuffs (Gallasch et al., 2010;Figure 3, 4, 5) or some kind of stimulation glove with pressurized sections at the fingertips including flat shaped heat pipes for quick cooling and warming. For the usage as a clinical tool, further multicenter studies with standardized stimulation protocols have to be carried out. Such studies are necessary to establish stable stimulus-response relationships independent of a certain scanner type.

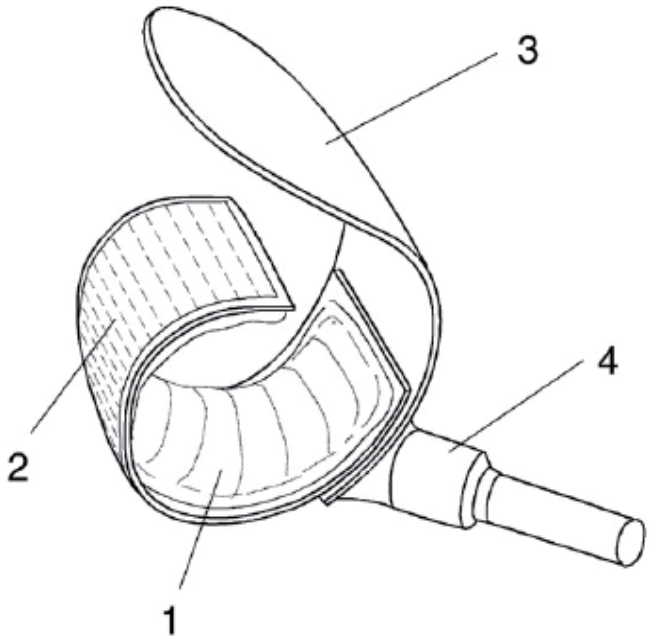

Fig. 3. Drawing of finger cuff with inflatable air bladder (1), flexible Welco strips (2, 3) and air connector (4)

Fig. 4. Stimulator system consisting of twin finger cuff, valve box and microprocessor unit.

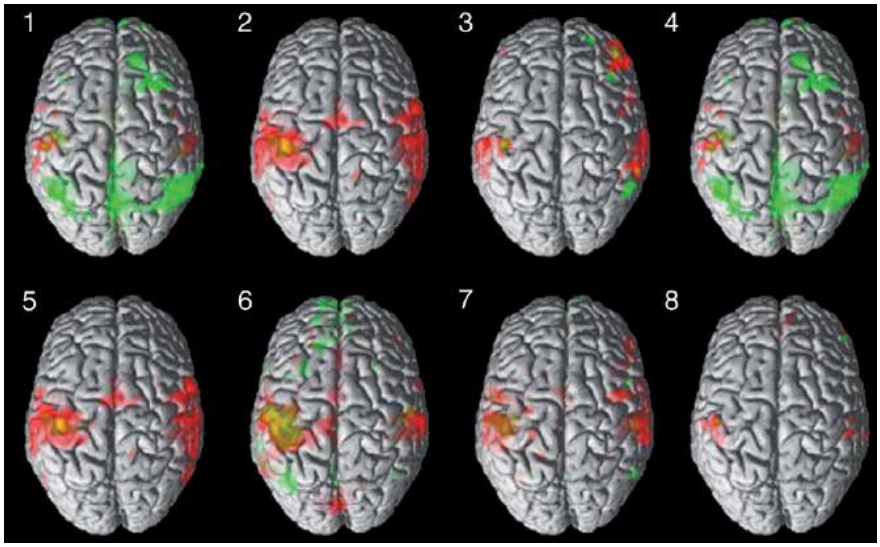

Fig. 5. Single subject analysis: fMRI maps of eight single subjects (1-8) applying pneumatic cuff somatosensory finger stimulation with fixed (fixed simulation FS, green) and random (random stimulation RS, red) presentation of vibrotactile stimuli with a mean frequency of 4 Hz over all blocks. Yellow spots represent activation overlap between FS and RS maps

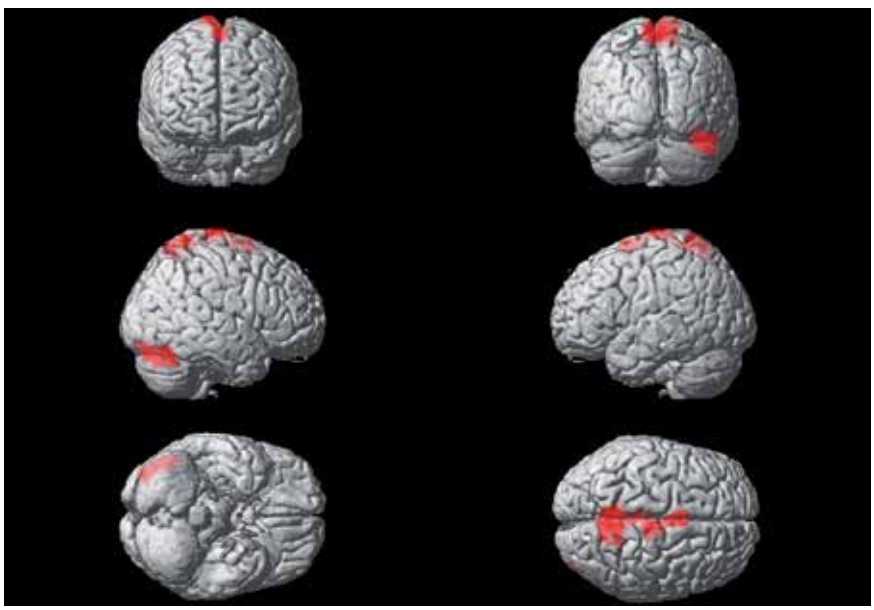

Fig. 6. Patient in vegetative state 14 days post hypoxia. Vibration stimulation with a moving magnet actuator system delivered to the sole of the left foot (Gallasch et al., 2006;Golaszewski et al., 2006) elicits brain activation contra- and ipsilaterally within the primary and secondary sensorimotor cortex and especially within the premotor cortex, the center for predefined movement loops, and the supplementary motor area that represents the superior center for motor planning. Functional brain mapping in this patient proved an intact somatosensory channel to the sensorimotor system for a targeted therapeutic approach in neurorehabilitation.

5. Perspective of the application of somatosensory stimulation within the clinical environment

In the studies of Gelnar, Harrington, and Stippich et al., brain activation within the postcentral gyrus and superior and inferior parietal lobule have been found (Gelnar et al., 1998a;Harrington et al., 2000a;Stippich et al., 1999a). Furthermore, brain activation within Brodmann area 3a was detected due to somatosensory stimulation (Geyer et al., 1999;Geyer et al., 2000;Kurth et al., 2000), which can be explained by the fact that Brodmann area 3a receives input from the deep and from the proprioceptive receptors (Ibanez et al., 1989;Iwamura et al., 1993;Kaas et al., 1979;Maldjian et al., 1999a;Recanzone et al., 1992;Tharin and Golby, 2007). BOLD response in the primary motor cortex due to vibrotactile stimulation is an important finding, because the stimulation does not require the collaboration of the subject under examination. In an fMRI study with mechanical vibration, BOLD response in primary sensorimotor cortex was found in all of the investigations (Golaszewski et al., 2002a,b). Motor cortical activation caused by vibration, is presumably based on the co-stimulation of cutaneous mechanoreceptors and muscle spindles that requires sufficient displacement amplitudes and vibration frequencies. Similar to the finger-to-thumb-tapping paradigm, vibration led to contralateral brain activity in postcentral gyrus in ten out of ten subjects. Vibration stimulation failed to consistently activate supplementary motor area and anterior cingular cortex since it represents a passive paradigm that does not involve motor cortical areas for planning of volitional movements. Vibratory stimuli are transmitted via the large afferents of the dorsal column to the thalamus and are relayed there to the brain cortex. This “information” originates from the extra personnel space that might be an explanation, why Brodmann area 9 in superior frontal gyrus responds with activation in some cases.

In functional brain imaging with certain somatosensory stimulation protocols the whole sensorimotor cortex can be addressed for functional brain mapping that offers the possibility of several clinical applications for somatosensory paradigms in Neuroradiology. Somatosensory paradigms can be used for preoperative functional brain mapping of the sensorimotor cortex in patients with perirolandic lesions. Further applications include the investigation of brain plasticity and reorganization (Pons et al., 1992) and investigation of patients in comatose and vegetative state (Kampfl et al., 1998).

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18

Neuroimaging Studies in Carbon Monoxide Intoxication

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1. Introduction

CO is a tasteless, odorless and colorless gas. The existence of endogenous CO in the human body arises from heme catabolism (Meredith and Vale 1988; Ernst and Zibrak 1998) and oxidation of organic molecules (Marilena 1997). Endogenous CO acts as a neurotransmitter for long-term potentiation, consequently playing a key role in memory and learning (Marilena 1997). It also plays a role in modulating inflammation, apoptosis, cell proliferation, mitochondrial biogenesis (Weaver 2009) and vascular relaxation (Marilena 1997).

Exogenous sources of CO intoxication include smoking, forest fires, pollutants, and improper usage of heaters or furnaces (Weaver 2009; Kumar, Prakash et al. 2010). CO intoxication usually indicates exposure to exogenous sources and is considered one of the most common causes of poisoning worldwide (Prockop and Chichkova 2007; Weaver 2009), with 1000 deaths annually in Britain (Meredith and Vale 1988), and 4000-6000 deaths annually in the United States (Tibbles and Perrotta 1994; Ernst and Zibrak 1998; Weaver 1999). In Asia, the exact epidemiology remains unclear. In Japan, Hong Kong and Taiwan, a common CO etiology of intoxication is charcoal burning suicide (Lee, Chan et al. 2002). In Japan, poisoning by charcoal burning is the most lethal form of suicide and is a highly prevalent method among men aged 25-64 years of age (Kamizato, Yoshitome et al. 2009), in contrast to a high rate of drug poisoning as a method of suicide in women. In Hong Kong, the risk factors of suicide by charcoal burning are male and living alone with financial stress (Lee and Leung 2009). In Taiwan, charcoal burning was not a common method of suicide before 1998, with a rate of only 0.14 per 10^5 people per year (Lin and Lu 2008). With the dissemination of media and the internet, the rate of charcoal burning suicides dramatically increased by 40-fold, reaching a rate of 5.38 per 10^5 people per year in 2005 (Lin and Lu 2008).

2. Mechanisms of CO intoxication

2.1 Tissue hypoxia

CO competes with oxygen in binding with hemoglobin to form carboxyhemoglobin. The affinity between CO and hemoglobin is 200 times higher than that of oxygen (Ernst and Zibrak 1998; Piantadosi 2002; Weaver 2009). The production of carboxyhemoglobin shifts the oxygen-hemoglobin curve to the left and dissociates oxygen from hemoglobin (Ernst and Zibrak 1998). These reactions consequently reduce oxygen delivery to tissues and result in a hypoxic microenvironment.

2.2 Oxidative stress

In brief, CO intoxication leads to oxidative stress through the following mechanisms:

1. CO increases cytosolic heme levels leading to increased heme oxygenase-1 protein, causing intracellular oxidative stress and direct cellular injury (Ernst and Zibrak 1998; Weaver 2009).
2. CO binds to cytochrome c oxidase and impairs mitochondrial function. Cytochrome c oxidase is one of the mitochondrial complexes involved in electric chain transport and is essential for energy production. Binding of CO to cytochrome c oxidase can lead to activation of hypoxia-inducible factor 1α or production of reactive oxygen species with direct cellular injury. Related downstream reactions include apoptosis, lipid peroxidation, lymphocyte proliferation, inflammation and necrosis (Weaver 2009).
3. CO binds to platelet heme protein and induces biogenesis of nitric oxide peroxynitrite, consequently leading to enhanced adhesion of neutrophils to the vascular lining, neutrophil aggregation and release of myeloperoxidase. All of these reactions not only trigger inflammatory processes but also produce more reactive oxygen species (Ernst and Zibrak 1998; Weaver 2009).

2.3 Reoxygenation injury

H_2O_2 production has been noted to increase extensively in brain tissues during reoxygenation after CO intoxication (Zhang and Piantadosi 1992). Salicylate hydroxylation products and 2,3- and 2,5-dihydroxybenzoic acid are also significantly increased during reoxygenation. During this period, CO still binds to cytochrome c oxidase and inhibits the mitochondrial electron transport chain. If the reaction exists in iron-rich regions such as the basal ganglia, it causes persistent acidosis and active iron, which can further damage cells (Zhang and Piantadosi 1992).

2.4 Mechanisms related to central nervous system (CNS) injury

2.4.1 Acute CNS injury

In animal models, an initial cerebral blood flow increment after CO exposure is thought to maintain the baseline energy state (MacMillan 1975). A change of blood flow depends on both the reaction of the cerebrovasculature and cardiac function in CO intoxication. In either failure of cerebrovasculature dilatation or impairment of cardiac pumping function, there is no compensatory blood supply increase in the status of acute carboxyhemoglobin elevation and oxyhemoglobin reduction. (Raub and Benignus 2002). After initially compensated hyperperfusion, focal hypoperfusion has been noted in several studies (Choi, Lee et al. 1992; Choi and Lee 1993) which might be related to clinical manifestation (Sesay, Bidabe et al. 1996). Hypoperfusion over the basal ganglion (Sesay, Bidabe et al. 1996; Kao, Hung et al.

1998), cerebral cortical (Choi, Lee et al. 1992; Kao, Hung et al. 1998), and white matter (WM) (Sesay, Bidabe et al. 1996) areas have been noticed. Cerebral WM and the globus pallidum (GPi) were noted to have relatively low cerebral blood flow after acute CO intoxication in one animal study (Okeda, Matsuo et al. 1987).
Hypoxia in the CNS induces decreased adenosine-5'-triphosphate, influx of Ca2+ and Na+, release of glutamate, noradrenaline and acetylcholine and causes cell swelling and death (Weinachter, Blavet et al. 1990; Kluge 1991). Increased glutamate with both neuronal necrosis and apoptosis was noted immediately after CO intoxication in one animal study (Piantadosi, Zhang et al. 1997). However, how hypoxia affects the CNS in the acute stage of CO intoxication has not been well established (Piantadosi, Zhang et al. 1997; Gorman, Drewry et al. 2003). Aside from changes of cerebral blood flow and hypoxia, increasing intracranial pressure and brain tissue necrosis have been noted in animals and humans after acute CO intoxication (Jiang and Tyssebotn 1997; Piantadosi, Zhang et al. 1997; Uemura, Harada et al. 2001; Lo, Chen et al. 2007).

2.4.2 Chronic CNS injury

The pathogenesis of delayed CNS injury in CO intoxication is complicated. Hypoperfusion (Sesay, Bidabe et al. 1996; Watanabe, Nohara et al. 2002; Chu, Jung et al. 2004) and hypoxia (Opeskin and Drummer 1994) still play an important role. Demyelination (Murata, Kimura et al. 2001; Kamijo, Soma et al. 2007; Ide and Kamijo 2008), cytotoxic edema (Kim, Chang et al. 2003; Chu, Jung et al. 2004; Kwon, Chung et al. 2004), hemorrhage (Ramsey 2001) and infarction (Schwartz, Hennerici et al. 1985; Sung, Yu et al. 2010) have also been associated with delayed neurological deficits. Hypoperfusion and cytotoxic edema in delayed CNS injury have been noted in WM areas and the cerebral cortex (Chu, Jung et al. 2004), and ischemia and necrosis have been noted in the globus pallidus (Chang, Han et al. 1992). Although demyelination and axonal damage might co-exist in CO intoxication, demyelination more than axonal damage is suggested in the literature (Chang, Han et al. 1992; Murata, Kimura et al. 2001; Kamijo, Soma et al. 2007; Ide and Kamijo 2008).

2.5 Other mechanisms

CO also inhibits a number of proteins essential for cells. Myoglobin in the heart and skeletal muscle systems, neuroglobin in the brain, cytochrome P450 (Weiner 1986), dopamine and tryptophan oxygenase (Raub and Benignus 2002) have all been reported to be affected. A high CO concentration transforms xanthine dehydrogenase to xanthine oxidase and produces more free radicals in tissues (Piantadosi, Tatro et al. 1995). Inhibiting the normal function of these intracellular proteins causes further damage or systemic injury in CO intoxication.

3. Clinical manifestation

3.1 The diagnosis of CO intoxication

The diagnosis of CO intoxication is based on the clinical history of exposure or elevated carboxyhemoglobin level (> 10%) (Handa and Tai 2005; Chang, Lee et al. 2009). There is currently no definition of clinical staging in CO intoxication in the literature, although the pathophysiology follows that of hypoxic–ischemic encephalopathy (Gutierrez, Rovira et al.).

3.2 Symptoms in the acute phase

Tightness across the forehead, headache, throbbing in the temples, nausea, vomiting, dimness of vision, dizziness, general weakness, syncope, convulsion, and coma are commonly found in patients with CO exposure within one day (Choi 2001). Cortical blindness with initially normal visual evoked potentials has also been reported in a case (Katafuchi, Nishimi et al. 1985). The pathogenesis contributing to the clinical manifestations includes change of blood flow (Penney 1990; Lo, Chen et al. 2007), hypoxia (Lo, Chen et al. 2007), and neurochemistry abnormalities (Penney 1990).

3.3 Symptoms in the late phase

Following initial neurological deficits after acute CO intoxication, some patients experience progressive neurological deterioration, while others nearly complete recovery of symptoms. Some patients have a delayed onset of neurological deficits after an initial symptom-free period (Lee and Marsden 1994). The latter is often termed as delayed neuropsychiatric sequela in CO intoxication. The lucid interval after acute CO poisoning, on average, is around 20 days, varying from one to 240 days (Choi 1983; Lee and Marsden 1994; Ernst and Zibrak 1998; Pavese, Napolitano et al. 1999; Hsiao, Kuo et al. 2004), with a prevalence of 0.2-40% (Hsiao, Kuo et al. 2004; Otubo, Shirakawa et al. 2007). Delayed neuropsychiatric sequelae include parkinsonism (Lee and Marsden 1994), chorea (Park and Choi 2004), akinetic mutism (Lee and Marsden 1994), increased irritability, verbal aggressiveness, violence, impulsiveness (Meredith and Vale 1988), mood disorders (Weaver 2009), dementia (Meredith and Vale 1988; Ernst and Zibrak 1998; Weaver 2009), psychosis (Ernst and Zibrak 1998), sleep disturbances (Weaver 2009), cortical blindness (Quattrocolo, Leotta et al. 1987; Senol, Yildiz et al. 2009) and incontinence (Ernst and Zibrak 1998).

The cognitive deficits are often very diverse (Hurley, Hopkins et al. 2001; Parkinson, Hopkins et al. 2002; Raub and Benignus 2002) including impairment in verbal or visual episodic memory, language, visuospatial ability, executive function and calculation (Chang, Chang et al. 2010). No specific neuropsychiatric battery has been designed for the cognitive deficits in CO intoxication. For general cognitive performance, most researchers apply the mini-mental state examination (Folstein, Folstein et al. 1975) or Wechsler Adult Intelligence Scale (Dorken and Greenbloom 1953) for evaluation. Chang *et al*. (Chang, Lee et al. 2009) used the clinical dementia rating scale (Morris 1997) to evaluate the functional capability of these patients since they may have physical disabilities. Tasks that have been used for evaluation are as follows: Alzheimer's Disease Assessment Scale-Cognitive word-recognition test (Rosen, Mohs et al. 1984) for verbal episodic memory; recollection of Rey-Osterrieth complex figures for visuospatial ability (Boone 2000); Boston naming test for language ability (Boone 2000); digit span, digit-symbol, digit backward (Cronholm and Viding 1956; Sherman and Blatt 1968; Rudel and Denckla 1974); Trail Making Part A and Part B, block design, and design fluency (Gieseking, Lubin et al. 1956; Arbuthnott and Frank 2000) for executive function; and neuropsychiatric inventory for behavioral changes (Cummings, Mega et al. 1994).

4. Neuroimaging study results of CO intoxication by anatomical classification

4.1 Basal ganglion lesions emphasized on the globus pallidus (GP)

The basal ganglion includes the putamen, caudate nucleus, and GP. GP lesions are often considered as pathognomonic signs for patients with CO intoxication, however the

prevalence differs among studies (Silver, Cross et al. 1996; O'Donnell, Buxton et al. 2000). One study showed 63% of abnormal lesions in the GP with 26% in the rest of the basal ganglia (O'Donnell, Buxton et al. 2000). Another study with 73 patients revealed only one patient (1.4%) with basal ganglia lesions scanned two weeks after CO poisoning (Parkinson, Hopkins et al. 2002).

4.1.1 Imaging features suggesting edematous change in the acute phase

Low density GP lesions, commonly seen in computed tomography (CT), are considered as characteristic findings in patients with CO intoxication (Kanaya, Imaizumi et al. 1992; Gotoh, Kuyama et al. 1993; Uchino, Hasuo et al. 1994; Chu, Jung et al. 2004; Kinoshita, Sugihara et al. 2005; Hopkins, Fearing et al. 2006). Low density lesions of the putamen and caudate nucleus, in contrast, have only been reported in one case (Ferrier, Wallace et al. 1994). The nature of GP lesions has been studied further by diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping (Chu, Jung et al. 2004; Kinoshita, Sugihara et al. 2005). One case report interpreted low ADC values and high intensity GP lesions on DWI as restriction of water diffusion (i.e. cytotoxic edema) (Kinoshita, Sugihara et al. 2005). Vasogenic edema can also be visualized on ADC and DWI as increased signal intensity lesions (Chalela, Wolf et al. 2001). The high signal on DWI is due to the T2 shine-through effect.

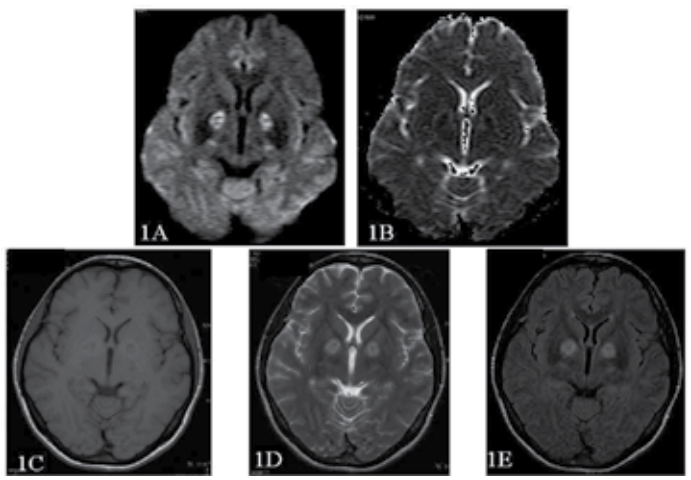

Fig. 1. Magnetic resonance imaging study in the acute stage of carbon monoxide intoxication.

Six days after CO intoxication, a 42-year-old woman with a globus pallidus interna lesion with hyperintensity in diffusion weighted imaging (1A), hypointensity in apparent diffusion coefficient (1B), hypointensity in T1 weighted image (WI) (1C), hyperintensity in T2WI (1D), and hyperintensity in fluid-attenuated inversion recovery (1E).

4.1.2 Imaging features suggesting necrosis

Imaging studies showing cavity-changes by T1 or T2WI often suggest necrosis of the GP (Mendelsohn and Hertzanu 1983; Pulst, Walshe et al. 1983; Ko, Ahn et al. 2004). Autopsies of patients with CO intoxication have confirmed the histology of necrosis and/or neuronal degeneration of the GP (Jones, Lagasse et al. 1994). The pathogenesis of necrosis is believed to be due to edema-induced ischemia or hemorrhage transformation (Chang, Han et al.

1992). Follow-up GP images often show volume shrinkage (Vieregge, Klostermann et al. 1989; Kanaya, Imaizumi et al. 1992).

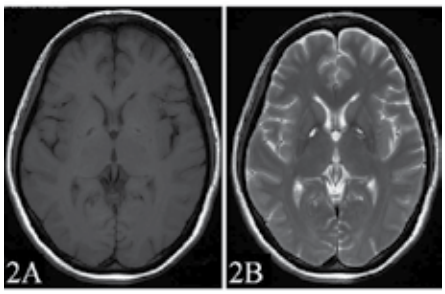

Fig. 2. Magnetic resonance imaging in the delayed stage of carbon monoxide intoxication.

Four years after CO intoxication, a 41-year-old woman with a globus pallidus lesion showed hypointensity in T1 weighted image (T1WI) (2A) and cavity changes with hyperintensity in T2WI (2B).

4.1.3 Imaging features suggesting hemorrhage

Hemorrhage of the GP is seen both in the acute and delayed stages after CO intoxication (Silverman, Brenner et al. 1993; Bianco and Floris 1996), while only one case report has demonstrated putaminal hemorrhage by CT (Schils, Cabay et al. 1999). Temporal sequences in conventional MRI have been noted to be similar to intracranial hemorrhage (Bradley 1993). Hemorrhage may occur within days after CO intoxication with high signal intensity in T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) (Bianco and Floris 1996). High T1WI and low T2WI signals have been observed up to two months after intoxication, suggesting delayed hemorrhage (Yoshii, Kozuma et al. 1998). One case report described abnormal signals in the GP, with shorter T1 characteristics and longer T2 characteristics suggesting a prior focal hemorrhage three years after CO intoxication (Silverman, Brenner et al. 1993). In one study, widespread multiple pin point hemorrhages in the thalamus and GP were found in 40% of postpartum autopsies (Mehta, Niyogi et al. 2001).

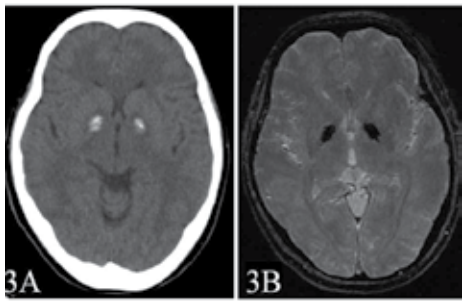

Fig. 3. Computed tomography and gradient echo T2WI after carbon monoxide intoxication.

Two days after CO intoxication, a 57-year-old woman with hemorrhage in the globus pallidus showed hyperdensity in CT (3A) and a follow-up one month later with low signal intensity on gradient echo (3B).

4.1.4 Imaging features suggesting calcification

Calcification of the GP has also been reported in the literature (Illum 1980; Lugaresi, Montagna et al. 1990; Adam, Baulac et al. 2008). The clinical presentations included acute neurological deficits with loss of initiative and slowness of thinking and acting (Adam, Baulac et al. 2008), and delayed neurological deficits with personality changes and akinesia (Lugaresi, Montagna et al. 1990). However one case was free of any neurological sequelae after 48 years of follow-up (Illum 1980).

4.1.5 Functional imaging features suggesting hypometabolism

[^{18}F]fluorodeoxyglucose (FDG) PET has been used to evaluate glucose metabolism activity. Decreased metabolism in the basal ganglion and frontal lobe has been frequently reported (Tengvar, Johansson et al. 2004; Hon, Yeung et al. 2006). The largest series on PET and CO intoxication with basal ganglion lesions included eight patients with their behavioral and MRI patterns (Laplane, Levasseur et al. 1989). Seven patients revealed hypometabolism of the prefrontal cortex in relation to other parts of the brain, leading to a concept of prefrontal-pallidum circuit dysfunction. A functional study using [^{18}F] F-DOPA showed presynaptic dopaminergic deficits in one case with parkinsonism symptoms after CO intoxication (Rissanen, Paavilainen et al. 2010). In this case, normal uptake of [^{11}C] raclopride implicated normal postsynaptic dopaminergic function (Rissanen, Paavilainen et al. 2010).

Single photon emission computed tomography (SPECT) provides perfusion patterns of GM and the basal ganglion (Chang, Liu et al. 2008) with tracers such as 99mTc-ethylcysteinate dimer and 99mTc-Hexamethylpropyleneamine oxime. (99mTc-ECD) brain SPECT is considered to be more sensitive than brain CT for the early detection of hypoperfusion status (Wu, Changlai et al. 2003). In the acute stage, 50% to 85% of the patients with CO intoxication have been reported to have basal ganglion hypoperfusion (Wu, Changlai et al. 2003; Pach, Hubalewska et al. 2004).

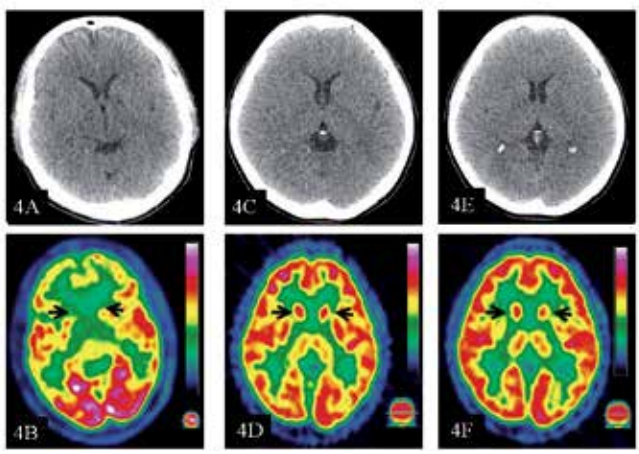

Fig. 4. [^{18}F]fluorodeoxyglucose positron emission tomography (PET) of two patients after CO poisoning.

Two and a half months after CO intoxication, a 33-year-old patient's CT showed low intensity of the globus pallidus (4A) on brain computed tomography (CT) while PET revealed a remarkably reduced uptake of FDG in bilateral striatum (arrows) and thalamus (4B). Five months after CO intoxication, another 36-year-old patient's CT showed no

obvious lesions (4C, 4E) while PET revealed normal FDG uptake in bilateral striatum (4D, 4F arrows) and normal thalamic uptake.

4.1.6 Imaging features suggesting pallidoreticular damage

In CO intoxication, pallidoreticular damage specifically targeting the fiber tract along the pallidum and substantia nigra pars reticulata was first described by Auer and Benveniste (Auer and Benveniste 1996). One case report revealed cytotoxic edema of bilateral GP with concurrent substantia nigra pars reticulata involvement in a patient scanned 12 days after CO intoxication (Kinoshita, Sugihara et al. 2005). Two case reports revealed pallidoreticular distribution after one year showing hyperintensities on T2WI and hypointensities on T1WI (Kawanami, Kato et al. 1998; Gandini, Prockop et al. 2002). The authors suggested that these two iron rich regions had selective tissue vulnerability due to the high affinity of CO to heme molecules (Kawanami, Kato et al. 1998; Gandini, Prockop et al. 2002; Kinoshita, Sugihara et al. 2005).

4.2 WM lesions

An increasing number of studies have established that WM lesions are the most common findings in CO intoxication patients, either in the acute phase or in those with delayed neuropsychiatric sequelae (Miura, Mitomo et al. 1985; Chang, Han et al. 1992; Choi, Kim et al. 1993; Lee and Marsden 1994). The largest study included 129 patients, and 33% of them had WM lesions on brain CT (Choi, Kim et al. 1993). In patients with improvements of neurological deficits, resolution of WM changes have also been noted (Klostermann, Vieregge et al. 1993; Matsushita, Takahashi et al. 1996; Pavese, Napolitano et al. 1999). Lesions of the WM area are believed to be associated with clinical outcomes (Miura, Mitomo et al. 1985; Vieregge, Klostermann et al. 1989; Choi, Kim et al. 1993).

4.2.1 Imaging features suggesting WM cytotoxic/vasogenic edema

In a pathological series, cytotoxic and vasogenic edema after CO intoxication were often mixed within three months, and the presence of cytotoxic edema was often noted to be in the acute phase (Ginsberg, Myers et al. 1974; Ginsberg 1985; Thom, Bhopale et al. 2004). The presence of cytotoxic edema lesions can be detected as early as the first day of CO intoxication (Sener 2003) or during the delayed phase (Murata, Kimura et al. 2001; Kim, Chang et al. 2003; Chu, Jung et al. 2004). Imaging features suggesting cytotoxic edema of the

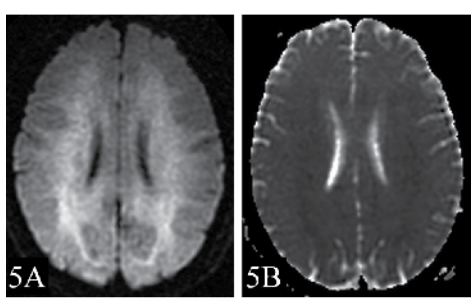

Fig. 5. Diffusion weighted image (5A) and apparent diffusion coefficient (5B) in one case presenting as delayed neuropsychiatric sequelae after carbon monoxide intoxication.

WM area show low ADC values with high DWI intensities, while vasogenic edema shows high signals on both sequences.
One month after CO intoxication, a 41-year-old woman with white matter hyperintensity in DWI (6A) and iso- to low-signal intensity in ADC (6B) indicating cytotoxic edema.

4.2.2 Imaging features suggesting WM demyelination or axonopathy

The prevalence of imaging features suggesting WM demyelination or axonopathy range from 12% to 100% in CO intoxication (Chang, Han et al. 1992; Parkinson, Hopkins et al. 2002). The largest MRI study focusing on WM included 73 patients scanned on day 1, 2 weeks and 6 months after CO intoxication (Parkinson, Hopkins et al. 2002). Semiquantitative scores were rated on bilateral periventricular and centrum semiovale areas (Parkinson, Hopkins et al. 2002). Twelve percent of the patients had WM hyperintensities on T2WI on day 1 (Parkinson, Hopkins et al. 2002) with significantly more periventricular, but not centrum semiovale distributions as compared with age-matched controls. The WM lesions in the CO group did not change from day 1 to 6 months follow-up, however the hyperintensities in the centrum semiovale were related to worse cognitive performance. The study revealed no correlation between WM hyperintensities and carboxyhemoglobin level, or duration of CO exposure at any of the three scan times (Parkinson, Hopkins et al. 2002).
Hyperintensities in T2WI and fluid-attenuated inversion recovery (FLAIR) and hypointensities in T1WI often suggest WM demyelination or axonopathy (Chang, Han et al. 1992; Pavese, Napolitano et al. 1999; Parkinson, Hopkins et al. 2002). From a pathological perspective, myelin damage is constant and can vary from discrete perivascular lesions to extensive periventricular demyelination and/or axonal destruction (Funata, Okeda et al. 1982; Prockop and Chichkova 2007). An autopsy study after CO intoxication showed that diffuse WM hyperintensities reflected apoptosis of oligodendrocytes (Akaiwa, Hozumi et al. 2002). Another autopsy study of brains three days after CO intoxication revealed a normal cortex and injured WM with disrupted myelin and pyknotic oligodendroglia, whilst the axons, astrocytes and capillaries were normal (Foncin and Le Beau 1978).

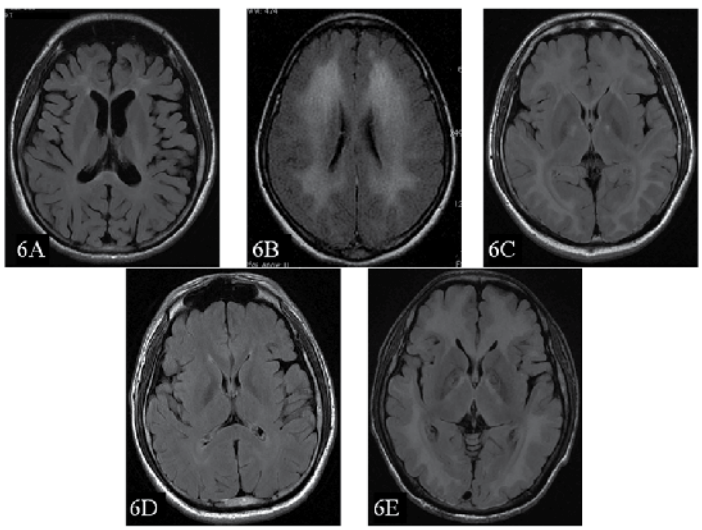

Fig. 6. A wide spectrum of white matter hyperintensities in fluid-attenuated inversion recovery after carbon monoxide intoxication with cognitive deficits.

Focal white matter hyperintensities (WMHs) over bilateral frontal horns in a 29-year-old woman, two years after CO exposure (6A). Diffuse and confluent WMHs in a 42-year-old woman, one and a half months after CO exposure (6B). Prominent subcortical U fiber hyperintensity with globus pallidus hyperintensity in a 35-year-old man, one and a half months after CO exposure (6C). A 31-year-old woman presented in a confused state without obvious WMHs four days after CO intoxication (6D). Extensive subcortical WMHs with globus pallidus hypointensity two years later (6E).

A study by Weaver (Weaver, Valentine et al. 2007) suggested that cognitive sequelae at six weeks benefited from hyperbaric oxygen (HBO) in patients aged 36 years and older, or who were exposed to CO for a duration of 24 hours or more. Two studies explored changes of fractional anisotropy (FA) in CO intoxication after HBO. Both studies revealed lower FA values in the patient group compared to that of controls three months after HBO (Lo, Chen et al. 2007; Chang, Lee et al. 2009). The mini-mental state examination scores completely recovered after three months of follow-up in all evaluated patients in one study (Lo, Chen et al. 2007), while another study showed that HBO treatment may not reverse the damage caused by CO intoxication (Chang, Lee et al. 2009). A longitudinal study used diffusion tensor imaging (DTI) and compared the changes of diffusion measurements in CO intoxication patients including mean diffusivity, axial diffusivity and radial diffusivity with follow-up scans three months and 10 months later. Extensive changes found in the FA maps at both three and 10 months in the CO group were attributed to initial increments of radial diffusivities, while a decrement of axial diffusivities were found at 10 months follow-up (Chang, Chang et al. 2010). The study suggested that changes in diffusion parameters might reflect WM demyelination at three months followed by subsequent axonopathy.

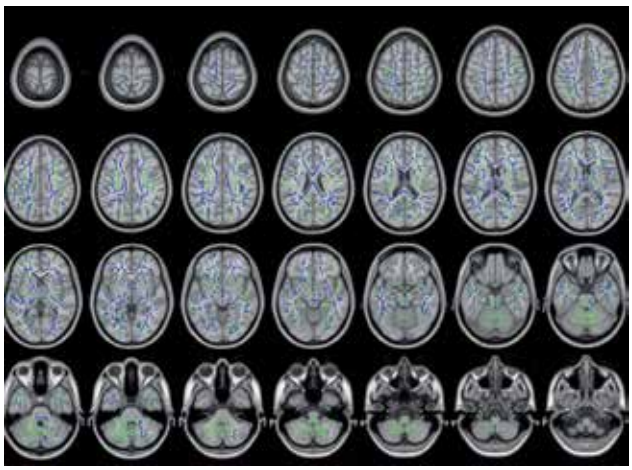

Fig. 7. An example of Tract Based Spatial Statistics with decreased Fractional Anisotropy (FA) (blue) overlaid on the mean FA skeleton (green) in a sample of carbon monoxide intoxication (n=30) as compared with age-matched controls. Diffuse white matter damage was detected including the subcortical areas, brain stem and cerebellum.

White matter insults after CO intoxication lead to transient or permanent injuries, which consequently lead to decreased WM volumes. Diffusion indices including mean diffusivity, axial diffusivity and radial diffusivity reflect WM injuries earlier than volume reduction, while the major regions of WM atrophy in one study were in the periventricular WM areas (Chang, Chang et al. 2010).

4.2.3 Imaging features suggesting WM hemorrhage

In the acute phase, petechial hemorrhages of the WM, particularly the corpus callosum, are common (Funata, Okeda et al. 1982; Finelli and DiMario 2004; Weaver and Hopkins 2005). Gradient echo T2WI uses a shorter repetition time than spin-echo T2WI and can detect metal material such as ferritin and ferritin-containing substances such as hemosiderin, thus detecting hemorrhages and microbleeds (Atlas, Grossman et al. 1988; Bradley 1993). Susceptibility-weighted imaging (SWI) is a heavy T2*-weighted gradient-recalled 3-D fast low-angle shot sequence with full flow compensation in all three directions (Sehgal, Delproposto et al. 2005). Microhemorrhages have been reported in patients with CO intoxication with the complimentary information provided by gradient echo T2WI and SWI (Finelli and DiMario 2004; Weaver and Hopkins 2005). In gradient echo T2WI, hemorrhages along the nerve fibers are distributed predominantly over the posterior WM (Finelli and DiMario 2004).

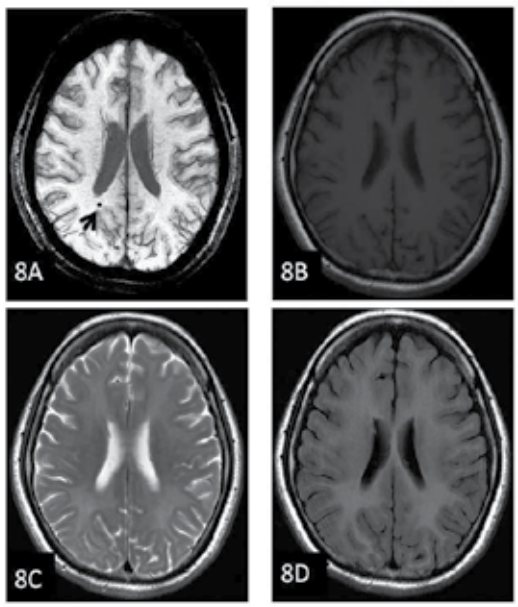

Fig. 8. Microhemorrhage shown on susceptibility-weighted imaging.

Four months after carbon monoxide intoxication, a 53-year-old woman with a low signal intensity lesion on susceptibility-weighted imaging (8A, arrow) suggesting microhemorrhage of white matter which was invisible on T1 (8B), T2 (8C), and fluid-attenuated inversion recovery (8D).

4.3 Cortex

4.3.1 Imaging features suggesting cortical injury and atrophy

Pure cortical involvement without concurrent WM lesions in CO intoxication is not common (Choi, Kim et al. 1993). Using DWI, imaging features suggesting cortical cytotoxic edema were described in bilateral posterior temporal lobes and bilateral occipital lobes in one patient, bilateral posterior temporal lobes and left parietal lobe in

another patient, and right frontal, temporal and parietal lobes in another (Hon, Yeung et al. 2006). Hippocampal involvement has been linked with anterograde amnesia, with pathological findings of necrosis and apoptosis (Uemura, Harada et al. 2001; Mahmoud, Mestour et al. 2009).

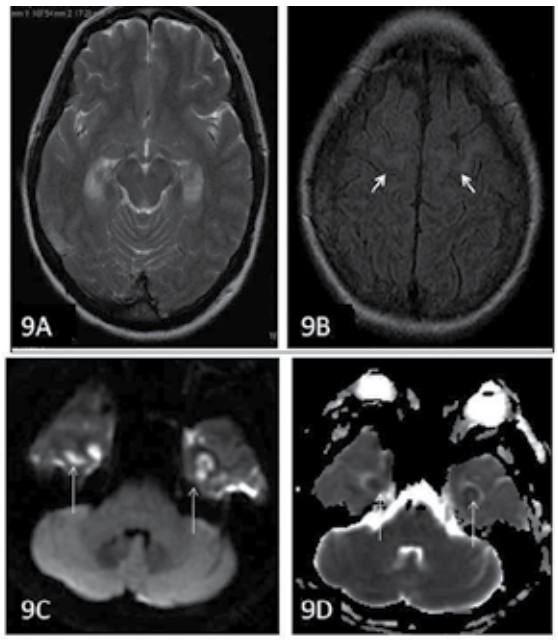

Fig. 9. Cortical injuries after CO intoxication.

Four days after CO intoxication, a 37-year-old woman with hyperintensities in bilateral hippocampi in a T2-weighted image (9A). Six days after CO intoxication, a 42-year-old woman with hyperintensities in bilateral superior frontal gyrus in fluid-attenuated inversion recovery (9B). Another 28-year-old female five days after CO intoxication showed bilateral medial temporal region high signal intensity lesions (9C, diffusion weighted image, arrows) with corresponding low intensity lesions on apparent diffusion coefficient map (9D, arrows) suggesting cytotoxic edema.

Cortical volume reduction is a late consequence of CO intoxication. Significant ventricle and sulcus dilatation in comparison with the controls were found in all 34 patients evaluated during the chronic phase of CO intoxication in a study by Kono et al. (Kono, Kono et al. 1983), with a 19-year interval from CO intoxication. In a case report several months after CO intoxication, brain MRI revealed bilateral atrophy of lateral temporal lobes and the clinical deficits included severe cognitive impairment and a transient Klüver-Bucy-like behavior (Muller and Gruber 2001). Voxel based morphometry (Ashburner and Friston 2001) enables the quantification of grey and WM volume changes between groups. In one study using voxel based morphometry, no significant differences in the GM were found in the patient group compared to age-matched controls ten months after CO intoxication (Chang, Chang et al. 2010), while atrophy of WM was evident in the periventricular areas. In another study of 13 patients with brain MRI studies 25 years after CO poisoning, the parieto-occipital region was most frequently involved, and six of the 13 patients had dilated temporal horns (Uchino, Hasuo et al. 1994).

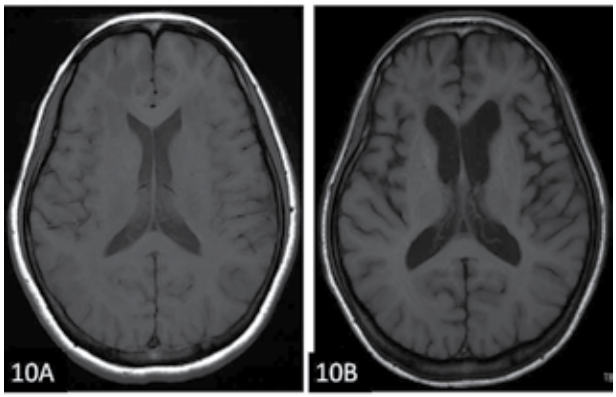

Fig. 10. Cortical atrophy after carbon monoxide intoxication revealed in T1-weighted image.

A 47-year-old woman with rapid cortical atrophy after CO intoxication as revealed in T1WI three months (9A) and 20 months (9B) after CO exposure.

4.3.2 Imaging features suggesting cortical hemorrhage

Hemorrhage in the cortical areas has also been reported in CO intoxication. One 28-year-old man had achromatopsia five months after CO intoxication (Fine and Parker 1996). Brain MRI revealed hemorrhage in the bilateral temporal and occipital lobes (Fine and Parker 1996). Another case demonstrated a 7-year-old boy who had generalized convulsions, coma and right hemiparesis on the day of CO intoxication (El Khashab and Nejat 2009). Brain CT on the same day revealed a left temporal hemorrhage (El Khashab and Nejat 2009). Micro-vascular impairment and brain reperfusion injury were the suspected pathogenetic mechanisms causing the damage (El Khashab and Nejat 2009).

4.3.3 Imaging features suggesting cortical hypoperfusion and hypometabolism

Six studies have reported SPECT findings in the evaluation of cortical blood flow after CO intoxication (Choi, Lee et al. 1992; Choi, Kim et al. 1995; Watanabe, Nohara et al. 2002; Pach, Hubalewska et al. 2004; Huang SH, Chang Chiung Chih2 et al. 2005; Pach, Urbanik et al. 2005). The largest one included 20 cases with 85% of the patients showing hypoperfusion over the frontal-parietal cortex (Pach, Hubalewska et al. 2004). In a study on follow-up SPECT in patients with CO intoxication, six of seven patients had improvement of hypoperfusion throughout the cortex, while their clinical conditions also improved concomitantly (Choi, Kim et al. 1995). In a comparison between those with delayed neuropsychiatric sequelae and those without sequelae, significant hypoperfusion was noted over bilateral frontal lobes, bilateral insula and right temporal lobe in patients with delayed neuropsychiatric sequelae, whilst only bilateral frontal lobe hypoperfusion was noted in those without neuropsychiatric sequelae (Watanabe, Nohara et al. 2002).

To date, there have only been a limited number of reports on [^{18}F] FDG-PET in the evaluation of metabolic dysfunction in the cortical areas of patients with CO intoxication (Tengvar, Johansson et al. 2004; Senol, Yildiz et al. 2009). One case report of a middle-aged man revealed hypometabolism of bilateral frontal lobes and anterior cingulate cortices (Tengvar, Johansson et al. 2004), and his neurological deficit of akinetic mutism was regarded as the consequence of

the hypometabolism state of the involved regions (Tengvar, Johansson et al. 2004). In a study of serial [18F] FDG-PET follow-up scans, persistent hypometabolism of bilateral frontal lobes was found in a 29-year-old woman who demonstrated impaired responsiveness to stimuli for one year after CO poisoning (Shimosegawa, Hatazawa et al. 1992). In another case report on a 21-year-old woman who had coma, seizure and cortical blindness within three days after CO poisoning, the neurological deficit of cortical blindness remained. A subsequent [18F] FDG-PET four years later still showed hypometabolism of bilateral posterior temporal and occipital lobes (Senol, Yildiz et al. 2009).

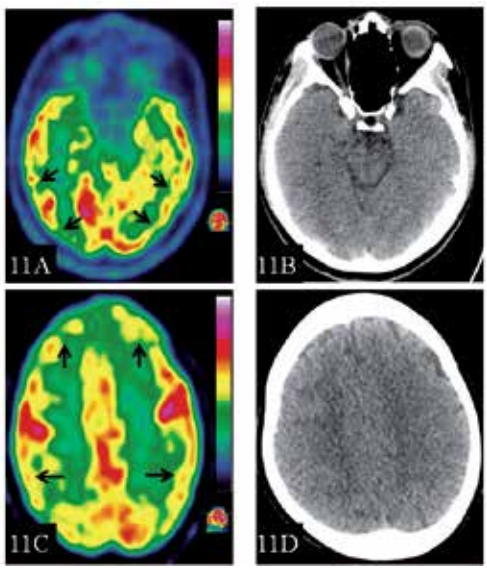

Fig. 11. [18F]fluorodeoxyglucose positron emission tomography of two patients after carbon monoxide intoxication.

One month after CO intoxication, a patient's (age: 30) PET revealed reduced uptake of FDG in bilateral temporal and occipital lobes (11A, arrows), while the brain CT (11B) did not detect any hypodense lesions over the corresponding areas. One month after CO intoxication, another patient's (age: 58) PET revealed reduced uptake of FDG in bilateral frontal and parietal lobes (11C, arrows) with negative findings on the CT scan (11D).

5. Nerves and muscles

Although peripheral neuropathy has been reported in CO intoxication (Choi 1982), only electrophysiological studies but not neuroimaging studies are available (Choi 1982).
Skeletal muscle injuries have been reported in CO intoxication. In one case report, skeletal muscle MRI was performed showing hyperintensity lesions in T2WI of the thigh muscles three months after CO intoxication (Chen, Huang et al. 2010). The muscle biopsy in this patient proved the diagnosis of heterotopic ossification selectively involving the iliopsoas, the tensor fascia lata, rectus femoris, sartorius and quadriceps muscles. Another study using Tc99m-sestamibi SPECT to evaluate the skeletal muscular injuries in 25 patients after CO intoxication showed decreased uptake in the patient group as compared with the controls (Huang, Chang et al. 2011). The low uptake was related to mitochondrial dysfunction.

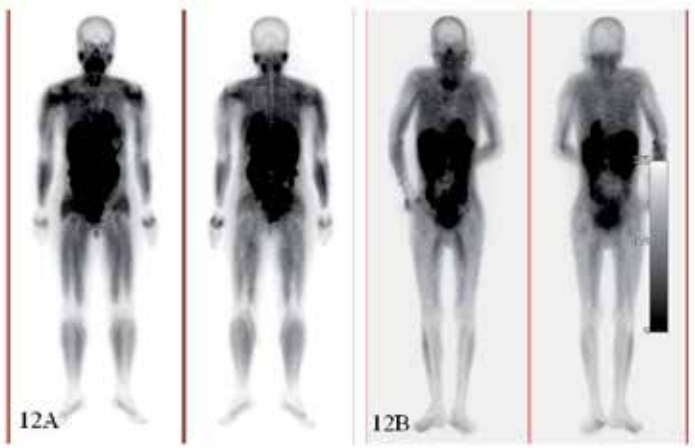

Fig. 12. Planar view of technetium-99m-sestamibi (^{99m}Tc-MIBI) in the evaluation of muscle injury in a patient with carbon monoxide intoxication.

Compared with muscle ^{99m}Tc-MIBI of a normal control (12A), a 59-year-old man showed decreased ^{99m}Tc-MIBI uptake in the thigh muscles two months after CO intoxication (12B).

6. Conclusion

Damage to the neurological system after CO intoxication includes the basal ganglia, cerebral WM, cortex and muscles. The mechanisms of damage can be identified by MRI and correlated with clinical features. Apart from MRI, functional imaging can provide information about brain perfusion and metabolism in CO intoxication. With muscle MIBI, mitochondrial function can be assessed in patients with CO intoxication.

7. Acknowledgments

The study was supported by grants CMRPG 880951, 890871 and 860171 from Kaohsiung Chang Gung Memorial Hospital.

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19

Graphical Models of Functional MRI Data for Assessing Brain Connectivity

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1. Introduction

1.1 Brain connectivity and fMRI

Modern neuroimaging technologies have allowed researchers to non-invasively observe indirect markers of brain activity *in vivo* (Fig. 1). This has resulted in a rapid growth of studies trying to ascertain what brain loci are associated with certain cognitive, sensory and motor tasks. In particular, the recent development of functional magnetic resonance imaging (fMRI) has allowed researchers to non-invasively investigate brain activity at excellent spatial resolution and relatively good temporal resolution. While probing aspects of brain function is typically under the domain of neuroscientists, fMRI work is inherently interdisciplinary: it involves MR physicists who determine MRI sequences sensitive to small changes in the brain, neuroscientists who design the behavioural experiments and interpret the observations, statisticians to assess significance of changes, and increasingly, people with signal processing expertise to derive more and more information from the time series extracted.

Analysis of fMRI data sets represents a special challenge for traditional statistical methods that were originally designed for a large number of samples of low-dimensional data points. The number of "voxels" (ie. representing a specific locus in the brain) to be analyzed are large ($\approx 10^5$), yet the number of time points ($\approx 10^2$) is relatively small. Most early fMRI analysis methods were designed to ascertain the regions where brain functions are localized by performing voxel-wise analysis.

Even when simple tasks are performed in the MRI scanner, widespread activation can be observed in the brain with fMRI. These and other studies suggest that the brain is active at multiple spatial and time scales supporting both segregated and distributed information processing (Bassett & Bullmore, 2006). In fact, the advent of non-invasive functional neuroimaging has re-ignited a centuries-old debate about whether or not cognitive and motor tasks are encoded in discrete loci or are more diffusely and fluidly represented, the latter emphasizing the importance of assessing brain connectivity (Catani & ffytche, 2005).

While connectivity appears to be of critical importance for understanding and assessment of brain function, it can be difficult to define in a rigorous sense with current technologies that can only probe brain activity at certain spatial and temporal scales (see Fig. 1). Conventionally, brain connectivity can be studied at three levels: anatomical, functional, and effective connectivity (see Fig. 2). Anatomical connectivity refers to actual physical connections

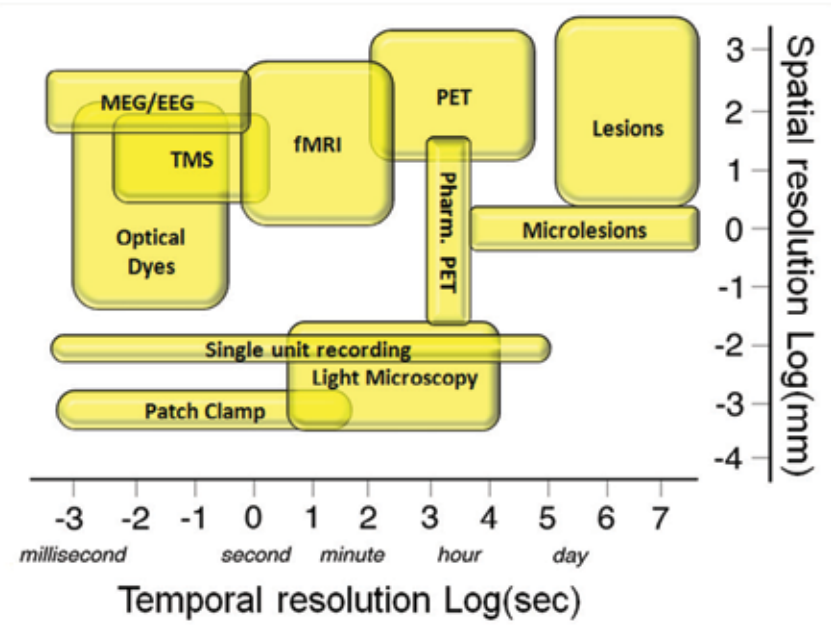
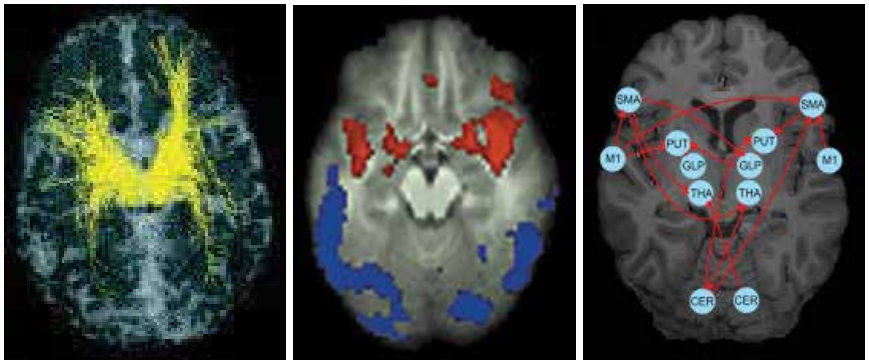


Fig. 1. Temporal and spatial resolution of current neuro-imaging technology. TMS: transcranial magnetic stimulation, MEG: magnetoencephalography, EEG: electroencephalography, PET: positron emission tomography, and Pharm.: pharmacological. (Adapted from: Churchland, Patricia, and Terrence Sejnowski (1992) The Computational Brain. Cambridge, MA: MIT Press.)

between brain structures. It can be determined with the help of rich anatomical studies that have been developed over decades, or more recently, using MR techniques such as Diffusion Tensor Imaging (DTI). Functional connectivity is defined as the significant mutual information between the time series found at distinct loci in the brain. However this raises several problems. If two regions have similarities between their respective time series, is this because one region influences the other, or there is a third region affecting both (Figs. 4 and 5)? Thus the term effective connectivity has been used to imply the causal influence that activity in one brain region exerts over the activity of another. The importance of assessing brain effective connectivity is also related to the fact that brain connectivity impairments are associated with many neuropsychiatric diseases such as depression (Schlösser et al., 2008), schizophrenia (Schlösser et al., 2008), Alzheimer's (Supekar et al., 2008) and Parkinson's disease (Palmer et al., 2009).

1.2 Graphical models for brain effective connectivity

Many methods for inferring connectivity from the four-dimensional fMRI data (three spatial dimensions and one temporal dimension) have been suggested. Proposed methods include correlation thresholding (Cao & Worsley, 1999), linear decomposition (Calhoun et al., 2001; McKeown, 2000), structural equation models (SEM) (Bollen, 1989), multi-variate auto-regression (Valdes-Sosa et al., 2005), dynamic causal models (Friston et al., 2003), Bayesian networks (Li et al., 2008; Zheng & Rajapakse, 2006), wavelet analysis (Bullmore et al., 2004), and clustering (Heller et al., 2006).



(a)* (b)** (c)

Fig. 2. Conventionally, brain connectivity is studied at three levels: (a) anatomical, (b) functional, and (c) effective connectivity. Anatomical connectivity is actual physical connections between brain structures. Functional connectivity is defined as the significant mutual information between the time series found at distinct loci in the brain. Effective connectivity has been used to imply the causal influence that activity in one brain region exerts over the activity of another. * Sub-figure (a) is from P. Hagmann, J.-P. Thiran, L. Jonasson, P. Vandergheynst, S. Clarke, P. Maeder and R. Meuli (2003) DTI mapping of human brain connectivity: statistical fibre tracking and virtual dissection, NeuroImage 19(3): 545–554. ** Sub-figure (b) is from Daniel S. Margulies, A.M. Clare Kelly, Lucina Q. Uddin, Bharat B. Biswal, F. Xavier Castellanos and Michael P. Milham (2007) NeuroImage 37(2): 579–588.

Correlation thresholding (Cao & Worsley, 1999) directly examines the correlation between the activities of brain regions. If the correlation is so strong that it is extremely unlikely based on chance, then the two regions are considered connected, though not necessarily directly. Linear decomposition approaches, e.g. principal component analysis and independent component analysis (ICA) (Calhoun et al., 2001; McKeown, 2000), assume that observed brain activities are a combination of underlying psychological processes that spatially recruit different brain regions or temporally have unrelated behaviours. Regions involved in the same psychological process as revealed by the decomposition is considered as connected, though not necessarily directly. Both correlation thresholding and linear decomposition are designed for discovering functional connectivity, and neither can distinguish whether two regions interact directly or indirectly through a third region (Kaminski, 2005). Though correlation thresholding and linear decomposition are generally not considered as graphical model, actually both can be related to graphical models (Roweis & Ghahramani, 1999).

Unlike correlation thresholding and linear decomposition whose results can be visualized as brain images at the voxel level, structure equation models[1](Bollen, 1989), dynamic causal models (Friston et al., 2003), multivariate auto-regression (Valdes-Sosa et al., 2005), and Bayesian networks (Zheng & Rajapakse, 2006), are another category of methods that normally work at the level of regions, and whose results can be visualized as graphs where nodes usually represent brain regions and edges represent connections. The brain regions are typically defined anatomically, and some automatic or manual segmentation of brain

[1] Structure equation models allow reciprocal connections, and normally are not considered as classical graphical models. As advanced graphical models, their Markov property and equivalence classes have been explored in (Ali et al., 2009; Richardson, 2003; Spirtes et al., 1998).

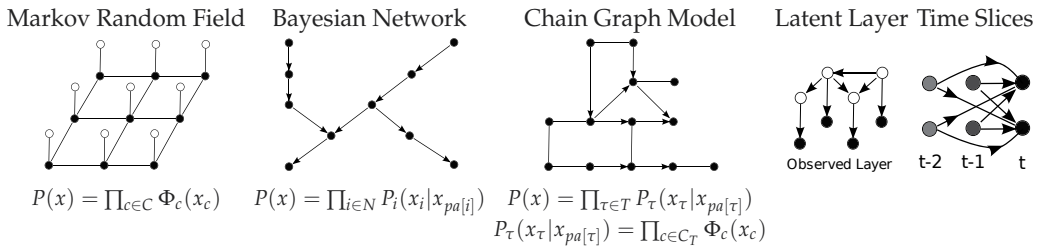


Fig. 3. Examples of the structures of classical graphical models. The structure of a Markov random field is an undirected graph. The joint probability is decomposed as the product of clique potential functions $\Phi_c(x_c)$ where c is a clique in the graph and x_c is the variables associated with the nodes in c. The structure of a Bayesian network is a directed acyclic graph. The joint probability is decomposed as the product of node conditional probabilities $P_i(x_i|x_{pa[i]})$ where i is a node in the graph and $pa[i]$ is the parent nodes of node i. Chain graph models unify Markov random fields and Bayesian networks. They allow both directed and undirected edges, but forbid directed cycles. The joint probability is decomposed as the product of chain-component conditional probabilities $P_\tau(x_\tau|x_{pa[\tau]})$ where τ is a chain component and $pa[\tau]$ is the parent nodes of the component. The chain-component conditional probability $P_\tau(x_\tau|x_{pa[\tau]})$ can be further decomposed as clique potential functions $\Phi_c(x_c)$ where c is a clique in the moral graph derived from the chain component τ. Dynamic causal models (Friston et al., 2003) can be regarded as non-linear Bayesian networks with an observed layer and a latent layer. Multi-variate auto-regression (Valdes-Sosa et al., 2005) can be regarded as linear Bayesian networks with many time slices and directed edges from slices at time $t-1, t-2, \cdots$ pointing to the slice at time t.

structures is required to act as nodes in the model. According to the interaction relationships specified by the graph, the joint probability of node random variables can be decomposed as the product of many local potential functions or local conditional probabilities, as shown in Fig. 3. A node variable usually depends on its neighbor variables and/or parent variables. For example, in Bayesian networks, the activity of a region A is usually modeled as a stochastic function of the activities of its "parent" regions, as in Eq. (1)

$$X_A = f(X_{pa_1[A]}, X_{pa_2[A]}, \ldots, X_{pa_n[A]}) \tag{1}$$

where X_A is the activity of region A and $pa_i[A]$s are the parent nodes of A in the graph. The graph structure of the model is not just for visualization, but encodes conditional-independence relationships among the activities of brain regions. A network structure can be translated to a set of conditional-independence relationships according to the Markov properties and vice versa, with certain assumptions, a set of conditional-independence relationships can also be encoded by a network structure (Lauritzen, 1996).

1.3 Pair-wise and conditional correlation

Graphical models are suitable for modelling brain connectivity, not only because their structures can be easily visualized as a network, but more importantly, their fundamental feature, namely conditional independence, is a key concept for differentiating effective connectivity from functional connectivity. When two brain regions show similar activation patterns, they can be somehow connected with several underlying possibilities, as illustrated in Fig. 4:

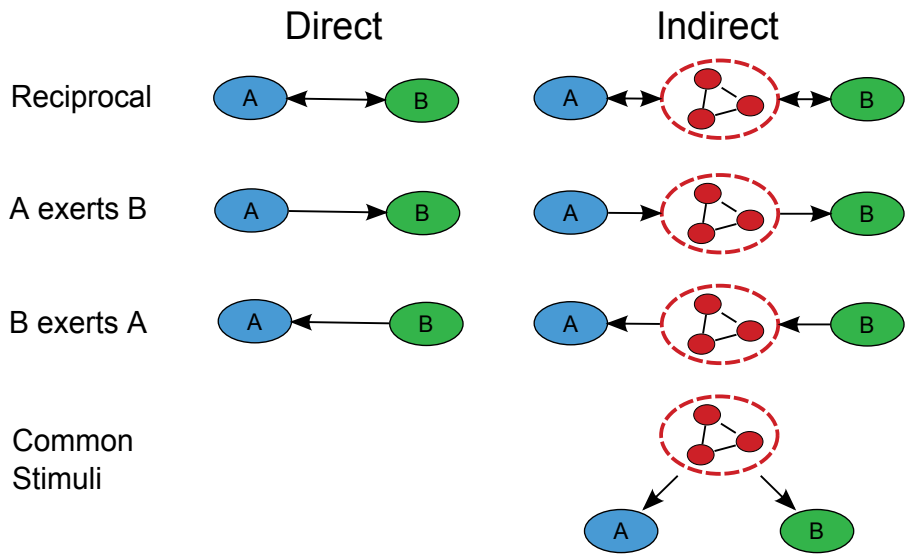


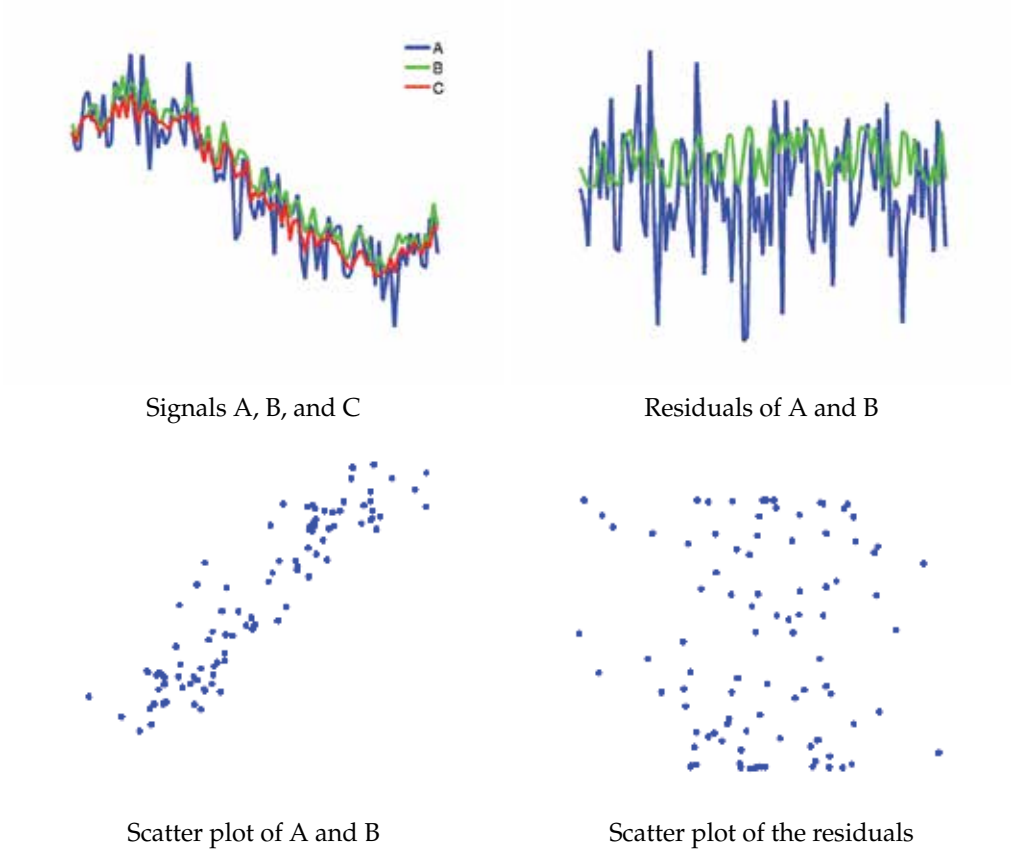
Fig. 4. When two brain regions show similar activation patterns, they can be connected with different underlying possibilities: (1) they directly reciprocally communicate with each other; (2) one region directly exerts the other; (3) they indirectly reciprocally communicate with each other via other brain regions; (4) one indirectly exerts the other via other regions; (5) they both are driven other regions; (6) they communicate with a combination of (1)–(5).

1. they directly reciprocally communicate with each other;
2. one region directly exerts the other;
3. they indirectly reciprocally communicate with each other via other brain regions;
4. one indirectly exerts the other via other regions;
5. they both are driven other regions;
6. they communicate by a combination of the above possibilities.

Pair-wise correlation can only tell that two regions is probably connected, but cannot distinguish among the above possibilities. To distinguish between direct and indirect connections, conditional independence must be considered. The example in Fig. 5 clearly explains this motivation. The two signals A and B show strong pair-wise correlation, but if we consider a third signal C, then the residuals of A and B after C is extracted from them hardly show any correlation. In this example, A and B are conditionally independent if given C, and maybe both are driven by C, as illustrated in the indirect common-stimuli case in Fig. 4. It must be noted that conditional independence alone without temporal information is not enough to determine causal relationships, ie. the direction of connections. To infer the direction, criteria considering temporal information, such as Granger causality (Granger, Aug., 1969), can be employed.

1.4 Challenges in modeling brain connectivity

Biomedical research explores the highly complex and diverse realm of living organisms and often incorporates clinical needs such as diagnosis and treatment design. Analysis



centering

Fig. 5. Two signals A (blue) and B (green) show strong pair-wise correlation, but with a third signal C (red) being considered, the residuals of A and B after removing the projection onto C hardly show any correlation.

of biomedical data typically emphasizes such features of reliability, interpretability and generality of reported results.

For example, when brain connections are reported, it is important to control or assess error rates in the claimed discoveries, addressing questions such as "how many among the reported connections are actually true connections?" and "how many true connections can be detected?"

Additionally, the ultimate goal of a biomedical experiment is usually a population inference applicable to a group of people, such as patients with a particular disease. However, subjects classified to the same experimental group according to the factor of interest can still be highly diverse with respect to other factors, such as gender, age, or race. Even repetitive experiments with the same subject can still be affected by various physical or psychological factors, such as drowsiness or stress. It is therefore important to integrate the information from separate experiments to make inference on the target topic, and to keep a balance between commonality and diversity.

Finally, as a multidisciplinary field, end users of connectivity analysis reports are often biomedical researchers or clinicians who focus on the biological implication of the results and the effects of medication. Therefore, it is undesirable to simply generate a vast network of

potential connections or just report abstract statistical scores, without providing an intuitive interpretation. Rather, clinicians prefer interpretable, informative and human-understandable results, for example, which brain regions play the central role in conducting a functional task, or which connections are normalized by a pharmacological manipulation. These considerations have implications for interpretation and feature extraction from graphical models.

As a response to the above common challenges in biomedical research (ie. reliability, generality and interpretability), in the following sections, we will focus on three topics: error control in learning brain connectivity, group analysis taking into account the enhanced inter-subject variability typically seen in patient populations, and brain network analysis. Finally, for completeness, we also briefly overview several popular software packages suitable for assessing fMRI brain connectivity in the Appendix.

2. Error control in structure learning

In real world applications, especially in modelling brain connectivity, graphical models are not only a tool for operations such as classification or prediction, but more often than not, it is the network structure of the model itself which is of particular interest. Thus a desirable graphical model of fMRI data should not only statistically fit the overall data well, but also accurately reflect the internal brain connectivity structure. Structure-learning algorithms must therefore control or assess the error rate of the connections/edges detected by them.

2.1 Criteria for error control

There are two basic types of statistical errors: type I errors, ie. falsely claiming connections when they actually do not exist; and type II errors, ie. failure in detecting connections that truly exist. Since real data are not free from noise, limited samples may appear to support the existence of a connection when it does not exist, or vice versa. It is therefore impossible to absolutely prevent the two types of errors simultaneously, but rather keep a balance between them. This can be done by, for example, minimizing a loss function associated with the two types of errors according to Bayesian decision theory.

There are several criteria available for error-rate control (see Table 2). Generally there is no single criteria that is universally superior if the research scenario is not specified. Selecting the error rate is largely not an abstract question "which error rate is superior over others?", but a practical question "which error rate is the researchers' concern?". One error-rate criterion may be favored in one scenario while another may be right in a different scenario, for example:

- We are diagnosing a serious disease whose treatment has serious potential side effects. Due to the risk of the treatment, we hope that less than 0.01% of healthy people will be falsely diagnosed as affected by the disease. In this case, the type I error rate should be controlled under 0.01%.
- We are diagnosing a disease with high mortality, e.g. a type of cancer. Because failure in detecting the disease will have catastrophic consequences, we hope that 95% of subjects with the disease will be correctly detected. In this case, the type II error rate should be controlled under 5%.
- In a pilot study, we are selecting candidate genes for a genetic research on Parkinson's disease. Because of limited funding, we can only study a limited number of genes, so when selecting candidate genes in the pilot study, we hope that 95% of the selections are

Test Results	Truth		
	Negative	Positive	Total
Negative	TN (true negative)	FN (false negative)	R_1
Positive	FP (false positive)	TP (true positive)	R_2
Total	T_1	T_2	

Table 1. Results of multiple hypothesis testing, categorized according to the claimed results and the truth.

Full Name	Abbrev.	Definition
False Discovery Rate (Benjamini & Yekutieli, 2001)	FDR	$E(\mathrm{FP}/R_2)$*
Positive False Discovery Rate (Storey, 2002)	pFDR	$E(\mathrm{FP}/R_2 \mid R_2 > 0)$
Family-Wise Error Rate	FWER	$P(\mathrm{FP} \geq 1)$
Type I Error Rate (False Positive Rate)	α	$E(\mathrm{FP}/T_1)$
Specificity (True Negative Rate)	$1-\alpha$	$E(\mathrm{TN}/T_1)$
Type II Error Rate (False Negative Rate)	β	$E(\mathrm{FN}/T_2)$
Power (Sensitivity, True Positive Rate)	$1-\beta$	$E(\mathrm{TP}/T_2)$
Positive Predictive Value	PPV	$E(\mathrm{TP}/R_2)$

Table 2. Criteria for multiple hypothesis testing. Here $E(x)$ means the expected value of x, and $P(\mathcal{A})$ means the probability of event $\mathcal{A}$. Please refer to Table 1 for related notations. * If $R_2 = 0$, FP/R_2 is defined to be 0.

truly associated with the disease. In this case, the FDR will be chosen as the error rate of interest and should be controlled under 5%.

- We are selecting electronic components to make a device. Any error in any component will cause the device to run out of order. To guarantee the device functions well with a probability higher than 99%, the family-wise error rate should be controlled under 1%.

Since the scenario favoring the false discovery rate (FDR) (Benjamini & Yekutieli, 2001; Storey, 2002) is common in exploratory research, the FDR has become an important and widely used criterion in many fields, such as in inferring brain connectivity. Simply controlling the type I and type II error rates at specified levels does not necessarily keep the FDR sufficiently low, especially in the case of large and sparse networks. For example, suppose a network includes 40 nodes where each interact in average with 3 other nodes, i.e. there are 60 edges in the network. Then an algorithm with the *realized* type I error rate = 5% and the *realized* power = 90% (i.e. the *realized* type II error rate = 10%) will recover a network with $60\times90\%$ = 54 correct connections and $[40 \times (40-1)/2 - 60] \times 5\% = 36$ false connections, which means that $36/(36+54) = 40\%$ of the claimed connections do not exist in the true network.

2.2 Structure-learning methods with error controlled

Score-based search methods (Heckerman et al., 1995) look for a suitable network structure by optimizing a certain criterion of goodness-of-fit, such as the Akaike information criterion (AIC) (Akaike, 1974), the Bayesian information criterion (BIC) (Schwarz, 1978), or the Bayesian Dirichlet likelihood equivalent metric (BDE) (Heckerman et al., 1995)), with a random walk (*e.g.* simulated annealing) or a greedy walk (*e.g.* hill-climbing). However, scores do not explicitly reflect the error rate of edges, and the sample sizes in real world applications are usually not enough to guarantee asymptotic performance.

Both classical and Bayesian approaches are available for controlling errors during network learning (Listgarten & Heckerman, 2007). Classical approaches are based on the Markov

property of graphical models, and treat error control as a problem of multiple testing. Since a graphical model is a graphical encoding of conditional-independence relationships, the non-adjacency between two nodes is tested by inspecting their conditional independence given other nodes. Conditional-independence relationships among node variables are tested one by one in a certain order, and p-values about the existence of each edge are estimated. Error control procedures, such as Bonferroni correction for the family-wise error rate, or the Benjamini-Hochberg procedure for the FDR, or without-correction for the type-I error rate, are applied to the p-values to set the cut-off threshold of accepting or rejecting the existence of edges.

Recently, a series of papers have addressed the problem using the classical approach. Listgarten and Heckman (Listgarten & Heckerman, 2007) proposed a permutation method to estimate the number of spurious connections in a graph learned from data. The basic idea is to repetitively apply a structure learning algorithm to data simulated from the null hypotheses with permutation. In general, this method will work with any structure learning method, but permutation may make the already time-consuming structure learning problem even more computationally expensive, limiting its practical usage. Kalisch and Bühlmann (Kalisch & Bühlmann, 2007) in 2007 proved that for Gaussian Bayesian networks, by adaptively decreasing the type I error rate, as the sample size approaches infinity, the PC algorithm (Spirtes et al., 2001) can, without errors, recover the equivalence class of the underlying sparse directed acyclic graphs, even if the number of nodes grows exponentially as the sample size does. Tsamardinos and Brown (Tsamardinos & Brown, July, 2008) in 2008 applied the FDR-procedure separately to edges related to each node. Li and Wang (Li & Wang, 2009) in 2009 applied FDR-control procedures globally to all connections of interest, and proved that with mild conditions, their method is able to asymptotically control the FDR of the "claimed" edges. They showed by empirical experiments that in the cases of moderate sample size (about several hundred), the method is still able to control the FDR under the user-specified level.

Bayesian approaches control errors by inferring the posterior probability of edges given the data. If G is the learned graph and G_i is the true graph, then the spurious edges in G are those of $G \setminus G_i$, ie. the sub-graph of G after edges in G_i are removed. In this case, the *realized* FDR is $|G \setminus G_i|/|G|$ where $|\bullet|$ denotes the number of edges in a graph, and the *realized* type-I error rate in this case is $|G \setminus G_i|/|G_{full} \setminus G_i|$ where G_{full} is the fully connected graph. Since Bayesian inference assigns a probability to each possible model, the error rate of G given data D should be integrated over all possible G_i according to their posterior possibilities (Listgarten & Heckerman, 2007). Therefore we have:

$$FDR(G|D) = \sum_{G_i} \frac{|G \setminus G_i|}{|G|} P(G_i|D), \tag{2}$$

where $P(G_i|D)$ is the probability of a model structure G_i given data D. Similarly the posterior type-I error rate is:

$$\alpha(G|D) = \sum_{G_i} \frac{|G \setminus G_i|}{|G_{full} \setminus G_i|} P(G_i|D). \tag{3}$$

As in many other Bayesian procedures, the most difficult part of the inference is not the formulation, but rather the calculation, and especially the integration. Because the number of possible graphs increases super-exponentially as the number of nodes increases (Steinsky, 2003), it is impractical to enumerate all the possibilities and sum them up. For certain prior distributions, given the order of nodes, Friedman and Koller (Friedman & Koller, 2003) in

2003 derived a formula that can calculate the exact posterior probability of a structure feature with the computational complexity bounded by $O(N^{D_{in}+1})$, where N is the number of nodes and D_{in} is the upper bound of node in-degrees. Considering similar prior distributions, but without the restriction on the order of nodes, Koivisto and Sood (Koivisto & Sood, 2004) in 2004 developed a fast exact Bayesian inference algorithm based on dynamic programming that is able to compute the exact posterior probability of a sub-network with the computational complexity bounded by approximately $O(N2^N)$. In practice, this algorithm runs fairly fast when the number of nodes is less than 25. For networks with more than about 30 vertices, the authors suggested setting more restrictions or combining with inexact techniques. For general situations, the posterior probability of a structure feature can be estimated with Markov chain Monte Carlo (MCMC) methods (Madigan et al., 1995). As a versatile implementation of Bayesian inference, the MCMC method can estimate the posterior probability given any prior probability distribution. However, MCMC usually requires intensive computation and the results may depend on the initial state.

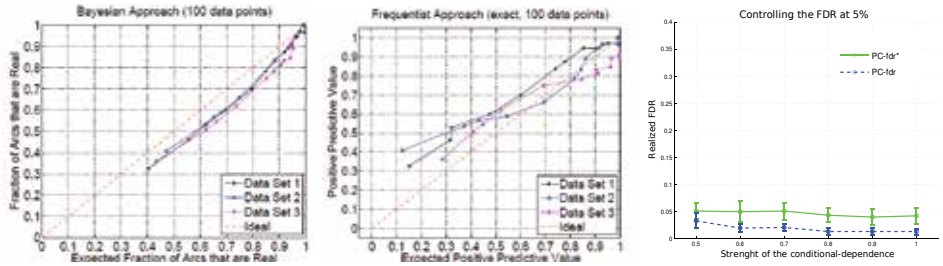
In Listgarten and Heckman's simulation (2007) (Listgarten & Heckerman, 2007), the error-control curves of the Bayesian approach was smoother and more favorable than those of the classical approach, as show in Fig. 6-A and Fig. 6-B. However, it was also pointed out that in practice the expected FDR of interest usually is very small, within a narrow range near 0, and that the classical approach showed reasonable performance in this range. (The axes of Fig. 6-A and Fig. 6-B are marked with the positive predictive value (PPV) instead of the FDR. The relationship between PPV and FDR is $PPV = 1 - FDR$, as in Table 2.) In Li and Wang's simulation (2009) (Li & Wang, 2009), to control the FDR at the conventional level of 5%, their classical approaches, the $\mathrm{PC}_{\mathrm{fdr}}$ algorithm and its heuristic modification, the $\mathrm{PC}_{\mathrm{fdr}^*}$ algorithm, controlled the FDR satisfactorily around the expected level 5%, as shown in Fig. 6-C. For inferring brain connectivity, since brain regions are not just algebraically isolated variables, but rather located in a three-dimension space with complex geometric structure, it may be important in the future to exploit such geometric information for improving error control.

3. Group analysis

Biomedical experiments are usually conducted to verify or discover knowledge about a population characterized by health or certain disease state. However, subjects classified to the same group can still be highly diverse with respect to factors such as gender, age, or race. With careful experiment design, the effect of these confounding factors can be reduced, but inter-subject variability still plays an important role and remains a challenge. Even studies on a single subject may still face challenges related to variability. For example, EEG recordings conducted at different times from the same subject can be affected by the subject's physical or psychological state, such as drowsiness or stress. Thus in this paper, the term "group analysis" is not restricted to the analysis of a group of people, but generalized to the inference by integrating the information distributed in separate experiments and affected by cross-experiment variability.

3.1 Commonality and diversity at different levels

Two basic concepts in group analysis are *commonality and* diversity. For example, all doctors learn professional knowledge related to medicine, but a doctor could be a pediatrician, a surgeon or a physician. Each one has their own speciality and this is the diversity among them. Commonality and diversity usually co-exist, and are revealed at different levels, depending on the perspective and scale we study the problem.



A B C

Fig. 6. Simulation results of the FDR control with the Bayesian and classical approaches. Sub-figure A and B are results in (Listgarten & Heckerman, 2007). Their x-axes and y-axes are the expected and realized positive predictive values (PPV) respectively. (The relationship between PPV and FDR is PPV = 1 - FDR.) The curves of the Bayesian approach was smoother and more favorable than those of the classical approach. When the expected PPV is high, or equivalently the expected FDR is low, the classical approach performed reasonably well. Sub-figure C is the result in (Li & Wang, 2009) to control the FDR at the conventional level of 5% with the classical approach. The x-axis is the strength of the conditional-dependence relationships among node variables, and the y-axis is the realized FDR. The PC_{fdr} algorithm controlled the FDR under 5%, and its heuristic modification, the PC_{fdr*} algorithm, controlled the FDR satisfactorily around 5%. For details of the two simulation studies, please refer to (Listgarten & Heckerman, 2007) and (Li & Wang, 2009).

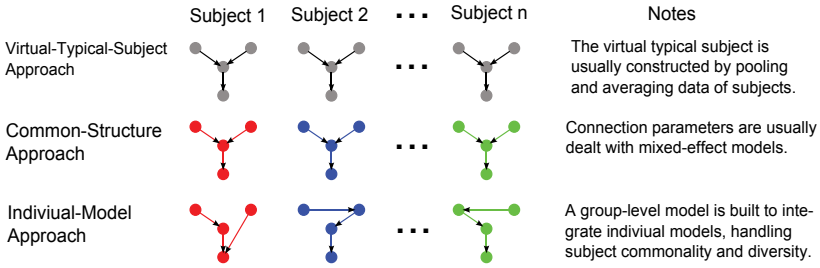


Fig. 7. Three broad categories of group-analysis methods. The "virtual typical" approach constructs a typical subject to represent the whole group, usually by pooling or averaging data of subjects. The "common-structure" approach imposes the same network structure to the model of every subject, and usually uses mixed-effect models to handle the parameter variability among subjects. The "individual-model" approach allows each individual subject to have its own model, and integrates the individual models with a group-level model.

Since graphical models combine network structures and probability descriptions, the group analysis needs also accommodate commonality and diversity with both model structures and probability parameters. A review of the literature shows that current group-analysis methods based on graphical models can be classified into three broad categories (see Fig. 7), as discussed as follows (Li et al., 2008).

First, we could ignore subject diversity, and assume that the brains of all the subjects are structured and function in a similar way, as if there is a virtual typical subject able to satisfactorily represent the whole group. This can be called the "virtual typical subject" approach. In this approach, the model for every subject has the same structure, and the

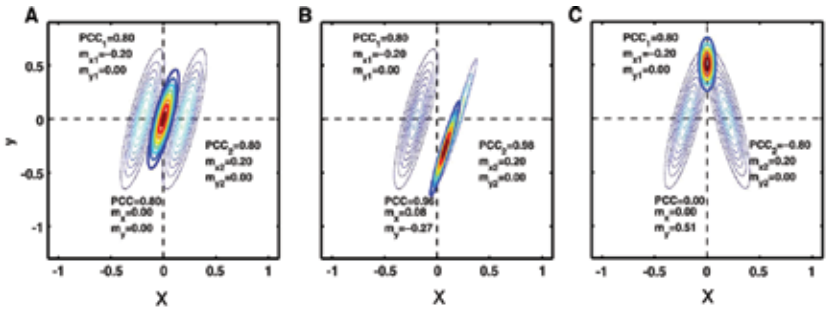


Fig. 8. Product of two Gaussian distributions. Thin lines are the contour of two bivariate Gaussian distributions, and the bold lines are the contour of their product. If the parameter likelihood for the data of two subjects is the two bivariate Gaussian distributions, then the parameter likelihood for the pooled data is the product distribution. In sub-figures B and C, the center of the product distribution is located off the x-axis, while neither of the two bivariate Gaussian distributions is centred off the x-axis. This is an undesirable and misleading phenomenon for data pooling. PPC is the abbreviation for partial correlation coefficient; m_x is the mean of x, and m_y is that of y. This figure is from (Kasess et al., 2010).

same parameters as well. The "virtual-typical" subject is usually constructed by pooling or averaging the group data, and then one model is learned from the data. Technically this degrades group analysis to learning a model for a single subject, for which both classical (Heckerman et al., 1995) and Bayesian (Neumann & Lohmann, 2003) approaches have been developed. When the group is homogeneous or inter-subject variability follows certain regular distributions, this approach could increase detection sensitivity, because pooling can build a relatively large data set, and averaging can enhance the signal-to-noise ratio (Kasess et al., 2010). However, when the group becomes more heterogeneous, this approach could lead to undesirable and misleading results (Kasess et al., 2010). Fig. 8 shows that by pooling data together, the group estimation of connection parameters could be located far way from the center of individual estimations.

The other extreme is that we assume subjects can be completely different from each other – the "individual-model approach". In this approach, the model of each subject can be completely different. This approach is related to the concept of functional degeneracy, ie. "the ability of elements that are structurally different to perform the same function or yield the same output" (Edelman & Gally, 2001), or more plainly "there are multiple ways of completing the same task" (Price & Friston, 2002). Because subjects in the same group are considered to share similarity, their individual models must be linked together in a certain way, usually by a second-level group model built over the individual models.

The most straight-forward implementation of the "individual-model approach" is to directly input separately learned individual models as subject features into a second-level analysis. For example, structural features of the network of individual models can be selected with classification and cross-validation procedures at the group level, as applied in (Li et al., 2008). A theoretically elegant approach is to build a group-level model to describe the diversity distribution in a group, and the group-level and the individual-level models form a big model over the group data. Usually this big integrated model should be learned from the batch of group data, which would require an intensive computation. The Bayesian group model proposed by Stefan, etc. (Stephan et al., 2009) provides a rigorous theoretical background and is able to break the model learning into two separate stages, the individual and group stages.

This property allow the group to be updated incrementally without re-learning individual models when new data are added. Niculescu-Mizil and Caruana proposed a heuristic method to link individual models (Niculescu-Mizil & Caruana, 2007). They allow network structures to be different across subjects, and punish excessive diversity among the structures with a tunable parameter.

A trade-off between the two extremes is assuming that subjects' brains are structured similarly, but function with considerable difference. This can be referred as the "common-structure" approach (Mechelli et al., 2002). In this approach, the model of every subject share the same network structure, but the parameters can be different from subject to subject. When the common model structure is specified, this approach focuses on dealing with the model parameters across subjects. The standard method is the mixed-effect model (Mumford & Nichols, 2006) as follows. Consider an experiment where there are n subjects and for each subject, indexed by k, a regression parameter β_k modeling the relationship between a response variable Y_k and an explanatory variables X_k. The first-level model for each individual subject is

$$Y_k = X_k\beta_k + \epsilon_k, \text{ for } k = 1, 2, \cdots, n, \tag{4}$$

where ϵ_k is the within-subject randomness following Gaussian distribution $N(0, V_k)$. The second-level model for group parameters is

$$\beta = \begin{bmatrix} \beta_1 \\ \vdots \\ \beta_n \end{bmatrix} = X_g\beta_g + \epsilon_g, \tag{5}$$

where β_g is the group-level parameter, X_g is the group design matrix and ϵ_g is the cross-subject randomness following Gaussian distribution $N(0, V_g)$. The combination of Eqs. (4) and (5) is called a mixed model, because both the within-subject and the cross-subject randomness are considered in the model. A notable issue in mixed-effect models is that the cross-subject variance V_g could be negative in maximum likelihood estimation. To avoid this undesirable and counter-intuition phenomenon, the random-effect variance is usually enforced to be positive. The mixed-effect model in practice usually is solved with the summary-statistics approach that reformulates the model as Eqs. (6) and (7):

$$\hat{\beta}_k = (X_k^T V_k^{-1} X_k)^{-1} X_k^T V_k^{-1} Y_k, \tag{6}$$

$$\begin{aligned} \hat{\beta} &= \begin{bmatrix} \hat{\beta}_1 \\ \vdots \\ \hat{\beta}_n \end{bmatrix} = X_g\beta_g + \epsilon_g + \hat{\beta} - \beta \\ &= X_g\beta_g + \epsilon_g^*, \end{aligned} \tag{7}$$

where $\hat{\beta}_k$ is the least-square-estimation of the parameter for each subject, and $\epsilon_g^* = \epsilon_g + \hat{\beta} - \beta$ following $N(0, V_g^*)$. Given V_g^* (the variance of ϵ_g^*), β_g can be solved from the estimation of β_ks, unnecessarily from β_ks. The summary-statistics approach decomposes a complicated model into two relatively easy stages, and retains the estimation for each single subject even when new subjects are added into the analysis. The summary-statistics approach assumes that V_g^* is known, but in practice it should be estimated from the data. The estimation, including both its value and its degree of freedom, is challenging and has attracted much research attention. Methods such as Restricted Maximum Likelihood (Harville, 1977), Smoothing with

fixed-effect model (Worsley et al., 2002) , and Markov Chain Monte Carlo (Woolrich et al., 2004) have been developed.
Though the aforementioned methods deal with group commonality and diversity with various techniques, most take or can be considered to be in a two-level framework: a lower level of models for each individual subject, and a group level integrating individual models and describing inter inter-subject commonality and diversity. The group level could enforce strong commonality, like the "virtual-typical" approach, or model group diversity probabilistically, like the "individual-model" approach in (Stephan et al., 2009). Models able to technically decouple the computation of the individual and the group levels are favoured.

3.2 Desirable features of graph analysis methods

To set clear goals for the future development of more advanced group-analysis methods, we suggest three highly desirable features: being modular, being incrementally updatable, and being scalable. Being modular means that a group-analysis method is not only designed for a particular type of single-subject model, but versatile and applicable to different types of single-subject models. For example, both Bayesian networks and structural equation models are applicable at the subject level, so the group-analysis method should not be restricted to only one of them, but should be able to work with both of them, though not necessarily with a mixture of them. If the group-level model just needs inputs such as the likelihood of individual models, then it is free from the specific format of the individual models. If a group-analysis model can be a module of itself, then it will be able to handle multi-level hierarchical group structures.
Being incrementally updatable means that group-inference results can be summarized as summary statistics and used for further analysis involving newly collected data. This feature is very useful in research practice because experimental data are usually collected incrementally. For example, after a study on eighty subjects half a year ago, twenty more subjects might be recruited. In this case, it may require cumbersome computation to analyze the entire data of one hundred subjects. However, if the group inference is incrementally updatable, it may need much less computation to include the additional twenty subjects.
Being scalable means that a group-analysis method can handle fast growing diversity among subjects. Because modern exploratory research usually involves investigation of a large number of candidate models, scalability has become a highly desirable feature for group analysis. For example, if the connectivity between ten brain regions is studied with Bayesian networks, then a group-analysis method should be able to handle the diversity of about 3.1×10^{17} (Steinsky, 2003) possible network structures.

4. Network analysis

Modelling is only the first step to investigate a system, following which human-understandable information should be further extracted from models to provide insightful understanding. For example, as final readers of a report on brain connectivity, neurologists might be interested in questions such as "which brain regions play the central role in conducting a functional task?", "in what patterns are cognitive functions segregated and integrated among brain regions?" or "how does this brain connectivity network react to the presence of a disease?" Simply reporting a vast and plain network without any highlights does not answer these questions. Graphical models notably have visualized network structures, so it is natural to analyze their structures as an important post-processing

in their applications in brain connectivity, as discussed in (Bullmore & Sporns, 2009; Stam & Reijneveld, 2007).

The history of graph theory can be traced back to nearly three hundred years ago, marked by preeminent Swiss mathematician Euler's paper on the Seven Bridges of Königsberg. Its application to real-world complex networks was boosted at the end of last century by a series of discoveries on the architecture of world-wide-web, social networks, cellular networks, etc. These systems, despite their tremendous variety, share certain common properties, such as the "small world" (Watts & Strogatz, 1998), the "scale free" (Barabasi & Albert, 1999) and the "self-similarity" (Song et al., 2005) properties. These properties might hint how these networks evolve and grow, and are also related to their functions and interactions with the environment (Watts & Strogatz, 1998).

Some well-know properties such as the "scale-free" or "self-similarity" properties are more suitable for large networks, than for networks of moderate size (with dozens of nodes), because their statistics need large scale observations. However, the number of time points of an fMRI scan is relatively small, approximately several hundred, and cannot support reliably discovery of large scale networks. Therefore, in this section, we focus on network analysis suitable for brain connectivity networks of moderate size.

4.1 Network measures

Graphs can be studied at different levels from basically nodes and edges, to paths, or more intricately, sub-graphs. According to the object of interest, network measures can be broadly classified into two categories: (1) local measures that focus on local objects in the network, for example, a node, an edge, or a sub-graph, and (2) global measures that feature the pattern of the overall architecture. Local measures usually, yet not necessarily, put a local object in the global view. For example, the importance of a node could be defined as the proportion of communication in the whole network that must go through it. Vice versa, global measures are usually built on local features. For example, the "scale-free" property is about the distribution of node degrees. Fig. 9 illustrates those network measures listed below. Most network measures are ultimately linked to fundamental concepts such as node degree and path length.

- **Centrality and local contribution to network communication.** A local object, for instance a node or an edge, that plays an important role in network communication is considered to be central in the network. The centrality of a node can be measured by its relay of the communication between other nodes. For example, betweenness centrality (Freeman, 1977) is based on the number of shortest paths between other nodes passing through a node. It can also be assessed by the geodesic distance to other nodes, as closeness centrality (Beauchamp, 1965) does, or by deleting a node and then comparing the connectivity loss of the "impaired" network, as Shapley ratings (Kötter et al., 2007) do. Similar ideas can be applied to define the centrality of an edge or a sub-graph. Some measures are not as intuitive as the aforementioned ones: for instance, eigenvector centrality (Bonacich, 1972) and sub-graph centrality (Estrada & Rodrguez-Velzquez, 2005) are also implemented for the same concept.
- **Modularity and brain function organization.** It is believed that various cognitive functions are localized in different brain regions, and that these distributed functions are integrated together for complicated information processing. Such a perspective on brain function organization naturally leads to a network structure where some nodes are densely clustered and form function modules. The "small-world" property, at the global level,

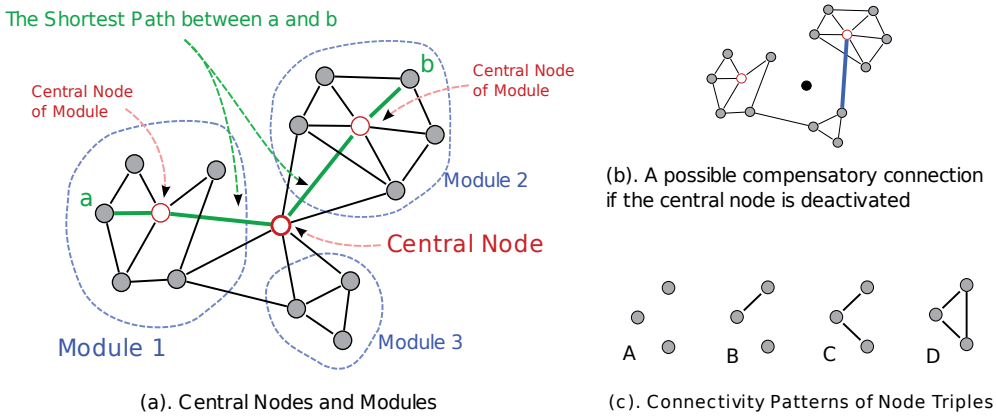


Fig. 9. Network measures suitable for graphs of moderate size. A central node, as the red nodes in sub-figure (a), plays an important role in network communication. Nodes densely clustered form modules, as those circled by dotted lines in sub-figure (a). The blue edge in sub-figure (b) is a possible compensatory edge to restore the connectivity impaired by deactivation of the central node (thick black). Sub-figure (c) shows the possible connectivity patterns of node triples. Connectivity patterns appear significantly more frequently than those in random graphs are called "network motif".

features systems that are highly locally clustered, like regular lattices, but still have small geodesic diameter, like random graphs (Watts & Strogatz, 1998). Modules can be detected by hierarchical clustering algorithms that groups node from the most linked pairs to the least pairs, or by community detection algorithms (Girvan & Newman, 2002) that draw module boundaries by breaking unimportant edges one by one.

- **Perturbation and compensation mechanisms.** It is believed that as a dynamic system, the brain will respond to impairment such as that induced by disease, by recruiting other neural resources to compensate the partially disabled function. This compensation mechanism is an important hypothesis of neuro-rehabilitation, and also related to many neurological diseases. Network analysis for the compensation mechanism can take a perturbation-and-recovery approach: deleting a connection or deactivating a node, and then searching for the most efficient changes that are needed to restore the impaired connectivity. Such mechanism could be developing a new connection other than the deleted one, or increasing the functionality of the most central node of the "lesioned" network (Kötter et al., 2007).
- **Motif and connectivity pattern.** Inter-connected nodes are building blocks of a big network, and the connectivity patterns among neighboring nodes characterize how information is processed at the local level. It has been found that in real-world networks certain patterns of inter-connections occur much more frequently than in random networks, and these "signature" local patterns are called network "motif" (Milo et al., 2002; Sporns & Kötter, 2004). Another network measure related to the "small-world" property is clustering coefficient, which is a function of the counts of pattern C and pattern D in Fig. 9-(c).

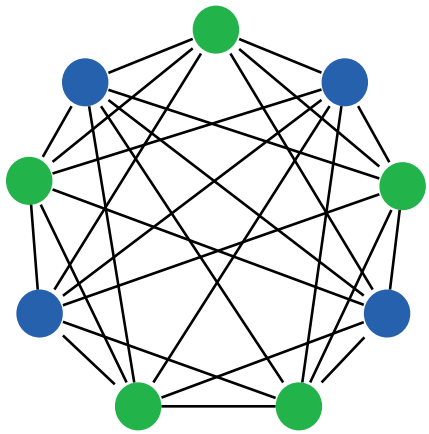


Fig. 10. An example of the discriminability of different centrality measures. With the betweenness, the closeness and the eigenvector centrality, all the nodes are identical, while with the sub-graph centrality, the nodes are distinguishable, with score 45.696 for blue nodes, and 45.651 for green nodes. This example is from (Estrada & Rodrguez-Velzquez, 2005).

4.2 Discriminability of network measures

When using network measures to quantitatively reveal the differences with respect to a certain network concept, we naturally expect that the measure could sensitively detect even subtle differences. As various calculation methods could be proposed to quantify the same network concept, this raises the concern of the discriminability of these calculation methods. For example, to measure the centrality of a node, there are options such as the betweenness (Freeman, 1977), the closeness (Beauchamp, 1965), the sub-graph (Estrada & Rodrguez-Velzquez, 2005), and the eigenvector centrality (Bonacich, 1972). As Fig. 10 shows, certain difference can only be detected by some measures.

This situation motivates the future development of theoretical criteria for rigorously comparing network measures and guiding their design, besides just evaluating them empirically. Theoretically, it is possible to use just a real number to uniquely represent a binary graph, achieving perfect discriminability. For instance, the adjacency matrix can be lined straight as the binary coding of a rational number. Though this simple mapping may not be meaningfully related to any network concept, it at least shows that with a single index all graphs can be distinguished.

For network measures of a graph, an available criterion is the mutual information between the measure and the "isomorphic" class of graphs (Corneil & Gotlieb, 1970). Two graphs G_1 and G_2 are isomorphic if and only if there is a one-to-one mapping f between the nodes of G_1 and G_2 such that for every adjacent node pair a and b in G_1, their mirrors in G_2, ie. $f(a)$ and $f(b)$, are also adjacent, and vice versa. Similarly, for network measures about a node in a graph, their discriminability can quantified with the mutual information between the measure and the "isomorphic" class of the nodes. Two nodes a and b in a graph G are isomorphic if and only if there a permutation p of the nodes of G such that $p(a) = b$ and $p(b) = a$ and that for every adjacent node pair c and d (which can be a or b), $p(c)$ and $p(d)$ are also adjacent. It is of great theoretic and practical importance to further pursue criteria for rigorously comparing the discriminability of network measures.

5. Concluding remarks

In this article, we reviewed the application of graphical models for inferring brain connectivity from fMRI data. We have described and provided signal processing solutions for the challenges raised in this highly interdisciplinary and innovating research field related to model reliability, generality and interpretability.

The importance of error control during brain network structure learning has been increasingly recognized, with a series of papers being published since 2005. These papers proposed solutions from the perspective of both classical and Bayesian statistics, and provided some theoretical conclusions. Because brain regions are not just algebraically isolated variables, but rather located in a three-dimension space with complex geometric structure, a desirable future direction is to exploit this geometric information for improving the error control.

Group analysis is a frequently encountered requirement in biomedical research. Graphical models introduce inter-subject diversity at both the parameter level and the structure level. Most existing methods can be considered to take a two-level framework: a lower level of models for each individual subject, and a group level integrating individual models and describing inter-subject commonality and diversity. Being modular, incrementally updatable, and scalable is highly desirable, yet not well implemented features for current group analysis.

Network analysis is an important post-processing for extracting interpretable and human-understandable information from graphical models. Network concepts such as centrality, modularity, connection patterns, the "small-world", "scale-free" property have been actively explored in the analysis of brain connectivity. As various calculation methods could be proposed to quantify the same network concept, it is of great theoretic and practical importance to further pursue criteria for rigorously comparing the discriminability of network measures.

6. Appendix

Software and databases

The interest on modeling brain connectivity using fMRI has been experiencing an increasing, important growth in the signal processing community during the last decade. One of the factors of this success is the availability of public-available software and databases. As a reference for interested readers, here we provide an overview of several widely used computer programs related to fMRI brain connectivity analysis. This list is by no means complete.

- **Statistical Parametric Mapping (SPM)**: Developed by the Wellcome Trust Centre for Neuroimaging.
  Website: `http://www.fil.ion.ucl.ac.uk/spm`
  Brief description: The SPM software package, probably the most popular one, has been designed for the analysis of brain imaging data sequences. The sequences can be a series of images from different cohorts, or time-series from the same subject. The current release is designed for the analysis of fMRI, PET, SPECT, EEG and MEG.
- **LONI Software**: Developed by the Laboratory of Neuro Imaging at the University of California, Los Angeles.
  Website: `http://www.loni.ucla.edu/Software`
  Brief description: The popular LONI Software is a comprehensive library for neuroimaging analysis, including pipelines for automated processing, web-based applications, tools for image processing and visualization, etc.

- **FMRIB Software Library (FSL)**: Developed mainly by the FMRIB Analysis Group at the University of Oxford.
  Website: `http://www.fmrib.ox.ac.uk/fsl`
  Brief description: FSL is a comprehensive library of analysis tools for fMRI, MRI and DTI brain imaging data.
- **MRIcro**: Developed by Professor Chris Rorden's group at the University of South Carolina.
  Website: `http://www.sph.sc.edu/comd/rorden`
  Brief description: MRIcro allows efficient viewing and exporting of brain images. It can create Analyze format headers for exporting brain images to other platforms, such as SPM. In addition, it allows neuropsychologists to identify regions of interest (ROIs).
- **FreeSurfer**: Developed by the Athinoula A. Martinos Center for Biomedical Imaging.
  Website: `http://surfer.nmr.mgh.harvard.edu`
  Brief description: FreeSurfer is a set of automated tools for reconstruction of the brain cortical surface from structural MRI data, and overlay of functional MRI data onto the reconstructed surface.
- **Brain Connectivity Toolbox (BCT)**: Developed mainly by the Computational Cognitive Neuroscience Laboratory at Indiana University.
  Website: `http://www.brain-connectivity-toolbox.net`
  Brief description: This toolbox provides an access to a large selection of complex network measures in Matlab. Such measures aim to characterize brain connectivity by neuro-biologically meaningful statistics, and are used in the description of structural and functional connectivity datasets.

There are normally fMRI datasets associated with the above software. Here we also briefly mention a few publicly-available fMRI databases. Details related with the experiment, design and data content are available in the associated website links.

- **fMRI Data Center (fMRIDC)**: Funded by the National Science Foundation, the W. M. Keck Foundation.
  Website: `http://www.fmridc.org`
- **Biomedical Informatics Research Network (BIRN) Data Repository**
  Website: `http://nbirn.net/bdr`
- **The Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC)**: Funded by the National Institutes of Health Blueprint for Neuroscience Research.
  Website: `http://www.nitrc.org`

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20

Event-Related Potential Studies of Cognitive and Social Neuroscience

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1. Introduction

In this chapter, we assess the role of Event-Related Potentials (ERP) in the field of cognitive neuroscience, particularly in the emergent area of social neuroscience. This is new ground that combines approaches from cognitive neuroscience and social psychology, highlighting the multilevel approach to emotional, social and cognitive phenomena, and representing one of the most promising fields of cognitive neuroscience (Adolphs, 2003, 2010; Blakemore, Winston and Frith, 2004; Cunningham and Zelazo, 2007; Decety and Sommerville, 2003; Frith and Frith, 2010; Insel, 2010; Lieberman and Eisenberger, 2009; Miller, 2006; Ochsner, 2004; Rilling and Sanfey, 2011; Sanfey, 2007; Singer and Lamm, 2009; Zaki and Ochsner, 2009).
The technique of ERPs is a precise tool regarding time resolution (on the order of milliseconds). ERPs are useful not only for their excellent temporal resolution but because recent advances (e.g., dense arrays, single trial analysis, source localization algorithms, connectivity and frequency measures, among others) provide multiples sources of brain activity in response to cognitive events.
First, a definition of ERPs and an explanation about the recordings and features of main components (P1, N1, N170, VPP, EPN, N2, P2, P3, N400, N400-like LPC, LPP, P600, ERN, fERN, CNV, RP; LRP, MP, RAP) are detailed (including a description of their generating sources when available). We then introduce some representative examples of cognitive and social neuroscience: contextual approaches to language, emotions and emotional body language; empathy; and decision-making cognition. All these areas are reviewed, highlighting their relevance for cognitive neuroscience and clinical research (neuropsychiatry and pathophysiology). Finally, important issues, such as sleep research, intracranial ERPs recordings, source location in dense arrays and co-recordings with fMRI, are discussed.

2. Event-Related Potentials (ERPs)

The technique of ERPs is a precise tool regarding time resolution (on the order of milliseconds) that incorporates the recording of ongoing electrophysiological activity using

electroencephalography (EEG). ERPs result from the synchronous activation of neural subpopulations that occur in response to events (sensory, motor or cognitive). ERPs are useful not only for their excellent temporal resolution but because recent advances (e.g., dense arrays, single-trial analysis, source localization algorithms, connectivity and frequency measures, among others) provide multiples sources of brain activity in response to cognitive events.

To measure the brain activity, the ERP quantifies electrical fields through the skull and scalp. This last procedure is named electroencephalography (EEG). ERPs are the ongoing electrophysiological activity resulting from the synchronous activation of several neural subpopulations that occur in response to sensory, motor or cognitive events (Hillyard and Picton, 1987). ERPs are the summed activity of excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP) activated in response to each new stimulus or subject response. The ERPs are less precise for the anatomical localization of the neural generators than the neuroimaging techniques. Nonetheless, this technique has an exceptional temporal resolution of milliseconds (Kutas and Federmeier, 2000). An ERP's spatial distribution on the scalp is not indicative of its brain-source generators (although some mathematical tools for source algorithm localization can enhance the spatial precision).

Electrodes are attached to diverse points on the scalp relative to bony landmarks. Using a standardized EEG-measurement technique to determine the correct spots, the entire head is measured. Normally, the participants are placed in front of a computer screen with electrodes fixed onto the scalp and connected to electric amplifiers and auditory headsets displaying a pattern of stimuli. One computer records and amplifies the electrical peaks elicited by each stimulus onset (or the participant response).

The EEG activity is time-locked to several presentations of similar events (stimuli or participants responses), and the averaging of these segmented EEG traced together is the usual procedure. The average decreases the influence of noisy activity (i.e., EEG not related to experimental events or background noise) while maintaining the event-related activity. Several signal processing steps, such as filtering (e.g., 0.5 to 30 hz), segmentation, artifact detection and correction, bad channel replacements, re-referencing, baseline correction and averaging, are usually required to obtain a suitable signal-to-noise ratio (see Figure 1). After these processing steps, positive or negative changes of voltage constitute ERPs that appear at specific latencies after the stimulus presentation. Most ERP components are referred to by a preceding letter (e.g., "N"), indicating polarity followed by the typical peak latency in milliseconds (e.g., the "N400" ERP component is described as a negative voltage deflection occurring approximately 400 ms after the stimulus onset). The timing of the brain processing is measured by the timing of these cortical responses.

The simplest ERP parameters are latency (how long after the event they appear), direction (positive or negative), amplitude (the strength of the voltage change) and topological distribution of the component on the surface of the head (frontal, parietal, occipital, etc.). The standard procedure to visualize and measure the ERP activity consists of quantifying the amplitude and latency (measured in microvolts and milliseconds, respectively) of the waveform associated with a specific stimulus or response. By means of this procedure, different stimuli or conditions can be contrasted in terms of amplitude or latency. It is usually stated that a given ERP "is modulated by," "is sensitive to" or "discriminates" a given condition when statistically significant differences are found in latency, amplitude or morphology, respectively, as a function of such condition manipulation.

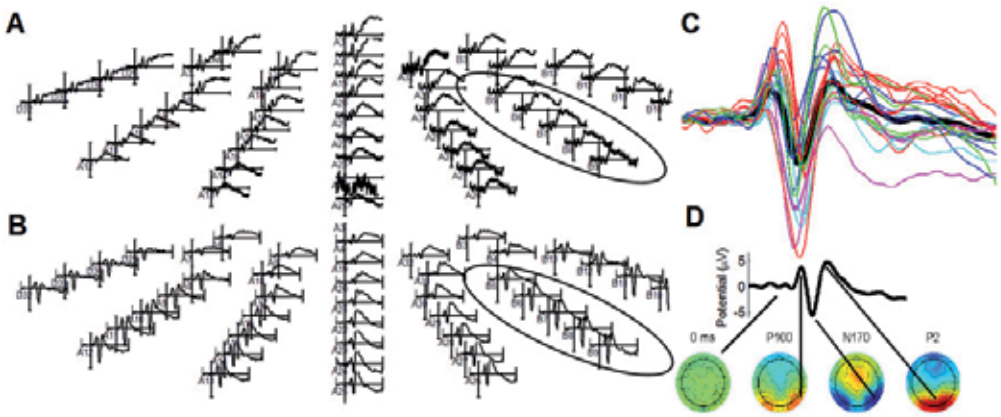

Fig. 1. ERP signal-to-noise ratio. A) ERPs at temporo-occipital scalp in response to face stimuli without preprocessing and (B) with preprocessing. Note how the N170 can be clearly observed after preprocessing over the right occipito-temporal sites (comparing both ellipses). C) N170 estimation over a representative electrode (T8) demonstrating the signal-to-noise ratio reduction in between the subject's average waveform (black line). D). Voltage map reconstruction by interpolation showing the scalp activity at 0, P100, N170, 200 and P2 after the presentation of face stimuli.

A continuous reconstruction of electrical activity on the scalp, normally based on spatial interpolation of the electrode sites, is termed a topographical map (or a voltage map or topomap). Each component usually has a relatively specific topographic distribution. The so-called long latency components (cognitive components or endogenous components) occur after 100 ms and are sensitive to changes in cognitive processing, as the meaning of the stimulus, or resources of processing required in the task performed (Hillyard, 2000). In the following section, we provide a succinct description of several components.

3. A selective description of main components

3.1 P100 and N100 (P1 and N1)

Eason et al. (1969) found that visual stimuli situated in visual fields with focused attention elicited components with larger amplitude (approximately 100 ms after stimulus onset, P1 and N1), compared with ignored or unnoticed stimuli. This amplitude enhancement is at its maximum in the temporal-occipital region, contralateral to the localization of the stimuli and is sensitive to the specific localization of the stimuli in the visual field (Mangun et al., 1993). Comparable results were obtained in the auditory modality by a dichotic listening paradigm (Hillyard et al., 1973). This auditory early-attention effect reflects a response increase of the auditory primary cortex (Woldorff et al., 1993). The P1 and N1 components are also modulated by several factors in the attentional task, such as emotional saliency, relevance or familiarity.

3.2 P200 (or P2)

Is a positive deflection occurring approximately 200 ms after the onset of the stimulus? P200 has been interpreted as reflecting selective attention (Hackley, Woldorff and Hillyard, 1990) and visual-feature detection processes (Luck and Hillyard, 1994). Similarly, P2 has been

shown to be sensitive to orthographic/phonological tasks, semantic categorization tasks, reward-punishment discrimination and lexical decision tasks.

3.3 N200 (or N2)

Is a negative deflection resulting from a deviation in form or context of a prevailing stimulus? Normally, N2 is evoked 180 to 235 ms following the presentation of a specific visual or auditory stimulus. Additionally, the N2 is considered to be a family of different components, but its classic consideration can be elicited through an experimental oddball paradigm and is sensitive to perceptual features (Bentin et al., 1999). This component is also associated with conflict detection during the regulation of successful behavior (Nieuwenhuis, Yeung, Van Den Wildenberg and Ridderinkhof, 2003). The source of N2 modulation compromises the anterior cingulate cortex (ACC hereafter, a brain area susceptible to social monitoring of conflict) and other prefrontal cortex areas (Nieuwenhuis et al., 2003).

3.4 N170/Vertex Positive Potential (N170/VPP)

The N170/VPP complex is a negative peak around 170 ms in the temporal-occipital regions and simultaneously one central-frontal positivity (VPP), functionally equivalent (Joyce and Rossion, 2005). The source of N170 compromises the inferior temporal gyrus and the fusiform gyrus (two neural areas associated with specific face processing). Its amplitude is greater for human faces, compared with objects or other stimuli (Bentin, Allison, Puce, Perez and McCarthy, 1996; Jeffreys, 1989). During the face-processing task, N170 is sometimes followed by a P2, a N250 and an LPP component modulated by other variables. The N170 component has shown amplitude/latency modulation based on race cues (Ibanez et al., 2010c; Ito and Ulrand, 2005; Gonzales et al., 2008), emotional variables (Ashley, Vuilleunier and Swick, 2004) and contextual effects (Ibanez et al. 2011d).

3.5 Early Posterior Negativity (EPN)

The EPN is a middle-latency component that has been associated with different stages of valence information processing and affective discrimination (Schupp et al., 2004a, 2004b). Di Russo, Taddei, Apnile and Spinelli (2006) suggested that EPN would reflect early valence discrimination and response selection processes. Additionally, Schupp et al. (2004a) have stated that the processing indexed by the EPN is modulated by perceptual features that facilitate further evaluation of arousing stimuli. Different studies have found a modulation differing from the neutral for both emotional (pleasant, unpleasant) categories of pictures (e.g., Dufey et al., 2010; Cuthbert, Schupp, Bradley, Birbaumer and Lang (2000). Nevertheless, specific effects (task or stimuli-dependent) on EPN in relation to valence and the influence of arousal should be further assessed.

3.6 P300 (or P3)

This component has been described as engaging higher-order cognitive operations related to selective attention and resource allocation (Donchin and Coles, 1988). The P3 amplitude may serve as a covert measure of attention that arises independently of behavioral responding (Gray et al., 2004). The component has also been related to a post-decisional "cognitive closure" mechanism (Desmedt, 1980; Verleger, 1998); and to the access of information for consciousness (Picton, 1992). Its amplitude generally varies as a function of the temporal

distance between a target and a preceding outgoing stimulus (e.g., Cornejo et al., 2007). There are two sub-components (P3a and P3b). The P3a has a more frontal distribution and is observed after an unexpected event, regardless of the relevance of the stimulus. Usually, it is associated with automatic attentional modulation. The P3b is related to attention, working memory and superior cognitive functions and is observed at centro-parietal sites. This ERP is affected by several psychological processes, the most important of which are motivation and sustained attention.

3.7 Late Positive Components (LPP, PPC, P600)

The late positive potential (LPP) is considered to be a family of components (although initially was described by Sutton in 1965 as a unique, frontal bilateral positivity). This late component (300 to 700 ms) is sensitive to stimuli valence and to the previous emotional context (Cacioppo et al., 1994, Schupp et al., 2000). Its amplitude, according to several studies, increases in response to motivationally relevant stimuli (i.e., pleasant or unpleasant images; Cuthbert et al., 2000; Schupp et al., 2000; Schupp, Junghofer, Weike and Hamm, 2004). The amplitude, latency and topography of LPP are modulated by the semantic emotional valence of stimuli (Cunningham et al., 2007) and contextual information (Cornejo et al., 2009; Hurtado et al., 2009). The late positive complex (LPC) is a component similar to LPP and has been related to the process of re-analysis of the incongruent situation produced by inconsistent meaning (Ibanez et al., 2010a, 2011b; Sitnikova, Kuperberg and Holcomb, 2003). The P600 is considered to be an index for second pass-parsing processes of information processing, having much in common with working memory operations. It is associated with superior frontal, temporal and parietal regions, which are believed to contribute to some aspects of information processing during recognition memory.

3.8 N400 and N400-like

The N400 is a negative component that appears around 400 ms after the presentation of semantically unrelated information between two words or between a context and a word. Although this component was first studied in the linguistic field, recent studies have extended previous results to richer action sequences and pictorial stimuli (sometimes called N350 or N400-like), such as congruent-incongruent pictures or videos of gestures, actions and motor events (Aravena et al., 2010; Cornejo et al., 2009; Proverbio et al., 2010; Ibañez et al., 2010b, 2011; Guerra et al., 2009; Sitnikova et al., 2003). Although spatial resolution provided by ERP does not allow a precise localization of N400 neural generators, evidence from lesion studies, MEG and intracranial recordings converge to implicate temporal areas (left superior/middle temporal gyrus, the anterior-medial temporal lobe, the PHC and anterior fusiform gyrus) as the possible sources of N400 (Van Petten and Luka, 2006). This N400 points to a distributed and multimodal system that is simultaneously open to verbal and nonverbal meanings (Kutas and Federmeier, 2000).

3.9 Contingent Negative Variation (CNV)

CNV is an extended and prolonged negative potential recorded during simple, warned reaction time paradigms from central and parietal scalp fields. Its scalp distribution always begins bilaterally and symmetrically at the midline of the precentral-parietal regions, approximately 1.000 to 1.500 ms before response movement. CNV is a correlate of anticipation of the latter presentation of a stimulus target (Picton and Hillyard, 1988; Walter, Cooper, Aldridge, McCallum and Winter, 1964).

3.10 Error-Related Negativity (ERN) and Feedback Error-Related Negativity (fERN)

The ERN is a component observed 50 to 100 ms after a response characterized as being of high conflict in which a dominant response is inconsistent with respect to the correct response (Hohnsbein, Falkenstein and Hoormann, 1995 and others). The ERN is an index for the general sensitivity of the conflict monitoring system, which can be used to predict successful patterns of control (Yeung, Botvinick, and Cohen, 2004). Feedback error-related negativity (fERN) has been referred to as a negative deflection in the event-related potential (ERP), which distinguishes between wins/losses or correct/error trials in terms of expected and unexpected outcomes (e.g., San Martin et al., 2010). In correct (ERN) or win trials (fERN), similar components have been named Correct Related Negativity (CRN) and

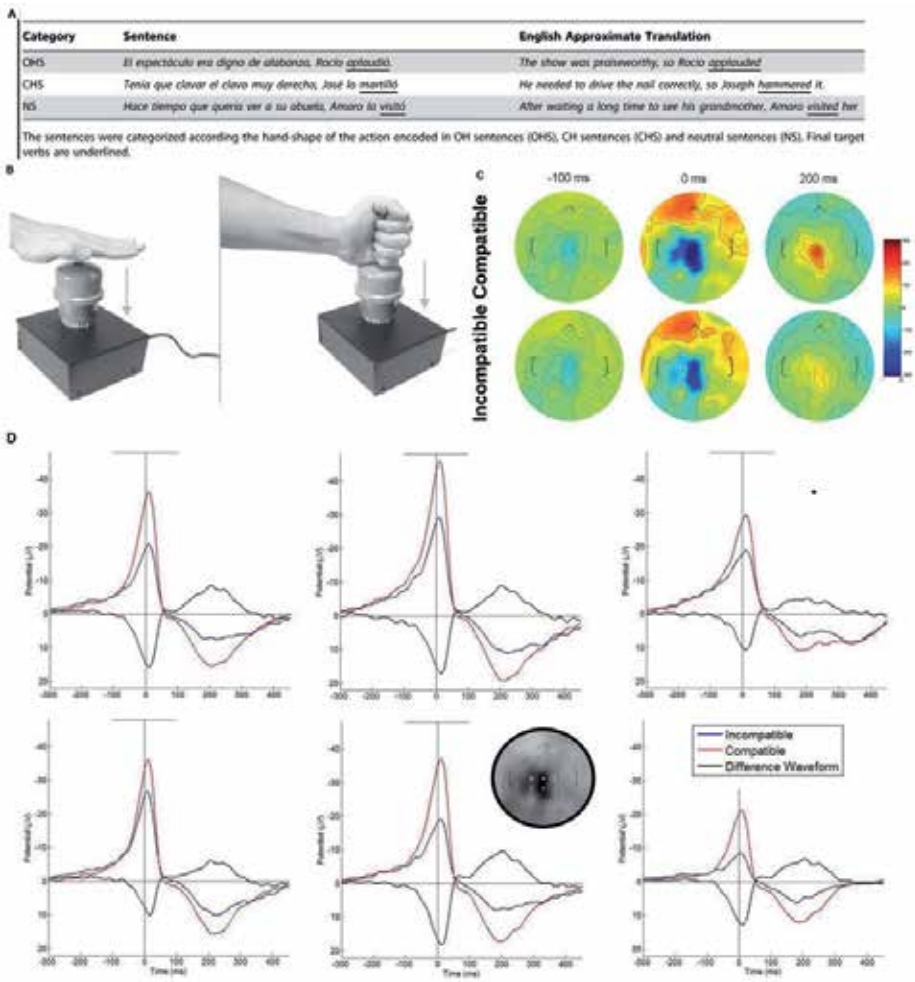

Fig. 2. Motor potential (MP and RAP) modulated by compatibility with semantic stimuli. A) Verbal stimuli used in an action-sentence compatibility paradigm. B) Participants' open- and close-hand responses. C) Scalp topography of the motor response at baseline, zero-time response and 200 ms after the response. D) Motor potential (MP and RAP) modulated by the compatibility between the participant motor responses (open or close) and the semantic stimuli (sentences containing open- or close-hand actions). Modified from Aravena et al., 2010.

feedback correct-related positivity (fCRP), respectively. According to an extended theory called the "reinforcement learning theory of ERN," both forms of ERN/fERN reflect the function of a generic, high-level error-processing system in humans (Holroyd and Coles, 2002). Both the ERN and fERN have a main source on the cingulate cortex, the anterior and the posterior division.

3.11 Motor components (RP, LRP, MP, RAP)

The movement-related cortical potentials (MRCP) associated with self-paced movements are considered to be a measure of motor cortex excitability and allow the exploration of cortical changes related to motor preparation and execution. The readiness potential (RP, or in its original German name, Bereitschaftspotential) precedes voluntary muscle movement and represents the cortical contribution to the pre-motor planning of volitional movement. The RP was first described in 1964 by Hans Helmut Kornhuber and Lüder Deecke. The lateralized readiness potential (LRP) is a particular form of RP in response to certain movements of one side (left or right) of the body. Being related to RP, another negativity measured over Cz beginning shortly before the response onset (-90 ms) has been named the motor potential (MP) or late motor-related potential (late MRP; Aravena et al., 2010). The MP is likely to represent pyramidal neuron activity in the primary cortex (M1) at motor execution. MP amplitude modulation has been associated with the rapidness and precision of movement and also with short-term training effects. Finally, another component with a peak over Cz after movement onset (200-300 ms) has been named the re-afferent potential (RAP). RAP is an index of movement-related sensory feedback to the primary sensory-motor cortex and is considered an indicator of attention (Aravena et al., 2010, see Figure 2).

4. Representative areas of social cognitive neuroscience

4.1 Contextual approaches to language

Context-dependence effects are pervasive in everyday cognition (Barutta et al., 2011; Cosmelli and Ibañez, 2008; Ibanez and Cosmelli, 2008; Ibanez et al., 2010a), especially in the case of language (Ledoux, Camblin, Swaab and Gordon, 2006; Rodriguez-Fornells, Cunillera, Mestres-Misse and de Diego-Balaguer, 2009). We listen and say words within other streams of words. We perceive the emotion of a face altogether with the emotional body language, the semantics, the prosody and other cues from the situation. Language use can be tracked by assessing the influence of context parameters (such as intonation, lexical choice, prosody, and paralinguistic clues) in a current communicative situation. ERPs studies of early (N170 and ELAN) and late components (N400, LPC, LPP) have provided important insights about the temporal brain dynamics of contextual effects in language. For instance, important issues, such as automaticity of contextual effects, multimodal blending of meanings, action-sentence coupling, language-like gesture processing, language and social information coupling, and early emotional word processing have been demonstrated within ERP research (Aravena et al., 2010; Cornejo et al., 2009; Hagoort, 2008; Ibanez et al., 2006, 2009, 2010b, 2010c, 2011b; 2011c, 2011d, 2011e, Van Petten and Luka, 2006). Contextual effects in language assessed with ERPs is a relevant topic in diverse areas of neuropsychiatric research, such as schizophrenia (Guerra et al., 2009; Ibanez et al., 2011c), Alzheimer's disease and mild cognitive impairment (Schwartz et al., 2003; Taylor and Olichney, 2007), focal basal ganglia lesions (Paulmann, Pell and Kotz, 2008) alcoholism (Roopesh et al., 2009) and aphasia (Wassenaar and Hagoort, 2005), among other conditions.

4.2 Emotion and emotional body language

Today, it is well known that complex social skills depend on basic emotional processing and inference (Grossmann, 2010). Moreover, facial emotional expressions can provide an automatic and rapid shortcut to alarm signals, mentalizing and inter-subjective communication. Important issues in emotion research, such as face emotional processing (Eimer and Holmes, 2007), emotion regulation (Hajcak, MacNamara and Olvet, 2010) and the intertwining of attention and emotion (Schupp, Flaisch, Stockburger & Junghofer, 2006) have a long tradition in ERP research.

Early, automatic and unaware processing of emotion in faces, words and pictures have been demonstrated within ERP research (Guex et al., 2011; Ibanez et al., 2010c, 2011d, In press, Submitted b, see Figure 3.A). Theoretical models of emotion perception (Vuilleumier and Pourtois, 2007) propose a parallel and interactive system indexing object recognition (e.g., triggered by the fusiform gyrus) and emotional discrimination (e.g., triggered by the amygdala). Emotional signs that can denote confidence or danger may occur before and parallel to the process of object codification. In other words, emotional significance can be processed before a stimulus is completely identified. At the same time, processing of complex social stimuli intermixed with emotional processing has been reported at late stages, indexed with the LPP and LPC (Dufey et al., 2010; Hurtado et al., 2009; Ibanez et al.,

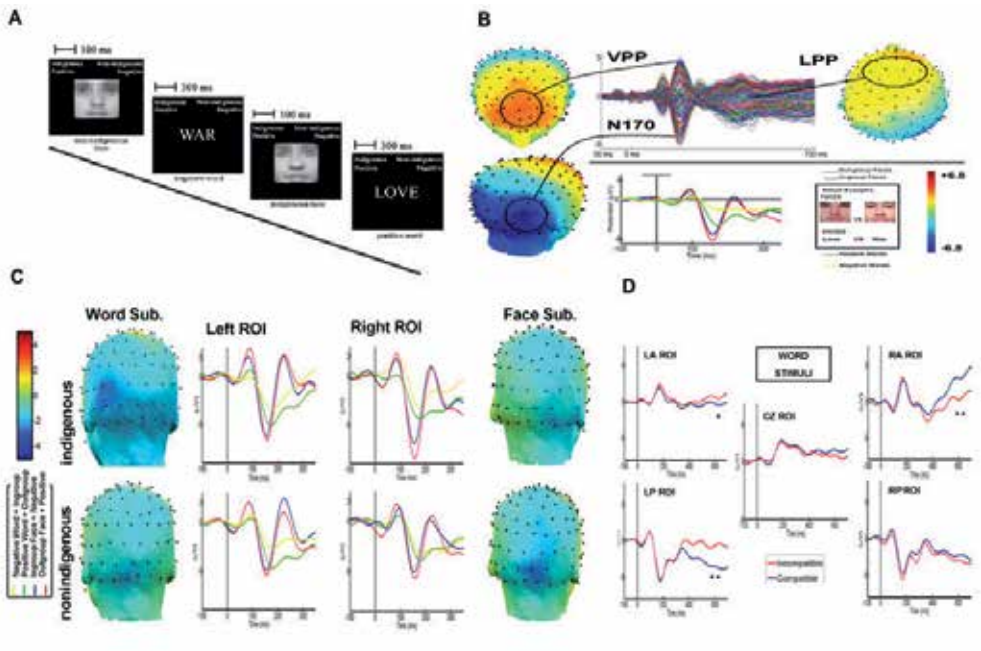

Fig. 3. Early and late emotional-cognitive processing. A) Implicit association test (IAT) schematic representation. Both ingroup and outgroup faces, along with words of positive and negative valence, are presented. The subject is required to classify each stimulus to the left or to the right according to labels displayed on top of the screen. B) Early (N170) and late (LPP) effects of IAT. C) N170 contextual modulation based on valence and membership stimuli. D) Late processing (LPP) of semantic stimuli compatibility. Modified from Hurtado et al. 2009 and Ibanez et al 2010c.

2009, 2010b, 2011b, see Figure 3.B). Emotional body language (EBL) is another emergent area in neuroscience research (de Gelder, 2006). Neuroimaging studies have shown that the EBL activates similar areas of emotional face processing, such as amygdala and fusiform gyrus. EBL signals are automatically perceived and influence emotional communication and decision making. ERP research has demonstrated that EMB (a) is automatic and processed early in the brain; (b) influences the emotional recognition of face processing; and (c) is processed in an integrated way with face processing (de Gelder et al., 2006; Meeren, van Heijnsbergen and de Gelder, 2005).

4.3 Empathy

A large number of studies using functional MRI, and more recently electrophysiology, have used the presentation of stimuli depicting people in pain (i.e., people suffering from physical injuries or expressing facial expressions of pain) to characterize the neural underpinnings of empathic processing (Botvinick et al., 2005; Jackson et al., 2006; Cheng et al., 2008a; Fan et al., 2008; Han et al., 2008; Akitsuki and Decety, 2009, Decety et al., 2010c). The results from these studies suggest that empathy for pain involves a somatosensory resonance mechanism between other and self that draws on the affective and sensory dimensions of pain processing (Jackson et al., 2006). This mechanism provides crucial and rapid information to help us understand the affective states of others and respond to them (Decety and Lamm, 2006).

ERP studies of empathy for pain showed an N1 differentiation (neutral pictures eliciting greater negative amplitudes) over the frontal area, as well as a late P3 over the centro-parietal region (pain pictures producing greater positive amplitudes; Fan et al., 2008; Han et al., 2008; Decety et al., 2010). These ERPs studies have shown early modulation by contextual reality of stimuli and late modulation based on cognitive regulatory and task demands (Fan and Han, 2008; Han et al., 2008; Decety et al., 2010c; Li and Han, 2010), as well as 'other-related' information, such as priming for treat signaling (Ibanez et al. 2011e). ERP studies have provided important insights regarding the context-dependent processing and differences in automatic-controlled processing on empathy for pain research.

4.4 Decision making and reward

The current neuroscience of decision making has assessed multiple processes engaged in this complex cognitive ability. Evidence from animals, healthy human volunteers and neuropsychiatric patients (e.g., Bechara and van Der Linden, 2005; Brand et al., 2006; Camerer et al. 2008; Gleichgerrcht et al. 2010; Kable and Glimcher, 2009; Glimcher and Rustichini, 2004; Rangel 2008; Rangel, Rushworth et al., 2007) highlights the role of frontostriatal and limbic loops in decision making. Despite some discrepancies between different models, three main systems are thought to be involved in frontostriatal and limbic loop: a stimulus-encoding system (orbitofrontal cortex), a reward-based action-selection and monitoring system (cingulate cortex) and an expected-reward system (basal ganglia and amygdala). We have shown (Gleichgerrcht et al., 2010) that these systems are crucial in the decision-making process in normal voluntaries, as well as in neuropsychiatric disorders, such as neurodegenerative diseases (Figure 4). The action-selection and monitoring system can be tracked directly with the P2, the ERN and the fERN, opening a new branch of research (Nieuwenhuis et al., 2004, 2005). Gambling and decision-making tasks can be assessed with ERPs (e.g., San martin et al., 2010). Behavioral measures of affective and risky

decision-making tasks would be not so sensitive as to assess subtle deficits in decision making in disorders such as adult attention deficit hyperactivity disorder and bipolar disorders. Conversely, ERP abnormal neural processing of valence and magnitude of rewards in a gambling task in those disorders may help to integrate reward, action-selection and monitoring systems, providing an excellent shortcut to goal-directed action (Ibanez et al., Submitted a). ERP research on gambling tasks provides both a clinical and a theoretical branch of research linking decision making, soft frontal diseases, monitoring-reward systems and psychiatry.

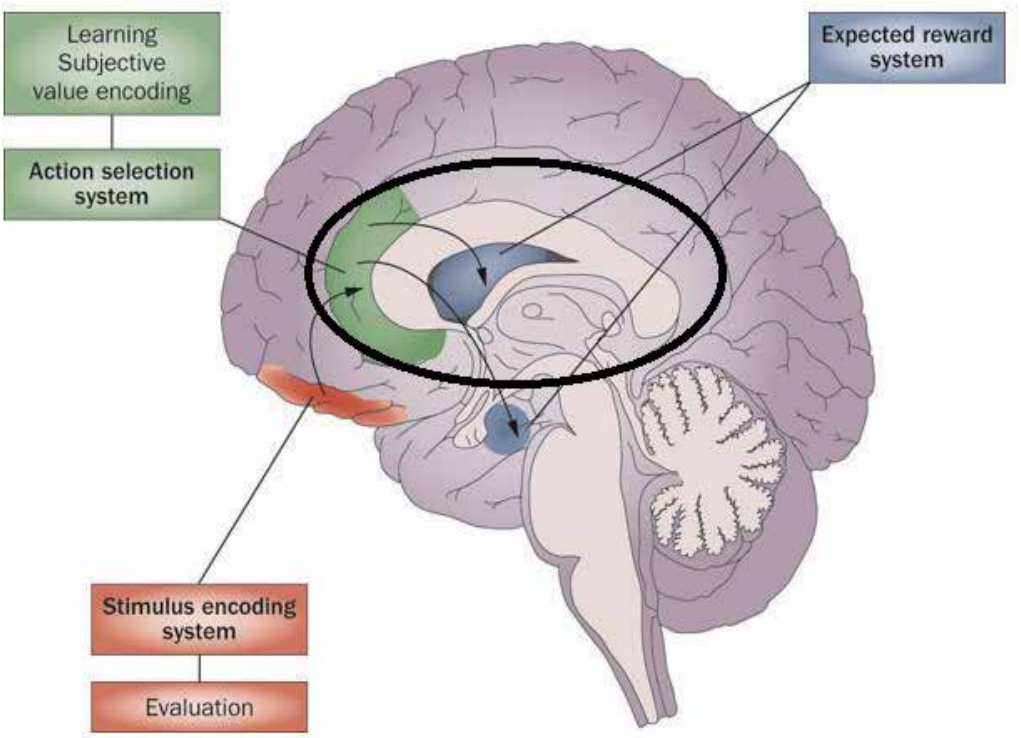

Fig. 4. A neuroanatomical model of decision making. Three main systems are thought to be involved in decision making: a stimulus-encoding system (orbitofrontal cortex shown in red), an action-selection system (anterior cingulate cortex shown in green) and an expected-reward system (basal ganglia and amygdala shown in blue). The anterior, medial and posterior cingulate cortex, together with basal ganglia (ellipse), seem to modulate the ERN and fERN in gambling and error-monitoring tasks. Modified from Gleichgerrcht et al., 2010.

5. Complementary issues

We have described several ERP components involved in studies of social and cognitive neuroscience. Now, in this section we review some methodological approaches of ERP research that complement and improve the advances in traditional ERP assessment: sleep research, intracranial recordings, source location analysis and co-recordings with fMRI.

5.1 Sleep research

The study of cognitive processing during sleep is a topic of great interest because ERPs allow the study of stimulation with passive paradigms (without conscious or behavioral response), opening multiple research possibilities during different sleep phases (Ibanez et al., 2008a). Different cognitive discriminations during sleep related to the learning, frequency, intensity, duration, saliency, novelty, proportion of appearance, meaning and even sentential integration of stimuli are topics of intense research (e.g., Ibanez et al., 2006). Methodological control of ERP sleep research, such the use of qualitative and quantitative measures of sleep stages (see Figure 5), the control of the so-called first night effect and the assessment of sleep disturbances are important factors for improving this research area (Ibanez et al., 2008b). Better control of experimental paradigms is relevant for the growth of the neuroscience of sleep.

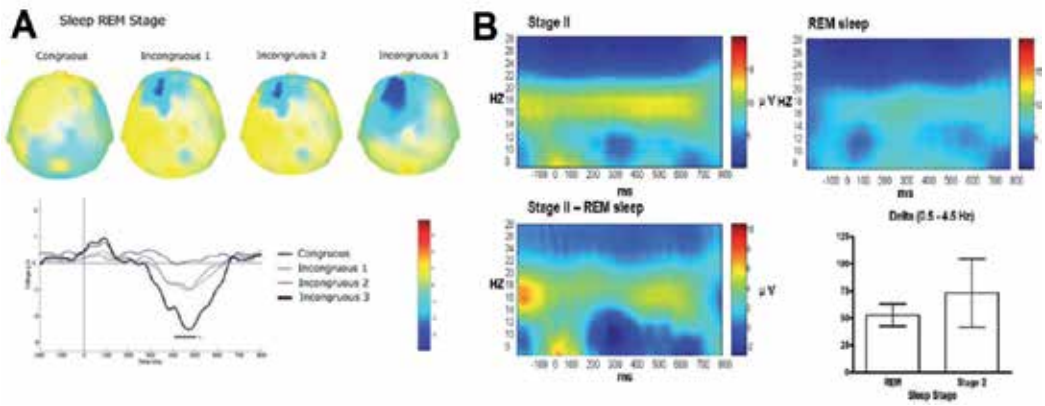

Fig. 5. Quantitative assessment of sleep stages during ERP recordings. A) The voltage maps and N400 waveform modulation of contextual semantic discrimination during REM sleep. B).Comparison of frequency bands between sleep stages (time-frequency charts for stage II sleep, REM sleep and stage II-minus-REM subtraction). Microvolt differences (mean and standard deviations) of delta band activity during stage II and REM (right bottom). Modified from Ibanez et al., 2006, 2008b.

5.2 Intracraneal recordings

The use of local field potentials (LFP) and electrocorticography (ECoG) in patients with surgically implanted electrodes (Figure 6) have provided a recent, new pathway to study the spatiotemporal brain dynamics of cognition. Intracraneal recordings help to diagnose and treat neurological conditions, such as epilepsy, Parkinson's disease and tumors. LFP and ECoG are measures of direct brain activity that have better (combined) temporo-spatial resolution than any other human neuroscience method. The ERP assessment, together with evoked oscillatory activity, has provided important insights on working memory, episodic memory, language, face processing, consciousness and spatial cognition (Jacobs and Kahana, 2010; Lachaux et al., 2003).

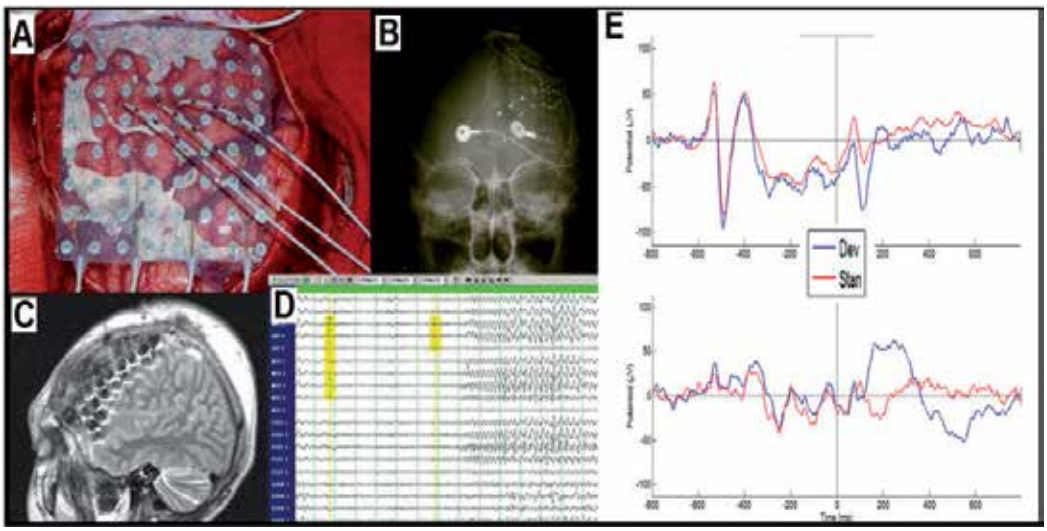

Fig. 6. Intracranial recordings. A) Grid of 63 electrodes for electrocorticography in a patient with refractory epilepsy. B) X-ray computed tomography (CT) and C) MRI showing the electrode grid and deep electrodes for local field potentials. D) Intracranial EEG. E) iERP recordings of deviant (DEV, Blue) and standard (STA, Red) stimuli during a global-local oddball task. Selected electrodes demonstrated an N2 and P3 modulation at the frontal (above) and parieto-temporal sites (below).

5.3 Source location in dense arrays

The current use of dense arrays of electrodes (from 64 to 256 channels) allows a better characterization of field potentials and improves the estimation of cortical brain sources, which generates the ERPs. The source estimation reduces the spatial imprecision of ERPs and links the temporal information with low-resolution anatomical measures. Important advances on parametric and non-parametric methods have been developed recently (Grech et al., 2008). Several engineering solutions of an inverse problem to find ERP sources using parametric and non-parametric approaches are available (e.g., LORETA, sLORETA, VARETA, S-MAP, ST-MAP, Backus-Gilbert, LAURA, SLF, SSLOFO and ALF; BESA, MUSIC and FINES). Methods of distributed sources (Figure 7), including biophysical and psychological constraints (e.g., LAURA), can produce more relevant results. Finally, principal-component analysis (PCA) and independent-component analysis (ICA) are now accessible for ERP source localization. The development of distributed EEG/MEG source analysis using statistical parametric mapping of MRI promises further advances in social-affective neuroscience (e.g., Junghofer, Peyk, Flaisch and Schupp, 2006).

5.4 FMRI-ERP simultaneous recordings

FMRI provides a fine spatial resolution but measures indirect brain signatures (hemodynamic response) and has poor temporal resolution. ERPs are a direct measure of cortical activity but have poor spatial resolution. Combining fMRI and ERPs provides a spatial and temporal fine-ground resolution of cognitive brain activity (Gore, Horovitz, Cannistraci and Skudlarski, 2006). Recently, removal algorithms of fMRI artifacts on ERPs

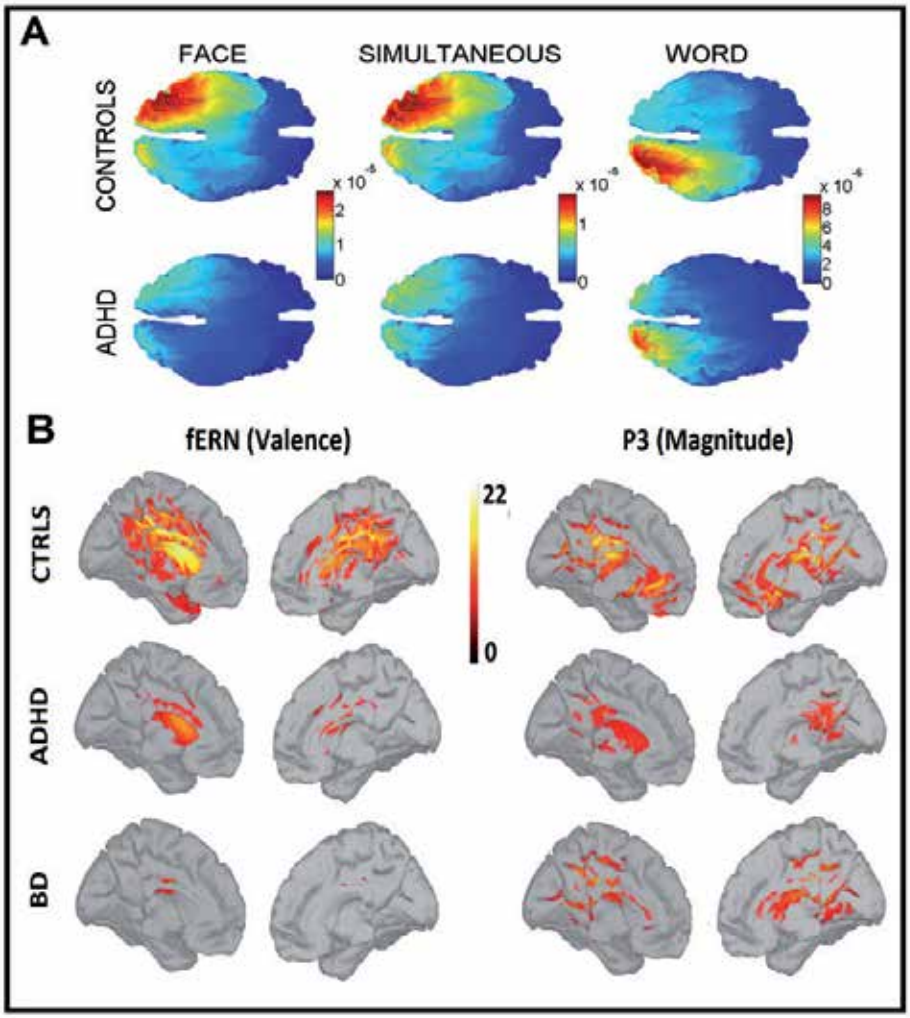

Fig. 7. ERP source estimation using distributed dipole modeling (N170 and fERN). A) N170 source imaging estimation of fusiform gyrus for faces, words and face-word simultaneous stimuli in controls (above) and patients (below) with ADHD. Average values of estimated, standardized current density power at maximum peaks of activation. B) Cortical current density mapping of valence and reward magnitude. The source estimation of distributed valence dipoles (fERN, left) and magnitude effects (P3, right) for controls, patients with ADHD and those with bipolar disorders (BD). Color-map values represent the t-values of comparisons between signal and noise. Modified from Ibanez et al., Accepted, Submitted a.

have been developed, facilitating the combined use of both methods. For instance, ERP/fMRI co-recording allows an enhanced study of origins and locations of ERP neural generators. For example, the spatial (face-processing brain areas) and temporal brain dynamics (N170) of face processing in the human brain have been reported with this methodology (Sadeh et al., 2008)

6. Conclusions

In this chapter, we highlighted the role of ERP research in the field of cognitive and social neuroscience. We introduced the ERP methodology and then a selective description of main components was developed. Subsequently, some representative fields of ERP research on the neural basis of language, emotion, empathy and decision-making cognition were presented. Finally, complementary methodological approaches (sleep research, intracranial recordings, source location in dense arrays and fMRI-ERP co-recordings) were introduced, highlighting the broad horizons of ERP research. By providing the fine, temporal brain dynamics of social and cognitive processes in normal, psychiatric and neurological participants, ERP research constitutes an important branch of human neuroscience.

7. Acknowledgments

This work was partially supported by grants CONICET and FINECO. The authors have no conflicts of interest related to this article.

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21

Neuroimaging Outcomes of Brain Training Trials

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1. Introduction

The brain remains plastic throughout the human lifespan. This unique property holds great promise for the better treatment of cognitive disorders, and forms the basis for behavioural interventions aimed at promoting mental function that may help delay and prevent the onset of dementia. Brain training (BT) is a direct method for targeting brain plasticity that employs repetitive cognitive exercises. Over the past decade increasing evidence has accumulated that BT can lead to clinical and cognitive benefits in psychiatric samples (McGurk et al., 2005, 2007), as well as in healthy older individuals (Valenzuela & Sachdev, 2009). However, the neurobiological mechanisms underlying these clinical benefits are not well understood. Advances in neuroimaging therefore has potential for revealing the complex *in vivo* structural, functional and metabolic brain changes that accompany BT. The aim of this systematic review was to compare and integrate results of several recent clinical trials of BT that have employed Magnetic Resonance Imaging (MRI), with a particular emphasis on design and technical issues. These studies are beginning to provide fascinating insights into the nature of BT effects on the human brain.

2. Definition of brain training

The wider cognitive intervention field abounds with multiple ill-defined terms that have hampered their development and validation, and can also explain mixed findings to date (Gates & Valenzuela, 2010). Clare and Woods divide this general area into 'cognitive rehabilitation', 'cognitive stimulation', or 'cognitive training' (CT) (Clare & Woods, 2004). We have proposed a specific operational definition for cognitive training (CT) to include cognitive interventions that meet the following four criteria: 1) involves repeated practice, 2) on tasks with an inherent problem, 3) using standardized exercises, and 4) that specifically target a cognitive domain (Gates & Valenzuela, 2010) . Here, the terms BT and CT are identical and are used interchangeably.

3. Method

3.1 Search strategy

The Medline (1996 – 04/2011) database was searched for original research articles in English that met the following criteria. (a) 'brain training', 'cognitive training', 'cognitive

intervention', 'cognitive exercise', 'mental exercise', 'cognitive activity' or 'cognitive stimulation', and (b) 'individuals', 'adults', 'persons', 'subjects', but no 'children' or 'teenagers', and (c) 'Magnetic Resonance Image', 'MRI' or 'brain scans'. Combined intervention, subject, and method terms were searched across all fields and produced 144 studies. The title and abstract of these studies were reviewed to identify potentially relevant trials, and these were supplemented by manual checking through reference lists of published reports.

3.2 Inclusion criteria & study quality

Studies were selected for review if they met the following criteria: i) comprised a longitudinal clinical trial with either a randomized controlled trial (RCT) design or uncontrolled clinical trial design (UCT), ii) sample included only healthy individuals not selected against clinical psychiatric criteria, iii) had MRI assessment at least at baseline (before training) and at post-training, and iv) the nature of the intervention met our definition for cognitive training (described above). The qualities of included studies were assessed against CONSORT 2001 criteria for clinical trials (www.consort-statement.org).

4. Results

4.1 Search results

After reviewing the 144 abstracts returned by our search, nine studies containing ten trials met our criteria. These included 7 RCT and 3 UCT. Details are provided in **Table 1**.

4.2 Study quality

Quality of studies varied between 13.5 and 19.5 (out of a maximum of 24). The main limiting factors were unspecified sample size calculations, or details about method of randomizing and blinding. CONSORT criteria scores for RCTs are provided in **Table 1** (maximum = 25).

4.3 Subjects

There were a total of 309 subjects included in the ten identified trials, split between training (N=168) and control groups (N=138). Sample size varied from 10 (Dahlin et al., 2008; Takeuchi et al., 2010) to 58 (Mozolic et al., 2010). Studies divided into three main groups based on age of participants: five studies of young adults with average age of 20-30 years (Dahlin et al., 2008; Erickson et al., 2007a; Olesen et al., 2004; Takeuchi et al., 2010), three studies of elderly subjects with mean age over 60 years (Engvig et al., 2010; Mozolic et al., 2010; Valenzuela et al., 2003), and two studies that combined both elderly and young adult age groups (Erickson et al., 2007b; Lovden et al., 2010). Recruitment source was also variable: young adult subjects were mainly university students, while elderly subjects were from the community based on newspaper advertisements (Dahlin et al., 2008; Engvig et al., 2010; Lovden et al., 2010). All subjects were cognitively-intact.

4.4 Nature of brain training

Because two studies used the same BT protocols (Erickson et al., 2007a, 2007b), a total of nine protocols were reviewed. These could be distinguished on the basis of implementation, either computer-based exercises (Dahlin et al., 2008; Erickson et al., 2007a, 2007b; Lovden et al., 2010; Olesen et al., 2004; Takeuchi et al., 2010), or non-computerized 'paper-and-pencil' exercises (Engvig et al., 2010; Valenzuela et al., 2003). Computerized BT most commonly

Citation	Intervention Summary	Targeted Cognitive Domain	Difficulty Level	Delivery	Time per Session	Frequency	Training Period	CONSORT Scores
Erickson 2007a Erickson 2007b	Pure or combined colour discrimination or letter discrimination tasks	Memory and decision	RT feedback	Computer	60 mins	Five sessions in total across 2-3 weeks		17.5 17.5
Lovden 2010	Three working memory tasks, three episodic memory tasks, and six perceptual speed tasks	Memory and perceptual speed	Adjusted automatically by performance	Computer	60 mins	Average of 101 sessions in 6 months		18
Olesen 2004 (Experiment I)	Three working memory tasks: visuo-spatial working memory task, a backwards digit span task and a letter span task	Memory	adjusted automatically by performance	Computer	35-45mins	Daily	5 weeks	N/A
Olesen 2004 (Experiment II)	Three spatial memory tasks only: Grid, Grid rotation and 3D Grid (Cogmed cognitive medical systems)	Memory	adjusted automatically by performance	Computer	35-45mins	Daily	5 weeks	N/A
Takeuchi 2010	Computer based working memory training	Memory	adjusted automatically by performance	Computer	25 mins	Daily	2 months	N/A
Mozolic 2010	Visual and auditory tasks with visual and auditory distracters	Detecting classifying and sequencing	adjusted automatically by performance	Computer	60 mins	Once per week	2 months	15.5
Dahlin 2008	One letter memory criterion task and five other updating tasks	Memory and updating	adjusted automatically by performance	Computer	45 mins	3 sessions per week	5 weeks	13.5
Engvig 2010	MOL(method of loci) verbal recollection memory task	Memory strategy	lengthen the word list	Group session +homework	60 mins	5 sessions per week	2 months	19.5
Valenzuela 2003	MOL, remember a list of unrelated concrete nouns	Memory strategy	lengthen the word list	Group session	15-20 mins	Once per week	5 weeks	16

Table 1. Summary of brain training interventions with MRI outcomes.

consisted of different memory-based exercises (i.e., unidomain) (Dahlin et al., 2008; Erickson et al., 2007a, 2007b; Lovden et al., 2010; Olesen et al., 2004; Takeuchi et al., 2010). BT exercises were generally custom-designed by the research group, although one study investigated a multi-domain commercial program which included detecting, classifying, and/or sequencing with audio and visual distracters (Mozolic et al., 2010). Non-computerized BT studies used a specific mnemonic strategy known as the Method of Loci (MoL) (Engvig et al., 2010; Valenzuela et al., 2003). Further BT details are available in **Table 1**.

For most of the computerized BT interventions, difficulty level was automatically adjusted based on performance on previous tasks, whereas the Erickson group utilized continuous real-time feedback (response time) to help motivate and challenge subjects (Erickson et al., 2007a). Across all studies, training was session-based, varying form 20 minutes to 60 minutes per session. Frequencies of BT also varied from one session per week to daily. The duration of interventions were generally around two months) (Dahlin et al., 2008; Engvig et al., 2010; Mozolic et al., 2010; Olesen et al., 2004; Takeuchi et al., 2010; Valenzuela et al., 2003), except for one 6 month training study (Lovden et al., 2010) and two 2-week training studies (Erickson et al., 2007a, 2007b).

Definition of control training in RCTs was predominantly a no-intervention wait-and-see condition in 6 studies, whilst one study used an active control training condition, which comprised an educational lecture program and quizzes (Mozolic et al., 2010).

4.5 Types of MRI

Five studies used an event-related fMRI approach, employing in-scanner tasks either identical or highly similar to the offline training exercises (Erickson et al., 2007a, 2007b; Olesen et al., 2004). One fMRI study is unique for investigating functional BT-related changes related to both the trained task as well as to non-trained tasks within the scanner (Dahlin et al., 2008). Two studies investigated BT-induced changes to white matter fractional anisotropy (FA) and mean diffusivity (MD) using DTI (Lovden et al., 2010; Takeuchi et al., 2010). Another study used perfusion MRI (pMRI) to investigate BT effects on whole-brain cerebral blood flow (Mozolic et al., 2010). Finally, one study employed MR spectroscopy (MRS) to explore biochemical change before and after BT in several cortical and subcortical areas (Valenzuela et al., 2003).

Whilst all studies were selected for employing a baseline and post-training scan, one study conducted dual baseline scans in one experiment, and 5 serial scans over 5 weeks during BT in another experiment (Olesen et al., 2004). T1 structural MRI (sMRI) were common to all studies, however only two studies have specifically reported structural BT outcomes (Engvig et al., 2010; Lovden et al., 2010). Three out of ten studies used a 3 Tesla scanner, remaining studies used 1.5 Tesla field strength. No study specifically reported the presence or absence of hardware scanner changes or upgrades during the follow-up period.

4.6 Approaches to MRI pre-processing

Three main software platforms were used to perform MRI preprocessing: Four papers used different versions (SPM99, SPM2, SPM5) of Statistical Parametric Mapping (SPM, http://www.fil.ion.ucl.ac.uk/spm/) (Dahlin et al., 2008; Mozolic et al., 2010; Olesen et al., 2004; Takeuchi et al., 2010), two studies used FSL (FMRIB Software Library http://www.fmrib.ox.ac.uk/fsl/) (Erickson et al., 2007a, 2007b), and one study was based on Freesurfer (http://surfer.nmr.mgh.harvard.edu/) (Engvig et al., 2010). Further MRI pre-processing information is summarized in **Table 2**.

Citation	MRI	MRI assessment point	Main MRI protocol	Scanner info	Pre-processing platform	Pre-processing steps
Erickson 2007a	2	Pre- and Post training	fMRI (training tasks)	3T	FSL	Slice timing, motion-corrected, temporally filtered (1.5s-50s) and smoothing (7mm)
Erickson 2007 b	2	Pre- and Post training				
Lovden 2010	2	Pre- and Post training	DTI	1.5T	Semi-auto algorithm	Motion correction, generating MD and FA maps and semi-auto corpus callosum (CC) segmentation
Olesen 2004 (Experiment I)	3	twice at Pre- and once at Post training	fMRI (lowload working memory task and control task)	1.5T	SPM99	Motion correction, normalized by using T1 localizer and smoothing (6mm)
Olesen 2004 (Experiment II)	5	5 scans during 5 weeks (day 0, 2,4,8 23)	fMRI(highload and lowload memory tasks and control tasks)			
Takeuchi 2010	2	Pre- and Post training	DTI	3T	SPM5	Optimised VBM, intra-subject coregistration and smoothing (10mm)
Mozolic 2010	2	Pre- and Post training	perfusion MRI and structural MRI	1.5T	SPM5	Optimised VBM and smoothing (8mm)
Dahlin 2008	2	Pre- and Post training	fMRI (letter memory, n-back and Stroop)	1.5T	SPM2	Slice timing, realigned and unwarped, normalized and smoothing (8mm)
Engvig 2010	2	Pre- and Post training	Structural MRI	1.5T	Freesufer	Tissue segmentation, cortical thickness measures, subtraction of pre BT from post BT after coregistration to mid point and smoothing (30mm)
Valenzuela 2003	2	Pre- and Post training	MRS at right hippocampus, left frontal lobe and occipital-parietal	1.5T	Not applicable	N-acetylaspartate, choline and phosphocreatine relative to internal water peak corrected by cerebral spinal fluid percentage using voxel segmentation and white matter hyper-intensity volume

Table 2. Hardware and preprocessing information of reviewed studies.

Irrespective of MRI modality or research interest, the goal of preprocessing should be to prepare data so that further analytical assumptions are valid (Klein et al., 2009). For example, motion correction and spatial normalization maximizes the likelihood that a particular voxel property comes from same location across subjects. In the ten studies reviewed, fMRI preprocessing procedures were similar, including slice timing, motion correction, normalization, and smoothing. pMRI, DTI and sMRI studies created sample-specific template for coregistration and normalization purpose. Two studies (Mozolic et al., 2010; Takeuchi et al., 2010) followed the Optimized VBM (Good et al., 2001) approach, and one study created subject-specific templates by averaging image pairs across pre- and post-sessions (Engvig et al., 2010). Finally, the Lovden group used a semi-automatic algorithm for analysis of the corpus callosum (Niogi et al., 2007).

MRS studies require no geometric preprocessing. Rather, quantitative MRS assessment of neurometabolites may be influenced by scanning parameters such as shimming and receiver gain. MRS studies generally report relative metabolic signal intensity against a reference signal, and creatine is by far the most common reference signal. However, because subclinical degenerative disease and the intervention itself could hypothetically alter resting state phosphocreatine-creatine turnover (Valenzuela & Sachdev, 2001), we have used tissue-water as a more reliable reference signal in studies of ageing and BT (Valenzuela et al., 2003).

4.7 Approaches to MRI statistical inference

The General Linear Model (GLM) assumes an individual's MRI signal of interest is a function of a 'ground truth' signal modified by one or more experimental conditions and affected by error. The strengths (Friston et al., 2007) and weaknesses (Haynes, 2011) of the GLM approach therefore apply generally to the present set of fMRI, sMRI and DTI studies. In the context of longitudinal BT studies, statistical inference was mainly geared at testing Group (BT vs control) × Time (Pre vs Post-BT) interactions. In addition, one study carried out a regression analysis when analyzing DTI, using total BT amount (completed sessions) as the covariate of interest (Takeuchi et al., 2010).

When testing the null hypothesis, BT MRI studies have generally adopted a 'mass univariate' voxel-by-voxel test, either across the whole-brain or restricted to some ROI defined by prior knowledge. This approach assumes each voxel (or larger cluster of voxels) is necessarily an independent observation, an assumption that contradicts brain biology and introduces a significant multiple-comparison problem (Nichols & Hayasaka, 2003). Four studies used cluster-level correction (Dahlin et al., 2008; Erickson et al., 2007a, 2007b; Mozolic et al., 2010; Olesen et al., 2004), and one study voxel-level correction (Engvig et al., 2010). Some studies designed an initial experiment, and such first-level results were consequently used as an explicit mask for the next experiment (Dahlin et al., 2008; Erickson et al., 2007a, 2007b; Mozolic et al., 2010; Olesen et al., 2004). In this case, close attention is required to avoid non-independence errors (Kriegeskorte et al., 2009; Vul et al., 2009). Interestingly, one study used a split-half validation approach that uses a more relaxed multiple-correction threshold in one half of the sample to generate hypotheses for rigorous (but more constrained) testing in the other half of the sample (Engvig et al., 2010). Notably, alternative network approaches that consider covariance patterns across and between ensembles of brain locations (Haynes 2011), including Partial Least Squares analysis (Krishnan et al., 2011), Independent Components Analysis (Biswal & Ulmer, 1999; Calhoun et al., 2001), or graph-based analysis (Bullmore & Sporns, 2009), have not yet been applied to BT studies. Further details are available in **Table 3**.

Table 3. Post-processing and statistical correction details.

Citation	Post-processing steps	Multiple Correction Approach
Erickson 2007a	1. Extract the mean signal from first level task-contrast activation and test interaction with time × group 2. Whole brain voxel wise interaction analysis 3. Test correlation between activity change and performance improvement.	1. Threshold cluster at $z<2.33$ ($p<0.01$) uncorrected, then use p(corrected)<0.01 to define ROI 2. Threshold cluster at $z<3.1$ ($p<0.001$) uncorrected, then p(corrected)<0.01
Erickson 2007 b	1. Extract the mean signal from first level task-contrast activation and test interaction with time × group 2. Whole brain time × group analysis 3. Test other interaction (time × group × condition × age) on these regions from step2	To define ROI: $z>3.1$($p<0.001$)uncorrected=>cluster level correction at p=0.01
Lovden 2010	1. Time × Group × Age interaction test of the FA and MD of 5 segments of Corpus Callosum (CC) 2. Test correlation of performances and DTI result 3. Structure change of voxel for each segmented CC	Not involved
Olesen 2004 (Experiment I)	Whole brain time × group analysis	Threshold at $z<2.33$($p<0.01$) uncorrected, then threshold at $p<0.01$ cluster level correction
Olesen 2004 (Experiment II)	1. First level analysis (task-control task) 2. Regression analysis on the level one contrast with individual working memory capacities	Threshold at $t>2.44$ ($p<0.022$) uncorrected, then threshold at $p<0.01$ cluster level correction
Takeuchi 2010	1. Pre- and post-training groups paired-t analysis 2. Regression analysis between different fractional anisotropy (FA) map and the total amount of BT within step 1 regions 3. Test correlation between total BT and mean FA changes within step 1 regions	Threshold at $p<0.005$ uncorrected, then threshold at $p<0.05$ cluster level correction
Mozolic 2010	1. Whole brain time × group interaction test on cerebral blood flow (CBF) map 2. GM time × group interaction test within ROI from step1 3. Test correlation on changes of CBF and performance improvements	1. p(uncorrected)<0.001, then extent p(corrected)<0.05; 2. Biological Parametric Mapping toolbox to correct
Dahlin 2008	1. First level pre-training scans for three tasks 2. Second level time × group interaction analysis for each tasks 3. A conjunction analysis of letter memory task and 3-back tasks	1. p(FDR)<0.01 for two tasks, p(uncorrected)<0.005 for Stroop task; 2, p(uncorrected)>0.05
Engvig 2010	1. Time × group interaction whole brain 2. Split-half validation 3. Memory improvement correlates with the mean ROI GM thickness change	1. p(FWE)<0.05 peak level; 2. p(uncorrected)<0.05 and overlap the two split-half results
Valenzuela 2003	Regression analysis in SPSS	Not involved

MRI	Citation	Regions	Main Results
fMRI	Erickson 2007a	Bilateral dorsolateral prefrontal cortex (DLPFC)	↑ activation
		Right inferior frontal gyrus, right superior parietal lobule, right dorsal inferior frontal gyrus and left superior parietal lobule (trend)	↓ activation
	Erickson2007 b	Left ventral prefrontal cortex, bilateral DLPFC	↑ activation
		Right ventral prefrontal cortex	↓ activation
	Olesen 2004 (Experiment I)	Right middle frontal gyrus, right inferior parietal cortex, and bilateral intraparietal cortex	↑ activation
		Cingulate sulcus	↓ activation
	Olesen 2004 (Experiment II)	Left middle frontal gyrus; bilateral superior parietal cortex, bilateral inferior parietal cortex, left intraparietal cortex, thalamus, and right caudate head	↑ activation
		Cingulate suclus; right inferior frontal sulcus and left postcentral gyrus	↓ activation
	Dahlin 2008	Bilateral putamen, right temporal lobe, and right occipital lobe	↑ activation
		Right frontal lobe, right parietal lobe	↓ activation
		Left frontal lobe, left parietal lobe, left temporal lobe and left putamen	↑ activation
DTI	Takeuchi 2010	WM adjacent to the inferior parietal sulcus; the border between the frontal lobe and parietal lob; adjacent to the intraparietal suclus; anterior part of the corpus callosum	↑ fractional anisotropy
	Lovden 2010	Segment 1 (anterior) of corpus callosum	↑ fractional anisotropy and voxels
pMRI	Mozolic 2010	Right inferior prefrontal cortex	↑ cerebral blood flow
sMRI	Engvig 2010	Right insular, right lateral orbitofrontal cortex, right fusiform cortex, and left lateral orbitofrontal cortex	↑cortical thickness
		Global	↑ right hemisphere thickness
MRS	Valenzuela 2003	Hippocampus (right)	↑ creatine and choline

Table 4. Summary of MRI results of brain training in healthy adults.

4.8 Neuroimaging outcomes in BT trials

All MRI studies have to date revealed significant training-induced brain changes. Moreover, there is some overlap between studies in terms of topographical distribution. Training-related adaptation in the frontal lobe is most common. In fact, frontal lobe functional changes were reported in all fMRI studies, although the direction of changes was not consistent, and the precise localization of differences also varied (see **Table 4**). Even in the same experiments, there was evidence of both increased and reduced activation in distinct frontal lobe areas (Erickson et al., 2007a, 2007b). These functional changes are also supported by BT-related increments to cerebral blood flow (Mozolic et al., 2010), and in one study, increased cortical thickness (Engvig et al., 2010). Since all BT (either explicitly or implicitly) requires repetitive high-load engagement of working memory, it is not altogether surprising that frontal lobe plasticity is consistently implicated. Differences in BT design may help explain regional heterogeneity in these fMRI studies.

Another working-memory related area is the parietal lobe (Osaka et al., 2007), also implicated in multimodal integration (Fogassi et al., 2005), and hence potentially relevant to BT. Greater superior or inferior parietal lobe activity was detected in five fMRi studies after training compared with the untrained groups (Dahlin et al., 2008; Erickson et al., 2007a, 2007b; Olesen et al., 2004), with the exception of one study which found reduced activation in the right superior parietal lobe (Dahlin et al., 2008). Furthermore, a DTI study found increased fractional anisotropy (FA) in white matter regions adjacent to the inferior parietal sulcus, as well as at the border between the frontal and parietal lobe (Takeuchi et al., 2010).

Two studies have investigated the corpus callosum (CC) using DTI, and both revealed increased FA of the anterior CC after BT (Lovden et al., 2010; Takeuchi et al., 2010). Finally, only one study has focused on BT-related changes in the hippocampus, arguably the brain's most plastic area (Burke & Barnes, 2006; Gage et al., 2008), using MRS after a five-week Method of Loci trial (Valenzuela et al., 2003). Increased phosphocreatine was found in the hippocampus, but not other grey and white matter areas, suggestive of an activity-dependent upregulation of cellular-energy resting state, potentially of neuroprotective benefit (Brustovetky et al., 2001) in an area highly susceptible to degeneration.

There were also several differences in outcomes between studies, and so it is important to consider possible moderating factors. Session number or frequencies are unlikely to have had a major impact as they were relatively consistent between studies. Age, however, may be salient to BT outcomes. For example, in Erickson and colleagues' study (Erickson et al., 2007b), whilst a significant group × time interaction was for both elderly and young subjects at the dorsal prefrontal cortex bilaterally, the direction of the effects were opposite: in the older subjects there was reduced activation after BT, and increased activation amongst young subjects. Age differences have also been observed in a DTI study, whereby FA increased after BT only in the older group (Lovden et al., 2010).

5. Discussion

5.1 A biological insight into the trained brain

One of the major unresolved challenges for the BT field is to adequately demonstrate transfer or generalizability of outcomes (Gates & Valenzuela, 2010; Valenzuela & Sachdev, 2009). Individuals will predictably improve on almost any trained task – in clinical terms this is rather trivial unless gains can also be demonstrated in non-trained tasks. Neuroimaging studies are only beginning to address this issue. For example, one study

found that the effect of training in one task translates to functional brain changes in non-trained tasks (Dahlin et al., 2008). Brain imaging studies can therefore provide independent biological evidence about the impact of BT on brain structure, function and biochemistry.

So far, BT studies have been universally positive, each study reporting at least one significant brain imaging outcome. It is of course impossible to assess the role of publication bias, as null studies may have been self-censored by authors, or rejected by editors and reviewers. The field is also manifestly young, only 10 studies were found following a systematic search, across a mix of BT designs, approaches, MRI modalities and subjects. Nevertheless, a number of studies point to the key role of frontal lobe plasticity in potentially mediating BT benefits. All fMRI studies have so far found changes in this region, and as mentioned, this may reflect the heavy working memory demands of BT itself. Interestingly, repetitive practice of working memory problems does not necessarily lead to straightforward increases (in terms of signal change or spread of suprathreshold voxels) in task-related functional activity. Rather, a complex series of increases and decreases in brain activity have been observed. BT may therefore lead to two major types of functional adaptations including (Lustig et al., 2009): i) task-related hyperactivation, where the network of brain regions that normally subserves a given task becomes primed to activate, and ii) efficiency gains, where for a less extensive brain response, the same (or increased) cognitive proficiency is possible.

The cellular and molecular mechanisms that underlie BT-related frontal lobe plasticity are currently not known. Environmental enrichment, (in part) a model for BT in animals, is known to produce a wide range of neurobiological changes, including enhanced synaptic plasticity, neurogenesis and angiogenesis, as well as macroscopic structural changes including increased brain volume (Nithianantharajah & Hannan, 2006; Valenzuela et al., 2007). Interestingly, one sMRI has found that extensive memory training (2 months, 5 days a week) can translate into increased cortical thickness in the frontal lobe (Engvig et al., 2010), and two DTI studies further suggest frontal lobe structural plasticity in the form of increased FA in the anterior corpus callosum (Lovden et al., 2010; Takeuchi et al., 2010). The temporal dynamics of such structural BT changes are not understood, but studies of mental activity outside of our BT definition do provide some clues. Knowledge acquisition amongst college students led to persistent hippocampal volumetric increases even 3 month after the end of study (Draganski et al., 2006), whilst motor training studies suggest gray matter volume reaches a zenith after just 7 days of training and gains are reversed three months later (Boyke et al,. 2008; Driemeyer et al., 2008). With sufficient practice, functional BT effects may transform into detectable structural brain changes. From a practical viewpoint, sMRI plasticity may take longer to develop, or simply produce subtle changes, and hence studies with this outcome in mind need to pay attention to adequate BT dosage, power and sample size.

5.2 Limitations and challenges for the field

Whilst BT research has so far employed the full range of MR modalities, the field conspicuously lacks multi-modal studies. Each modality has its strengths and weaknesses, and so combining MR approaches will allow the clearest insight into putative neurobiological mechanisms. Use of network-based analyses will also help integrate findings across modalities, as well as recognize the interconnected and dynamic nature of human brain plasticity (Bullmore & Sporns, 2009). However, of more fundamental concern is the absence of any active control group in almost all reviewed RCTs. Since BT typically involves participants coming into a centre for some level of person-to-person instruction, as

well as often undertaking training in group sessions, receiving personalized feedback, and a host of other non-specific stimulatory factors, it is altogether unclear whether results so far reflect the benefits of BT specifically, or the neural manifestation of social contact, motivation, generic mental activity, and other Hawthorne effects. Future studies must employ active control conditions to ensure that valid neurobiological inferences are possible. Similarly, whilst BT often implicates working memory-related brain regions such as the prefrontal lobe, few studies have demonstrated a clear correlation between MRI-changes and BT-induced cognitive benefits (Engvig et al., 2010; Erickson et al., 2007a, 2007b). Of course, when testing for such links there are numerous technical MR processing pitfalls that could lead to spurious results. This has been graphically illustrated by Thomas et al., 2009, who found that a period of mirror-reading training led, alternatively, to either nil, modest, or widespread structural brain changes depending on which Voxel-Base-Morphometry assumptions were made, or even which software package was chosen. Recently, a systematic comparison of different sMRI software platforms found each had strengths and weaknesses, depending on the nature of the question (de Bresser et al., 2011). Clearly, for the field to advance on solid ground, claims of BT-related plasticity should not be pipeline-dependent (Valenzuela, et al., *in press*), and the strongest results will be those with some level of cross-validation, either though the use of multiple imaging modalities, verification by manual methods, or parameter-based sensitivity testing.

Finally, a technical factor that is often overlooked is the role of hardware MRI upgrades during the intervention period (Ridgway et al., 2008). These routinely occur, often outside the control of the investigator, and become increasingly relevant in longitudinal studies. Reporting of any hardware changes during a BT trial should be standard, and if this change selectively affects some subjects but not others, at a bare minimum this information should be added to analyses as a nuisance covariate.

6. Conclusions

Neuroimaging studies of BT emphasize the brain's potential to adapt and change during the whole of life. Functional BT changes are most frequently implicated, with consistent findings of altered activity patterns in frontal and parietal lobe areas. Cross-validation of these results is also emerging with MR studies reporting BT-induced structural, blood flow and biochemical adaptation. Multimodal imaging investigation of BT is needed, recognizing that structural BT-related plasticity may be subtle and have a different time course to functional BT-related plasticity. A major challenge for the field is to start to draw connections between BT-related changes in brain structure and function to the cognitive benefits increasingly evident in clinical studies. Future studies should also take care to design active control conditions, as well as ensure that results are not overly influenced by arbitrary processing decisions.

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EEG-Biofeedback as a Tool to Modulate Arousal: Trends and Perspectives for Treatment of ADHD and Insomnia

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1. Introduction

EEG-biofeedback (EBF) is a method to provide information about a person's brain state using real-time processing of electroencephalographic data (Budzynski, 1973; Morin, 2006). The idea behind EBF training is that by giving the participant access to a physiological state she will be able to modulate this state in a desired direction. As such EBF makes use of a brain-computer interface (BCI), in itself a field of study that has seen rapidly growing interest over recent years (Felton et al., 2007; Kübler, Kotchoubey et al., 2001; Leuthardt et al., 2006; Schalk et al., 2007). There is a distinction between using BCI to gain control over an external device or to use it to modify the internal state of the user. The former has seen fascinating applications in facilitating control of prosthetics (Nicolelis, 2003) or in offering new channels of communication to the paralysed (Birbaumer et al., 1999; Krusienski et al., 2006; Krusienski et al., 2008). EEG biofeedback belongs to the latter category as it aims to provide a means for the user to modify her own cognition or behaviour through feedback on specific EEG characteristics (Fig. 1). EBF therapy should, after repeated training, result in improved brain states or an effective internalized strategy to invoke such a brain state.

EEG-biofeedback (EBF) was first used in operant conditioning studies on cats in the 1960s. By rewarding the generation of the sensori-motor rhythm (SMR, Table 1), cats learned to increase SMR by suppression of voluntary movement (Roth et al., 1967; Sterman et al., 1969; Sterman & Wyrwicka, 1967; Wyrwicka & Sterman, 1968). Interestingly, a lasting effect of the biofeedback training became apparent when the same cats were later used in a dose-response study of an epileptogenic compound in which they showed significantly elevated seizure thresholds (Sterman, 1977; Sterman et al., 1969). These serendipitous findings motivated the use of biofeedback in research on humans with epilepsy (Sterman, 2006). Because the EEG is altered in several other disorders, biofeedback research has expanded to a range of clinical disorders including addiction (Passini et al., 1977; Peniston & Kulkosky, 1989; Saxby & Peniston, 1995), anxiety (Angelakis et al., 2007), attention-

deficit/hyperactivity disorder, autism (Coben & Padolsky, 2007; Pineda et al., 2008), depression (Baehr et al., 1997; Hammond, 2005), post-traumatic stress disorder (Peniston & Kulkosky, 1991), and sleep disorders (Cortoos et al., 2009). More recently, research has explored the potential of biofeedback to enhance normal cognition, e.g. to improve attention (Egner et al., 2002; Gruzelier et al., 2006), working memory (Hoedlmoser et al., 2008; Vernon et al., 2003), or athletic performance (Egner & Gruzelier, 2003; Vernon, 2005).

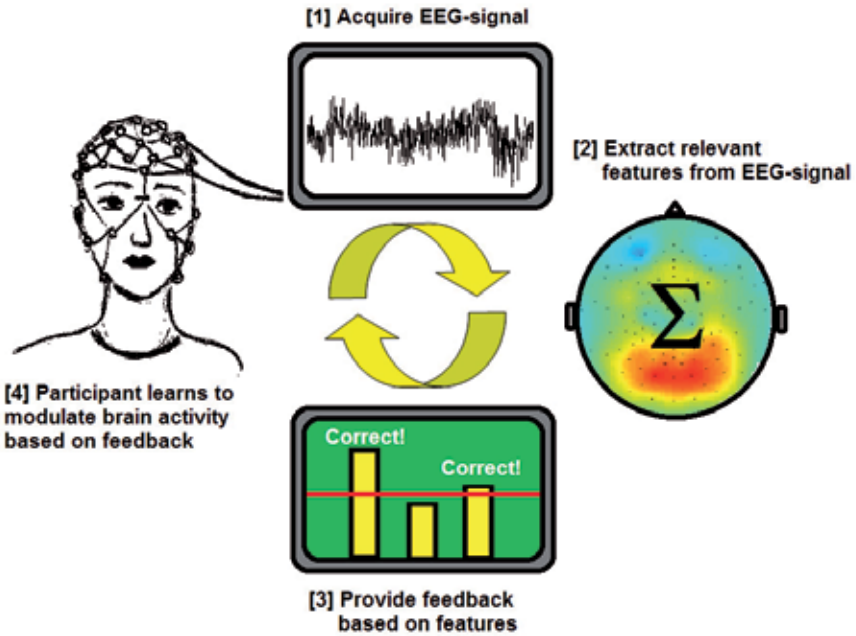

Fig. 1. The concept of EEG-biofeedback. The EEG is recorded [1], a suitable EEG-biomarker is extracted [2] and made available to the participant and correct changes in brain activity are rewarded by, e.g., a visual stimulus indicating success [3]. With repetition, this enables the participant to learn what strategies to employ in order to change brain activity in the desired direction [4].

In spite of the many studies using EBF to improve a clinical condition, the concept awaits a solid theoretical framework and the efficacy of EBF therapy requires further validation to gain widespread acceptance. Nevertheless, EBF holds the prospects to become an alternative to pharmaceutical intervention, where side-effects and dependency are prominent risks. An efficient EBF protocol that enables learning with a moderate number of sessions, will not only be more cost-effective but may bear additional psychological benefits such as avoiding certain stigmata (requiring psychiatric consultation or medication) and giving the participant more control over his/her own treatment. It is also conceivable that the mechanism with which EBF training exerts its therapeutic action is distinct from drug treatment as has been observed, e.g., when comparing neurobiological changes following successful treatment of depression using either cognitive behavioural therapy (CBT) or medication (Kumari, 2006).This would raise the perspective that EBF could be of help to those patients that do not respond to medication.

In this chapter, we focus on two disorders that share a characteristic arousal component, which EEG-biofeedback therapy attempts to modulate: attention-deficit hyperactivity disorder (ADHD) and insomnia.

Band	Frequency range (Hz)	Hallmark
δ	0.1–4	Sleep (stages N3-N4)
θ	4–8	Drowsiness, Sleep (stages N1-N2)
α	8–13	Relaxed wakefulness, cortical idling
σ	12–14	Spindle range (N2)
SMR	12–15	Sensorimotor rhythm
β	13–30	Cognitive effort, alertness

Table 1. All EEG bands from delta to beta have proven relevant for EBF in ADHD and insomnia.

ADHD has been described as a disorder of decreased CNS arousal and cortical inhibition, partially explaining the symptom normalizing effect psychostimulants have in the treatment of ADHD (Satterfield et al., 1974). These arousal deficits become manifest in lowered skin conductance levels (Barry et al., 2009; Raine et al., 1990; Satterfield et al., 1974), EEG deviations (e.g. increased theta but less beta activity) (Barry et al., 2003a; Barry et al., 2003b; Clarke et al., 2002; Clarke et al., 2001) and are related to CNS dopamine systems and associated genes (Li et al., 2006).

Insomniacs in contrast, exhibit elevated (cognitive) arousal effectively delaying the transition from wakefulness to sleep or resulting in frequent awakenings, oftentimes directly related to persistent (psychological) stressors (Bonnet, 2010; Bonnet & Arand, 1997; Bonnet & Arand, 2005; Cortoos et al., 2006; Drake et al., 2004; Drummond et al., 2004; Jansson & Linton, 2007; Nofzinger, 2004; Perlis, 2001). Brain areas involved in sleep regulation, arousal and attention are closely related (Brown et al., 2001) possibly explaining the observation that 50% of ADHD children also have difficulties falling asleep and 20% report recurring severe sleep problems (Ball et al., 1997; Stein, 1999). The association between arousal and sleep has classically been described using the EEG, where elevated arousal is associated with beta and gamma (>30 Hz) activity, whereas decreases in arousal are associated with enhanced delta and theta band activity (Alkire et al., 2008; Rechtschaffen & Kales, 1968; Steriade et al., 1993).

Here we propose that for EBF to have a therapeutic effect it is required that (1) EEG can index (disease-)relevant states of the brain, (2) one can learn to modulate these brain states, (3) training the modulation of brain states causes (lasting and desired) changes to the brain, and (4) EBF-related changes to the brain have cognitive and/or behavioral correlates. In the following, ADHD and insomnia are treated as case examples of disorders that have been proposed to benefit from EEG-biofeedback therapy. We present the evidence that EBF has a therapeutic effect on these disorders and outline trends and perspectives by reviewing recent progress in the design of EBF for pre-clinical research.

2. EEG-biofeedback in ADHD

Attention deficit/ hyperactivity disorder (ADHD) is a psychiatric disorder, characterized by symptoms of inattention and/or impulsivity and hyperactivity. These symptoms frequently co-exist with emotional, behavioural and learning deficits such as conduct disorder and oppositional defiant disorder, anxiety disorders and major depressive disorder (Barry et al., 2003). Prevalence in school-aged children is fairly high (3–12%) (Brown et al., 2001) and 30–50% of these children will continue to experience symptoms into adulthood (Barry et al., 2003; Monastra, 2005). DSM-IV criteria allow the distinction of three ADHD subtypes: (1) the predominantly inattentive type, (2) the predominantly hyperactive-impulsive type and (3) the combined type, which exhibits symptoms of both inattention and hyperactivity-impulsivity (DSM-IV-TR; American Psychiatric Association, 2000).

Pharmacological intervention based on psychostimulant medication leads to a reduction of ADHD symptoms by increasing CNS arousal (Satterfield et al., 1974), but lacks long-term efficacy (Faraone & Buitelaar, 2010; Faraone & Glatt, 2010; Molina et al., 2009) and introduces adverse effects in 20-50% of the patients (Charach et al., 2004; Efron et al., 1997; Goldstein & Goldstein, 1990). Still, 35–45% of the patients with an "inattentive" type of ADHD and 10–30% of those diagnosed as "combined" type do not respond to medication, limiting the effectiveness of pharmaceutical intervention (Barkley, 1998; Hermens et al., 2006; Swanson et al., 1993). EEG biofeedback therapy for ADHD is one proposed alternative treatment and aims at restoring CNS arousal imbalances by training participants to suppress EEG rhythms associated with underarousal and enhance those rhythms associated with attention (J. F. Lubar & Shouse, 1976; Monastra et al., 2005; Thompson & Thompson, 1998).

2.1 Training duration and feedback

An EBF training session consists of repeated training blocks of typically 3 minutes, each starting with a measure of baseline activity, like 5 minutes eyes-closed rest (J. O. Lubar & Lubar, 1984), within the specified frequency band in order to establish a target threshold value (Table 2). The participant will then attempt to match or exceed this value during a subsequent feedback trial by modulating activity within the set frequency band. The participant need not be aware of the underlying parameter(s) and is merely instructed to meet/exceed the threshold. Participants are encouraged to find their own optimal strategy to alter the brain activity. When the participant successfully exceeds the threshold, e.g., for 0.5 s (Monastra, 2005), a reward signal indicating success (e.g. a bonus point that can be traded for money or toys) is presented to reinforce learning. ADHD patients prefer smaller and immediate rewards to delayed, but larger ones (Loo & Barkley, 2005; Marco et al., 2009; Tripp & Alsop, 2001) and as the ADHD population largely consists of children, feedback protocols often involve video games where success is rewarded instantly (Drechsler et al., 2007; Leins et al., 2007).

2.2 Target brain activity

Spontaneous (resting-state) EEG profiles of ADHD children differ significantly from those of normally developing children, especially increased theta/beta ratio but also lowered alpha band activity has been reported (Barry & Clarke, 2009; Barry et al., 2003; Barry et al., 2009; Barry et al., 2003; Clarke et al., 2002; Clarke et al., 2001).

The increased theta/beta ratio has been proposed as a characteristic biomarker for CNS underarousal (Mann et al., 1992), whereas the SMR has been classically described as reflecting motor inhibition (Sterman & Friar, 1972; Sterman et al., 1970). The vast majority of EBF studies has been inspired by a two-phase protocol of Lubar et al. (1984), in which participants where first trained to increase their SMR and later to inhibit theta activity while simultaneously increasing beta activity (Beauregard & Levesque, 2006; Carmody et al., 2000; Fuchs et al., 2003; Gevensleben et al., 2009; Heywood & Beale, 2003; Holtmann et al., 2009; Kaiser, 1997; Kaiser & Othmer, 2000; Kropotov et al., 2005; La Vaque et al., 2002; Leins et al., 2007; Levesque et al., 2006; Linden et al., 1996; J.F. Lubar et al., 1995; Monastra et al., 2002; Rossiter, 2004; Rossiter, 1998; Rossiter & La Vaque, 1995; Strehl et al., 2006; Thompson & Thompson, 1998).

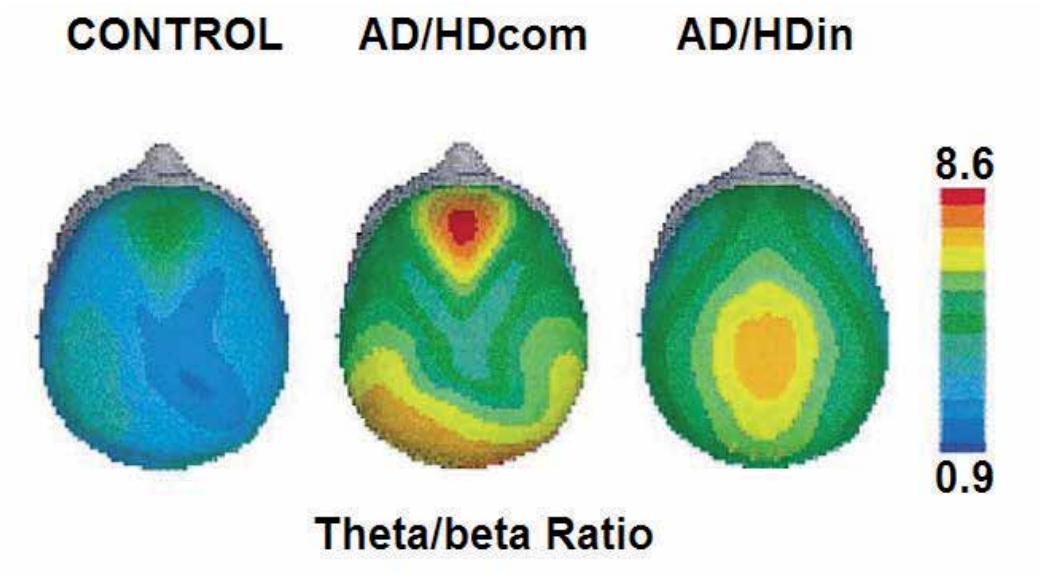

Fig. 2. Brain activity profiles in children with ADHD differ from healthy controls. Theta/beta-band activity ratio is strongly elevated in ADHD, but differs in spatial localization between combined (AD/HDcom) and inattentive (AD/HDin) subtypes. (From: Barry et al., 2003.).

In recent years, however, an interesting new target for EBF has been found in the form of slow cortical potentials (SCPs). These slow event-related DC shifts represent excitation thresholds of large neuronal assemblies and training ADHD patients to increase SCPs robustly improves symptoms of ADHD (Doehnert et al., 2008; Drechsler et al., 2007; Gevensleben et al., 2009; Heinrich et al., 2007; Kropotov et al., 2005; Leins et al., 2007; Siniatchkin et al., 2000; Strehl et al., 2006).

Study	Control P/R/B*1)	N (m)	Age	Electrodes /Ref	Freq.	Stim/ Reward	#Ses./ Dur.
Monastra et al., 2002	-/-/-	[1] 49(40) [2] 51 (43)	[1] 10.0± 3.7 [2] 10.0± 3.1	CPz & Cz/A2	β ↑ θ ↓	Visual & auditory /Money	43 (34–50) / 30–40 min
Fuchs et al., 2003	-/-/-	[1] 12(12) [2] 22(21)	[1] 9.6±1.2 [2] 9.8±1.3	C3 or C4/A1+A2	SMR↑ /β ↑ θ ↓	Visual & auditory /Points	36 / 30-60 min
Rossiter, 2004	-/-/-	[1] 31(21) [2] 31(22)	[1] 16.7±12.5 [2] 16.6±12.7	C3/A2 or C4/A1	β ↑ θ ↓	Visual & auditory	40 or >60 /30 or 36 min
Lévesque et al., 2006	+/+/-	[1] 5(5) [2] 14(11)	[1] 10.2±0.8 [2] 10.2±1.3	Cz/A1	SMR↑ θ ↓	Visual & auditory (video game)	40 / 60 min
Drechsler et al., 2007	-/-/-	[1] 13(10) [2] 17(13)	[1] 11.2±1.0 [2] 10.5±1.3	Cz/A1+A2	SCP↑/↓	Visual /Points	2x15 /2x45 min
Leins et al., 2007	-/+/+	[1] 16(13) [2] 16(13)	[1] 9.16±1.43 [2] 9.16±1.53	[1] CF3,CF4/ A1+A2 [2] Cz/A1+A2	[1] β ↑ θ ↓ [2] SCP↑/↓	Visual /Points	30 /60 min
Doehnert et al., 2008	-/-/-	[1] 12(10) [2] 14(12)	[1] 11.4±0.9 [2] 10.8±1.3	Cz/A1+A2	SCP↑/↓	Visual /Points	2x15 /2x45 min
Gevensleben et al., 2009	-/+/-	[1] 35(26) [2] 59 (51)	[1] 9.3± 1.16 [2] 9.8± 1.25	Cz/A1+A2	β ↑ θ ↓ SCP↑/↓	Visual	2x9 /2x 50 min

***1) P/R/B= Placebo/Randomized/Blind (- = no, + = yes). N(m):** Number of participants (males)**, Freq.:** Target frequency ↑/↓ (increase/decrease) of EBF condition(s).

Table 2. EBF therapy focused at treating ADHD is an active field of research.

2.3 Efficacy of EEG-biofeedback in the treatment of ADHD

The first study of EBF in ADHD (J. F. Lubar & Shouse, 1976) reported improved attention and normalized levels of arousal, together with improved grades and achievement scores for the (eight) children under treatment. Subsequent studies have reported similarly positive results, showing improvements of behaviour, attention and impulsivity (Alhambra et al., 1995; Carmody et al., 2000; Drechsler et al., 2007; Gevensleben et al., 2010; Gevensleben et al., 2009; Heinrich et al., 2004; Kaiser & Othmer, 2000; Kropotov et al., 2005; Leins et al., 2007; Linden et al., 1996; J.F. Lubar et al., 1995; J. F. Lubar, 1991; Rossiter, 1998; Rossiter & La Vaque, 1995; Strehl, et al., 2006; Thompson & Thompson, 1998; Doehnert et al., 2008). Efficacy of EBF is comparable to psychostimulant medication and group (CBT) therapy programs with effects lasting 6 months and longer (Fuchs et al., 2003; Gani et al., 2009; Gevensleben et al., 2010; Kaiser, 1997; Leins et al., 2007; Linden et al., 1996; J.F. Lubar et al., 1995; Monastra et al., 2002; Rossiter & La Vaque, 1995; Thompson & Thompson, 1998). Overall, EBF treatment results in clinical improvement in about 75% of the cases, without any reported adverse effects so far (Leins et al., 2007; Monastra et al., 2005).

It should be noted, however, that the use of the theta/beta ratio as marker of general arousal has been questioned, because it does not correlate with skin conductance level (R.J. Barry & Clarke, 2009; R.J. Barry et al., 2009). Similarly, SCPs are no direct correlates of arousal but rather represent attentional processes (Siniatchkin et al., 2000). This raises the interesting notion that in ADHD, EBF may not restore or modulate arousal systems per se, but compensate underarousal by strengthening cognitive functions that have been negatively affected by the arousal dysfunction.

3. EBF as treatment of insomnia

Insomnia is a most pervasive disorder, affecting about 15% of the general population while 6% meet clinical (DSM-IV) criteria (Ohayon, 2002) and interferes with cognition, quality of life, job performance and represents a multi-billion dollar burden on healthcare providers (Daley et al., 2009; Ebben & Spielman, 2009; Edinger et al., 2004). Insomnia can be subdivided into primary and co-morbid insomnia with the most salient symptoms being difficulty initiating and/or maintaining sleep (Espie, 2007). Causes of primary insomnia include physiological, cognitive and behavioural factors (Espie, 2007). Symptoms and duration are related to severity and persistence of stressors (Morin et al., 2006).

To better understand the possible therapeutic targets of insomnia, the so-called "3P model" has been proposed (Ebben & Spielman, 2009). This model specifies three categories of factors influencing the risk at developing or worsening insomnia: predisposing, precipitating and perpetuating factors. The first category constitutes genetic factors or personality traits, such as increased basal level of anxiety or hyperarousal (Drake et al., 2004), whereas precipitating events represent work and educational stress together with health and emotional problems (Bastien et al., 2004). Finally, perpetuating factors, such as continuous stress and poor sleep hygiene, may cause the actual transition to chronic insomnia and complete the vicious circle.

Pharmacological treatment of insomnia with sedative-hypnotic agents has seen a steady decline over the past (Aldrich, 1992; Walsh & Schweitzer, 1999), because of side effects, discontinuation discomfort, and the risk of developing drug tolerance or dependency (Ebben & Spielman, 2009; Walsh & Schweitzer, 1999). Alternative treatment options that have been met with success are cognitive-behavioural therapy (CBT) (Ebben & Spielman, 2009; Espie, 1999; Morin et al., 1999; Morin et al., 1994; Murtagh & Greenwood, 1995; Siebern & Manber, 2010) or treatments

increasing body temperature (e.g., physical exercise, hot bath before bed), which has recently been shown to hasten sleep onset (Van Someren, 2006). Whereas CBT causes sustained improvements and reduces sleep complaints, one fifth of the patients does not respond to the intervention (Cortoos et al., 2010; Harvey & Payne, 2002; Morin, 2006). EBF therapy for insomnia could be a safer alternative to medication and may offer treatment where CBT fails.
The EEG profile of insomniacs (Fig. 3) consists of increased levels of beta activity especially during the sleep-onset period and early sleep stages (Merica et al., 1998). These observations may be interpreted as evidence of cognitive hyperarousal, which is in line with the often reported 'racing thoughts' of insomniacs (Bastien et al., 2003; Buysse et al., 2008; Buysse et al., 2008; Freedman, 1986; Harvey & Payne, 2002; Jacobs et al., 1993; Lamarche & Ogilvie, 1997; Merica, et al., 1998; Merica & Gaillard, 1992; Nofzinger et al., 1999; Perlis et al., 2001). In addition, elevated levels of alpha activity at sleep onset (Besset et al., 1998; Krystal et al., 2002) as well as a decrease in delta activity during non-REM sleep (Merica et al., 1998; Merica & Gaillard, 1992) have been reported. Furthermore, it has been demonstrated that insomniacs produce less spontaneous waking SMR activity than controls (P. Hauri, 1981; Krystal et al., 2002). One interesting aspect about the SMR is that it lies in the same frequency range as sleep spindles (Sterman, et al., 1970). Spindles are the hallmark waveform of stage 2 sleep, and their occurrence is reduced in insomniacs (Besset et al., 1998), possibly resulting in lighter and more fragmented sleep (Glenn & Steriade, 1982; Perlis et al., 2001).

3.1 Training duration and feedback

Protocols for EEG-biofeedback in insomnia are quite similar in many respects to the ones used in the treatment of ADHD, e.g. patients usually receive feedback and reward in the form of auditory and/or visual stimuli and are encouraged to search for their own

Study	Conds.	Control P/R/B*1)	N (m)	Age	Electrodes /Ref	Freq.	Stim/ Reward	#Ses./ Dur.
Hauri,1981	[1] EBF+EMG [2] EBF [3] EMG [4] Control	-/+/-	[1]12 [2]12 [3]12 [4]12	Total: 41.3±14.6	C3 /A2	θ ↑ SMR↑	Visual	24.8 (15-62) / 60 min
Hauri et al.,1982	[1] EBF(θ) [2] EBF(SMR)	-/+/-	[1]8(5) [2]8(5)	50.1 47.4	T7&C3/A2	θ ↑ SMR↑	Visual	25.4/ 60 min 27.8/60 min
Berner et al., 2006	EBF/Sham	+/+/+	11(4)	20.8±2.8	Cz / FCz	σ ↑	Visual & Auditory	1 / 4x10 min
Hoedlmoser et al., 2008	[1] EBF [2] Sham	+/+/+	[1]16(?) [2]11(?) Total: 27(13)	Total: 23.6±2.7	C3 /A2	SMR↑	Visual & Auditory	10/ 24 min
Cortoos et al., 2009	[1] EBF [2] EMG [3] Control	-/+/-	[1] 9(6) [2] 8(5) [3]12(7)	41.5±9.5 43.8±9.5 44.4±7.8	FPz & Cz /A2	SMR↑ θ ↓ β ↓	Visual	20/ 20 min

*1) **P/R/B**= Placebo/Randomized/Blind (- = no, + = yes). **N(m)**: Number of participants (males), **Freq.**: Target frequency ↑/↓ (increase/decrease), **?** = data unavailable

Table 3. Overview of EBG group studies aimed at improving sleep.

individual strategies (Berner et al., 2006; Cortoos et al., 2009; Hauri et al., 1982; Hoedlmoser et al., 2008). Training sessions (Table 3) are usually blocked (e.g., 3 minute intervals) during which a threshold of activity expressed as a percentage of, or within a predefined band around the baseline, must be maintained for 250–500 ms (Berner et al., 2006; Cortoos et al., 2010; Hoedlmoser et al., 2008).

3.2 Target brain activity

Insomniacs differ from good sleepers in terms of their EEG profile (Fig. 3), especially exhibiting large spectral decreases in the lower frequency bands (delta, theta) (Merica et al., 1998) and attenuated sigma activity, corresponding to less occurrences of sleep spindles (Besset et al., 1998). These findings have led to the design of EBF therapies aimed at either increasing theta activity, due to its close relationship with drowsiness and early sleep stages, or SMR activity, as this rhythm overlaps with the sigma range and is believed to stimulate sleep spindle occurrence which in turn is key to further progression into deeper sleep stages

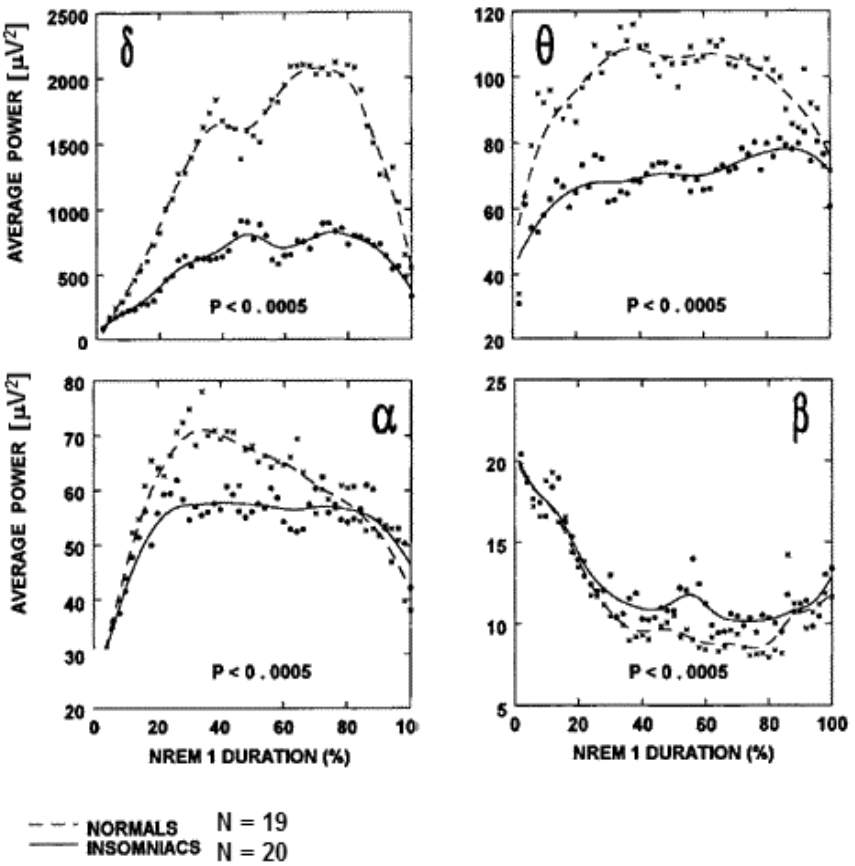

Fig. 3. Insomniacs and normal sleepers have different EEG during stage 1 sleep. Insomniacs (solid line) have reduced delta, theta and alpha activity, but higher levels of beta activity compared to normal sleepers (dashed line) during early stages of sleep. Y-axis: average power over all participants in specific frequency band. X-axis: normalized duration of sleep stage 1, each of the 50 dots marks a 2% interval. From: Merica et al., 1998.

(Berner et al., 2006; Budzynski, 1973; Hauri, 1981; Sittenfeld, 1972; Steriade, 2003). The application of either protocol depends on the insomnia sub-population: theta feedback (enhancement training) is used for patients with difficulty initiating sleep, whereas SMR/sigma feedback is best used on patients that have problems maintaining sleep. The importance of disentangling insomnia subtypes is further illustrated by the studies of Hauri et al. (1981,1982). Even though all participants showed a trend towards improvement, the experimental groups (i.e. theta feedback, SMR feedback) did not differ, which could be attributed to participants having received treatment unsuitable to the underlying symptoms (Hauri, 1981; et al., 1982).

3.3 Efficacy of EEG-biofeedback in the treatment of insomnia

A pioneering case study used theta training to treat an insomnia patient and observed a near doubling of theta activity by the end of the 11-week (one session per week) EBF training, together with vastly decreased sleep-onset latency (from 54 to 16 minutes), an increase in total sleep time and a halving in intrusive thoughts (Bell, 1979). Recent studies have compared SMR training with pseudo-EBF training and reported positive results with respect to the total sleep time and the sleep latency (Berner et al., 2006; Hoedlmoser et al., 2008). Cortoos et al. (2009) compared electromyography (EMG) biofeedback, aimed at reducing muscle tension and relaxation, with an EBF protocol of SMR increase and simultaneous theta-, and beta-band suppression. Both groups showed decreases in sleep latency (-8.5 and -12.3 minutes respectively) and time awake after sleep onset. It is noteworthy that participants were trained to apply electrodes and initiate training in their home environment and experimental control was established remotely through the internet, making this "tele-neurofeedback" protocol an interesting example of fusing established knowledge with advanced technology.

In contrast to the case of ADHD where subjective ratings largely define outcome measures (Table 2), efficacy and validity of EBF-therapy for insomniacs is easier to assess through objective measures such as total sleep time, sleep-onset latency and the number of nightly awakenings. In 1998, the American Academy of Sleep Medicine recommended biofeedback in general, including EMG-biofeedback, as treatment for insomnia and classified it as "probably efficacious", based on the Guidelines for Evaluation of Clinical Efficacy of Psychophysiological Interventions (Table 3). In the update of 1999–2004, this rating was maintained (Morgenthaler et al., 2006; Morin et al., 2006; Morin et al., 1999).

4. Conclusion

The methodology of EBF studies has often been subject to criticism (Kline et al., 2002; Loo & Barkley, 2005; Pelham & Waschbusch, 2006; Ramirez et al., 2001; Rickles et al., 1982). While some concerns are undoubtedly warranted, much effort has been put in establishing strict guidelines for EBF therapy and this has been met with positive results (Arns et al., 2009; La Vaque et al., 2002). Double-blind, randomised and placebo controlled experiments are unfortunately not always an option. Blinding requires a control condition that is indistinguishable from the treatment condition, which is often technically not feasible. Randomisation, while powerful, is only useful when the target sample is either well-known or homogenous to avoid samples being treated with inadequate protocols (Hauri, 1981; Hauri et al., 1982). Finally, a placebo condition, especially in the case of ADHD, is problematic from an ethical viewpoint, as denying patients a standard and efficacious

treatment (i.e., medication) is in conflict with the Declaration of Helsinki (Vernon et al., 2004). Employing sham (random frequency) feedback (Hoedlmoser et al., 2008; Logemann et al., 2010) is therefore not always an option when treating patients. Thus, apart from reaching certain endpoints of treatment, the further validation of EBF therapy is likely to depend on the observation of complimentary physiological changes, e.g., obtained from neuroimaging experiments or other biomarker assays (Frank & Hargreaves, 2003).

Motivation and cognitive strategies are also important aspects to consider (Bregman & McAllister, 1982; Meichenbaum, 1976). If participants are motivated and rewarded for their success they will put effort into the therapy, whereas lack thereof leads to frustration and possibly resignation (Huang et al., 2006). Good methodology can compensate for possible expectancy effects, i.e., improved symptoms like decreases in sleep onset latency induced by the sheer hope of becoming better through therapy (Hauri et al., 1982). However, providing sham feedback, which lacks obvious rewards, bears the risk of the participant becoming unmotivated, ceasing effort and thus confounding the comparison between control and experimental condition (Logemann et al., 2010). In addition, the instructions given to participants in the EBF studies reviewed here do not go beyond the direction to meet some specified criterion, i.e., increasing an onscreen bar towards a target value. The general idea is that participants need to search for their own strategies to modulate their brain activity. In our view, this is unfortunate, because good instructions/guidance can increase participant compliance and speed of learning (Weinert et al., 1989). While individual strategies are likely to vary greatly, an opportunity for future research presents itself in the collection of these strategies and finding patterns that may be useful to guide participants towards success more efficiently. Interestingly, Gevensleben et al. (2009) report on having queried individual strategies of their participants (albeit without further analysis), making future compilation of strategies feasible.

Technological advances have made it possible to record high-density EEG data from several hundred electrodes at once (Dornhege et al., 2006). However, current EBF studies seldom record from more than two active electrodes (Tables 2 and 3). With ongoing developments towards ever more powerful and cost-effective computational equipment, it is feasible that future research should focus on the opportunities these advances can offer EBF, possibly in combination with tools from the field of BCI (e.g., more sophisticated algorithms, spatial filtering allowing feedback on localized anatomical structures and less artefacts). Despite some (methodological) issues that have subjected the field to scepticism, recent developments give rise to optimism, as stricter guidelines are increasingly being adhered to and new avenues continue to be explored (e.g., SCP feedback and tele-neurofeedback as in Cortoos et al., 2009). Overall, from the studies reviewed here we conclude that EBF is a promising tool for treating disorders of arousal, which offers many opportunities for future research.

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23

Deconstructing Central Pain with Psychophysical and Neuroimaging Studies

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1. Introduction

The IASP has defined central pain as initiated or caused by a primary lesion or dysfunction of the central nervous system (CNS)" (Merskey, 1986). A more recent and specific definition describes central pain as "pain arising as a direct consequence of a lesion or disease affecting the central somatosensory system" (Treede et al., 2008). This definition recognizes that a disturbance of the central somatosensory system is the essential feature of central pain. A disturbance of this system applies to all central pain conditions, although they exhibit great variability across different etiologies. This chapter includes structural and functional imaging results, as well as the results of psychophysical studies, as they complement the imaging results. There is some overlap between the content of this chapter and our previous reviews of this topic (Veldhuijzen et al., 2007;Greenspan et al., 2008;Veldhuijzen et al., 2011).

2. Prevalence of sensory abnormalities in central pain?

Patients with central pain (CP) inevitably show stimulus-evoked sensory abnormalities which include negative symptoms such as hypoesthesia and hypoalgesia, as well as positive symptoms such as hyperalgesia Hyperalgesia is increased pain evoked by a stimulus which can be painful, such as deep pressure over a muscle which has been injured or bruised. Another positive symptom is allodynia which is pain evoked by a stimulus which is not normally painful, such as pain evoked by light touch following a sunburn.
When studied by quantitative sensory testing (QST, Table 1), patients with central post-stroke pain (CPSP) exhibit hypoesthesia for cold in 85-91% of patients, for warmth in 85-100%. Decreased sensation for pain (hypoalgesia) is found for cold pain in roughly 45% of patients, and for heat pain in 7-91% (Boivie et al., 1989;Leijon et al., 1989;Andersen et al., 1995;Vestergaard et al., 1995;Greenspan et al., 2004). As shown in Table 1, CPSP patients show decreased tactile sensibility in 27-52% of cases. These results demonstrate that decreased sensation or negative sensory signs vary widely across the CPSP patient population. Overall, these patients do not show sensory deficits for all types of thermal and

	(Ohara et al., 2004)	(Boivie et al., 1989;Leijon et al., 1989)	Clinic (Vestergaard et al., 1995) QST (Andersen et al., 1995).
Burning cold/cold pain	53% overall; 38%, burning & cold; 15%, hot and cold;	59%, 16/27	38%, 6/16 (freezing 3/16)
Mechanical pain	77% overall 33%, sharp/stab; 23%, pressure heavy; tight/ squeezing 7% each	Aching 30%, Pricking 30%, lacerating 26%.	86%, 23/27.
Pain rating	7.1 mean, 2.0 SD	2.5-7.9 mean by stroke location	3.3 median (0-7)
Touch – method	**Von Frey for threshold; brushes for allodynia**	**V Frey for threshold; Pin prick for hyperalgesia**	**V Frey hair, V Frey.**
Normal threshold	50%, 5/10	48%, 13/27.	54%, 6/11.
Hypoesthesia	50%, 5/10	52%, 14/27	27%, 3/11.
Allodynia/ hyperalgesia	54% 7/13.	16/27, 59% - hyperalgesia	1/11-hyperalgesia to rotating von Frey hair
Cool – method	**Peltier Medoc**	**Peltier Somedic, warm minus cool threshold**	**Peltier Somedic**
Normal threshold	15%, 2/13	0/27	9%, 1/11.
	85%, 11/13, 3 with equal bilateral hypoesthesia	Diff in cool-warm thresholds 17/27; larger change in cool 2/27	91%, 10/11.
Cold pain – method	**As above**		
Normal threshold	31%, 4/13	7% normal difference between cold & heat pain threshold	18%, 2/11-unaffected side lower
Hypoalgesia	46%, 6/13 (2 indeterminate)	93% abnormal difference between cold & heat pain threshold	45%, 5/11 (4/11-bilateral)
Allodynia	23%, 3/13	No abnormally sensitive thresholds, but 5/22 (23%) reported discomfort to metal at room temperature	0/11
Warm – method	**As above**		
Normal threshold	15%, 2/13	-	-
Hypoesthesia	85%, 11/13	Diff in cool-warm thresholds, 17/27; larger change in warm threshold 8/27	11/11

Heat pain – method	**As above**		
Normal	93%, 12/13	7% normal difference between cold & heat pain threshold	9%, 1/11.
Hypoalgesia	7%, 1/13 (2 indeterminate)	93% abnormal difference between cold & heat pain threshold	91%, 10/11.
Allodynia	0/13 (2 borderline)	No abnormally sensitive thresholds.	0/11

Table 1. Summary of QST and descriptors of CPSP. The fourth column included both clinical findings (n=16) (Vestergaard et al., 1995) and quantitative sensory testing (n=11) (Andersen et al., 1995). Similarly, the third column included both clinical (Leijon et al., 1989) and sensory testing results (both N=27) (Boivie et al., 1989). Another very large series could not included because quantitative sensory testing results were not described as population statistics, (Bowsher, 1997).

painful stimuli, but they do show decreased sensitivity to at least some submodality of thermal or noxious stimuli.

Another important observation is that some patients with injuries or disease of the central nervous system (CNS) may experience thermal hypoesthesia or hypoalgesia as a result of a CNS lesion without developing central pain. This has been demonstrated for patients with lesions of the spinal cord (Ducreux et al., 2006;Finnerup et al., 2003), and brain (Andersen et al., 1995;Garcia-Larrea et al., 2010).

In the case of cortical lesions, the results of a recent study demonstrate warm and cold hypoesthesia based on QST thresholds in all subjects with lesions of parietal or insular cortex or both (Veldhuijzen et al., 2009). The largest degree of thermal hypoesthesia by threshold measures was found in the subject with the largest lesion, which involved extensive parietal and insular lobar lesions (see also (Greenspan et al., 1999). Suprathreshold measures demonstrated that sensory loss for painful and nonpainful hot and cold modalities was maximal for the largest parietal lesions.

Subjects with relatively small lesions restricted to the posterior insula and retroinsula showed central pain and cold allodynia, based on thresholds and clinical assessment. Cold allodynia based on thresholds but not on clinical assessment were observed in patients with parietal lesions sparing the insula. Similarly, a study of two patients with lesions of the insula and adjacent cortical lobes confirmed normal heat pain thresholds but increased ratings of heat pain compared to controls (Starr et al., 2009). These results suggest that non-painful cold and heat sensations are jointly mediated by parietal and insular cortical structures, while thermal pain sensation is more robust, requiring larger cortical lesions of these same structures to produce hypoalgesia. In addition, these studies dramatically demonstrate that neither the presence nor the extent of abnormal thermal sensation nor cold allodynia following a CNS lesion predicts the presence or the characteristics of central pain syndromes.

The variability of negative and positive symptoms and signs in patients with central pain raises the possibility that the level of spontaneous pain is correlated with the extent of sensory loss in patients with central pain. Such a relationship has been reported among patients with central pain resulting from spinal cord injury (SCI) (Ducreux et al., 2006). Specifically, two differences were observed between syringomyelia patients with or without allodynia. Those with allodynia tended to have 1) lesser thermosensory deficits and 2) more

asymmetrical thermosensory deficits than those without allodynia. The intensity of the spontaneous burning pain was correlated with the degree of thermal sensory loss. Additionally, thermal deficits were less severe in patients with cold allodynia compared to those with tactile allodynia. Therefore, the pattern of thermal sensory loss may differentially influence different features of central pain.

Another study of SCI secondary to syringomyelia compared diffusion tensor imaging (DTI) and electrophysiological potentials between patients with and without neuropathic pain and healthy controls (Hatem et al., 2010). Among those SCI patients with neuropathic pain, higher average daily pain intensity correlated with the extent of structural damage to the spinal cord tracts. Additionally, the number of intact nerve axons within the whole spinal cord was inversely correlated with deep spontaneous pain and dysaesthesias. Patients with both spontaneous and evoked pain had less structural spinal cord damage by morphological and electrophysiological criteria compared to patients with only spontaneous pain. Therefore, in patients with SCI there was strong evidence that the extent of structural lesions is strongly correlated with the expression of spontaneous and evoked pain, or hypersensitivity (Hatem et al., 2010).

Based on the sample of 30 central pain patients (mostly CPSP) evaluated with QST at our research center, we found no relationship between the extent of thermosensory loss (based on cool or warm thresholds), and the level of ongoing pain. Therefore, thermal hypoesthesia may manifest differently in patients with different etiologies of central pain.

3. Central pain and cold allodynia

Cold allodynia is often associated with central pain even though it is not found in the majority of patients with CPSP (Table 1). The expression of cold allodynia is variable, which suggests that there is more than one mechanism for cold allodynia in different patients. In our recent study of seven patients with isolated parietal and/or insular lesions, 4/7 patients had cold allodynia based on thresholds, but only two of these had central pain and clinical cold hyperalgesia based on increased ratings of a painful cold waterbath stimulus (Veldhuijzen et al., 2009). Overall, these results suggest that posterior insular/retroinsular lesions in isolation can lead to cold allodynia as assessed by clinical, threshold and suprathreshold measures.

The matter is further complicated by differences in cold allodynia measured by different QST techniques. Cold allodynia can be evoked by touching the patient with a cool object, such as metal, at room temperature. In this case, the obligatory tactile stimulus may contribute to allodynia sensation, particularly in subjects with tactile allodynia. During QST, cold allodynia is often measured by thresholds for cold pain using a probe which is held on the skin while the temperature decreases until the patient reports pain perception. Surprisingly, the pain with a cold object contact often does not correspond to the pain evoked by the contact probe at the same temperature.

These phenomena have been observed in an early study which reported that 5/22 central pain patients had clinical cold allodynia but none had cold allodynia as measured with a contact temperature probe (Boivie et al., 1989). A similar observation was made in a more recent study (see Table 1). In the same study, 2 patients showed increased sensitivity to cold pain by thresholds, which met experimental criteria for cold allodynia, but the patients did not exhibit cold allodynia during clinical exams.

3.1 Ongoing pain

No relation between the size or location of a lesion and the presence or intensity of central pain has been found, although CP requires an impairment of thermosensory pathways or nociceptive pathways or both (see Table 1) (Boivie et al., 1989;Leijon et al., 1989;Andersen et al., 1995;Vestergaard et al., 1995;Greenspan et al., 2004;Lewis-Jones et al., 1990). In addition, studies of patients with central pain secondary to SCI show that the spinothalamic tract is not differentially affected in pain-free patients as opposed to patients with ongoing central pain (Ducreux et al., 2006;Finnerup et al., 2003). Therefore, lesions involving the spinothalamic pathway and its cortical connections, while necessary, are not sufficient to explain the development of central pain.

In a large series of patients (n=270) investigated for somatosensory abnormalities following stroke, five subjects were identified that presented with central pain and pure thermoalgesic sensory loss contralateral to the cortical stroke. All of these patients had involvement of the posterior insula and inner parietal operculum. Lemniscal sensory modalities and somatosensory evoked potentials to non-noxious inputs were preserved, while thermal and pain sensations were profoundly altered, and laser-evoked potentials were abnormal in all (Garcia-Larrea et al., 2010).

The nature of neural abnormalities in central pain is poorly understood. It has been proposed that thalamic bursting (low-threshold spike or LTS pattern) occurs at a higher rate among neurons in the region of the Ventral caudal (Vc) nucleus in patients with central pain as opposed to those with movement disorders (Jeanmonod et al., 1996;Lenz et al., 1989;Lenz et al., 1994). Another report found no difference in the thalamic burst rate between patients with chronic pain as opposed to those with movement disorder (Radhakrishnan et al., 1999). In the latter report, most of the neuronal recordings were made outside Vc in patients with peripheral neuropathic pain rather than central pain. Thus, this latter report does not speak directly to the mechanism of central pain. Electrical stimulation in the area of Vc evoked pain more commonly in central pain patients with allodynia, versus those without allodynia (Lenz et al., 1998;Davis et al., 1996). Overall, these studies suggest that reorganization of the region of Vc contributes to the symptoms of central pain.

In a study of MR spectroscopy, concentrations of markers for neurons (N-acetyl aspartate, NA) and glial cells (myo-inositol, Ins) in the thalamus were significantly different between patients with versus without central pain after SCI (Pattany et al., 2002;Stanwell et al., 2010). NA concentrations and NA/Ins ratios were lower in patients with pain versus those without, while Ins concentrations were higher for pain patients. In addition, NA concentrations were inversely correlated with VAS pain intensity, and Ins was directly correlated with pain intensity in the pain group. These results suggest that in SCI patients, dysfunction or loss of thalamic neurons is greater among SCI patients with central pain than among those without.

A recent study of SCI patients used a sophisticated wavelet-based analysis of the entire MRS signal to identify differences between SCI patients and intact controls, and between SCI patients with versus without central pain (DiPiero et al., 1991;Hsieh et al., 1995;Iadarola et al., 1995). Signals from the thalamus best discriminated between SCI patients and intact controls, yet signals from regions of the anterior cingulate and prefrontal cortex, but not the thalamus, highly discriminated between SCI patients with versus without central pain. While such an approach cannot identify the specific molecular differences, it does reveal which brain regions exhibit neurochemical differences that relate specifically to neuropathic central pain.

Neuroimaging studies of CP patients have most often reported thalamic hypoactivity, but some have observed thalamic hyperactivity. PET (positron emission tomography) studies

have found a decrease in thalamic cerebral blood flow (CBF) on the same side as the lesion in patients with central pain patients at rest (Ness et al., 1998). The spatial resolution of these studies does not permit identification of the specific thalamic nuclei which were involved. This decrease in activity could be reversed by stimulation of the motor cortex (Peyron et al., 1995), or therapeutic intravenous infusion of lidocaine (Cahana et al., 2004). A similar decrease in thalamic bloodflow has been reported in patients with central and peripheral neuropathic pain combined. Specifically, the thalamus opposite the affected body region had lower bloodflow than the thalamus on the same side as the affected region in patients with SCI and central pain (Lenz et al., 2010). However, a single photon emission CT (SPECT) study found bilateral increased thalamic metabolism associated with pain of high intensity, but decreased blood flow associated with pain of low intensity (Cesaro et al., 1991).

Finally, PET results from CP patients show decreased thalamic bloodflow in both medial and lateral thalamus. Both SPECT and PET studies demonstrate increased thalamic activity contralateral to stimulation of the allodynic sites compared to non-allodynic sites in CPSP patients with or without unilateral allodynia (Lenz et al., 2010). The brain metabolic and bloodflow differences estimated by PET or SPECT reflect both inhibitory and excitatory synaptic activity. Therefore, decreased thalamic bloodflow in patients with CP might reflect decreased inhibitory synaptic activity, which may be related to loss of neurons, as suggested by the MR spectroscopy study reviewed above (Fukumoto et al., 1999). This decrease in bloodflow could occur despite the increased spontaneous thalamic firing rates, since spontaneous activity may not be reflected in metabolic or bloodflow imaging studies of the brain.

It is also possible these results are due to adaptive changes in the thalamus following the inciting lesion. For example, in patients with complex regional pain syndrome a SPECT study found increased thalamic bloodflow in patients with symptoms at 3 to 7 months after the injury, while decreased bloodflow occurred with long-term symptoms (24–36 months after) (Fukumoto et al., 1999).

Finally, ongoing pain in patients with CP might be related to changes in the opiodergic intrinsic modulatory system. These patients show decreased binding of the non-selective opioid binding ligand, diprenorphine, versus healthy controls, which indicate higher levels of binding sites occupied by opioids originating in the brain's intrinsic opioid system (Willoch et al., 2004). These reductions in opioid receptor binding within the "medial nociceptive system" were most pronounced in the dorsolateral prefrontal cortex (Brodmann area 10), anterior cingulate cortex (Brodmann area 24), insular cortex, and the medial thalamus. There were also reductions in binding in the lateral nociceptive system including the inferior parietal cortex (Brodmann area 40). Similar but more extensive decreases in binding were found in a study which included parietal cortex, cingulate and midbrain gray matter; these decreases were independent of the lesion locus which caused CP (Head and Holmes, 1911).

3.2 Mechanisms of cold allodynia in patients with central pain

An often cited hypothesis of cold allodynia suggests that it is the result of disinhibition of the medial nociceptive system following disruption of the lateral nociceptive system (Lenz et al., 2010). An approximate version of this hypothesis was proposed long ago (Head and Holmes, 1911), but the more recent version proposes that the medial system (ACC and medial thalamus) is critical to the mechanism of both central pain and cold allodynia.

This hypothesis was tested by a PET study which reported the bloodflow activity resulting from cutaneous stimulation with a cool, tactile stimulus (ice in a plastic container) in patients with central pain due to lateral medullary stroke (Wallenberg) syndrome (Peyron et al., 1998). This stimulus produced differential activation of structures contralateral to the

affected side but not when it was applied to the unaffected side. These structures included: the primary sensory and motor cortex (contralateral to stimulation), the lateral thalamus (contralateral to stimulation), inferior parietal lobule (bilateral), and the frontal inferior gyrus. Notably, allodynic stimulation failed to evoke responses in medial thalamus or the portion of the ACC associated with pain. This study, then, did not support the model of disinhibition of the medial nociceptive processing system, but rather supported an amplification of the lateral nociceptive processing system as a basis for central pain allodynia.

A single subject PET study of a patient with central pain resulting from an infarct of the thalamus revealed a dramatic increase in sensory and motor cortical activation contralateral to allodynic cold stimulation of the affected hand (Kim et al., 2007). These increases may indicate disruption of a modulatory effect of the insula upon sensorimotor cortex which occurs in the normal brain. A study of two patients with large insular lesions but without central pain found that activation of S1 cortex ipsilateral to the lesioned insula was dramatically increased in response to painful heat stimulation (Starr et al., 2009).

Cold allodynia was associated with BOLD (blood oxygen level dependent) activation in the posterior insula, ACC, bilateral anterior insula, inferior parietal cortex, and supplementary motor cortex contralateral to the stimulus, and in the ipsilateral frontal gyrus of patients with syringomyelia (Ducreux et al., 2006). Brain activation in response to cold allodynic stimulation was much greater than usually evoked by the normally innocuous stimulus, and was comparable to the activation evoked by painful stimuli in controls without sensory abnormality. As noted above, a PET study of patients with Wallenburg strokes did not find activation of the ACC in response to stimuli which produced allodynia (Peyron et al., 1998), although such activation is often found in response to acute pain stimuli in healthy controls (Apkarian et al., 2005;Lenz et al., 2010). A combined PET and fMRI study of a unique patient with strokes of both the ACC and parietal cortex demonstrated cold allodynia, in the absence of hyperactivity in the remaining ACC (Peyron et al., 2000).

In contrast, one fMRI study of a patient with CPSP resulting from a stroke of the postero-lateral thalamus and adjacent internal capsule found activation of the ACC, the posterior parietal cortex, and the putamen during allodynia evoked by a cool stimulus (Seghier et al., 2005). Another fMRI study examined cold allodynia in normal controls evoked by cutaneous application of menthol, which rendered the skin hypersensitive to normally non-painful cold stimuli (Seifert and Maihofner, 2007). Stimulation of the sensitized skin was compared with the same intensity evoked by a normal cold pain stimulus. The pain evoked during allodynia resulted in more activation in dorso-lateral prefrontal cortex, bilateral anterior insula, and in parts of the brainstem. This range of results limits our ability to understand the mechanism of cold allodynia in terms of structures in the brain, particularly the ACC.

3.3 Mechanisms of tactile allodynia in patients with central pain

Tactile hypoesthesia and allodynia are common features of central pain as measured by use of von Frey hairs and camel hair brushes. Hypoesthesia for tactile sensation are associated with lesions of the dorsal columns, while such sensory loss is not found with lesions of the STT which spare the dorsal columns (Finnerup et al., 2007).

One recent study provided the first evidence that A-beta fibers are involved in dynamic mechanical allodynia (Landerholm and Hansson, 2010) In a portion of the central pain patients, dynamic allodynia occurred during a compression nerve block transitioning to a sensation of dysethesia. The remaining patients transitioned directly to the absence of allydynia following the block. In a subset of patients with central pain, concurrent changes in cold, but not warm, perception were found indicating A-delta involvement as well.

In contrast, tactile allodynia was more often associated with normal tactile thresholds than with tactile hypoesthesia in a study of CPSP patients (Hofbauer et al., 2006). Therefore, tactile allodynia may be the result of abnormal forebrain processing of signals transmitted through a relatively intact dorsal column – medial lemniscal system. This is consistent with reports of dysesthesias, which can be evoked by activation of afferents projecting through the dorsal column – medial lemniscal pathway in patients with post-stroke dysesthesias, a variation of CPSP (Triggs and Beric, 1994).

Cortical activation associated with tactile allodynia has been examined in experimental allodynia and peripheral neuropathic pain. A study of experimental allodynia resulting from application of capsaicin treatment in normal volunteers found that S1 and S2 activation occurred during nonpainful stimulation using von Frey filaments (Lorenz et al., 2002). When stimulating the area with mechanical allodynia, significant activation was found in the prefrontal cortex, as well as middle and inferior frontal gyri. There was no activation of the ACC.

In a patient with peripheral neuropathic pain after a peroneal nerve injury ongoing burning pain and tactile allodynia were observed; tactile stimuli evoked a deep pain, despite decreased tactile sensation (Hofbauer et al., 2006). Tactile allodynic sensations of the involved foot were compared with brush stimulation of the non-involved foot, and were associated with higher BOLD signals in S2, ipsilateral anterior insula, and ACC. Increased BOLD signals in S1 or ipsilateral posterior insula were not associated with stimulation of the involved foot, although such increased signals were observed after stimulation of the non-involved foot.

In a group of patients with complex regional pain syndrome, mechanical stimulation of the involved side evoked hyperalgesia and larger than control BOLD signals in several pain-related brain regions, including contralateral S1, bilateral S2, bilateral insula, inferior parietal lobule, and widespread ACC (Maihofner and Handwerker, 2005). Allodynia to a moving brush stimulus has also been studied in patients with traumatic peripheral nerve injury of the extremities, who suffered from ongoing pain and tactile allodynia (Witting et al., 2006). In these patients, allodynia in the affected limb yielded higher bloodflow than in the non-affected limb in contralateral orbitofrontal cortex and ipsilateral anterior insular cortex. Brushing of normal skin in the mirror image of the allodynic area produced a distinctly different pattern with increased bloodflow in contralateral S1 and posterior parietal cortex.

One imaging study has examined BOLD activation by tactile allodynia in patients with central pain secondary to syringomyelia (Ducreux et al., 2006). Tactile allodynia evoked by repeated brushing with a soft brush produced a pattern of brain activation distinct from that produced in normal controls with the same brushing, or with cold allodynic stimulation in these same patients. In all groups, activation was observed in the contralateral S1 and S2, and in parietal association areas. Tactile allodynia specific BOLD activation was elicited in the contralateral thalamus, bilateral middle frontal gyrus, and supplementary motor area, but was not observed in the insula or in the anterior and middle cingulate cortexes.

4. Conclusions

Based upon the data available today, it is not possible to draw any more than tentative conclusions. A frequent observation from PET and SPECT studies is that of thalamic hypometabolism in the painful resting state. At the same time, allodynic stimulation can evoke a stronger thalamic signal than normal. Both observations can be explained by a partially denervated thalamus and by a major disruption of GABA-mediated inhibition (Rausell et al., 1992). There is also some evidence that dysfunction of the thalamic nucleus Vc is involved in the mechanism of central pain (Montes et al., 2005;Kim et al., 2007).

The cortical regions associated with central pain can vary considerably among studies and symptoms of central pain. A recent study has suggested that CPSP occurred only in individuals with lesions including posterior insula/retroinsula, which spare the anterior and posterior parietal cortex (Veldhuijzen et al., 2009). Evidence from neuroimaging studies suggests that the parietal lobe is involved in the mechanism of CPSP and CPSP-associated allodynia in subjects with strokes of the lateral medulla (Wallenberg syndrome)(Peyron et al., 1998), and the thalamic nucleus Vc which projects to the parietal cortex (Kim et al., 2007). In both studies, a combined cold and mechanical cutaneous stimulus produced allodynia, and was associated with intense bloodflow activation of contralateral sensorimotor (frontal and parietal) cortex. In addition, pain sensations are evoked in subjects with CPSP by electrical stimulation of S1 cortex (Katayama et al., 1994;Nguyen et al., 2000;Brown and Barbaro, 2003) or of thalamic nucleus Vc, which projects to it (Lenz et al., 1998;Davis et al., 1996). Lesions of parietal cortex can dramatically relieve pain in subjects with CPSP resulting from thalamic lesions (Soria and Fine, 1991;Helmchen et al., 2002;Canavero and Bonicalzi, 2007). Consideration of these observations suggests the hypothesis that a network of insular and sensorimotor cortex is specifically disrupted in central pain, leading to increased activity in sensorimotor cortex, particularly with respect to the expression of allodynia.

5. Acknowledgement

This work was supported by the National Institutes of Health – National Institute of Neurological Disorders and Stroke (NS38493 and NS40059 to FAL NS-39337 to JDG). We thank C. Cordes and L. H. Rowland for excellent technical assistance.

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Edited by Peter Bright

The rate of technological progress is encouraging increasingly sophisticated lines of enquiry in cognitive neuroscience and shows no sign of slowing down in the foreseeable future. Nevertheless, it is unlikely that even the strongest advocates of the cognitive neuroscience approach would maintain that advances in cognitive theory have kept in step with methods-based developments. There are several candidate reasons for the failure of neuroimaging studies to convincingly resolve many of the most important theoretical debates in the literature. For example, a significant proportion of published functional magnetic resonance imaging (fMRI) studies are not well grounded in cognitive theory, and this represents a step away from the traditional approach in experimental psychology of methodically and systematically building on (or chipping away at) existing theoretical models using tried and tested methods. Unless the experimental study design is set up within a clearly defined theoretical framework, any inferences that are drawn are unlikely to be accepted as anything other than speculative. A second, more fundamental issue is whether neuroimaging data alone can address how cognitive functions operate (far more interesting to the cognitive scientist than establishing the neuroanatomical coordinates of a given function - the where question).

ISBN 978-953-51-6996-3

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