Neuroimaging of Consciousness

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Editors

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ISBN 978-3-642-37579-8 ISBN 978-3-642-37580-4 (eBook)
DOI 10.1007/978-3-642-37580-4
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013943114

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

…by night the glass
Of *Galileo* … observes
Imagined lands and regions in the moon.

John Milton
Paradise Lost, Book 5, lines 261–263

Science and technology are inextricably intertwined and this is particularly true for the field of neuroscience. Thanks to considerable advances in neuroimaging techniques, the past two decades have witnessed an unprecedented increase in the number of studies on the structure and function of the human, which have deepened our understanding of how neural networks subserve our mental life. This scientific endeavor, in turn, is leading to a reappraisal of the very notion of human nature. However, neuroscientists have just begun to unravel the secrets of the brain. In a sense, we are in the same position as sixteenth-century scientist Galileo Galilei when he first pointed his spyglass at the night sky to scrutinize the cosmos and better define the place of man in the wider perspective. Just like Galileo peered into the depths of the sky to see new worlds with the help of his telescope, we can now peer into the brain to see the living patterns of the mind in action with the help of increasingly more ingenious tools. In fact, neuroimaging gives us the privilege to see and analyze pictures of a hidden world – the inner life of the brain – that was until recently paradoxically inaccessible, despite its near and intimate location.

Neuroscientists are the privileged explorers of this vast landscape, and as a result of their investigations, they have realized that the fabric of mind is deeply complex, sometimes bewildering, but also extremely fascinating. During the last 25 years, they have been able to produce images of almost every nook and cranny of the brain, thereby collecting a wealth of data on the whole spectrum of mental functions. Among all cognitive functions, consciousness is arguably the one which has gained the highest interest and attention, because of its implications for the individual's presence of self, as well as human culture and society. What is progressively coming into view from the neuroscientific studies of consciousness is that this essential property of human nature seems to behave like a temporal glue that keeps together information processed by different neural subsystems, in order to construct a unified and coherent flow of sensations, thoughts, and feelings. We can realize how delicate and multifaceted this process is when the conscious glue is disrupted or altered in

specific pathologies of the brain. Particularly in regard to the study of the pathological and altered states of consciousness, brain imaging proves to be an invaluable tool for guiding paradigm shifts in neuroscience research for the new millennium.

The aim of this book is to provide the reader with the state of the art in the field of neuroimaging studies of consciousness. The book is divided into four parts, in order to minimize overlap between highly interlinked topics. Part I is an introductory tour of the historical, theoretical, and methodological aspects of the application of neuroimaging to consciousness studies. Parts II–IV focus on the role of neuroimaging in shedding light on the clinically relevant alterations of consciousness across neuropsychiatric conditions: epilepsy (Part II); coma, sleep, and anesthesia (Part III); and other neuropsychiatric disorders associated with alterations of consciousness (Part IV).

Part I is an overview of brain imaging and pathologies of consciousness. The part opens with a chapter by Nani, Seri, and Cavanna on *Consciousness and Neuroscience*, which outlines the recent historical background of the modern scientific approach to the study of consciousness by using ever more sophisticated neuroimaging techniques. The Chap. 2 (*Consciousness: Theoretical Approaches*), by Bayne and Hohwy, reviews some of the central theoretical challenges confronting the search for the neural correlates of consciousness and develops a conceptual framework for tackling these challenges. Chap. 3 (*Functional Brain Imaging and Consciousness*, by Bagshaw and Khalsa) introduces the reader to a consistent observation in brain imaging studies of altered conscious states: the modification of activity and functional connectivity in distributed cortical and subcortical networks. These findings have led to the description of specific perturbation in resting-state networks (especially the so-called default mode network) across a range of pathologies of consciousness.

Part II discusses brain imaging and alterations of consciousness in epilepsy, beginning with a chapter on neuroimaging and mechanisms of impaired consciousness in focal temporal lobe epilepsy (*Temporal Lobe Seizures* by Furman and Blumenfeld). Next is a chapter on localized components of consciousness which may be selectively impaired and analyzed through functional neuroimaging in absence epilepsy (*Absence Seizures* by Gotman and Kostopoulos). This is followed by a chapter on cortical and subcortical changes in generalized tonic-clonic seizures identified through neuroimaging (*Brain Imaging and Alterations of Consciousness in Epilepsy: Generalized Tonic-Clonic Seizures* by Paige and Cavanna). Part II concludes with a chapter on intracranial electroencephalography and pathological synchrony in partial seizures (*Consciousness, Epilepsy and Intracranial EEG* by McGonigal and Bartolomei).

Part III discusses imaging and alterations of consciousness in coma, sleep, and anesthesia. This part opens with a chapter entitled *Neuroimaging of Consciousness in the Vegetative and Minimally Conscious States*, reviewing studies on residual brain function in very severe pathological alterations of consciousness, by Schnakers, Laureys, and Boly. These studies emphasize the critical role of frontoparietal network connectivity for the emergence of conscious awareness. Next, physiological alterations of consciousness, encompassing sleep and dreaming, are being extensively discussed in terms of neural mechanisms assessed by EEG, PET, fMRI, and TMS-EEG measurements (*Sleep and Consciousness*, by Nir, Massimini, Boly, and

Tononi). Finally, changes in brain function during pharmacological alterations of consciousness as seen in general anesthesia are being presented (*Anesthesia*, by Bonhomme, Boveroux, and Brichant).

Part IV closes the book with three chapters on relatively novel and promising applications of neuroimaging to neuropsychiatric conditions characterized by altered consciousness. Chap. 11 (*Neuroimaging Studies of Interoception and Self-Awareness*, by Garfinkel, Nagai, Seth, and Critchley) explores the insights gained from neuroimaging studies into the brain substrates and mechanisms underlying metacognitive aspects of consciousness which allow the mental representation of the body and self-recognition. In Chap. 12 (*Neuroimaging of Functional Neurological Symptoms*), Carson, Edwards, and Stone illustrate the new era of structural and functional brain imaging studies of conversion disorder, or functional neurological symptoms. The unconscious/subconscious production of symptoms resembling the consequences of organic neurological pathology has been a medical conundrum for centuries, and neuroimaging holds promise in unraveling psychophysiological mechanisms which have proven elusive to previous investigation techniques. The final chapter (*Neuroimaging Studies of the Dwindling Self: Neurodegenerative Dementias*, by Nani and Cavanna) focuses on the link between disrupted anatomical and functional networks and the progressive loss of the sense of self which accompanies different forms of neurodegenerative dementias. These are arguably among the pathologies of consciousness where new developments in the technology of in vivo neuroimaging can more directly translate into clinically relevant applications.

We hope that this book will provide the reader with novel concepts and insightful ideas, in addition to up-to-date information from the leaders in their fields. The present renaissance of consciousness studies is likely to persist and reverberate in the future decades because of their crucial clinical applications and intrinsic fascination. The enterprise inaugurated by Galileo with his telescope is continued by the modern explorers of the mysteries of consciousness, as increasingly more sophisticated brain imaging techniques are getting closer to provide us with the ultimate picture of human nature.

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Contents

Part I

Brain Imaging and Pathologies of Consciousness

Andrea Nani and Andrea E. Cavanna

Consciousness and Neuroscience

1

Andrea Nani, Stefano Seri, and Andrea E. Cavanna

Abstract

Neuroscience has received a strong impulse from brain imaging techniques. For the first time, neuroimaging made it possible to study the brain in vivo and thereby associate mental processes with distinctive patterns of cerebral activity. Moreover, functional images of the living brain have provided a powerful instrument for the scientific study of consciousness. Advances in imaging techniques have proved invaluable for obtaining high-resolution maps of the functional and anatomical brain connectivity. Over the last few years, the notion that cerebral regions work together to form a functional network at rest was substantiated by functional imaging studies. These resting-state networks show a high level of spontaneous coupling of ongoing neuronal activity. Among the functional networks identified thus far, the so-called default mode network exhibits particularly interesting features, which might play an important role in the promotion and maintenance of conscious states, especially with regard to the level of consciousness (arousal).

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_1, © Springer-Verlag Berlin Heidelberg 2013

The objective level of arousal and the subjective contents of awareness appear to be the two planes within which the neural correlates of consciousness can be interpreted. With regard to the content dimension, which has traditionally been the most elusive to scientific exploration, a theory of conscious access should incorporate five essential concepts: a supervisory system, a serial processing, a coherent structure of recurrent neural loops, a global neuronal workspace capable to differentiate and integrate the various contents of experience, and a complex system of topological properties which identifies crucial hub nodes.

1.1 Introduction

Over the last two decades, the development of new scientific techniques has provided powerful tools for studying the human brain in a way that was unattainable before. For the first time, high-resolution pictures of the brain in vivo offered a "physiological window into the human mind" (Dolan 2008). This, in turn, contributed to the current renaissance of neuroscience: crossroads of interconnected disciplines that aim to study the nervous system under specific but also converging aspects (molecular, cellular, developmental, structural, functional, evolutionary, computational, and clinical).

The discovery of the blood oxygen level-dependent contrast in gradient-echo magnetic resonance images (Ogawa et al. 1990) led the way for a new approach to human brain mapping. This technique rapidly became the preferred tool for noninvasive investigation of brain activity surpassing positron emission tomography due to its greater spatiotemporal resolution and minimal invasiveness. Furthermore, a novel analysis framework and sophisticated data mining methods made it possible to construct statistical maps of the brain from functional imaging data (Fox et al. 1988a; Friston et al. 1991).

The high-resolution visualization of the normal brain's functional anatomy has been one of the major achievements of the brain imaging era. This instrument led to the exciting discovery that the execution of simple tasks is associated with recruitment of more widespread networks of brain areas than previously thought based on postmortem data of patients with cerebral lesions. Neuroscientists have found that the bases of cognitive performances depend on both the functional differentiation (due to localized neuronal modules) and the integration of brain regions able to form distributed functional networks. This finding has led to two fundamental questions: how do functional distributed brain areas interact while executing a cognitive task? And how can we identify and assess the causal influence of a cerebral region over others? In the endeavor to understand these crucial issues regarding the organization of the brain-mind, we have literally witnessed an explosion of neuroimaging studies (Buchel and Friston 2001; Bullmore and Sporns 2009; Friston 1994; McIntosh and Gonzalez-Lima 1994). Many aspects of the human mind have been investigated. Motor learning (Karni et al. 1998) memory (Courtney et al. 1998; Fletcher et al. 1995; Jonides et al. 1993; Shallice et al. 1994; Wagner et al. 1998), perception (Haxby et al. 1991, 1996), attention (Kastner et al. 1998), executive functions (Baker et al. 1996; Owen et al. 1996), emotions (Phan et al. 2004; Vuilleumier and Pourtois 2007),

and decision making (Elliott et al. 2000; Sanfey et al. 2003) are but a few of the numerous topics that went under the lens of neuroscience. A torrent of neuroscientific findings has thus spread in various directions and affected entire research fields which until then had been kept separate, such as ethics (de Quervain et al. 2004), economics (Kable and Glimcher 2007), law (Hsu et al. 2008), and aesthetics (Winston et al. 2007) with significant cross-fertilization.

As a result of the flourishing of neuroimaging studies, the way we consider the human mind has profoundly changed. Several commonsense principles on which we founded the way we thought of ourselves and of our mental faculties have been challenged, and old philosophical questions regarding these concepts have taken new shapes (Churchland 2008). In particular, consciousness – traditionally the object of philosophical inquiry – became a focus of the attention of neuroscientists. Historically, philosophers tried to decipher the intimate nature of man by exploiting the explanatory power of the sole reason and indeed produced ideas that are still of invaluable inspiration in our time. As we shall see, however, bringing consciousness under empirical investigation revealed aspects that were inaccessible to conceptual analysis alone.

1.2 The Functional Connectivity of the Brain

The fundamental tenet of the neuroimaging approach is that discrete states of mind can be investigated with measurements of brain activity. In principle, every mental event should find a correlate in a specific cerebral process. Although it is as yet debatable whether the neural correlate of a mental state is necessary *and* sufficient or necessary *but not* sufficient for the mental state to take place, there are robust empirical data to suggest that changes in one's state of mind are invariably accompanied by changes in measures of brain function. Based on these observations, the standard view in neuroscience assumes that mental activity is supported by neuronal activity (Shulman 2001). However, most modern functional imaging methods do not measure brain activity directly, as the detected signal is derived from physiological measures of energy consumption (i.e., changes in blood flow, glucose consumption, and glucose oxidation).

In the average adult, the brain is about 2 % of the body weight, although the energy required to maintain its functions amounts to about 20 % of its resting metabolic rate (McKenna et al. 2006). Remarkably, the metabolic activity of the brain is constant over time, despite variation in mental and motor performances. This is explained by the fact that the resting state normally needs considerable energy for maintaining membrane potentials. Approximately 75 % of energy utilized by brain is related to signaling, whereas the remaining 25 % of energy consumption serves to maintain indispensable nonsignaling cellular activity, including protein synthesis and degradation, nucleotide turnover, axoplasmic transport, and mitochondrial proton leak (Attwell and Laughlin 2001).

Since the brain is characterized by a high metabolic rate both when we are cognitively and behaviorally "passive" (resting state) and when we are actively engaged

in tasks, the physical properties of the imaging techniques are as important as the meaning of term "activation" (Raichle and Gusnard 2002) in determining the sensitivity of the different techniques to transient changes in brain activity. Brain activation can be distinguished from the resting metabolic activity based on blood flow and oxygen consumption measures. This relationship can be measured by PET as the fraction of available oxygen and has a remarkable spatial uniformity in the resting state, i.e., when the subject lies quietly in a scanner with eyes closed but fully awake (Raichle et al. 2001). In the normal brain, however, the balance between oxygen delivery (i.e., blood flow) and oxygen consumption is altered to a measurable degree when "activations" take place (i.e., when cerebral areas transiently change their activity level) during the performance of specific behaviors (Raichle and Mintun 2006). Significantly, the changes in blood flow are greater than the accompanying changes in oxygen consumption. As a result, the amount of oxygen supply increases more than the oxygen demand. On the other hand, while oxygen utilization increases less than blood flow, glucose consumption increases proportionally to the change in blood flow, because part of the increase in the metabolism is supposedly due to glycolysis (Fox et al. 1988b). As both glucose consumption and blood flow increase more than oxygen utilization, brain activation can be precisely distinguished from resting metabolic activity.

These methodological grounds make it possible to design functional imaging experimental protocols to measure differences in the detected brain signal between two behavioral conditions. In one condition (the control task), the subject lies at rest in absence of stimulation, while in the other condition he or she is engaged in accomplishing a specific task. Subsequently, images of functional activation patterns obtained at rest are compared to those gathered during the task performance, in order to look for statistically significant changes in the brain signals that identify brain regions predominantly associated with a specific state of mind or a mental process. It is important to take into consideration, however, that the same brain area could serve more than one function. In the neuroscientific literature this phenomenon has been called "neuronal context" (McIntosh 1998) or "functional context" (Bressler and Kelso 2001). In addition, results from single-cell studies have revealed that neuronal firing patterns frequently depend on several combined factors rather than on single stimulus or response parameters. Effective connections, therefore, are expected to be context sensitive (Buchel and Friston 1997). In this view, the contribution of a particular neuronal population or single cell to a specific function is markedly influenced by the state of other anatomically related elements, in so far that the same level of activity in a given brain area may contribute to different mental processes depending on what other regions are temporarily coactive (McIntosh 1999).

The neuronal or functional context has considerable implications for interpreting brain distributed activation profiles, especially in the study of higher-order psychological functions, where a great overlap in the functional patterns for different cognitive operations is expected (McIntosh et al. 2001). It is well established that at rest, brain areas are consistently found to activate together, so as to constitute a variety of functional networks. These resting-state networks show a high level of spontaneous baseline neuronal activity. So far, neuroimaging studies have identified

at least ten functional networks (Beckmann et al. 2005; Fransson 2005; Salvador et al. 2005; van de Ven et al. 2004; van den Heuvel et al. 2008). These sets of connections include the motor network, the visual network, two lateralized networks composed of superior parietal and superior frontal regions, a network composed of bilateral temporal insular and anterior cingulate cortex regions, the dorsal attention network, and the default mode network (DMN). The DMN is a widespread network encompassing the posterior cingulate cortex (PCC) and precuneus in the posteromedial parietal cortex, the temporoparietal junction, the medial prefrontal cortex, the parahippocampal gyri, the superior frontal sulci, and the nonspecific nuclei of the thalamus (Buckner and Vincent 2007; Fox and Raichle 2007; Fox et al. 2005; Raichle and Snyder 2007).

The connectivity patterns observed in functional neuroimaging studies are supposed to be mirrored in the structural connections between these same brain regions. The structural connections are white matter tracts that directly link large ensembles of spatially segregated neurons. These pathways convey large traffic of data between functionally related brain areas. In effect, converging lines of research suggest a direct association between functional and structural connectivities in the brain (Hagmann et al. 2008; Honey et al. 2007, 2009; Koch et al. 2002). Multimodal imaging obtained by combining resting-state fMRI with structural diffusion tensor imaging (DTI) is the method of choice to visualize functional and anatomical connections. DTI is an MRI-based technique that enables to reconstruct white matter pathways by measuring the diffusion profile of free water molecules in the brain tissue. This technique exploits the property of water molecules, which diffuse in preferential directions along white matter tracts, due to the compact shape of axonal fibers. Combined fMRI-DTI studies have revealed that almost all the brain regions which are functionally linked in the observed resting-state networks are also structurally connected by white matter pathways (Van den Heuvel et al. 2009). Therefore, current neuroscientific data support the existence of an intimate relationship between functional and structural connectivities on a whole brain scale (Damoiseaux and Greicius 2009).

Among the functional networks identified so far, the DMN has particularly interesting implications for consciousness studies. In contrast to the other networks, the DMN shows a high level of activity during rest compared to active engagement in cognitive tasks. This peculiar aspect suggested that its activity could represent a default state of human brain activity at baseline (Gusnard and Raichle 2001; Raichle and Snyder 2007). Originally proposed as a system for evaluating "information broadly arising in the external and internal milieu" (Raichle et al. 2001), the DMN has since been thought to underpin a variety of functions: episodic memory (Greicius and Menon 2004), memory consolidation (Miall and Robertson 2006), social and self-related cognition (Buckner and Carroll 2007; Iacoboni et al. 2004; Uddin et al. 2005, 2007; Wicker et al. 2003), integration of cognitive and emotional processing (Greicius et al. 2003), and task-unrelated free thoughts or mind wandering (Mason et al. 2007; McKiernan et al. 2006). Given this different array of functions, it is likely that the DMN may be composed of functionally different, yet strongly overlapping, subnetworks (Uddin et al. 2009). Nevertheless, although it is not possible to link the brain intrinsic activity to a specific activity or cognitive process, converging

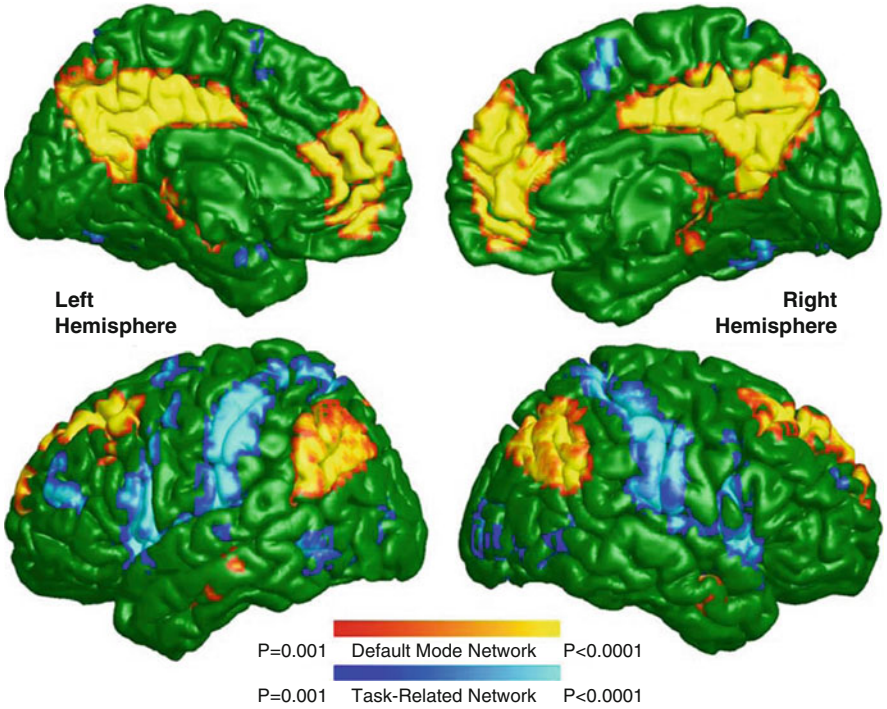

Fig. 1.1 Default mode and task-related maps in healthy controls. On a *green* background, the default mode network is highlighted in warm colors (*red* and *yellow*), and the task-related network is highlighted in cold colors (*blue* and *light blue*) depending on the *p*-value of one sample *t*-test (From Shim et al. (2010). © 2010 Biomed Central Ltd. http://creativecommons.org/licenses/by/2.0)

findings suggest that DMN functioning can be altered or disrupted in neuropsychiatric disorders characterized by specific dysfunction in selective cognitive processes, including self-reflection and self-awareness (Damoiseaux et al. 2007; Garrity et al. 2007; Greicius 2008; Rombouts et al. 2009; Shim et al. 2010). Figure 1.1 illustrates the contrast between the DMN and a task-related network activation pattern (social cognition task).

Despite the wide array of hypotheses which have been put forward, the exact role of brain intrinsic activity dynamics remains elusive. A unifying account proposes that the synchronous spontaneous activity of connected cerebral regions might maintain functional systems in an active state, helping to improve performance whenever any cognitive or motor task is to be undertaken (van den Heuvel and Hulshoff Pol 2010). In addition to the maintenance of an optimum level of brain functionality, the spontaneous fluctuations of the DMN could reflect a combination of conscious activity and internal neuronal dynamics, which is critical to the emergence of sophisticated behavioral functions (Buckner 2010; Rosazza and Minati 2011). In light of this interpretation, the DMN activity appears to be an essential ingredient for promoting consciousness and self-oriented cognition.

1.3 The Neuroscientific Coordinates of Consciousness

Neurophysiological and neuroimaging studies provide converging evidence that the neural correlates of consciousness can be better interpreted in the light of a bidimensional model, based on the two different axes: the objective level and subjective content of consciousness (Cavanna et al. 2011; Laureys et al. 2004; Monaco et al. 2005; Nani and Cavanna 2012). Within this framework, the level evaluates the structures necessary for control of the quantitative features of consciousness, while the content addresses the structures involved in producing the qualitative features of subjective awareness (Blumenfeld 2009; Plum and Posner 1980; Zeman 2001). The level of arousal reflects the degree of wakefulness, which can range from full alertness through drowsiness and sleep to coma (Baars et al. 2003; Laureys and Boly 2008). The functional and structural integrity of ascending ponto-mesodiencephalic reticular pathways and widespread thalamocortical projections is essential for igniting and maintaining the level of consciousness (Steriade 1996a, b). The contents of conscious experience are composed of sensations, emotions, thoughts, memories, intentions, and all the feelings that color our inner world ("qualia" in neuro-philosophical terms). The contents are likely to be determined by the interaction between exogenous factors coming from the environment and endogenous factors (e.g., focal attention). Subjective experiences are also bound to visceromotor reactions and are accompanied by a degree of emotional salience, which appears to be modulated by temporolimbic activity (Critchley 2005; Johanson et al. 2003).

On the basis of these two parameters, we can also distinguish an intransitive from a transitive use of the terms "conscious" and "consciousness." In the intransitive use (e.g., "The patient never regained consciousness"), the term refers to the state of awareness or vigilance. By contrast, in the transitive use (e.g., "She was suddenly conscious of the alarm clock"), the term refers to the conscious processing of a specific block of information.

With regard to the contents of consciousness, it is important to highlight that, at any given moment, we have conscious access only to a limited amount of information, which can then be reported verbally or by intentional behavior. However, a number of other brain processes remain totally out of consciousness. Different studies have investigated how a piece of information can gain access to consciousness by aiming at isolating the neural correlates and the physiological properties of a specific conscious experience. In order to study the moment of the conscious access, researchers have developed experimental paradigms which generate a minimal contrast between conscious and nonconscious stimuli (Kim and Blake 2005). We can therefore distinguish whether a nonconscious stimulus is subliminal or preconscious (Dehaene et al. 2006; Kanai et al. 2010). A stimulus is subliminal when the bottom-up information is so reduced as to make it unnoticeable, even though the attention is inwardly focused. On the contrary, a preconscious stimulus is potentially detectable as its intensity and duration are such that it may be perceived, although it is not actually perceived because of inattention or distraction.

Masking is often used as a method for subliminal presentation: the conscious vision of a stimulus is diminished or prevented by presenting other stimuli working

as "masks" in near spatial and temporal contiguity (Breitmeyer 2006). The same effect can also be achieved by the experience of *binocular rivalry*, in which the image of one eye turns out to be subliminal by competition with a rivaling image shown to the other eye. Participants typically report that the two images alternate between each other, so that they can consciously see only one image at a time. On the other hand, in the *continuous flash suppression* paradigm, which is a variant of binocular rivalry, an image can be maintained invisible by presenting repeated flashing figures to one eye (Tsuchiya and Koch 2005).

A vast assortment of techniques is similarly used to explore the effect of preconscious presentation. In *inattentional blindness* a potentially visible stimulus is not reported when participants focus their attention on another task (Mack and Rock 1998; Simons and Ambinder 2005). A variant of this phenomenon is the *attentional blink*: a first stimulus blocks the conscious experience of a second stimulus, which is showed a few milliseconds after the first one in a rapid serial visual presentation (Raymond et al. 1992). Related to this effect is the *psychological refractory period*, in which the second stimulus is eventually detected and processed but only after a delay during which it still remains nonconscious (Corallo et al. 2008; Marti et al. 2010). Both the attentional blink phenomenon and the psychological refractory period underline the limits of conscious processing, which therefore appears to be intrinsically serial (Marti et al. 2010; Wong 2002).

fMRI and PET are eminently suitable to investigate the relationship between consciousness and attention. Although attention normally represents the gate for conscious access, empirical evidence has convincingly put forward that these processes are related but dissociable activities of the brain. On the one hand, selection can occur without conscious processing (Koch and Tsuchiya 2007); on the other hand, conscious access can occur independently of selection, in simple displays with a single target (Wyart and Tallon-Baudry 2008). Indeed, consciousness and attention have different functional roles. Consciousness has been conceptualized as a global process capable of elaborating information in order to give a survey of what is going on inside and outside the body, while attention seems to identify with the ability of shifting between mental states in order to appreciate the sensory relevance or salience from one perception to another, thereby assigning voluntarily or involuntarily priority to some parts of the information that is available at a given moment (Cavanna and Nani 2008).

The difference between consciousness and attention is expected to reflect into segregated neural correlates. With regard to attention, most neuroimaging studies have revealed the involvement of a distributed system of brain regions that control selection by enhancing the processing of attended aspects of information. Converging data showed that the most consistent activation pattern for attention is within the bilateral parietal and dorsolateral prefrontal cortex (Pessoa et al. 2003). With regard to conscious access, brain imaging studies suggest an amplification in the activity of the occipital cortex and other higher-order visual areas (such as the fusiform gyrus) in the case of conscious vision (Polonsky et al. 2000; Williams et al. 2008) or in bilateral temporal areas in case of conscious hearing (Sadaghiani et al. 2009), along with the activation of a distributed set of regions, ranging from bilateral parietal and

prefrontal cortices (van Gaal et al. 2011). Similar results have also been found with regard to conscious tactile perception (Boly et al. 2007). Overall, consciousness and attention appear to be essentially separate functional processes, which are however characterized by partially overlapping neural correlates within frontoparietal association networks (Cavanna and Nani 2008).

Association networks within the frontoparietal regions appear to play a central role also for action awareness. In fact, consciousness of one's own action is far from directly arising from primary and premotor areas activation: it has been associated with higher-order representation of intention, which involves prefrontal and parietal cortices (especially the angular gyrus), and its expected consequences (i.e., sensory feedback) (Desmurget et al. 2009; Farrer et al. 2008). Back in 1890, William James already noted that both selective attention and conscious effort are necessary in order to learn and control the execution of novel nonroutine sequential tasks, but are no longer required or even disadvantageous once the routine has been established. Indeed, an extensive network consisting of inferior and dorsolateral prefrontal, anterior cingulate, and lateral parietal and intraparietal regions is activated when the subject is engaged in performing single or dual tasks (Marois and Ivanoff 2005). In contrast, the activation of this network decreases as a result of training (Dux et al. 2009). Remarkably, such brain activity rapidly collapses as soon as the subject acquires a routine mode of task execution (Landmann et al. 2007; Procyk et al. 2000). Other neuroimaging data have revealed that frontoparietal networks can also be isolated during spontaneous brain activity in absence of explicit goal-directed tasks (Mantini et al. 2009; Vincent et al. 2008).

As illustrated in the previous section, the DMN appears to be primarily involved in mind wandering as well as in episodic memory and self-oriented reflection (Christoff et al. 2009; Smallwood et al. 2008). Over the last few years, the DMN has received increasing interest in neuroimaging studies, especially with focus on altered states of consciousness. One intriguing question is how this intrinsic baseline activity of the brain relates to conscious awareness, given that it has been observed, to some extent, even in sleep (He et al. 2008), vegetative state (Boly et al. 2009), and sedation in both humans (Greicius et al. 2008) and monkeys (Vincent et al. 2007). Moreover, during light sleep, no measurable change in DMN connectivity was observed (Larson-Prior et al. 2009). In contrast, however, during deep sleep and propofol anesthesia, the coherence of spontaneous activity within DMN and other functional networks exhibits a significant reduction in the connectivity between prefrontal and parietal cortices (Horovitz et al. 2009; Schrouff et al. 2011). Moreover, voxel-based analyses have found selective alterations of the normal co-activation patterns of associative fronto-parieto-cingulate areas in other altered states of consciousness, such as coma, epileptic seizures, and somnambulism (Baars et al. 2003; Laureys 2005).

A possible way to reconcile these apparently conflicting data is to hypothesize a two-layer structure in the connectivity of the DMN (Vanhaudenhuyse et al. 2010). According to this view, one layer of the DMN connectivity would persist independently of the level of consciousness, as it is associated with underlying anatomical connectivity (Greicius et al. 2009), while the other layer of the DMN would be

tightly related to the degree of awareness and conscious cognitive processes. The DMN could therefore be a candidate for subserving basic functions related to consciousness (Boly et al. 2008). Thus far, analyses of neuroimaging data and clinical practice both suggest that the progressive decrease in awareness between normal wakefulness, minimally conscious, vegetative state, and coma is nonlinear (i.e., the level of consciousness shown by vegetative-state patients is closer to the level of consciousness shown by comatose patients than to the level of consciousness shown by minimally conscious-state patients). Interestingly, the peak region of significance for the correlation between the degree of connectivity and level of consciousness has been located in the PCC/precuneus. The degree of activation in this area was also found to discriminate the minimally conscious patients from the unconscious ones (Vanhaudenhuyse et al. 2010).

These neuroimaging findings suggest a particularly strong relationship between the activity of PCC/precuneus and the patients' level of consciousness (Cavanna 2007; Cavanna and Trimble 2006; Cavanna et al. 2008; Laureys et al. 2004). The precuneus, consequently, appears to have a pivotal role in the DMN architecture, from both the functional and the structural points of view (Fransson and Marrelec 2008; Hagmann et al. 2008). Indeed, this brain region shows the highest resting metabolic rate among the DMN, consuming around 35 % more glucose than any other area of the cerebral cortex in humans (Gusnard and Raichle 2001) and in other species (Harley and Bielajew 1992).

In light of the recent neuroscientific data presented here, it is likely that the brain default mode connectivity may have a precise functional significance for consciousness. However, more studies on the physiological (e.g., sleep), pharmacological (e.g., anesthesia), and pathological alterations of consciousness are needed before we can understand the exact nature of the relationship between DMN activity and conscious processing.

1.4 A Conceptual Framework for Consciousness

The scientific investigation of the brain based on clinical data and functional imaging studies provides us with a conceptual framework for consciousness. At least five essential concepts can be singled out (Achard et al. 2012; Dehaene and Changeux 2011).

1.4.1 A Supervision System

Information is consciously processed when it is represented within a supervisory attentional system, which is in control of the lower-level sensory-motor routines or schemes (Posner and Rothbart 1998; Shallice 1972, 1988; Norman and Shallice 1980). In fact, although several chains of sensory, semantic, and motor functions can occur without awareness, conscious focus is needed for the flexible control of their execution, as well as their onset, termination, inhibition, repetition, and for the acquisition of novel routines. The supervision system seems to require the essential support of

attentional processes, which are associated with the activity of subsystems in prefrontal and inferior parietal cortices (Shallice and Cooper 2011).

1.4.2 A Serial Processing System

Consciousness seems to have a limited capacity channel (Broadbent 1958), so that we can be fully conscious of only one thing at a time. Effects such as the attentional blink and the psychologically refractory period corroborate the serial nature of consciousness: the first stimulus temporarily prevents us to consciously perceive other shortly subsequent stimuli. Thus, despite the fact that the brain can implement several perceptual and cognitive processes in parallel and unconsciously, conscious access of information is thought to take place serially through a central bottleneck (Pashler 1994) or a second processing stage of working memory consolidation (Chun and Potter 1995).

1.4.3 A Consistent Structure of Reentrant Loops

A fundamental component for creating a unified percept is *reentry*, defined as the bidirectional exchange of information along parallel and functionally linked cortical neuronal assemblies which elaborate different aspects of the same object (Edelman 1987). The hypothesis is that this reentrant functional connectivity can form temporary consistent structures (i.e., dynamic cores) which are able to distinguish and to integrate the different aspects of a perceptual scene, in order to construct a coherent and unified representation in which the whole has more information than the sum of its parts (Tononi and Edelman 1998). According to this hypothesis, consciousness would essentially be a modality of integrated information, which is achieved by the neural dynamic core (Tononi 2008) and originates as the stable and global activity of neural coalitions (Crick and Koch 1995, 2003, 2005). Within these coalitions, top-down or feedback signals elaborated in recurrent loops would play a fundamental role for conscious visual access (Lamme and Roelfsema 2000; Supèr et al. 2001). Also fundamental for the emergence and the maintenance of consciousness would be the property of neurons to be intrinsically active within thalamocortical closed loops (Llinás et al. 1998; Llinás and Paré 1991).

1.4.4 A Global Workspace Architecture

Conscious access to information can be made possible in a mental space where the current conscious content is represented and transferred by input processors to other processors (Baars 1989). The activation of the ascending reticular formation of the brainstem and midbrain, the outer shell of the thalamus, and the set of neurons projecting from the thalamus to the cerebral cortex would be fundamental for the emergence of the global workspace. An improved version of this model is represented by

the *global neuronal workspace* (GNW) (Changeux and Dehaene 2008; Dehaene and Changeux 2005; Dehaene et al. 2006; Dehaene and Naccache 2001). According to this proposal, coalitions of cortical pyramidal neurons with long-range excitatory axons, which populate the prefrontal, cingulate, and parietal areas, together with the thalamocortical loops, could maintain a mental workspace that interlinks specialized, automatic, and nonconscious neuronal modules. In virtue of their abundant connections, GNW neurons may sustain and globally broadcast specific conscious contents to other brain processes, such as verbal reports, memories, plans, and intentional actions. Consequently, this global availability of information would constitute what we subjectively experience as a conscious state (Dehaene and Naccache 2001).

1.4.5 Neurotopography

It has recently been suggested that human brain networks share topological properties with other complex systems (Achard et al. 2012). Using a methodology based on graph theory, it is possible to explore what aspects of brain network organization are critical for distinctive functional properties of the brain, such as consciousness. Interestingly, results from fMRI data in patients with severely impaired consciousness showed that many global network properties (including global efficiency, clustering, small-worldness, and modularity) were conserved in comatose patients (Achard et al. 2012). However, imaging data from patients with impairment of consciousness showed evidence of a radical reorganization of high-degree or highly efficient "hub" nodes between the healthy and pathological states. These preliminary findings are promising and intriguing, as they suggest that global topological properties of complex brain networks may be homeostatically conserved under extremely different clinical conditions, while preservation of consciousness might depend on the anatomical location of crucial hub nodes in human brain networks.

Conclusion

Neuroimaging techniques have provided an invaluable insight into the human mind. Indeed, it is apparent that every manifestation of human cognition can in principle find a specific neural correlate in the brain. The gap between mind and body has, therefore, begun to reduce, thanks to the evermore sophisticated exploration of brain activity. As we have seen, the impact of brain imaging has been crucial for the recent development of research studies into the nature of consciousness, which in turn has now become a respectable topic for scientific inquiry. This empirical enterprise has moved along the two coordinates of the level and content of consciousness and has revealed that the functional connectivity of the brain plays a central role with regard to both of them. In particular, the so-called DMN may subserve the conditions for maintaining and promoting consciousness as well as help define more precisely the boundaries of altered states of awareness. It is, therefore, becoming evident that consciousness, in its various features, requires the support of a vastly distributed set of recurrent

networks in the brain. The future pathways will be to achieve a thorough understanding of this intimate relationship with the help of a more refined technology so as to open ever-clearer views into the mind.

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Consciousness: Theoretical Approaches

2

Tim Bayne and Jakob Hohwy

Abstract

This chapter reviews some of the central theoretical challenges confronting the search for the brain basis of consciousness and develops a conceptual framework for tackling these challenges. At the heart of the search for the neural basis of consciousness is the notion of a neural correlate of consciousness. Identifying the neural correlates of consciousness requires that we acknowledge the various aspects of consciousness, for each of the aspects of consciousness raises its own set of methodological challenges. We examine the question of whether an account of the neural correlates of consciousness can be used to ascribe consciousness to creatures that lack the capacity to report their experiences, and we ask whether it is possible to go beyond the neural correlates of consciousness by providing neurally-based explanations of consciousness.

2.1 Introduction

In this chapter, we review three aims of the science of consciousness for which neuroimaging is potentially relevant. The first aim is that of identifying the neural correlates of consciousness (NCCs), where a neural correlate of consciousness is a neural state that suffices for a certain kind of conscious state. The second aim is that

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_2, © Springer-Verlag Berlin Heidelberg 2013

of developing robust tools for the ascription of consciousness. The hope is that once we have identified the neural correlates of consciousness we can use our knowledge of them to determine whether or not a target creature is in a particular kind of conscious state. A third aim for the science of consciousness is to go beyond the identification of the neural correlates of consciousness by providing mechanistic explanations of consciousness. We will consider how neuroimaging might bear on each of these three aims, but first we present a framework for thinking about consciousness that informs our discussion of these issues.

2.2 A Conceptual Framework for Consciousness

A central distinction is that between *specific* conscious states and the *generic* state of being conscious (what is sometimes called 'creature consciousness'). Specific conscious states are individuated in terms of their content. For example, we can distinguish the state of smelling a rose from the state of smelling coffee, and we distinguish each of these states from the state of seeing a face. We can say that a creature is in the generic state of consciousness if, and only if, it is in some conscious state or another.

For the most part the scientific study of consciousness has focused on the study of specific conscious states. For example, a typical paradigm for investigating consciousness employs binocular rivalry, where a conscious monkey or human is shown different stimuli to the two eyes and the conscious content of their experience changes between what is shown to the two eyes. The aim, using various neuroimaging techniques, is to identify the changes in neural activity that correlate with the changes in conscious experience. Here, investigators are not interested in the domain-general mechanisms that underlie consciousness as such, but are instead interested in the particular mechanisms that are implicated in having certain contents in consciousness (namely, those that characterise the content of binocular rivalry).

Most discussions of specific conscious states focus on phenomenal consciousness. A mental state is phenomenally conscious if there is 'something it is like' for the creature in question to be in that state (Nagel 1974; Chalmers 1996). Phenomenal consciousness is most closely associated with various forms of sensory experiences, such as perceptual states, bodily sensations, and affective states. However, not all conscious states are sensory, for consciousness also includes thoughts of various kinds—beliefs, desires, and intentions. It is controversial whether conscious beliefs, desires, and intentions are forms of phenomenal consciousness or whether—as many theorists believe—such states are conscious only in some non-phenomenal sense (Bayne and Montague 2011). At any rate, a full account of consciousness must accommodate all kinds of specific conscious states, both sensory and non-sensory.

Although the science of consciousness has tended to focus on specific conscious states, in recent years there has been increased interest in the mechanisms that underpin the generic state of being conscious. Some research groups have employed neuroimaging to explore the contrast between the presence and absence of consciousness in the persistent vegetative state (Laureys 2005; Bekinschtein et al. 2009;

Boly et al. 2011), whereas others have used neuroimaging to examine the global changes to the conscious states that are seen in anaesthesia (Alkire et al. 2008).

In addition to specific conscious states (the 'contents of consciousness') and the generic state of being conscious, we need also to recognise a third aspect of consciousness: what we will call *modes* of consciousness. We can think of modes as non-specific states of consciousness. Distinct modes of consciousness are associated with normal wakefulness, REM dreaming, hypnosis, mild anaesthesia, epileptic absence seizures, and the states associated with various kinds of consciousness-altering drugs such as LSD.

Modes of consciousness are not defined in terms of their content in the way that specific conscious states are, but are instead characterised by appeal to the subject's cognitive and behavioural capacities (or the lack thereof). For example, in some modes of consciousness the subject might have introspective access to and attentional control over their specific conscious states whereas in other modes these capacities might be disrupted or even altogether absent. Modes of consciousness are often referred to as 'levels of consciousness' or 'background states of consciousness'. We find both terms problematic: the former suggests that modes of consciousness involve different degrees of consciousness (which they may not do), and the latter suggests that modes are recessive features of the field of consciousness against which the contents of consciousness stand out (which they aren't).

Although we have distinguished these three aspects of consciousness (specific states, modes, and the generic state of being conscious), we do not mean to suggest that these three aspects of consciousness are independent of each other. On the contrary, it is clear that there are deep and important relations between these three aspects of consciousness and that a full account of consciousness will involve identifying these relations. Indeed, one of the ways in which the neuroscience of consciousness might contribute to our understanding of consciousness is by advancing our understanding of these relations. We return to this point shortly.

2.3 The Neural Correlates of Consciousness

We turn now to the notion of a neural correlate of consciousness (NCC). An NCC for a conscious state kind C_1 is a neural state that is minimally sufficient for instances of C_1 in the members of a certain population (Chalmers 2000; Hohwy 2007). The qualification of *minimal* sufficiency is included in order to 'screen off' those neural states that are of only causal relevance to the presence of C_1. The overall state of an individual's brain may suffice for one of its conscious states (C_1), but such a state would not, intuitively, qualify as an NCC for C_1 insofar as it would contain a great deal of neural activity that wasn't directly required for C_1.

Note a couple of general features concerning the NCCs. Firstly, the term 'correlate' is employed in order to leave open the precise relationship between neural states and conscious states. Although there is general agreement that the neural correlate of C_1 is not a *cause* of or *causal precondition* for C_1, there is debate about whether the relation between conscious states and their neural correlates is that of

identity, constitution, or realisation or whether—as some dualists hold—conscious states are merely correlated with neural states.

Secondly, it is important to recognise than an NCC holds only relative to a certain population. Some NCCs might hold with respect to a number of species, others might hold only with respect to a particular species, and still others might hold only with respect to the neurotypical members of a species. Indeed, we shouldn't rule out the possibility that the neural basis of consciousness might be quite variable even across the neurotypical members of a single species and that the neural correlate of C_1 in one person might differ in non-trivial ways from the neural correlate of C_1 in another person. We return to this topic below.

In light of the distinctions that we made in the previous section, we can see that there will be at least three different types of NCCs: there will be NCCs associated with specific conscious states of various kinds (such as smelling a rose), there will be NCCs associated with conscious modes of various kinds (such as normal waking awareness or dreaming), and there will be NCCs associated with the generic state of being conscious. Thus, there will be minimally sufficient neural correlates for distinct aspects of consciousness, and each of these NCCs will raise its own set of issues.

An important (but poorly understood) distinction that bears on specific NCCs concerns a contrast between two components of such correlates, what we might call their *differentiating* components and the *non-differentiating* components. The differentiating component of a specific NCC will be that component of its correlate that is selectively implicated in its content. For example, there is evidence that activation of MT/V5 is implicated in conscious experiences of visual motion; thus, this might qualify as a differentiating correlate for the conscious state of seeing movement. But it is highly unlikely that MT/V5 itself suffices for experiences of visual motion, for one wouldn't expect MT/V5 activation that was causally isolated from all other activity in the brain to generate experiences of visual motion. In order to function as a full correlate of experiences of visual motion, MT/V5 activity must be suitably integrated with certain kinds of non-specific activity, activity that is implicated in many kinds of conscious states. In other words, the *full* neural correlates of specific conscious states will have non-specific components that do not differentiate between the contents of those states.

The distinction between differentiating and non-differentiating correlates has important methodological implications. The study of specific NCCs involves the use of individuals who are conscious throughout the procedure. For example, in binocular rivalry paradigms, the contrast is between the subject's being in one specific conscious state (e.g. seeing a face) and another specific conscious state (e.g. seeing a house); similarly, in a masking paradigm, the contrast is between conscious and nonconscious content processing in participants who are conscious throughout the experiment. It seems plausible that some of the stable neuronal activity that is seen in these experiments—and which underwrites the fact that the participants are conscious—functions as a non-differentiating NCC for each of these specific conscious experiences. Thus, there is reason to think that such studies are capable of revealing only the differentiating correlates of consciousness and are necessarily

unable to reveal the non-differentiating components of a conscious state's full neural correlate (Hohwy 2009).

What about the NCCs of the various modes of consciousness? Here there is an important distinction to be made between the modes of consciousness in which subjects retain robust access to their conscious states from those modes in which first-person access to consciousness is seriously impaired or even completely lost. This latter category includes not just those modes that occur in disorders of consciousness (such as the minimally conscious state or epileptic absence seizures) but also certain modes that occur in healthy individuals, such as those seen in light anaesthesia or REM dreaming. In order to identify the NCC of these modes of consciousness, we need so-called 'objective' measures of consciousness, and there is notoriously little agreement about what such measures might look like (or indeed whether there even are any such measures that can be trusted).

Finally, what about generic NCCs—the neural correlates of the state of being conscious as such? Because it is a trivial truth that any creature that is in a specific conscious state is itself conscious, any specific NCC will also be a generic NCC. However, there may also be generic NCCs that are not also specific NCCs. If there are such states, then we might be able to use them as markers of consciousness as such without needing to rely on specific NCCs.

One method neuroscience can use to reveal generic NCCs is to form hypotheses about what all specific NCCs have in common (this would presumably include the non-differentiating NCCs) and then contrast conditions where this invariant part of NCCs is present with conditions where that part of the NCC is absent (i.e. states where unconsciousness is assumed, such as disorders of consciousness, some seizures, and anaesthesia). Without this contrast between wholly conscious and wholly unconscious creatures, it cannot be ruled out that a candidate for being the generic NCC is in fact unrelated to the presence of consciousness. Methodologically, this calls for manipulating both the contents of consciousness *and* the overall state of the creature, preferably in a full-factorial design. This is a non-trivial task because it is difficult to conceive of conditions that would yield either overall conscious states without specific contents or overall unconscious states with specific contents (for discussion, see Bayne 2007; Hohwy 2009). This task is further complicated by the fact that the subject's modes of consciousness may change during experimental manipulations and thereby affect the way in which their conscious contents are modulated.

It is an open question whether there are such generic NCC states. Although there could be neural systems that are implicated in all forms of consciousness, it is also possible that consciousness is highly disjunctive from a neural point of view and that the neural correlates of different kinds of specific conscious states involve distinct systems that may have little to nothing in common. 'Global' accounts of consciousness of the kind that have been defended by Baars and Dehaene (Baars 2005; Dehaene and Changeux 2011) would point towards the former possibility, whereas 'local' accounts of consciousness of the kind defended by Zeki (2007) and van Gaal and Lamme (2011) would point in the latter direction.

2.4 The Ascription of Consciousness

Arguably, an account of the NCCs would be of relatively little interest in its own right. Instead, its importance would reside in what we might be able to do with it. One idea that motivates much of the interest in the NCCs is the thought that we might be able to use an account of the NCCs as a tool for the ascription of consciousness.

The markers for consciousness that we currently possess are problematic in various ways. Perhaps the most important of these markers are reports. We lean heavily on a person's reports—or surrogates for such reports, such as button presses—in order to determine what conscious contents ('I see a face'; 'I smell coffee') the person in question is enjoying. However, there are a number of respects in which verbal reports in general—and introspective reports in particular—have shortcomings when it comes to the ascription of consciousness. Firstly, many creatures are unable to produce any kind of report, let alone introspective reports. This is obviously true of most non-human animals and prelinguistic infants, but it also applies to many mature human beings who may have suffered from brain damage of some kind. Secondly, even creatures that are able to produce introspective reports may not always be reliable when it comes to describing or even detecting their own conscious states (Bayne and Spener 2010; Hohwy 2011; Schwitzgebel 2008). In some cases—as in emotional experiences—the content of the conscious state might be obscure and difficult to form an accurate judgement about. In other cases subjects form introspective judgements in conditions that are unlikely to be conducive to introspective reliability. A much-discussed example of this kind of problem is raised by Sperling displays, in which subjects are briefly presented with a grid of alphanumeric items. Although subjects are able to report only some of the figures, many subjects have the impression that they had been conscious of each of the presented items. As Ned Block (2007) has put it, many people have the impression that the contents of consciousness 'overflow' what is accessible to the systems responsible for verbal report and short-term memory. Block and others have argued that in such cases subjects may have conscious states to which they lack introspective access.

So, we need ways of measuring the presence and absence of consciousness that don't involve introspective report. In some contexts, behavioural measures of various kinds might provide us with tools for the ascription of consciousness. For example, clinicians employ a patient's capacity for voluntary agency as a guide to the presence of consciousness when dealing with patients who have suffered serious brain trauma. However, even the most optimistic assessment of the power of non-verbal behaviour measures will grant that there are many contexts in which their capacity to provide us with an accurate account of a creature's state of consciousness is questionable.

It is tempting to hope that neuroscience in general and neuroimaging in particular might provide us with some assistance here. If we could identify the NCCs, then—the thought is—we could use information about an individual's neural states in order to identify its state of consciousness. It is unlikely that such measures would

supplant standard measures of consciousness that we currently employ, but they might be used when current methods are either silent or of dubious reliability.

How might neuroimaging be used as a measure for the presence of consciousness? The most straightforward line of argument involves what is known as a 'reverse inference' (Poldrack 2006). Reverse inferences proceed in two steps. One first identifies the neural correlate (N_1) for a certain kind of conscious state (C_1) in a population. One then argues that if an arbitrary member of that population is in state N_1, then there is good reason to ascribe C_1 to that individual. The strength of this reason will depend on a number of things, most notably the robustness of the correlation between N_1 and C_1 in the relevant population.

We will shortly examine a number of significant challenges to reverse inferences of this kind, but let us first note that at best arguments of this form will provide us with evidence that a creature *is* in a certain kind of conscious state. They cannot be used to show that a creature is *not* in a certain kind of conscious state. This is because the existence of robust mapping from N_1 to C_1 in a population is compatible with the *lack* of a tight mapping from C_1 to N_1 in that same population. For example, it could be that conscious state C_1 is multiply realised in the relevant population and that in some individuals C_1 is correlated with N_1, whereas in other individuals C_1 is correlated with neural states N_2 and N_3. If this were the case, then the fact that a member of this population was in N_1 might give us good reason to think that it was also in C_1, but the fact that it was not in N_1 would not necessarily give us good reason to think that it was not in C_1 (for the individual in question might be in either N_2 or N_3). So, inferences from the absence of an NCC to the absence of a conscious state can be precarious. (If we knew that the mapping from C_1 to N_1 was as robust as the mapping from N_1 to C_1, then the discovery that the creature was not in N_1 *would* give us reason to think that it was not in N_1, but this would involve knowing more than just that N_1 is an NCC of C_1.)

Let us return to the challenges facing the use of reverse inferences to ascribe conscious states to an individual. We can explore the most pressing of these challenges by considering the following striking study by Adrian Owen and colleagues, in which the brain of a vegetative-state patient was scanned while she was instructed to either imagine herself playing tennis or visiting the rooms of her home (Owen et al. 2006). They found that the fMRI signal in the areas that are preferentially implicated in these tasks (SMA for the tennis imagery and PMC/PPC/PPA for spatial navigation) was indistinguishable from that seen in 12 healthy controls. On the basis of this finding, the authors declared that there is little doubt that the patient was conscious, even though she was not at the time able to produce either introspective reports or overt voluntary behaviour of any kind.

This interpretation of the data can be—and indeed has been—challenged on a number of grounds. One question is whether the neural states appealed to in this study are full NCCs. Let us focus just on the relationship between SMA activity and conscious experiences of motor imagery. There is evidence that SMA activity is correlated with motor imagery in conscious individuals, but it doesn't follow from this that SMA activity is itself sufficient for an experience of motor imagery. Instead, it could be the case that SMA activity is only a *differentiating* correlate of such

experiences and that a full correlate of such experiences may involve neural states of which SMA activity is only one component (the other component being the 'non-differentiating' correlate of consciousness). This is an important point here, because for all we know vegetative-state patients may not have the capacity for the neural activity required for non-differentiating correlates of consciousness. In short, SMA activity might constitute good evidence for experiences of motor imagery when dealing with conscious individuals, but it may not provide such evidence in the context of individuals in which the very presence of consciousness is uncertain.

Even if SMA activity is a full correlate of conscious motor imagery in normal human beings, it is a further question whether SMA activity is correlated with conscious motor imagery in *this* patient. The reason for this is that it is not clear whether this patient is a member of the population with respect to which this NCC holds. Is the relevant population for this NCC *adult human beings*, or is it *adult human beings who have not suffered serious brain damage*? The case for thinking that there is a correlation between SMA activation and experiences of motor imagery is based on studies of neurologically unimpaired individuals—individuals who are able to report their conscious states—but of course this patient is neither unimpaired nor is she able to report her conscious states. So, even if there is a robust correlation between SMA activation and experiences of motor imagery in neurologically unimpaired individuals, it is an open question whether that correlation extends to individuals who have suffered significant brain damage. We might call this the 'population problem'.

The population problem might arise even when it comes to the ascription of consciousness to neurotypical individuals, for there is mounting evidence that individual differences in perception and aspects of consciousness can be predicted by individual and local grey and white matter differences (Kanai and Rees 2011). If there are aspects of consciousness for which it is possible to identify only NCCs that are 'individually tailored' (or at least relativised to rather select populations), then the population problem will be even more acute, for it may be difficult to know which population to assign an arbitrarily selected individual to.

A third challenge—one that is intimately related to that just discussed—concerns a worry about circularity. The problem is this: given that one must employ markers for the ascription of consciousness in order to discover the NCCs, how could the NCCs themselves function as independent evidence of consciousness? One might think that the evidential power of an NCC could, of necessity, only be as strong as that of the markers that were used to identify it in the first place and thus that information about an individual's neural state could never provide one with independent grounds for the ascription of consciousness. One might think that to the extent that there is a sound inference from an individual's neural states to consciousness, there must also be a sound inference from some other property that that individual possesses (e.g. a behavioural property) to consciousness. In other words, as far as the ascription of consciousness goes, the worry is that neuroimaging data is either ungrounded or redundant.

This last challenge raises what is perhaps the most acute challenge for any attempt to use neuroimaging to ascribe consciousness, and the jury is still out on whether it can be given a satisfactory response. The most promising responses to it invoke *inference to the best explanation*, a pattern of justification that is ubiquitous

in science. The idea is that we might be justified in regarding a certain type of neural state N_1 as a more robust marker of any set of pre-theoretical markers of consciousness—markers that were employed in identifying N_1—on the grounds that N_1 provides a unifying account of why those markers tend to co-occur in the way that they do (Shea 2012).

Thus far we have focused on direct forms of the reverse inference argument, but the reverse inference model can also be deployed in less direct ways. One might argue that neuroimaging data provides evidence of consciousness in virtue of providing evidence of some cognitive capacity which is itself good evidence of consciousness. For example, one might argue that the fMRI data obtained by Owen and colleagues is evidence of consciousness insofar as it is evidence of intentional agency (it was sustained for 30 s and was time-locked to the imagery instructions given to the patient) and intentional agency is itself evidence for consciousness (Shea and Bayne 2010). According to this reconstruction of the argument, neuroimaging data justifies an inference to consciousness not because it concerns particular neural areas but because of its duration and relationship to the patient's environment.

This indirect version of the argument is also open to challenge. For one thing, some theorists have argued that the activation seen in this patient was not a manifestation of intentional agency but was merely automatically triggered, even though it lasted for 30 s and was time-locked to the experimental instructions (Naccache 2006). Even if it is granted that the patient was engaged in an intentional action, one might argue that it is a further question whether intentional agency is a reliable indicator of consciousness (Levy 2008). A form of the population problem arises here too, for even if the presence of intentional agency is correlated with consciousness in the healthy population, such a correlation might not hold when it comes to individuals with disorders of consciousness (Hohwy and Fox 2012). It goes beyond the scope of this chapter to evaluate these important but difficult issues further. Our aim is only to draw attention to the fact that there is more than one way in which one might mount a case for consciousness on the basis of neuroimaging data.

2.5 The Explanation of Consciousness

We turn now to the question of whether an account of the NCCs might point us in the direction of an explanation of consciousness. It is one thing to know that a certain kind of neural state is correlated with a certain kind of conscious state, but can we go beyond correlations to explanations?

There is very good reason to think that certain kinds of mental phenomena can be explained in neural terms. In memory research, for example, neuroscience has uncovered neural mechanisms such as long-term potentiation that explain how functional features of memory arise from brain activity. An understanding of these mechanisms provides us with a reductive account of memory—it removes any of the mystery surrounding memory (Craver 2007). Might an account of the NCCs also provide—or at least point the way towards providing—a reductive explanation of consciousness? Might it remove the mystery surrounding consciousness?

There are reasons for skepticism. To use Joseph Levine's (1983) famous phrase, there seems to be an *explanatory gap* between neural states and conscious states. Information about the neural states that underlie consciousness seems unable to explain why such states are accompanied by conscious states. Assume that we have identified not only neural correlates for every aspect of consciousness but also neural mechanisms that explain every functional and structural feature of consciousness. Such an explanation would seem to leave something unexplained—it would seem to leave an explanatory gap. In fact, there are two kinds of explanatory gaps to grapple with here: a *generic* gap and a *specific* gap. The generic gap concerns the question of why some neural states are accompanied by conscious states of any kind, while the specific gap concerns the question of why N_1 is accompanied by the specific kind of conscious state that it is (say, the smell of coffee) rather than another (say, the visual experience of a face). Why is there 'something it's like' to be in N_1, and why is what it's like to be in N_1 like *this* rather than like *that*? Neural states appear able to explain only the structural and functional features of mental phenomena, and yet an account that appeals only to structure and function seems doomed to omit the 'phenomenal feel' of consciousness. On the face of things, a robot could exemplify the functional and structural aspects of consciousness without there being anything 'that it's like' for the robot to be the robot it is.

Broadly speaking, there are four kinds of responses to the explanatory gap in the literature. Some theorists (e.g. Dennett 1991) deny that there is anything more to consciousness than structure and function and thus hold that neuroscience possesses the conceptual tools required to explain every aspect of consciousness. Other theorists (e.g. Searle 2004) allow that consciousness involves more than structure and function, but they hold that neuroscience will develop the conceptual tools needed in order to explain these additional aspects of consciousness. A third group of theorists (e.g. McGinn 1989) hold that there is a perfectly natural account of how consciousness emerges from neural activity, but they hold that our cognitive limitations prevent us from grasping that account. A final group of theorists (e.g. Chalmers 1996) argue that the explanatory gap is a manifestation of an underlying metaphysical gap between consciousness and the physical world: neuroscience will not be able to explain how consciousness emerges from neural activity because consciousness doesn't emerge from neural activity—it is merely correlated with it.

The debate between these four positions cuts to the heart of some of the deepest and most obscure questions in philosophy, and we are not minded to engage with it here. Even if a reductive treatment of consciousness in its entirety is beyond our ken, neuroscience may be able to provide reductive explanations of those aspects of consciousness that do involve structural and functional properties. For example, by providing an account of how neural states might implement certain computational states, we can begin to see how it might be possible to explain the relationship between consciousness and other mental phenomena such as attention, memory, intention, and reasoning. We will bring this chapter to a close by considering certain aspects of this explanatory project.

One aspect of consciousness that may well succumb to reductive explanation is its modal nature. As we noted earlier, the various modes of consciousness differ

from each other in terms of the cognitive and behavioural capacities with which they are associated. For example, various disorders of consciousness (such as those seen in epileptic absence seizures) are associated with reduced availability of the contents of consciousness to the 'high-level' consuming systems involved in reasoning, intentional control, and introspection. There is every reason to expect that a detailed analysis of the neural correlates of consciousness will point the way towards mechanistic accounts of why the various modes of consciousness are associated with their distinctive cognitive and behavioural profiles. Such an account might not bridge the explanatory gap, but it would mark a very considerable advance in our understanding of the nature of consciousness. By revealing the neural mechanisms underlying this aspect of consciousness, we may learn something new about consciousness—something that introspection would not be able to reveal.

Recent research in this area is beginning to make some progress. For example, using Bayesian model selection, Boly and colleagues provide evidence that top-down message passing in the brain is implicated in the contrast between the modes of consciousness seen in disorders of consciousness and those seen in the state of normal wakefulness (Boly et al. 2011). Research like this provides a promising glimpse of the kind of mechanism that might constitute such modes of consciousness. Moreover, large-scale, top-down modulation of neural activity seems to be the kind of mechanistic process that could begin to *explain* the generation of an overall conscious state because its functional profile fits with the idea that consciousness involves integrating a number of low-level processing streams under a single, unified global model of the world.

What we begin to see here is a marriage of neuroimaging findings from the search for the NCC with computational and information theoretical approaches to the neural systems making up NCCs (e.g. in terms of information integration (Tononi 2005), which is being incorporated into the global neuronal workspace theory (Dehaene and Changeux 2011) or prediction error minimisation (Friston and Stephan 2007)). This means that the neural activity correlating with conscious states can begin to be understood in its own right, without being picked out only via its correlation with conscious states. This in turn improves the chances of identifying *systematic* NCCs where we can use our new theoretical, mechanistic understanding of the NCC to predict its behaviour under new types of experimental interventions on both contents, modes, and overall state. For example, using transcranial magnetic stimulation of NCCs, based on our understanding of its computational properties, it may be possible to produce new types of conscious states. This is something that cannot be done as long as the NCC is exclusively picked out as the correlates of conscious states with no understanding of their mechanistic and computational function.

In his influential treatment of the NCCs, Chalmers (2000) noted the desirability of identifying systematic correlations between neural states and consciousness rather than mere 'raw' or 'one-off' correlates (2000). Contemporary computational and information theoretical work is paving the way for the realisation of this aim. There is reason to believe that the combination of traditional NCC approaches for contents, modes, and generic conscious states with computational theory will be a main contributor to our understanding of how these aspects of consciousness interact

with each other. There is thus considerable reason to think that neuroscience will be able to explain many of the structural and functional aspects of consciousness. We may not be able to close the explanatory gap, but we will certainly be able to narrow it.

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Functional Brain Imaging and Consciousness

3

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Abstract

The neurobiological mechanisms underlying the maintenance of the conscious state have been extensively investigated with functional brain imaging techniques, in particular in relation to the alterations to consciousness associated with sleep and neurological and neuropsychiatric disorders. A consistent observation in these studies is the modification of activity and connectivity in distributed networks of cortical and subcortical brain regions, often associated with resting-state networks (RSNs). Several RSNs can be identified from functional imaging data, with separate networks associated with primary sensory domains and higher-level cognitive functions. One of the RSNs that has been consistently implicated in alterations to consciousness is the default mode network (DMN), with studies across diverse neurological and neuropsychiatric disorders identifying differences in DMN connectivity between control subjects and patients. While the data required to examine resting functional networks is easily acquired, and the functional networks themselves are reproducible and reliable, quantifying networks of distributed brain activity and identifying the most informative features in a particular disorder remains a challenge. Progress has been made in

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_3, © Springer-Verlag Berlin Heidelberg 2013

this direction in recent years, with the adoption of mathematical tools from network engineering, and the hope is that these methods will lead to additional techniques for the diagnosis and management of neurological and neuropsychiatric disorders of consciousness.

3.1 Introduction

Neuroscientific study of the brain mechanisms underlying consciousness is an active field and one which is far from being resolved (Crick and Koch 1998). Despite this, and the inherent problem in defining what is meant by consciousness itself, clinically it is clear that in certain situations consciousness is altered. Impairment of consciousness is the major distinguishing factor between complex and simple partial seizures in patients with epilepsy, while the descent into sleep involves a reduced ability to interact with the external environment. In addition to these transient and reversible alterations to consciousness, more long-term changes are seen in patients in a coma or conditions such as locked-in syndrome. Standard clinical examinations in these situations rely on behavioural responsiveness and need to be interpreted cautiously since unresponsiveness may be the result of selective impairment of normal brain functions needed to make a response (e.g. regions responsible for language, memory or motor performance), rather than a disruption to the processes underlying consciousness itself. The challenge for imaging neuroscience if it is to become a part of routine clinical management is to provide tools which can give a much more direct indication of the integrity of the brain activity that is necessary for the conscious state. However, if measures of brain function are to be taken as surrogate markers of consciousness, there are at least two fundamental challenges which need to be addressed.

Firstly, a coherent explanation for how brain activity underlies the subjective experience of being conscious needs to be provided. As will be outlined in this chapter, some considerable steps have been made in identifying the 'neural correlates of consciousness' (NCC), the set of brain regions which must be acting both individually and collectively in order for consciousness to be preserved. The second challenge is to understand how this activity is disrupted in different clinical syndromes. Only by developing non-invasive methods that are capable of shedding light on the neurobiology of consciousness can clinical tools be provided that will make a difference to the management of patients with disorders of consciousness.

Functional brain imaging techniques have made considerable advances in localising brain regions that are involved in the performance of various tasks, but in studying something as complex as consciousness, a different approach is needed. Consciousness is almost certainly better conceptualised as arising from the coordinated activity of multiple interconnected brain regions, and therefore tools which can investigate how distributed regions interact and reciprocally modify their activity are needed. In the vocabulary of imaging neuroscience, tools to study and quantify functional connectivity and complex brain networks, and to link them with observable behaviour, will be required. While ultimately this may prove beyond the capabilities of existing or potential methods, it is certainly the case that imaging

neuroscience is in the process of undergoing a conceptual shift that points in this direction. In the current chapter, we will summarise how recent developments in functional brain imaging data can shed light on the neurobiological mechanisms behind clinical alterations of consciousness.

3.2 Functional Connectivity and Resting-State Networks

Historically, most functional neuroimaging studies have employed tasks to identify brain regions whose activity responds to a certain category of stimuli or is different for two different categories. However, there is another way of analysing brain imaging data and of conceptualising brain function, which is to move away from a sole emphasis on stimulus responses towards an examination of the brain's intrinsic functional properties (Raichle 2010). This approach relies upon the definition of functional connectivity, or the identification of how regions coordinate their activity and interact, and has become an increasingly important approach for understanding the neural underpinnings of sensation and cognition (Fox and Raichle 2007; Raichle 2010; Bressler and Menon 2010). Crucially, the brain's functional architecture can be characterised in the absence of any specific external input (i.e. while the subject is at rest), which is a considerable advantage when dealing with patient groups.

Functional connectivity can be studied with any of the available non-invasive methods that probe human brain function (i.e. nuclear imaging methods (positron emission tomography (PET) and single-photon emission computed tomography (SPECT)), electrophysiological methods (electro- and magnetoencephalography (EEG/MEG)) or functional MRI (fMRI)). We will concentrate mainly on fMRI, since in the research setting it is now the most widely used tool for studying human brain function and has some advantages over the other techniques in terms either of spatial and temporal resolution or sensitivity to cortical and subcortical structures. It also has the potential to be widely available clinically, since clinical MRI scanners can be used. In terms of fMRI data, functional connectivity is generally defined by examining correlations between regions in the low-frequency (<0.1 Hz) part of the signal (Fox and Raichle 2007). Analytically, this can be done in two main ways. On the one hand, an initial 'seed' region can be defined based on some previous anatomical or functional prior information, and its activity correlated with all other brain regions. For example, functional connectivity of the hippocampus can be examined in patients with temporal lobe epilepsy. Alternatively, multivariate techniques such as independent component analysis (ICA, Beckmann and Smith 2004) can be used. ICA decomposes the data into multiple components based purely on its statistical properties with no prior functional or anatomical constraints. This has proved particularly powerful for identifying brain networks for which no previous hypotheses exist.

The primary discovery that has arisen out of this approach is that the brain is intrinsically organised into a series of networks (resting-state networks (RSNs), also known as intrinsic connectivity networks (ICNs) to avoid the assumption that they are only seen in data acquired at rest). While the precise neuronal and physiological

mechanisms that coordinate low-frequency haemodynamic fluctuations over spatially distributed regions remain unclear, the overwhelming body of research now suggests they are a direct result of neuronal activity. Around ten RSNs can be identified with fMRI, ranging from regions known to be involved in motor function (the sensory-motor network) and primary sensory processing (auditory phonological and visual processing networks) to those involved with higher-level cognitive functions such as executive functioning, memory, awareness and conscious self-perception (the default mode network (DMN) and dorsal attention network (DAN), Smith et al. 2009). The activity of RSNs has been shown to have functional significance, explaining variability in behavioural performance and evoked responses between and within subjects (Fox et al. 2006, 2007). They are also robustly and reliably identified from short fMRI scans in individual subjects (Anderson et al. 2011), and, as will be discussed below, their activity is modified in a range of neurological and neuropsychiatric conditions as well as in the different stages of sleep.

3.3 Functional Imaging in Alterations of Consciousness

The examination and quantification of functional connectivity has proved to be a valuable addition to the methods available for the analysis of functional neuroimaging data and has led to some important insights particularly into how ongoing brain processes interact with and define stimulus responses (Bressler and Menon 2010; Fox and Raichle 2007; Raichle 2010; Smith et al. 2009). The RSN that has been linked most closely with alterations to consciousness is the DMN. The DMN was the first RSN to be established and was identified from PET data as a set of regions which were consistently deactivated across a range of tasks (Shulman et al. 1997; Raichle et al. 2001). It consists of the posterior cingulate/precuneus cortex (PCC), bilateral inferior parietal lobule (IPL) and the mesial prefrontal cortex (mPFC). Other regions such as the thalamus and lateral and medial temporal lobes are also sometimes included. Activity in the DMN is considered to be instrumental in promoting awareness and conscious self-perception and has been linked with several cognitive processes that are fundamental to consciousness (e.g. self-oriented mental activity, conceptual processing, self-reflection). The PCC seems to play a particularly important role within the DMN, particularly in relation to the maintenance of the conscious state (Cavanna and Trimble 2006; Cavanna and Monaco 2009). It has the highest level of metabolic activity at rest (Gusnard and Raichle 2001) and has widespread cortical and subcortical connectivity (Cavanna and Trimble 2006; Cauda et al. 2010). It has been proposed that when an individual is awake, but not actively engaged in a cognitive task, the PCC promotes information gathering and representation of oneself within the world. Conversely, when an individual focuses on a goal-directed task, these processes are disrupted (Raichle et al. 2001; Gusnard and Raichle 2001; Cavanna 2007; Leech et al. 2011, 2012).

Some of the most detailed work in identifying the brain regions necessary for maintaining consciousness has been done using SPECT in patients with epilepsy. Although this work has not generally investigated RSNs as such, it gives a crucial

insight into how distributed brain networks are affected by alterations of consciousness and has allowed the definition of a set of regions comprising the NCC. One of the advantages of SPECT is that it can be used to measure brain activity during seizures, even when the seizure has a motor component which would largely preclude fMRI studies. This is because although the radionuclide is injected as soon as possible following the start of a seizure, the patient is only taken to the scanner once the seizure ends, meaning that routine clinical care can be given during the seizure itself.

SPECT studies have investigated the NCC by identifying brain regions which are selectively more involved in CPS compared with SPS, since impairment of consciousness is used as the major factor to distinguish between the two types of seizure. Several studies in patients with temporal lobe epilepsy (TLE) have suggested that CPS lead to blood flow increases in widespread, bilateral cortical and subcortical regions, often involving the temporal lobe ipsilateral to the seizure focus and bilateral subcortical midline structures (medial thalamus, basal ganglia and upper brainstem). Blood flow decreases are often seen in bilateral orbitofrontal cortex, anterior and posterior cingulate regions and frontal and parietal association cortices. SPS show much more limited changes primarily involving the temporal lobe itself (Blumenfeld et al. 2004). Although the temporal resolution of SPECT is relatively low compared with fMRI, functional connectivity can be investigated by analysing signal correlations across regions. This has led to the observation that frontoparietal hypoperfusion is correlated with midline subcortical structures, including the thalamus, resulting in the 'network inhibition hypothesis' (Englot and Blumenfeld 2009). The network inhibition hypothesis suggests that consciousness is disrupted when seizure activity propagates to subcortical structures responsible for cortical activation. These normal processes are disrupted, leading to cortical deactivation. Interestingly, many of the regions identified in this way as being associated with the NCC have clear overlap with known RSNs, in particular those involved with conscious self-perception and awareness (i.e. the DMN and DAN). The relationship between the NCC and RSNs remains to be clarified, but several other lines of evidence support the idea that disruption to RSNs may underlie clinical alterations of consciousness.

Experimental evidence that RSNs are affected by epilepsy comes from several studies combining fMRI with EEG to investigate the consequences of interictal epileptiform discharges (IEDs). In patients with epilepsy, fMRI is mostly restricted to the time between seizures (i.e. the interictal period) rather than seizures themselves, because of safety concerns within the restricted scanning environment. Interictal studies have consistently identified deactivation of the DMN in response to bursts of generalised spike and wave (GSW, Gotman et al. 2005), the electrophysiological correlate of absence seizures. Similar observations have been made for focal IEDs (Laufs et al. 2007), while RSNs other than the DMN also seem to be affected by GSW (Yang et al. 2012). However, even in the absence of IEDs, the activity of RSNs has been shown to be modified in patients with epilepsy. The DMN has decreased connectivity in patients with generalised tonic-clonic (Song et al. 2011) or absence (Luo et al. 2011) seizures and similarly in patients with TLE (Liao et al. 2010, see Seri et al. (2011) and Bagshaw and Cavanna (2011) for recent reviews on

the relationship between the DMN and alterations of consciousness in generalized and focal seizures). As well as this modification of RSNs in patients with epilepsy, other alterations to functional connectivity have been observed in several studies in TLE (Bettus et al. 2009; Negishi et al. 2011; Pittau et al. 2012) suggesting more widespread disruptions to ongoing brain function as a result of the epileptogenic process.

For investigating the sleeping brain, PET has been the most widely applied functional imaging tool. One of the considerable advantages of PET is that several different radioligands can be used, allowing different physiological processes to be investigated (see Maquet 1997, 2010; Dang-Vu et al. 2010 for review). For example, Nofzinger et al. (2004) examined cerebral glucose metabolism in patients with insomnia and found that compared to controls, they had increased global glucose metabolism during sleep and while awake. From a different physiological viewpoint, Volkow et al. (2008, 2012) demonstrated a reduction in dopamine D2/D3 receptor availability following sleep deprivation in the ventral striatum. This kind of physiological specificity offers a fascinating insight into the sleeping human brain as well as being a reminder of the complexity of the biological processes that maintain a level of consciousness. While fMRI is receiving an increasing amount of attention because of its relative ease of use, it offers a restricted view of brain function based on changes in blood oxygenation and flow. There are clearly many other physiological variables which may be equally, if not more, important when trying to provide a coherent explanation for how the brain mediates the conscious state.

EEG-fMRI has been used to examine changes in the activity of RSNs as a function of sleep stage, with the EEG providing the information necessary to perform sleep staging. Generally, these have suggested that connectivity may be maintained in light sleep (Horovitz et al. 2008; Larson-Prior et al. 2009), but that it reduces as deeper stages of sleep are reached (Horovitz et al. 2009; Sämann et al. 2011; Spoormaker et al. 2010), although this is not universally seen (Koike et al. 2011). One of the more consistent results seems to be a reduction in connectivity between the anterior and posterior regions of the DMN (Horovitz et al. 2009; Sämann et al. 2011), and DMN connectivity is also altered in the waking state following sleep deprivation (Gujar et al. 2010). Consistent with the idea that maintenance of the conscious state requires coordination of widespread and distributed brain regions, Boly et al. (2012) identified an increase in modularity in non-rapid-eye-movement sleep, indicating a fragmentation of large-scale brain networks which might underlie the reduced ability to process information and maintain a conscious state. As will be discussed below, this type of advanced analysis, and the use of analytical tools designed to characterise distributed network activity, has considerable potential for future clinical uses of functional connectivity data.

One of the advantages of EEG-fMRI in the study of sleep is that it can be used to study the haemodynamic consequences of the paroxysmal discharges of sleep (vertex sharp waves, K-complexes, sleep spindles). These electrophysiological transients are central to the definition of sleep stages, which in turn are characterised by differing levels of responsiveness, but their functional purpose remains largely obscure. Several studies have identified regions selectively activated as a result of

sleep paroxysms as well as during the prolonged and synchronised electrophysiological activity recorded in slow-wave sleep (Schabus et al. 2007; Dang-Vu et al. 2011; Caporro et al. 2012; Jahnke et al. 2012), potentially providing a more fundamental understanding of their functional role .

Resting-state functional imaging has been relatively widely applied to the study of neuropsychiatric disorders (for reviews, see Greicius 2008; Broyd et al. 2009). This is in keeping with the concept that in many such disorders the clinical manifestations, in particular in relation to complex phenomena such as alterations of consciousness, are the result of disrupted connectivity or ineffective interactions between different brain regions. Schizophrenia is perhaps the archetypal example of this. There is evidence that the DMN is disrupted in patients with schizophrenia, although not all studies have been in agreement. This literature has been reviewed extensively elsewhere (see, e.g. Calhoun et al. 2009; Williamson and Allman 2012). Disruptions to other RSNs have also been observed, and, as with all of the other alterations to consciousness discussed here, it may be that rather than concentrating on single networks, the relationships between networks will prove to be a fruitful line of enquiry (Woodward et al. 2011). Symptom-specific changes in connectivity have been observed, for example, patients with auditory-verbal hallucinations have reduced functional connectivity in speech-related networks (Vercammen et al. 2010), although more widespread alterations have also been seen (Wolf et al. 2011).

Other conditions such as depression, non-epileptic attack disorder and autism spectrum disorder (ASD) have been characterised with functional imaging. ASD has been hypothesised to be the result of underconnectivity of posterior and anterior brain regions. This hypothesis was supported by an early PET study (Horwitz et al. 1988) as well as subsequent resting fMRI studies (see Schipul et al. 2011 for a review). However, again the situation may be more complicated than initially suspected, with at least some evidence of increased connectivity of the DMN at rest (Monk et al. 2009; Weng et al. 2010).

As has been briefly reviewed here, a significant amount of imaging research has been performed during alterations to consciousness, and considerable advances have been made in identifying the brain regions involved in the maintenance of consciousness. Much of this research points towards the crucial importance of interactions between multiple networks as well as between regions of individual networks. The idea that modifications to the activity of multiple interacting networks might be necessary to understand the complex and diverse behavioural symptoms associated with disorders of consciousness is relatively new, but could be a powerful motif for linking behaviour with the alterations to functional connectivity that have been observed in many neurological and neuropsychiatric disorders.

3.4 Future Directions

Functional imaging has led to considerable advances in our understanding of the conscious state and how it is maintained and mediated by brain activity. In a variety of situations where consciousness is altered, functional imaging markers have been

identified that differentiate between normal and altered consciousness. These markers are specific to the underlying cause of the alteration to consciousness, whether occurring as a result of normal or pathological processes, which is the prerequisite for working with individual patients in a clinical setting. However, diagnosis, assessment, prognosis and efficacy of treatment are still heavily reliant on clinical history and psychopathology, rather than functional imaging. While functional imaging tools are not intended to replace the clinical skills that are successfully applied now, they have the potential to provide additional information that can be used to optimise clinical decision making. Before this can be achieved, some challenges remain.

One of these is inherent to the type of brain activity that has been identified as necessary for the maintenance of consciousness, namely, distributed cortical and subcortical regions which must maintain a certain level and coherence of interaction. The current trend in clinical radiology is to identify abnormalities on individual subjects' images by visual inspection. Clearly, the success of this approach is heavily dependent on the previous experience of the reporting radiologist and of the expectations the radiologist brings to the interpretation of the scan regarding potential abnormalities in a particular syndrome. Visual inspection of functional imaging data, even after the extensive statistical processing that can identify functional activations or RSNs, is not likely to be a viable approach given the richness of the data sets. Methods to quantify this type of data, and hence to produce validated and accurate metrics which can reliably distinguish between different clinical syndromes, are therefore of the utmost importance.

One methodology which has received a considerable amount of attention in the last few years, and which has already been used in several of the patient studies discussed above, is graph theory. Graph theory has been adopted from network and communications engineering and provides a set of mathematical tools and techniques which can be used to summarise the properties of distributed networks (Bullmore and Sporns 2009). By simplifying the large and complex data sets acquired by human functional imaging into a set of nodes (regions involved in a particular network) and edges (connections between them), differences between subjects and/or patient groups can be identified. The extracted network parameters can then be combined with classification techniques to characterise a particular scan and assign it to a particular behavioural or clinical grouping (e.g. a 'patient' or 'control' scan). While imaging neuroscience is at present still at the stage of understanding how network properties are related to behaviour and how they might be disrupted by a particular pathological process, these tools have shown considerable promise as a way of characterising the large data sets that functional neuroimaging produces.

At the same time that fMRI, PET and SPECT have been employed to examine the functional basis of alterations to consciousness, similar studies have been ongoing using structural MRI. One of the most promising techniques, certainly from the viewpoint of understanding the structural connectivity of distributed brain networks, is diffusion-weighted imaging (DWI, Jones and Cercignani 2010). DWI characterises the brain based on the diffusion properties of water. Within and between the axons of white matter, water can diffuse with comparable ease along the direction of the fibres, but diffusion perpendicular to the fibres is much more restricted. From

this basic physiological structure, information can be gained about the microstructural integrity of white matter, and estimates of the predominant fibre connections between regions can be made using tractography (Dell'acqua and Catani 2012). Analysis of the structural differences between control subjects and patient groups provides an alternative window on the mechanisms of alterations of consciousness, but the relationship between these structural changes and the functional connectivity that has been discussed here remains unclear.

Understanding the relationship between functional and structural connectivities is an active area of research (Guye et al. 2008; Damoiseaux and Greicius 2009). The goal of this research is to understand how underlying brain structure and the modifications to structure brought about by disease processes affect functional networks and behaviour. An indication of how this combined information might help in the understanding of brain disorders is given by a recent study looking at patients with idiopathic generalised epilepsy (Zhang et al. 2011). Taking a graph theoretical approach to network characterisation, Zhang et al. (2011) demonstrated that patients had disrupted functional and structural networks compared to controls and that the degree of coupling between structure and function was decreased in patients and dependent on the duration of epilepsy. Such a synthesis of structural and functional information could prove extremely powerful at identifying brain abnormalities in patient groups and providing a coherent explanation for the observed clinical and behavioural symptomatology.

This chapter has introduced some of the basic ideas behind the use of functional imaging to shed light on the mechanisms of disorders of consciousness. Many of the methods and approaches are at an early stage, but show considerable promise as ways of understanding human neurobiology non-invasively. The hope is that these methods can lead to viable clinical tools which can be used to characterise individual patients and inform the management of the clinical problems they face.

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Part II

Brain Imaging and Alterations of Consciousness in Epilepsy

Hal Blumenfeld

Temporal Lobe Seizures

4

Moran Furman and Hal Blumenfeld

Abstract

Focal temporal lobe seizures often cause loss of consciousness. Whereas abnormal function of the temporal lobe is expected to cause memory loss, it is unclear why it should impair consciousness. Recent advances in neuroimaging, behavioral, and electrophysiological techniques spanning both human patients and animal models have revealed new and exciting insights into this old question. Impaired consciousness in temporal epilepsy (TLE) is correlated with large-amplitude slow electroencephalogram (EEG) activity and decreased metabolic activity in the frontal and parietal association cortices, similar to other states of impaired consciousness such as sleep, coma, and deep anesthesia. According to the "network inhibition hypothesis," supported by imaging and electrophysiological data, cortical dysfunction during temporal lobe seizures results from inhibition of subcortical arousal structures which are required for maintaining the cortex in an alert and awake state. Advances in our understanding of impaired consciousness in epilepsy will hopefully pave the way toward novel treatments to prevent this profoundly debilitating side effect of seizures.

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_4, © Springer-Verlag Berlin Heidelberg 2013

4.1 Altered Consciousness in Epileptic Seizures

Epileptic seizures are episodes of excessive, highly synchronized neural discharges in the brain. Epilepsy is one of the most common neurological disorders, affecting roughly 1 % of the population (Kobau et al. 2008). In the public's mind, epilepsy is often associated with *grand mal* or *generalized tonic-clonic seizures* and the dramatic convulsions that accompany them (Chap. 7). In reality, however, epileptic seizures are very diverse in terms of their physiological and behavioral markers. *Absence seizures*, for instance, are brief episodes of unresponsiveness, characterized by generalized 3–4 Hz spike-wave discharges on the EEG and seen most commonly in young children (Chap. 6). Despite their differences, generalized tonic-clonic seizures and absence seizures share an important and debilitating side effect: impaired consciousness. A third class of epileptic seizures causing impaired consciousness is *complex partial seizures*, involving focal seizures most commonly originating from the temporal lobe and characterized behaviorally by staring and automatic repetitive movements. Impaired consciousness in temporal lobe epilepsy (TLE) is the focus of this chapter.

A key idea emerging from recent neuroimaging studies is that despite the limited spread of temporal lobe seizures, altered consciousness in TLE results from abnormal activity in widespread brain networks. In addition to imaging, intracranial EEG studies have elucidated important aspects of the pathophysiology of impaired consciousness in epilepsy (see also Chap. 8); and neurostimulation techniques, including optogenetics, would hopefully lead to mechanistic, microcircuit-level insights into impaired consciousness in epilepsy and pave the way to novel therapeutic strategies for this debilitating side effect of seizures (Tønnesen et al. 2009; Fisher et al. 2010; Kahane and Depaulis 2010; Lega et al. 2010; Kokaia and Ledri 2012).

4.2 Behavioral Correlates of Loss of Consciousness During Complex Partial Seizures

Epileptic discharges in the mesial temporal lobe evoke a wide range of behavioral and cognitive symptoms. These symptoms include amnesia for the event, fear, autonomic changes, neuroendocrine changes, a rising epigastric sensation, dystonic posturing of the limbs, and automaton-like movements referred to by Penfield as "automatisms" (Marks and Laxer 1998; Bauer 2001; Park et al. 2001; Quigg et al. 2002; Janszky et al. 2003; Engel and Pedley 2008). Since many of these symptoms relate to functions attributed to the temporal lobe/limbic system, their occurrence during mesial temporal lobe seizures may be expected. Surprisingly, however, mesial temporal lobe seizures often cause, in addition to the abovementioned symptoms, behavioral unresponsiveness and impaired consciousness (Bagshaw and Cavanna 2011; Blumenfeld 2012).

How is ictal unconsciousness measured and characterized? Until recently, epileptic unconsciousness was characterized mainly through retrospective and nonstandardized methods (Bell et al. 1998; Inoue and Mihara 1998; Lee et al. 2002;

Lux et al. 2002; Blumenfeld et al. 2004a, b; Guye et al. 2006). In the last years, a number of studies have made important steps toward more systematic characterization of impaired consciousness during seizures. Cavanna and colleagues (2008) developed a scale of ictal alternations of consciousness, the "Ictal Consciousness Inventory" (ICI). ICI is based on a 20-item self-report questionnaire that quantifies a patient's level of general awareness or responsiveness and the vividness of ictal experiential phenomena during epileptic seizures. Arthuis et al. (2009) used a consciousness seizure scale (CSS)-based video recordings of seizures. The CSS testing battery includes criteria for unresponsiveness, impaired attention, altered behavior, and amnesia, resulting in a consciousness score from 0 to 9. Recently, to allow externally based prospective testing and online monitoring during seizures, a "Responsiveness in Epilepsy Test" (RES-I) was proposed (Yang et al. 2011; McPherson et al. 2012). This testing battery was derived from the JFK Coma Recovery Scale-Revised (Giacino et al. 2004) and modified to enable testing within the typical 1–2 min time frame of seizures (Afra et al. 2008). To accomplish this, RES-I testing begins with higher-level questions and commands, proceeds adaptively to more basic sensorimotor responses depending on patient performance. RES-I continues postictally with memory testing. A major challenge in developing standardized ictal behavioral testing is the rapidly changing time course of behavioral impairments during seizures. The adaptive nature of the RES-I testing procedure was intended to maximize information obtained in the shortest time possible. However, adaptive testing schemes require highly trained and skilled testing personnel. To overcome this limitation, a modified and simplified nonadaptive testing scheme was recently developed (RES-II) (Bauerschmidt et al. 2013). RES-II has been designed to be faster and less error prone to administer while retaining the diverse range of cognitive and sensorimotor functions evaluated.

Testing batteries such as RES, combined with inpatient continuous video/EEG (cVEEG) monitoring, will help to identify brain networks underlying specific components of impaired consciousness in seizures.

4.3 Human Imaging of TLE

The temporal lobe has long been implicated in functions such as memory and semantic processing, but not in maintaining consciousness or alertness (e.g., Milner 1972). Why then do focal temporal lobe discharges often impair consciousness? A number of studies proposed that temporal lobe seizures impair consciousness when seizure activity spreads from the ipsilateral mesial temporal lobe to involve the bilateral temporal cortex (Gloor et al. 1980; Pedley 1992; Bancaud et al. 1994). However, even bilateral temporal lobe dysfunction is not expected to cause, by itself, loss of consciousness. If so, perhaps bilateral temporal lobe seizure activity is *correlated* with impaired consciousness rather than directly mechanistically linked to it (Englot et al. 2010). In particular, bilateral temporal seizure spread could mark the disruption of other downstream bilateral networks directly involved in

consciousness. Examining this hypothesis requires monitoring widespread changes in brain activity during seizures.

Imaging techniques such as fMRI or O-15 PET are not usually feasible for use during seizures in humans, due to safety concerns as well as methodological difficulties such as movement artifacts. In contrast, single photon emission computed tomography (SPECT) has the unique ability to take a "snapshot" of cerebral blood flow (CBF) during seizures, by injecting the SPECT radioisotope at the time of the seizure and carrying out the imaging at a later time point. Using SPECT imaging during complex partial seizures, a number of studies revealed abnormal increases in CBF in the upper brainstem and medial diencephalon and decreases in frontoparietal cortical regions (Lee et al. 2002; Van Paesschen et al. 2003; Blumenfeld et al. 2004a; Tae et al. 2005; Hogan et al. 2006; Van Paesschen et al. 2007). Furthermore, CBF increases in the medial thalamus are directly correlated with CBF decreases in the frontoparietal cortex during temporal lobe seizures (Fig. 4.1; Blumenfeld et al. 2004a). These findings raise the intriguing possibility that temporal lobe seizures impair consciousness not because of abnormal discharges in the temporal lobe itself but by affecting subcortical arousal systems, including the upper brainstem and medial diencephalon (Penfield and Jasper 1954; Blumenfeld 2002). The involvement of subcortical structures in impaired consciousness during complex partial seizures as suggested by altered CBF has been also confirmed by direct electrical recordings (Guye et al. 2006; Arthuis et al. 2009).

If subcortical arousal systems are indeed implicated in loss of consciousness during limbic seizures, one would expect, physiologically, a transition of cortical activity into a sleep-like state, characterized by slow-wave oscillations in the EEG (Steriade et al. 1993; Haider et al. 2006). Notably, large-amplitude 1–2 Hz slow-wave activity has indeed been observed in the frontal and parietal neocortices during and immediately following complex partial seizures (Lieb et al. 1991; Blumenfeld et al. 2004b) but not during simple partial seizures, in which consciousness is intact (Englot et al. 2010). As can be seen in the intracranial EEG data shown in Fig. 4.3 (*right panels*), slow-wave activity recorded from the frontoparietal association cortex (*bottom*) contrasts with the fast polyspike activity in the temporal lobe (*top*), indicating (1) lack of seizure activity in the frontoparietal cortices and (2) a transition of the neocortex to a sleep-like, depressed state. The transition of the frontoparietal network into slow-wave activity during complex partial seizures is further supported by animal studies (Englot et al. 2008, 2009). As described later in this chapter, these animal models have provided direct, mechanistic evidence for the remote effect of the temporal lobe on frontoparietal cortices during complex partial seizures.

It is also possible that apart from or in addition to neocortical slow-wave activity, other mechanisms play a role in impaired consciousness in TLE. In particular, Arthuis et al. (2009; see also Chap. 7) have argued for a role of synchronization between brain structures that are critical for awareness, particularly the thalamocortical loop, in ictal unconsciousness. More generally, these findings relate to the "global workspace" theory of consciousness (Dehaene et al. 2003; Baars 2005), in which information becomes consciously available via synchronized

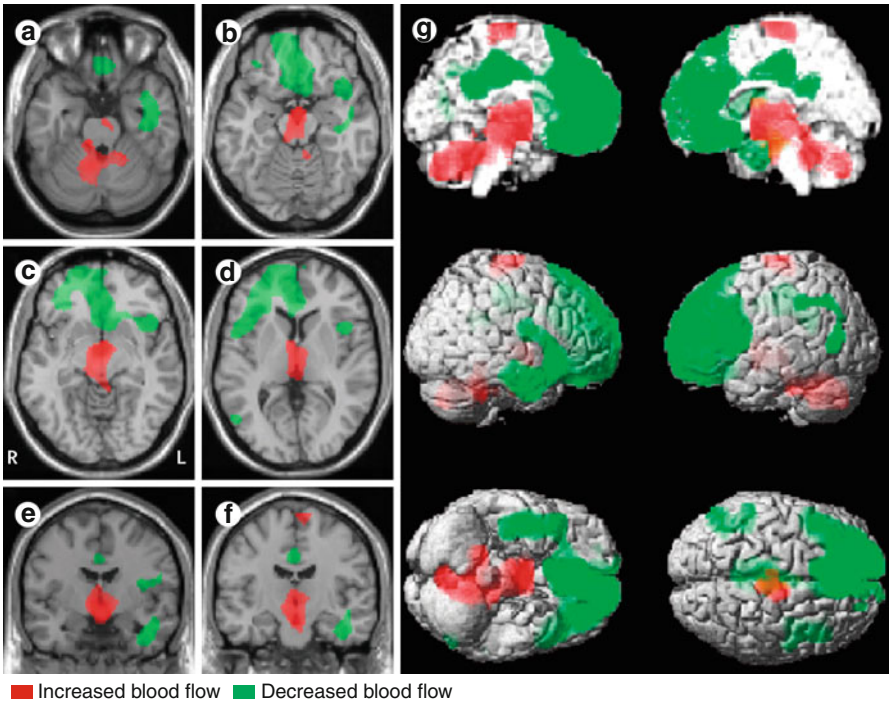

Fig. 4.1 SPECT imaging of cerebral blood flow during temporal lobe complex partial seizures. Complex partial seizures arising from the temporal lobe are associated with significant increases and decreases in cerebral blood flow (CBF) in widespread brain regions. Statistical parametric maps depict SPECT increases and decreases. Changes ipsilateral to seizure onset are shown on the *left side* of the brain and contralateral changes on the *right side* in images from ten patients. Data are from >90s after seizure onset, when consciousness was markedly impaired. At earlier times, SPECT increases were seen in the ipsilateral mesial temporal lobe (not shown). (**a**–**d**) Horizontal sections progressing from inferior to superior and (**e**, **f**) coronal sections progressing from anterior to posterior showing CBF increases in the bilateral midbrain, hypothalamus, medial thalamus, and midbrain. Decreases are seen in the bilateral association cortex. (**g**) Three-dimensional surface renderings show increases mainly in the bilateral medial diencephalon, upper brainstem, and medial cerebellum, while decreases occur in the frontal and parietal association cortices (same data as a–f). Extent threshold k = 125 voxels (voxel size 2 × 2 × 2 mm). Height threshold $p = 0.01$ (Reproduced with permission from Blumenfeld (2012), after Blumenfeld et al. (2004a))

activity within neuronal modules, often widely distributed throughout the brain. Within this framework, frontoparietal cortical slow activity during ictal unconsciousness is interpreted as preventing information processed by sensory regions from accessing awareness.

Interestingly, the networks affected during complex partial seizures largely overlap with the "default mode network" (DMN), a network of specific brain regions that are consistently activated at rest (either passive viewing or lying with eyes closed) compared to goal directed behaviors (Raichle et al. 2001; Cavanna and Trimble 2006; Cavanna and Monaco 2009; Danielson et al. 2011). Notably, cortical

slow-wave activity associated with decreased CBF and metabolism in the DMN, as observed during complex partial seizures, is commonly observed in other states of impaired consciousness including coma, encephalopathy, and deep sleep (Steriade et al. 1993; Cowan and Wilson 1994; Laureys 2005; Haider et al. 2006; Vincent et al. 2007; Laureys and Tononi 2009). However, during temporal lobe seizures, prominent slow-wave activity and decreased CBF also occur in regions not classically part of the DMN, such as lateral and orbital frontal cortex (Englot et al. 2008, 2009). As discussed next, both CBF changes and neocortical slowing associated with ictal unconsciousness have been also observed in animal models of TLE, providing insight into the mechanisms for these changes both in the DMN and other cortical networks.

4.4 Imaging in Animal Models of TLE

Animal models, particularly rodents, have been playing an important role in clarifying network mechanisms underlying loss of consciousness in TLE. Despite their more limited behavioral repertoire and lack of verbal communication, these animal models allow the application of both functional magnetic resonance imaging (fMRI) which is not feasible for routine use during complex partial seizures in humans due to safety concerns and motion artifacts and other invasive techniques which are inapplicable in humans in general.

Englot et al. (2008, 2009) have generated a rat model of TLE which recapitulates key aspects of ictal unconsciousness in human. This rat model has provided an important link for directly relating imaging data to electrophysiological recordings. Focal hippocampal seizures are initiated in the rat model using electrical stimulation or pharmacological manipulations. In acute fMRI experiments, Englot et al. (2008, 2009) found that complex partial seizures in epileptic rats were associated with BOLD signal increases in the bilateral hippocampus, as well as the thalamus and septal nuclei (Fig. 4.2). In contrast, prominent BOLD decreases were seen in downstream cortical regions such as the orbitofrontal, anterior cingulate, and retrosplenial/posterior cingulate cortices. CBV measurements in the same animals, after injection of exogenous paramagnetic contrast, closely mirrored BOLD signal alterations. Specifically, partial seizures showed increased CBV in the hippocampus, thalamus, and septal nuclei, along with decreased CBV in the orbitofrontal, cingulate, and retrosplenial cortices. These imaging results show that like in humans, partial limbic seizures in the rat have a remote network effect leading to deactivation of cortical regions including the orbitofrontal cortex, specifically in seizures involving behavioral arrest and unresponsiveness.

Recordings from the hippocampus, septum, and medial thalamus demonstrate fast, polyspike activity associated with increased neuronal firing during hippocampal seizures, whereas frontal cortex showed slow oscillations with decreased neuronal firing (Englot et al. 2008, 2009). Notably, transecting the fornix, the major route from hippocampus to subcortical structures, abolished the cortical slowing and

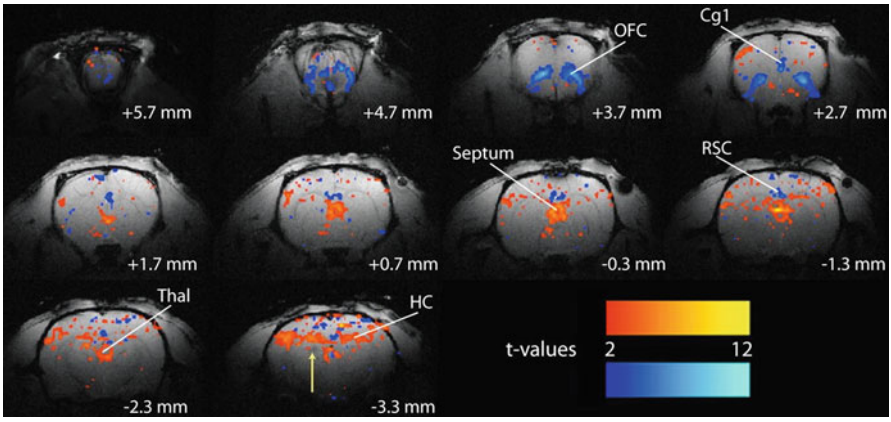

Fig. 4.2 BOLD changes during electrically stimulated partial limbic seizure in the rat. During partial limbic seizures, BOLD fMRI signal increases are observed in the hippocampus, thalamus, and septal nuclei. Prominent BOLD decreases are seen in the orbitofrontal, anterior cingulate, and retrosplenial/posterior cingulate cortices. The *arrow* indicates the hippocampal electrode artifact. *t*-maps are shown for the first 30s of seizure activity (ten consecutive fMRI images acquired every 3 s) versus 30s baseline and are superimposed on high-resolution anatomical images. Slices are shown from anterior to posterior, with approximate coordinates relative to bregma (Paxinos and Watson 2007). *Color bars* indicate *t*-values for increases (*warm colors*) and decreases (*cold colors*). The display threshold is $t=2$. *Cg1* anterior cingulate cortex, *HC* hippocampus, *OFC* orbitofrontal cortex, *RSC* retrosplenial/posterior cingulate cortex, *septum* septal nuclei, *Thal* thalamus (Reproduced with permission from Englot et al. (2008))

behavioral arrest during seizures. Thus, propagation of seizure activity into adjacent subcortical structures appears to be crucial for mediating the remote effect of the hippocampus on the neocortex. Furthermore, stimulation of the septal area, but not hippocampus or medial thalamus, in the absence of seizure activity resulted in cortical deactivation with slow oscillations and behavioral arrest, resembling changes seen during limbic seizures. As discussed further below, these findings suggest that hippocampal seizure activity propagates into subcortical inhibitory structures, including the lateral septum, that in turn inhibit neural activity in brainstem arousal structures such as the pedunculopontine tegmental nucleus (PPT), which are crucial for maintaining the cortex in an awake state.

To further examine the subcortical networks involved cortical dysfunction during seizures, Motelow et al. have recorded from identified single units in the PPT (Motelow et al. 2012). Intriguingly, cholinergic neurons, but not other types of neurons of the PPT, were suppressed during hippocampal seizures. Since cholinergic PPT neurons are part of the subcortical arousal system which maintains the cortex in an awake and alert state, inhibition of these neurons during seizures is likely to be mechanistically linked to ictal dysfunction of the neocortex. Advances in molecular-genetic tools (Witten et al. 2011) and optogenetic stimulation techniques (Cardin 2012) pave the way for testing the role of specific neuronal pathways in mediating cortical dysfunction during seizures.

4.5 Recapitulation: Why Is Consciousness Impaired in Complex Partial Seizures?

The temporal lobe has long been known to support an array of cognitive functions such as memory and language but is not crucial for maintaining alertness, behavioral responsiveness, or consciousness. Why then do focal temporal lobe seizures often cause impaired consciousness?

Findings from human and animal studies reviewed above have led to the "network inhibition" hypothesis for ictal unconsciousness in TLE (Norden and Blumenfeld 2002; Blumenfeld and Taylor 2003; Blumenfeld et al. 2004a, b; Englot and Blumenfeld 2009; Blumenfeld 2012). According to the network inhibition hypothesis, ictal unconsciousness represents a depressed cortical state, resembling coma, deep sleep, or other forms of impaired consciousness. Furthermore, this depressed cortical function occurs when temporal lobe seizures propagate to neighboring structures such as the lateral septum which in turn inhibit subcortical arousal systems (Fig. 4.3). During consciousness, these subcortical arousal systems interact with the cortex to maintain alertness and responsiveness. When consciousness

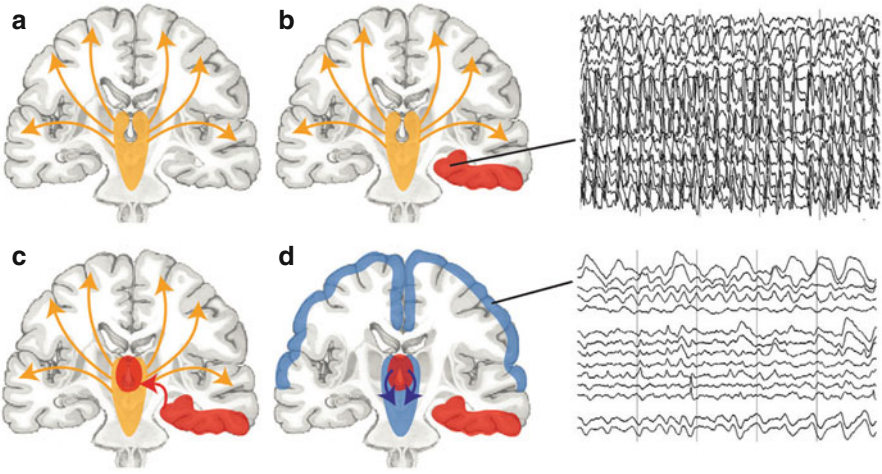

Fig. 4.3 Network inhibition hypothesis for impaired consciousness in temporal lobe complex partial seizures. (**a**) Under normal conditions, the upper brainstem and diencephalic activating systems interact with the cerebral cortex to maintain normal consciousness. (**b**) A focal mesial temporal lobe seizure. Intracranial electroencephalographic recordings (*right, upper inset*) show fast polyspike activity in the temporal lobe. If the seizure remains localized, a simple partial seizure will occur without impairment of consciousness. (**c**) Seizure activity often spreads from the temporal lobe to midline subcortical structures. Often, propagation also extends to the contralateral mesial temporal lobe (not shown). (**d**) Inhibition of subcortical activating systems leads to depressed activity in bilateral frontoparietal association cortex and to loss of consciousness. Intracranial electroencephalographic recordings (*right, lower inset*) from the frontoparietal association cortex show slow-wave activity that resembles activity during deep sleep (Reproduced with permission from Blumenfeld (2012), after Englot et al. (2010))

is impaired, the arousal systems are "shut off," resulting in a sleep-like mode of cortical activity.

Conclusions and Future Directions

Brain imaging studies have revealed network changes linked to loss of consciousness during temporal lobe seizures. In both human patients and animal models, ictal unconsciousness involves neocortical dysfunction, characterized by decreased CBF and slow-wave activity in the EEG. This transition of the neocortex into a sleep-like mode is likely to be caused by inhibition of subcortical arousal structures which are required for maintaining wakefulness and alertness. Technological advances, such as small-animal high-resolution fMRI, molecular-genetic techniques, and optogenetics, will help to mechanistically link specific brain networks to ictal unconsciousness and hopefully pave the way to new therapeutic approaches to this debilitating side effect of seizures. Understanding impaired consciousness in temporal lobe epilepsy may also shed light on more general network mechanisms contributing to other disorders of consciousness.

Acknowledgments This work was supported by NIH R01NS055829 and R01NS066974 and the Betsy and Jonathan Blattmachr Family.

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Absence Seizures

5

Jean Gotman and George Kostopoulos

Abstract

Absence seizures are usually considered to present a short suspension of consciousness, concomitant with the 3-Hz spike and wave seen in the EEG. For this reason, mechanisms of generation of spike-and-wave discharges have long been negatively associated with mechanisms of consciousness. We present a review of the various theories that have been developed to explain the generation of spike-and-wave discharges, concluding that hyperexcitable components of the cortico-thalamocortical circuit are likely to explain the EEG discharge. Behavioral analysis of absence seizures points to the possibility that it is not consciousness, as a unitary integrating concept, that is disrupted but rather various components of behavior, such as sensory perception, motor output, attention, and memory, that are suspended. Functional imaging studies of metabolic changes during the discharges point to the involvement of the thalamocortical system but also to the suspension of the default mode network as well as involvement of various cortical regions. Taken altogether, these studies point to the possibility that rather than a diffuse attenuation of consciousness, absence seizures result in the suspension of variable "pieces of consciousness" depending on which cortical, subcortical, and thalamocortical networks are primarily involved. It may be that consciousness itself is more amenable to study if it is conceived in terms of its component pieces rather than a unitary concept.

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_5, © Springer-Verlag Berlin Heidelberg 2013

5.1 Introduction

One of the most common types of epileptic seizure is the so-called absence, in which the patient appears to the observer as abruptly disconnected from his or her environment, suddenly absent and frozen in his activities, and suddenly present and active again when the seizure ends. The patient is often said to have had a brief loss of consciousness, based on the fact that he often stops doing whatever he may have been doing and stops interacting with the environment. In this chapter, we will examine how the study of this type of seizure has informed the study of consciousness (Panayiotopoulos 2008). It is therefore through the loss of consciousness that we will approach the study of consciousness. The objective hallmark of the absence seizure is the typical and easily recognized generalized spike-and-wave discharge (GSWD) seen in the electroencephalogram (EEG). This pattern (Fig. 5.1) consists in the alternation of sharp and short waves (the spike) and slow waves, forming a spike-and-wave complex; the complex repeats approximately three times per second for several seconds. It is recorded over most head regions but most prominently in frontal regions, and it appears symmetrically over both hemispheres. It starts and stops abruptly and largely coincides with the clinical manifestations of the absence, with its abrupt onset and offset. Absence seizures constitute a common type of epilepsy, and their concomitant EEG signature is considered the hallmark of the genetic tendency towards all epilepsies (Berkovic et al. 1987).

There has been considerable investigation in the last 80 years of the mechanisms generating the GSWD, particularly in experimental animals in which absences were induced by various procedures. Because of the apparent loss of consciousness dur-

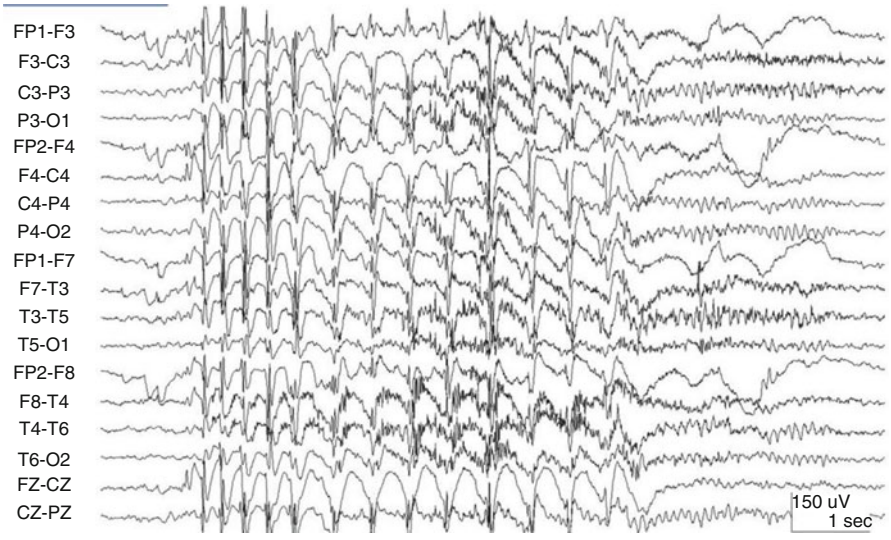

Fig. 5.1 EEG during a typical absence seizure. The pattern consists of an abrupt onset and offset of a succession of spike-and-wave complexes repeating at an approximate rate of 3/s. The activity is symmetrical in both hemispheres and predominates in anterior head regions. As in this example, it often slows down as it progresses

ing absences, the mechanisms of GSWD generation have been linked to mechanism of loss of consciousness. We will first review the succession of theories that have been put forward as underlying GSWD, starting with the centrencephalic theory of Penfield and Jasper, followed by the cortico-reticular theory of Gloor and ending with the most recent cortical focus theory (Meeren et al. 2002). We limit our review to models where animals have GSWD when awake and have been shown to have behavioral impairments similar to that of humans with absences, typically manifest in animals as a behavioral arrest. We will then discuss the actual behavioral changes occurring in patients during GSWDs and see if we can equate these to loss of consciousness. Finally, we review the recent evidence obtained by functional imaging studies, which have the unique advantage of being able to examine noninvasively the function of the whole human brain during a GSWD. Our main conclusion will be that it may be interesting to think of consciousness as a mosaic of pieces rather than as a unified concept.

5.2 Neural Correlates of Losing Consciousness in Absence Seizures

The astonishingly sudden onset and termination in apparently all brain regions of the GSWD justified a very early (1933) interest on conditions of ictogenesis of absences rather than on the mechanisms of their epileptogenesis. As recently reviewed by Avoli (2012), one of the first such conditions is the level of arousal, and some peculiar condition of the midline thalamus was held responsible for GSWD by Jasper and Kershman already in 1941. The debate however flourished since then around the localized versus global nature of the mechanisms, which turn on and off this clocklike EEG phenomenon. Eighty years later, the debate continues enriched by many more ambitious collateral questions and exciting new research possibilities allowed by modern technology. The debate started with a bold assertion that the brainstem reticular system makes conscious experience possible by integrating the activity of both hemispheres (Penfield and Jasper 1954), and this *centrencephalic hypothesis* was supported by lesions and stimulation experiments. Rhythmical stimulation of reticular nuclei of thalamus produced GSWD. It was however subsequently demonstrated that the experimentally isolated cortex is also capable of sustaining autonomous GSWD. Taking into account all the evidence, Gloor (1968) proposed the *cortico-reticular theory*, which for the generation of GSWD assigns essential roles to both the cortex and the reticular system of thalamus and brainstem. The hypothesis was further refined with an animal model in which intramuscular penicillin in the cat induces GSWD and simultaneous movement arrest. Experiments in this model suggested several elements of a proposed mechanism for the emergence of GSWD (Avoli 2012; Kostopoulos 2000, 2001). GSWDs were proposed to emerge from the same circuit that normally paces sleep spindles (Gloor 1978) under conditions of diffuse cortical hyperexcitability. The observation that under special experimental conditions pentobarbital spindles would be gradually replaced by GSWD of a little higher than half or a third of the spindle frequency (most importantly the change in frequency was steplike) allowed to further hypothesize that the

specific rhythm of GSWD may result from the intervention of feedback inhibition due to this hyperexcitability. Both the cortical hyperexcitability and the increased recurrent inhibition were experimentally demonstrated (Avoli et al. 1990; Avoli 2012; Kostopoulos 2000, 2001).

Two important developments followed in the mid-1980s: a better understanding of thalamocortical pacing mechanisms and the development of several rodent models of absence seizures. Rodolfo Llinas and colleagues employing in vitro preparations revealed the membrane ionic mechanisms which endow pacemaker properties to thalamic neurons, while Steriade and colleagues demonstrated in vivo the two modes of thalamocortical neuronal firing (tonic for awake and rhythmically bursting during sleep) and the importance of the nucleus reticularis thalami and its activation by the cortex in the generation and spread of the spindle rhythm (see Steriade and Llinas 1988). This concept was refined as the "thalamic clock" theory (Buzsáki 1991), and it explained the bursting mode as a result of an interplay between the mutually interconnected GABAergic inhibitory neurons of the reticular nucleus of thalamus and the thalamocortical neurons, their intrinsic properties, and their influence by cortical as well as brainstem ascending inputs.

This new knowledge was exploited very productively in many labs working in vivo and in vitro with mostly genetic but also pharmacological rodent models of absence seizures, which revealed several ionic channel and transmitter systems involved in the generation of the EEG rhythm of GSWD by extending the general scheme of physiological mechanisms supporting TC bursting mode of spindles into pathology (Avanzini et al. 1993; Crunelli and Leresche 2002; Depaulis and van Luijtelaar 2005).

Towards an understanding of the mechanisms underlying GSWD, one has to consider several possibly distinct candidate mechanisms for their electrical generators, sudden start and stop, how they get paced and how they spread, augment, get synchrony, and maintain it.

There is no doubt that the current sources of the GSWD are cortical and specifically elementary electrical dipoles generated on pyramidal neurons by EPSPs and IPSPs, respectively, underlying the spike and the wave of any GSWD in widespread cortical areas. However, the pace of GSWD is determined in the thalamocortical reverberating circuits by the duration of the IPSPs in bursting neurons.

Cortical hyperexcitability demonstrated in both animal models and humans with absences (see ref. in Kostopoulos 2000; Badawy et al. 2007) has been claimed to be responsible for the instigation (via excitation of neurons from the nucleus reticularis of the thalamus) as well as augmentation and generalization of GSWD (via recurrent and transcortical excitation).

Connectivity of brain regions is of obvious relevance to the neural correlates of consciousness as well as to the generalized nature of GSWD. MEG studies of patients with absences found an increase in clustering and a decrease in path length preceding GSWD onset and a rhythmic pattern of increasing and decreasing connectivity during GSWDs. A consistent low-frequency frontal cortical source appeared prior to the first GSWD, which was preceded by a low-frequency occipital source (Gupta et al. 2011). Another MEG study from controls and patients with absences but outside the GSWD (Chavez et al. 2010) showed that control brains show modular connectivity with sparse connection between modules, while absence

patients show more intermodular connections. High connectivity may characterize the brains of patients with absences and may facilitate GSWD. On the other hand, consciousness may require high connectivity (Dehaene and Changeux 2011), but also its availability to normal brain communication, which is lost during GSWD.

EEG activity *synchronization* was once the prime distinguishing criterion of the degree of loss of consciousness – as defined for studies of sleep, coma, and anesthesia. Although today we know that several cognitive functions depend on specifically localized high-frequency synchronization, it still holds that consciousness demands the absence of the slow synchronized EEG rhythms of NREM sleep and absence seizures when consciousness is lost. The question arises whether synchronization precedes and partakes in the causes of GSWD and the loss of consciousness. The transition to absence seizures can be accompanied by increased rhythmicity with augmented synchronization between several structures, especially bilateral homotopic areas (Niedermeyer et al. 1979). MEG recordings showed cortical synchronization near frontal and precentral areas to precede GSWDs (Amor et al. 2009; Aarabi et al. 2008) found an unexpected decrease in synchronization just prior to absences compared to the interictal period (63 %, while 31 % exhibited increase and 6 % no change). With the start of GSWD, synchronization of course increased suddenly but was also persistent for some time after the GSWD.

5.2.1 Comparing Two Ways of Losing Consciousness

The simplest definition of consciousness was probably given by Gerald Edelman (2004): "it is what you lose when you fall into a deep dreamless *sleep* and what you regain when you wake up." Also research in absence seizures is related to that of sleep and arousal in many ways (see Kostopoulos 2009; Halász 2012) since the almost parallel development in the 1940s of the centrencephalic theory of Penfield and Jasper and the brainstem reticular activating system proposal of Moruzzi and Magoun. It appears therefore justified for a study of the neural correlates of consciousness to compare the two ways of losing consciousness.

The definition of "Consciousness as information integrated" (Tononi 2010) leads to the question: When consciousness is lost, is this because the brain loses its dynamic complexity or its capacity to integrate the enormously diverse patterns of its activity into a consciously perceived whole? The answer undoubtedly differentiates the loss of consciousness in sleep from that in absence seizures: In the case of NREM sleep, we increasingly recognize brain activity rich in spatiotemporal differentiation of high-frequency activations (Ioannides et al. 2009; Valderrama et al. 2012) possibly supporting cognitive functions (Diekelmann and Born 2010) and dynamic interactions between its microstructure elements (Kokkinos and Kostopoulos 2011). It is therefore more likely that consciousness is lost because in NREM sleep, brain connectivity is decreased (Massimini et al. 2012). Inversely, in absence seizures, brain connectivity is increased (see above), but the pattern of connectivity is less complex (Babloyantz and Destexhe 1986). Whether information entry is gated in absences in the same way as in sleep needs to be seen. In NREM sleep, incoming information is impeded by three "gates": the bursting from hyperpolarization state of thalamocortical neurons, the bistability of cortical neurons (up and down states),

and what may be called the negotiable gates, i.e., K-complexes, microarousals, and cyclic alternating pattern (Parrino et al. 2012), since they are suggested to represent brain reactions to stimuli which vary depending on the stimuli salience features and the sleep pressure. Although GSWDs appear preferentially at phase A of the cyclic alternating pattern (Bonakis and Koutroumanidis 2009), during GSWD, sensory gates appear as nonnegotiably closed. However, the lack of responses does not necessarily reflect lack of sensation or even perception. In fact, a direct test showed that rats respond robustly to mild tactile stimulation during bouts of 7–12 Hz oscillations in S1, "contradicting the absence interpretation" (Wiest and Nicolelis 2003). Also during GSWD, we do not have atonia as in NREM sleep, so the absent or minimal body movements concurrent with the very intense activation of most neurons may also suggest a defect in brain's motor output. Finally, upon waking from sleep, we often report dreaming or other mentation (internally generated), indicating cognitive functions during both REM and NREM, not so after absences. At least partly different mechanisms are therefore underlying the suspension of consciousness in sleep and in absence seizures with GSWD. The latter mechanisms are certainly beyond – at a higher level than – but somehow dependent on arousal mechanisms: When GSWDs occur in awake patients, it is usually in transitional periods or in drowsiness; when GSWDs occur during NREM sleep – when consciousness is lost – they occur preferentially at times of sleep instability.

A final comment in the comparison of the ways consciousness is lost in absences and in sleep stems from the observation that the GSWDs have maximum amplitude in the midline anterior frontal region and possibly the precuneus (Blumenfeld 2012). It is interesting that in healthy humans, these two areas are gradually activated as sleep progresses from awake to light to deep NREM to REM sleep (Ioannides et al. 2009). Specifically, these MEG studies showed that during normal sleep when consciousness is lost, two areas, the left dorsomedial prefrontal cortex (DMPFC) and precuneus, sustain gamma band EEG activation of higher power than in wakefulness. Recent studies showed that lesions in the left DMPFC cause insomnia (Koenigs et al. 2010), while it has been suggested that this region may contribute the content to dreaming consciousness (Ioannides et al. 2009; Domhoff 2011). These areas lie about the areas of the default mode network, which is important for internally directed processing and supporting the state of consciousness (Raichle et al. 2001; Heine et al. 2012) and which has been shown to be activated just before and then sustains profound and long-lasting deactivation during absence seizures (Gotman et al. 2005; Sakurai et al. 2010).

5.2.2 Focal Features in Absence Seizures

Meeren et al. (2005) demonstrated a consistent cortical site of initiation of GSWD within the perioral region of the somatosensory cortex in a genetic rat model. Electrophysiological (EEG, MEG) and metabolic (fMRI) imaging studies in patients with different types of idiopathic generalized epilepsy (IGE) in accord with previous reports (Niedermeyer 1999; Pavone and Niedermeyer 2000; Vuilleumier et al.

2000) have shown SWDs in discrete, mainly midfrontal and parietal cortical regions before they appear over the rest of the cortex (Holmes et al. 2004; Blumenfeld 2012). The focal EEG paroxysms, which one often observes along with GSWD in childhood absence epilepsy, have been suggested (Koutroumanidis et al. 2012) not to contradict the fundamental generalized nature of absences but to reflect a multifocal nonlocalizing and unstable system of cortical areas that under various facilitatory influences can foster corticothalamic volleys of sufficient strength to instigate 3-Hz GSWDs. Depending on prevailing conditions, the GSWDs may be sustained and have behavioral consequences. The continuous pacing of GSWD however demands a chronically established physiological system (the thalamocortical) and its vulnerability to synchronous oscillations at around 3 Hz. This requirement in the absence of any demonstrable brain lesion or other cause besides the hereditary predisposition places absence seizures with the system epilepsies (Avanzini et al. 2012). The dysfunction may lie with the thalamocortical system itself or with various influencing factors, which may work alternatively or in synergy to define the pacing at around 3 Hz and to instigate, augment, synchronize, spread, and stop this rhythm.

Regardless of the underlying mechanisms, the demonstration of a pivotal role of midfrontal areas in GSWD may suggest that absences represent an interference with a function ascribed to them, i.e., the executive functions rather than the information processing, the top-down modulation by attention (see Kostopoulos 2001), the default system, and the system related to theory of mind and other self-related functions. Prefrontal cortex has been proposed to mediate attention control through its influence on the reticular nucleus of thalamus (Yingling and Skinner 1976; Guillery et al. 1998), which is essential in the cortico-thalamocortical processes generating GSWD. An excessive such influence during GSWD could hinder the interaction of discrete cortical areas with their homologous part of reticular nucleus (Guillery et al. 1998), which is necessary for selecting specific cortico-thalamocortical sectors for attention (Montero 1999). Unresponsiveness produced in this way could be restricted to specific modalities. It remains however for future electroclinical studies to investigate any possible correlation between the localization of focal EEG paroxysms accompanying GSWD and partial losses of consciousness.

5.3 Behavioral Manifestations of Absences

From observing a patient during an absence seizure, the behavioral manifestations consist primarily of an arrest of behavior (immobility) with a fixed blank stare. This is sometimes accompanied by mild clonic movements of the eyelids, corners of the mouth, or upper extremities. Absences are also but rarely accompanied by tonic or atonic components. When they are of long duration, they may include automatisms not unlike those of partial complex seizures (Berkovic and Benbadis 2001). The presence of these various motor manifestations points to the possibility that different parts of the brain are differentially involved in different patients.

In a 1986 essay, Gloor lays the foundation for the main points we would like to develop here (Gloor 1986), discussing epilepsy and consciousness. He argues that it

may not be possible to define consciousness and that in fact this may not be a useful scientific concept because it cannot be observed. His main argument is that consciousness is essentially something that is perceived by the subject, who can communicate and describe only his or her consciousness but cannot describe a lack of consciousness. It is not possible to observe consciousness per se but only to observe some of its "pieces." Gloor describes "aspects of conscious experience such as perception, cognition, memory, affect, and voluntary motility that are open to neurobiological research." He also argues that during absences and other epileptic seizures, it is critical to tease out which are the aspects of consciousness that are impaired and which are preserved. Gloor gives the example of a patient with typical absences whose only real deficit appears to be the inability to make a movement and therefore a motor response, but whose auditory perception, verbal comprehension, memory, and ability to say monosyllabic words are preserved. Such a patient appears unconscious, but only one small piece of what one might think constitutes consciousness is affected. It has also been observed that the most severe behavioral unresponsiveness is associated with GSWD of pronounced amplitude, duration, rhythmicity, midfrontal distribution, and generalization (Blumenfeld 2012). Some sensory modalities or memory trace or the hedonic value of a stimulus may survive a long absence seizure (Gloor 1986; Drinkenburg 1995; Drinkenburg et al. 2003; Moeller et al. 2010a; Rémi et al. 2011). Different patients with absences have variable "pieces of consciousness" affected. We will see below that imaging findings can be interpreted in agreement with this view. This is a very important finding, consistent with a defect in most but not necessarily all corticothalamic sectors.

The study of Vuilleumier et al. (2000) gives credence to this view: in two patients, prolonged spike-and-wave bursts (absence status) predominating in fronto-mesial cortex were associated with selective impairment in the initiation of response and self-generated action, whereas short-term storage of external information was fully preserved. In two other patients with typical absences and a complete lack of retention for information given during the discharges, topographic mapping found a more lateral frontal involvement. Although spike-and-wave bursts often have a grossly similar spatial distribution, fine interindividual differences may explain the different symptomatologies. This was also the case in the study of Berman et al. (2010), where it was found that spike-and-wave bursts with preserved responsiveness resulted in different patterns of BOLD activation compared to bursts accompanied by absence of responsiveness (see below).

5.4 Functional Imaging Studies of Spike-and-Wave Discharges: The Default Mode Network and Generalized Epilepsy

We have seen that experimental studies have proposed a variety of possible mechanisms to explain the generation of GSWDs and their associated modifications in consciousness. Patients with medically intractable focal epilepsy are commonly investigated with intracerebral electrodes exploring a number of brain regions, and

this has led to an excellent understanding of the origin and propagation patterns of focal seizures. This is not the case, however, for patients with generalized epilepsy, since there is no known surgical cure when the disease is medically intractable; in some extreme cases, section of the corpus callosum has been performed, but this does not require the use of intracerebral electrodes. We therefore do not know what happens in the different parts of the human brain during the GSWDs of primary generalized epilepsy. Although it is not possible to have the knowledge of the electrophysiological phenomena occurring in various brain regions during GSWDs, it is possible to know about metabolic changes throughout the brain by using the combination of EEG and functional MRI (fMRI). The application of this method to epilepsy is reviewed in several publications (Gotman et al. 2006; Laufs and Duncan 2007; Jackson et al. 2012). In brief, it allows the measurement of the BOLD (blood oxygenation level-dependent) changes that occur in the whole brain as a result of spike-and-wave discharges. The EEG is recorded while the patient is scanned and a statistical analysis is performed to indicate where in the brain there are BOLD increases or decreases following the start of spike-and-wave discharges, compared to a baseline free of epileptic discharges. It is presumed in this analysis that the BOLD changes reflect changes in neuronal activity, primarily in postsynaptic potentials (Logothetis et al. 2001). If epileptic activity is visible in the scalp EEG, the EEG-fMRI method therefore allows the evaluation of the BOLD changes everywhere in the brain around the time of the scalp-recorded activity. Because GSWDs are such a prominent scalp EEG pattern, this method was applied to this condition from the early days of its development.

Early applications of EEG-fMRI to GSWDs studied small groups of patients, analyzed individually. Archer at al. (2003) evaluated five patients and noted a relatively consistent deactivation in the posterior cingulate gyrus and an activation in precentral regions. Studying one patient with prolonged absences, Salek-Haddadi et al. (2003) found a thalamic activation and widespread frontal deactivations. In a set of 15 patients, Aghakhani et al. (2004) found a response in the thalamus in 80 % of patients and an inconsistent pattern of activation and deactivation in frontal and posterior areas; cortical and thalamic responses were usually symmetrical in the two hemispheres. The thalamic response is in agreement with the involvement of this structure in all experimental models. It has been difficult, however, to reconcile the cortical findings with the EEG pattern, which clearly predominates in the anterior head regions.

The patients of the Aghakhani et al.'s (2004) study were subsequently subjected to a group analysis on the basis of the fact that they all had a relatively similar condition, from the medical and from the EEG point of view. The purpose of such an analysis was to determine if there were regions that showed a consistent response, despite the apparent heterogeneity of the primary responses. Some regions could, for instance, show a response that is too small to be significant in individual subjects but consistent enough to become significant in the group analysis. The results of this group analysis (Gotman et al. 2005) can be divided into activations and deactivations. The activations (Fig. 5.2) were most significant in the thalamus bilaterally and also present in the mesial frontal region, in bilateral insulae, and in the cerebellum.

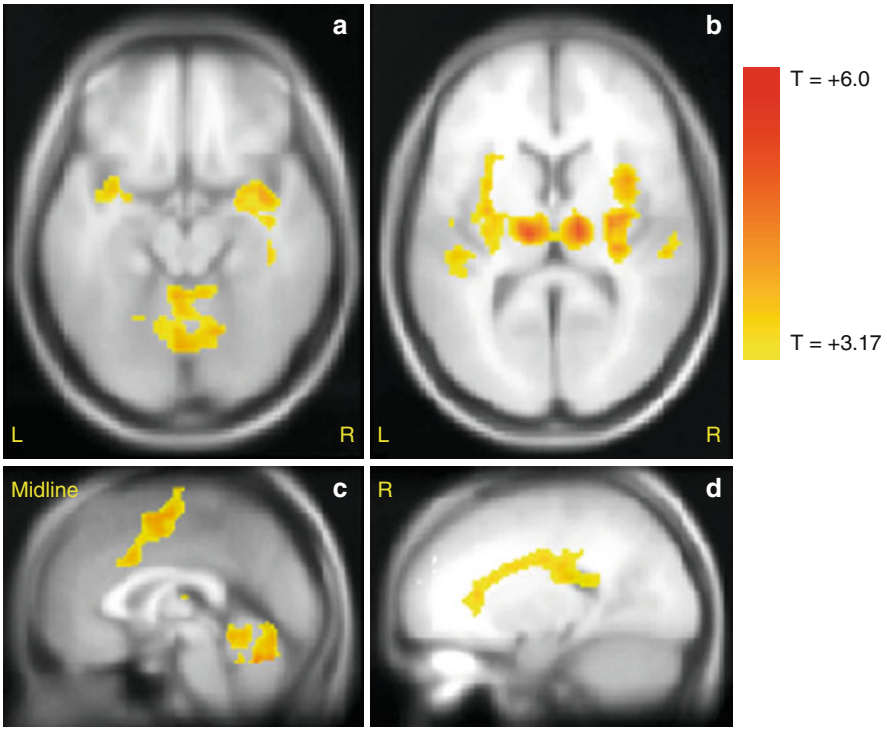

Fig. 5.2 Significant positive BOLD response observed from the group analysis of 15 IGE patients obtained using the HRF peaking at 5 s (**a**–**c**) and at 7 s (**d**), corrected $P<0.05$ for spatial extent. (**a**) Axial view showing activation in the cerebellum and inferior part of the insula. (**b**) Axial view showing the largest cluster involving the thalami and insulae. (**c**) Sagittal interhemispheric view showing an activation along a wide band of mesial frontal cortex and within the cerebellum. (**d**) Sagittal view of the right hemisphere 2 cm away from the midline showing an activation within the ventricles. This activation was bilateral and followed the ventricles until the temporal horn (From Gotman et al. 2005)

The thalamic and mesial frontal response was consistent with the thalamocortical network hypothesized by experimental studies (above). The involvement of the insulae and cerebellum was surprising and did not fit well with the thalamocortical framework, but one has to notice that these regions have rarely been studied in experimental animals at the time of GSWD. The results also showed a response in the third ventricle. This is obviously not a genuine activation but is likely representing an artifact caused by a change of shape of the ventricle related to the GSWD; this change could result from a large change in blood volume in the whole brain, compensated by a change in the volume of the ventricles.

The deactivations (Fig. 5.3) were surprising in the context of what was thought to be an intense neuronal discharge corresponding to the large GSWD. This result was consistent with the findings of Archer et al. (2003), who had observed a deactivation in the posterior cingulate gyrus. The pattern of deactivation, including

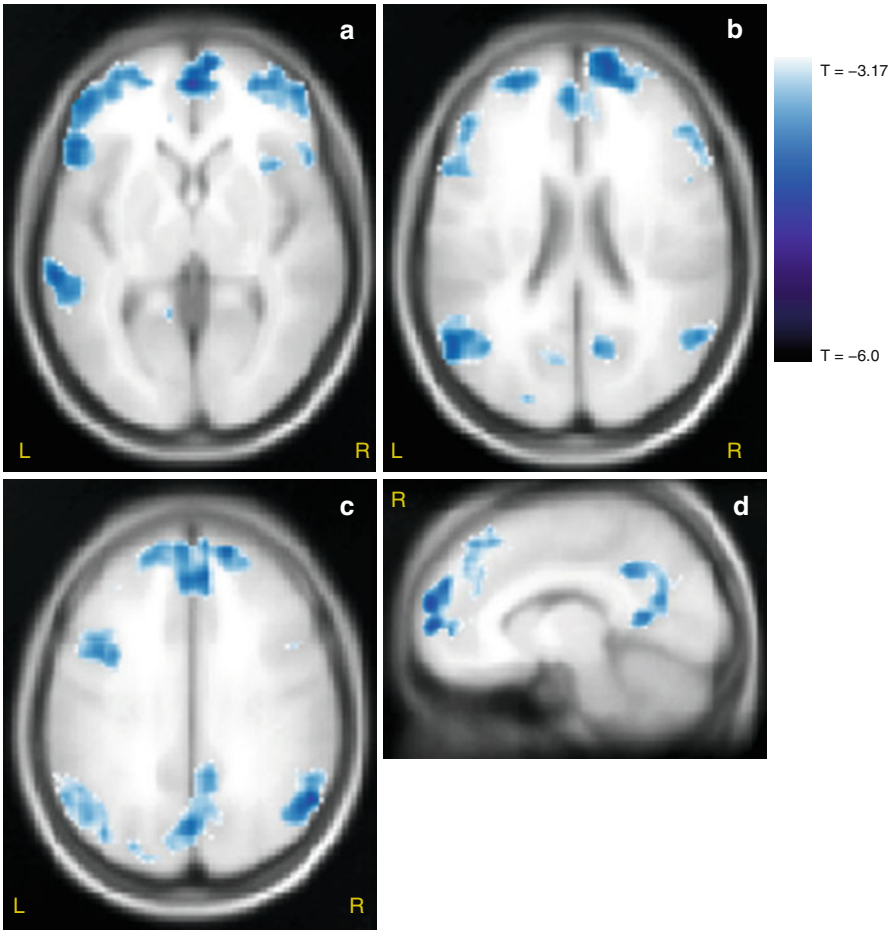

Fig. 5.3 Significant negative BOLD response observed from the group analysis of 15 IGE patients obtained using HRF peaking at 9 s, corrected $P<0.05$ for spatial extent. (**a**) Axial view showing bilateral deactivations in mesial and lateral anterior frontal areas and in the left posterior temporal area. (**b**) Axial view 1 cm higher than the previous one showing deactivations in frontal regions, in parietal areas, and in the posterior cingulate gyrus. (**c**) Axial view 2 cm above the previous one showing the same frontal and parietal clusters. (**d**) Sagittal view of the right hemisphere 1 cm away from the midline showing a deactivation within the mesial prefrontal area and the posterior cingulate gyrus (From Gotman et al. 2005)

posterior cingulate and bilateral parietal and anterior frontal regions, strikingly reminded us of the regions involved in the default mode of brain function, as they were defined by Raichle and collaborators (2001). We will make a small aside to review this concept.

The default mode of brain function was first described by Raichle and collaborators (2001). Their multiple studies with positron emission tomography and fMRI "suggest the existence of an organized, baseline default mode of brain function that is

suspended during specific goal-directed behaviors." The set of regions active during this default mode of brain function, which become deactivated during goal-directed behavior, have become known as the default mode network (DMN). A recent review of this concept can be found in Raichle (2010). In addition to its involvement in task-related experiments, the DMN has also been prominent in fMRI-based functional connectivity studies, which have discovered that, at rest, the regions of the DMN form a real network of regions with synchronously fluctuating BOLD signals (see Power et al. 2010 for a review). It has also been shown that there are spatially specific electrophysiological changes in parallel with BOLD changes at the time of deactivation of the DMN (Jerbi et al. 2010; Ossandón et al. 2011); these consist primarily of decreases in the gamma band activity, while gamma band activity is increased in task-specific regions.

It therefore appears that during GSWDs, as at the time of a task-specific response, there is a deactivation of the DMN. How could this be related to the frequently observed decreased consciousness or responsiveness seen during GSWDs? One can hypothesize that the function of the DMN is to allow us to be aware of our environment without concentrating on a specific task. When we concentrate on a task, we become less aware of our environment, and the DMN is deactivated. During GSWDs, the DMN is deactivated as a result of the discharge, thus resulting in less awareness of the environment. This is not caused by a specific task but by the spike and wave. In this way, one could consider that the deactivation of the DMN is fully or partially responsible for diminished self-awareness during spike-and-wave discharges. In addition, there is an abnormally active thalamus, and this may contribute to a partial blocking of sensory information reaching normally the cortex, thus reducing the awareness of the external world. The study of Berman et al. (2010) confirms that BOLD changes during GSWDs were more marked in the cases where responsiveness was impaired compared to the episodes where it was preserved.

The question arises as to the mechanism responsible for deactivating the DMN, given the primary importance of thalamocortical mechanisms in the generation of spike-and-wave discharges. Blumenfeld and collaborators (Danielson et al. 2011) invoke a "network inhibition hypothesis" in which excessive cortical and thalamic activity results in activated inhibition of brainstem arousal mechanisms, thus resulting in reduced arousal or awareness.

The study of Moeller et al. (2010b), in which BOLD changes were studied dynamically and compared across several GSWDs of the same patient, showed that BOLD spatial and temporal response patterns were very consistent between discharges of the same patient, but quite different from patient to patient. Examples from two patients are shown in Figs. 5.4 and 5.5. In particular, different parts of the DMN were deactivated, and different cortical regions were activated. Different parts of the DMN have been associated to different aspects of awareness and information processing (see Danielson et al. (2011) for a review). The focal cortical activations may be related to the focal cortical theory of generation of spike and wave in WAG/Rij rats described above, which was confirmed with fMRI studies of these rats (Nersesyan et al. 2004). These various focal effects may reflect how different aspects of what one can globally call consciousness may be affected in different individuals, as has been observed in individual patient behavioral testing (see above).

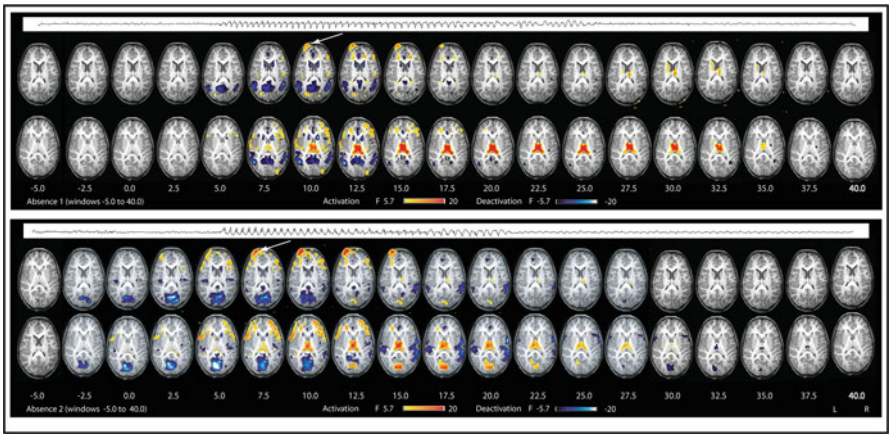

Fig. 5.4 Sliding window analysis for two absences of a patient (windows 0–52.5 s). First activation consistent for both absences was found in the right inferior frontal cortex (*white arrows*). In the first absence, this activation started 2.5 s after the onset; for the second absence, it coincided with the onset. The thalamic activation and deactivation in default mode areas and caudate nucleus started between 5 and 7.5 s after onset. BOLD signal changes in the thalamus and default mode areas exceeded the duration of the absence by several windows. Thalamic activation was followed by thalamic deactivation in both absences

Note for Figs. 5.4 and 5.5; The duration of the absence is indicated by one EEG channel (Fp2 with average reference), the onset is indicated by a black arrow. Please note that the EEG onset of the absence is shifted 5 s to account for the hemodynamic delay of the BOLD response and allow a direct comparison of absence duration and associated BOLD signal changes. White arrows indicate areas of the earliest cortical activation which were consistent if more than one absence were recorded (From Moeller et al. 2010b)

Conclusion

Absences are attributed to a presumably hereditary vulnerability of the thalamocortical system which under various influences, like cortical (often midfrontal) hyperactivity, an unstable interface level of arousal and changes in metabolic activity or synchronization of wide brain areas, sustain ~3 Hz GSWD, during which most cortical neurons fire intensely at this rhythm. This abnormal firing pattern during an absence suffices to explain the unresponsiveness and cognitive impairment of the subjects, which have been likened to suspension of consciousness. However, from patient observation and from neurophysiological and imaging studies of GSWDs in experimental animals and in patients, one could conclude that it is not consciousness as a whole that is impaired but rather "pieces of consciousness" (e.g., attention, ability to perceive, memory, emotion, responsiveness), pieces that differ with every patient and that are reflected by different patterns of BOLD activation and deactivation and by the involvement of different parts of the thalamocortical system. It may be that it is easier to define consciousness as the ensemble of many measurable components or pieces rather than as a unitary and standalone entity that cannot be observed or measured.

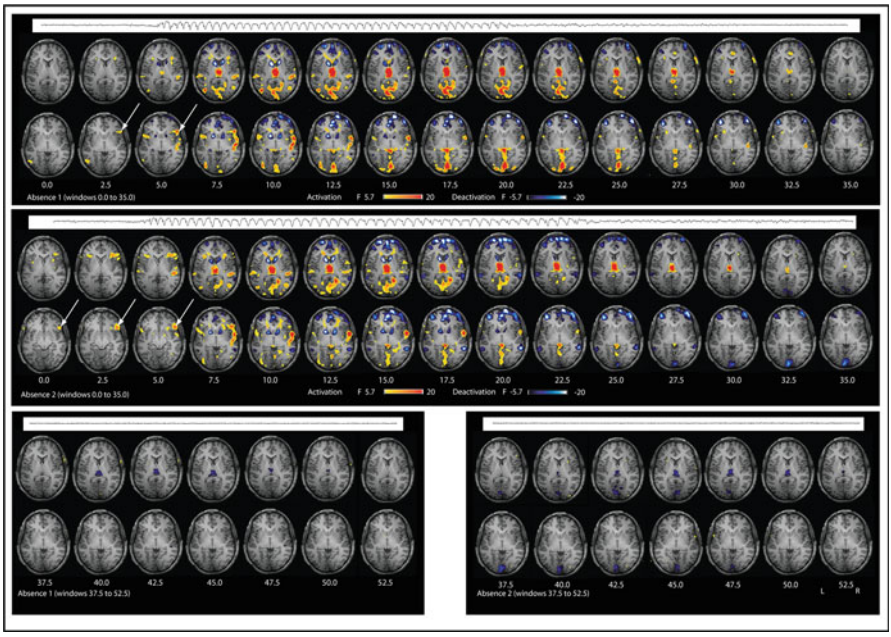

Fig. 5.5 Sliding window analysis for both absences of another patient (windows -5–40 s). First activation consistent for both absences was found in the left frontopolar cortex (*white arrows*). In the first absence, this activation started 10 s after the onset; for the second, it started 5 s after onset. The thalamic activation started 7.5 s after onset in both, deactivation in the caudate nucleus 5 s after onset and deactivation in default mode areas 5 s after onset in the first and 2.5 s before onset in the second. BOLD signal changes in the thalamus and default mode areas exceeded the duration of the absence by several windows. In the second absence, thalamic activation was followed by thalamic deactivation; see note in legend of Fig. 5.4 (From Moeller et al. 2010b)

Acknowledgements The research lab of G.K. Kostopoulos is currently funded by the European Commission under the Programme FP7/2007–2013, grant ARMOR, agreement 287720.

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Generalized Tonic–Clonic Seizures

6

A. LeBron Paige and Andrea E. Cavanna

Abstract

Generalized tonic–clonic seizures (GTCs) have long been assumed to produce their dramatic clinical effects through a widely distributed and uniform dysfunction of the human cerebral cortex. However, evidence from a diversity of sources is mounting that GTCs actually exert their influence through discrete cortical and subcortical brain areas, while leaving the intervening structures unaffected. This dysfunction may be produced directly through spatially circumscribed seizure activity or remotely through propagated network dysfunction. Specialized imaging and analysis methods have identified the distinct brain areas affected by GTCs as those also implicated in maintaining both the level of consciousness and its content. The subcortical areas identified in these imaging studies likely play a critical role in the characteristic motor manifestations of GTCs, as well as the complete disruption of alertness. A notable strong cerebellar activation of the late-ictal and postictal period may be the source of dramatic postictal confusion with GTCs, mediated by its strong inhibitory connections to the thalamus. By propagating this inhibitory influence through its divergent thalamocortical connections, the thalamus may effectively deactivate broad areas of the cortex. These deactivated cortical areas correspond conspicuously with those implicated in the so-called default mode network, the widely distributed network of functional units thought to be responsible for personal awareness and conscious processing of environmental inputs.

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_6, © Springer-Verlag Berlin Heidelberg 2013

> Why should not a carefully observed convulsion … associated with central disease so local as a tumor … be considered as an anatomical and physiological experiment, although a rough one, on the part of the brain? (Critchley and Critchley 1998)
>
> John Hughlings Jackson

6.1 Introduction

The previous two chapters have shown that absence and complex partial seizures can dramatically impact awareness even as they allow preserved wakefulness. While generalized tonic–clonic seizures (GTCs) involve a similar profound loss of awareness, they are also well known for their very dramatic motor features and complete loss of consciousness (Cavanna and Ali 2011). Until recently, the intensity of the clinical and electrical features of GTCs, as the terminal phase of some epileptic events, led to the conclusion that they are produced by a widespread and uniform process within the cortex of the brain. However, any effort to expand our understanding of consciousness through the study of GTCs can only be a nontrivial exercise if it is demonstrated that GTCs have some structure, i.e., are not truly generalized. That is to say GTCs do not simply obliterate consciousness by their diffuse and uniform impact on the whole brain. Not only must a nonuniform pattern of GTC seizure activity exist, but it must be demonstrated to have some correlation with the brain's pattern of hypothesized consciousness-producing regions. Based on our recent understanding of the components of consciousness, one might generally predict GTCs to impact both cortical and subcortical areas. Disruption of alertness, or level of consciousness, would logically place a portion of GTCs' impact in the subcortical structures, where centers of activation having strong relay relationships with the cortex are known to reside. The disruption of understanding, or content of consciousness, most notable in the GTCs postictal period, would predict effects on the broadly distributed association areas of the medial and lateral surfaces of the frontal and parietal lobes. Finally, the dramatic motor effects of GTCs would imply involvement of either the bilateral motor cortex or specific subcortical regions.

As it turns out, the term generalized seizure may in fact be a technical misnomer when used to describe GTCs. Evidences from a range of sources such as animal models of epilepsy, human ictal semiology, intracranial EEG, and imaging in human epilepsy all indicate that discrete regions of the brain are active during GTCs, while other areas are relatively spared (Seri et al. 2011). The most compelling of this evidence comes from human functional imaging studies with group statistical analysis. These studies have demonstrated an emerging but consistent nonuniform pattern of sequential brain activations and deactivations during GTCs. Further analysis of these activation–deactivation patterns suggests that they are the same cortical and subcortical brain areas thought to play a role in the loss of consciousness with absence and complex partial seizures (Kalamangalam 2001).

6.2 The Generalized Tonic–Clonic Seizure

GTCs, also frequently called "grand mal" seizures, are well-known dramatic and dangerous convulsions that are responsible for much of the social stigma, morbidity, and mortality associated with epilepsy (Danielson et al. 2011). These events are characterized clinically by whole body stiffening and shaking, during which the patient is rendered deeply unconscious with no responsiveness to external or internal stimuli and no recall of events. Two categories of GTCs may be distinguished based on the clinical mode of onset: generalized ab initio ("from onset") and secondarily generalized. The former event begins with abrupt onset without warning and immediate loss of awareness. Conversely, secondarily generalized events are the terminal phase of partial-onset seizures that have outstripped the brain's ability to confine the seizure to its lobe of origin. The initial clinical effects of the ictal pre-generalization phase of these events may be very subtle, with features that depend on the exact brain region of onset. Whether generalized at onset or as the terminal phase of a partial-onset seizure, GTC events are stereotyped and begin clinically with diffuse sustained tonic stiffening. This posture is seen as a symmetric extension of most of the joints of the upper and lower extremities, with the exception of flexion of the wrists, fingers, and toes. Within 10–20 s this stiffening begins to progressively break down into initially high-frequency tremulousness that slowly evolves into discrete jerks. At first these discrete clonic jerks have a frequency of 4–5 Hz, but there is a progressive slowing to 1–0.5 Hz before offset in a final discrete jerk. With offset of the seizure event after a total duration of 60–90 s, the postictal period begins with eyes closed, deep breathing, and flaccid unresponsiveness. Recovery of spontaneous movements and responsiveness may take more than an hour and is typically associated with poor motor coordination and marked disorientation. Occasionally, a return of alertness may precede the return to normal content of thought, and the deeply confused patient may become aggressive or inappropriately try to leave. Isolated GTCs not associated with epilepsy may also occur, typically in the setting of various provoking physiologic derangements such as electrolyte imbalance, hypoglycemia, toxic exposure, and electric shock (Blumenfeld 2011).

As with the clinical aspects of GTCs, their electroencephalographic characteristics define two categories: primary and secondary GTCs. Primary GTCs begin electrographically with an abrupt transition from normal waking or sleep background rhythms to the high-frequency relatively low-amplitude desynchronization of the tonic phase of the seizure event (Fig. 6.1). Secondarily generalized events typically begin with a focal ictal pattern that grows and becomes more rhythmic and sharply contoured as it spreads to affect an increasing subset of adjacent EEG electrodes. Eventually the entire electrode montage is impacted by a high-frequency desynchronized chaotic pattern associated with the sustained tonic limb extension described above. The clonic phase is characterized by discrete polyspike bursts separated by rhythmic intervals of low-amplitude suppression. The transition to this pattern is gradual, with the appearance of initially very brief and indistinct intervals of suppression seen in the continuous pattern of the tonic phase (Fig. 6.2). Once

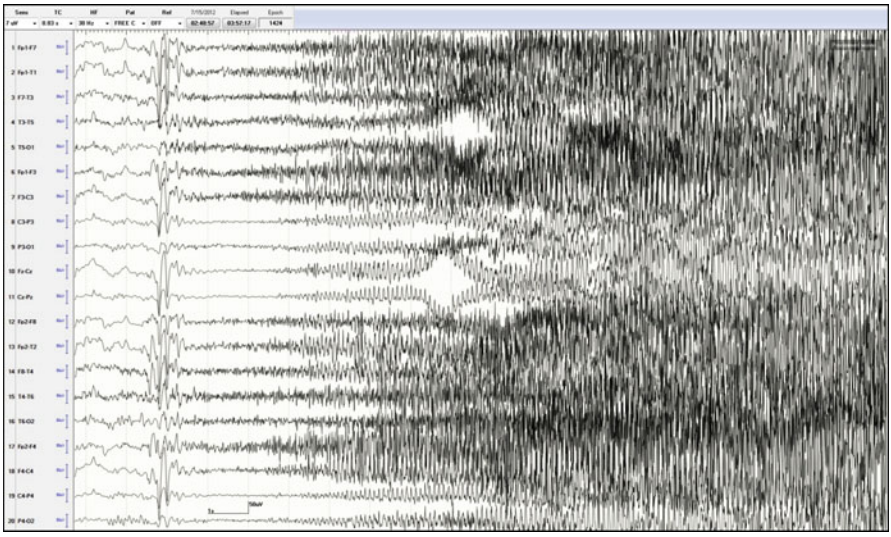

Fig. 6.1 EEG showing the onset of primary GTCs. There is an abrupt transition from normal sleep rhythms to high-amplitude sentinel discharges. The initial portion of the seizure is characterized by a low-amplitude desynchronized pattern which gradually builds into high-amplitude diffusely distributed 9–10 Hz rhythmic spike waves and muscle artifact

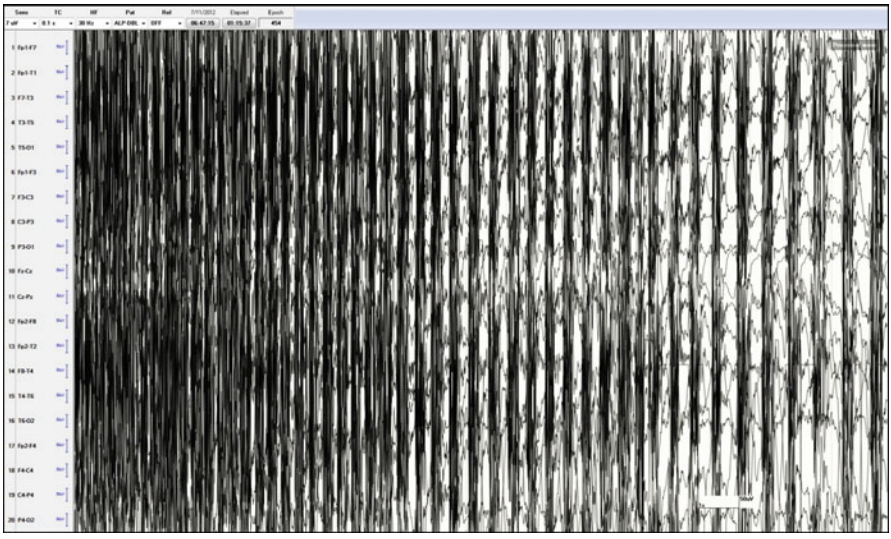

Fig. 6.2 EEG recording of the transition from tonic to clonic phases of GTCs. The start of the transition is noted as very brief and initially indistinct intervals of suppression in the almost continuous spiking and high-amplitude muscle artifact. Once these periodic polyspike bursts develop, there is a progressive slowing in their rate. Muscle artifact almost completely occludes the electrographic profile of the rhythmic spiking and polyspike burst activity throughout this portion of the recording

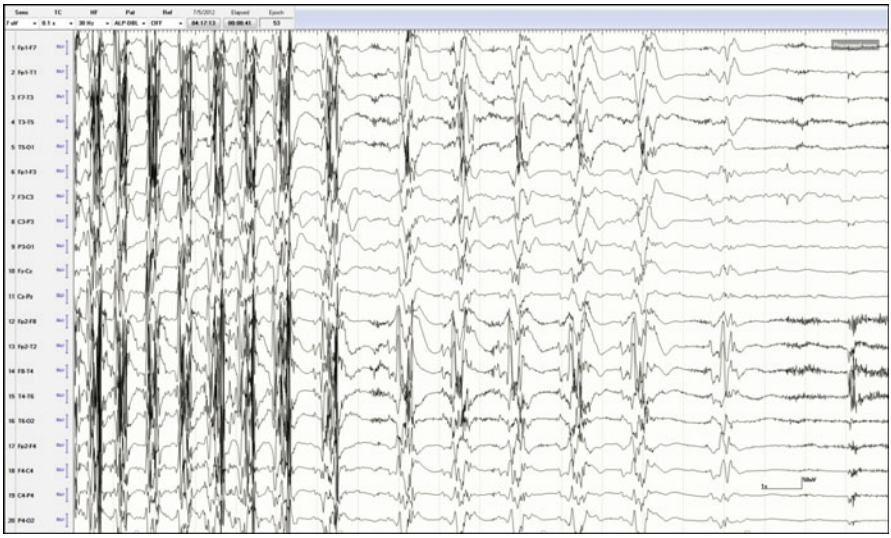

Fig. 6.3 EEG recording of the termination and postictal slowing characteristic of GTCs. Progressive slowing of the polyspike bursts leads to <1 Hz rate just prior to seizure offset. Muscle artifact is seen to diminish with the last few bursts, as the last few clinical jerks weaken. A final less complex burst signifies seizure offset and the start of marked background slowing and suppression typical of the GTCs postictal phase

clearly established at 4–5 Hz, the frequency of discrete polyspike bursts and their accompanying jerks gradually diminishes to around 1–0.5 Hz, stopping abruptly with a final discrete polyspike complex (Fig. 6.3). Postictally there is prominent slowing and generalized background suppression with reduced amplitude that gradually resolves over several minutes to hours.

6.3 Historical Perspective: GTCs and Consciousness

The modern mechanistic perspective on loss of consciousness during GTCs begins with the eminent nineteenth-century British neurologist John Hughlings Jackson (1835–1911). His meticulous observations of clinical seizures and postmortem anatomical studies lead to his belief that the brain's organization is functionally hierarchical yet anatomically discrete. His theory holds that the brain's hierarchy consists of primitive processes that are subordinate to various higher levels of increasingly complex integrative processes. Ultimately this organization leads to "the highest stratum" that, through its processing and control of the body's various inputs and outputs, mediates consciousness. Only through the direct impact of seizure spread to key anatomic regions comprising this stratum would the seizure produce complete loss of consciousness. This concept would become the historical foundation for the idea that GTCs exert their dramatic effects on consciousness through their

influence on discrete consciousness-producing regions of the brain (Yu and Blumenfeld 2009; Eadie and Bladin 2001; Critchley and Critchley 1998).

Like Hughlings Jackson almost a century before, Wilder Penfield and Herbert Jasper made groundbreaking contributions to our understanding of epilepsy, as well as laying much of the foundation of modern epilepsy surgery. Through their study of postoperative epilepsy patients, they began to realize that extra-cortical areas of the brain must play an essential role in consciousness. Their rationale was based on observations of preserved consciousness after even the largest of cortical resections or corpus callosotomy. Further evidence came from those cases of diffuse cortical damage that leave the patient with an apparently normal level of arousal but no demonstrable content of thought. They formulated their beliefs into a "centrencephalic theory," identifying the brainstem and diencephalon as critical players in integrating the activity of the two hemispheres as a mechanism for the modulation of conscious states (Penfield 1958; Jasper 1991; Eadie and Bladin 2001). The work of contemporaries and others since has led to the identification of specific subcortical structures and their projections, e.g., ascending reticular fibers and reciprocal thalamocortical projections, which support the modulatory role of the brainstem and diencephalon in human consciousness.

The most recent chapter in this journey to understand the neural correlates of consciousness has been the identification of a highly interconnected frontoparietal associative network with a very unique property. This network is characterized by the observation that its component regions exhibit their highest metabolic activity only during the inactive conscious restful and reflective state (Raichle et al. 2001; Gusnard et al. 2001). These same regions – especially the precuneus and surrounding posteromedial parietal areas – characteristically show functional deactivations during non-self-directed cognitive tasks ("task-independent decreases") and pathological states of altered consciousness (Cavanna and Trimble 2006; Broyd et al. 2009; Cavanna 2011). These regions have been referred to as the "default mode network" (DMN) because of this consistent activity pattern, which points towards a possible central role in subserving consciousness processes in humans (Cavanna 2007; Crone et al. 2011; Soddu et al. 2011).

6.4 GTCs as Discrete Multifocal Brain Process

In the modern era, evidence from controlled clinical trials and case reports has come together to more seriously bring into question the widely held belief that GTCs are anatomically homogeneous cortical events. Observational studies of ictal semiology during GTCs have shown that most of these events demonstrate some asymmetric features, even during the final clonic stages of seizure offset. It has also been found that even among primary GTCs a significant portion may demonstrate asymmetric semiology (Niaz et al. 1999; Walser et al. 2009). Secondarily GTCs, studied through careful observation of ictal semiology, have been shown to exhibit significant variability within extremely homogeneous groups of patients and even in the same patient during subsequent seizures. There appears to be not

only semiologic variability among homogeneous groups of seizure patients but also specific semiologic patterns that arise from diverse patient groups suffering different types of secondarily GTCs. These identifiable patterns tend to develop later in the process of a seizure's secondary generalization (Theodore et al. 1994; Jobst et al. 2001; Kotagal et al. 2000). Even the observation of Todd's paralysis supports the notion of an apparent sparing of some brain areas with secondarily GTCs (Rolak et al. 1992). Interestingly, there are rare reports in the literature of seizure events with dramatic bilateral motor manifestations yet preservation of consciousness (Botez et al. 1966; Weinberger and Lusins 1973; Bell et al. 1997). These results taken together may indicate the presence of multiple cortical and subcortical spread patterns and may explain postictal focal neurological deficits. Further confirmation of nonuniformity in cortical activation during GTCs comes from intracranial EEG recordings as part of epilepsy surgery evaluations. One study concluded that up to 26 % of secondarily generalized seizures demonstrate some EEG channels in which no ictal pattern is recorded during any stage of the seizure (Schindler et al. 2007).

6.5 Functional Imaging of GTCs in Animal Models

Although more direct than these observational approaches, imaging the brain during human GTCs is fraught with practical difficulties, most notably the unpredictable seizure timing and significant movement artifact. Many of these complexities may be avoided by employing the many animal models of generalized epilepsy that have been developed. Although there are limitations on the applicability beyond the species studied, animal models of epilepsy have contributed significantly to our understanding and treatment of human epilepsy (Fisher 1989). Some of the earliest animal studies that focused on GTCs activity employed techniques such as intracellular potential recording with EEG recording, metabolic mapping using ^{14}C-2-deoxyglucose autoradiography, and blood flow mapping using ^{14}C-iodoantipyrine autoradiography (Matsumoto and Marsan 1964; Engel et al. 1978; McCown et al. 1995; Handforth and Treiman 1995; Andre et al. 2002). These studies produced variable and somewhat controversial results showing diffuse and confluent brain activation during GTCs. However, other studies that also employed ^{14}C-2-deoxyglucose autoradiography were able to demonstrate, in these same rat models, discrete regional changes during GTCs (anterior neocortex, striatum, and thalamus). Interestingly, these discrete regional effects in animals were not appreciated in human subjects using the PET scanners of the day (Ackermann et al. 1986; McIntyre et al. 1991). Confirmation of these results has come from subsequent functional MRI (fMRI) studies using high-strength animal magnets (7T & 9.4T). Although some question remains about the fundamental relationships between the electrical activity of the brain and the interpretation of the blood–oxygen-level-dependent (BOLD) signals, fMRI offers higher temporal resolution than autoradiography and higher spatial resolution than neurophysiologic methods (Blumenfeld 2007; Schridde et al. 2008). Indeed, some of the pioneering studies in which Ogawa et al. validated fMRI as an imaging method employed animal models of kainic acid-induced seizures (Ogawa and Lee 1992).

Studies that have employed simultaneous EEG–fMRI in rats during pentylenetetrazole (PTZ)-induced seizures have demonstrated repeatable progressive positive and negative BOLD contrast changes in discrete cortical and subcortical areas (Van Camp et al. 2003; Keogh et al. 2005; Brevard et al. 2006). Other EEG–fMRI studies that used the $GABA_A$ antagonist bicuculline to induce GTCs in rats have produced images that show subtle pre-ictal increases in the somatosensory cortex, thalamus, and brainstem tegmentum, along with decreases noted in the hippocampi. They also noted that in the postictal period there was a transition to widely distributed cortical and subcortical decreases, most significant in the hippocampi (Nersesyan et al. 2004; DeSalvo et al. 2010). Other fMRI studies in both rat and mouse bicuculline models have employed intravenous magnetite nanoparticles to improve resolution. These studies have confirmed the initial contrast increases in the cortex but have also documented late-ictal cerebellar increase, as well as thalamic increases which persisted throughout the seizure (Reese et al. 2000; Mueggler et al. 2001). The sum contribution of GTCs imaging studies in animal models has been to confirm the discrete effects GTCs have on the brain and to establish a sequence of early cortical, thalamic, and brainstem activation; progression into the cerebellum; and ultimately a late-ictal transition to diffuse cortical decreases in perfusion.

6.6 New Methods in Imaging Human GTCs

Unlike the well-controlled and invasive studies in animal models of epilepsy described above, the systematic study of human GTCs is complicated by their clinical features. Specifically, the unpredictable timing and dramatic motor involvement of these events renders most neuroimaging studies, including PET and fMRI, impractical. However, specialized studies and advanced image-processing algorithms, originally developed for their clinical utility, have been enlisted to address these difficulties, with some success. Ictal SPECT is a nuclear scan that employs radiopharmaceuticals to noninvasively image regional cerebral blood flow at the time of a seizure, relying on its known proportional linkage to synaptic activity for seizure localization. The particular advantage of ictal SPECT is that radiopharmaceutical injection may be performed at the time of the seizure, with the subsequent scan delayed until the seizure has ended and the patient is stabilized, usually up to 2 h later. This very useful practical feature is accomplished through the rapid (single pass) absorption and stabilization of the radiopharmaceutical within cerebrovascular endothelial cells. Once stabilized within these cells, the radiotracer forms a virtual image of rCBF, written in radioactivity at the time of the seizure.

In recent years, the analysis of SPECT images using software such as Statistical Parametric Mapping (SPM) has allowed the objective comparison of groups of scans (Friston 1994). This technique relies on coregistration of a variable number of SPECT images into a standard three-dimensional space, along with normalization of their intensity. Once standardized in this way, SPM uses the general linear model to generate a single voxel-wise statistical representation, or 3D parametric map, of the group of SPECT scans. This group map may be compared to maps similarly derived from

other groups of scans, typically from a reference cohort of healthy normal subjects. The intensity of each voxel in the resulting comparison image, or Z-map, represents a Z-score. This quantity shows how statistically significant a change in the study group's ictal perfusion is, when compared to the variance of the corresponding voxel in the other group's parameterized data. The use of thresholding to display only those voxels with high significance changes, greater than a user-specified p-value, e.g., $p<0.01$, adds additional clarity. Optionally, a second-order threshold, the cluster size, is used to eliminate small physiologically irrelevant clusters by displaying only those significant voxels that are also in contiguous clusters larger than a specified "extent parameter," e.g., $k=125$ voxels. Finally, coregistration of this dual thresholded significance image to the standard MRI is performed, allowing precise anatomical localization of significant ictal activity. A growing number of studies have demonstrated that the SPM approach provides objective and accurate analysis of ictal–interictal SPECT data in patients with temporal lobe and extratemporal epilepsy (Chang et al. 2002; Knowlton et al. 2004; McNally et al. 2005).

Another clinical method that has simplified the imaging studies of the human GTCs is the treatment for severe depression known as electroconvulsive therapy (ECT). Clinically, this treatment has not only been established as safe but is widely accepted as the most effective treatment for those cases of depression deemed severe and medically refractory. Multiple treatments (8–12) performed on separate days are typically required to effect the desired antidepressant response. The implementation of this therapy is based on delivering an electrical stimulus via scalp electrodes with current levels adequate to induce GTCs in the anesthetized and pharmacologically paralyzed patient. The predictable timing of ECT-induced seizures allows for ictal SPECT radiopharmaceutical injection with very precise control of the injection latency, defined as the time from seizure onset to injection completion. SPM group analysis of SPECT images, each obtained at the same specified injection latency, has been used to study the rCBF patterns of onset and progression in ECT-induced GTCs (Kim et al. 2010).

6.7 Functional Imaging of ECT-Induced GTCs in Humans

The earliest imaging studies to explore human GTCs used PET scanning in ECT-induced seizures (Ackermann et al. 1986; Engel et al. 1982). These studies were able to discern only global increases or decreases with ictal and postictal states, respectively. These results were likely due to PET's inadequate temporal resolution to capture the sequence of brain activations that occur during GTCs. However, subsequent evidence from numerous qualitative studies, most using SPECT images obtained from secondarily GTCs, has suggested that human GTCs produce nonuniform cortical and subcortical areas of discrete activation (Lee et al. 1987; Rowe et al. 1989; Green and Buchhalter 1993; Shin et al. 2002; Koc et al. 1997). More recent quantitative studies of ECT-induced GTCs have employed SPM group analysis of SPECT imaging (Blumenfeld et al. 2003b; McNally and Blumenfeld 2004; Enev et al. 2007). The earliest of these studies compared various ECT-stimulating

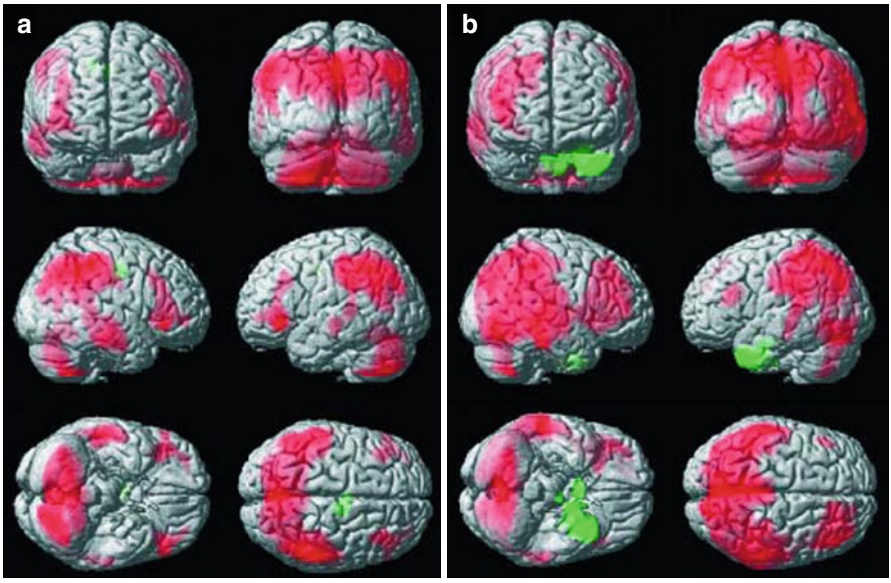

Fig. 6.4 SPM group analysis of SPECT images obtained from ECT-induced generalized tonic–clonic seizures with 30 s injection latency. Red areas represent significant areas of increased rCBF and green areas decreased rCBF compared to an interictal scan performed on a separate day. (**a**) Right unilateral ECT-stimulating electrode configuration, (**b**) bilateral temporal ECT-stimulating electrode configuration (Blumenfeld et al. 2003b)

electrode configurations (bitemporal, bifrontal, right unilateral frontal) (Blumenfeld et al. 2003b). They analyzed rCBF changes in groups of images obtained with 30 s injection latency relative to pre-ECT–SPECT images obtained on a different day. Both electrode configurations produced a nonuniform pattern with prominent areas of discrete cortical increases and notable sparing of the intervening cortical structures. These increases were most prominent in the frontal and parietal lobes, but smaller areas in the temporal lobe, pontine tegmentum, brainstem, and cerebellum were also seen (see Fig. 6.4).

More detailed scrutiny of these images also reveals asymmetries in these increases in both cortical and subcortical areas, reflecting the stimulating electrode configuration used, i.e., right unilateral frontal stimulation produced a relative sparing of increases in the left frontal and temporal regions as well as in the left thalamus. A separate study that employed ^{15}O-PET to image rCBF of patients undergoing ECT also found areas of discrete increases at the time of ECT compared to pre-ECT (Takano et al. 2007). These areas included the inferior frontal and temporal lobes, as well as subcortical increases in the cerebellar vermis, thalamus, amygdala, basal ganglia, midbrain, and pontine tegmentum. They also found residual postictal increases in the thalamus and decreases in the anterior cingulate. Thus, from these single time-point ECT studies, a pattern of early activation is seen to coincide with those cortical regions (frontal and parietal) known to be involved in high-level consciousness-producing integrative function. The more revealing temporal aspect of

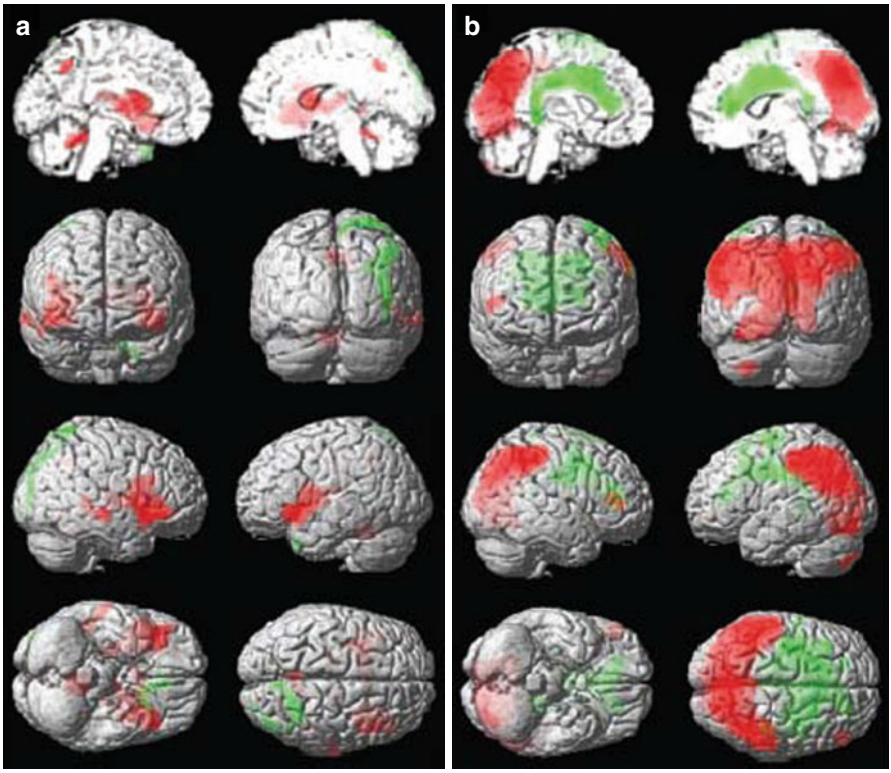

Fig. 6.5 SPM group analysis of SPECT images obtained from ECT-induced generalized tonic–clonic seizures at two injection latencies. Red areas represent significant areas of increased rCBF and green areas decreased rCBF compared to an interictal scan performed on a separate day. (**a**) Early SPECT injection completed simultaneous to ECT-induced seizure onset. (**b**) Late injection completed at 30 s after onset of ECT-induced seizure (Enev et al. 2007)

ECT-induced GTCs has been investigated by Enev et al., who performed group analyses on SPECT images obtained at two injection latencies relative to seizure onset (Enev et al. 2007). One group had radiopharmaceutical injection performed simultaneous with electrical stimulation, and the other group was injected 30 s after the onset of stimulation, with each subject having a pre-ECT scan obtained on a separate day (see Fig. 6.5). The 30 s interval between injections was rationalized to be the approximate temporal resolution of the SPECT method. As with previous studies, the early group result confirmed that initial regions of increased cortical perfusion are related to the configuration of the stimulating electrodes (McNally and Blumenfeld 2004; Blumenfeld et al. 2003a, b; Takano et al. 2007).

Although no areas of significant decreases were noted in the early group, the late injection images showed loss of the initial frontal cortex increases and new increases in the lateral and medial parietal and occipital cortex bilaterally. Again, the intervening regions of cortex between the initial frontal and later parietal activation remained unaffected. This seems to show that an anterior-to-posterior propagation

may have led to the frontal parietal increases noted in the single-time sample imaging of prior studies (Blumenfeld et al. 2003b). This pattern supports the idea that the differences in activation from early to late may have come about through propagation rather than contiguous spread. The authors propose cortico-cortical network propagation through known long association fiber pathways such as the superior longitudinal fasciculus. They also suggest an indirect cortico-thalamocortical mechanism of seizure propagation through recruitment of subcortical projection sites that then spread the activation to other cortical regions. Support for the role of the thalamus in this second mechanism is provided by the noted early thalamic activation and the thalamus' known broadly distributed network of recurrent projections. Significant late rCBF decreases noted in the bilateral cingulate and left dorsolateral frontal cortex also confirm similar findings in earlier ECT studies.

6.8 Functional Imaging of Spontaneous GTCs in Humans

Although ECT as a model for studying human GTCs offers well-defined seizure timing and a homogeneous seizure type, this method suffers from the possibility that important mechanistic differences exist between induced and spontaneous seizure events, particularly in the setting of anesthetized subjects. Although less well controlled, the more representative secondarily GTCs of localization-related epilepsy are available for study through the clinical practice of epilepsy presurgery evaluation. Blumenfeld et al. investigated the temporal progression of secondarily GTCs using SPM group analysis of 59 ictal–interictal SPECT image pairs from 53 patients (Blumenfeld et al. 2009). This set of clinically obtained images had randomly distributed injection latencies ranging from 0 to 300 s. Images were divided into three analysis groups based on which electrographic phase the patient was in at the time of radiotracer injection: ictal pre-generalization, generalization, or postictal.

They found that these secondarily GTCs, as with ECT-induced GTCs, involve intense rCBF changes in specific discrete brain regions with relative sparing of other areas (see Fig. 6.6). Images from the ictal pre-generalization group demonstrated significant cortical rCBF increases that reflected the region of seizure focus, as well as decreases in the bilateral superior frontal association areas and bilateral mid-cingulate. This is consistent with the findings in ECT-induced seizures described above. In the next group, injected during seizure generalization, analysis showed that the initial onset-related regional increase seen in the pre-generalization group had been replaced by areas of strongly reduced rCBF affecting the bilateral medial, superior, and orbital frontal cortex. There were also bilateral posterior cingulate and precuneus decreases that were significant at the voxel level, but these did not reach significance at the cluster level. Subcortical structures that had remained unaffected until the generalization phase demonstrated increased rCBF, specifically in the superior medial cerebellum, basal ganglia, and thalamus. The images from the final group, those patients injected postictally, showed an intensification and spread of both the diffuse cortical decreases and the cerebellar increases noted in the earlier generalization phase. In the postictal phase the now more intense cortical decreases had also expanded to affect the bilateral

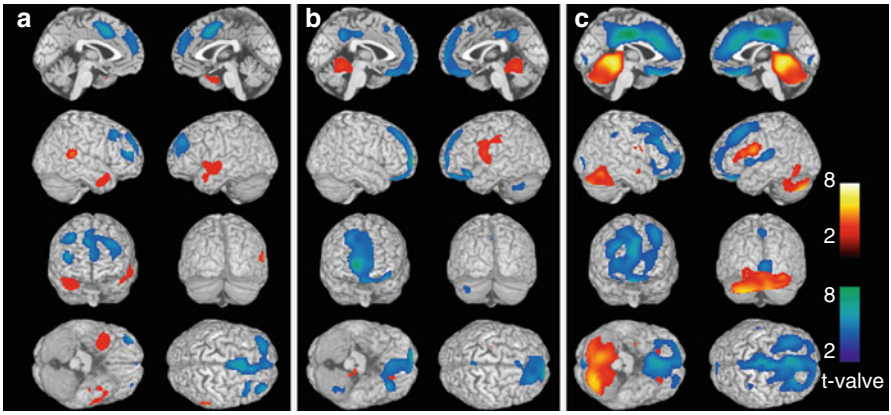

Fig. 6.6 SPM group analysis of SPECT images obtained from secondarily GTCs grouped by injection latency epochs: (**a**) ictal pre-generalization, (**b**) generalization, and (**c**) postictal. Warm colors represent significantly increased rCBF relative to the patient's interictal scan performed on a separate day, and cool colors represent significant rCBF decreases (Blumenfeld et al. 2009)

orbitofrontal, middle frontal, cingulate, and precuneus. However, the most striking feature of the postictal phase data was the marked extension of the cerebellar increases to encompass the entire cerebellum and dorsal midbrain. When the postictal images were further subdivided into early, mid, and late postictal groups, these changes were noted to progress well into the late postictal period. A voxel-wise whole-brain correlation analysis showed that the cerebellar increases of the ictal and particularly postictal periods were most highly correlated with remote increases in the thalamus and basal ganglia and with the widespread decreases in cortical rCBF.

6.9 Summary/Conclusion

The sequence of abnormal GTCs activity that is emerging through the imaging studies presented above begins with the regional cortical activation of seizure onset. Seizure generalization brings activation of the brainstem, midbrain tegmentum, and cerebellum. Since the cortical areas of motor control appear to be spared, this spread into subcortical structures may be responsible for the dramatic motor effects of the GTCs. Progressive cerebellar and dorsal midbrain activation late in the seizure is likely responsible for strong inhibition of the thalamus, which in turn affects a widespread reduction in cortical activity through diffusely divergent thalamic projections. Support for this strong inhibitory influence of the cerebellum is evident in neurophysiologic studies of animals that have demonstrated sustained high-rate firing of inhibitory Purkinje cells well into the postictal period of GTCs (Salgado-Benitez et al. 1982). This strong and broadly distributed inhibitory influence on the cortex may be in part responsible for seizure termination. It also adequately explains both the EEG slowing and impairment of thought characteristic of the GTCs postictal state.

GTCs have long been assumed to bring about their various dramatic clinical effects through a widely distributed and uniform dysfunction of the human cerebral cortex. However, evidence from a diversity of sources is mounting that GTCs actually exert their influence through discrete cortical and subcortical brain areas, while leaving the intervening structures unaffected. This dysfunction may be produced directly through spatially circumscribed seizure activity or remotely through propagated network dysfunction. Specialized imaging and analysis methods have identified the distinct brain areas affected by GTCs as those also implicated in maintaining both the level of consciousness and its content. The subcortical areas implicated in these imaging studies likely play a critical role in the characteristic motor manifestations of GTCs, as well as the complete disruption of alertness. A notable strong cerebellar activation of the late-ictal and postictal period may be the source of dramatic postictal confusion with GTCs, mediated by its strong inhibitory relay connections through the thalamus and diverse projection to the cortex. By propagating this inhibitory influence through its divergent thalamocortical connections, the thalamus may effectively deactivate broad areas of the cortex. Interestingly, there is a striking correlation between these deactivated cortical areas and those implicated in the so-called DMN (Cavanna and Monaco 2009; Danielson et al. 2011). This widely distributed network of functional units is thought to be responsible for personal awareness and conscious processing of environmental inputs, functions that are dramatically defective during GTCs and the associated postictal period.

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Consciousness, Epilepsy and Intracranial EEG

7

Aileen McGonigal and Fabrice Bartolomei

Abstract

Intracranial stereoelectroencephalography (SEEG), carried out during epilepsy presurgical assessment, offers high temporal resolution coupled with a three dimensional vision of network dynamics, this latter aspect representing a specific advantage of SEEG over subdural EEG recording. Study with SEEG of patients presenting transient, reversible altered consciousness in the context of epileptic seizures thus affords a unique opportunity to study the dynamics of cerebral substrates of consciousness, since clinical signs can be recorded on video, quantified using validated consciousness scales, and correlated with changes in intracerebral EEG activity. Whereas earlier epileptology studies by Penfield, Gloor, Munari and others looked mainly at lobar localisation and duration of seizure activity associated with impaired consciousness, research since the end of the 20th century has rather begun to investigate the distributed network

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_7,

dynamics underlying consciousness, notably the global workspace hypothesis. This concept posits the role of widely distributed networks including frontal, parietal and subcortical (thalamic) structures. Partial seizures producing altered consciousness could be seen as acting at the « modular » level of the global workspace and provide an intriguing paradigm for investigating this hypothesis. SEEG studies in patients with temporal lobe seizures have demonstrated the importance of cortico-thalamic coupling in altered consciousness, showing long-distance synchronisation between the local zone of seizure organisation and both distant cortical (e.g. posterior cingulate gyrus) and subcortical (thalamus) structures. In addition an association between the degree of long distance synchrony and the degree of altered consciousness has been shown in parietal seizures. Analysis of intracranial EEG obtained through recording epileptic seizures thus represents an important and unique tool in the investigation of consciousness. Future work should include evaluation of the specific role of prefrontal and parietal cortex in consciousness networks.

7.1 Introduction

The ability to record directly from brain structures using electrodes has had a major impact on understanding of cerebral function. Apart from experimental approaches in animal models, the use of intracranial recording is carried out in human subjects in the context of specific clinical situations, notably presurgical evaluation of intractable epilepsy. While the primary purpose is to ascertain electro-clinical localisation of epileptic seizures within the brain, the intracerebral electroencephalography (EEG) data thus obtained are clearly very valuable from a research point of view. Epileptic seizures, which are brief, paroxysmal episodes of alteration of cerebral function produced by abnormal brain electrical activity, provide a quite unique opportunity for in vivo analysis of reversible loss of consciousness (LOC), since ictal EEG recording and functional neuroimaging techniques allow investigation of the networks involved.

7.2 Intracranial Recording of Epileptic Seizures

In order to optimally study the neural correlates of consciousness, high temporal resolution on a millisecond scale is required (Crick and Koch 2003), and EEG offers an advantage over functional neuroimaging methods such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) in this respect. Compared to surface EEG, intracranial recording has a much higher degree of anatomical precision and fewer artefacts when studying signal changes. Depending on the chosen method of intracranial recording, a variable number of brain structures can be simultaneously recorded from. Intracerebral electrodes are placed during a surgical procedure under general anaesthesia, their position having been previously selected according to clinical hypotheses of likely localisation of seizure activity. A period of recording with digital video EEG in a specialised monitoring unit is then performed over several days, often with reduction of the

patient's usual antiepileptic medication, with the goal of recording several habitual seizures. In addition stimulation of certain electrodes carried out in the course of this recording period can help to better characterise the role of different structures in seizure production as well as delineate functional zones for language and motor function.

Different methods of intracranial recording exist, including subdural grid or strip recordings in which an array of electrodes is placed usually over the cortical convexity, sometimes accompanied by one or more depth electrodes. The stereoelectroencephalography (SEEG) method as conceived and developed by Bancaud and Talairach in Paris (Bancaud et al. 1965) uses multiple (usually between 5 and 15) implanted orthogonal electrodes, each with 8–15 recording contacts (Fig. 7.1). This offers certain advantages over subdural recording, notably the ability to record simultaneously from medial and lateral structures in several different brain regions, including deep or buried cortex. Through comparison of the evolution of the spatiotemporal pattern of electrical activity in relation to the emergence of clinical signs, electro-clinical-anatomical correlations can be made, allowing estimation of the likely network organisation of the seizure (Talairach et al. 1974; Bartolomei et al. 2002). The chosen method of intracranial recording is clearly an important point when considering anatomical and functional substrates of consciousness in seizures since the networks involved are likely to simultaneously involve multiple distant cortical and subcortical regions. Although technically feasible using depth electrodes,

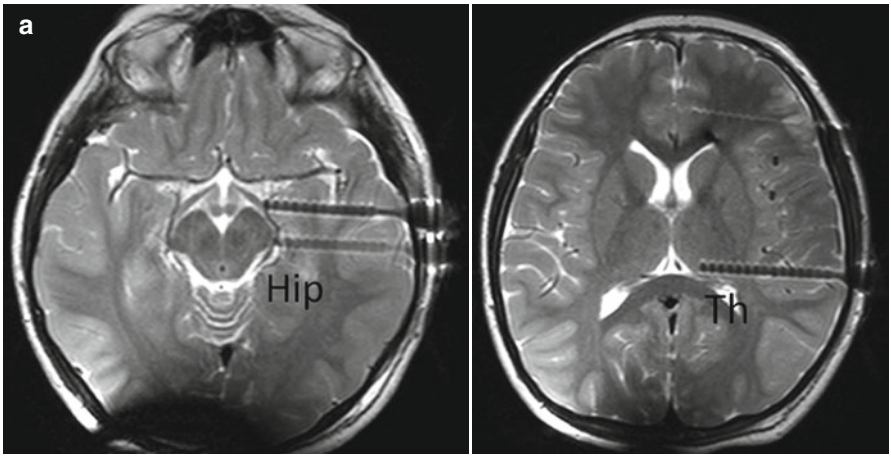

Fig. 7.1 (**a**) MRI in a patient with electrodes reaching the hippocampus (Hip) (*upper part*) or the thalamus (Th) (*lower part*) during SEEG recordings. (**b**) Two different seizures with alteration of consciousness (*group C*) and without alteration of consciousness (*group A*). Intracerebral recordings are obtained from multiple contacts electrodes placed according to Talairach's stereotactic method. Four regions are shown: *hip* anterior hippocampus, *EC* entorhinal cortex, *Th* thalamus (pulvinar), and *Pa* posterior parietal cortex. Seizures started in the medial temporal lobe before affecting thalamus and parietal cortex. The estimation of synchrony used nonlinear regression (h^2) between pairwise signals. Increase in h^2 values is particularly marked for seizure from group C affecting not only the mesial temporal interactions (*EC-hip, red line*) but also the other interactions represented. Seizure from group A is mainly characterised by increase in h^2 values between entorhinal cortex and hippocampus (*red line*) (Adapted from Arthuis et al. 2009, with permission)

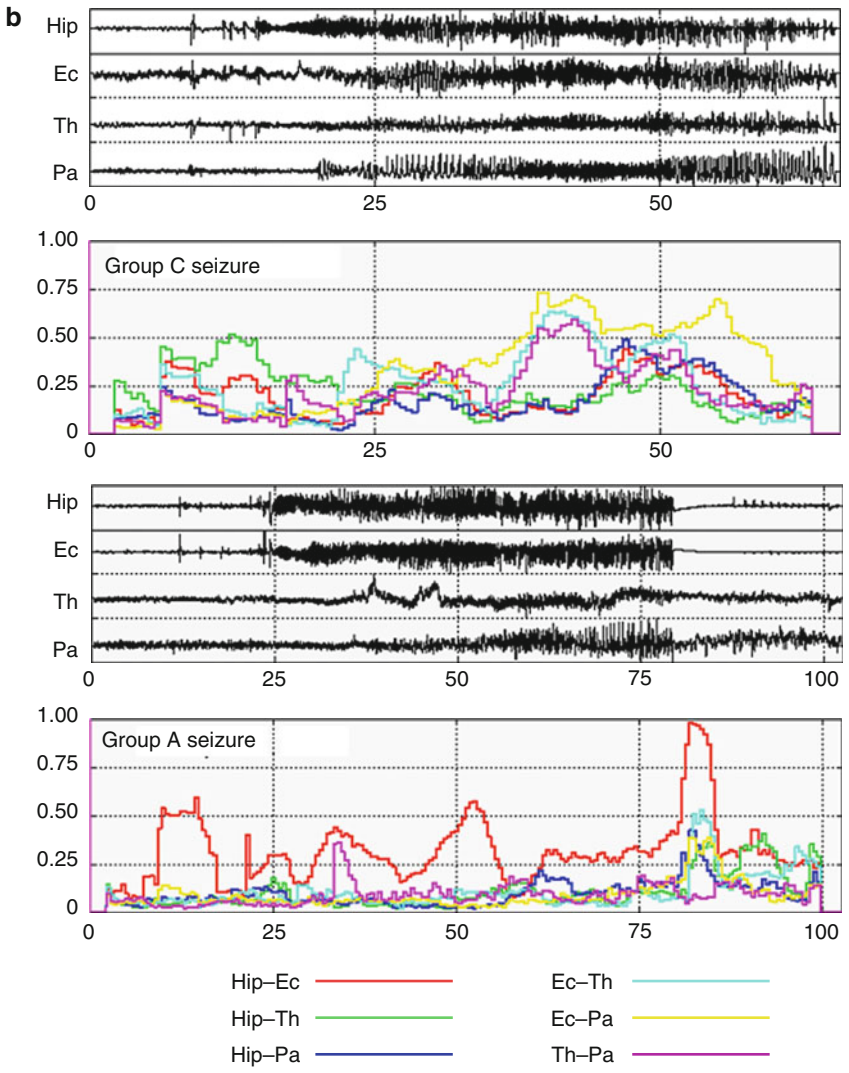

Fig. 7.1 (continued)

subcortical structures are however rather infrequently sampled in a clinical epileptology context since the goal of the exploration is always successful identification of the extent of the likely (cortical) epileptogenic zone (Chauvel et al. 1996) and the possibility of curative surgery. The medial contacts of certain electrodes, notably those implanted to explore lateral temporal cortex, may reach thalamic nuclei, but this is not in general a primary goal of the implantation unless (rarely) a subcortical lesion is present (Rosenberg et al. 2006; Guye et al. 2006). It has long been considered likely that the anatomical substrate of consciousness involves subcortical brain

structures, notably the thalamus (Penfield and Jasper 1954). Thalamo-cortico-thalamic loops are indeed considered to have a central role within the neuronal basis of the global workspace model (Baars 1988; Newman et al. 1997). In clinical studies thalamic involvement in circuits underlying consciousness has been demonstrated in epileptic subjects with ictal altered consciousness using surface EEG and SPECT in partial seizures (Lee et al. 2002; Blumenfeld et al. 2004) as well as simultaneous surface EEG and fMRI recording during absence seizures (Aghakani et al. 2004; Gotman et al. 2005). Recent reports of SEEG recordings with intra-thalamic electrodes have shed further light on the interactions between cortical and thalamic structures during seizures, discussed below (Guye et al. 2006; Arthuis et al. 2009).

7.3 Consciousness in the Context of Epileptic Seizures

According to current seizure classification proposed by the International League Against Epilepsy (ILAE) (Berg et al. 2010), seizures are considered "partial" if arising within a region of one hemisphere or "generalised" if associated with initial simultaneous epileptic discharge over both hemispheres (although the acknowledged reality is probably better described by a continuum between these). This chapter deals only with partial seizures since patients with generalised epilepsies do not as a rule undergo intracranial exploration.

Alteration of consciousness, despite inherent difficulties in assessing and quantifying this entity (Gloor 1986), remains a key clinical sign in clinical classification since so-called complex partial seizures are defined by the presence of altered consciousness (or the commonly used epileptological term "loss of contact") and "simple partial seizures" by the absence of this sign (Berg et al. 2010). However, the nature of altered consciousness in seizures and how best to assess this empirically is much debated, since the definition of consciousness varies depending on whether subjective experience or outward physical signs are taken as the main viewpoint (Ali et al. 2012). Indeed, the distinction between altered content and altered level of consciousness (Plum and Posner 1980; Zeman 2001) seems particularly relevant in epileptology (Monaco et al. 2005) since both aspects may independently occur in seizures. However, epileptology classifications employing altered consciousness as a clinical sign are based on an operational definition, and this chapter will likewise deal with altered level rather than content of consciousness during seizures.

7.4 How Is Conscious Level Assessed in Epileptic Seizures?

The operational definition is based on observing objective clinical signs that indicate that the patient is no longer fully aware of or in contact with his or her environment, as evaluated by lack of interaction with the examiner and by lack of memory for what has occurred during the seizure. This is distinct from altered vigilance, since patients usually keep their eyes open and appear "awake" during the seizure, although the postictal period may often be associated with a sleepy or even

Table 7.1 The consciousness seizure scale (CSS)

Criteria	Assessment of the criteria
1. Unresponsiveness (0 or 1)	The patient does not execute simple verbal commands (e.g. "clap your hands", "open the mouth", "close your eyes")
2. No visual attention (0 or 1)	The patient presents no adequate visual response to external stimuli (e.g. the patient does not look at the examiner during examination)
3. No interaction with the examiner (0 or 1)	The patient does not present any signs (other than visual attention) of response to the examiner
4. No consciousness of the seizure (0 or 1)	The patient does not report to be in seizure state at any time of the seizure course (e.g. he/she does not call the examiner at the beginning of the seizure)
5. Inappropriate behaviour (0 or 1)	The patient presents with an automatic, uninhibited behaviour or an unreactive state
6. Postictal amnesia (0 or 1)	The patient does not remember his/her seizure
7. Amnesia of the seizure events (0 or 1)	The patient does not remember the events that have occurred during the seizure
8. Global appreciation of consciousness by an experienced physician (0,1 or 2)	1. No alteration 2. Middle alteration 3. Complete alteration

comatose state. If no observer is present to interact with the patient as the seizure unfolds, then level of consciousness cannot be reliably ascertained, hence the need for highly trained and available staff who are able to perform appropriate ictal examination. It has been emphasised that impairment of language, cognitive and/or motor functions due to the seizure may well impair ability to respond, and failure to obey simple commands, for example, cannot in itself be considered a marker of altered consciousness (Gloor 1986). Nevertheless, it is usually possible to form a clinical impression of whether a patient retains contact or not during a seizure, if necessary by repeated viewing of video recording of seizures in which an examiner has been able to intervene. To try to render this process more reliable and quantifiable, previous studies have identified clinical criteria for ictal unconsciousness, based on inability to carry out verbal instructions, amnesia of the seizure episode and inability to recall memory items given during a seizure (Lux et al. 2002; Lee et al. 2002; Blumenfeld et al. 2004). A validated 20-point scale detailing subjective features of level and content of consciousness has been described (Cavanna et al. 2008). Another group has recently evaluated a standardised 3-level procedure for ictal examination, modified from an existing coma recovery scale (Yang et al. 2012). Our own work has been based on a clinical 8-point "Conscious Seizure Score" (CSS) (Arthuis et al. 2009, see Table 7.1) which we have found practicable and robust. This takes into account not only response to verbal instruction and amnesic features but also visual attention, inappropriate behaviour and the examining physician's overall impression of the patient's state, with good intra-rater and inter-rater agreement having been shown (Arthuis et al. 2009).

7.5 Intracranial EEG and Altered Consciousness During Seizures: Evolving Concepts

Following the development of EEG recording in the 1920s, it became possible for the first time to demonstrate changes in cerebral activity according to altered clinical states including sleep, coma and epileptic seizures. Herbert Jasper and Wilder Penfield were the first to use intracranial EEG to record from the brains of epileptic patients in the 1950s and reported for the first time experiential phenomena (such as déjà vu) elicited by intraoperative cortical stimulation of temporal lobes (Penfield 1958). Penfield and Jasper's huge body of clinical research led them to conclude that two main components contributed to the cerebral substrate of consciousness: localised functions of speech, memory and affect and a more diffuse, subcortical system, the "diencephalon", including the thalamus, that was responsible for awareness and conscious integration.

Directly influenced by his training with Penfield and Jasper in the Montreal Neurological Institute, Gloor subsequently contributed important data from intracranial recordings. In 1980, he reported 14 patients with a total of 72 partial temporal lobe seizures associated with loss of consciousness, of which the majority (74 %) had bilateral and widespread temporal lobe involvement; only rarely did loss of consciousness occur with discharge limited to either limbic or temporal neocortical structures (Gloor et al. 1980). These data thus corresponded to earlier observations by Jasper and also Bancaud and colleagues (1994) that bilateral temporal ictal involvement is frequently associated with loss of consciousness (complex partial seizures), but not obligatory for loss of consciousness to occur. The importance of limbic structures in maintaining contact with the environment was highlighted since loss of consciousness provoked by stimulation of temporal lobe generally occurred with stimulation of limbic rather than neocortical structures. Gloor pointed out the marked contrast between the "loss of contact" of temporal seizures and the loss of consciousness seen with higher brainstem dysfunction, the latter more often characterised by altered vigilance than by altered contact. The opinion of Penfield and Jasper of the role of "integrating circuits" within the higher brainstem in producing the altered consciousness of temporal lobe seizures was thus somewhat difficult to reconcile with the clinical picture since seizures typically do not produce sleep-like states. For Gloor the clinical signs were more suggestive of specific impairment of temporal lobe functions in terms of the processing and stocking of visual and auditory sensory information in relation to past experience and associated emotional states. He hypothesised that seizure activity abnormally activating these memory and perception systems, via the production of experiential hallucinations or even "white noise" in the same circuits, could monopolise attentional processes, thus cutting off access to normal environmental cues (Gloor et al. 1980). However, the questions of why such altered contact should be able to occur with unilateral temporal lobe seizure activity, and why amnesia should be so complete, remained unanswered. In fact Gloor subsequently expressed the view that since unconsciousness was essentially indefinable and since clinical "altered consciousness" encompasses such a heterogeneous set of perceptive and behavioural changes including impaired

motor response or aphasia, the search to understand "consciousness" as a neurobiological concept, via the study of seizures, was unlikely to be fruitful (Gloor 1986).

Around the same time, Munari and colleagues also studied altered consciousness in temporal lobe seizures using SEEG, reporting a large series with 100 patients and a total of 388 seizures, of which 178 showed altered ictal consciousness (Munari et al. 1980). Interestingly, since the patient group was sufficiently large, comparison was possible not only of individual seizures but also groups of patients (those who lost consciousness at the onset of every seizure versus those who never lost consciousness). Patients who lost consciousness were also more likely to present complex semiology such as dyspraxic automatic activity as well as extra-temporal semiology including lateralised motor signs and subsequent generalisation, associated with a longer duration of ictal discharge (on average 90 s). In contrast those who never lost consciousness were more likely to present subjective epigastric sensation at seizure onset in the context of a shorter discharge limited to unilateral temporal structures. Like Gloor, the authors found a higher occurrence of loss of consciousness in seizures involving bilateral temporal structures. However, unlike Gloor their conclusion was that LOC was not per se a characteristic of temporal lobe seizures, but rather a phenomenon that occurred principally when ictal activity was prolonged (average seizure duration of 90 s when LOC occurred, in contrast to 47 s for seizures without LOC); in addition, over half of cases with LOC showed propagation to contralateral hemisphere, especially contralateral temporal lobe.

Few subsequent intracranial studies at the end of the twentieth century looked specifically at the issue of altered consciousness during seizures. However, a study of 142 consecutive patients undergoing subdural EEG for presurgical exploration of partial seizures of all localisations (both temporal and extra-temporal origin) (Inoue and Mihara 1998) studied the usefulness of loss of consciousness as a defining clinical sign in seizure classification. The authors found a high prevalence of LOC in all subgroups (frontal, temporal and posterior epilepsies) with around 70 % of patients demonstrating some degree of impaired responsiveness during ictal examination and therefore complex rather than simple partial seizures using the operational definition. On the other hand, using patients' descriptions of subjective experience during the seizure, the authors noted that around 80 % retained some degree of awareness, highlighting the difference between objective and subjective measures of consciousness as previously discussed. In concordance with Munari and Gloor, this study also found more prevalent LOC in bilateral rather than unilateral temporal involvement.

In the 1990s, the introduction of digital EEG recording systems opened up important new possibilities for analysing intracranial EEG signals, notably the ability to compute power spectra. This development coincided with resurgence in neuroscientific interest in consciousness as a neurobiological entity that could be objectively studied using modern imaging and neurophysiological techniques (Frith et al. 1999). The ability to record EEG from within brain structures and to analyse the modulation and interaction of activity from different structures according to changes in clinical state was thus to provide a crucial tool for studying the cerebral substrates of consciousness.

7.6 Intracranial EEG and Global Workspace Theory

Perhaps as a consequence of the rather pessimistic views expressed by Gloor in the 1980s, emerging techniques in digital intracranial EEG did not immediately lead to new research into these questions. However, converging theories of consciousness, notably the global workspace model and its neuronal network basis, has led to renewed interest over the last decade in using epileptic seizures as a useful model with which to study the cerebral basis of reversible loss of consciousness. This has been largely centred on temporal lobe and absence seizures, with some recent SEEG data from our team looking at temporal and extra-temporal seizures, described below.

The global workspace model (Baars 1998, 2002, 2005; Newman et al. 1997) has become accepted across many disciplines as a useful way of conceptualising consciousness. According to this model, the multitude of available incoming information will reach conscious awareness only if three conditions are met (Dehaene and Naccache 2001; Dehaene et al. 2006; Gaillard et al. 2009): the information must be detected by cortically represented systems (such as visual, auditory or memory processing), corresponding to "modules" or "local experts" (Newman et al. 1997); this information must then be "amplified" by a higher level of cortical processing dominated by prefrontal cortex; and lastly the information is then "broadcast" throughout a widely distributed network characterised by coherent neural activity within many different brain structures. In this model the vast majority of cognitive processes do not therefore reach conscious awareness; priority is given to stimuli that are new, threatening or highly relevant to an active goal or process (Newman et al. 1997). An important aspect is thus attentional resource allocation (Posner 1994). (The notion that attention to sensory information represents a key component of consciousness is not entirely recent, since this idea was indeed suggested by John Hughlings Jackson in the late nineteenth century, largely through his meticulous observation of epileptic seizures (Hogan and English 2012)).

Another modern concept is that of "binding", allowing for seamless integration of multifaceted information (Newman and Baars 1993; Engel and Singer 2001). The likely core neural basis for this model is the thalamo-cortico-thalamic circuit, with connections to specialised cortical regions, notably executive attentional processing in prefrontal regions and sensory processing in posterior regions. This might approximately correspond to the notion of "the front of the brain looking at the back of the brain" (Crick and Koch 2003). Under physiological conditions, consciousness representations are associated with transient synchrony between different cortical regions (Dehaene and Changeux 2011). For example, visual consciousness is associated with increased synchrony between areas extending outside the limits of the visual system (Gaillard, et al. 2009; Rodriguez, et al. 1999). The gamma band of neuronal activity (40–150 Hz) seems to be especially important for local binding (Hermann et al. 2004), while beta synchrony was found to be important for long-distance "dialogue" (Gaillard et al. 2009). Defining the activity of different components of the global workspace thus becomes a goal that might be partly reached through analysis of intracranial EEG data from seizures with LOC.

7.7 The Pathophysiological Role of Synchrony

Hypersynchrony within cortico-thalamic circuits occurs during periods of altered vigilance, having been extensively studied in normal sleep (Steriade 2000) and known to occur in unconscious states provoked by anaesthesia (Supp et al. 2011). In the awake state hypersynchrony of brain rhythms, particularly in the gamma band, appears to be a fundamental physiological mechanism of neural processing for cognitive tasks at all levels including top-down effects (Engel et al. 2001) and modulation of attentional and vigilance systems (Engel and Singer 2001). It has been suggested that hypersynchronisation may be a direct pathophysiological mechanism of altered consciousness, through reduction of the diverse repertoire of highly differentiated neural states normally present in the alert state (Tononi and Edelman 1998).

Epileptic seizures produce hypersynchronisation of a zone of neuronal tissue that may be very focal or conversely widespread, measurable with EEG. The clinical effect of this abnormal neuronal activity depends on many factors including the brain structures involved and both the frequency and duration of the discharge. It can be hypothesised that loss of consciousness will occur during a seizure only if a large enough volume of cortical tissue within critical areas is involved by a hypersynchronised discharge, which disrupts normal local functioning and/or deactivates distant structures necessary for regulation of attention, perception and vigilance. In terms of the global workspace model, cortico-thalamic pathways should be particularly affected, with certain cortical regions such as prefrontal and parietal cortex playing a specific role (Bartolomei and Naccache 2011). Partial seizures that produce altered consciousness through transient abnormal functioning of local brain areas could be seen as acting at the "modular" level of the global workspace (Newman et al. 1997). Seizures therefore present an interesting paradigm for looking at neuronal network changes underlying reversible alteration of conscious level, with intracranial EEG allowing investigation of both spatial (anatomical regions) and temporal (signal dynamic) aspects.

7.8 Exploring Thalamo-cortical Circuits with Intracranial EEG

Converging evidence from animal and human studies of absence seizures, generalised tonic-clonic seizures and partial seizures suggests that loss of consciousness in all these seizure types probably shares a similar anatomical basis involving fronto-parietal cortex and thalamus, since clear correlations in functional activity have been shown between these regions in association with altered conscious level (Blumenfeld et al. 2003). Previous studies using ictal SPECT and intracranial recording of temporal lobe seizures (Blumenfeld et al. 2004) have indicated increased thalamic activity associated with rapid discharge within temporal lobe structures, as well as decreased fronto-parietal activity. Fronto-parietal slow wave activity has been described in intracranial recording of temporal lobe seizures (Englot et al. 2010), suggested to represent an inhibitory effect indicating deactivation of cortical circuits, with perhaps a causal role in altered consciousness since

this was quantitively related to the presence of altered consciousness and resembled the slowing seen in sleep and coma states.

Using SEEG, our group has studied in vivo the relation between cortical seizure discharge and intra-thalamic EEG signal (Guye et al. 2006; Arthuis et al. 2009) during temporal lobe seizures producing altered conscious level. Twelve patients were retrospectively studied who underwent SEEG for presurgical evaluation of temporal lobe epilepsy, with at least one electrode within thalamic nuclei and at least one in parietal lobe as well as medial and lateral temporal lobe structures (Arthuis et al. 2009). Thirty-five seizures allowed for adequate analysis of ictal conscious level using the eight-point scale described above. Seizures with and without loss of consciousness were compared in terms of degree of broadband signal synchronisation (0.5–90 Hz) between temporal and extra-temporal structures, these having been pre-selected as regions of interest based on the global workspace hypothesis. Analysis was performed using nonlinear regression analysis (Pijn and Lopes Da Silva 1993; Wendling et al. 2003). A very clear difference emerged between the two groups: seizures with no loss of consciousness showed expected levels of synchronisation, in keeping with known dynamics of the epileptogenic zone (Bartolomei et al. 2004), limited to the local intra-temporal region, whereas seizures with altered consciousness showed marked long-distance synchronisation within extra-temporal structures, notably the thalamus, the posterior cingulate gyrus and the lateral parietal cortex (Fig. 7.1). In addition, the seizure-related, pathological synchronisation differed from the transient, physiological cortico-cortical synchronisation known to occur during normal cognitive processes, since during seizures thalamo-cortical synchronisation was abnormally stable and prolonged. Interestingly pathological synchronisation never occurred immediately at seizure onset but rather in the middle and late parts of the seizure, corresponding to the period after the end of the rapid temporal lobe discharge and also to the clinical appearance of altered contact. This tends to suggest that the structures underlying altered consciousness are not the same as those responsible for seizure production. In addition, the degree of LOC as measured by the clinical scale was statistically correlated to the degree of dependence between extra-temporal structures. This therefore provides very compelling evidence for the existence of a widely distributed network subserving consciousness, with a crucial role for thalamus and parietal structures, notably posterior cingulate gyrus. Frontal structures were not explored in this particular series because of clinical factors; if the results reported here support the hypothesis of a global workspace, then synchronisation should also logically exist within a parieto-frontal network. In particular it could be hypothesised that the degree of synchronisation between parietal and frontal structures during the seizure would influence the level of consciousness, which remains to be confirmed by future work.

Parietal seizures are less prevalent than temporal lobe seizures and rather more difficult to study since the clinical and electrophysiological features are less well characterised. However, the key role of parietal structures, especially posterior cingulate gyrus, in the global workspace model makes these an apposite subject for study. We retrospectively selected 29 seizures from 10 patients having undergone SEEG for presurgical evaluation of parietal epilepsy, in whom altered conscious level could be assessed using previously described parameters (Arthuis et al. 2009)

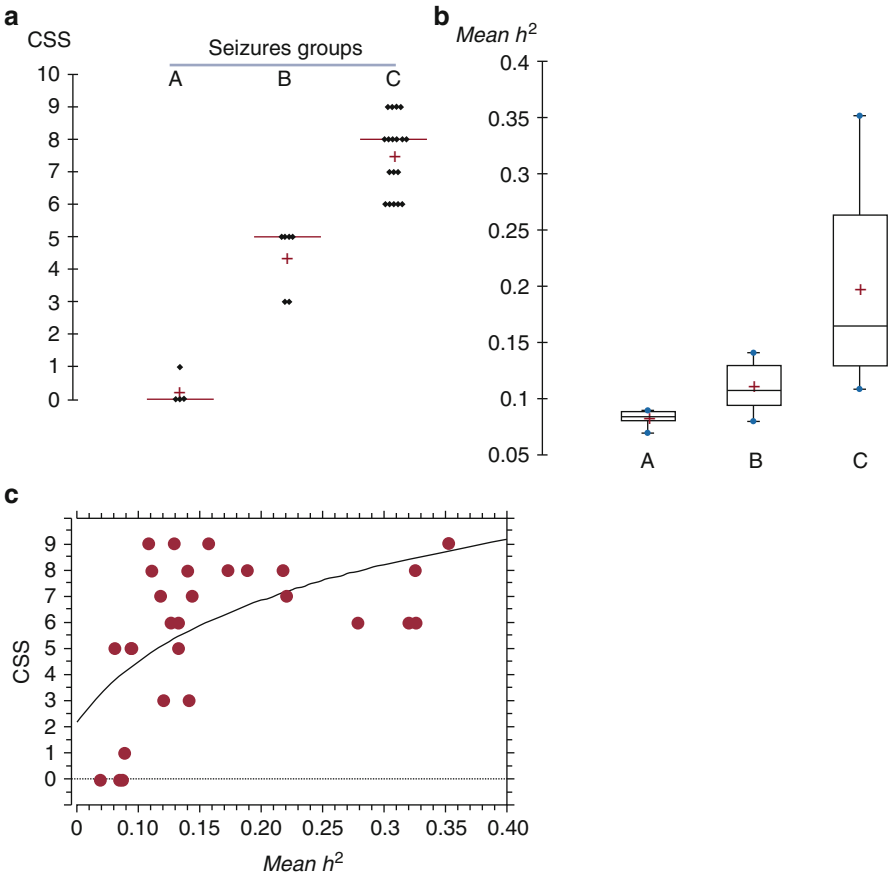

Fig. 7.2 Relationship between changes in SEEG synchrony and consciousness in parietal seizures. (**a**) Analysis of the loss of consciousness (LOC) using the CSS according to the three defined groups of seizures (*A* no LOC, *B* intermediate LOC, *C* complete LOC) in patients with parietal seizures. (**b**) Box plots representation of the correlation values (h^2 values averaged from all interactions) in these three groups of seizures. Values are maximal in group C and minimal in group A and disclosed intermediate levels in group B. (**c**) There is a significant relation between h^2 values and CSS scores during these seizures. This relation follows a sigmoid curve suggesting a nonlinear bistable function for consciousness (Adapted from Lambert et al. 2012)

and in whom electrodes were placed in at least one frontal and one parietal lobe region (Lambert et al. 2012). Based on the degree of altered consciousness as measured by the Consciousness Seizure Scale (CSS) (Arthuis et al. 2009), the patients could be divided into three groups (no alteration (CSS <1), partial (CSS 2–5) or maximal LOC (CSS >6)). Using an averaged value of synchrony (h^2) compared across regions for each seizures, similar to the method used in previous work (Arthuis et al. 2009), a significant difference was seen between the three groups: the greater the level of long-distance synchrony, the greater the degree of altered consciousness

(Fig. 7.2). In addition significant differences were seen when comparing averaged synchrony across different regions with consciousness score: frontal lobe ($p = 0.0009$) and lateral parietal lobe ($p = 0.01$) showed more significant correlation with consciousness score than medial parietal lobe ($p = 0.04$) and temporal lobe regions ($p =$ NS). Some weaknesses of the study are due to the clinical nature of the explored cases, since only a limited number of frontal lobe structures and contralateral regions were explored according to epileptological indications; data from thalamic structures were not available in this series. In addition it was not possible to distinguish the temporal relation between the onset of LOC and the level of synchronisation, since in these parietal seizures, conscious level appeared to be affected more or less at seizure onset, as far as could be determined by clinical examination. Nevertheless, this study contributes additional evidence for a causal role of abnormal long-distance synchronisation, especially within parieto-frontal networks in seizure-related LOC.

Frontal seizures present even more difficulties for analysis due to characteristically short seizure duration, rapid evolution of clinical signs (often making clinical testing of consciousness difficult) and rapid and widespread propagation. However, initial analysis of a series of over 50 patients with frontal lobe seizures explored by SEEG in our centre indicates a difference between frontal seizures predominantly affecting precentral and premotor regions and those predominantly affecting prefrontal regions, since prefrontal seizures always manifested early altered consciousness as a semiological feature (unpublished data). This is in keeping with previous observations that primary cortex appears not to be functionally affected during altered consciousness (Blumenfeld et al. 2004; Gotman et al. 2005).

Conclusion

Intracranial recording of epileptic seizures represents an important tool for studying pathophysiological mechanisms of altered consciousness. The role of pathological synchronisation within widespread networks, particularly thalamo-cortical and fronto-parietal circuits, has been confirmed by recent studies using SEEG, in line with the global workspace hypothesis. Future work will include better characterisation of the role of specific frontal and parietal regions within these networks, with some evidence in favour of preferential involvement of lateral parietal and prefrontal structures.

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Part III

Brain Imaging and Alterations of Consciousness in Coma, Sleep and Anesthesia

Steven Laureys

Neuroimaging of Consciousness in the Vegetative and Minimally Conscious States

8

Caroline Schnakers, Steven Laureys, and Melanie Boly

Abstract

Differentiating reflex from voluntary activity is one of the most challenging task facing clinicians involved in the care of patients presenting disorders of consciousness such as vegetative and minimally conscious states. Behavioral assessment is considered as the main way to detect signs of consciousness but may often be complicated by verbal and motor impairments. As misdiagnosis can lead to serious consequences, especially, in terms of pain treatment and end-of-life decision-making, objective paramedical tools have to be used to assess remnant brain functioning and detect brain activity linked to consciousness. We therefore here review the current state of clinical behavioral assessment and functional neuroimaging paradigms as these may offer complementary information to bedside examination findings.

Differentiating reflex from voluntary activity is one of the most challenging tasks facing clinicians involved in the care of severely brain-injured patients. Behavioral assessment is considered as the main way to detect signs of consciousness and, hence, to determine diagnosis. However, behavioral assessment is complicated by the presence of motor impairments, tracheostomy, high fluctuations in vigilance, or ambiguous and rapidly habituated responses. Because of these compromising factors, accurate diagnosis can rapidly become difficult to make. As misdiagnosis can lead to serious consequences, especially, in terms of pain treatment and end-of-life decision-making, additional tools have to be used to assess remnant brain functioning and detect brain activity linked to consciousness. Functional neuroimaging techniques such as positron-emission tomography (PET) and functional magnetic

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_8,

resonance imaging (fMRI) can provide an objective index of brain activity at rest and during active cognitive processing. These techniques are well equipped to identify covert cognitive processes in patients who are otherwise incapable of intelligible or sustained behavioral responses and offer complementary information to bedside examination findings. In this context, we here review the current state of clinical behavioral assessment and functional neuroimaging studies in patients presenting disorders of consciousness such as vegetative and minimally conscious states.

8.1 Differentiating Disorders of Consciousness

8.1.1 Coma

Plum and Posner defined coma as a pathological state marked by severe and prolonged dysfunction of vigilance and consciousness (Plum and Posner 1966). This state results from global brain dysfunction (most often due to diffuse axonal injury following traumatic brain injury) or from a lesion limited to brainstem structures involving the reticular activating system. The distinguishing feature of coma is the continuous absence of eye-opening (spontaneously or following stimulation). There is no evidence of visual fixation or pursuit, even after manual eye-opening. No voluntary motor or verbal (even vocalization) response is observed and behaviors are limited to reflex activity only. This state must last at least 1 h to be differentiated from a transient state such as syncope, acute confusion, or delirium. Prolonged coma is rare as this condition usually resolves within 2–4 weeks, most often evolving into a vegetative state or a minimally conscious state (The Multi-Society Task Force on PVS 1994).

8.1.2 Vegetative State

The term "vegetative" indicates relatively preserved physiological functions (e.g., cardiac or respiratory) without clear signs of consciousness (Jennett 2005). In a sense, the body works without the mind. The vegetative state (VS) often results from injury involving the white matter or from bilateral lesions in the thalamus in the presence of preserved brainstem, hypothalamus, and basal ganglia. VS patients open their eyes spontaneously or in response to stimulation, but they only show reflex behaviors, unrelated to the environment (The Multi-Society Task Force on PVS 1994). Behaviorally, there is no response to verbal order, and although moaning may occur, there is no intelligible speech. Infrequently, behaviors such as inappropriate smiling, crying or grimacing, and even randomly produced single words have been reported in patients diagnosed with VS (Working Party of the Royal College of Physicians 2003). When this state lasts 1 month or more, the term "persistent VS" may be applied. When there is no recovery after a specified period (3 months for nontraumatic etiologies or 1 year for traumatic etiology), this state can

be declared permanent, and only then, the ethical and legal issues around treatment withdrawal can be discussed. Note that, given the negative connotation of the term "vegetative state," the European Task Force on Disorders of Consciousness has recently proposed to use the term "unresponsive wakefulness syndrome" rather than "vegetative state" (Laureys et al. 2010).

8.1.3 Minimally Conscious State

The minimally conscious state (MCS) is characterized by the presence of inconsistent but clearly discernible behavioral signs of consciousness (Giacino et al. 2002). Command-following, recognizable yes-no responses, and intelligible verbalizations represent the clearest evidence of conscious awareness. In fact, recent findings tend to subcategorize the MCS in two clinical entities, MCS+ and MCS−, based on language production and comprehension, as different functbuional neuroanatomy was observed (Bruno et al. 2012a). In contrast to patients in VS who may display random episodes of crying or smiling, in MCS, these behaviors occur in contingent relation to appropriate environmental triggers. Reemergence of visual pursuit appears to be an early behavioral marker of the transition from VS to MCS. Patients may grasp and manipulate objects even though inappropriately. Although behavior may fluctuate across examinations, at least one of these signs must be replicated within a given examination to meet the diagnostic criteria for MCS. Regarding prognosis, the probability of functional recovery at 1 year is more favorable relative to VS for either traumatic or nontraumatic etiology (Bruno et al. 2012b. Some patients in MCS progress slowly, while others remain in this condition permanently. Unlike VS, clearly defined temporal parameters for recovery do not yet exist, and there is wide heterogeneity in the degree of functional recovery ultimately attained. Emergence from MCS occurs when the patient is able to reliably communicate through verbal or gestural yes-no responses or is able to demonstrate the use of two or more objects (e.g., hairbrush, cup) in a functional manner on two consecutive assessments (Giacino et al. 2002).

Two additional conditions characterized by behavioral unresponsiveness must be differentiated from clinical entities presented above. In the first, consciousness is retained, while in the second, it is permanently lost.

8.1.4 Locked-In Syndrome

The locked-in syndrome (LIS) is marked by tetraplegia and anarthria in the setting of near-normal to normal cognitive function. This state is caused by a lesion involving the ventral pons and, in 60 % of cases, is due to basilar thrombosis. Because patients with LIS have spontaneous eye-openings, but are unable to speak or move the extremities, this state can be confused with VS because of the confluence of behavioral signs. Classic LIS consists of complete paralysis of the orobuccal musculature and all four extremities; however, vertical eyes movements are spared, allowing

nonverbal communication through directional gaze. Perceptual functions are also usually spared as ascending corticospinal axons remain intact (American Congress of Rehabilitation Medicine 1995). Bauer has described multiple varieties of LIS, including the incomplete form in which there is residual motor activity (frequently, finger or head movements) and total LIS, in which there is complete immobility including both horizontal and vertical eye movements (Bauer et al. 1979). Data on life expectancy suggest that some patients with LIS live 12 or more years post-onset. Surprisingly, chronic LIS patients rate their quality of life similarly to the healthy population. In the absence of other structural or functional brain abnormalities, patients with LIS are generally able to make independent decisions and communicate their preferences (Laureys et al. 2005b).

8.1.5 Brain Death

The definition of death has evolved from cardiorespiratory-centered diagnosis to neurocentric diagnosis. Besides the presence of apnea and the lack of any voluntary or oriented behavioral responses, in UK, the diagnostic criteria for brain death are limited to the absence of brainstem function, whereas, in USA, brain death is considered as a condition in which there is "irreversible unconsciousness with complete loss of brain function" (Wijdicks 2012). This last definition is accepted in most countries around the world. Generally, an electroencephalogram is completed to demonstrate an isoelectrical signal reflecting the absence of electrical brain activity. Transcranial Doppler studies reveal the absence of cerebral blood flow. After excluding brain dysfunction due to drug toxicity or hyperthermia, a final diagnosis can be established after 6–24 h. Note nevertheless that the US definition of brain death is still debated as it may lead to the use of derivative terms such as higher brain death (cortical structures) which would include permanent vegetative state and would facilitate organ transplantation (Laureys 2005a).

8.2 Bedside Consciousness Assessment

One of the few ways we have to differentiate these patients from conscious patients is to observe their spontaneous behaviors and their reactions to stimuli occurring in their environment. This behavioral assessment requests thorough expertise on behalf of the clinician. It also depends on the physical and mental capacities (particularly, the vigilance level) of the patient at the time of assessment. Missing signs of consciousness is not a rare fact and diagnostic errors are frequent (i.e., around 40 %) (Schnakers et al. 2009b). The diagnosis is however crucial. It influences the way the patient's care will be oriented and the way end-of-life decisions will be considered with the patient's family. Developing valid and sensitive behavioral scales to detect the presence of signs of consciousness, even subtle, therefore represents a real challenge. In this section, we briefly review commonly used behavioral instruments for the assessment of consciousness.

8.2.1 The Glasgow Coma Scale (GCS)

The GCS (Teasdale and Jennett 1974) remains the most widely used tool in traumatic and acute care settings. The GCS was the first validated rating scale developed to monitor levels of consciousness in the intensive care unit. This scale is relatively brief and can be easily incorporated into routine clinical care. It includes three subscales that address arousal level, motor function, and verbal abilities. Subscale scores are added and yield a total score ranging from 3 to 15. The GCS has been extensively investigated for its prognostic value. Despite its widespread use, the GCS has been criticized for variable inter-rater agreement and problems deriving scores in patients with ocular trauma, tracheostomy, or ventilatory support (McNett 2007).

8.2.2 The Full Outline of Unresponsiveness Scale (FOUR)

The FOUR was recently developed to replace the GCS to assess severely brain-injured patients in intensive care (Wijdicks et al. 2005). The scale includes four subscales assessing motor and ocular responses, brainstem reflexes, and breathing. The total score ranges from 0 to 16. Unlike the GCS, the FOUR does not assess verbal functions to accommodate the high number of intubated patients in intensive care. A score of 0 on the FOUR assumes the absence of brainstem reflexes and breathing and, therefore, helps to diagnose brain death. The scale also monitors recovery of autonomic functions and tracks emergence from VS. The FOUR is specifically designed to detect patients in a locked-in syndrome as it uses oculomotor commands that detect vertical eye movements and eye blinks, both being preserved in LIS.

8.2.3 The Wessex Head Injury Matrix (WHIM)

The WHIM (Shiel et al. 2000) was developed to capture changes in patients in VS until emergence from post-traumatic amnesia. This tool is particularly sensitive to detect changes in patients in MCS not captured by traditional scales such as the GCS. Shiel et al. longitudinally followed 97 severely brain-injured patients recovering from coma to create the WHIM. The 62 items were ordered according to the mean sequence of recovery observed in these patients; they assess arousal level and concentration, visual consciousness (i.e., visual pursuit), communication, cognition (i.e., memory and spatiotemporal orientation), and social behaviors. The WHIM score represents the rank of the most complex behavior observed.

8.2.4 The JFK Coma Recovery Scale (CRS-R)

The CRS-R was originally developed by investigators from the JFK Johnson Rehabilitation Institute in 1991. The scale was revised and published in 2004 as the JFK Coma Recovery Scale-Revised (CRS-R) (Giacino et al. 2004). The purpose of

the CRS-R is to assist with differential diagnosis, prognostic assessment, and treatment planning in patients with disorders of consciousness. The scale consists of 23 items that comprise six subscales addressing auditory, visual, motor, oromotor, communication, and arousal functions. CRS-R subscales are comprised of hierarchically arranged items associated with brainstem, subcortical, and cortical processes. The lowest item on each subscale represents reflexive activity, while the highest items represent cognitively mediated behaviors. Scoring is standardized and based on the presence or absence of operationally defined behavioral responses to specific sensory stimuli. Psychometric studies indicate that the CRS-R meets high standards for measurement and evaluation tools designed for use in interdisciplinary medical rehabilitation. The CRS-R can be administered reliably by trained examiners and produces reasonably stable scores over repeated assessments. Validity analyses have shown that the CRS-R is capable of discriminating patients in MCS from those in VS (even better than the GCS, the FOUR and the WHIM) which is of critical importance in establishing prognosis and formulating treatment interventions (Seel et al. 2010).

8.2.5 Pain Assessment: The Nociception Coma Scale

Patients recovering from coma are unable to communicate their feelings and their perception of pain. It is therefore important to develop sensitive instruments to assess pain perception in these patients. Even if scales were developed to assess different types of noncommunicative populations (such as demented elderly and newborns), none of these are adapted to detect pain in severely brain-injured patients. In this context, the Nociception Coma Scale (NCS) was recently developed (Schnakers et al. 2010). This scale includes the observation of motor, verbal, and visual responses as well as facial expression. The total score varies from 0 to 12. A validation study of the NCS was performed by observing the responses of 48 VS and MCS patients following a nociceptive stimulation (nail pressure). Results showed a good inter-rater agreement and concurrent validity between NCS and other pain scales validated for demented elderly patients and newborns. However, in contrast to these scales, the total score of the NCS significantly differed according to the level of consciousness. Higher scores were observed in MCS vs. VS patients, suggesting that the scale is particularly adapted to assess pain in patients recovering from coma. The NCS hence represents a valid tool adapted for detecting pain behaviors in severely brain-injured patients (Schnakers et al. 2012).

8.3 Behavioral Assessment and Diagnostic Errors

Differentiating between MCS and VS can be challenging as voluntary and reflexive behaviors can be difficult to distinguish and subtle signs of consciousness may be missed. The recent development of diagnostic criteria for MCS (Giacino et al. 2002)

would reasonably be expected to reduce the incidence of misdiagnosis relative to the rates reported before these criteria were established (Childs et al. 1993; Andrews et al. 1996). However, a recent study found that 41 % of patients believed to be in VS were misdiagnosed. This study also found that the majority of cases with an uncertain diagnosis were in MCS (89 %), not in VS. Another 10 % diagnosed with MCS had actually emerged from this condition (Schnakers et al. 2009b).

The high rate of misdiagnosis reported by Schnakers and collaborators likely reflects different sources of variance. Variance in diagnostic accuracy may result from biases contributed by the examiner, patient, and environment. Examiner error may arise when the range of behaviors sampled is too narrow, response-time windows are over- or under-inclusive, criteria for judging purposeful responses are poorly defined, and examinations are conducted too infrequently to capture the full range of behavioral fluctuation. The use of standardized rating scales offers some protection from these errors, although failure to adhere to specific administration and scoring guidelines may jeopardize diagnostic accuracy. The second source of variance concerns the patient. Fluctuations in arousal level, fatigue, subclinical seizure activity, occult illness, pain, cortical sensory deficits (e.g., cortical blindness/deafness), motor impairment (e.g., generalized hypotonus, spasticity, or paralysis), or cognitive disturbance (e.g., aphasia, apraxia, agnosia) constitute a bias to the behavioral assessment and therefore decrease the probability to observe signs of consciousness. Finally, the environment in which the patient is evaluated may bias assessment findings. Paralytic and sedating medications, restricted range of movement stemming from restraints and immobilization techniques, poor positioning, and excessive ambient noise/heat/light can decrease or distort voluntary behavioral responses.

Some sources of error can be avoided, but this is not always possible or within the examiner's control. This is particularly troubling as clinical management, from treatment of pain to end-of-life decision-making, often depends on behavioral observations. To address this problem, neuroimaging procedures have begun to assume an adjunctive role in the diagnostic assessment of patients with disorders of consciousness.

8.4 Functional Neuroimaging Studies in MCS and VS Patients

While the distinction between MCS and VS at the bedside is still challenging, there is considerable evidence for the existence of major differences in brain function between these patient populations (Fig. 8.1). Positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies showed that MCS patients present extended cerebral processing of external stimuli such as noxious (Boly et al. 2008) or self-related auditory stimuli (Qin et al. 2010). Resting-state fMRI studies showed that MCS patients also display preserved functional connectivity in a self-related associative network, the default network (Soddu et al. 2012; Vanhaudenhuyse et al. 2010). Recent structural studies revealed that brain white matter integrity and gray matter volume (Fernandez-Espejo et al. 2010, 2011) are

also more preserved in MCS as compared to VS – corresponding to the better prognosis observed in MCS (Luaute et al. 2010).

Recently, functional and structural MRI studies have also recently been used to identify prognostic markers in DOC patients. Several fMRI studies have identified a correlation between the extent of activation in individual brain-damaged patients, for example, in response to the patient's own name, and a favorable clinical outcome (Coleman et al. 2009; Di et al. 2007). White matter integrity in various subcortical and brainstem white matter regions has also been correlated with patients' outcome (Perlbarg et al. 2009). In VS, there can exist variations depending on the etiology (Newcombe et al. 2010): both traumatic and nontraumatic VS patients display decreased supratentorial subcortical white matter integrity, but only trau-

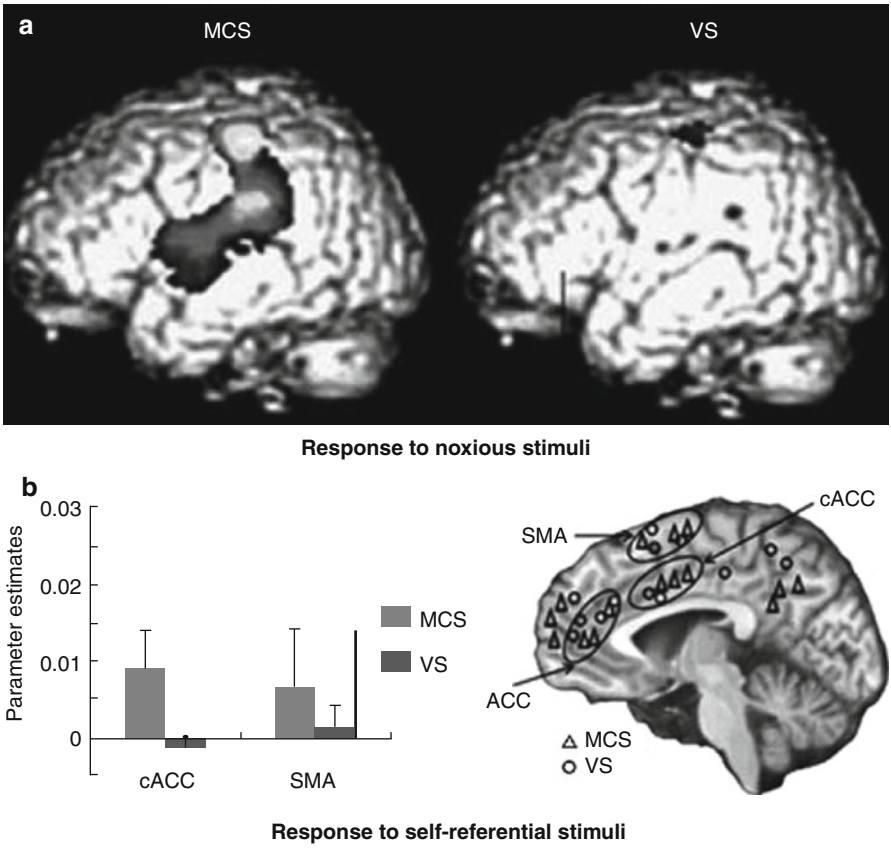

Fig. 8.1 MCS patients show more preserved brain response to noxious (**a**) or self-related external stimuli (**b**), greater resting-state default network connectivity (**c**), and white matter structural integrity (**d**) as compared to vegetative state patient populations. *aACC* anterior part of anterior cingulate cortex, *cACC* caudal part of anterior cingulate cortex, *MCS* minimally conscious state, *SMA* supplementary motor area, *VS* vegetative state (Adapted with permission from Boly 2011)

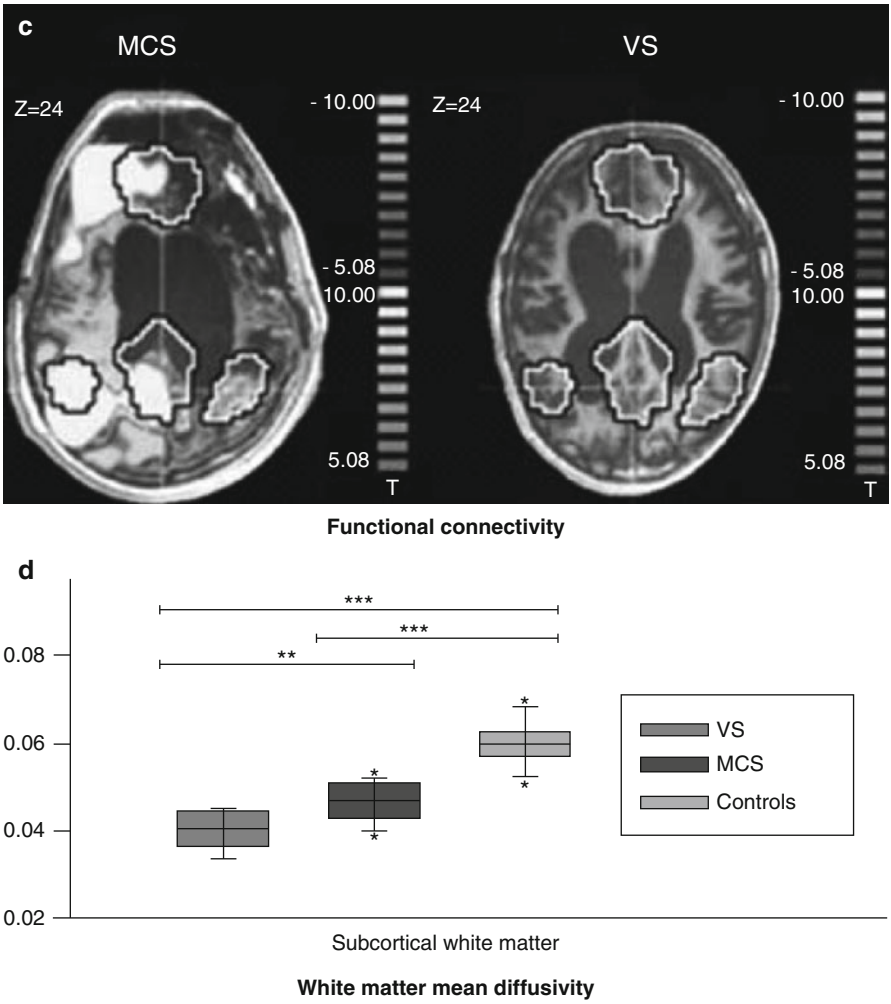

Fig. 8.1 (continued)

matic VS patients show lesions in the brainstem. In addition, the patients' fMRI activations in response to linguistic stimulation correlate with supratentorial white matter integrity, but not to brainstem lesions (Newcombe et al. 2010). These data provide a first link between structural lesions and functional impairment in individual brain-damaged patients, both showing some correlation with the patients' prognosis.

Finally, there have been recent attempts to automatically classify patients' neuroimaging findings according to their level of consciousness, without requiring an examiner's intervention. Multivariate classification of PET scan data could differentiate VS from LIS patients at the individual level (Phillips et al. 2011). Additionally, new resting-state fMRI data analysis procedures (Soddu et al. 2012) may provide an

observer-independent method to classify brain connectivity patterns at the single-subject level. These studies have however to be further validated on larger populations of patients, involving not only LIS and VS but also MCS, before their clinical utility can be fully determined.

8.4.1 Interpreting Neuroimaging Results at the Single-Subject Level

At the clinical bedside, the only way we can infer the presence or absence of consciousness is by observing the patients' responses in various controlled examination conditions. Any clinical assessment of the level of consciousness therefore equates awareness with some form of motor responsiveness. Importantly, decreased bedside motor responses could also be observed due to the patients' motor impairment, rather than due to an altered level of consciousness. In fact, motor impairment can be expected to be relatively frequent in severely brain-damaged patients. fMRI- and EEG-based active paradigms search for a response to command using brain activity rather than a bedside motor response, for consciousness diagnosis. Recently, such active paradigm studies confirmed that some VS patients can retain some degree of awareness (Owen et al. 2006) or even communicate (Monti et al. 2010). Similarly, responses to command using EEG-based paradigms have been reported in a rare case of total locked-in syndrome (Schnakers et al. 2009a) and in several clinically VS patients (Cruse et al. 2011). These findings suggest that even gold-standard bedside examination can be insufficient to sensitively detect consciousness in DOC patients. These studies also show that all VS patients cannot anymore be considered as totally lacking awareness. This fact probed clinical experts to suggest renaming VS as "unresponsive wakefulness syndrome" (Laureys et al. 2010). It is important to notice that to date, there is still a true need of further validation and inter-rater variability assessment for each of these active paradigm techniques, before they can be considered to deserve a more widespread clinical use (Nachev and Hacker 2010; Rafii and Brewer 2010). Further research should also aim at developing efficient brain-computer interfaces; in order to ensure a proper follow-up in the patients, a capacity of communication is evidenced. Such communication tools would also allow evaluating more precisely which cognitive functions are genuinely preserved in each individual patient and better guide rehabilitation needs.

Even if they are promising techniques, fMRI- or EEG-based active paradigms cannot, however, be considered sufficient on their own to replace the bedside examination of DOC patients. Indeed, Bardin et al. (Bardin et al. 2011) investigated fMRI-based response to command and communication in six severely brain-damaged patients and compared neuroimaging findings to bedside behavior. In this study, brain-injured subjects dissociated bedside and fMRI imaging-based, command-following and communication capabilities in various ways. In particular, fMRI-based communication could not be established with a locked-in syndrome patient, which was reliably communicating at the bedside, even if the patient reported after the experiment having actually tried to perform the task. This result illustrates that fMRI active paradigms are intrinsically

prone to false-negative results at the single-subject level. A same risk of false negative has been reported for EEG-based active paradigm studies (Cruse et al. 2011). In fact, false-negative results in these studies can also appear due to various factors other than impaired consciousness, though also linked to the patients' clinical state (Rafii and Brewer 2010), e.g., the presence of aphasia, neglect, or merely a lack of will of collaboration from the patient's side. In fact, cohort studies show that results come back negative in about 90 % cases, when an active fMRI paradigm is performed in individual MCS and VS (Monti et al. 2010). If a negative result comes out of these tests, one must thus be very cautious in its interpretation.

In summary, current evidence suggests that while being certainly complementary, both clinical examination and fMRI/EEG-based active paradigms present the risk to miss the presence of consciousness in individual brain-damaged patients. Assessing the presence or absence of awareness by searching for a response to command is also challenging because it requires the subjects' collaboration, which is often deficient in DOC patients. Ideally, in the search for a generic paraclinical diagnostic marker of consciousness, one should design a test which does not require the patients' volitional collaboration – in this context, neuroimaging "passive paradigms" are very promising. We will discuss them in the next section.

8.4.2 Towards the Use of Neuroimaging Paradigms as Diagnostic Tools

Compared to active paradigms, passive paradigms have advantage of not requiring the patients' collaboration. However, as long as there is no definite certainty concerning neural correlates of consciousness (NCC), results obtained using these paradigms can be difficult to interpret (Coleman et al. 2009; Fischer et al. 2010; Rodriguez Moreno et al. 2010). Research aiming at identifying NCC faces the problem that these NCC can vary depending on the clinical condition generating unconsciousness. Integrating the different conditions all together helps identifying generic mechanisms for a link between conscious perception and the brain. For example, a number of studies (Boly et al. 2009b; Silva et al. 2010; Soddu et al. 2012; Vanhaudenhuyse et al. 2010; Zhou et al. 2011) have shown that coma and VS states are characterized by decreased large-scale cerebral connectivity, in proportion to the patients' impairment of consciousness. In contrast, epileptic-induced unconsciousness is accompanied by a diffuse increase in connectivity between distant brain areas (Arthuis et al. 2009; Guye et al. 2006). Taking these two conditions together, consciousness cannot be merely considered to be proportional to the strength of connectivity in the human brain. It could rather be suggested that consciousness requires both functional integration and preserved information capacity in the brain (i.e., some specificity of each brain area performing its function) (Boly et al. 2009a; Tononi 2008) – both conditions being provided by balanced connectivity patterns. Conceptual theories of consciousness such as global workspace (Dehaene et al. 2006) or information integration (Tononi 2008) frameworks are currently developed to give a more precise mechanistic account of these observations. Working on such

theoretical frameworks in parallel to experimental data acquisitions helps precising the links between consciousness and the brain. This should allow in the future the design of practical neuroimaging markers able to optimally assess the presence of consciousness in various patients' populations.

A general observation in unconscious conditions is a privileged impairment of higher-order frontoparietal cortices activity, contrasted to a relative preservation of lower-level sensory areas (Boveroux et al. 2010; Bruno et al. 2011). This observation can be linked to findings of recent functional (Buckner et al. 2009) or structural (Hagmann et al. 2008) studies pointing out frontoparietal areas as the most connected regions of the normal human brain, likely being critical hubs on the brain's avenues to integrate information. Impairing the function of major hubs of cerebral connectivity likely has dramatic consequences on global brain functions, such as the ability to generate consciousness. In VS and MCS patients, a major disruption of brain hub connectivity likely hinders the possibility for normal conscious perception.

For future studies, assessing both integration and information content in the activity of the patients' frontoparietal cortices constitutes a promising theoretically grounded marker for detecting conscious perception. Techniques such as transcranial magnetic stimulation combined with high-density EEG (Ferrarelli et al. 2010; Massimini et al. 2009; Rosanova et al. 2012) nowadays allow an exhaustive study of brain dynamics. Integrating passive and active neuroimaging paradigms with bedside findings will also help to further improve our understanding of the significance of brain activity patterns in DOC patients and of their residual ability for various cognitive functions.

Conclusion

Both clinical and neuroimaging studies recently allowed considerable progress in our understanding of brain function in VS and MCS. Future validation work is still needed before any attempt to use neuroimaging studies as a potential consciousness diagnostic tool. On a long-term basis, a combination of clinical examination and neuroimaging will probably be advised in order to fully evaluate noncommunicative brain-damaged patients' conscious states. Up to now, behavioral assessment however remains the gold standard.

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Sleep and Consciousness

9

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Abstract

Sleep offers a unique opportunity to relate changes in brain activity to changes in consciousness. Indeed, if it were not for sleep, when consciousness fades in and out on a regular basis, it might be hard to imagine that consciousness is not a given but depends somehow on the way our brain is functioning. At the same time as changes in consciousness occur, brain activity undergoes major changes through an orderly progression of sleep stages, which can be identified by recording the electroencephalogram (EEG), eye movements (EOG), and muscle tone (EMG). Within each sleep stage, there are frequent, short-lasting electrophysiological phenomena, such as slow oscillations and spindles representing moments at which brain activity undergoes important fluctuations. There are also orderly spatial changes in the activation of many brain regions, as indicated by imaging studies. Importantly, similar brain activities occur in animals, and this has spearheaded detailed studies of the underlying neural mechanisms.

This chapter will first examine how sleep is traditionally subdivided into different stages that alternate in the course of the night. It will then review the dreaming events we experience across sleep. Next, it will consider the neural

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_9, © Springer-Verlag Berlin Heidelberg 2013

correlates of sleep and wakefulness – the brain centers that determine whether we are asleep or awake and the mechanisms giving rise to the electrophysiological activities across sleep. It will review functional imaging studies of human sleep including research of regional metabolism using positron emission tomography (PET), functional magnetic resonance imaging (fMRI) correlates of spontaneous brain rhythms, as well as resting-state functional connectivity studies. It will review recent experiments combining transcranial magnetic stimulation (TMS) and EEG that allow perturbing directly cortical neurons and recording with millisecond resolution the response across the cortical mantle in sleep and wakefulness. It will then discuss recent intracranial studies in humans that have provided evidence for the local occurrence of sleep oscillations in both the sleeping and the waking brain. The demonstration of local sleep changes the traditional view of sleep as a monolithic, all-or-none behavioral state and suggests that mixed and dissociated states are not just found in pathological conditions. This chapter ends with some open questions: when and why do we lose consciousness in sleep? Is consciousness in sleep (dreaming) more akin to perception (bottom-up) or imagination (top-down)? And why is sleep consciousness largely disconnected from the external environment?

9.1 Sleep Stages and Cycles

In the course of the night, the EEG, EOG, and EMG patterns undergo coordinated changes that are traditionally used to distinguish among different sleep stages (Fig. 9.1a).

9.1.1 Wakefulness

During wakefulness, the EEG is characterized by waves of low amplitude and high frequency. This kind of EEG pattern is known as low-voltage fast activity or activated. When eyes close in preparation for sleep, EEG alpha activity (8–13 Hz) becomes prominent, particularly in occipital regions. Such alpha activity is thought to correspond to an "idling" rhythm in visual areas. The waking EOG reveals frequent voluntary eye movements and eye blinks. The EMG reveals tonic muscle activity with additional phasic activity related to voluntary movements.

9.1.2 Falling Asleep: Stage N1

Falling asleep is a gradual phenomenon of progressive disconnection from the environment. Sleep is usually entered through a transitional state, stage 1, characterized by loss of alpha activity and the appearance of a low-voltage mixed-frequency EEG pattern with prominent theta activity (3–7 Hz). Eye movements become slow and rolling, and muscle tone relaxes. Although there is decreased

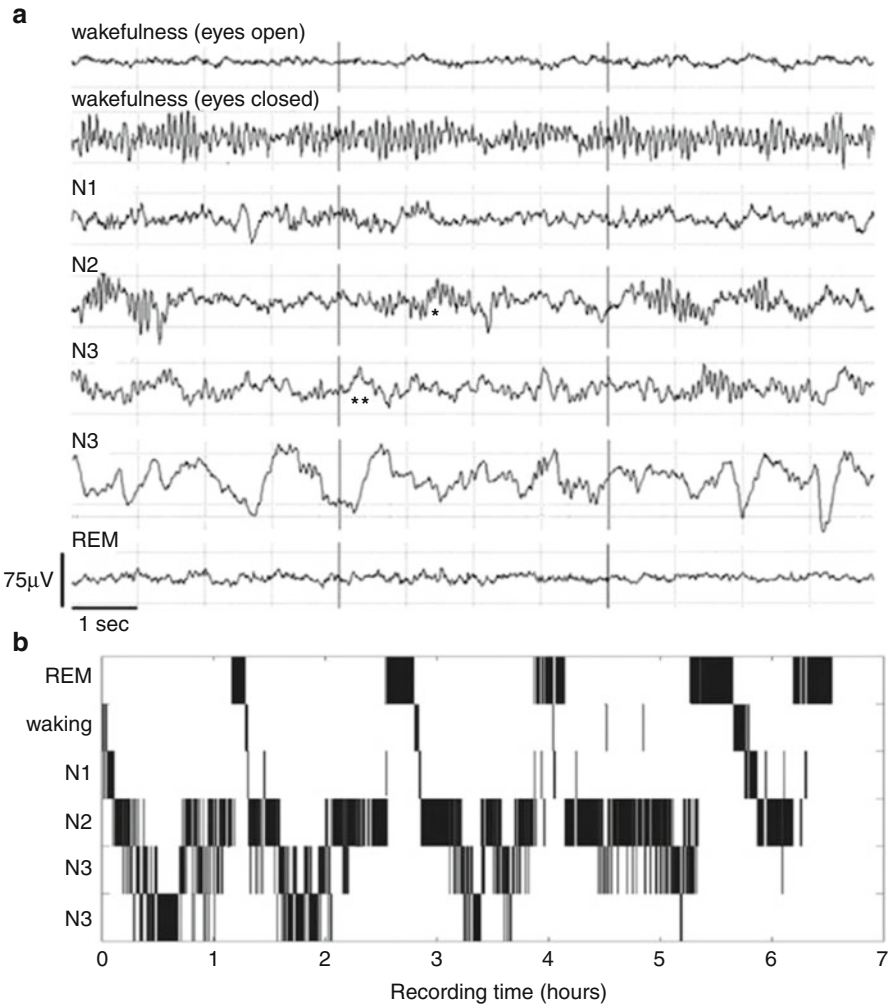


Fig. 9.1 Sleep stages and cycles. (**a**) EEG wave form during wakefulness with eyes open and closed and during the different stages of sleep. (**b**) Average times and sequences of sleep cycles during the night

awareness of sensory stimuli, a subject in stage N1 may deny that he was asleep. Motor activity may persist for a number of seconds during stage N1. Occasionally individuals experience sudden muscle contractions (hypnic jerks), sometimes accompanied by a sense of falling and dreamlike imagery. Individuals deprived of sleep often have "microsleep" episodes that consist of brief (5–10 s) bouts of stage 1 sleep; these episodes can have serious consequences in situations that demand constant attention, such as driving a car.

Sleep is traditionally categorized into non-rapid eye movement (NREM) sleep and REM sleep. Human NREM sleep, in turn, is divided into stages N2 and N3.

9.1.3 NREM Sleep: Stage N2

After a few minutes in stage N1, people usually progress to stage N2 sleep. Stage N2 is heralded in the EEG by the appearance of K-complexes and sleep spindles, which are especially evident over central regions. K-complexes are made up of a high-amplitude negative sharp wave followed by a positive slow wave and are often triggered by external stimuli. Sleep spindles are waxing and waning oscillations at around 12–15 Hz that last about 1 s and occur 5–10 times a minute. Eye movements and muscle tone are much reduced. Stage N2 qualifies fully as sleep because people are partially disconnected from the environment, meaning that they do not respond to the events around them – their arousal threshold is increased. If stimuli are strong enough to wake them up, people in stage N2 will confirm that they were asleep.

9.1.4 NREM Sleep: Stage N3

Stage N2 is followed, especially at the beginning of the night, by a period called stage N3, during which the EEG shows prominent slow waves in the delta range (<2 Hz, >75 μV in humans). Eye movements cease during stage N3 and EMG activity decreases further. Stage N3 is also referred to as slow-wave sleep (SWS), delta sleep, or deep sleep, since the threshold for arousal is higher than in stage N2. The process of awakening from slow-wave sleep is drawn out, and subjects often remain confused for some time.

9.1.5 REM Sleep

After deepening through stages N2 to N3, NREM sleep lightens and returns to stage N2, after which the sleeper enters REM sleep (Aserinsky and Kleitman 1953; Dement and Kleitman 1957a), also referred to as paradoxical sleep (Jouvet 1962, 1965, 1998) because the EEG during REM sleep is similar to the activated EEG of waking or of stage N1. Indeed, the EEG of REM sleep is characterized by low-voltage fast activity, often with increased power in the theta band (3–7 Hz). REM sleep is not subdivided into stages, but is rather described in terms of tonic and phasic components. Tonic aspects of REM sleep include the activated EEG and a generalized loss of muscle tone, except for the extraocular muscles and the diaphragm. REM sleep is also accompanied by penile erections. Phasic features of REM include irregular bursts of rapid eye movements and muscle twitches. Behaviorally, REM sleep is deep sleep, with an arousal threshold that is nearly as high as in slow-wave sleep.

9.1.6 The Sleep Cycle

The succession of NREM sleep stages followed by an episode of REM sleep is called a sleep cycle and lasts approximately 90–110 min in humans. As shown in Fig. 9.1b, there are a total of 4–5 cycles every night. Slow-wave sleep is prominent

early in the night, especially during the first sleep cycle, and diminishes as the night progresses. As slow-wave sleep wanes, periods of REM sleep lengthen and show greater phasic activity. The proportion of time spent in each stage and the pattern of stages across the night is fairly consistent in normal adults. A healthy young adult will typically spend about 5 % of the sleep period in stage N1, about 50 % in stage N2, 20–25 % in stage N3 (slow-wave sleep), and 20–25 % in REM sleep.

9.1.7 Sleep During the Life Span

Sleep patterns change markedly across the life span (Carskadon et al. 2002; Peirano et al. 2003; Carskadon et al. 2004; Jenni and Carskadon 2004; Ohayon et al. 2004). Newborn infants spend 16–18 h/day sleeping, with an early version of REM sleep, called active sleep, occupying about half of their sleep time. At approximately 3–4 months of age, when sleep starts to become consolidated during the night, the sleep EEG shows more mature waveforms characteristic of NREM and REM sleep. During early childhood, total sleep time decreases and REM sleep proportion drops to adult levels. The proportion of NREM sleep spent in slow-wave sleep increases during the first year of life, reaches a peak, declines during adolescence and adulthood, and may disappear entirely by age 60.

9.2 Dreaming Across Sleep

Dreams show that vivid conscious experience is possible despite the sensory and motor disconnection from the environment and the loss of self-reflective thought (see (Nir and Tononi 2010) for review). Studying mental experiences during sleep offers a unique opportunity to explain how changes in brain activity relate to changes in consciousness (Hobson et al. 1998; Rees et al. 2002; Nir and Tononi 2010). In fact, if it were not for sleep, when consciousness fades in and out on a regular basis, it might be hard to imagine that consciousness is not a given but depends somehow on the way our brain is functioning. Traditionally, studies have focused on differences among reports obtained after awakenings from different sleep stages or at different times of night. When REM sleep was initially distinguished from NREM sleep (Aserinsky and Kleitman 1953), it was reported that 74–80 % of REM sleep awakenings produced vivid dream recall, compared to only 7–9 % of awakenings from NREM sleep (Dement and Kleitman 1957a, b). It was only natural to conclude that, compared to NREM sleep, the distinct physiology of REM sleep, and especially its fast, low-voltage EEG resembling that of wakefulness, was the reason why we are conscious in REM sleep, and not in NREM sleep (Hobson et al. 1998). Indeed, for some time, reports of mental activity upon awakenings from NREM sleep were assumed to be recalls of earlier REM sleep dreams, or considered analogous to sleep talking (Hobson 1988), or treated as confabulations made up by subjects confused upon awakening (Rechtschaffen 1973; Nir and Tononi 2010). However, by simply changing the question from "tell me if you had a dream" to "tell me anything that was going through your mind just before you woke up," reports of

conscious experiences in NREM sleep ranged between 23 and 74 % (Rechtschaffen 1973). Subsequent studies demonstrated clearly that NREM sleep awakenings yielded reports of mental activity (Foulkes 1962; Nielsen 2000).

Specifically, reports from sleep stage N1 are extremely frequent (80–90 % of the time), though they are very short (Foulkes 1966). Usually people report vivid hallucinatory experiences, so-called hypnagogic hallucinations. In contrast to typical dreams, hypnagogic hallucinations are often static – like single snapshots (Hobson et al. 2000; Hobson and Pace-Schott 2002) – and usually do not include a self-character (Foulkes 1985). Some activities performed before sleep (e.g., video games) may influence the content of hypnagogic dreams (Stickgold et al. 2000; Wamsley et al. 2010). Awakenings from NREM sleep stages N2 and N3 yield reports about some experienced content 50–70 % of the time (Nielsen 2000), although there is great variability throughout the night and between subjects. Early in the night, when stage N3 is prevalent and many large slow waves dominate the EEG, awakenings yield few reports (Stickgold et al. 2001). Moreover, these reports are often qualitatively different than typical REM sleep reports, being usually short, thought-like, less vivid, less visual and more conceptual, less motorically animated, under greater volitional control, more plausible, more concerned with current issues, less emotional, and less pleasant (Rechtschaffen 1973; Hobson et al. 2000; Fosse et al. 2001). Also, the average length of REM sleep reports increases with the duration of the REM sleep episode, while this is not true for NREM sleep reports (Stickgold et al. 2001). However, late in the night, NREM sleep reports are considerably longer and more hallucinatory. Indeed, 10–30 % of all NREM sleep reports are indistinguishable by any criteria from those obtained from REM sleep (Monroe et al. 1965; Antrobus et al. 1995). Since NREM sleep accounts for 75 % of total sleep time, this means that full-fledged NREM sleep dreams actually account for a significant portion of all typical dreams.

Thus, the initial equation of a physiological state (REM sleep) with a mental state (dreaming) was incorrect, or at best, an oversimplification. Moreover, neuropsychological evidence indicates that dreaming and REM sleep can be dissociated: forebrain lesions may abolish dreaming and spare REM sleep, whereas brainstem lesions may nearly eliminate overt features of REM sleep without abolishing dreams (Solms 2000; Nir and Tononi 2010). But if dream reports can be elicited during any stage of sleep (Cavallero et al. 1992; Hobson et al. 2000; Nielsen 2000; Hobson and Pace-Schott 2002; Suzuki et al. 2004), and conversely some awakenings may yield no report, no matter in which sleep stage they were obtained (Nielsen 2000), where do we stand today with respect to the relationship between brain activity and consciousness during sleep? The one thing that seems clear is that we need to move beyond the REM/NREM sleep dichotomy and beyond traditional sleep staging. Though staging is useful, it treats brain activity as uniform in space (only a few electrodes are used) and in time (for 30 s epochs). Inevitably, subtler features of brain activity, which may well influence the presence, degree, and reportability of consciousness, are missed both in space and in time.

In the spatial domain, increasing evidence suggests that different brain regions may be in different states at the same time, and this notion will be discussed in

Sect. 9.4 below. Along this line, dreaming in NREM sleep may be related to "covert" REM processes that occur locally (Nielsen 2000). Thus, refined spatial analysis using fMRI or high-density EEG (hd EEG) could potentially identify regionally specific predictors of dreaming and possibly indicate, in real time, whether dream reports will be obtained.

In the temporal domain, some attempts have been made to relate transient, phasic activities to dreaming. For example, various studies have tried to link dream recall to eye movements (Roffwarg et al. 1962; Moskowitz and Berger 1969), PGO waves (Pivik 1991), and EEG power bouts in specific frequency bands (Esposito et al. 2004), but limited success has been achieved, and little has been done for NREM sleep (Hobson et al. 2000; Pivik 2000). We now know that slow waves in NREM sleep reflect a slow oscillation of cortical neurons between UP and DOWN states (Sect. 9.3.2). Perhaps long UP states are necessary for dreaming to occur. This is normally the case in REM sleep since slow waves are absent. As for NREM sleep, we would expect that higher occurrence of recalls, and especially of typical dreams in the morning hours, would reflect longer UP periods upon dissipation of sleep pressure (Vyazovskiy et al. 2009b). In general, focusing on (rather than avoiding) "gray zones" where it is more difficult to predict whether a dream report will be obtained, for example, in early REM sleep or late NREM sleep, may be a promising strategy for identifying psychophysiological correlates that go beyond traditional staging.

9.3 Neural Correlates of Sleep and Wakefulness

9.3.1 Brain Centers Regulating Wakefulness and Sleep

9.3.1.1 Wakefulness System

Maintenance of wakefulness is dependent on several heterogeneous cell groups extending from the upper pons and midbrain (the so-called reticular activating system, RAS) (Lindsley et al. 1949; Moruzzi and Magoun 1949) to the posterior hypothalamus and basal forebrain. These cell groups are strategically placed so that they can release, over wide regions of the brain, neuromodulators and neurotransmitters that produce EEG activation, such as acetylcholine, histamine, norepinephrine, glutamate, and hypocretin (Fig. 9.2, red). Cholinergic cells are located in the basal forebrain and in two small nuclei in the pons: the pedunculopontine tegmental and lateral dorsal tegmental nuclei (PPT/LDT). Both basal forebrain and pontine cholinergic cells fire at high rates in wakefulness and REM sleep and decrease or stop firing during NREM sleep (Hobson et al. 1975; el Mansari et al. 1989; Lee et al. 2005b). Pontine cholinergic cells project to the thalamus, where they help depolarize specific and intralaminar thalamic nuclei. The latter, which are dispersed throughout the thalamus and project diffusely to the cortex, fire at very high frequencies during both wakefulness and REM sleep and help to synchronize cortical firing in the gamma (>28 Hz) range (McCormick 1989; Steriade 2004; Jones 2005a). Cholinergic cells in the dorsal brainstem and nearby non-cholinergic cells also

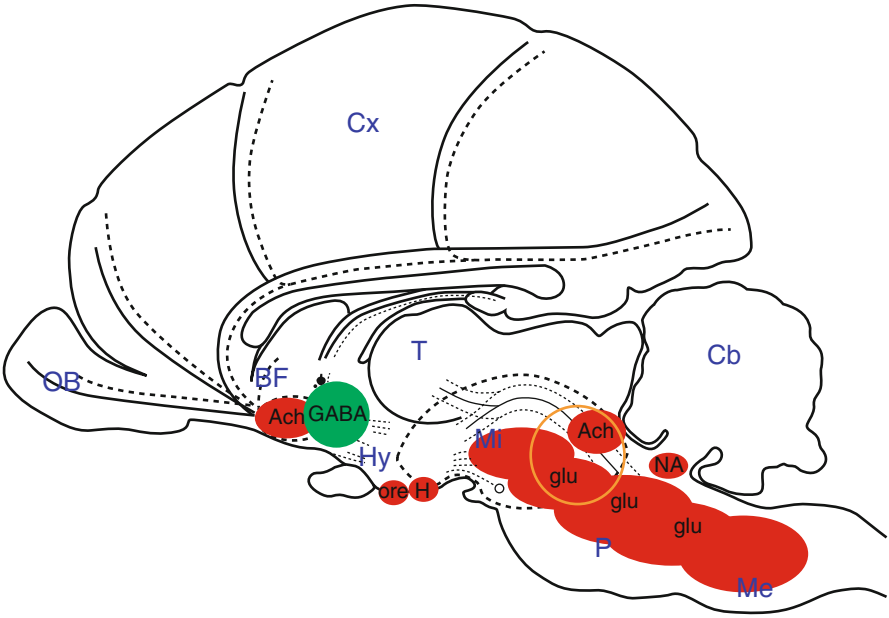


Fig. 9.2 The major brain areas involved in initiating and maintaining wakefulness (*red*), NREM sleep (*green*), and REM sleep (*orange*) (From Tononi 2009)

project to other cholinergic and non-cholinergic cells (many of them glutamatergic) in the basal forebrain, which in turn provide an excitatory input to the entire cortex (Jones 2003, 2005a, b).

Cholinergic neurons in the pons also project to the posterior hypothalamus, where histaminergic neurons are located in the tuberomammillary nucleus (Brown et al. 2001). Histaminergic neurons, which project throughout the cortex, fire at the highest rates during wakefulness and are inhibited during both NREM and REM sleep (Takahashi et al. 2006). Probably the largest contingent of the wakefulness-promoting system is made up by cells dispersed throughout the brainstem reticular formation and the basal forebrain that do not release conventional neuromodulators, but rather the ubiquitous neurotransmitter glutamate. By binding to metabotropic receptors, glutamate can act as a neuromodulator and influence the excitability of target cells. The firing patterns of these glutamatergic cells are not well characterized (Jones 2003, 2005a, b). Noradrenergic cells are concentrated in the locus coeruleus in the upper pons, from where they project throughout the brain (Foote et al. 1980; Aston-Jones and Bloom 1981a, b; Berridge and Abercrombie 1999; Aston-Jones and Cohen 2005). They fire tonically during wakefulness and emit short, phasic bursts of activity during behavioral choices or salient events (Hobson et al. 1975; Foote et al. 1980; Aston-Jones and Bloom 1981a, b; Berridge and Abercrombie 1999; Aston-Jones and Cohen 2005). By contrast, locus coeruleus neurons decrease their firing during NREM sleep and cease firing altogether during REM sleep. Serotonergic cells from the dorsal raphe nucleus also project widely throughout the

brain and, like noradrenergic neurons, fire at higher levels in waking and lower levels in NREM sleep and fall silent during REM sleep. However, in contrast to noradrenergic neurons, serotonergic neurons are inactivated when animals make behavioral choices or orient to salient stimuli and are activated instead during repetitive motor activity such as locomoting, grooming, or feeding (McGinty and Harper 1976; Jacobs et al. 2002). Dopamine-containing neurons located in the substantia nigra and ventral tegmental area, which innervate the frontal cortex, basal forebrain, and limbic structures (Monti and Monti 2007), do not appear to change their firing rate depending on behavioral state, though blocking dopamine reuptake is known to promote arousal (Monti and Monti 2007). Finally, the peptide hypocretin (also known as orexin) is produced by cells in the posterior hypothalamus that provide excitatory input to all components of the waking system (Sakurai 2007). These cells, too, are most active during waking, especially in relation to motor activity and exploratory behavior, and almost stop firing during both NREM and REM sleep (Lee et al. 2005a; Mileykovskiy et al. 2005). Altogether, the main mechanism by which these neuromodulators and neurotransmitters produce cortical activation is by closing leakage potassium channels on the cell membrane of cortical and thalamic neurons, thus keeping cells depolarized and ready to fire.

9.3.1.2 Sleep System

At sleep onset, wakefulness-promoting neuronal groups are actively inhibited by antagonistic neuronal populations located in the hypothalamic and basal forebrain (Fig. 9.2, green). Decreasing levels of acetylcholine and other waking-promoting neuromodulators and neurotransmitters lead to the opening of leak potassium channels in cortical and thalamic neurons, which become hyperpolarized and begin oscillating at low frequencies. Cell groups scattered within the anterior hypothalamus, including the ventrolateral preoptic area (VLPO, (Sherin et al. 1996; Szymusiak et al. 1998) and the median preoptic nucleus (Suntsova et al. 2002), as well as in the basal forebrain, are involved in the initiation and maintenance of sleep. These neurons tend to fire during sleep and stop firing during wakefulness. When they are active, many of them release GABA and the peptide galanin and inhibit most waking-promoting areas, including cholinergic, noradrenergic, histaminergic, hypocretinergic, and serotonergic cells. In turn, the latter inhibit several sleep-promoting neuronal groups (Szymusiak et al. 2001; McGinty and Szymusiak 2003; McGinty et al. 2004; Saper et al. 2005). This reciprocal inhibition provides state stability, in that each state reinforces itself as well as inhibits the opponent state.

9.3.1.3 REM Sleep Generator

This consists of pontine cholinergic cell groups (LDT and PPT) that are part of the wakefulness system and nearby cell groups in the medial pontine reticular formation and medulla (Jouvet 1962; Hobson et al. 1975; McCarley 2004; Siegel 2005). Lesions in these areas eliminate REM sleep without significantly disrupting NREM sleep. Pontine cholinergic neurons produce EEG activation by releasing acetylcholine to the thalamus and to cholinergic and glutamatergic basal forebrain neurons that in turn activate the limbic system and cortex. However, while during wakefulness,

other waking-promoting neuronal groups, such as noradrenergic, histaminergic, hypocretinergic, and serotonergic neurons, are also active, they are inhibited during REM sleep. Other REM active neurons in the dorsal pons are responsible for the tonic inhibition of muscle tone during REM sleep. Finally, neurons in the medial pontine reticular formation fire in bursts and produce phasic events of REM sleep, such as rapid eye movements and muscle twitches.

9.3.2 Spontaneous Neuronal Activity in Sleep: Animal Studies

9.3.2.1 Wakefulness

The waking EEG, characterized by the presence of low-voltage fast activity, is known as activated because most cortical neurons are steadily depolarized close to their firing threshold (Fig. 9.3) and are thus ready to respond to the slightest change in their inputs. The readiness to respond of cortical and thalamic neurons enables fast and effective interactions among distributed regions of the thalamocortical system, resulting in a continuously changing sequence of specific firing patterns. Superimposed on the low-voltage, fast-activity background of wakefulness, one frequently observes rhythmic oscillatory episodes within the alpha (8–13 Hz), beta (14–28 Hz), and gamma (>28 Hz) range, which are usually localized to specific cortical areas. These waking rhythms are due to the activation of oscillatory mechanisms intrinsic to each cell as well as to the entrainment of oscillatory circuits among excitatory and inhibitory neurons.

9.3.2.2 NREM Sleep

The EEG of NREM sleep differs markedly from that of wakefulness because of the occurrence of slow waves (<2 Hz in humans), K-complexes, and sleep spindles. The opening of leakage potassium channels due to the reduced levels of acetylcholine and other neuromodulators draws cortical and thalamic cells toward hyperpolarization and triggers a series of membrane currents that produce the slow oscillation (Fig. 9.3) (Steriade et al. 2001). As shown by intracellular recordings, the slow oscillation is made up of a hyperpolarization phase or down state, which lasts a few 100 ms, and a slightly longer depolarization phase or up state. The down state is associated with the virtual absence of synaptic activity within cortical networks. During the up state, by contrast, cortical cells fire at rates that are as high or even higher than those seen in waking and may even show periods of fast oscillatory activity in the gamma range.

The slow oscillation is found in virtually every cortical neuron and is synchronized across brain regions by corticocortical and thalamocortical connections, which is why the EEG records high-voltage, low-frequency waves. Human EEG recordings using 256 channels have revealed that EEG slow waves behave as traveling waves that sweep across a large portion of the cerebral cortex (Massimini et al. 2004; Murphy et al. 2009). Most of the time, the sweep starts in the very front of the brain and propagates front to back. These sweeps occur very infrequently during stage N1, around five times a minute during stage N2, and more than ten times a minute in stage N3. Thus, a wave of depolarization and intense synaptic activity, followed by a wave of hyperpolarization and synaptic silence, sweeps across the

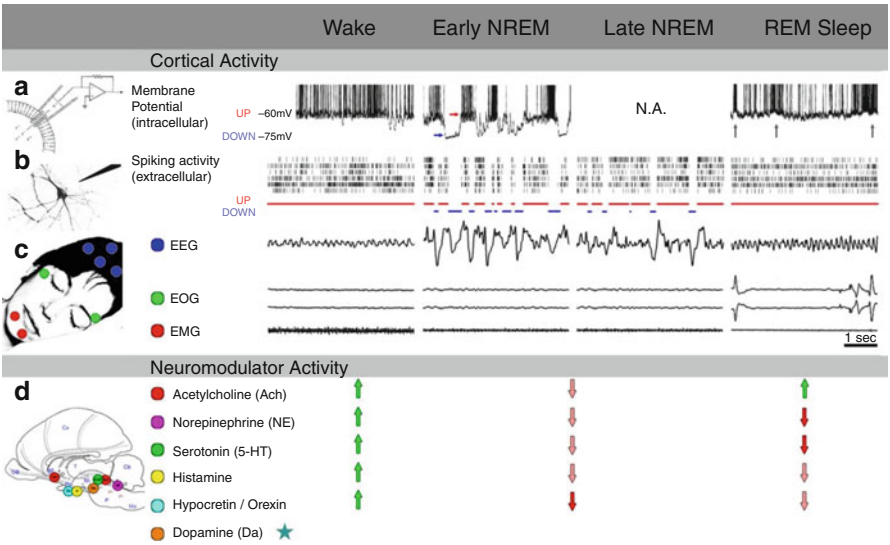


Fig. 9.3 Neurophysiology of wake and sleep states. A comparison of cortical activity (**a**–**c**) and neuromodulator activity (**d**) in wake, early NREM (when sleep pressure is high and dream reports are rare), late NREM (when sleep pressure dissipates and dream reports are more frequent), and REM sleep (when dreams are most common). (**a**) Intracellular studies. The membrane potential of cortical neurons in both wake and REM sleep is depolarized and fluctuates around −63 and −61 mV, respectively (Steriade et al. 2001). In REM sleep, whenever phasic events such as rapid eye movements and PGO waves occur (*gray arrows*, events not shown), neurons increase their firing rates to levels that surpass those found in wake (Yamamoto and Nakahama 1983; Steriade et al. 2001). In early NREM sleep, neurons alternate between two distinct states, each lasting tens to hundreds of milliseconds: UP states (*red arrow*) are associated with depolarization and increased firing, whereas in DOWN states (*blue arrow*), the membrane potential is hyperpolarized around −75 mV, and neuronal firing fades (Steriade et al. 1993a; Destexhe et al. 2007). Intracellular studies focusing specifically on late NREM sleep are not available (N.A.). (**b**) Extracellular studies. Spiking of individual neurons in REM sleep reaches similar levels as in active wake. In both wake and REM sleep, neurons exhibit tonic irregular asynchronous activity (Evarts 1964; Noda and Adey 1970; Hobson and McCarley 1971; Destexhe et al. 1999; Steriade et al. 2001). Sustained activity in wake and REM sleep can be viewed as a continuous UP state (Destexhe et al. 2007) (*red bars*). In early NREM sleep, UP states are short and synchronous across neuronal populations and are frequently interrupted by long DOWN states (*blue bars*). In late NREM sleep, UP states are longer and less synchronized (Vyazovskiy et al. 2009b). (**c**) Polysomnography. Waking is characterized by low-amplitude, high-frequency EEG activity (>7 Hz), occasional saccadic eye movements, and elevated muscle tone. In early NREM sleep, high-amplitude slow waves (<4 Hz) dominate the EEG. Neuronal UP (*red*) and DOWN (*blue*) states correspond to positive and negative peaks in the surface EEG, respectively (Vyazovskiy et al. 2009b). Eye movements are largely absent and muscle tone is decreased. In late NREM sleep, slow waves are less frequent, whereas spindles (related to UP states and surface EEG positivity) become more common. Eye movements and muscle tone are largely similar to early NREM sleep (Werth et al. 2002). In REM sleep, theta activity (4–7 Hz) prevails, rapid eye movements occur and muscle tone is reduced. (**d**) Neuromodulator activity. Subcortical cholinergic modulation is active in wake and REM sleep (*green arrows*) and leads to sustained depolarization in cortical neurons and EEG activation (Steriade et al. 2001). Wake is further maintained by activity of monoamines, histamine, and hypocretin/orexin (*green arrows*). In sleep, monoaminergic systems, including norepinephrine and serotonin, reduce their activity (*pink arrows*) and are silent in REM sleep (*red arrows*). Whereas dopamine levels do not change dramatically across the sleep–wake cycle (*asterisks*), phasic events and regional profiles can differ (Monti and Monti 2007). Data are pooled across different species for illustration purposes (From Nir and Tononi 2010)

brain more and more frequently just as NREM sleep becomes deeper. Slow waves can originate at short intervals at multiple cortical sites, in which case they superimpose or interfere, leading to EEG waves that are shorter and more fractured. Topographically, slow waves are especially prominent over the dorsolateral prefrontal cortex. K-complexes, which are usually triggered by external stimuli and appear particularly prominent because they are not immediately preceded or followed by other slow waves, are most likely the EEG correlate of global slow oscillations due to the near-synchronous activation of the cortical mantle by the reticular activating system (as opposed to a single cortical source; Riedner et al. 2011).

Sleep spindles occur during the depolarized phase of the slow oscillation and are generated in thalamic circuits as a consequence of cortical firing. When the cortex enters an up state, strong cortical firing excites GABAergic neurons in the reticular nucleus of the thalamus. These in turn strongly inhibit thalamocortical neurons, triggering intrinsic currents that produce a rebound burst of action potentials. These burst percolate within local thalamoreticular circuits and produce oscillatory firing at around 12–15 Hz. Thalamic spindle sequences reach back to the cortex and are globally synchronized by corticothalamic circuits, where they appear in the EEG as sleep spindles.

9.3.2.3 REM Sleep

During REM sleep, the EEG returns to an activated, low-voltage fast-activity pattern that is similar to that of quiet wakefulness or stage 1 (Fig. 9.3). As in wakefulness, the tonic depolarization of cortical and thalamic neurons is caused by the closure of leakage potassium channels. In fact, during REM sleep acetylcholine and other neuromodulators are released again at high levels, just as in wakefulness, and neuronal firing rates in several brain areas tend to be higher.

9.3.3 Metabolism and Functional Brain Imaging in Humans

9.3.3.1 PET Studies

Recently, the data obtained by recording the activity of individual neurons have been complemented by imaging studies that provide a simultaneous picture of neuronal activity over the entire brain, although at much lower resolution.

NREM Sleep

PET studies show that metabolic activity and blood flow are globally reduced in NREM sleep compared to resting wakefulness (Braun et al. 1997; Hofle et al. 1997; Maquet et al. 1997; Kajimura et al. 1999). During slow-wave sleep, metabolic activity can be reduced by as much as 40 %. Metabolic activity is mostly due to the energetic requirements of synaptic transmission, and its reduction during NREM sleep is thus most likely due the hyperpolarized phase of the slow oscillation, during which synaptic activity is essentially abolished. At a regional level, activation is especially reduced in the thalamus, due to its profound hyperpolarization during NREM sleep. In the cerebral cortex, activation is reduced in dorsolateral prefrontal cortex, orbitofrontal, and anterior cingulate cortex (Braun et al. 1997; Hofle et al.

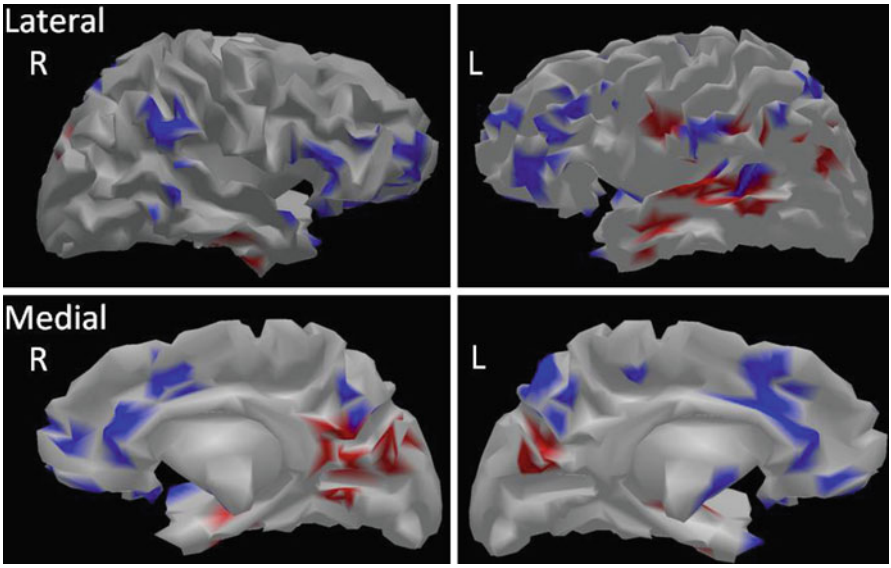


Fig. 9.4 Functional neuroanatomy of human NREM sleep: a meta-analysis of PET results. Meta-analysis of regions showing relatively decreased (*in blue*) and relatively preserved (*in red*) cortical activity during NREM sleep as compared to wakefulness, as seen with PET imaging using $H2^{15}O$ measurements of regional cerebral blood flow (rCBF) (Maquet et al. 1997; Hofle et al. 1997; Braun et al. 1998; Kajimura et al. 1999). *Top row*: cortical surface, lateral view. *Bottom row*: cortical surface, medial view. Analysis is based on Talairach coordinates of significant foci published in Maquet et al. (1997), Hofle et al. (1997), Braun et al. (1998), and Kajimura et al. (1999). *Blue areas* denote decreased activity in precuneus/posterior cingulate, medial prefrontal cortex/anterior cingulate, superior and inferior parietal gyri, superior and inferior frontal gyri, orbitofrontal cortices, anterior medial and posterior inferior temporal gyri, insula, angular and supramarginal gyri. Red areas denote preserved regional activity in calcarine sulcus, fusiform and lateral occipital gyri, superior temporal and anterior middle/inferior temporal gyri, superior temporal sulcus, inferior parietal lobule, and pericentral cortices

1997; Maquet et al. 1997; Kajimura et al. 1999). This deactivation is in line with the observation that slow waves are especially prominent in these areas (Murphy et al. 2009). Parietal cortex, precuneus and posterior cingulate cortex, as well as medial temporal cortex also show relative deactivations (see Fig. 9.4, in blue). As discussed in other chapters, the deactivation of thalamus and associated frontoparietal networks is seen in other conditions characterized by reduced consciousness, such as coma, vegetative states, and anesthesia. By contrast, visual, somatosensory, and auditory cortices are not deactivated compared to resting wakefulness (see Fig. 9.4, in red). Basal ganglia and cerebellum are also deactivated, probably because of the reduced inflow from cortical areas.

REM Sleep

During REM sleep absolute levels of blood flow and metabolic activity are high, reaching levels similar to those seen during wakefulness, as would be expected

based on the tonic depolarization and high firing rates of neurons. There are, however, interesting regional differences (Maquet et al. 1996; Braun et al. 1997; Nir and Tononi 2010). Some brain areas are more active in REM sleep than in wakefulness. For example, there is a strong activation of limbic areas, including the amygdala and the parahippocampal cortex (see Fig. 9.5). Cerebral cortical areas that receive strong inputs from the amygdala, such as the anterior cingulate and the parietal lobule, are also activated, as are high-order visual areas. By contrast, the rest of parietal cortex, precuneus and posterior cingulate, and dorsolateral prefrontal cortex are relatively deactivated. These regional activations and inactivations are consistent with the differences in mental state between REM sleep and wakefulness: REM sleep dream mentation is indeed associated with vivid sensory imagery and emotional content, in the presence of decreased cognitive control and decreased recall (Nir and Tononi 2010).

9.3.3.2 EEG–fMRI Studies: Neural Correlates of Specific Spontaneous Sleep Events

NREM Sleep

By using simultaneous EEG and event-related functional magnetic resonance imaging (fMRI), some recent studies have shed light on brain-wide correlates of phasic activity associated with characteristic sleep electrophysiological events such as slow waves and spindles. Dang-Vu et al. (2008) characterized the transient changes in brain activity consistently associated with slow waves (>140 μV) and delta waves (75–140 μV) during NREM sleep in non-sleep-deprived normal human volunteers. Significant increases in activity were associated with these waves in the inferior frontal, medial prefrontal, precuneus, and posterior cingulate areas. Compared with baseline activity, slow waves were also associated with significant activity in the parahippocampal gyrus, cerebellum, and brainstem, whereas delta waves were rather related to frontal activations. No decrease in activity was observed. Schabus et al. (2007) investigated neural correlates of spindle activity in the same cohort of subjects. They showed an activation pattern common to both slow (11–13 Hz) and fast (13–15 Hz) spindles involving the thalamus, anterior cingulate cortex, insular cortices, and superior temporal gyri. No thalamic difference was detected in the direct comparison between slow and fast spindles, although some thalamic areas were preferentially activated in relation to either spindle type. Beyond the common activation pattern, the increases in cortical activity differed significantly between slow and fast spindles. Slow spindles were associated with increased activity in the superior frontal gyrus. In contrast, fast spindles recruited a set of cortical regions involved in sensorimotor processing, as well as the mesial frontal cortex and hippocampus (Schabus et al. 2007). A recent independent EEG–fMRI study likewise showed an involvement of thalamus, posterior cingulate, precuneus, putamen, paracentral cortex, and temporal lobe in sleep spindles (Caporro et al. 2012). The finding of a hippocampal involvement during spindle activity is also in line with a recent EEG–fMRI study showing increased hippocampal/neocortical connectivity during stage N2 sleep spindles (Andrade et al. 2011).

To date, three EEG–fMRI studies investigated neural activity associated with K-complexes evoked by external stimuli. Using an auditory oddball paradigm,

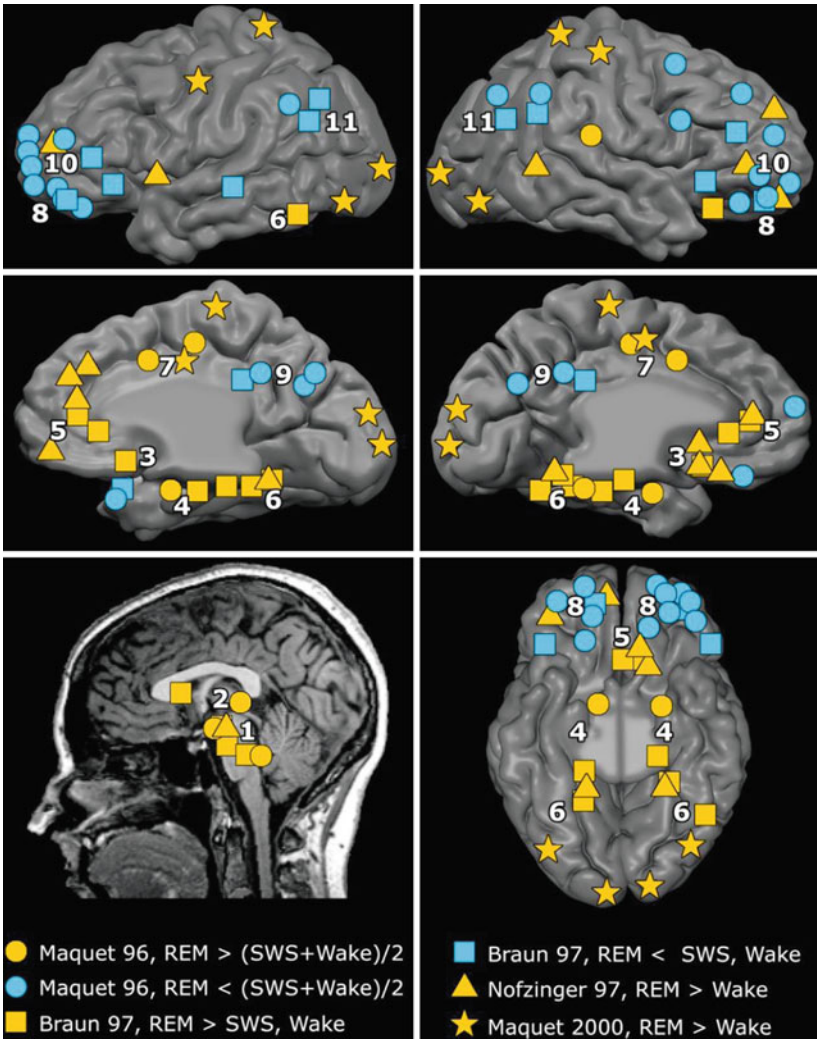


Fig. 9.5 Functional neuroanatomy of human REM sleep: a meta-analysis of PET results. Meta-analysis of relative increases and decreases in neuronal activity during REM sleep as seen with PET imaging using $H2^{15}O$ measurements of regional cerebral blood flow (rCBF) (Maquet et al. 1996; Braun et al. 1997; Maquet et al. 2000) or [18F]-fluorodeoxyglucose measurements of glucose metabolism (Nofzinger et al. 1997). *Top row*: cortical surface, lateral view. Middle row: cortical surface, medial view. *Bottom row*: subcortical foci (*left*) and ventral view of cortical surface (*right*). Analysis is based on published Talairach coordinates of foci whose activity was significant at $p<0.001$ corrected (Z-score >3.09). *Circles*, *squares*, *triangles*, and *stars* denote activity foci as reported in Refs Maquet et al. (1996, 2000), Braun et al. (1997), Nofzinger et al. (1997), respectively. Each symbol marks the center of mass of a region regardless of its spatial extent. *Yellow symbols* denote increased regional activity in the (1) mesopontine tegmentum and midbrain nuclei, (2) thalamus, (3) basal forebrain and diencephalic structures, (4) limbic MTL structures including amygdala and hippocampus, (5) medial prefrontal cortex, (6) occipitotemporal visual cortex, and (7) anterior cingulate cortex. Cyan symbols denote decreased activity in the (8) orbitofrontal cortex, (9) posterior cingulate and precuneus, (10) dorsolateral prefrontal cortex, and (11) inferior parietal cortex (From Nir and Tononi 2010)

Czisch et al. (2009) showed that sleep K-complexes evoked by rare tones activated the auditory cortex, hippocampus, superior and middle frontal gyri, and posterior cingulate. Caporro et al. (2012) showed that auditory K-complexes were correlated with increased BOLD signal in thalamus, superior temporal lobes, paracentral gyri, and medial regions of the occipital, parietal, and frontal lobes. Jahnke et al. (2012) found that auditory evoked K-complexes were associated with positive BOLD signal changes in brainstem, thalamus, sensory and motor midline regions, and the default-mode network (DMN). Negative K-complex-related responses were found in the anterior insula. Additionally, connectivity analyses using dynamic causal modeling suggest that the primary auditory cortex may be the first region affected by K-complexes and that midline regions would activate successively from front to back (Jahnke et al. 2012). Using EEG–fMRI, activation of mostly primary cortices (bilaterally in central, precentral, posterior superior temporal, and medial occipital cortex) has also been found during vertex sharp waves (Stern et al. 2011).

REM Sleep

A number of neuroimaging studies are beginning to shed light on the neural correlates of ocular saccades occurring during REM sleep (REMs) as compared to wakefulness. Using H(2)(15)O positron emission tomography, Peigneux et al. (2001) identified activations in the right geniculate body and in the primary occipital cortex in relation to REMs during paradoxical sleep as compared to wakefulness. Using EEG–fMRI, Wehrle et al. (2005) subsequently confirmed fMRI BOLD signal increases in the posterior thalamus and occipital cortex co-occurring with REMs during human paradoxical sleep. Subsequently, several EEG–fMRI studies revealed that not only the posterior thalamus and primary visual cortex but also several other subcortical and cortical areas were activated during paradoxical sleep-associated REMs. Miyauchi et al. (2009) found REM-associated activation during sleep in the pontine tegmentum, putamen, anterior cingulate, parahippocampal gyrus, and amygdala. In line with the results of Peigneux et al. (2001), self-paced saccades in total darkness did not produce activity in the visual cortex during wakefulness. Hong et al. (2009) also found additional REM-locked activation in the thalamic reticular nucleus, claustrum, retrosplenial cortex, fusiform gyrus, anterior cingulate cortex, frontal eye field, motor cortex, language areas, and in the ascending reticular activating system, including basal forebrain. In this study, REMs were also associated with BOLD decreases in periventricular subregions matching the distribution of the serotonergic supraependymal plexus.

9.3.3.3 Resting-State fMRI Connectivity Studies

NREM Sleep

A number of studies have investigated changes in functional connectivity, as assessed by BOLD signal correlation techniques, during human NREM sleep as compared to wakefulness. A typical finding is that NREM sleep-induced reduction of consciousness is reflected in altered correlation between DMN components and most notably a reduced involvement of frontal cortex (Horovitz et al. 2009).

This decrease in DMN connectivity is however stage dependent. It was observed that in the transition from wakefulness to light sleep, thalamocortical connectivity is first sharply reduced, whereas corticocortical connectivity is increased; corticocortical connectivity subsequently breaks down mainly in slow-wave sleep (Spoormaker et al. 2010). With increasing sleep depth, contributions of the posterior cingulate cortex, parahippocampal gyrus, and medial prefrontal cortex to the DMN further decrease (Larson-Prior et al. 2011; Samann et al. 2011). Connectivity in task-positive networks, involving lateral parietal and frontal cortices, was also observed to be lower in NREM sleep stages as compared to wakefulness (Spoormaker et al. 2012). Additionally, there is a loss of anti-correlation between the DMN and the "task-positive networks" during NREM sleep as compared to wakefulness (Samann et al. 2011).

EEG–fMRI studies using graph theory tools also show that slow-wave sleep is characterized by a strong hierarchical clustering of brain activity in local sub-modules as compared to wakefulness (Spoormaker et al. 2012). While local clustering values are closest to random values in light sleep, slow-wave sleep is characterized by the highest clustering ratio (Spoormaker et al. 2010). During NREM sleep, brain activity is thus characterized by a modification of the hierarchical organization of the brain's large-scale networks into smaller independent modules (Boly et al. 2012). This reorganization is however independent from markers of the slow oscillation, as far as can be inferred from scalp EEG. An increase in delta power per se is rather associated with a further breakdown of connectivity in DMN and lateral frontoparietal cortices (Boly et al. 2012). Recently, an fMRI-based multivariate classification approach has been applied to differentiate between NREM sleep and wakefulness. Inputs to the classifier were the BOLD signal correlation values between 20 cortical regions and two regions in the thalamus. This classification approach achieved accuracies over 0.8 in the binary classification between NREM sleep and wakefulness, based on changes in functional connectivity values obtained for epochs as short as 60s (Tagliazucchi et al. 2012). Taken altogether, these results support a marked reorganization of brain connectivity architecture between NREM sleep and wakefulness.

REM Sleep

A recent EEG–fMRI study investigated DMN resting-state functional MRI connectivity during REM sleep as compared to NREM sleep (Koike et al. 2011). Results showed that during REM sleep, the connectivity between the anterior cingulate cortex, the dorsomedial prefrontal cortex, and the inferior parietal lobule on one hand and the medial temporal cortex on the other hand was significantly stronger than in NREM sleep. In contrast, functional connectivity between the dorsomedial prefrontal and the precuneus was significantly weaker in REM sleep as compared to NREM sleep. The authors suggest that such lack of co-activation between the precuneus and medial prefrontal cortex in REM sleep could prevent autobiographic memory from being incorporated into dream content (Koike et al. 2011). To shed further light on this question, additional studies of functional connectivity changes in REM sleep as compared to wakefulness are warranted.

9.3.4 TMS–EEG Studies

9.3.4.1 NREM Sleep

As was discussed above, the level and quality of conscious experience can vary dramatically across the sleep–wake cycle. For example, during NREM sleep early in the night, consciousness can nearly vanish (Pivik and Foulkes 1968; Hobson and Pace-Schott 2002; Suzuki et al. 2004) despite periods of persistent neural activity in the thalamocortical system (Steriade et al. 2001) and despite preserved levels of neuronal synchronization (Bullock et al. 1995; Duckrow and Zaveri 2005). In order to better understand how information transmission/processing within thalamocortical changes across the sleep–wake cycle, a series of recent experiments employed a combination of transcranial magnetic stimulation and electroencephalography (TMS/EEG) (Fig. 9.6a). This technique allows perturbing directly a subset of cortical neurons and recording with millisecond resolution the response of this initial activation in the rest the brain. Therefore, TMS/EEG represent a suitable method to evaluate directly the ability of different areas of the cerebral cortex to engage in complex patterns of causal interactions (effective connectivity), a theoretical requirement for information integration and consciousness (Tononi 2004).

In a first set of experiments, TMS/EEG measurements were carried out during the transitions from wakefulness into NREM sleep early in the night (Massimini et al. 2005, 2007). Figure 9.6b shows the typical response obtained after direct cortical stimulation (rostral premotor cortex) in an awake subject. During wakefulness, TMS triggers a series of low-amplitude, high-frequency (25–30 Hz) waves associated with cortical activations that propagate along long-range ipsilateral and transcallosal connections. Remarkably, the exact same stimulation, applied 15 min later during sleep stage N3, results in a very different picture (Fig. 9.6c). In this case, TMS elicits a larger, lower-frequency wave, associated with a strong initial cortical activation, which does not propagate to connected brain regions and dissipates rapidly. This finding was extremely reproducible, could be generalized to any cortical area, and suggested that during sleep stage N3 thalamocortical networks – despite being active and reactive – lose their ability to sustain long-range causal interactions.

TMS/EEG measurements not only indicate that during slow-wave sleep the thalamocortical system tends to break down into isolated modules, but they also show that the ability of thalamocortical circuits to produce differentiated responses is impaired. Indeed, while during wakefulness different cortical areas react to TMS with a pattern of activation which has a characteristic shape and frequency content (Rosanova et al. 2009), this distinction is clearly obliterated during sleep; the local response to TMS becomes, in all cases, a simple positive–negative wave (Massimini et al. 2007). Interestingly, this positive–negative component resembles a full-fledged sleep slow wave when TMS is delivered at high intensities in a scalp region around the vertex. Also in this case, the complexity of the response obtained during wakefulness is lost; indeed, while the pattern of cortical activation associated with the full-fledged slow waves is global, it is also simple and stereotypical (Fig. 9.6d). In summary, TMS/hd–EEG measurements suggest that during NREM sleep early in the night, when consciousness vanishes, the only way the brain can react to a direct

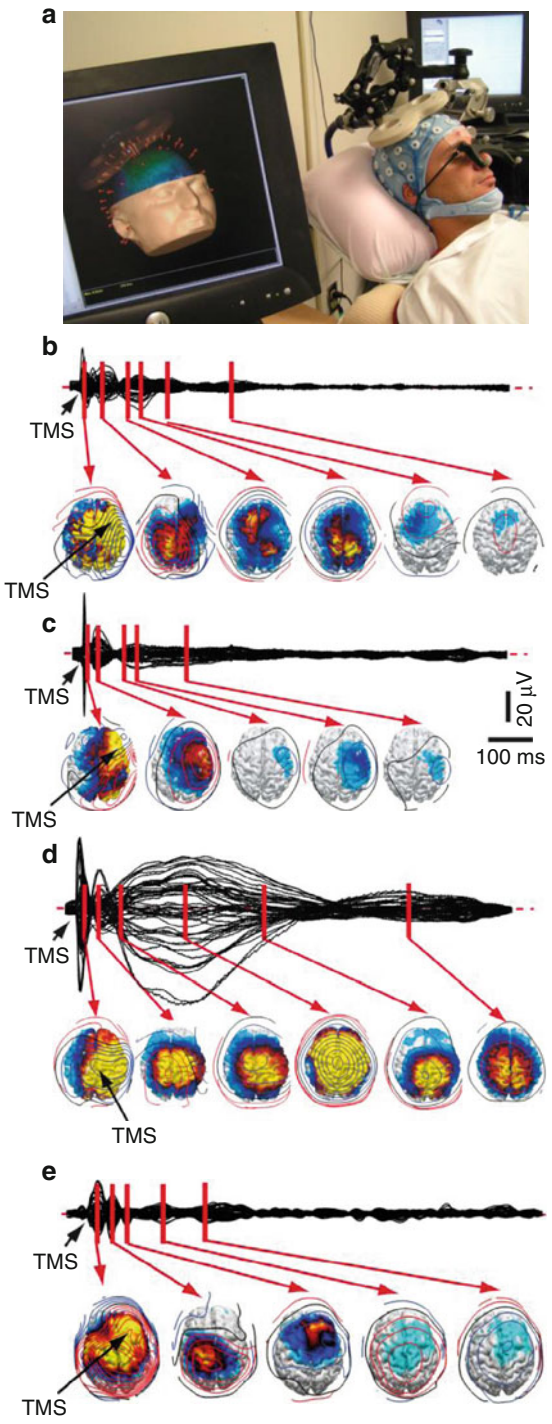


Fig. 9.6 Spatiotemporal cortical current maps of TMS-induced activity during wakefulness, NREM, and REM sleep. (**a**) The experimental setup including the TMS coil, a 60-electrode EEG cap, and an MRI-based neuronavigation system. From the EEG data, current sources corresponding to periods of significant activations were plotted on the subject's MRI. (**b**) TMS during wakefulness elicits rapidly changing patterns of activation, lasting up to 300 ms and involving several different areas (right premotor cortex stimulation is shown, but similar results are observed for other stimulation sites, including midline centroparietal regions). (**c**) TMS during NREM sleep elicits either a brief activation that remains localized to the area of stimulation (right premotor cortex stimulation) or (**d**) a global wave of activation that affects indiscriminately and stereotypically the entire cortex (midline centroparietal stimulation) (**e**) for TMS during REM sleep; a balanced pattern of activation and a significant resumption of effective connectivity are observed (From Massimini et al. 2005, 2007, and Tononi and Massimini, unpublished data)

cortical perturbation is by producing a slow wave that is either local or global but nonspecific and stereotypical. Hence, the thalamocortical system, despite being active and reactive, either breaks down in causally independent modules (producing a local slow wave) or bursts into an explosive and nonspecific response (a full-fledged, global slow wave). In no case, during NREM sleep, did TMS result in a balanced, long-range, differentiated pattern of activation. The possible mechanisms for this apparent breakdown of complex interactions within the thalamocortical system will be discussed in Sect. 9.5.

9.3.4.2 REM Sleep

As was also mentioned, complete loss of consciousness during sleep is the exception rather than the rule, and many awakenings yield dream reports (Casagrande et al. 1996; Stickgold et al. 2001; Fagioli 2002; Nir and Tononi 2010), suggesting that during much of sleep thalamocortical circuit may retain a high capacity to integrate information. In a recent study TMS/EEG was employed to evaluate intracortical communication during REM sleep (Massimini et al. 2010), when dreaming is most frequently reported upon awakening. In this case, TMS-evoked EEG potentials were recorded during the first REM sleep episode. These measurements showed that during the transition from NREM to REM, while subjects were still behaviorally asleep, the brain's response to TMS recovered fast oscillatory components and became similar to the one obtained during wakefulness, especially during the first 100–150 ms post-stimulus. Source modeling revealed that, as in wakefulness, the resumption of fast oscillations during REM sleep was associated with a pattern of activation that was more complex and widespread compared to one of NREM sleep (Fig. 9.6e). This observation corroborates the hypothesis that cortical effective connectivity may play a role in the shifts of conscious experience that occur during sleep. Notably, the persistence, to some degree, of long-range corticocortical effective connectivity has been also reported during stage 1 (see Fig. S2 in Massimini et al. 2005), another sleep stage associated with frequent dream reports (Foulkes 1966). In future work, it would be interesting to systematically collect TMS/EEG measures of thalamocortical effective connectivity during the whole night and to correlate them with dream reports. This approach may help to clarify the neural correlates of consciousness during sleep on a finer timescale, beyond the REM/NREM sleep dichotomy and beyond traditional sleep staging.

9.3.5 Intracranial Recordings in Humans

Until recently, our understanding of neuronal activity in sleep reflected a massive gap between functional imaging and behavioral studies in humans and electrophysiological investigations typically carried out in cats and rodents. Direct brain recordings during sleep in patients with intractable epilepsy, implanted with depth electrodes for potential surgical treatment, constitute an invaluable opportunity for bridging this gap. Such studies permit the investigation of simultaneously recorded neuronal activity from multiple brain areas bilaterally and provide sampling of

activity across cortical and subcortical structures that is rarely achieved in animal studies. Naturally, recording sites are dictated by clinical considerations and usually encompass mostly medial limbic structures. Fortunately, these brain regions play a pivotal role in supporting many activity patterns in sleep such as slow waves (Murphy et al. 2009; Nir et al. 2011) and sleep spindles (Andrillon et al. 2011).

9.3.5.1 Sleep Slow Waves

The most prominent electrophysiological events in sleep are slow waves and related K-complexes – isolated high-amplitude waves that are triggered by external or internal stimuli (Colrain 2005). Animal studies established that such waves reflect a bistability of thalamocortical neurons undergoing a slow oscillation (<1 Hz) between active ("UP") and inactive ("DOWN") states and that these waves group and modulate other neuronal oscillations (Steriade et al. 1993b; Contreras and Steriade 1995; Destexhe et al. 2007; Crunelli and Hughes 2010). Recently, microelectrode studies confirmed that, in humans, slow waves are similarly associated with underlying neuronal bistability (Fig. 9.7) oscillating between active and inactive states (Cash et al. 2009; Csercsa et al. 2010; Le Van Quyen et al. 2010; Nir et al. 2011), as was found in natural sleep of rodents (Vyazovskiy et al. 2009b) and cats (Chauvette et al. 2011).

Importantly, such studies also revealed some important features of sleep slow waves that had not been evident in previous work. While slow oscillations are remarkably synchronous when examined in brain slices (Sanchez-Vives and McCormick 2000) and in animals under anesthesia (Chauvette et al. 2011), human studies focusing on natural sleep and recording in many regions in parallel revealed that most sleep slow waves and the underlying active and inactive neuronal states occur locally (Fig. 9.7e, f), where some regions can be active while others are silent (Nir et al. 2011). It was also found that slow waves have a tendency to propagate along typical paths (Fig. 9.3d), from medial prefrontal cortex to the medial temporal lobe (MTL) through the cingulate gyrus and neighboring structures (Nir et al. 2011), which constitute an anatomical backbone of anatomical fibers (Hagmann et al. 2008). Such propagation was previously suggested by high-density EEG and animal studies (Massimini et al. 2005; Volgushev et al. 2006; Murphy et al. 2009; Vyazovskiy et al. 2009a; Riedner et al. 2011). Slow waves also exhibit complex propagation patterns at a local scale (Hangya et al. 2011).

In addition, important insights were gained about slow-wave propagation *within* the MTL, where noninvasive imaging is limited. By and large, cortical slow waves precede hippocampal waves, revealing a sequential propagation from the parahippocampal gyrus, through entorhinal cortex, to hippocampus (Nir et al. 2011), in line with previous animal studies (Sirota et al. 2003; Isomura et al. 2006; Hahn et al. 2007; Ji and Wilson 2007) and with a recent study of human depth EEG (Wagner et al. 2010). As for the direction of cortico-hippocampal dialogue in sleep (Buzsaki 1998), it was found that at times of hippocampal ripples (associated with the "replay" of activity in cell assemblies during sleep in rodents (Diekelmann and Born 2010)), local effects of hippocampal output can be observed within the MTL in terms of increased unit activity (Nir et al. 2011) as well as gamma bursts in parahippocampal

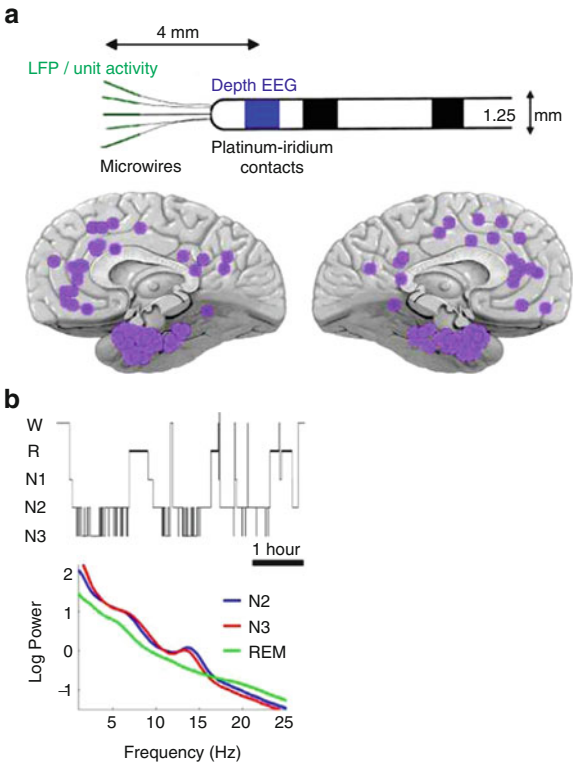
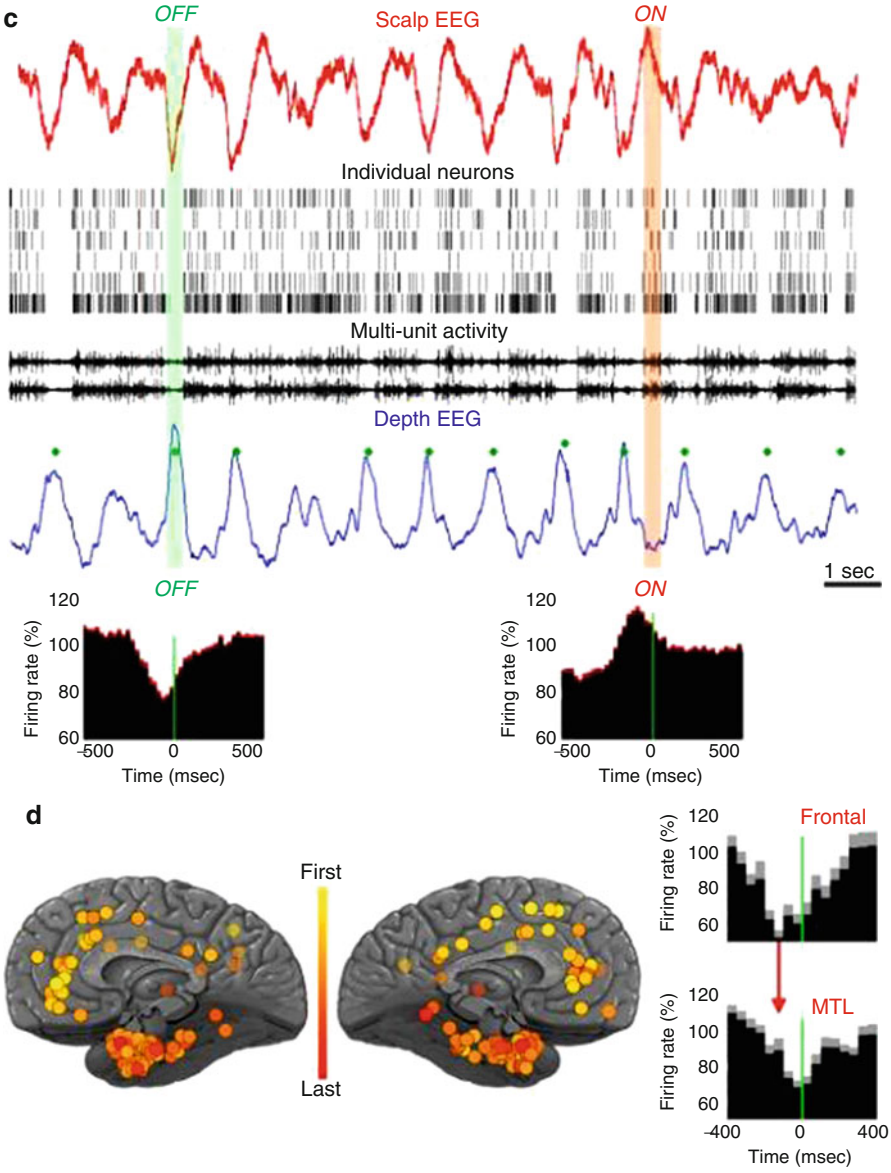


Fig. 9.7 (**a**) (*Top*) Diagram of flexible probes used for concomitant recording of depth EEG (platinum contacts, *blue*) and unit activity (microwires, *green*) in microelectrode studies of human sleep. (*Bottom*) Overview of depth electrode locations in 13 individuals encompassing multiple brain regions seen from medial view. (**b**) Hypnogram (*top*) and average power spectra of scalp EEG (*bottom*) in one representative individual indicate that sleep measures in epilepsy patients are in general agreement with typical findings in healthy young adults (*W* wake, *R* REM sleep; N1–N3, NREM sleep, stages 1–3). (**c**) Neuronal activity underlying slow waves in human sleep. Electrical brain activity across 15 s of deep NREM sleep. Top (*red*), scalp EEG; bottom (*blue*), intracranial depth EEG in entorhinal cortex. Green dots, individual slow waves that are automatically detected and separated from pathological events. *Black*, MUA and action potentials of six neurons. Vertical *green bar*, OFF periods of inactivity. *Orange green bar*, ON periods of neuronal silence. *Bottom insets*, an analysis across 600 units confirms that neurons increase and decrease their activity in concert with local electrical fields. (**d**) Slow waves have a tendency to propagate along typical paths. Left, each *circle* denotes a depth electrode and its color marks the typical slow-wave timing at that location. Right, average unit activity in frontal cortex (top, $n=76$) and MTL (*bottom*, $n=155$), triggered by the same scalp slow waves. Note that on average slow waves and underlying neuronal activity occur earliest in the frontal lobe, about 200 ms later in the temporal lobe and finally in the hippocampus. (**e**) An example of local sleep slow waves occurring at different times in left and right posterior cingulate cortices. Rows (*top* to *bottom*) depict activity in scalp EEG (Cz, *red*), left and right posterior cingulate. *Blue*, depth EEG; *green*, MUA; *black lines*, single-unit spikes. *White* shadings mark local OFF periods. (f) The vast majority of slow waves occur locally. Distribution of slow-wave involvement (percentage of monitored brain structures expressing each wave) shows that global slow waves are quite rare (From Nir et al. 2011)



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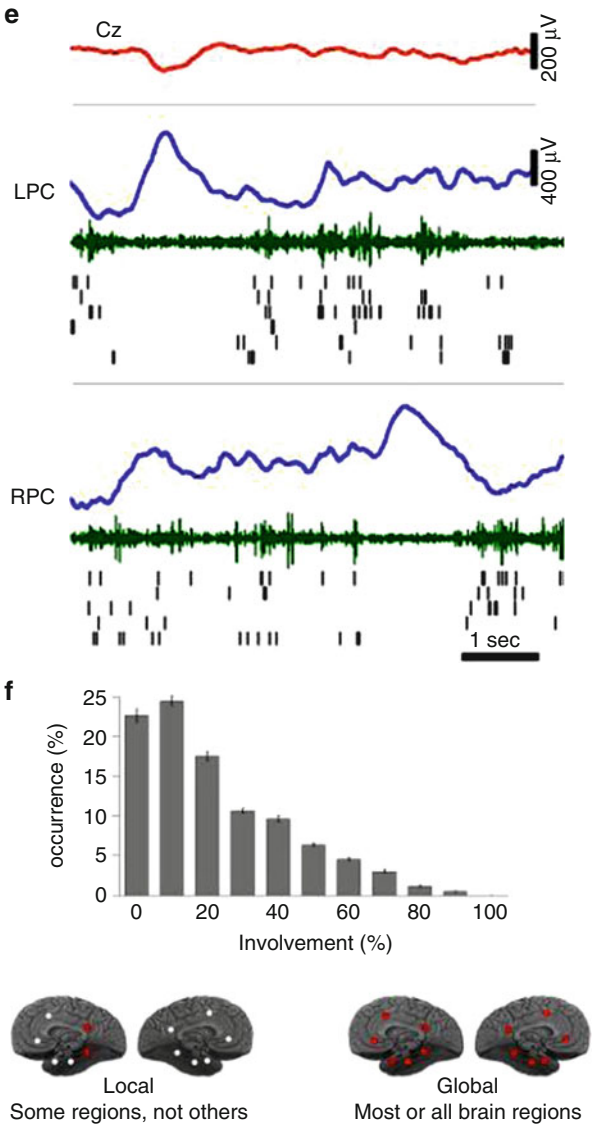

Fig. 9.7 (continued)

gyrus (Le Van Quyen et al. 2010). However, ripples were not associated with detectable effects in the medial prefrontal cortex (Nir et al. 2011), a primary projection zone of hippocampal output in primates. On the whole, during NREM sleep neural activity propagates predominantly from the neocortex to the hippocampus. Future studies are needed to determine whether within this robust cortico-hippocampal broadcast, there may be islands of hippocampo-cortical transmission that may be functionally relevant for memory consolidation.

9.3.5.2 Sleep Spindles

Sleep spindles are the other hallmark oscillation of NREM sleep; they are waxing-and-waning 10–16 Hz oscillations lasting 0.5–2 s and are believed to mediate many sleep-related functions (De Gennaro and Ferrara 2003). Recent intracerebral human studies (Andrillon et al. 2011; Peter-Derex et al. 2012) revealed that spindle frequency is topographically organized with a sharp transition between fast (13–15 Hz) centroparietal spindles and slow (9–12 Hz) frontal spindles occurring 200 ms later on average (Fig. 9.8). Moreover, like slow waves, most spindles occur locally, thereby showing that constrained intracerebral communication is an important feature of NREM sleep. It was also found that spindle frequency changes along with sleep depth, reflecting the level of thalamocortical hyperpolarization at any given time and that robust firing rate modulations were surprisingly weak during sleep spindles (Andrillon et al. 2011). On the whole, patient studies revealed changes in spindle occurrence, frequency, and timing between regions and across sleep (Andrillon et al. 2011; Peter-Derex et al. 2012). Some of this heterogeneity (e.g., slow frontal vs. fast centroparietal spindles) was observed also with noninvasive scalp measurements (Anderer et al. 2001; De Gennaro and Ferrara 2003; Schabus et al. 2007; Ferrarelli et al. 2010), whereas several other novel aspects such as timing differences between brain regions, frequency changes across sleep, and the lack of robust firing rate modulations (Andrillon et al. 2011) were previously unknown.

9.3.5.3 Gamma and Ripple Oscillations During Slow-Wave Sleep

Gamma oscillations (40–120 Hz) are usually associated with waking functions such as sensory binding (Singer and Gray 1995), attention (Fries et al. 2001), or encoding/retrieval of memory traces (Montgomery and Buzsaki 2007) and have been shown to be closely related to correlated neuronal activity in humans during wakefulness (Nir et al. 2007). These oscillations are also present during SWS, as shown by extensive evidence from in vivo (Steriade et al. 1996; Grenier et al. 2001; Isomura et al. 2006; Mena-Segovia et al. 2008) and in vitro recordings of the rodent and feline cortex (Dickson et al. 2003; Compte et al. 2008). These experiments have shown that gamma oscillations occur preferentially during the active (UP) component of the slow wave – characterized by rhythmic cycles of synaptically mediated depolarization – and disappear during the hyperpolarized (DOWN) phase. Recent microelectrode studies in the human cortex during sleep have confirmed that gamma oscillations are reliably associated with EEG slow waves and with a marked increase in local cellular discharges (Cash et al. 2009; Le Van Quyen et al. 2010). Also, coincident firings with millisecond precision between cells within the same cortical area were shown to be strongly enhanced during gamma oscillations (Le Van Quyen et al. 2010). Cortical gamma patterns in sleep have been suggested to briefly restore "micro-wake" activity (Destexhe et al. 2007; Haider and McCormick 2009) and may be important for consolidation of memory traces acquired during previous wakefulness. Along this line, coupling between parahippocampal gamma oscillations and hippocampal ripple/sharp-wave complexes has been reported in humans (Le Van Quyen et al. 2010); Fig. 5C). Ripple oscillations (80–160 Hz) are known to coincide with reactivation of hippocampal activity patterns (Wilson and McNaughton

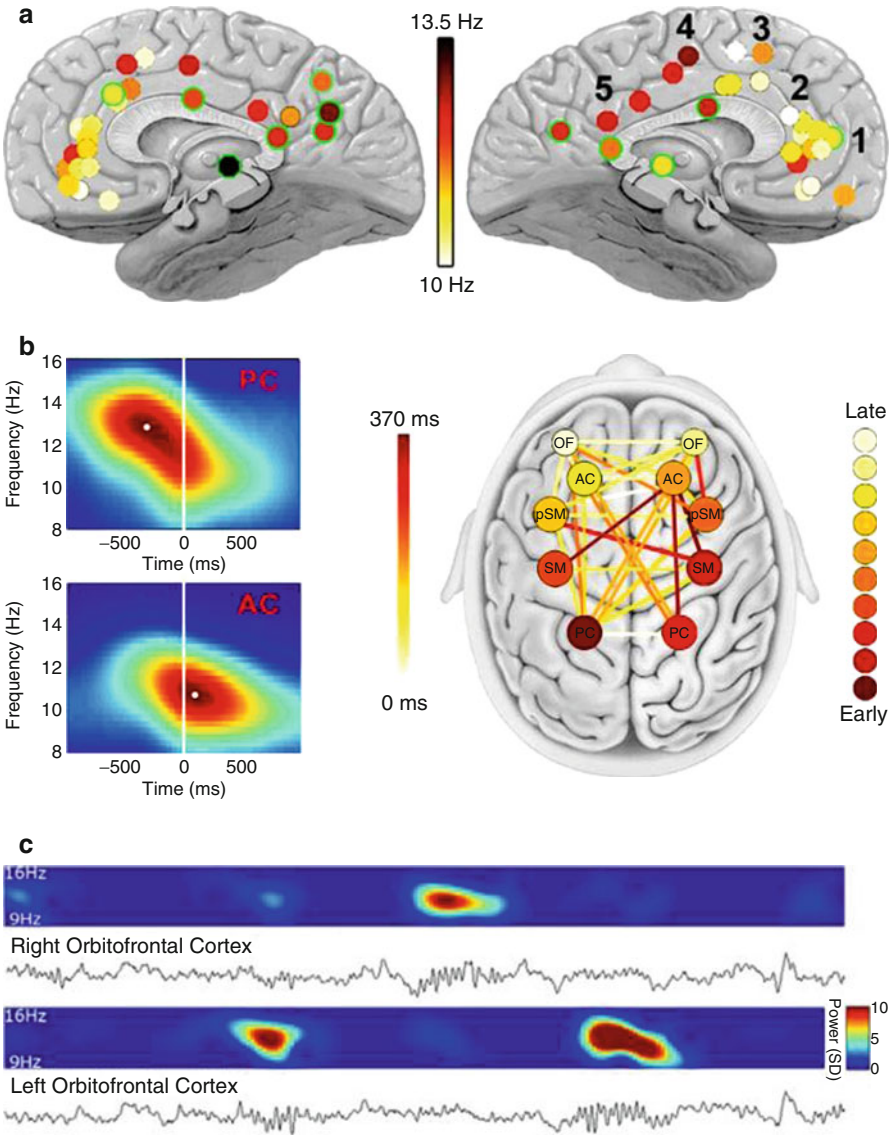

Fig. 9.8 (**a**) Average frequency of spindles across the medial brain; note the contrast between slow (9–12 Hz) frontal spindles and fast (13–16 Hz) centroparietal spindles. (**b**) Fast centroparietal spindles precede slow frontal spindles by 200 ms on average; (*left*) an example of differences in timing and frequency between early, fast spindles in posterior cingulate (*PC*) and late, slower spindles in anterior cingulate (*AC*). (*Right*) a graph showing a quantitative analysis of the order in which spindles are detected across multiple regions (*node color*) and the mean temporal delays between each pair of regions (*edge color*). (**c**) Example of a local sleep spindle as seen in depth EEG across bilateral orbitofrontal cortex along with corresponding spectrograms in the spindle frequency range (9–16 Hz) during 15 s of slow-wave sleep. (**d**) Spindle frequency reflects sleep depth. Representative time course of slow-wave activity (SWA) and spindle frequency dynamics throughout sleep in the anterior cingulate of one individual. Note that spindle frequency is lowest in deep sleep when SWA is highest and increases toward transitions to REM sleep (From Andrillon et al. 2011)

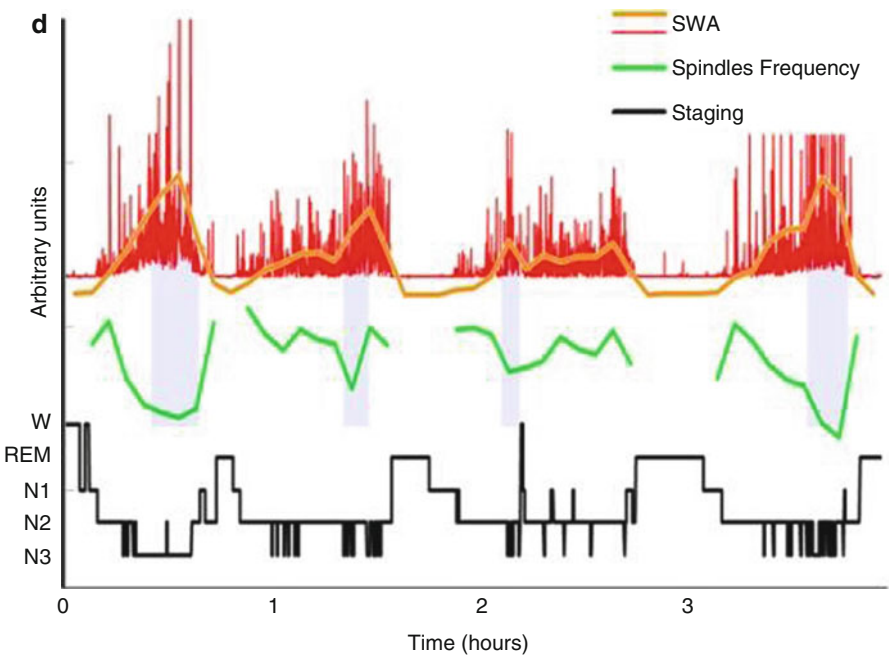

Fig. 9.8 (continued)

1994) which could reflect information flow from the hippocampus to the cortex. In the human hippocampus and entorhinal cortex, ripples are similar to those described in non-primate CA1 and CA3 in terms of duration and spectral frequency, bilateral occurrence in hippocampal areas, highest probability of occurrence during NREM sleep, and minimal occurrence during REM sleep (Buzsaki et al. 1992; Staba et al. 2004; Le Van Quyen et al. 2008). Thus, human microelectrode studies show that high-frequency gamma and ripple oscillations robustly occur and modulate single neuron firing during sleep. Moreover, slower fluctuations such as slow waves group and modulate faster "nested" oscillations such as cortical spindles, gamma events, and hippocampal ripples (Clemens et al. 2007; Le Van Quyen et al. 2010; Andrillon et al. 2011; Nir et al. 2011) confirming findings in animal studies (Sirota et al. 2003; Battaglia et al. 2004; Steriade 2006).

9.3.5.4 Ultraslow Resting-State Fluctuations in Sleep and Wakefulness

Although perception and action occur on the sub-second timescale, it has long been recognized that cortex also shows fluctuations in electrical activity with slower dynamics. As discussed in Sect. 9.3.3, resting-state ultraslow fluctuations (<0.1 Hz, at the timescale of tens of seconds) in blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signals have gained attention as a powerful tool to study functional brain networks in health and disease (Fox and Raichle 2007). However, the extent to which such waves reflect neuronal activity or may stem from nonneuronal sources (e.g., cardiac, respiratory) remained unclear. Recent intracerebral recordings (He et al. 2008; Nir et al. 2008) established that spontaneous

ultraslow neuronal activity can indeed be detected in direct cortical recordings and that it exhibits significant correlations between nodes within the same functional system. An important open question in this field is whether such resting-state waves may reflect cognitive processes such as mind wandering, shifts in attention or mental imagery, or whether they may be more closely related to basic maintenance of synaptic contacts (Balduzzi et al. 2008). Interestingly, ultraslow waves in humans were found to persist and grow stronger in sleep. They are also present in anesthesia (Vincent et al. 2007) and to some extent in vegetative patients (Ovadia-Caro et al. 2012) thus arguing against involvement of such waves in conscious processes.

In summary, by analyzing simultaneous activity across multiple brain regions, microelectrode studies of human sleep demonstrated that slow waves and sleep spindles (Nir et al. 2011) as well as gamma bursts (Le Van Quyen et al. 2010) are mostly local. The local nature of sleep slow waves has recently been confirmed in animal studies (Vyazovskiy et al. 2011; see also Sirota and Buzsaki 2005; Mohajerani et al. 2010). Thus, an important new theme that has emerged from single-unit human studies is that sleep oscillations are much more heterogeneous than initially assumed (Magnin et al. 2010; Andrillon et al. 2011; Hangya et al. 2011; Nir et al. 2011). Regional diversity in occurrence, spectral, and temporal aspects of sleep oscillations were hardly observable with noninvasive human imaging, when recording from a limited number of brain regions in rodents or when using anesthesia as a model for sleep.

9.4 Local Sleep and Dissociated States

9.4.1 Local Sleep: Mixed States, Sleep Onset, and Sleep Inertia

The main new finding put forward by recent intracranial studies of human sleep is that most sleep slow waves and the underlying active and inactive neuronal states occur locally, and this is also the case for sleep spindles (Nir et al. 2011). The demonstration that sleep oscillations typically occur in a local manner highlights the notion that at a fundamental level, electrophysiological features associated with particular vigilance states such as sleep or wakefulness may regularly occur independently in different brain regions. This finding in normal sleep adds to several lines of evidence supporting the notion of mixed states and their underlying local activities and offers a new emerging perspective on behavioral states and underlying brain activities (Nobili et al. 2012).

While mammalian sleep is typically associated with distinct electrophysiological markers, it is important to note that sleep is first and foremost defined as a reversible state of reduced behavioral responsiveness (Carskadon and Dement 2005). Given the primacy attributed to behavior, the global changes in neuromodulation (Jones 2005a), and the clear-cut changes in the EEG (driven in large part by central subcortical arousal networks such as the reticular activating system (Moruzzi and Magoun 1949)), sleep has been traditionally regarded as a global phenomenon.

However, it has been proposed that sleep may be fundamentally a local property of neuronal ensembles and that behavioral sleep emerges only when local sleep

emerges over sufficiently large cortical regions (Krueger et al. 2008; Rattenborg et al. 2012). Along this line, there is evidence that electrophysiological signatures of sleep and wakefulness can be restricted to small populations such as individual cortical columns (Pigarev et al. 1997; Rector et al. 2005). Along this line, naturally occurring sleep patterns in dolphins (Mukhametov and Rizzolatti 1970), seals (Siegel 2009), and birds (Rattenborg et al. 2001) suggest that parts of the brain can be awake while others are asleep, a condition that may have evolved in those species in order to facilitate continuous flying or swimming in the face of dissipating sleep need.

Furthermore, slow waves can be locally regulated so that their intensity varies among cortical regions. Prolonged waking induces an increase in slow-wave activity (SWA; EEG power <4 Hz), which is largest over the frontal cortex (Werth et al. 1997; Finelli et al. 2001). Sleep slow waves can be locally regulated as a function of prior use and plastic processes (Vyazovskiy et al. 2000; Huber et al. 2004, 2006). Local gradients of SWA intensity and SWA regulation are also coherent with the spatiotemporal dynamics of slow waves during full-fledged NREM sleep. As we have seen (Fig. 9.3d), slow waves originate more frequently at anterior cortical regions and tend to propagate from medial prefrontal cortex to the MTL through the cingulate gyrus and neighboring structures (Massimini et al. 2004; Volgushev et al. 2006; Murphy et al. 2009; Vyazovskiy et al. 2009a; Nir et al. 2011; Riedner et al. 2011).

In further support of mixed states consisting of coexisting wake-like and sleep-like activity patterns, recent intracranial studies of human sleep demonstrated long-lasting (10–120 s) local awakenings within the sleeping brain. For example, local activation as indicated by abrupt increases in high-frequency EEG power within the motor cortex occurs synchronously with deep-sleep EEG patterns in the dorsolateral prefrontal cortex and scalp EEG (Nobili et al. 2011). As noted in the earlier sections, primary cortices are often reported to be the least deactivated brain regions in NREM sleep (Braun et al. 1997; Dang-Vu et al. 2005), and it has been hypothesized that this pattern may have been evolutionary selected to increase the probability of survival by facilitating motor behaviors in case of sudden awakenings (Nobili et al. 2012). Such local cortical awakenings could also underlie confusional arousals (Terzaghi et al. 2009), as discussed in more detail below in the section on dissociated states.

Conversely, sleep-like activities may occur during wakefulness. During prolonged wakefulness, the EEG gradually shows a progressive increase in slow frequency activities reflective of increased homeostatic sleep pressure (Finelli et al. 2000; Vyazovskiy and Tobler 2005). Indeed, it was noted that sleep-deprived monkeys may be able to activity control behavior with some neural circuits, while others are idle (Pigarev et al. 1997). More recently, it was demonstrated directly that in freely behaving rats, after a long period of wakefulness, cortical can go briefly "off-line" exactly as in sleep (i.e., showing brief OFF periods resembling those of the sleep slow oscillation) in one cortical area but not in another (Vyazovskiy et al. 2011). The incidence of such local OFF periods increases with the duration of the awake state, while rats are active and display an "awake" EEG. However, they are progressively impaired in a sugar-pellet-reaching task.

Another condition where mixed states seem to be particularly prevalent is during sleep onset. Magnin et al. (2010) showed that when falling asleep, the emergence of slow waves is highly asynchronous across brain regions, such that the thalamic deactivation precedes that of the cortex by several minutes. Moreover, several minutes before sleep onset, sleep spindles emerge in the hippocampus along with early slow-wave activity in the anterior thalamic nuclei (Nobili et al. 2012). Within cortex, anterior frontal regions are the first to show synchronized sleep EEG signatures (De Gennaro et al. 2001). Interestingly, frontal cortex shows the strongest slow-wave activity throughout sleep (Werth et al. 1997). Since SWA is an established marker of sleep intensity, it seems that frontal cortex possesses the strongest sleep need and consequently "falls asleep" before other regions do. Interestingly, many subjects awakened from early stage N1 sleep claim that they had been awake. Such mismatch between subjective reports of sleep onset and the electrophysiological markers of scalp EEG may not be surprising given that sleep does not seem to begin simultaneously in all cortical and subcortical areas. In addition, such sleep onset asynchrony may help explain in part the long sleep latency in patients with insomnia and paradoxical insomnia (Nobili et al. 2012).

Mixed patterns of activities reflecting local wakefulness and sleep could also be related to the phenomenon of sleep inertia (Ferrara et al. 2006; Marzano et al. 2011) – the subjective feeling of grogginess accompanied by decreased levels of cognitive and behavioral performance which typically follows the awakening. For example, a PET study (Balkin et al. 2002) demonstrated that post-sleep waking patterns of regional CBF were reestablished at different rates in different brain areas, most rapidly in centrencephalic regions (e.g., brainstem and thalamus) and then in the anterior cortical regions (prefrontal association cortices) across the ensuing 15 min of wakefulness. In an EEG study (Ferrara et al. 2006), the first 10 min after awakening was characterized by increased EEG power in the 1–9 Hz range especially over parieto-occipital range and decreased power in the beta range (18–24 Hz) especially over occipital areas, suggesting that posterior brain areas may take longer to become fully "awake."

9.4.2 Dissociated States

The next section will consider a number of conditions that lie in between waking and sleep: They partake of some features typical of waking consciousness as well as of some characteristic of consciousness in sleep – that is, they represent dissociated states (Mahowald and Schenck 2005). Some of these conditions, such as daydreaming and lucid dreaming, are perfectly normal and can even be learned; others occur in the context of sleep disorders that provide further striking examples that sleep and wakefulness might be simultaneously present in different cerebral regions. These clinical conditions, known as parasomnias, include some of the most remarkable examples of pathological dissociation between consciousness, awareness of the environment, reflective consciousness, and behavior.

9.4.2.1 Daydreaming

A common definition of daydreaming is "a dreamlike musing or fantasy while awake, especially of the fulfillment of wishes or hopes." For experimental purposes, daydreaming can be defined as "stimulus independent mentation," that is, as waking images and thoughts that are independent of the task at hand (Singer 1993). Daydreaming is extremely common. Indeed, no matter how hard one concentrates on the task at hand, a surprising amount of time is spent drifting off into fantasies and interior monologues of one kind or another. If subjects are periodically interrupted for thought sampling during a signal-detection task, they report stimulus-independent mentation at least 35 % of the time, even under heavy processing loads. Their reports also indicate discontinuities and scene changes that are more frequent than in REM sleep. There have been attempts at further categorizing waking mental activities and validating such categories using questionnaires and factor analysis. Relevant dimensions are (1) directed or operant vs. non-directed or respondent thought (the former voluntarily directed toward accomplishing a task), (2) stimulus bound vs. stimulus independent, (3) realistic vs. fanciful, (4) well integrated (orderly, connected, coherent) vs. degenerated, and (5) vivid vs. non-vivid. A prototypical daydream would be non-directed, stimulus independent, fanciful, and non-integrated. Recall of waking images and thoughts experienced while daydreaming can be as poor as dream recall, possibly because, just as dream images, daydreaming images cannot be referenced by external events.

The neural circuits involved in daydreaming are beginning to be studied. For instance, using both thought sampling and brain imaging (Mason et al. 2007), a recent study showed that mind wandering is associated with activity in the same default network of cortical regions that are active when the brain is not actively engaged in a task (Raichle et al. 2001). Regions of the default network that exhibited greater activity during mind wandering included bilateral medial prefrontal cortex, anterior cingulate, posterior cingulate, precuneus, insula, left angular gyrus, as well as superior temporal cortex. In addition, individuals' reports of the tendency of their minds to wander were correlated with activity in this network (Mason et al. 2007). Based on these results, however, it would seem that the circuits activated during daydreaming may actually be different from those involved in dreaming, given that, for instance, posterior cingulate, precuneus, and lateral parietal cortex are relatively deactivated during REM sleep (Maquet et al. 1996; Braun et al. 1997; Nir and Tononi 2010).

9.4.2.2 Lucid Dreaming

Dreams usually involve loss of self-reflection and of reality testing. Hallucinations and delusions in dreams are typically thought to be real rather than dreamt up. Sometimes, however, a dreamer can become aware that he is dreaming (LaBerge 2000). Under such circumstances, the dreamer is able to remember the circumstances of waking life, to think clearly, and to act deliberately upon reflection all while experiencing a dream world that seems vividly real. Lucid dreaming can be cultivated, typically by a pre-sleep autosuggestion procedure: the key is to remember that if one is experiencing something bizarre, such as floating in space, it must

be a dream rather than a waking experience. In fact, lucid dreamers often attempt to fly: If they succeed, they know they are probably dreaming. Lucid dreaming has been extensively studied in the laboratory by asking trained subjects to carry out distinctive patterns of voluntary eye movements when they realize they are dreaming. The prearranged eye movement signals appear on the polygraph records during REM sleep, proving that the subjects had indeed been lucid during uninterrupted REM sleep. This strategy has been used to demonstrate that time intervals estimated in lucid dreams are very close to actual clock time, that dreamed breathing corresponds to actual respiration, and that dreamed movements result in corresponding patterns of muscle twitching. Stable lucid dreams apparently only occur out of REM sleep, especially in the early morning, when REM sleep is accompanied by intense phasic phenomena. A recent EEG study (Voss et al. 2009) has shown that during lucid dreaming, gamma activity is higher than in typical REM sleep, especially over frontal cortex. Moreover, EEG coherence throughout the frequency spectrum in lucid dreaming is significantly higher than in REM sleep, even higher than in wake for the delta and theta band (but lower for the alpha band), especially over frontal areas. Thus, lucid dreaming may indeed be a distinctive state in its own right.

9.4.2.3 Sleepwalking

Sleepwalking refers to various complex motor behaviors, including walking, that are initiated during deep NREM sleep, typically during stage N3 (Bassetti 2009). Some episodes may be limited to sitting up, fumbling, picking at bedclothes, and mumbling. Patients usually stand up and walk around quietly and aimlessly. Sleepwalkers walk around with open eyes and sometimes speak, though slowly and often inarticulately. They behave as if they were wide awake though their awareness of their actions is very restricted. Occasionally, sleepwalkers become agitated, with thrashing about, screaming, running, and aggressive behavior. A highly publicized case is that of Ken Parks, a sleepwalker who, after falling asleep at home, arose to drive to his in-laws, strangled his father-in-law into unconsciousness, and stabbed his mother-in-law to her death.

Sleepwalking is frequent in children, but it can persist in up to 1 % of adults. In predisposed individuals, attacks can be precipitated by forced arousals, e.g., by placing the subject afoot. Sleepwalking is regarded as a disorder of arousal with frequent but incomplete awakening from slow-wave sleep. If awakened during an episode, sleepwalkers typically do not report any dreamlike mental activity, although in a few cases hallucinations have been reported. There is almost never any memory of the behaviors carried out while sleepwalking. The episodes begin while the EEG shows high-amplitude slow waves. During the episodes, the EEG decreases in amplitude and increases in frequency, usually leading to the appearance of mixed-frequency patterns typical of stage N1. There may also be rhythms resembling the alpha rhythm of waking, but slower by 1–2 Hz and not abolished by eye opening or visual stimulation. During short episodes of sitting up with eyes open and moving around, the EEG may show slow waves throughout – providing a clear-cut dissociation between observable behavior, brain activity, and consciousness.

A recent study has succeeded in performing neuroimaging during a sleepwalking episode using single-photon emission computed tomography, a variant of PET (Bassetti et al. 2000; Bassetti 2009). The patient, a 16-year-old man, stood up with his eyes open and a scared facial expression. After a few seconds, he sat down, pulled on the EEG leads, and spoke a few unintelligible words. The EEG showed diffuse, high-voltage rhythmic slow-wave activity. Compared to waking, regional cerebral blood flow was decreased during sleepwalking in frontoparietal associative cortices, just as it is in slow-wave sleep. This deactivation of prefrontal cortices during normal sleep and sleepwalking is consistent with the lack of self-reflective consciousness and recall that characterize both conditions. However, blood flow was higher during sleepwalking than in slow-wave sleep in the posterior cingulate cortex and anterior cerebellum, and the thalamus was not deactivated as it is during normal slow-wave sleep. Thus, at least in this patient, sleepwalking seems to arise from the selective activation of thalamo-cingulate circuits and the persisting deactivation of other thalamocortical systems. Normally, the entire forebrain is either awake or asleep. Sleepwalking thus appears to constitute a dissociated state where some brain areas are "awake" while others are "asleep." It is likely that, in different patients or at different times in the same patient, different areas may be awake or asleep. This interpretation is supported by a recent intracranial study (Terzaghi et al. 2009) in an epileptic patient suffering form confusional arousals – an NREM sleep parasomnia closely related to sleepwalking. During an episode of confusional arousal, the motor and cingulate cortices were precociously activated and displayed the same fast activity seen during wakefulness, while the frontoparietal associative cortices displayed an enhancement of delta activity.

Sleeptalking is a more frequent occurrence than sleepwalking, and it can occur both in NREM and REM sleep. The majority of sleep speeches contain at least a few words, but they range from a single, mumbled utterance to several minutes of perfectly intelligible talk, the latter more frequently associated with REM sleep. Sometimes sleeptalk is clearly a soliloquy; at other times, it may resemble telephone conversation. While there is some correspondence between sleeptalking and dream content, more often one has the impression of multiple, concurrent stream of mental activity that occur independently and in parallel. Such instances suggest that the speech-production system may be active in relative isolation from dream consciousness, thereby constituting another example of dissociation.

9.4.2.4 REM Sleep Behavior Disorder

This disorder, which affects mostly elderly males, is characterized by vigorous, often violent episodes of dream enactment, with punching, kicking, and leaping from bed (Mahowald and Schenck 2005). Patients often injure themselves or their spouses. For example, a male subject would dream of defending his wife, but in enacting his dream he would actually forcefully strike her in bed. In rare cases there can be well-articulated speech. Polysomnographic recordings demonstrate that such episodes occur during REM sleep. Unlike sleepwalkers, who usually have no recollection of what they were thinking or dreaming at the time of their actions, people with REM sleep behavior disorder can usually recall their dreams in detail.

Conscious experience during an episode is extremely vivid, as in the most animated dreams, and is fully consistent with the motor activity displayed.

Much before the clinical syndrome was recognized in humans, sleep researchers had observed that if certain regions of the pons that are normally responsible for inhibiting muscle tone and motor programs during REM sleep are lesioned, cats seem to "enact their dreams" of raging, attacking, fleeing, or eating while not responding to external stimuli (Sastre and Jouvet 1979; Morrison 1988). In humans, the disorder most often occurs without an obvious cause, but it is sometimes associated with neurological conditions. It may indeed result from minute lesions in the pons, it may anticipate the development of Parkinson's disorder, and it may be triggered acutely by certain drugs (certain antidepressants) or by withdrawal (ethanol).

9.4.2.5 Narcolepsy and Cataplexy

Narcolepsy is characterized by daytime sleepiness (sleep attacks), cataplexy (muscle weakness attacks), hypnagogic hallucinations, and sleep paralysis (Mahowald and Schenck 2005). Narcolepsy usually begins with excessive sleepiness and unintentional naps in the teens and 20s. Sleepiness is especially strong during periods of inactivity and may be relieved by short naps. When narcoleptics fall asleep, they usually go straight into REM sleep. Not surprisingly, patients complain that they have a short attention span, have poor memory, and sometimes behave in an automatic, uncontrolled way. The sleepiness seems to be due to a problem staying awake rather than to an increased need for sleep, since narcoleptics generally get enough sleep at night. In more than half of the cases, narcolepsy is accompanied by cataplexy. This is a sudden loss of muscle tone, typically brought on by strong emotions such as laughter or anger. The sudden weakness may be generalized and force the patient to collapse to the ground, or it may be localized to the voice, the chin, or a limb. Each episode generally lasts only a few minutes. Consciousness and awareness of the environment are preserved during cataplectic attacks, unless sleep intervenes. Hypnagogic hallucinations are dream-like hallucinations, mostly visual, that occur at sleep onset or when drowsy. Sleep paralysis is a frightening feeling of not being fully conscious but unable to move, which may occur on awakening or falling asleep, like a temporary version of the locked-in syndrome (Gosseries et al. 2009). Healthy individuals can experience hypnagogic hallucinations, especially when sleep deprived, and may also experience sleep paralysis. However, while laughter and other emotional stimuli can produce muscle relaxation in healthy individuals, cataplexy is definitely an abnormal phenomenon. Sleep paralysis and cataplexy are probably due to the inappropriate activation of the brainstem mechanisms responsible for abolishing muscle tone during REM sleep. Narcolepsy–cataplexy are known to be associated with a defect in the hypocretin/orexin system (Dauvilliers et al. 2007). Narcoleptic dogs and mice have a mutation in the gene for hypocretin or its receptors and, in the brain of narcoleptic patients, there is a loss of hypocretin cell groups in the posterior hypothalamus.

9.5 When and Why Do We Lose Consciousness in Sleep?

Sleep highlights several interesting paradoxes about the relationship between consciousness and the brain. For instance, it was first thought that the fading of consciousness during sleep was due to the brain shutting down. However, while metabolic rates decrease in some cortical areas (see Sect. 9.3.3), thalamocortical neurons may remain active also during slow-wave sleep, with mean firing rates comparable to those of quiet wakefulness (see Sect. 9.3.5.1; (Steriade et al. 2001; Nir et al. 2011)). It was also hypothesized that sensory inputs are blocked during sleep and that they are necessary to sustain conscious experience. However, we now know that, even during deep sleep, sensory signals continue to reach the cerebral cortex (Kakigi et al. 2003) where they are processed subconsciously (Portas et al. 2000). Gamma activity and synchrony have been viewed as possible correlates of consciousness, and some studies found them to be low in slow-wave sleep (Cantero et al. 2004; He et al. 2008). However, they may be equally low in REM sleep, when subjective experience is usually vivid, and they can be high in anesthesia (Vanderwolf 2000). On the other hand, intracellular recordings show that gamma activity and gamma coherence (Bullock et al. 1995) persist during slow-wave sleep. Interestingly, similar paradoxes, where neural activity levels, access to sensory information, and the degree of neural synchrony do not correlate with the level of consciousness, can be found in other conditions such as anesthesia, epilepsy, and brain-injured patients. In this sense, sleep may represent a physiological model to investigate why consciousness fades, transforms, and reappears in the brain.

The rapid succession of differentiated, unified conscious scenes that characterizes subjective experience is thought to rely on the ability of multiple, functionally specialized cortical areas to interact rapidly and effectively to form an integrated whole. Hence, an emerging idea in theoretical neuroscience is that consciousness depends on the ability of distributed cortical areas to engage in complex activity patterns that are, at the same time, spatially extended (integrated) and information rich (differentiated). As described in Sect. 9.3.4, TMS/EEG measurements show that, while in wakefulness TMS triggers a balanced response where different cortical areas become activated at different times giving rise to a complex pattern, during early NREM sleep cortical responses become a positive–negative wave that is either local or global and stereotypical, depending on stimulation intensity (Massimini et al. 2005). This finding suggests that this ability to integrate information is lost during NREM sleep early in the night, when reports of conscious experience upon awakening are least likely.

What prevents the emergence of a long-range, differentiated pattern of activation during sleep? It is possible that the mechanism underlying the impaired capacity of the sleeping brain to engage in complex activity patterns is the same mechanism that underlies the occurrence of spontaneous sleep slow waves, that is, bistability in thalamocortical circuits (Massimini et al. 2009). Upon falling asleep, brainstem activating systems reduce their firing rates, thus increasing the influence of depolarization-dependent K+ currents in thalamic and cortical neurons (McCormick et al.

1993). These hyperpolarizing K+ conductances become stronger after neurons have become depolarized and have fired action potentials. Due to these currents, neurons become bistable and tend to fall into a silent, hyperpolarized state (down state) after a short period of activation (up state), such as the one induced by TMS. As suggested by modeling studies, a shift in the balance of synaptic excitation and inhibition toward inhibition due to changes in the neuromodulatory milieu may also contribute to bistability (Esser et al. 2009). As a consequence, any local activation, whether occurring spontaneously or induced by a stimulus (like TMS), will converge into a silent neuronal down state and into a stereotypical EEG slow wave (Hill and Tononi 2005). Thus, the intense bistability with frequent and prolonged OFF periods during early NREM sleep (Vyazovskiy et al. 2009b) is likely to prevent the occurrence of sustained depolarization, a precondition for the establishment of sustained, complex thalamocortical interactions. Moreover, given the recent evidence that OFF periods in NREM sleep are mostly local, i.e., they occur asynchronously, especially in distant cortical areas (Nir et al. 2011), then interactions among distant cortical areas are particularly vulnerable to disruption by bistability, because longer reentrant loops involving multiple nodes can be interrupted by an OFF period in any node. If information integration among distributed cortical regions is indeed necessary for consciousness, then, it follows that consciousness during sleep should be maximally impaired when OFF periods are frequent and longer-lasting, as in early NREM sleep, and minimally so when OFF periods are largely absent, as in REM sleep, or rare and short, as in late NREM sleep (Vyazovskiy et al. 2009b).

Future studies, possibly employing intracranial perturbations and recordings in humans, are warranted in order to evaluate the role of bistability and cortical down states in reducing the information-processing capability of thalamocortical networks during NREM sleep. Is the breakdown of corticocortical effective connectivity actually associated with a neuronal down state as indicated by an actual suppression of neuronal discharge? Is the rebound of activation that follows the down state uncorrelated to the stimulus, suggesting a loss of causality in the temporal domain? Are the local slow waves revealed by intracranial recordings (Nir et al. 2011) preventing the propagation of activity to specific regions of the brain, resulting in functional disconnections? Are these roadblocks specific for different stages of sleep? What are the spatial relationships between spontaneous slow waves and covert bistability, as revealed by slow waves evoked by cortical stimulation? Hopefully, some of these questions may be answered in the next few years.

9.6 Is Consciousness During Sleep More Akin to Perception or Imagination?

Whether dreams are generated in a “bottom-up” or a “top-down” manner is a question that has been asked since at least Aristotle (350 B.C.). To put the question in a modern context, do dreams start from activity in low-level sensory areas, which is then interpreted and synthesized by higher-order areas, as is presumably the case in waking perception? Or do they begin as wishes, abstract thoughts, and memories

deep in the brain, which are then enriched with perceptual and sensory aspects, as in imagination? Of course, it is possible that such a dichotomy is misguided, and dreams may be best conceptualized as global attractors that emerge simultaneously over many brain areas. However, as we shall see, the available data do indeed suggest that there may be a privileged direction of dream generation (Nir and Tononi 2010).

In the nineteenth century, sensory experience was often regarded as the source of dreams, which were considered to be an attempt of the mind to interpret somatic nerve stimuli. A similar notion was later adopted by Allan Hobson (Hobson et al. 2000; Hobson and Pace-Schott 2002; Hobson 2009; Nir and Tononi 2010). According to his AIM model, internally generated signals originating in the brainstem during REM sleep, such as PGO waves, excite visual cortex and are later processed and synthesized by higher-order areas. High levels of acetylcholine in the absence of aminergic neuromodulation may enhance feed-forward transmission and suppress back-propagation (Hobson 1988; Hasselmo 1999). By contrast, Freud and some of his followers asserted that dreams originate from psychic motives that are later instantiated as sensory percepts, much like mental imagery (Freud 1900).

Deciding between these alternative views will most likely require difficult experiments in which the direction of signal flow during dreaming sleep is evaluated and compared to that during waking perception and imagery (Buzsaki 1996; Nir and Tononi 2010). However, various lines of evidence already suggest that dreaming may be more closely related to imagination than to perception. From lesion studies, we know that dreaming requires an intact temporo-parieto-occipital junction (Solms 1997, 2000), and lesions in this region also affect mental imagery in wakefulness (Kerr and Foulkes 1981). Cognitive studies indicate that the skill that maximally correlates with dream recall in adults is visuospatial imagery (Butler and Watson 1985). In children, dream recall develops hand in hand with visuospatial imagery (Nir and Tononi 2010). In epileptic patients, direct electrical stimulation in high-order regions such as the medial temporal lobe, rather than in visual cortex, can elicit "dreamlike" experiences (Penfield and Jasper 1954), although such patients are simultaneously aware of their surroundings. Other evidence comes from lucid dreamers (LaBerge 2000) who report that it is impossible to focus on fine-grain details of visual objects, as is the case in mental imagery (Finke and Kurtzman 1981). Perhaps top-down connections lack the anatomical specificity to support detailed representations. The rare occurrences of smells or pain in dreams may also be related to our difficulty in imagining them vividly when awake. However, one important difference between dreaming and mental imagery is that while imagining we are aware that the images are internally generated (preserved reflective thought).

If the flow of brain activity during dreaming were shown to be largely backward, as one would expect in imagery, rather than forward, as in perception, many of the seemingly bizarre properties of dreams, such as blended characters and scene switches, would be easier to explain, as they are standard features of our imagination. Such a top-down mode may disrupt the encoding of new memories and thus underlie dream amnesia. In addition, top-down mental imagery could obstruct the processing of incoming stimuli and disconnect us from the environment (see final section below). If this view is correct, waking consciousness is more like watching

the news in real time, while dreaming is more like watching a movie created by an imaginative director (Tononi 2009). As in some B-movies, the director is not particularly choosey and any actor, dress, means of transportation, or object that is readily available will do. Albert Einstein said that "imagination points to all we might yet discover and create," and indeed, dreaming may turn out to be the purest form of our imagination.

9.7 Why Is Sleep Consciousness Disconnected from the Environment?

The most obvious difference between consciousness during sleep and wakefulness is the profound disconnection from the environment. Such disconnection, of course, is a key feature of sleep: By definition a sleeping person shows no meaningful responses to external stimuli, unless they are strong enough to cause an awakening as may happen with the sound of an alarm clock. Such a high "arousal threshold" gradually increases with the succession of NREM sleep stages and persists also in REM sleep (Rechtschaffen et al. 1966; Neckelmann and Ursin 1993). Moreover, stimuli largely fail to be incorporated in the content of dreams (Rechtschaffen 1978; Nir and Tononi 2010), though some stimuli such as a spray of water, pressure on the limbs, and meaningful words have a slightly higher chance of incorporation (Dement 1958; Berger 1963; Koulack 1969). For example, if we are to sleep all night in front of the television, our dreams will have little, if anything, to do with the contents of the surrounding stream of sounds. This striking disconnection occurs even when subjects sleep with their eyes taped open and objects are illuminated in front of them (Rechtschaffen and Foulkes 1965). By and large, consciousness in sleep is remarkably disconnected from the external environment, posing an intriguing paradox – especially if one considers that it persists in REM sleep along with strong cortical activation and along with dreams involving vivid sensory experiences.

It has been suggested that during NREM sleep and anesthesia, disconnection is due to "thalamic gating" where a burst-silence mode of activity in the thalamus does not relay peripheral sensory inputs effectively to the cortex (McCormick and Bal 1994; Steriade 2003). Along this line, attenuated single-unit responses in NREM sleep have been reported in thalamic sensory relay nuclei (Mukhametov and Rizzolatti 1970; Livingstone and Hubel 1981; Mariotti et al. 1989; Edeline et al. 2001) and primary visual and somatosensory cortices (Evarts 1963; Gucer 1979; Livingstone and Hubel 1981). However, several lines of evidence suggest that thalamic gating can not sufficiently explain sleep disconnection. First, recent studies in the auditory system demonstrate that neuronal responses in primary auditory cortex (A1) are comparable in sleep and wakefulness (Pena et al. 1999; Edeline et al. 2001; Issa and Wang 2008; Nir et al. 2012). Second, functional imaging in humans reported comparable activation in wakefulness and NREM sleep at the level of A1 (Portas et al. 2000) although some challenge this view (Czisch et al. 2002). Third, event-related potential (ERP) studies in humans suggest that potentials that are attributed to sensory cortices are largely preserved during sleep (Colrain and Campbell 2007)

and that some semantic analysis of auditory stimuli remains possible in the sleeping human brain (Bastuji et al. 2002). Fourth, olfactory stimuli are not directly incorporated in dreams (Schredl et al. 2009) suggesting that we remain disconnected also from these stimuli, though they are not routed through the thalamus.

A related notion is that of a cortical "gate" leading to diminished inter-cortical propagation (Esser et al. 2009), as seems to be the case in the dissociation of primary visual cortex (V1) from high-order visual cortex in REM sleep (Braun et al. 1998). As discussed earlier, regional NREM sleep oscillations (Nir et al. 2011) may promote a state of functional disconnection that could prevent activity in primary sensory regions from effectively driving that in high-order cortical nodes (Massimini et al. 2005). Indeed, in those cases that reported comparable auditory responses in thalamus and A1 across sleep and wakefulness (Portas et al. 2000), sounds could not drive the activity of high-order (frontoparietal) networks as effectively in sleep.

Recent EEG–fMRI studies emphasize that the processing of auditory stimuli in sleep may also be largely dependent on momentary changes in underlying activity. Along this line, Dang-Vu et al. (2011) showed that acoustic responses in thalamus and A1 present during wakefulness persisted in NREM sleep except during spindles, during which responses became less consistent. When sounds induced a K-complex, activity in the auditory cortex was enhanced and responses in distant frontal areas were elicited, similar to the stereotypical pattern associated with slow oscillations. Schabus et al. (2012) also showed that responses to sounds outside A1 (at higher cortical levels) decreased when their presentation co-occurred with the negative going phase of the scalp EEG slow oscillation. Thus, in deep NREM sleep, the brain may be more responsive between spindles and during the positive going slope of the slow oscillation. Wehrle et al. (2007) found that auditory responses during phasic periods of REM sleep (with bursts of rapid eye movements and muscle twitches) were correlated with a lack of reactivity to sensory stimuli compared with tonic REM sleep. These findings are in line with the observation of a higher arousal threshold during phasic as compared to tonic REM sleep in humans (Ermis et al. 2010). Taken together, such recent findings highlight the significant heterogeneity in brain responsivity that exists during sleep, even during epochs occurring within the same sleep stage.

Another important consideration with regard to sleep disconnection is that the neuromodulatory milieu changes drastically in sleep (Fig. 9.3). Specifically, the levels of norepinephrine, serotonin, histamine, and hypocretin are greatly reduced in REM sleep compared to wake, so the presence of one or more of these neuromodulators may be necessary for external stimuli to be incorporated into our stream of consciousness. Two particularly relevant candidates are histamine – whose levels are correlated with our ability to incorporate sensory stimuli into conscious experience in the context of cataplexy (John et al. 2004; Nir and Tononi 2010) – and phasic activities of the locus coeruleus–norepinephrine (LC-NE) system which may be strongly tied to orienting to external stimuli and their subsequent processing (Nieuwenhuis et al. 2005). For instance, it could be that in wakefulness such neuromodulatory tone facilitates transmission of feed-forward sensory inputs in cortical layer 4, at the expense of backward signal propagation.

Other possibilities that could mediate sleep disconnection are the dominance of internally oriented, default-mode networks at the expense of externally oriented cortical networks (Fox et al. 2005; Golland et al. 2007) (see (Nir and Tononi 2010) for further discussion), and alterations in attention (analogous to states such as extreme absorption, hypnosis, and neglect). While the underlying mechanisms are unclear, frontoparietal cortices and the reticular thalamic nucleus are both important for directing and sustaining attention, and both undergo dramatic changes in activity in sleep (Guillery et al. 1998; Zikopoulos and Barbas 2007).

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Anesthesia

10

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Abstract

This chapter describes current knowledge about functional brain modifications observed during anesthesia-induced alterations of consciousness and places it into the context of consciousness physiology and anesthesia mechanisms. Anesthesia is a unique research tool for studying consciousness, insofar as it allows differentially and reversibly altering several of its constituents. Recent evidence suggests that anesthesia produces unconsciousness through a breakdown of connectivity into brain networks that are known to play a role in the emergence of mental content. These findings are in line with, and corroborate to some extent, current theories of conscious perception. Although anesthetic agents have effects on neural pathways controlling sleep and arousal, accumulating elements suggest that unconsciousness during general anesthesia occurs through mechanisms that are different from those of physiological sleep. Additional scientific exploration is still needed to understand the link between known biochemical targets of anesthetic agents, their effect on sleep-arousal systems, and

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_10,

the observed effects on consciousness networks. There is also a need for precising the exact sequence of events during transitions across consciousness states, for each type of anesthetic agents.

Abbreviations

BOLD	Blood oxygen level dependent
DMN	Default mode network
ECN	Executive control network
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging
Glycine R	Glycine receptor
HCN channels	Hyperpolarization-activated cation channels
HDEEG	High-density electroencephalography
m ACh R	Muscarinic acetylcholine receptor
n ACh R	Nicotinic acetylcholine receptor
N_2O	Nitrous oxide
Na channels	Presynaptic voltage-gated sodium channels
NIRS	Near-infrared spectroscopy
n-REM	Non-rapid eye movement
PET	Positron emission tomography
REM	Rapid eye movement
TMS	Transcranial magnetic stimulation
VLPO	Ventrolateral preoptic nucleus

10.1 Introduction: Anesthesia as a Tool for Studying Consciousness

Etymologically, anesthesia is a loss of the ability to experience sensations. When therapeutically applied, this large definition must be restricted to an operationally more convenient one. In that case, it corresponds to a reversible intervention aimed at allowing patients to tolerate painful or unpleasant invasive procedures. The anesthetic technique can be locoregional or general. General anesthesia produces a reversible alteration of consciousness, which is part of its multiple measurable effects, namely, its pharmacodynamic effects (Eger and Sonner 2006). Those effects are usually classified into three main non-mutually exclusive categories (Fig. 10.1). In addition, the alteration of consciousness during general anesthesia, or, in other words, the hypnotic effect of anesthesia, relates to several aspects of consciousness such as self-perception, inner speech, awareness of the environment, or memory. The nature and depth of the alteration depend on the properties of the

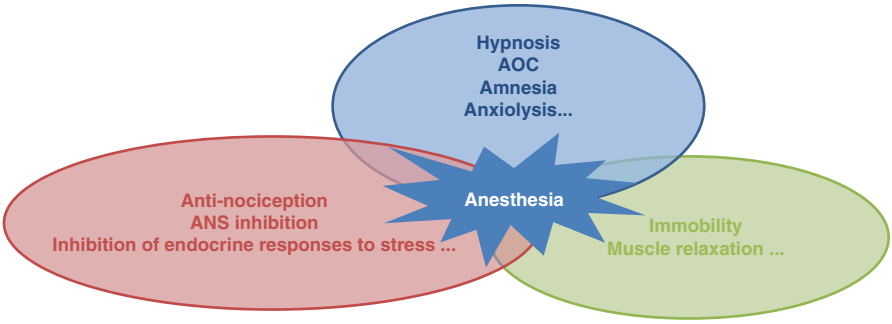

Fig. 10.1 Pharmacodynamic effects of general anesthesia. The pharmacodynamic effects of general anesthesia belong to three non-mutually exclusive categories: those producing an alteration of consciousness (hypnotic effects), those producing antinociception, and those producing immobility. Hypnosis encompasses effects on cognitive functions, including an alteration of several aspects of consciousness (*AOC*) such as self-perception or perception of the environment. Other cognition alterations may concern anxiety, forms of memory, et cetera. In an unconscious individual, antinociception consists in reducing the systemic consequences of noxious stimulation such as autonomic nervous system (*ANS*) reactions and hormonal responses to stress. Immobility concerns the suppression of movements, either spontaneous or stimulation evoked

anesthetic agents, their interactions, and dose. The other most important characteristic of consciousness alteration during general anesthesia is its reversibility. Hence, adequately choosing a specific anesthetic agent and appropriately dosing it allow specifically and reversibly altering behavioral components of consciousness, while looking at the brain functional repercussions of such alterations. Besides the interest of understanding a technique that beneficiates to thousands of patients every day in the world, this approach permits a unique virtual and reversible dissection of consciousness and, ultimately, the identification of functional systems involved in its generation. Noteworthy, the question to know if the relationship between anesthetic agent concentration in the body and effect on consciousness is continuous or is rather an on-off phenomenon is not solved, and the answer may be different for one component of consciousness or the other. The kinetics of that relationship and involved mechanisms may also not be the same during installation of anesthesia and recovery (Lee et al. 2011; Mantz and Hemmings 2011). According to recent publications, consciousness itself is probably a continuous phenomenon, and not on-off (Sandberg et al. 2011), but the relationship with anesthesia remains to be determined. When performing a study, these elements are important for interpreting the results.

The aim of this chapter is to detail the contribution of brain imaging studies to the understanding of anesthesia mechanisms and integrate those findings into knowledge acquired through other scientific techniques, as well as into current theoretical concepts describing consciousness, trying to make the link between these sources of information.

10.2 A Historical Quest

The quest for understanding anesthesia mechanisms originates a long time ago, in the nineteenth century with the paradigm of a unitary mechanism of anesthesia formulated by Claude Bernard (Perouansky 2012), later confirmed by the discovery by Meyer and Overton, at the end of the nineteenth century, that the potency of hypnotic agents increases with their solubility in lipids (Kopp et al. 2009; Meyer 1899; Overton 1899). The primary target of anesthetic agents was early identified as the central nervous system. Since then, there has been continuous evolution of mechanistic concepts (Fig. 10.2), both regarding biochemical sites of action and functional repercussions on the brain. At the molecular level, the idea of a direct effect on

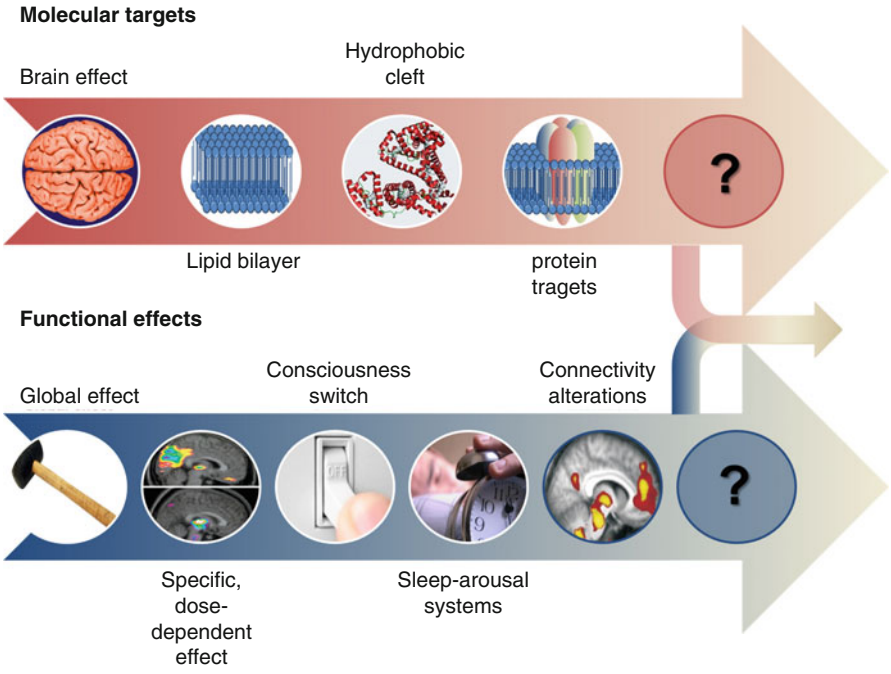

Fig. 10.2 Evolution of concepts regarding the two mechanistic levels of the mechanisms of anesthesia-induced alteration of consciousness. At the molecular level (*upper part of the figure*), the hypothesis of anesthetic agents directly acting on the lipid bilayer moved to the concept of ligation to a hydrophobic cleft within specific proteins. Those proteins were later identified as being receptors for specific neurotransmitters or ion channels. At the functional level (*lower part of the figure*), the initial hypothesis of a global depressing effect on brain function did not outlive the discovery of a dose-dependent effect of hypnotic agents on the activity of specific brain regions. This led to the search for a consciousness switch that would be operated by hypnotic anesthetic agents. That switch is still not identified, but would be a functional system or network rather than a precise anatomical structure. The systems controlling physiological sleep and arousal and functional connectivity networks involved in mental content generation could reveal to be that switch. Near future will probably see the link between the two mechanistic approaches of anesthesia mechanisms, as illustrated by the two merged *arrows* on the right

structure and conformation of the lipid bilayer membrane of neurons progressively led to the conviction that hypnotic agents were acting through their interaction with hydrophobic clefts into specific proteins (Franks 2006). Those proteins were later identified as being receptors for specific neurotransmitters and ion channels (Kopp et al. 2009). Regarding the effect of hypnotic agents on brain function, similarly to their biochemical site of action, the initial idea was holistic, considering that a global depression of brain function was responsible for the observed anesthetic effects. This "hammer hypothesis" was later reinforced by the demonstration of a global depressing effect on brain metabolism and electroencephalographic (EEG) activity by most anesthetic agents with hypnotic properties (Alkire et al. 1995, 1997; Alkire 1998; Cold et al. 1986; Forster et al. 1982; Newberg et al. 1983; Pierce et al. 1962). However, the observation that EEG depression was not uniform (Bennett et al. 2009; Rampil 1997) and that some hypnotic agents, such as ketamine, were also able to increase brain metabolism and EEG activity (EEG) (Hirota 2006; Langsjo et al. 2005) prompted scientists to propose a dose-dependent effect on specific brain regions or systems as well as to look for a sort of consciousness switch within the brain (Alkire et al. 2000; Cavanna 2007). As we shall see, the switch is still not identified, but seems to be a functional network rather than a precise anatomical structure. At that level, anesthesia seems to operate a dimmer rather than an on and off switch. Candidates for that role are systems controlling physiological sleep-wake cycles (Zecharia and Franks 2009) and functional connectivity networks potentially responsible for the generation of mental content (Bonhomme et al. 2011a). Knowledge about these mechanisms is still progressing, and we may soon see a day where the link between biochemical targets of hypnotic agents, their effects at the cellular level, and their repercussions on brain function will be made.

10.3 A Two-Side Approach

As mentioned above, two approaches govern scientific research dedicated to the understanding of anesthesia mechanisms. The first one focuses on identifying the biochemical targets of hypnotic agents, their effects at the cellular level, as well as on specific neural circuitry devoted to the control of wakefulness. It uses sophisticated biochemical and electrophysiological techniques on cell cultures, brain slices, or in vivo. It also juggles with agonists and antagonists, even in humans (Meuret et al. 2000), to precise the neurotransmission systems affected by anesthesia. This approach has evidenced that several biochemical targets and neurotransmission systems can be concerned, but transposition to the human brain is not easy. Although the obtained results poorly vary according to the studied species, at least in mammals, they merely depend on chosen end points, i.e., the definition of the loss of consciousness, and on concentration used (Franks 2006). A huge amount of neurotransmission systems have been shown to be potentially influenced by anesthesia, but only a small part of them have received enough experimental support to be definitely acknowledged as real mediators of anesthetic drug effects (Franks 2008). Given the extraordinary complexity of interactions between systems, isolating a

specific neurotransmission system in an experimental design and showing an effect of hypnotic agents on it do not necessarily mean that this effect is relevant in vivo. For example, it is possible to awaken volunteers using a cholinesterase inhibitor, which increases cholinergic neurotransmission, while keeping anesthetic agent concentration constant (Xie et al. 2011). It does not necessarily mean that the cholinergic system is a specific target of the chosen hypnotic agent. It may simply be that awakening is the result of an increased cortical arousal by boosted cholinergic neurotransmission, independently from the mechanisms having led to anesthesia-induced unconsciousness. This is also true for noradrenergic and dopaminergic neurotransmission systems (Chemali et al. 2012; Kelz and Sleigh 2012).

Hence, to complete the picture, there is a need for observing the functioning living brain during anesthesia. This is the purpose of the second scientific approach. Several techniques are now available to achieve it, including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), high-density electroencephalography (HDEEG), transcranial magnetic stimulation (TMS), near-infrared spectroscopy (NIRS), and combinations between them. They have permitted considerable progress in the understanding of anesthesia-induced loss of consciousness during the past 10–15 years. They are not only able to identify brain regions that modify their activity during anesthesia but also to detect changes in functional connectivity between them. However, those techniques have also made the picture more complex, and several elements remain a mystery, particularly the link between cellular effects, affected neurotransmission systems, and brain functional alterations.

10.4 Principal Functional Neuronal Proteins Targeted by Hypnotic Anesthetic Agents

The potential protein targets of anesthetic agents are numerous, and accumulating evidence suggests that only a few of them are relevant with regard to hypnosis (Franks 2008). Their main characteristic is a large distribution across the brain. Schematically, they can be assigned into two main categories (Table 10.1) (Kopp et al. 2009; Solt and Forman 2007): those whose activation promotes neuronal activity and those with an inhibitory effect on neurons. The N-methyl-D-aspartate (NMDA) glutamate receptor subtype (NMDA R), cholinergic receptors (Ach R), hyperpolarization-activated cation channels (HCN channels), and presynaptic voltage-gated sodium channels (Na channels) belong to the first category. The gamma-aminobutyric acid type A receptors (GABAA R), two-pore potassium (2P K) channels, and glycine receptors belong to the second one. Barbiturates, propofol, etomidate, and benzodiazepines are known to promote GABAergic neurotransmission. Other effects have been described for some of those molecules, including an effect on nicotinic and muscarinic cholinergic neurotransmission, as well as on HCN channels, but the GABA effect remains prominent. Halogenated compounds such as sevoflurane, desflurane, or isoflurane also promote inhibitory neurotransmission through an effect on 2P K channels (Franks and Honore 2004). Other described

Table 10.1 Functional neuronal proteins targeted by hypnotic anesthetic agents

	Hypnotic anesthetic agents and their known effect							
	Propofol	Benzodiazepines	Barbiturates	Etomidate	Vapors	Xenon	N_2O	Ketamine
$GABA_A$ R	+	+	+	+	+	0	0	
2P K channels	0	0	0	0	+	+	+	+
NMDA R					–	–	–	–
n and m ACh R	–		–		–	–	–	–
Glycine R					+			
HCN channels	–				–			
Na channels					–			

Reproduced with authorization from Bonhomme et al. (2011b)
+ activation, – inhibition, 0 no effect, *GABA* γ-aminobutyric acid, *$GABA_A$ R* GABA receptor type A, *NMDA* N-methyl-D-aspartate, *NMDA R* NMDA receptor, *2P K channels* two-pore potassium channels, *n and m ACh R* neuronal nicotinic and muscarinic acetylcholine receptor, *glycine R* glycine receptor, *HCN* hyperpolarization-activated cation channels, *Na channels* voltage-gated presynaptic sodium channels, *Vapors* halogenated vapors, *N_2O* nitrous oxide

effects of halogenated vapors are the promotion of GABAergic neurotransmission, inhibition of NMDA-mediated excitatory neurotransmission, inhibition of cholinergic neurotransmission, activation of glycine receptors, inhibition of HCN channels, and inhibition of Na channels. The volatile anesthetic agents xenon and nitrous oxide have no effect on GABAergic neurotransmission. They mainly act through their effect on 2P K channels, NMDA receptors, and cholinergic receptors. This is also true for ketamine.

Despite the heterogeneity of targets for hypnotic agents, the net result of their interactions is an alteration of consciousness, with subtle qualitative differences between agents though. After such an observation, one may conclude that there must be a final common mechanism responsible for the anesthesia-induced alteration of consciousness and that this pharmacodynamic effect results from a dose- and agent-dependent fine-tuning between effects on each of those biochemical systems (Changeux 2012). The only way to answer the question is to functionally explore either specific sleep-arousal and consciousness networks in animal models or the whole brain using functional neuroimaging techniques.

10.5 Functional Brain Alterations During Anesthesia

Most of experimental techniques allowing functional exploration of the brain have limitations. Animal models often give a truncated picture of the entire system, and transposition to the living human brain is not easy (Zecharia and Franks 2009). At the other extreme, functional brain imaging techniques and sophisticated whole-brain electrophysiological techniques have spatial and/or temporal resolution limitations. They are not always able to explore the highly complex functional interactions within the brain. In addition, functional brain imaging techniques are indirect measures of activity or of functional interactions. For example, fMRI is based upon the regional hemodynamic response to a change in activity, namely, upon the blood oxygen level-dependent (BOLD) signal. Connectivity studies rely on the statistical detection of synchronization between brain regions. Hence, information gathered from all kinds of techniques must be combined to complete and confirm findings and to finally end up with a reliable phenomenon's explanation.

10.5.1 Anesthesia and Endogenous Sleep-Arousal Pathways

A complex circuitry, mainly involving subcortical structures, governs the physiological sleep-wake cycle. Arousal pathways largely project to the cortex and sustain cortical arousal, which is a prerequisite for the emergence of the conscious experience (Franks 2008). They are cholinergic, noradrenergic, serotonergic, histaminergic, orexinergic, glutamatergic, and dopaminergic. During slow-wave sleep, GABAergic inhibitory systems go into action, provoking a widespread inhibition of arousal pathways. Tightly interconnected cortical and thalamic neurons enter into a hyperpolarized and burst-firing state, leading to thalamic oscillations and diffuse

synchronization of thalamic and cortical activity. These increasingly well-depicted mechanisms of sleep have legitimately inspired scientists regarding the mechanisms of anesthetic unconsciousness. They have postulated that it could be the result of a sleep-promoting activity enhancement, an inhibition of arousal systems, an alteration of thalamocortical interactions, or a combined effect. Indirect proofs of such implication have been obtained in animal models. The prevailing hypothesis remains the enhancement of GABAergic neurotransmission by hypnotic agents (Nelson et al. 2002; Zecharia et al. 2009), with consequences on cholinergic (Meuret et al. 2000; Plourde et al. 2003; Xie et al. 2011), noradrenergic, dopaminergic (Chemali et al. 2012), serotonergic (Franks 2008; Lu et al. 2008), orexinergic (Zecharia et al. 2009), and histaminergic (Luo and Leung 2009, 2011) arousal pathways. As discussed below, these experimental findings must be compared to pictures given by functional imaging techniques to derive temporal sequence of events and primary effects. Indeed, the question to know whether anesthesia is a top-down or bottom-up alteration of brain function is still not solved. Among the hypnotic agents, the α2-adrenergic agonists clonidine and dexmedetomidine are the most probable agents acting through sleep pathways. They inhibit the locus coeruleus and thwart its tonic inhibition on the GABAergic ventrolateral preoptic nucleus (VLPO), which in turn inhibit arousal pathways (Bonhomme et al. 2008; Nelson et al. 2003). However, their exact effects on cortical and cortico-subcortical connectivity still need to be investigated.

10.5.2 Anesthesia-Induced Electrophysiological Modifications

Electrophysiological studies are cornerstones of the understanding of anesthesia-induced alteration of consciousness. At the present time, those techniques have the best temporal resolution, allowing an almost online observation of changes associated with loss of consciousness. The multiplication of sensors and the use of sophisticated algorithms have improved spatial resolution and now permit the detection of functional connections between brain regions, as well as sources of activity (Barrett et al. 2012).

Surface EEG changes are not the same for all hypnotic agents. At low doses, barbiturates, propofol, benzodiazepines, etomidate, and halogenated vapors induce low-amplitude 13–30 Hz beta waves. With increasing doses, the EEG progressively slows down to high-amplitude 0.5–4 Hz delta waves (Murphy et al. 2011), near burst suppression, and isoelectricity (Tonner and Bein 2006) (Fig. 10.3). Contrarily, agents such as ketamine produce a totally different dose-dependent surface EEG pattern. Ketamine first reduces 8–13 Hz alpha activity. At moderate doses, it increases high-amplitude 4–8 Hz rhythmic theta activity, before inducing very large amplitude delta waves with scattered low-amplitude beta activity (Hirota 2006). Nitrous oxide administration switches alpha activity to activity in the upper part of the beta frequency range, while xenon produces similar changes as those induced by halogenated vapors. Alpha$_2$-adrenergic agonists produce electrophysiological changes that are very close to those of physiological slow-wave sleep (Bonhomme et al. 2008; Franks and Zecharia 2011).

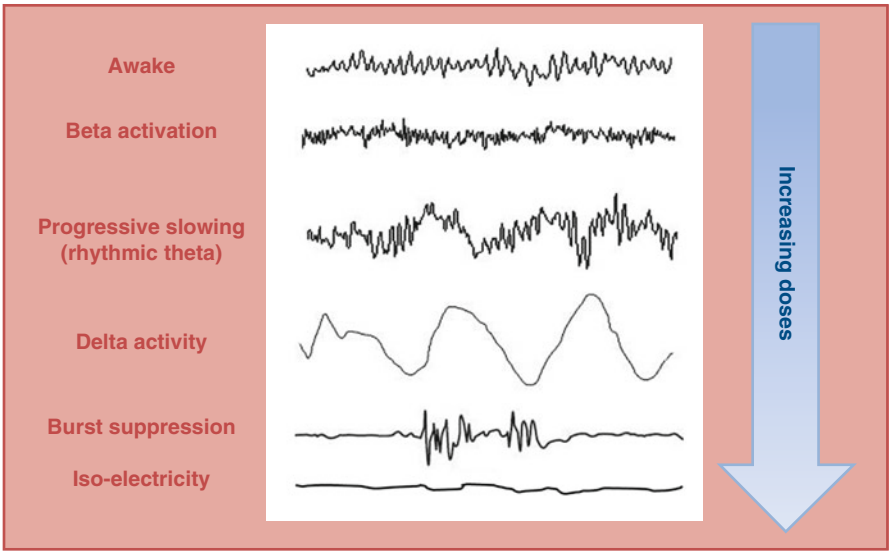

Fig. 10.3 Classical EEG changes observed during the administration of hypnotic agents such as barbiturates, propofol, etomidate, benzodiazepines, or halogenated vapors. As dose increases, a beta activation first appears (low amplitude, 13–30 Hz), followed by delta activity (high amplitude, 0–4 Hz), burst suppression, and eventually isoelectricity (Redrawn and adapted from Tonner and Bein (2006))

Despite undeniable interest in defining and monitoring depth of sedation, the above frequency domain description of EEG changes during anesthesia poorly helps in understanding the involved mechanisms. High-density EEG, its combination with TMS, and deep recordings in humans have recently opened a novel era in investigating functional brain modifications during anesthesia. Those techniques pave the way for a better definition of the sequence of events, localization of sources of activity, as well as of the alterations in functional interactions between brain regions, thereby nicely confirming and completing findings made by functional brain imaging studies (Fig. 10.4).

Regarding the sequence of events, an interesting discovery was that a cortical electrical activity change is concomitant to the loss of consciousness induced by propofol or sevoflurane, while electrical modifications in subcortical structures only occur at higher dosages (Velly et al. 2007). Electrophysiological studies were also among the first to demonstrate an anesthesia-induced alteration of functional connectivity between brain regions and particularly of the backward frontoparietal connectivity (Ferrarelli et al. 2010; Ku et al. 2011). This was recently confirmed for propofol, in addition to the demonstration that mild sedation is associated with a relative increase in thalamic excitability, while thalamocortical connectivity was preserved even in unresponsive individuals (Boly et al. 2012).

There is currently a need for repeating those experiments using hypnotic agents of other classes, where findings could be different, as suggested by animal studies (Kim et al. 2012).

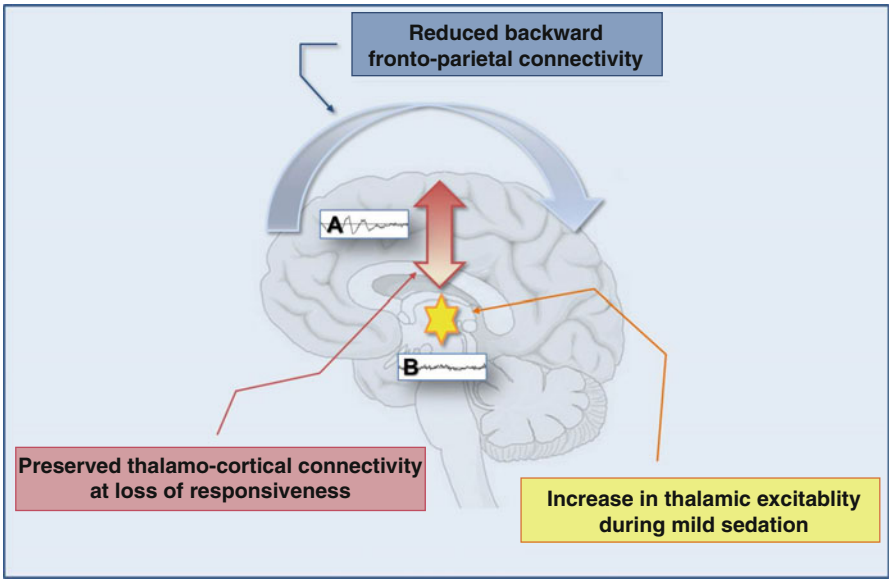

Fig. 10.4 Recent advances made by sophisticated electrophysiological studies in the understanding of functional brain modifications during anesthesia-induced alteration of consciousness. Cortical electrical activity is affected at the time of loss of consciousness (*A*), while brainstem is affected at higher doses of hypnotic agents (*B*). During propofol mild sedation, the thalamus shows increased excitability (*yellow*). Loss of consciousness is associated with ruptured backward frontoparietal connectivity (*light blue*), with preserved thalamocortical connectivity (*pink*) (Drawn from results of Velly et al. (2007) and Boly et al. (2012))

10.5.3 Functional Brain Imaging During Anesthesia

The brain functional exploration during anesthesia started during the mid-1990s, with the pioneer works of Fiset and Alkire. Using PET, they were the first to demonstrate that hypnotic agents have a dose-dependent effect on specific brain regions rather than a global depressing effect. Results of other studies later confirmed and completed these findings for a series of hypnotic agents including propofol (Fiset et al. 1999; Kaisti et al. 2002), halogenated vapors (Kaisti et al. 2003), barbiturates (Veselis et al. 2004), benzodiazepines (Veselis et al. 1997), xenon (Rex et al. 2006), and α_2-adrenergic agonists (Bonhomme et al. 2008). Interestingly, concerned brain regions are relatively similar for all those agents (Fig. 10.5) and include the thalamus, the cuneus-precuneus, the posterior cingulate cortex, and the frontoparietal association cortices. Similar brain activity alterations can be found during other altered states of consciousness, namely, in patients suffering from unresponsive wakefulness syndrome, during slow-wave sleep, and during the postictal phase of generalized seizures (Boveroux et al. 2008; Vanhaudenhuyse et al. 2010).

However, these regions cannot be considered as simple consciousness switches or dimmers, because totally different functional images are obtained with other hypnotic agents, also producing consciousness alterations. For example, ketamine activates

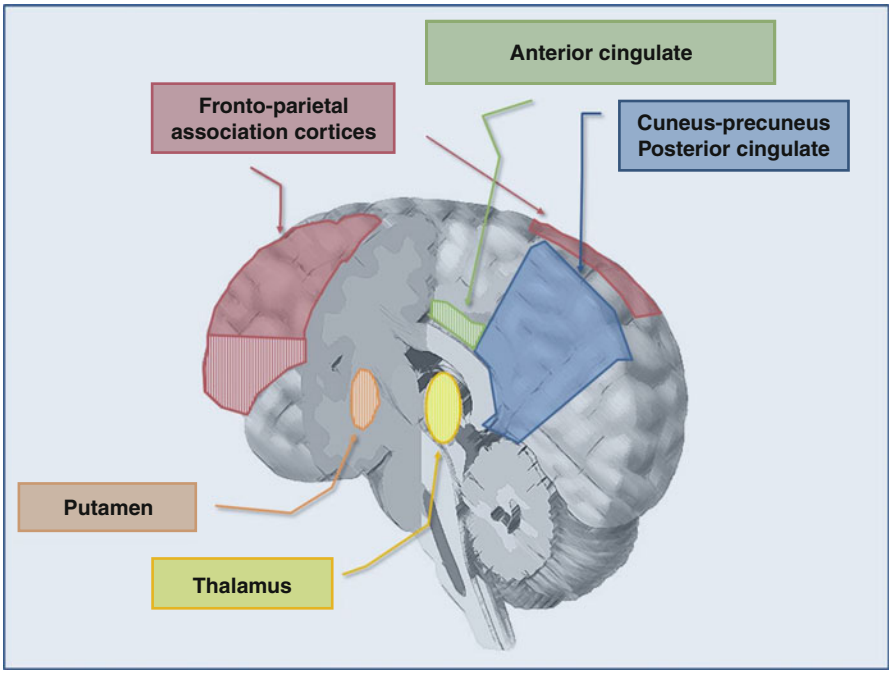

Fig. 10.5 The thalamus, cuneus-precuneus, posterior cingulate, and frontoparietal association cortices are brain regions shared by propofol, halogenated vapors, barbiturates, benzodiazepines, xenon, and α_2-adrenergic agonists in terms of a dose-dependent depressing effect on activity. These regions also show reduced activity during other altered states of consciousness such as slow-wave sleep and unresponsive wakefulness syndrome. Hatched surfaces (frontal cortex, thalamus, anterior cingulate, and putamen) show regions activated during a ketamine-induced alteration of consciousness (Drawn according to Boveroux et al. (2008) and Kaisti et al. (2003))

the anterior cingulate, the thalamus, the putamen, and the frontal cortex (Langsjo et al. 2003; Langsjo et al. 2004) (Fig. 10.5). In addition, a strong reduction in the activity of the above-listed regions may be found, while several cognitive brain functions are, at least, partially preserved (Bonhomme et al. 2008).

A step further can be reached using functional imaging of connectivity. In this case, mapping concerns brain structures that are functionally interconnected. In other words, mapped regions are those displaying synchronous activity. Recent work has demonstrated that several hypnotic anesthetic agents are able to disrupt connectivity into those brain networks that are thought to be essential for the emergence of mental content, namely, the default mode network (DMN, involved in self-awareness), the executive control networks (ECN, left and right, awareness of the environment), as well as in other higher-order networks (Alkire et al. 2008a) (Table 10.2). Hence, GABAergic-promoting agents, such as propofol, dose-dependently reduce connectivity into DMN and ECN, as well as the anti-correlation between the activity of those two networks (Boveroux et al. 2010; Martuzzi et al. 2010; Stamatakis et al. 2010). Connectivity into those networks and their anti-correlation

Table 10.2 Summary of currently demonstrated connectivity modifications by hypnotic anesthetic agents

Networks and type of connectivity	Hypnotic agents			
	Propofol	Halogenated vapors	Benzodiazepines	Ketamine
DMN	↓ and ↓↓ at LOR (Boveroux et al. 2010; Stamatakis et al. 2010)	?	↓ but preserved at low dose (Greicius et al. 2008)	?
ECN	↓ and ↓↓ at LOR (Boveroux et al. 2010)	?	?	?
DMN ∞ ECN	↓ and ↓↓ at LOR (Boveroux et al. 2010)	?	?	?
Thalamocortical connectivity	Preserved ↑ at LOR (Boly et al. 2012; Boveroux et al. 2010)	?	?	Preserved at low dose (Niesters et al. 2012)
Sensory networks	Preserved or ↑ altered cross-modal interactions (visual-auditory) (Boveroux et al. 2010)	Unchanged at low dose (Martuzzi et al. 2010)	Preserved or increased at low dose (Greicius et al. 2008)	↑ in visual and ↓ in somatosensory and auditory networks at low dose (Niesters et al. 2012)
Motor networks	?	?	Preserved or increased at low dose (Greicius et al. 2008)	?
Other networks	Putamen disconnection at low doses (suppression of responsiveness) (Mhuircheartaigh et al. 2010)	↓ in memory and pain networks at low dose (Alkire et al. 2008a; Martuzzi et al. 2010)	?	↓ pain processing (Niesters et al. 2012)

DMN default mode network, *ECN* executive control network, *DMN ∞ ECN* anti-correlation between DMN and ECN, *LOR* loss of responsiveness, ↓ lightly reduced, ↓↓ highly reduced, ∞ anti-correlation

disappear when consciousness is lost, while both become anti-correlated with thalamic activity (Boveroux et al. 2010). At lower concentrations, connectivity is preserved or even increased in motor networks, as well as in lower-order sensory networks (Greicius et al. 2008), but there exists cross-modal interaction alterations (Boveroux et al. 2010). Propofol also disrupts the ability of the brain to transfer information from lower-order sensory processing areas to higher-order ones (Liu et al. 2011). At low doses, it disconnects the putamen, thereby suppressing purposeful responsiveness to external stimulation, while the subject is still conscious to some degree (Mhuircheartaigh et al. 2010). Ketamine produces connectivity modifications as well. At sub-anesthetic doses, it increases connectivity into visual networks and decreases it into auditory and sensory networks and into networks involved in pain processing (Niesters et al. 2012). Several other hypnotic agents still need to be explored in that respect, as well as several other networks.

10.6 Is Anesthesia Pharmacological Sleep?

At first glance, general anesthesia resembles physiological sleep, but detailed analysis reveals substantial behavioral and electrophysiological differences (Bonhomme et al. 2011b; Sanders et al. 2012) (Table 10.3).

During slow-wave sleep, muscle tone is normal, spontaneous movements occur, and consciousness is altered at various degrees, including reduced environmental awareness, loss of the ability to respond to command, loss of self-awareness, and absence of mental imagery. Reversibility by external stimulation depends on sleep depth. Electrophysiologically, slow-wave sleep onset is characterized by spindle activities and K complexes, progressively switching to slow oscillations in the delta frequency range as sleep deepens.

During rapid-eye-movement sleep, muscle tone is reduced, and no movement occurs, except for specific movements of the eyes. Mental imagery, or dreaming, with virtual self-perception can be present, but awareness of the environment is altered. All these modifications can easily be reversed by external stimulation. Concomitant electroencephalographic recordings display low-voltage desynchronized fast activity and increased power in the theta frequency range, hence similar, but not identical to the wake state.

Contrarily to the well-defined sleep states, the anesthetic state is behaviorally and electrophysiologically much more heterogeneous. The above-depicted electrophysiological consequences of anesthesia may sometimes resemble those of sleep, but not always. Moreover, those consequences differ as a function of agent types. This is also true for behavioral observations. GABAergic-promoting agents blunt out awareness of the environment (or connectedness (Sanders et al. 2012)) and self-awareness. They also lessen muscle tone and movements. At high concentrations, reversibility by external stimulation is difficult. Dreaming can occur with these agents, particularly during emergence from anesthesia (Leslie et al. 2009). Ketamine and nitrous oxide produce unconsciousness while preserving signs of wakefulness such as opening of the eyes and preserved muscle tone. Patients under ketamine

Table 10.3 Behavioral and surface EEG comparison between sleep and general anesthesia

		Sleep		General anesthesia			
		n-REM	REM	Inhib. neurotrans.	Ketamine	Xenon	α_2-agonists
Wakefulness		Absent	Absent	Absent	Present	Absent	Reduced
Movements	Spontaneous	Present	Absent	Absent	Present	Absent	Reduced
	Evoked	Present	Absent	Absent	Absent	Absent	Reduced
	Purposeful	Present	Absent	Absent	Absent	Absent	Reduced
Muscle tone		Normal	Atonia	Reduced	Normal	Few effects	Normal
Environment awareness		Absent	Absent	Absent	Absent	Absent	Reduced
Response to command		Absent	Absent	Absent	Absent	Absent	Altered
Self-perception		Absent	Virtual	Absent	Absent/virtual	Absent	Altered
Mental imagery		Dreaming possible	Present	Absent Dreaming during emergence	Present	?	Altered
Reversibility		St.-dep.	Yes	No	No	No	Yes
EEG features		Spindles K-complex Delta	Des. fast Theta	Beta activation Theta, delta Burst suppression Isoelectricity Spindles	Reduced alpha Rhythmic theta Polymorphic delta Scattered beta	Similar to halogenated vapors	Spindles Delta and theta activity

Reproduced with authorization from (Bonhomme et al. 2011b)
n-REM non-rapid eye movement, *REM* rapid eye movement, *Inhib. neurotrans.* agents that promote inhibitory neurotransmission such as barbiturates, propofol, benzodiazepines, etomidate, and halogenated vapors, *α2 agonists* α2-adrenergic agonists, *St.-dep.* stage-dependent, *Des. fast* desynchronized fast activity

show spontaneous movements, loss of environmental awareness, inadequate self-perception, and intense dreams. As already mentioned above, the hypnotic agents producing the closest sleep-like state are the α_2-adrenergic agonists, both behaviorally and functionally (Bonhomme et al. 2008; Sanders and Maze 2011).

As one can see, sleep and general anesthesia generate a panel of different states. Hence, mechanistically comparing anesthesia to the promotion of sleep pathways' activity or to the inhibition of arousal pathways' activity is probably oversimplification.

10.7 The Hen and the Egg Problem

When considering the effects of hypnotic agents on sleep-arousal systems, temptation is high to consider that primary effects occur at the subcortical level and that the observed specific cortical effects are only secondary to the subcortical ones (Zecharia and Franks 2009). However, the inverse hypothesis, that is, a primary cortical effect with consequences on cortico-subcortical interactions and subcortical activity, could also reveal true. The literature provides us with arguments sustaining the latter. For example, lower doses of hypnotic agents are needed to observe cortical effects than those needed for subcortical effects (Bonhomme et al. 2001; Heinke and Koelsch 2005; Velly et al. 2007). In addition, higher-order processing cortical areas are more sensitive to the effect of hypnotic agents than lower-order ones (Dueck et al. 2005; Liu et al. 2011; Ramani et al. 2007). Hence, there is currently a need for studies exploring the exact sequence of subsystem alterations during anesthesia. The sequence is probably not the same for all anesthetic agents and during induction or recovery. The best way to proceed will probably be the use of combined functional exploring techniques with high temporal and spatial resolution.

10.8 Fitting with Current Consciousness Theories

Noteworthy, recent findings regarding the mechanisms of anesthesia-induced alteration of consciousness fit with current theories of conscious perception, thereby confirming some aspects of those theories. To avoid confusion, it is important to distinguish between consciousness, connectedness, and responsiveness (Sanders et al. 2012).

Consciousness refers to the presence of mental content. It may be present without connectedness (i.e., awareness of the environment) or without responsiveness (i.e., directed motor response to external stimulation), such as during dreams. It seems that each of those elements is sustained by specific functional networks, which may differentially be affected by anesthesia (Sanders et al. 2012).

Three main theories are currently proposed to explain mental content generation. The integrated information theory postulates that the corticothalamic system, which encloses the above-described resting state networks such as the DMN, integrates as a whole a large repertoire of information generated by functionally specialized

cortical areas (Tononi 2004). Experimental arguments suggest that anesthesia-induced alteration of consciousness, at least with GABAergic-promoting agents, is associated with a lack of integration (Schrouff et al. 2011), a reduced amount of information (Alkire et al. 2008b), or both. Connectivity modifications observed during anesthesia are in line with this hypothesis (Changeux 2012; Ku et al. 2011). For the global workspace theory, mental content is generated by attention processes highlighting some pertinent information among others that are shared in a global workspace (Baars et al. 2003). Corticothalamic consciousness networks are thought to be necessary for an available global workspace. The cognitive binding theory sustains that synchronization across corticothalamic networks, known as gamma oscillation, is necessary for binding together in a single percept the different features of an object (Mashour 2004). It has been proposed that anesthesia produces unconsciousness through a disruption of gamma oscillation within networks, hence through unbinding of information (John and Prichep 2005). During anesthesia, the concomitant alteration of connectivity into networks and loss of consciousness are compatible with all theories, although increases in gamma synchrony between some brain regions have been reported during propofol sedation (Barrett et al. 2012).

Connectedness would depend upon a cortical ventral attention network that receives noradrenergic innervation (Coull et al. 1999) and upon ECN (Vanhaudenhuyse et al. 2011). Alpha$_2$-adrenergic agonists would suppress connectedness through their effect on the ventral attention network (Coull et al. 1999), while GABAergic agents such as propofol would poorly affect that network, but rather act through an effect on the ECN (Schrouff et al. 2011).

Purposeful responsiveness to external stimulation is controlled by subcortical structures, including the amygdala and the putamen. The connectivity of those structures can be affected by anesthetic agents (Alkire et al. 2008a; Mhuircheartaigh et al. 2010). There are arguments to think that, in that case, connectivity modifications would be the result of the effect of hypnotic agents on sleep-arousal controlling systems and in particular the histaminergic system.

10.9 So Many Unresolved Questions

At this point, one must acknowledge that the picture is far from being totally understood. The amount of established scientific facts related to the mechanisms of anesthesia-induced alteration of consciousness is rapidly growing. In summary, they are that hypnotic anesthetic agents act through interactions with specific neuronal proteins, are able to influence subcortical sleep-arousal controlling systems, and affect the activity of specific consciousness-related networks. Although generalization helps in defining concepts, the diversity of anesthetic agents, their mode of action, and their diverse pharmacodynamic effects must incite to seek for a detailed description of mechanisms for each of their classes. In addition, the scientific vision of the phenomenon is currently relatively static, looking at what happens during steady states of consciousness. Future research will have to investigate the dynamic aspects of changes in consciousness states during anesthesia. This will be the only way to

better precise the link between biochemical targets, neurotransmission systems, and function within the brain. Furthermore, a complete understanding of anesthesia-induced alteration of consciousness will shed light on the physiological mechanisms of consciousness. It will allow us being conscious of our consciousness.

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Part IV

Brain Imaging and Alterations of Consciousness in Neuropsychiatric Disorders

Andrea E. Cavanna and Andrea Nani

Neuroimaging Studies of Interoception and Self-Awareness

11

Sarah N. Garfinkel, Yoko Nagai, Anil K. Seth, and Hugo D. Critchley

Abstract

Selfhood and self-awareness, at least in humans, can be dissected into many levels. At one level, self-awareness describes a metacognitive aspect of consciousness wherein higher-order thought is directed through attentional focus on the self-object and self-related matters. This chapter explores the insights gained from neuroimaging studies into the brain substrates and mechanisms underlying such "high-level" self-referential processing. At another level, selfhood is reflected in self-recognition processes which discriminate self-related stimuli from other similar stimuli. Here, we examine the relevant neuroimaging evidence, focusing on self-face recognition as an exemplar. At a more fundamental level, we review what is known about the mental representation of the body,

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_11, © Springer-Verlag Berlin Heidelberg 2013

focusing on studies suggesting that a primary sense of self is ultimately derived from the neural representation of the body via interoception. These studies emphasize the continuous mapping of dynamic changes in internal state, whereby physiological demands and homeostatic imperatives dictate motivations and shape the contents of cognition. Here, converging neuroimaging evidence suggests that brain regions involved in representing internal physiological processes and making them available to conscious appraisal contribute to self-referential cognitions. This link is further apparent in the neural correlates of cognitive control and detachment techniques, such as mindfulness, that increasingly find clinical utility. Ultimately, inferences from neuroimaging regarding selfhood and self-awareness must cohere with evidence from lesion studies and with an increasingly sophisticated understanding of the brain as a connected network generating self-representations via a range of overlapping mechanisms.

11.1 Overview

This chapter reviews how neuroimaging studies have helped illuminate the neural basis of selfhood and self-awareness in humans, at multiple levels of description. It begins by examining how neural substrates support the representation of the internal state of the body (interoception) and its accessibility to conscious appraisal (interoceptive sensitivity or awareness), motivated by influential conceptualizations of consciousness that propose a coherent representation of selfhood grounded on internal biological signals. Self-recognition, often used to infer the integrity of self-representation, and self-reference, including the capacity to objectify one's thoughts (and those of others), draw on an objectified cognitive model of self that involves specific neural substrates. The capacity for cognitive objectification of self appears to be trainable though techniques such as mindfulness that encompass awareness of concurrent bodily and mental processes. In these domains, neuroimaging studies are converging toward an understanding of cortical and subcortical brain systems supporting self. Such information requires integrating with methodological advances for understanding functional networks within the brain, as with evidence from lesion studies and psychopathology, and with emerging theoretical perspectives relating selfhood to predictive coding and self-modeling.

11.2 Neuroimaging of Interoception and Interoceptive Sensitivity

11.2.1 Overview

Interoception refers to sensitivity to stimuli originating from within the body. Interoception is distinct, in Sherrington's view, from exteroception and proprioception (Sherrington 1948). When compared to information from skeletomusculature or circulating (humoral) signals, more emphasis has been placed historically on

information from the visceral organs and vascular system carried by viscerosensory nerves forming the afferent limb of autonomic nervous regulation. Correspondingly, interoception is occasionally dismissed as a low-level homeostatic process. However, writings of William James and Carl Lange, ascribing emotional feelings to internal bodily responses (Lange and James 1967), and subsequent formulations relating internal bodily state to behavior and self-representation (Cannon 1927; Schachter and Singer 1962; Damasio et al. 1991; Lazarus 1991) have maintained psychological interest in interoception. These formulations further motivate a distinction between interoception per se and *interoceptive sensitivity*, which refers to access to interoceptive signals (e.g., as reflected in heartbeat detection tasks). In the field of biofeedback, the provision of conscious access to a previously covert involuntary (autonomic) process (e.g., by visually displaying a measure such as ongoing electrodermal or electroencephalographic activity) enables a participant to learn to control this signal voluntarily, typically without full understanding how it is achieved. Thus, awareness of internal bodily processes implies controllability. Interoceptive awareness also emerges within emotion science as an account for individual differences in affective experiences, behaviors, and vulnerability. Peripheral theories of emotion originating with James and Lange suggest that people who are more attuned to emotional bodily responses should experience emotions with greater intensity. In recent years, Craig has argued for a broader definition of interoception as "the sense of the physiological state of the body" including pain, sensual touch, and temperature signaling (Craig 2003), with the stable representation of (homeostatic) internal state providing the primary reference for a sense of self ("material me"). Indeed, Damasio, Craig, and others argue that consciousness is underpinned by interoception and its neural substrates (Craig 2002; Parvizi and Damasio 2001), with implications for models of selfhood and its disturbance (Seth et al. 2011). The relevance of interoception to self-representation is reinforced by the empirical observation that individual differences in laboratory measures of interoceptive sensitivity predict the extent to which illusory distortions of body ownership may be experienced (Tsakiris et al. 2011).

11.2.2 Brain Correlates Interoceptive Change

Neuroimaging studies have sought to define the brain substrates mapping internal bodily state in humans. Unsurprisingly, studies that evoke changes in interoceptive state, whether intentionally (by direct visceral stimulation) or unintentionally (through effort, emotion, or other processes coupled to autonomic responses), will evoke changes in the activity of viscerosensory brainstem, subcortical, and cortical brain regions (Bharat et al. 2005; Hobday et al. 2001; Paus et al. 1998; Critchley 2009; Gianaros et al. 2004). Cortical regions reliably engaged during states of enhanced bodily arousal include anterior cingulate and insula cortices, consistent with their respective visceromotor and viscerosensory roles apparent across mammalian species (Harrison et al. 2010; Critchley et al. 2003). Activity changes within subcortical regions such as amygdala, thalamus, hypothalamus, and dorsal pons

(parabrachial nucleus and periaqueductal gray matter) are more variably described in human neuroimaging studies (Harrison et al. 2006; Gray et al. 2009; Critchley 2009), while activity change within medullary centers is technically difficult to quantify reliably. Nevertheless, the importance of these other regions to the representation, signaling, and control of internal bodily state is established through other techniques. Neuroimaging investigations have further associated states of low physiological arousal (antisympathetic or parasympathetic "rest-and-digest" responses) with activity changes within ventral prefrontal and pre/subgenual cortical regions (Wager et al. 2009; Nagai et al. 2004) providing a physiological account of rostral default mode activity.

11.2.3 Brain Correlates of Interoceptive Sensitivity

Objective techniques for measuring individual differences in interoceptive sensitivity and awareness have, over the last 50 years, gravitated toward two measures of cardiac awareness: heartbeat detection (Whitehead et al. 1977; Katkin et al. 2001) and heartbeat counting (Schandry 1981). These assess how accurately a participant can gauge their heart beating at rest. Observed correlations between measures of cardiac and gastrointestinal awareness suggest a generalizability of inference across different viscerosensory axes (Whitehead and Drescher 1980). Thus, people who are aware of their heart beating at rest are assumed to be sensitive to other interoceptive processes. In the Whitehead method, and its modifications by Katkin, a series of lights or tones are presented and participants are asked to judge whether they are perceived as synchronous or delayed relative to their own heartbeat. Schandry's approach uses a mental tracking task, in which participants try to silently count their own heartbeats during a set time interval. Neither task is free from psychometric criticism, yet the validity of these approaches is reflected in their capacity to predict vulnerability to affective symptoms (notably anxiety: Schandry 1981), performance on implicit tasks that can be steered by internal arousal responses (Katkin et al. 2001), and other measures of emotional reactivity (Wiens et al. 2000).

Neuroimaging studies link both the process of heartbeat detection and overall performance on tests of interoceptive sensitivity to activation of anterior cingulate and insular cortices (Pollatos et al. 2005; Critchley 2004). These findings are consistent with a proposed role of these regions in autonomic control and, in the case of anterior insular cortex, as a substrate for conscious readout of changes in interoceptive state relevant to emotional processes (Critchley et al. 2003; Craig 2002, 2003). Individual differences in both the size and reactivity of anterior insular regions predict interoceptive sensitivity and experience of emotional symptoms, particularly anxiety (Critchley 2004; Paulus and Stein 2006) (Fig. 11.1).

Subsequent neuroimaging studies have honed in on the relationship between interoceptive ability, emotion, and autonomic reactivity. In one example, activation of insula, thalamus, anterior cingulate, and dorsomedial prefrontal and inferior frontal gyrus was engendered within individual participants by both interoceptive performance and by cardiovascular arousal associated with exercise (Pollatos et al. 2007).

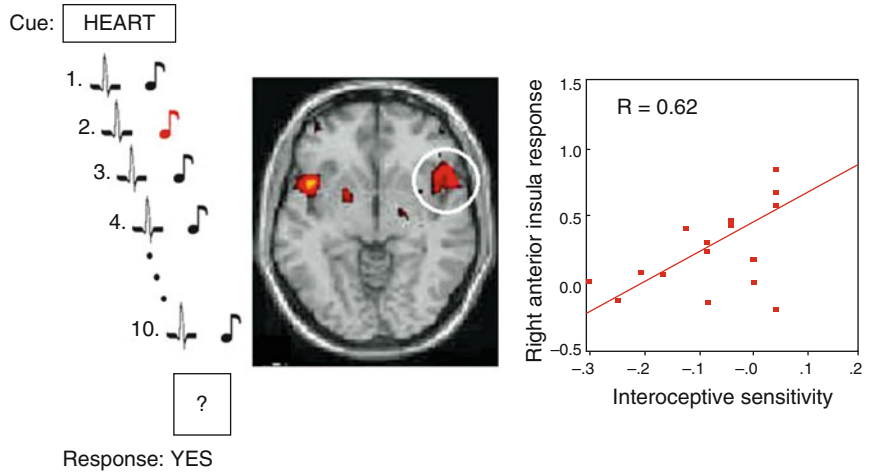

Fig. 11.1 Right insula cortex and performance on a heartbeat detection task (Critchley et al. 2004) The Katkin variation of the Whitehead heartbeat detection task was adapted to an fMRI experiment. Participants listened to a series of 10 notes, each triggered by occurrence of their heartbeat. When the preceding cue read "heart," the participants attended "interoceptively" to the timing of their own heartbeat in relation to the notes and decided whether the notes were coincident with their heartbeat or delayed by a fixed interval (here, 500 ms) (*left panel*). If the preceding cue read "note," participants attended "exteroceptively" only to the quality of the note, which during the sequence might include a rogue tone at a close but different frequency. A measure of interoceptive sensitivity was derived from overall relative performance on these trials (*x-axis of right panel*). Comparison of intero- and exteroceptive trials demonstrated greater activity in a set of brain regions including bilateral insula cortex, anterior cingulate cortex SI and SII somatosensory regions, and subcortical structures (*middle panel*). Activity within right anterior insula (*circled*) predicted interoceptive performance, interpreted as proxy for conscious interoceptive awareness. The activation and size of this region also predicted interindividual differences in other questionnaire measures of interoceptive sensitivity

Moreover, activation of dorsal cingulate and medial prefrontal cortex was observed also to relate to the experience of negative emotions. This study highlighted the interrelationship of interoceptive mapping of bodily changes and substrates for emotion. Using a similar approach, right anterior insula cortex activation was elicited during performance of an interoceptive awareness task, and critically the same region was also engaged when participants judged their own emotional reactions to emotional film clips (Zaki et al. 2012).

Together, these studies highlight anterior insular cortex, particularly on the right side, and its dependent link with anterior cingulate cortex, as a major neural substrate for interoceptive representations accessible to conscious awareness. Such representations further support affective feeling states and mediate influences of physiological state on subjective feelings and cognitive processes (Harrison et al. 2009). A compelling case, based largely on neuroimaging, can be made for conscious selfhood to be rooted in the interoceptive representation within insula and cingulate cortices (Craig 2009). Approaches other than neuroimaging (e.g., lesion studies) are needed to validate this proposal.

11.3 Neuroimaging of Self-Recognition

11.3.1 Overview

Intact self-recognition has often been interpreted as a marker for self-awareness, especially when assessed in pre- or nonlinguistic infants and animals. The canonical test for self-recognition is the Mirror Self-Recognition Test or Mirror Dot Task (Gallup and Capper 1970; Gallup 1982) which assesses whether the individual behaves to investigate a dye mark on their head (placed covertly) when looking in a mirror. In so doing, the individual indicates that he/she is able to deploy a coherent "projective" representation of self. Correspondingly, neuroimaging experiments have sought to determine the central neural correlates of self-representation through tests of self-recognition adapted for fMRI. Typically, these studies compare brain responses evoked by pictures of self (participant) with pictures of people familiar to the participant. Such tasks generally evoke distributed activity across cortical and subcortical regions, with some indication of right hemispheric dominance but without obvious specialization.

11.3.2 Brain Correlates of Visual Self-Recognition

When passively viewing photos of self, familiar faces, or unknown faces, regional brain activity associated with self-processing evokes activity enhancement within a variety of areas including right insula, basal ganglia, pregenual cingulate, left dorsolateral prefrontal cortex, and temporo-occipital cortices (Kaplan et al. 2008; Platek et al. 2004). Familiar faces, compared to other unknown faces, enhance activity within insula alone (Kircher et al. 2001). These findings can further be dissected according to relationships (e.g., kinship), social context, and cognitive and affective demands of the imaging task (Devue and Bredart 2011). Thus, the inferior frontal gyrus engagement is implicated in attention-driven abstracted evaluation of visual self, while engagement of medial frontal cortex appears more related to social context than to individual self-distinction (Sui and Han 2007). Engagement of insular cortex during visual self-recognition is interpretable in terms of integrative self-representations, grounded on interoception (e.g., Craig 2010), and in this context, anterior cingulate cortex is implicated in multimodal integration of information to derive self-representations for autobiographical narrative and a sense of agency (Karnath and Baier 2010; Medford and Critchley 2010; Seth et al. 2011). Similar accounts exist for the engagement of inferior and medial parietal cortices during visual self-recognition, consistent with both the impact of lesions to these areas on self-processing and a parallel body of neuroimaging work increasingly implicating precuneus and the temporoparietooccipital junction in somatic self-representation (Blanke 2012). Not unsurprisingly, activity within face and arousal-sensitive regions of early visual cortices (including fusiform cortex) is typically enhanced during the processing of self-images consistent with the salience of content (Devue and Bredart 2011).

11.3.3 Brain Networks in Visual Self-Recognition

Many of the above studies directly or indirectly implicate a distributed representation of self, drawing on multiple processes. However, a direct examination of the mechanisms underpinning recognition of self from visual information, as implied by the Mirror Dot Task, is still lacking. For the future, a critical experiment may involve the presentation of a single visual stimulus where in one context self is recognized and not in another. Surprisingly, while several appropriate techniques are available to neuroscientists interested in conscious processes, few studies have tapped into this critical aspect. Morphing of faces toward or away from the veracity of one's own face image provides some data; however, one weakness of this approach is that self-similarity blurs experimental boundaries, implicitly favoring an interpretation in terms of multiple neural self-representations. Furthermore, there remain to date very few neuroimaging studies that employ connectivity analyses to test how integrative information processing may support visual self-recognition. One such study describes right insula and right inferior parietal cortex activation during visual self-processing (Ramasubbu et al. 2011) and uses seed-based correlation analysis to identify distinct but interrelated networks supporting self-processing. Here, insula connectivity to frontostriatal regions and temporal cortex is distinguishable from superior temporal anterior cingulate and precuneus connectivity for the parietal network. These early findings suggest that self-face recognition preferentially implicates networks linking regions underpinning interoceptive sensitivity and sense of body ownership, in contrast to regions involved in higher-order autobiographical functioning.

11.3.4 Future Studies

Many experiments and a number of meta-analyses have explored neural correlates of visual self-representation. However, there remains much scope for further informative neuroimaging work in this area, capitalizing on advanced experimental designs for changing/alternating conscious perception and on advanced analytic methods including multivariate and connectivity approaches that are increasingly informative in studies of other areas of consciousness science. While it may be easy to dismiss visual self-recognition as a confused set of interacting complex processes, the mirror dot test remains a powerful motif with compelling surface validity and is ultimately tractable to detailed scientific understanding.

11.4 Neuroimaging of Self-Reference

11.4.1 Overview

Cognitive self-reference has close affinity with motivational and affective salience and supports executive functions including planning, decision making, and behavioral control. Importantly, it is frequently exaggerated across different psychiatric

conditions, notably depression and paranoia. Neuroimaging studies comparing thoughts about oneself to thoughts about other (objects or people) exhibit a remarkable consistency, highlighting the engagement of a medial cortical system involving cingulate and parietal cortices. Other regions become more or less engaged depending on the task at hand (e.g., dorsal anterior cingulate if effortful, dorsolateral prefrontal cortex and supplementary motor cortices if decisional, and insula, somatosensory, and temporoparietal junction if referenced to the internal body) (Herwig et al. 2012). Moreover, the weight of neuroimaging evidence points to the "default mode network" as most closely associated with self-referential processing (Gusnard and Raichle 2001).

11.4.2 Default Mode and Self-Reference

Many processes of interest to psychological, behavioral, or clinical neuroscience involve self-reference. Unsurprisingly, studies using cognitive subtraction designs when identifying neural substrates of affective or motivationally salient functions often contrast processes that are self-relevant with those that are not. Conversely, attention-demanding effortful tasks typically require a focus away from the self and active suppression of self-referential processing to engage and apply cognitive resources to external stimuli and actions. In these studies, the low-level baseline conditions encompass a more consistent representation of selfhood (Gusnard et al. 2001). Meta-analyses have been undertaken to synthesize evidence regarding neural substrates for self-referential processing across different tasks, sensory domains, and even "types of self-reference." In condensing this literature, nuances are typically lost and important differences (e.g., in the engagement of subcortical structures) are underplayed to derive a clear regional correlate in the brain of "core self." An analysis of 27 neuroimaging (PET and fMRI) studies between 2000 and 2004 encompassing spatial, perceptual, social, motor, and emotional domains was able statistically to dissect regional brain activations according to the nature of the self-processing engaged. This revealed the central contribution of cortical midline structures, notably anterior cingulate, medial prefrontal cortex, and medial parietal lobe, and their connectivity to subcortical and brainstem nuclei (Northoff et al. 2006). This ascription of self-referential processing to medial cortex was proposed to be consistent with the notion of "core, mental, or minimal" self. Core self bridges sensory self/other representations and higher-order processes including autobiographical, emotional, and verbal functions that draw selectively on self-representation (Northoff et al. 2006). These findings were independently endorsed by a meta-analysis of PET and fMRI studies that allowed comparison of both self versus baseline and self versus other processing (see Fig. 11.2). Here, self versus baseline processing strongly mapped to activations within posterior cingulate and precuneus, dorsal anterior cingulate cortex, medial and polar prefrontal cortex, and orbito-insular cortex. Activity distinguishing self versus other across studies was reliably found in pregenual cingulate regions, extending dorsally within ACC and rostrally into ventromedial prefrontal cortex (van der Meer et al. 2010).

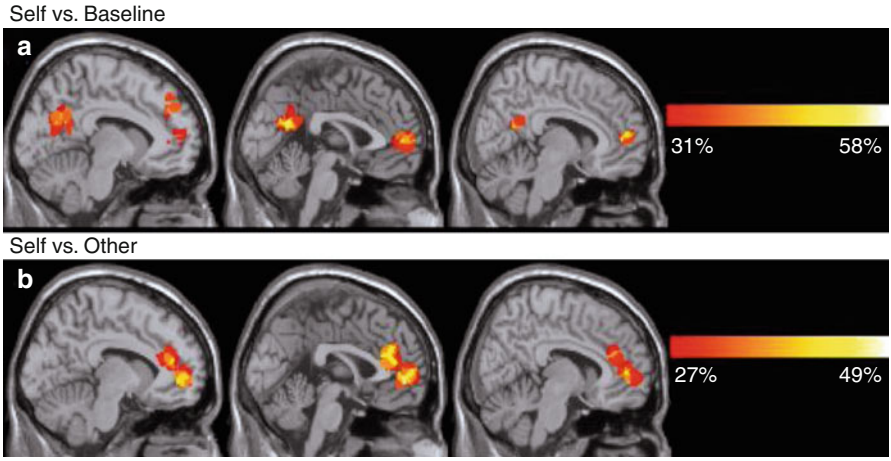

Fig. 11.2 Meta-analysis of brain activation involved in self-reflection vs. baseline (**a**) and self-reflection vs. other reflection (**b**) The score reflects the proportion of experiments reporting at least one activation peak within at local neighborhood of size $p = 10$ mm, weighted by study size, and FDR corrected. Sagittal slices at X [−8, 0, 8] for both (a) and (b) sections (Figure adapted from van der Meer et al. 2010)

11.4.3 Self-Referential Processing in Depression

The cortical midline system, highlighted above in self-referential processing, has particular relevance to the expression of depression where cognitions focus on the self and are coupled to negative attributions and critical ruminatory thoughts. Neuroimaging studies of depression implicate the subgenual cingulate cortex and its connectivity to amygdala and ventral striatum regions sensitive to social motivation (Johansen-Berg et al. 2008; Drevets et al. 2002; Mayberg et al. 1999). This same set of regions predicts negative changes in mood evoked by illness more generally (Harrison et al. 2009). The aberrant enhancement of self in depression is associated with increased engagement of this medial prefrontal cortex (Lemogne et al. 2012), which appears to arise from failure to deactivate these default mode regions during tasks that demand external focus and action (Wagner et al. 2006). The magnitude of depression reflected in clinical scores is predicted by engagement of rostral anterior cingulate during performance of effortful mental tasks (Wagner et al. 2012).

11.5 Neuroimaging of Metacognition

11.5.1 Overview

The conscious deliberate evaluation of perceptions, decisions, and judgments provides a form of self-monitoring that can shape subsequent behavior and appraisal. This form of metacognitive introspection may reduce basal levels of confidence or

self-doubt that frequently diverges from behavioral accuracy or the appropriateness of decisions. Metacognitive processes are associated through lesion studies and overlap with executive functions, with the integrity of prefrontal cortices. Thus, working memory, response selection, error monitoring and correction, and other aspects of self-regulation encompass metacognition and introspection at varying degrees of explicitness and are compromised by predominantly lateral prefrontal damage. Metacognition also includes mentalization: the capacity to evaluate and predict the thought processes of others, a process most strongly associated (through neuroimaging studies) with activation within mediodorsal prefrontal and paracingulate cortices.

11.5.2 Individual Differences in Introspection

Metacognitive ability can be operationally defined as the degree to which an individual's subjective sense of confidence mirrors their performance, e.g., in discriminating correct from incorrect decisions. Using this approach, structural imaging has shown a relationship between volume within right rostral prefrontal cortex (frontal pole) and metacognitive ability on a simple visual discrimination task. This effect was dissociable from both task accuracy and overall measures of self-confidence (Fleming et al. 2010). Intriguingly, left inferior temporal gyrus showed an inverse correlation with this ability.

11.5.3 Neural Correlates of Metacognition

Metacognitive ability, as noted, may be partitioned into different domain abilities associated with activation of distinct cortical regions, such that mentalizing engages medial prefrontal cortex (Gallagher and Frith 2003), whereas a sense of agency engages frontal polar cortex (Miele et al. 2011). Nevertheless, the frontal pole is involved in types of mentalization inferring intended strategy and in planning one's own strategy (Burgess et al. 2003). Meta-analyses of introspective/metacognitive processes (Schilbach et al. 2012) implicate medial prefrontal cortex together with medial parietal lobe across a broad range of introspective processes. There is notable overlap with brain regions subsumed within the "default mode network," particularly when appraising one's own affective feeling states, which is consistent with more general neuroimaging observations of self-referential processing that strongly implicate "default mode" ventromedial prefrontal and medial parietal cortex (see Sect. 11.4, above). In reviewing this literature, Frith emphasizes the social value of introspective metacognition (Frith 2012), grounding representation of self and other in social interchange, that in turn adaptively hones self-evaluative processes toward better perceptual and behavioral performance.

11.6 Neuroimaging of Mindfulness

11.6.1 Overview

Mindfulness describes one aspect of a set of meditative mental practices that originate in Eastern religious traditions, which has been reapplied in recent years to specific forms of psychological therapy and cognitive training in health settings (e.g., Kabat-Zinn 2003). In this context, mindfulness typically describes a mental focus on immediate present (mental and physical) experiences in the absence of mental or physical action. A distinction is sometimes made between mindfulness and concentration meditation, wherein attention is focused on a specific concept or process such as breathing, reciting a mantra, or visualizing an object. Nevertheless, mindfulness and concentration approaches are often combined to some degree across different styles of meditation (Ivanovski and Malhi 2007).

Therapeutic mindfulness approaches include mindfulness-based cognitive therapy, mindfulness-based stress reduction, acceptance and commitment therapy, and dialectical behavior therapy. These therapies attempt to change the personal impact of thoughts rather than their content, and in this way, they are distinct from other cognitive therapies. This is achieved through developing the capacity for passive observation of changes in mental events and processes within and outside the individual, without recourse to judgment or response. The capacity to achieve this state of non-evaluation, delayed reaction, and (arguably) affective detachment is fostered through training exercises which may combine a focus on bodily sensations. Ultimately, these techniques engage, develop, and adapt a number of psychological functions. Thus, the extent to which people practice mindfulness techniques reportedly predicts improved sustained attention and reduced distractibility, impulsivity, and startle response.

Various mechanisms have been proposed through which mindfulness might exert therapeutic effect (Holzel et al. 2011): (1) attention regulation, (2) bodily awareness, (3) emotional regulation through reappraisal, (4) emotional regulation through extinction learning and reconsolidation, and (5) change in perspective on "static" self. These different processes putatively engage different brain systems, such as (1) anterior cingulate and lateral prefrontal, (2) insula and temporoparietal junction, (3) dorsolateral prefrontal cortex, (4) orbitofrontal cortex and medial temporal lobe, and (5) medial prefrontal cortex and posterior cingulate.

Neuroimaging investigations of mindfulness can be divided up into those studies that focus on correlates on the practice of meditation and those that focus on the impact on symptoms. In the former, investigators have compared different forms of meditation and the effect of training and expertise on neural correlates. In the latter, longitudinal studies have begun to investigate structural and functional changes associated with symptom improvement (Holzel et al. 2010; Goldin and Gross 2010).

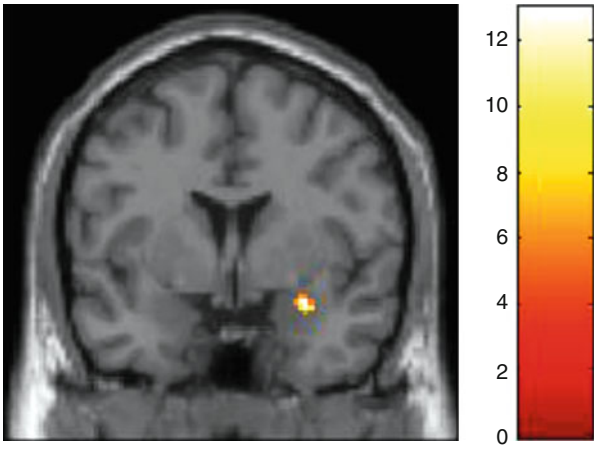

Fig. 11.3 Neural correlates underlying mindfulness focus on the present. Right amygdala activated while the minds of participants wandered to positive and negative events in the past but was not active during mindful focus on the present (Garfinkel and Critchley, pilot data in $N=7$ subjects, peak activation at [30 2–18], 26 voxels $Z=4.37$ threshold $p=.001$)

11.6.2 Neuroimaging Correlates of Mindfulness

Comparisons between meditative practice and relaxation or between different types of concentration or mindfulness meditation have been undertaken in a number of neuroimaging studies. Typically, these show widespread engagement of brain systems which include, particularly for meditation involving breath control, regions implicated in brain-body interactions and as interface between autonomic control and emotion. In a meta-analysis of ten functional neuroimaging studies involving expert meditators, including both mindfulness and concentration meditation, activation within caudate, insular sulcus/caudal orbitofrontal cortex (identified by authors as entorhinal cortex and frontal pole) was more reliably evoked by meditation compared to control conditions (Sperduti et al. 2012).

Mindfulness therapy trains the nonjudgmental awareness of experiences in the present moment, a strategy which can aid attentional control over mind wandering to aversive memories in the past or anxieties in the future. This refocusing of attention to the present moment is associated with reductions observed in emotion circuitry (see Fig. 11.3). Functional studies have implicated reduced amygdala activation associated with dispositional mindfulness (Creswell et al. 2007), while a course of mindfulness stress reduction was associated with quicker decreases in amygdala activation following symptom provocation in social anxiety patients (Goldin and Gross 2010).

Mindfulness meditation potentially exerts therapeutic effects (in part) through changes in emotion regulation. However, alterations in emotion regulation can encompass various processes such as attentional deployment, cognitive change, and response modulation (Gross 1998). In addition, attention training inherent within meditation could enhance capacity to disengage from aversive emotional stimuli (Lutz et al. 2008). These emotion regulation processes tap into distinct neurocircuitry (Ochsner and Gross 2005), and the exact regulation mechanisms/circuits through which mindfulness exerts therapeutic effects are still being understood. In an attempt to elucidate emotion regulation mechanisms in the context of mindfulness, individuals with social

anxiety disorder were given a course of mindfulness-based stress reduction and scanned reacting to negative self-beliefs while regulating negative emotions using either breath-focused attention or distraction-focused attention (Goldin and Gross 2010). Mindfulness was associated with improvements in anxiety, depression, and self-esteem scores. Notably, no neural changes were observed during distraction-based regulation. In contrast, changes associated with breath-focused attention regulation were observed in parietal and occipital brain regions associated with visual attention. Moreover, mindfulness-related reductions in social anxiety symptoms were associated with mindfulness-related neural responses in cuneus and occipital brain regions implicated in visual attention (Goldin and Gross 2010).

11.6.3 Structural Brain Correlates of Meditation and Mindfulness Practice

Structurally, experienced meditators are reported to show regional changes in brain morphometry in comparison with matched non-meditators. Some of these changes also reflect experience, i.e., they correlate with years of meditative practice. In healthy controls, regions that distinguish meditators from non-meditators *and* correlate with practice may perhaps be the most meaningful for understanding how meditation may exert putatively therapeutic effects. Here, even among the healthy population, individuals may choose to take up meditation for reasons that distinguish them from non-meditators: In the East, these may be subcultural, while in the West, there may be additional drivers including subclinical psychological or physiological health difficulties. These background effects may enhance or diminish (through increased variance) measurable group differences. Importantly, experience in meditation may either lead to divergence of neural correlates of adaptive brain processes or engender a normalization of dysfunctional systems leading to diminishment of group differences. Further care needs to be taken in interpreting effects, for example, in deciding whether to attribute neural changes to psychological adaptations or to "lower-level" physiological changes (slower breathing, increased baroreflex sensitivity) consequent upon the training in the volition control of respiration and muscle tone.

To date, structural imaging studies of mindfulness meditation report relatively inconsistent findings. The most reliable regional differences in gray matter are observed within right insula cortex (Lutz et al. 2008; Farb et al. 2007) and hippocampus (Lazar et al. 2000; Holzel et al. 2011). Diffusion tensor imaging (DTI) can provide insight into the structural connectivity of the brain, delivering a measure of white matter integrity (fractional anisotropy (FA)). Using this technique, more compelling differences arise when investigating older populations, suggesting that natural brain-based deterioration in FA induced by age may be reduced in individuals who meditate (although this effect could be driven by baseline differences in the innate prerequisites for initiating and/or continuing meditation). Nevertheless, the natural reduction of FA with age was lessened in elderly meditators in areas such as superior longitudinal fasciculus (SLF) and uncinate fasciculus (UNC) (Luders et al. 2011). The SLF traverses through the superior temporal gyrus, while the ventral

part of the UNC connects the orbital cortex with amygdala and hippocampal gyrus, areas which potentially accord with previous structural studies suggesting heightened gray matter volumes in orbital frontal cortex and larger hippocampal volumes (Luders et al. 2009; Holzel et al. 2011). In a longitudinal study investigating before and after effects of an 8-week mindfulness-based stress reduction course, greater declines in perceived stress levels were associated with enhanced reductions in gray matter concentration in the right amygdala (Holzel et al. 2010). To remove potential confounds of preexisting baseline differences between those who opt to meditate versus those who do not, more longitudinal studies are needed which incorporate an adequate (randomly allocated) control condition to help elucidate the brain-based effects of mindfulness therapy.

Conclusions

Consistent with the multiple axes of selfhood and self-awareness apparent in behavior and in consciousness, neuroimaging studies have identified a broad range of neural substrates implicated in self-processing. Distinct regions and networks emerge at basal levels associating interoception and interoceptive sensitivity with notions of "core self" and the "material me," as compared to areas implicated in higher-order metacognitively explicit self-related cognitions. Intermediate levels of self-processing, apparent in, for example, self-face recognition, self-referential cognition, and mindfulness, pick out still other substrates. Nonetheless, there is a broad systems-level convergence among the neural substrates for the representation of internal state; the capacity to appraise, evaluate, and predict internal bodily changes; and the perception of self, self-recognition, and self-referencing. Perhaps unsurprisingly, posterior cingulate, anterior insula, and ventromedial prefrontal and medial parietal cortices regions show this association, consistent with putative roles of these centers as interfaces between an embodied "core biology" and integrative cognitive processes involving associative cortices.

This evidence is consistent with perspectives arguing for the interoceptive primacy of self-representation, but goes little beyond this. To gain an advanced practical understanding of self-representation across levels of expression, new approaches are needed that go beyond regional neuroimaging correlates of stimulation and/or subjective phenomena. These could usefully include novel experimental designs contrasting conscious and unconscious self-related stimuli; emerging analysis methods foregrounding functional and effective connectivities within and between networks; integrated experimental setups leveraging combinations of neuroimaging, physiological recordings, and/or virtual/augmented reality manipulations of bodily experience; and finally integrative theories accounting for the subjective expression of selfhood (and its disorders) in terms of mechanistically explicit neural circuits. The personal, clinical, and societal impact of a comprehensive understanding of self-representation will be far-reaching.

Acknowledgments The authors are grateful to the Dr. Mortimer and Theresa Sackler Foundation for its support.

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Neuroimaging of Functional Neurological Symptoms

12

Alan Carson, Mark Edwards, and Jon Stone

Abstract

Functional neurological symptoms, or conversion disorders, have been described since the beginning of written medicine. Although originally attributed to a uterine disorder and first described as in a gynaecological text by the Middle Ages they were recognised as disorder of brain then of psyche. In the nineteenth century Charcot described them as being caused by a functional neurological lesion; one that evaded the availbel techniques of the day. A century on the technique shave become available that allow a search for these putative mechansims. In this chapter we review diagnosis and clinical presentation of functional symptoms which allows to speculate on potential mechanisms and hypothesise about potential target areas and paradigms for imaging. We then review all the imaging studies up until the end of 2012. To date the imaging conducted, both structural and functional, allow to be reasonably secure in concluding that functional neurological symptms are a genuine entity and not simply feigned. We cannot however make any claims that the underpinning mechansims of FNS have been resolved. We speculate that there are overly sensitive amygdala fear responses (i.e. abnormal response to stimuli (even objectively neutral stimuli), possibly conditioned

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_12,

by previous learning experiences) that drive changes in networks mediating perceptual experiences and/or movement plans. These changes, in the presence of abnormal self-directed attention (cf. prefrontal activations in functional imaging studies), are capable of producing movements or perceptual experiences which are not associated with a normal sense of self-agency and are therefore interpreted by patients as involuntary symptoms of an underlying disease.

12.1 Introduction

> The patient [says] "I cannot"; it looks like I will not; but it is "I cannot will" – James Paget 1873 (Merskey 1995).

Conversion disorder or functional neurological symptoms are a range of motor and sensory symptoms, which comprise the absence of normal or the presence of abnormal sensations or movement which suggest neurological impairment but display symptoms or signs which are either inconsistent or incongruent with the normal pathophysiological 'rules' of disease. Other terms used include 'psychogenic', 'non-organic', 'dissociative' and 'hysterical' neurological symptoms. They consist of a range of symptoms including anaesthesia, blindness, deafness, pain, weakness, abnormal gait, tremor, dystonia and seizures. Their display is attributed to an unconscious or preconscious mechanism, and it is assumed within this concept that they do not involve conscious deception of the examiner but truthful report of symptomatic experience.

Throughout medical history an association with emotional symptomatology has been noted, but following the seminal 1895 work of Breuer and Freud 'Studies on Hysteria' (Breuer and Freud 1955), the link was made explicitly with preconscious psychological trauma. The theory was that the production of a physical symptom resolved the distress caused by the repressed memories – the concept of *conversion disorder*. Treatment was by cathartic psychological therapy. This hypothesis proved remarkably robust throughout the twentieth century and was maintained within DSM IV (American Psychiatric Association 1994). However, it remains a hypothesis and confirmatory evidence, beyond striking case examples, has remained notably absent. Many patients with such symptoms present with no evidence of psychological troubles (Roelofs et al. 2005) – although proponents of conversion hypothesis would reply that these individuals do have psychological difficulties, it is just that they have repressed them more successfully. Many patients seem to improve in the absence of any explicitly psychological treatment either spontaneously or via physical treatments or purely on the basis of physically orientated reassurance – i.e. 'this is not a sinister illness' (Hoedeman et al. 2010). At the time of writing, DSM V (not yet finalised) appears to accept this anomaly and is overhauling its operationalised criteria based solely on the presence of symptoms that cannot be explained in terms of neurological disease rather than explicit psychological mechanisms (Kanaan et al. 2010; Stone et al. 2011). However, the concept of conversion disorder is deeply ingrained and whether this radical parting from Freudian dogma will survive remains to be seen. For the purposes of this chapter, we shall use

Table 12.1 Current proposed revised diagnostic criteria for conversion disorder: DSM V (functional neurologic symptom disorder)

A. One or more symptoms of altered voluntary motor or sensory function.
B. Clinical findings provide evidence of incompatibility between the symptom and recognised neurological or medical conditions.
C. The symptom or deficit is not better explained by another medical or mental disorder.
D. The symptom or deficit causes clinically significant distress or impairment in social, occupational or other important areas of functioning or warrants medical evaluation.

the proposed DSM V definition at the time of writing and will refer to the symptoms as functional neurological symptoms (FNS) (Sharpe and Carson 2001) (Table 12.1).

FNS are surprisingly common, accounting for 16 % of all outpatient attendees to neurology clinics (Stone et al. 2010). They are associated with significant disability, pain and distress (Carson et al. 2011). Approximately one third of cases resolve spontaneously and the remainder stay symptomatic often for a very prolonged course (Sharpe et al. 2010; Stone et al. 2003). Despite fears to the contrary (Slater 1965), the diagnosis can be made accurately with an error rate of somewhere between 0.4 and 4 % (Stone et al. 2005, 2009). Contrary to popular belief, their presentation and prevalence rate is surprisingly consistent, and there is little evidence of change in the clinical phenotype over the centuries. Another popular belief is that such symptoms are largely the product of 'secondary gain', i.e. there is monetary or explicit social reward for being ill. In the largest study, FNS patients had a slight excess of health-related unemployment and receipt of disability payments, but the most interesting finding was that the majority of patients were economically productive and not benefitting fiscally from their symptoms (Carson et al. 2011).

12.2 Diagnosis

The diagnosis of FNS is made on the basis of inconsistent or incongruent physical findings. The most notable feature of these is the central role of attention in generating symptoms. In diseases such as Parkinson's or stroke, the 'attentional spotlight' will have little effect on the presence of the tremor or hemiparesis. If anything, directing attention away from the affected limb may lead to a worsening of symptoms as active compensatory mechanisms are dispensed with. By contrast, in FNS shifting, the attentional focus towards the symptom typically leads to substantive worsening of symptoms (Zeuner et al. 2003).

These attentional phenomena underpin a range of techniques designed to distract attention from the limb or utilise reflex actions in order to make the diagnosis in patients with functional motor symptoms (Stone and Carson et al. 2012). For example, patients with functional tremor tend to focus visually on the tremulous hand (Van Poppelen et al. 2011) which typically gets worse whenever they are looking at it (and conversely may improve if they perform a (McAuley and Rothwell 2004) distracting motor task). Patients with functional leg weakness often have a positive

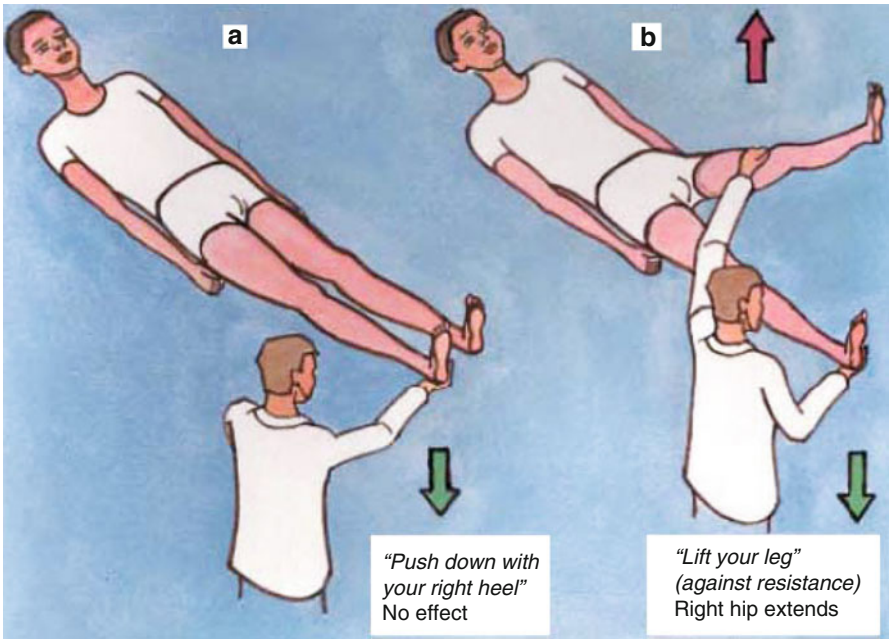

Fig. 12.1 Hoover's sign for functional weakness. (**a**) The patient has weak right hip extension. (**b**) Right hip extension returns to normal with left hip flexion against resistance

Hoover's sign (Ziv et al. 1998) in which hip extension weakness can be found to return to normal with contralateral hip flexion against resistance (see figure: McWhirter et al. 2011). Interestingly these findings remain despite explanation, and even with insight into the mechanisms, patient's symptoms continue to be dramatically influenced by attentional focus – many of our patients indeed find reassurance from conducting their own Hoover's test (Stone and Edwards et al. 2012) (Fig. 12.1).

The way that patients with functional neurological symptoms perceive a problem whenever they think about or look at a limb (but not necessarily when they do not) was experimentally demonstrated by Pareés et al. (2012). Patients with functional tremor wore an actigraph 'tremor watch' for a 5-day period while also filling in a daily diary of how much of the time they perceived themselves to be tremoring. Patients rated their tremor to be present at least 80 % of the waking day, even though tremor was only present for about 30 min each day. The patients' experience was that symptoms were there when they looked. Patients were fully aware of the purpose of the study and the fact the tremor watch was constantly recording their tremor, making malingering an unlikely explanation for these findings.

This necessary attentional spotlight for symptom production must also involve higher level cognitive processing as distraction, whilst conducting complex mental or motor tasks results in decreased symptoms expression. Again this finding survives explanation to the patient and many will use it therapeutically to help

control their symptoms. It follows that there will be a substantive executive 'top-down' component to the symptoms that involved capacity-limited conscious processing.

12.3 Aetiology

In terms of mechanisms, such findings however must coexist with a range of well-replicated aetiological findings which substantively increase the risk of developing FNS. It has been recognised since Briquet's *Treatise on Hysteria* (Briquet 1859) that aversive childhood and intercurrent life events confer an increased risk. Whilst such events are not essential for the development of FNS (Roelofs et al. 2005; Testa et al. 2012; Kranick et al. 2011) nor indeed as strong a risk as some assume, they are undoubtedly associated in some individuals. Broadly speaking, these risk factors are similar to the risks for anxiety and depressive disorders and do not answer the question of why someone should develop a weak leg or a shaking hand rather than an episode of low mood.

Roelofs and colleagues (Roelofs et al. 2003; Roelofs and Spinhoven 2007; Bakvis et al. 2009a, b) developed one of the more interesting hypothesis suggesting that part of the explanation may be an alteration in preconscious threat processing – a 'bottom-up' bias in vigilance in the environment towards threat and an associated misrepresentation of neutral stimuli as threatening. This model has the potential to be further mediated by genetic and epigenetic effects.

An integrated cognitive model was developed by Brown (2004) who suggested FNS may simply arise from distortions in self-awareness that can develop in the absence of emotional difficulties. By this view, FNS result from the overactivation of 'rogue' mental representations, with anything that fuels this activation contributing to symptom development and maintenance (see Fig. 12.2). This model accommodates the attentional mechanism described above but also allows for, but does not insist upon, modification of the rogue representations by cognitive schema shaped by abusive experience.

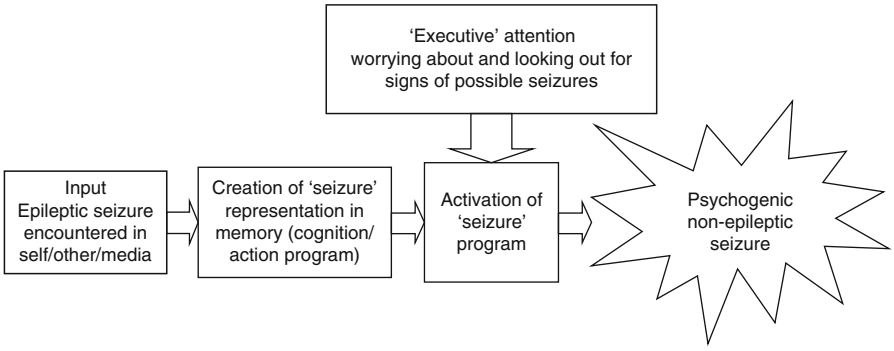

Fig. 12.2 After work of Brown R (With permission of JNNP Carson et al. (2011))

Edwards and colleagues (2012) described a Bayesian model of symptom generation based around Friston's positive entropy model of cerebral function. In this model, which accepts that the brain has a hierarchical structure which each level reciprocally connected, the organism aims to minimise surprise by generating sensory predictions on the basis of current sensory data derived from the environment and predictions about these data based on an internal model of the world built up over time via experience of interaction with the environment. Surprise is minimised by reducing prediction error by either action or changing the nature of the prediction based on perception. They describe the model as Bayesian because the hypotheses regarding the causes of sensory input are derived by an interaction between prior beliefs about the world encoded in 'top-down' backward connections and sensory evidence encoded in 'bottom-up' forward connections. The relative weights placed on these contributions to perception and action are not fixed, and in different circumstances, more weight might be placed on prior beliefs and less on sensory data, or vice versa.

This hypothesis is that FNS develop when there is a specific distortion in the relative weights given to sensory data and prior belief related to specific physical symptoms. The authors propose that physical triggering events, which are common at the onset of symptoms and are often associated with anxiety/panic responses, may act in concert with a number of other factors to cause a dramatic increase in the 'precision' (weight) associated with top-down beliefs associated with the novel sensory data occurring in the physical event. The argument is that these very strong top-down predictions, enhanced by self-directed attention, will produce perception and/or action consistent with these beliefs, overwhelming any sensory evidence to the contrary (Fig. 12.3).

The great attraction of this model is that it offers an underpinning neurobiological explanation not only for the clinical correlates of attention described above but also for the apparently crucial role of beliefs in the formation of FNS that has been demonstrated at both an individual and population level. It also explains why there may be such marked placebo responses in such patients and why treatments based around the study and alteration of beliefs, cognitive behavioural therapy explicitly (Sharpe et al. 2011; Goldstein et al. 2010) and hypnosis implicitly (Moene et al. 2002), appear to be effective treatments. It also provides a general framework for the development of all functional symptoms, rather than making a distinction, as some models do, between sensory and motor symptoms or positive (e.g. tremor, pain) and negative (e.g. paralysis, sensory loss) symptoms. This is consistent with the common co-occurrence of functional symptoms.

The evidence that beliefs make at least a material contribution to the aetiology of FNS is overwhelming. At individual patient level, distortions of beliefs and expectations can promote symptom development (Pennebaker 1982; Green et al. 2004) and also be predictive of outcome (Sharpe et al. 2010). This effect can also be seen at a population level, and the cultural beliefs of population can shape the presentation of syndromes, for instance, persistent symptoms following 'whiplash' injury is much rarer in countries where whiplash is not known and the expectation of outcome from

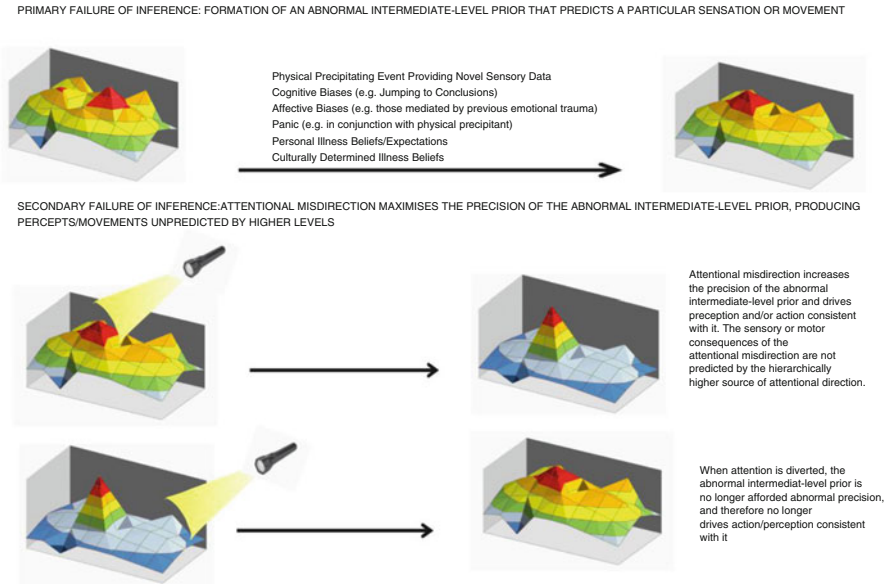

Fig. 12.3 Edwards et al. (2012) Baysian model suggests that very strong top-down predictions, enhanced by self-directed attention, will produce perception and/or action consistent with these beliefs, overwhelming any sensory evidence to the contrary (Reproduced with permission from *Brain*)

minor road traffic accidents described in population surveys closely mirrors the outcome of whiplash injuries (Ferrari et al. 2001). Not only can these effects be mediated by particular illness beliefs but also distorted by systematic bias from pathological mood states. The association between low mood and increased pain perception is well recognised (Berna et al. 2010).

12.4 Plasticity: Cause or Effect?

Imaging studies, in particular activation studies, provide a snapshot of brain function at a given time, but often, functional symptoms have been present for a prolonged period (often years), resulting in sustained alteration of sensorimotor signals. It is inherently unlikely that the brain will not adapt to this, resulting in changes to functional, and possibly structural, architecture. One might be most likely to see such effects in more sustained presentations such as the phenomenon of fixed dystonia (Schrag et al. 2004) where the hand or foot is held, over a prolonged period of time, in a dystonic posture which does not relax. Consideration of data from imaging studies needs to include the possibility that we are seeing the effect rather than the cause of functional symptoms.

12.5 Deception

A consideration of the backdrop to neuroimaging of FNS must take account of the possibilities of deliberate deception. At a population level, the phenomenological, historical and geographical consistency of presentations would appear to argue against deception – if explained by deception, one would predict that symptoms would vary enormously over time and correlate closely with the economic benefits of ill health, but such changes are notably absent. However, at an individual level, the impairments displayed resemble voluntary behaviour and the diagnosis is essentially based on an assumption that the individual is not feigning. Anyone who has practiced in a medico-legal setting will be aware just how fallible such impressions are. The great attraction of functional imaging studies is that they offer the potential to distinguish between genuine displays of FNS and deception. However, those engaged in deception in this context are usually healthy volunteers merely going along with an experiment. There is no indication that this form of temporary knowing deception in any way mirrors the more prolonged, maintained, emotionally or economically rewarding deception undertaken by a 'patient'.

Studies examining deception have shown that it is a cognitively complex, executive activity compared to truth telling which is straightforward (Spence et al. 2001). Deception involves suppression of truthful response as well as generation of a strategy for the deception. At an experimental level, activation of anterior cingulate gyrus has been shown in a number of experiments. This correlates with slower response times reflecting increased processing demands. Again, however, these studies involve healthy volunteer controls, and even when conducting paradigms such as gambling studies, the stakes are very low and the subject does not have much riding on the deception. One of the few reports of a real-life 'high-stakes' situation is a fascinating review of the behaviour of convicted murder filmed undergoing interrogation by police at different stages. It was noted that in the early stages of the interview whilst the subject was lying, there were increased response times and patterns of non-fluent speech disturbance mimicking the findings from experimental subjects but in a high-stakes, prolonged situation (Vrij and Mann 2001). This does offer at least some reassurance that similar mechanisms may underpin both the trivial experimental situation and the real-life equivalent.

12.6 Imaging Studies

12.6.1 Structural

Structural imaging studies in FNS have been limited. The traditional view is that structural imaging in FNS should be normal. One study found reduction in the volume of basal ganglia in ten patients with motor FNS compared to healthy controls, using a manual segregation technique (Atmaca et al. 2006).

Aybek et al. (2012) examined 15 patients with limb weakness due to FNS and compared them to 25 randomly selected healthy controls from general practitioner

lists. They used a voxel-based morphometry (VBM) and a voxel-based cortical thickness (VBCT) analysis to conduct comparisons. With VBM they found no differences when comparing all patients to controls but did note a trend towards increased grey matter volume in the right premotor cortex. A VBCT analysis also revealed no difference between all patients and all controls. However, a subanalysis (with all the inherent risks of false-positive results) did show a significant increase in cortical thickness in bilateral premotor cortex in hemiparetic CD patients compared to controls but not in paraparetic patients compared with controls. The authors hypothesise that this result may reflect recruitment of compensatory networks.

Partial support was offered from a recent study of response to immobilisation after upper limb injury which showed a decrease in cortical thickness, within 14 days, in contralateral primary motor and somatosensory areas and increase in ipsilateral motor cortex (Langer et al. 2012).

Labate et al. (2012) conducted a comparison of 20 patients with telemetry-confirmed psychogenic non-epileptic attacks (functional seizures) and 40 healthy controls. Using a VBM and a VBCT analysis, they found reduction in the volume of the motor and premotor regions in the right hemisphere and the cerebellum bilaterally. They noted the degree of atrophy correlated with the degree of depressive symptomatology. This raises the question whether they are imaging PNES specifically or the structural neural correlates of depression where reduction in volume of cortical structure is well recognised although it is more commonly the hippocampal, basal ganglia, orbitofrontal cortex and subgenual prefrontal cortex that are affected (Lorenzetti et al. 2009). In fact, all of these structural studies are problematic to interpret because of confounding with current and past comorbidity and uncertainties about cause and effect. Prospective studies with scanning of recovered patients could help to sort out which changes, if any, are specific to FNS.

12.6.2 Functional

Charcot's hypothesis of the underpinning mechanisms of hysteria, 'Not of the nature of a circumscribed organic lesion of a destructive nature…one of these lesions which escape our present means of anatomical investigation…we designate a dynamic or functional lesion' (Charcot 1877) encapsulates the logic and the aspirations underpinning functional imaging. It would appear as a tool ideally designed for studies of FNS. However, 17 years after the first study, the field remains small and the number of studies limited. In general, studies have been underpowered, and with some notable exceptions, the paradigms tested have often been unsophisticated. Furthermore, subjects have had a variety of different FNS phenotypes. The ability to draw comparison between studies is therefore limited.

In 1995, Tiihonen and colleagues (1995) published a single case study of a patient with left-sided paralysis and paraesthesia investigated with SPECT. The paradigm involved stimulation of the left median nerve when symptomatic and following recovery. They found increased cerebral blood flow in the right frontal

regions and decreased uptake in the right parietal regions when symptomatic that largely resolved on recovery.

Two years later, Marshall and colleagues (1997) reported on a single case PET study of a woman with left-sided hemiparesis without somatosensory loss. The onset of her symptoms followed an episode of psychological trauma. They contrasted preparation to move and actual attempted movement of the affected left leg to the same activities in the healthy right leg. The preparation to move either leg and actual movement of the good right leg were associated with activation of premotor and motor areas. By contrast, attempted movement of the paralysed leg was not associated with the expected activation of right primary motor cortex. However, the right orbitofrontal and right anterior cingulate cortex were significantly activated. The authors suggested that these areas were inhibiting prefrontal, 'willed' effects on the right primary motor cortex, preventing the movement of the left leg.

It seemed we were on the road. This data seemed to offer a 'top-down' explanation in which higher frontal areas inhibited normal sensorimotor activity.

Yazici (Yazici and Kostakoglu 1998) conducted a SPECT study on five patients with astasia-abasia (a condition in which the patient can move normally on the bed but is unable to stand upright or walk but lurches violently in all directions). They found perfusion defects (of greater than 10 % compared to other brain regions) in the left temporal regions in four patients and in the left parietal region in the remaining one. What a resting-state study of a dynamic process of movement actually means is difficult to interpret.

Spence and colleagues (2000) described two patients with left upper limb paralysis who were compared to two healthy subjects deliberately feigning symptoms and six healthy controls who conducted the task normally. They then repeated the paradigm on a further case who had *right* upper limb paralysis and two further feigners. The great attraction of this study is that it moved towards answering the question that most people wanted to know more than any other – 'when a patient with functional paralysis can't move their arm in a scanner, are they just pretending?' The subjects were asked to move a joystick with their hands in response to a paced auditory tone. Scans were taken during movement of affected hand, the unaffected hand and at rest. They found that relative to resting state, left-sided paralysis patients had hypoactivity of left dorsolateral prefrontal cortex (DLPFC). By contrast, feigners showed hypoactivity of the right anterior frontal cortex. Surprisingly when studying the right-sided paralysis patient, they found the same hypoactivity of the left DLPFC. They commented that the left DLPFC is specifically activated by the internal generation of choice, i.e. action and that FNS patients had a deficit of the required higher components of volition to 'will' themselves to act. The results were seductive, but with hindsight, the seeming simplicity of the dissociation between the patients and the feigners, based on only four subjects, may have been too good to be true and we suspect it was a chance finding.

In the most methodologically robust of the early studies, Vuilleumier and colleagues (2001) (using SPECT) studied seven patients with unilateral sensorimotor symptoms using bilateral passive vibratory stimulation. Patients were imaged whilst symptomatic and four of them were reimaged following recovery around 3 months

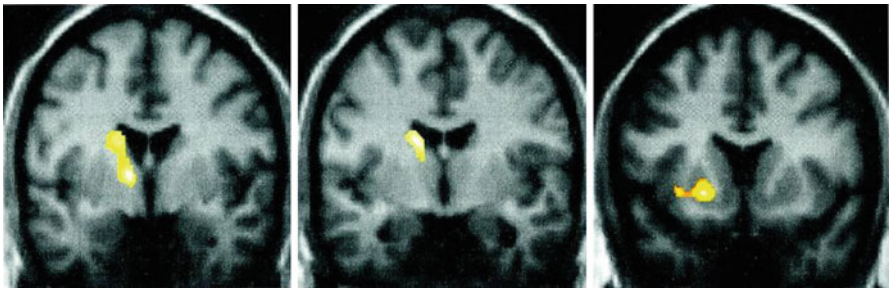

Fig. 12.4 SPECT of four patients with unilateral functional motor and sensory symptoms comparing the symptomatic state to the recovered state. The figures show hypoactivity in thalamus, caudate and putamen (Reproduced by permission from Brain, Vuilleumier et al. (2001))

later. They found a consistent decrease of regional cerebral blood flow in the thalamus and basal ganglia contralateral to the deficit (Fig. 12.4). The basal ganglia are part of a motor, sensory and cognitive network. In particular, structural lesions in the areas described, after stroke, for example, may produce similar hemisensory symptoms. Was this the dynamic lesion that Charcot had dreamed of? The findings held across a range of image analysis techniques and subcortical asymmetries were present in each subject. The persuasive and exciting finding however was that the contralateral basal ganglia and thalamic hypoactivation resolved after recovery. Furthermore, lower activation in contralateral caudate predicted poor recovery at follow-up. The authors concluded that their results 'suggest that hysterical conversion deficits may entail a functional disorder in striatothalamocortical circuits controlling sensorimotor function and voluntary motor behaviour. Basal ganglia, especially the caudate nucleus, might be particularly well situated to modulate motor processes based on emotional and situational cues from the limbic system. Remarkably, the same subcortical premotor circuits are also involved in unilateral motor neglect after organic neurological damage, where voluntary limb use may fail despite a lack of true paralysis and intact primary sensorimotor pathways'. They hoped the findings showed the way for a modern psychobiological theory of hysteria. Others in the field were impressed.

The newly emergent technology of fMRI was used in a number of small studies (Mailis-Gagnon et al. 2003; Werring et al. 2004; Burgmer et al. 2006) which produced conflicting findings. Mailis-Gagnon et al. studied chronic pain patients who reported non-dermatomal somatosensory deficits. They hypothesised that central factors would underpin these deficits and suspected that the supraspinal nuclei were a key area. They examined evoked brain responses to noxious and light brush stimulation. Unperceived stimuli (from touch in the non-dermatomal deficit areas) failed to activate the thalamus and the posterior regions of the anterior cingulate cortex (ACC) which were activated with perceived touch and pain. Unperceived stimuli were also associated with deactivations in the somatosensory cortex, posterior parietal cortex and prefrontal cortex. The unperceived stimuli activated the rostral anterior cingulate.

Werring et al. 2004 evaluated visual stimulation in five patients with functional visual loss, in an attempt to determine the underlying neural mechanisms. They used 8 Hz light stimulation versus darkness and found that patients did indeed

show reduced activation in visual cortices, but they had increased activation in the left inferior frontal cortex, left insula-claustrum, bilateral striatum and thalami, left limbic structures and left posterior cingulate cortex. They hypothesised that these findings could be indicative of either an inhibition of primary visual cortex or a shift to implicit visual processing.

Burgmer et al. (2006) used studied four patients with upper limb paralysis using an fMRI paradigm based on passive observation of a video clip of a moving hand or a hand at rest. They found patients showed decreased activation of cortical hand areas during movement observation that was specific to the side of their dissociative paralysis. No brain activation compatible with movement inhibition was observed. They considered this was suggestive of a deficit in the conceptualisation of movement as well as the initiation of an action.

It was difficult to compare data between these studies as they were on different phenotypes of FNS and used very different investigatory paradigms, but even allowing for this, there was no sense of an emergent common ground with contradictory patterns of activation emerging.

Ghaffar and colleagues (2006) tried to reconcile these opposing findings in an fMRI study of three patients with unilateral sensory deficits using a vibrating stimulus which was delivered either unilaterally or bilaterally. They found that stimulation of the affected limb did not activate the contralateral primary somatosensory cortex whereas bilateral limb stimulation did. They also found activation of the orbitofrontal cortex, anterior cingulate, putamen and thalamus.

Activation of the orbitofrontal and anterior cingulate cortex was becoming a consistent finding – the concern was that Vuilleumier's group had found similar patterns of abnormal activity in these regions in their patients when symptomatic and following recovery, suggesting that this was either some form of background trait or perhaps a feature of the stimulation paradigm but not a mechanism of the actual symptoms themselves.

Stone et al. (2007) revisited the comparison of patients with deliberate feigners, this time using fMRI to study four patients with unilateral ankle weakness and comparing them to four controls. They compared both 'good' and 'bad' limb and between patients and feigners. Plantar flexion of the affected ankle resulted in less and more diffuse activation of the contralateral motor cortex than the 'good' leg. In the comparison between feigners and patients, the feigners' activation pattern was relatively simple and involved primarily activity in the contralateral supplementary motor cortex, suggesting they were simply preparing to move (but not actually fulfilling), whereas the patients with FNS activated a more complex network which included the putamen and lingual gyri bilaterally, left inferior frontal gyrus, left insula and precuneus. The patients also showed deactivation of the right middle frontal and orbitofrontal cortices. The differences between the two groups were reassuring for those who believed FNS to be a genuine condition but presented a rather different set of findings from the earlier Spence study. Some might view the more complex, and less coherent, pattern of findings as inherently more plausible, but this particular study was troubled by a lack of a direct comparison between feigners and FNS and by subjects with different laterality to their symptoms.

Tanaka et al. (2007) echoed the earlier Yazici et al. paper by conducting a resting-state SPECT examination of four patients with hemiparesis due to FNS and found decreased uptake in the frontal regions. They concluded this reduced activity was responsible for the symptoms but somewhat bizarrely felt that if there was a biological correlation, the patient could no longer be viewed as having FNS and they reclassified such patients as 'pseudohysterical hemiparesis'. Aside from this minor Cartesian dispute, the real issue with this study was – could a resting-state study really add anything?

The same year also saw a change to more sophisticated experimental designs. De Lange's group (de Lange et al. 2007), informed by cognitive neuropsychology, reported an fMRI study of imagined movement in eight patients with unilateral upper limb paresis, analysed with a functional connectivity analysis. Motor imagery would be predicted to recruit similar circuitry to actual movement, and indeed, this is what they found with imagined movement of both the affected and unaffected limb. However, motor imagery of the affected limb was also associated with increased activation in the ventromedial prefrontal cortex and superior temporal cortex. They interpreted these differences as evidence that symptom production related to a failure to deactivate these regions and was therefore associated with heightened self-monitoring during action.

Richard Kanaan and colleagues (2007) also offered a novel and welcome departure, albeit in a single case study. To date, studies had concentrated on mechanism underpinning symptom expression. These 'how' studies offered insight into underpinning putative neural mechanism that could explain how it came to pass that an affected limb could not move. Kanaan by contrast made the first attempt at trying to explain 'why' this happened in the first place and linked an explicit aetiological risk factor to an explicit mechanism. They used the Freudian conversion hypothesis that preconscious memories of traumatic events were directly linked to symptom production. They used the Life Events and Difficulties Scale to interview a 37-year-old woman with a paralysed upper limb. They made objective ratings of events that they considered were most likely to be associated with symptoms onset that were associated with 'escape' cognitions and that appeared to be repressed. When these events were represented to the patient during fMRI scanning they regional brain activations characteristic of emotional arousal, including the amygdala and right inferior frontal lobe, when compared with an equally severe events from the patient's past, as rated by the LEDS. The recall event was also associated with decreased motor activity in the area corresponding to the subjectively paralysed limb. For the first time, there was an explicit experimental test of a cherished Freudian idea that to that date had failed Popper's notion of falsifiability. Not everyone in the field shares such an enthusiasm for the Freudian hypothesis, and the authors acknowledged that they had to conduct many assessment interviews in order to find a suitable subject indicating that the results may not be generalisable even if replicated. Nonetheless, this linking of 'why' and 'how' within one experiment was most welcome.

In 2009 Cojan and colleagues (2009) reported on an attempt to look further at the link between emotional situations and their potential to suppress motor pathways by excessive inhibitory signals. They compared a single case with functional left arm

paresis to 30 healthy controls feigning weakness. They utilised a 'go-no go' task design to investigate executive inhibitory circuits during preparation, execution and inhibition of movement. They found that preparatory activation arose, as predicted, in the right motor cortex, indicating preserved motor intentions; however, this was associated with increased connectivity and activation of the ventromedial prefrontal cortex, an area that would be more commonly associated with motivational and emotional processing. The patient's failure to actually move in the 'go' trials was associated with the activations in precuneus and ventrolateral frontal gyrus. When they examined data related to the unaffected arm during the 'no go' trials and compared that to activations in the affected limb during the 'go' trials, they found different patterns of activation. As anticipated, 'no go' on the right normal arm was associated with activation of the right frontal areas normally subserving inhibition, but this pattern was not mirrored with the affected left arm. The feigners, however, showed a similar pattern of inhibition during the 'no go' trials of their 'good' arm and the 'go' trails of their (simulated) 'bad' arm. This indicated that different patterns of inhibition of motor activation were present between patient and feigners. In the patient, the right motor cortex also showed enhanced functional connectivity with the posterior cingulate cortex, precuneus and ventromedial prefrontal cortex, suggesting that inhibition of movement in FNS is not mediated via traditional cognitive inhibitory structures but by activation of midline circuits associated with self-related representations and emotion regulation.

In a second study on eight patients, with upper limb paresis due to FNS, using imagined movement (mental rotation of a limb), de Lange and colleagues (2010) examined connectivity between the prefrontal cortex and sensorimotor regions. They made a comparison between functional connectivity patterns associated with imagined movement in the affected limb and the normal limb. They found distinct connectivity patterns for different parts of the prefrontal cortex. The ventromedial prefrontal cortex was not functionally connected to the motor system, but the dorsolateral prefrontal cortex was, a seemingly contradictory finding to Cojan et al.

Valerie Voon and colleagues from NIH published three reports of fMRI experiments in patients with functional motor symptoms. The first report was an elegant fMRI study on 16 patients with motor FNS of a variety of subtypes including paresis, tremors and dystonias (Voon et al. 2010a). The comparison was to 16 age- and sex-matched controls. They utilised an emotional Stroop test in which the subject was presented with a series of faces which had fearful, happy or neutral expressions. Previous healthy volunteer studies have previously demonstrated that presentation of 'emotional' faces is associated with amygdala activation compared to the neutral faces. The effect is greatest for faces with 'negative' emotional expression. The control subjects showed this pattern and also a degree of habituation of response over time to the stimuli. By contrast, the FNS patients showed a similar pattern of amygdala activation to all stimuli irrespective of content and had a relative failure to habituate. A connectivity analysis suggested that in the FNS patients, there was greater connectivity between the amygdala and the right supplementary motor area than in healthy volunteers (Fig. 12.5b). They concluded that this was a potential neural mechanism that may explain why psychological or physiological stressors can trigger or exacerbate FNS in some patients and that increased functional

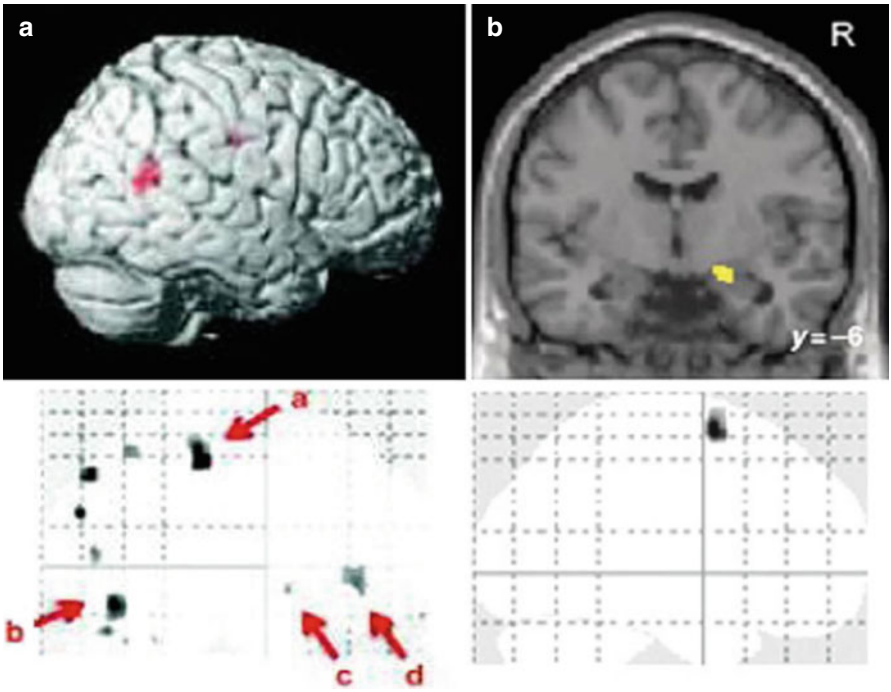

Fig. 12.5 (**a**) Conversion disorder patients had lower activity of the right temporoparietal junction (TPJ) (*top*) when comparing involuntary conversion tremor versus their own voluntary mimicked tremor. Patients also had lower functional connectivity between the right TPJ and bilateral sensorimotor cortices *a* bilateral cerebellar vermis *b*, left ventral striatum *c* and bilateral ventral cingulate/medial prefrontal cortex *d*. The TPJ is implicated in the feed forward model of motor control and suggested to act as a comparator of intended (sensory prediction) and the actual sensory outcome for online monitoring of movement. As sensory outcome is intact, the authors suggest that decreased TPJ comparator activity may be related to impaired generation of the intended sensory prediction during motor preparation. 75 (**b**) Conversion disorder patients had greater right amygdala activity to positive and negative affective stimuli compared with healthy controls (*top*) along with greater limbicemotor functional connectivity between the amygdala and a region involved in motor preparation, the supplementary motor area (*bottom*). Arousing stimuli might aberrantly influence motor preparation, providing a potential explanation for the influence of stress on motor function 76 (with permission from Neurology 82 and Brain 83)

connectivity of emotional processing in limbic regions and motor preparatory regions during states of arousal may underlie the pathophysiology of FNS. The difficulty with this study is that because it did not specifically study the correlates of the symptom, the findings may relate to other common state or trait changes in the FNS.

The group's second study explored the sensation of self-agency – the experience that one is the cause of one's own actions (Voon et al. 2010b) and did relate more directly to the symptom. They were interested in the apparent anomaly of functional motor symptoms that movement has characteristics associated with voluntary movement (e.g. tremor that stops with distraction, jerks of the limbs preceded by a premovement potential), but the symptoms are perceived as being involuntary. They

suggest that the feeling of self-agency comes from the comparison between the prediction of an action's consequences (feed-forward signal) and sensory feedback as to the actual consequence. This comparison is believed to involve recruitment of the right inferior parietal cortex. They examined eight patients with tremor due to FNS. The study had the advantage that the subjects acted as their own controls by performing a 'feigned' voluntary tremor at times when their functional tremor was not present. They found that, as predicted, the patients had right temporoparietal junction hypoactivity which was associated with decreased functional connectivity in sensorimotor regions and limbic regions (Fig. 12.5a). They concluded that FNS were associated with a failure to appropriately match sensory prediction signal and proprioceptive feedback and this computational failure could explain the perception that FNS were not self-generated.

The group's final study looked at motor preparation in 11 patients with weakness due to FNS (Voon et al. 2011). They found that compared with healthy volunteers, there was lower left supplementary motor area activity (implicated in motor initiation) and higher right amygdala, left anterior insula and bilateral posterior cingulate activity (implicated in assigning emotional salience). They linked this back to their earlier study of increased amygdala activation to suggest a theory 'in which previously mapped conversion motor representations may in an arousing context hijack the voluntary action selection system, which is both hypoactive and functionally disconnected from prefrontal top-down regulation'.

In 2010 Thomas-Aterion and colleagues (2010) published a single case study of prolonged dense retrograde amnesia with loss of personality. In one sense, this presentation is the classic psychogenic, dissociative state and the report is of therefore interest. However, we have always been troubled by such presentations and have often suspected factitious illness as a more likely explanation. In resting-state PET study compared to 47 healthy controls, they found left medial temporal and insular/opercular hypometabolism which would be consistent with some form of attentional disruption to verbal memory networks and retrieval of personal detail. Although one might have expected this to be more likely to occur on right-sided regions, which have a stronger association with autobiographical retrieval, they are able to cite a supportive case report from Hennig-Fast et al. (2008) who had reported similar findings in a similar case. The authors do however acknowledge that the results could be interpreted as the effects of long-term volitional suppression of personal identity.

Van Beilen et al. (2011) tried to reconcile a number of different finding in a complex analysis of an fMRI study of 9 patients (5 right sided and 4 left sided) with hemiparesis due to FNS who were compared to 21 normal controls and 13 feigners (7 right sided, 6 left sided). The paradigm involved both real and imagined movement of both 'good' and 'bad' limbs. They analysed within subjects and between groups with flipped and unflipped images. In truth, although the paper itself is well written comprehending the results is not straightforward, the results do appear to confirm the authors' conclusions of abnormal parietal activation which was specific for conversion paresis patients. Patients also showed reduced activity in the right dorsolateral prefrontal cortex, supramarginal gyrus and precuneus. The prefrontal activation included hemisphere-specific activation that was lateralised in the same

hemisphere, regardless of right- or left-sided paresis. They interpreted this right-sided prefrontal deactivation as being indicative of a failure of willed action based on free choice. Of interest they draw attention to this area's involvement in post-traumatic stress disorder. They acknowledge that these findings are different from a number of other reports which had shown increased prefrontal activation although did chime better with Spence et al.'s earlier study. They suggest that these differences are a methodological artefact of scan analysis rather than necessarily a true difference. They also report contralateral (to the paresis) prefrontal hypoactivity which they relate to failure of volitional movement, but this finding they acknowledge as being at odds with previous reports, although they say this may be explained by different activation paradigms used. The reports of contralateral(to the paresis) underactivation in the supramarginal gyrus in both real and imagined movement and the precuneus in real movement only could be related to a failure of areas involved in integrating movement with bodily and environmental awareness. The precuneus has been linked with multiple functions including retrieval of autobiographical memories, judging between self-relevant and self-irrelevant traits, and shows increased activation in default resting conscious state. They propose that the supramarginal gyrus deficit may be unique to the development of paresis, but the prefrontal and precuneus deficits may relate to a failure of willed volition more generally in FNS.

Van der Kruijs and colleagues (2012) conducted the only study we are aware of on patients with dissociative functional seizures. They compared 11 patients to 12 controls during an activation paradigm (cognitive tasks of picture encoding and the colour Stroop) and then a resting-state functional connectivity analysis using seed regions based on the activation tasks. They found patients had increased connectivity between the insula (an assumed emotional region), the inferior frontal gyrus and parietal cortex (both assumed to link to executive circuits) and the precentral sulcus (movement). The strength of the associations correlated well with the patients' tendency to dissociate (as measured by the questionnaire).

12.7 Summary

Disappointingly no coherent set of finding emerges from the set of studies to date. To some extent, this is to be expected given the range of different phenotypical expressions of FNS tested across a range of different scanning techniques and different activation paradigms. The fact that many studies are underpowered may add to the confusion with increased likelihood of false-positive and false-negative findings.

The biggest disappointment is the lack of coherence between studies suggestive of an inhibition hypothesis in which excessive activity of prefrontal regions, including anterior cingulate and dorsolateral prefrontal cortex, inhibits the planning stage of volitional movement and those studies suggestive of impaired volition in which underactivity in similar regions, and perhaps additionally the ventromedial prefrontal cortex, results in a failure to generate the necessary preplanning states for volitional movement.

An optimist might feel that there does seem to be some consistency to the findings of disrupted parietal activity although what role these regions play may be more questionable. Similarly, despite a lack of coherence to the findings, the idea emerges that there is some form of abnormal functional connectivity between regions primarily involved in emotional programming and regions involved in motor preplanning.

This would certainly fit with well-established epidemiological relationship and the clinical observation that many patients seem quite emotional. The possibility of reverse causality to this relationship must however be considered. These emotional risk factors often long predate the development of symptoms, and there may well be a need to separate out trait from state findings. There is clearly a need for groups to copy Vuilleumier's (2001) pre- and post-recovery approach to comparison. Finally, it is reassuring that studies repeatedly find differences between patients with FNS and those who are feigning symptom production even if there is a lack of consistency to the exact nature of the difference.

Many of the patients studied have had psychiatric co-morbidities in the form of post-traumatic stress disorder and depressive/anxiety illness, all of which may be influencing the findings on functional imaging. There is a need for more use of controls matched for psychiatric disorder but in the absence of specific FNS symptoms.

That said, a substantive minority of patients do not have any observable emotional disruption; by contrast, almost every patients has alteration of attention and distorted illness beliefs directed towards the affected area. Paradigms designed to test these features have been notably absent. Furthermore, FNS develop over time and the paradigms used to date, with the possible exception of Voon's emotional processing study, do not tend to look at (mal)adaptive learning.

Another issue which has been ignored by all the studies to date is the heterogeneity by which patients may actually produce their symptoms. For example, some types of functional tremor are identical in appearance and mechanism to a voluntary tremor; others arise from a process of co-contraction of agonists and antagonists as seen in shivering (Raethjen et al. 2004). In paralysis, some patients have no muscle contraction, while others appear to co-contract muscles when attempting to move. Such heterogeneity may be an important missing confounder in these studies. Finally, there is a clear need for more and larger studies.

Can we make any attempt at synthesising a unified message from these data? The simple answer is no. If pushed, one possibility is that there are 'overly sensitive amygdala fear responses (i.e. abnormal response to stimuli (even objectively neutral stimuli), possibly conditioned by previous learning experiences) that drive changes in networks mediating perceptual experiences and/or movement plans. These changes, in the presence of abnormal self-directed attention (cf. prefrontal activations in functional imaging studies), are capable of producing movements or perceptual experiences which are not associated with a normal sense of self-agency and are therefore interpreted by patients as involuntary symptoms of an underlying disease' (Carson et al. 2012).

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Neuroimaging Studies of the Dwindling Self: Neurodegenerative Dementias

13

Andrea Nani and Andrea E. Cavanna

Abstract

The term *dementia* was first introduced in the medical literature by the Roman physician Aulus Cornelius Celsus in his treatise *De Medicina* (20 AD) to indicate a generic pattern of alterations of intelligence and behavior. Until the eighteenth century, however, the term *dementia* was commonly used as a synonym of madness. In 1838 French psychiatrist Jean-Étienne Dominique Esquirol first distinguished dementia – defined as an acquired process characterized by loss of memory, ability to judge, and attention – from congenital mental deficit. At present, according to DSM-IV (American Psychiatric Association. DSM-IV-tr: diagnostic and statistical manual of mental disorders, 4th ed, text revision. American Psychiatric Association, Washington, DC, 2000), the essential characteristics of dementia include impairment in memory, plus at least in one other cognitive function (language, visuospatial skills, etc.), as well as substantial disturbance of work or social functioning resulting from cognitive deficits. These features should not occur as isolated features of delirium. Nonetheless, from a clinical point of view, the term *dementia* has to be considered a multifaceted syndrome rather than a single disease.

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A.E. Cavanna et al. (eds.), *Neuroimaging of Consciousness*,
DOI 10.1007/978-3-642-37580-4_13,

Lear: Where have I been? Where am I? Fair daylight,
I am mightily abus'd. I should e'en die with pity
To see another thus. I know not what to say.
I will not swear these are my hands. Let's see.
I feel this pin prick. Would I were assur'd
Of my condition!
Cordelia: O, look upon me, Sir.
And hold your hands in benediction o'er me.
No, sir, you must not kneel.
Lear: Pray, do not mock me.
I am a very foolish fond old man,
Fourscore and upward, not an hour more nor less;
And, to deal plainly,
I fear I am not in my perfect mind.
Methinks I should know you, and know this man;
Yet I am doubtful; for I am mainly ignorant
What place this is; and all the skill I have
Remembers not these garments; nor I know not
Where I did lodge last night. Do not laugh at me;
For (as I am a man) I think this lady
To be my child Cordelia.
W. Shakespeare, *King Lear*, Act IV, Scene VII

13.1 Introduction

The term *dementia* was first introduced in the medical literature by the Roman physician Aulus Cornelius Celsus in his treatise *De Medicina* (20 AD) to indicate a generic pattern of alterations of intelligence and behavior. Until the eighteenth century, however, the term *dementia* was commonly used as a synonym of madness. In 1838 French psychiatrist Jean-Étienne Dominique Esquirol first distinguished dementia – defined as an acquired process characterized by loss of memory, ability to judge, and attention – from congenital mental deficit. At present, according to DSM-IV (American Psychiatric Association 2000), the essential characteristics of dementia include impairment in memory, plus at least in one other cognitive function (language, visuospatial skills, etc.), as well as substantial disturbance of work or social functioning resulting from cognitive deficits. These features should not occur as isolated features of delirium. Nonetheless, from a clinical point of view, the term *dementia* has to be considered a multifaceted syndrome rather than a single disease.

The symptomatology of this syndrome includes both cognitive aspects (memory impairment, spatial and temporal disorientation, apraxia, aphasia, alexia, agraphia, abstract reasoning, acalculia, agnosia, visuospatial deficits) and behavioral aspects, such as delirium, hallucinations, affective disturbances (depression, euphoria, emotional lability), anxiety, neurovegetative symptoms (sleep, appetite, sexual behavior disorders), psychomotor activity disorders (vagabondage, afinalistic bustle, akathisia), agitation (physical and verbal aggressiveness, persistent vocalization), and personality alterations (indifference, apathy, disinhibition, irritability). The prevalence rate of dementia in the elderly (people over 65 years) is 5 %, and it nearly

doubles every subsequent 5-year period, with a peak of 40 % in subjects over 85. An almost exponential increase with age and a female predominance have been described. The incidence rate also rises with age, but epidemiological data are limited (Woods et al. 2003).

Medical literature has classically distinguished between cortical dementia (with prevalent cortical lesions and early alterations in symbolic, abstract thinking and memory) and subcortical dementia (with neuropathological damage in basal ganglia, thalamus, and rostral brainstem and involvement of frontal lobe projections, characterized by early cognitive impairment, personality alterations with depression, apathy, inertia, and motor slowdown). However, this distinction is no longer accepted because of the significant overlap of clinical manifestations and the impossibility of an accurate neuroanatomical differentiation. Moreover, it is worth noting that frequently cognitive deficits in the elderly can be related to depressive syndromes rather than neurodegenerative disorders (so-called *depressive pseudodementia*): in such cases, the differential diagnosis can be quite challenging. Clinical features like datable onset, rapid progression of cognitive symptoms, and impairment of consciousness can be useful elements for the clinician. Significantly, cognitive response to an antidepressive therapy is often indicative of pseudodementia (Lee and Lyketsos 2003).

Dementia may be caused by various diseases, each characterized by a particular constellation of symptoms in combination with a specific neuropathological substrate. Among the neurodegenerative disorders, Alzheimer's disease (AD) is the most frequent cause of dementia. Other common neuropathological causes include frontotemporal lobe degeneration and Lewy body disease. However, it is not always easy to differentiate between these subtypes of dementia. The next section provides an overview on the most common neurodegenerative forms of dementia (Table 13.1).

13.2 Degenerative Dementias

13.2.1 Alzheimer's Disease

Alzheimer's disease (or Alzheimer-Perusini's disease) is a primary dementia first described by the German psychiatrist Alois Alzheimer in a 1907 paper and in 1910 by the Italian neurologist Gaetano Perusini (Jarvik and Greenson 1987; Lucci 1998). Augusta D. was the first patient with this syndrome described by Alzheimer (Fig. 13.1). She was 51 when she developed a jealousy delusion coupled with progressive memory deficit. After her death at 55 years of age, Alzheimer demonstrated the presence of neurofibrillary tangles and neuritic plaques in the patient's brain tissue.

AD approximately accounts for 50–60 % of all cases of dementia (Yaari and Corey-Bloom 2007). It is a degenerative disease with an insidious onset and a fatal progression in about 10 years. AD exhibits a relatively predictable clinical pattern, characterized by three stages. In the early phases, the patient preserves consciousness of the progressive cognitive impairment. In the middle phases, it is common to observe spatial and

Table 13.1 Diagnostic criteria and clinical features of the main forms of neurodegenerative dementia

Alzheimer's disease (AD)	Frontotemporal dementia (FTD)	Dementia with Lewy bodies (DLB)
Core diagnostic criteria		
1. Presence of an early and significant episodic memory impairment that includes the following features:	1. Insidious onset and gradual progression	1. Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and frontal-subcortical skills and visuospatial ability may be especially prominent
Gradual and progressive change in memory reported by patients or informants over more than 6 months	2. Early decline in social interpersonal conduct	2. Two of the following are required for a diagnosis of probable dementia with Lewy bodies:
Objective evidence of significantly impaired episodic memory on testing: this commonly consists of recall deficit that does not improve or does not normalize with cueing or recognition testing and after effective encoding of information has been previously controlled	3. Early impairment in regulation of personal conduct	Fluctuating cognition with pronounced variations in attention and alertness
The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances	4. Early emotional blunting	Recurrent visual hallucinations which are typically well formed and detailed
	5. Early loss of insight	Spontaneous motor features of parkinsonism
Supportive features		
2. Presence of medial temporal lobe atrophy	(a) Behavioral disorder	(a) Repeated falls
Volume loss of hippocampi, entorhinal cortex, and amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well-characterized population with age norms) or quantitative volumetry or regions of interest (referenced to well-characterized population with age norms)	Decline in personal hygiene and grooming	(b) Syncope or transient loss of consciousness
3. Abnormal cerebrospinal fluid biomarker	Mental rigidity and inflexibility	(c) Neuroleptic sensitivity

Low amyloid β_{1-42} concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three	Distractibility and impersistence	(d) Systematized delusions
Other well-validated markers to be discovered in the future	Hyperorality and dietary change	(e) Hallucinations in other modalities
4. Specific pattern on functional neuroimaging with PET	Utilization behavior	
Reduced glucose metabolism in bilateral temporal parietal regions	(b) Speech and language	
Other well-validated ligands, including those that foreseeably will emerge such as Pittsburgh compound B of FDDNP	Altered speech output (aspontaneity and economy of speech, press of speech)	
5. Proven AD autosomal dominant mutation within the immediate family	Stereotypy of speech	
	Echolalia	
	Perseveration	
	Mutism	
	(c) Physical signs	
	Primitive reflexes	
	Incontinence	
	Akinesia	
	Rigidity	
	Tremor	
	Low/labile blood pressure	
	(d) Investigations	
	Neuropsychology: impaired frontal lobe test; no amnesia or perceptual deficits	
	EEG: normal on conventional EEG despite clinically evident dementia	
	Brain imaging: predominant frontal and/or anterior temporal abnormality	

(continued)

Table 13.1 (continued)

Alzheimer's disease (AD)	Frontotemporal dementia (FTD)	Dementia with Lewy bodies (DLB)
Criteria for definite AD		
AD is considered definite if the following are present:		
Both clinical and histopathological (brain biopsy or autopsy) evidence of the disease, as required by the NIA-Reagan criteria for the postmortem diagnosis of AD; criteria must both be present		
Both clinical and genetic evidence (mutation on chromosome 1, 14, or 21); criteria must both be present		

Fig. 13.1 Auguste D., the first patient described by Dr. Alois Alzheimer (Photo taken in 1902)

temporal disorientation and failure of anterograde episodic memory. Language skills decline as the illness progresses with paraphasias, anomy, circumlocution, and comprehension deficits. Ideomotor apraxia, insomnia, lack of appetite, bradykinesia, and extrapyramidal signs are other typical manifestations of this stage. The late phases of AD are characterized by complete impairment of cognitive activities with remote memory loss for familiar faces and places. Language is critically impaired up to mutism. Rigidity, myoclonus, and seizures commonly occur. The patient can also be aggressive, often becomes incontinent, and in the terminal stage is confined to bed and needs artificial feeding, being no longer able to communicate.

13.2.1.1 Etiopathology

Amyloid senile plaques are a characteristic finding in AD; however, it is unclear if these plaques are the cause rather than an epiphenomenon of the neurodegenerative process. Neurotoxic plaque deposits are widely distributed throughout the cerebral cortex (Hardy and Selkoe 2002). A linkage to chromosome 21, which hosts the APP gene (amyloid protein precursor), was discovered in some early-onset families with AD (Richards and Hendrie 1999). The presenilin 1 gene (on chromosome 14) is responsible

for 50 % of the early-onset forms of familiar Alzheimer's disease (Van der Flier and Scheltens 2005). From a neuroanatomical perspective, the whole cortex with the possible exception of the occipital lobe is generally affected by atrophy, while the medial part of the temporal lobe (primarily the hippocampus) is more atrophic than other cortical areas. Microscopic examination reveals extracellular deposits of a peptide known as β-amyloid and neurofibrillary tangles, skein-like aggregates of filamentous material, largely composed of hyperphosphorylated tau proteins (Braak and Braak 1996).

13.2.1.2 Diagnosis

Only a postmortem examination can confirm a definite diagnosis of AD. In vivo indicators of probable AD can be derived from clinical examination, laboratory tests, neuropsychological tests, and neuroradiology (Growdon 1999). The diagnostic evaluation for dementia includes the patient's complete history, physical and neurological examination, neuropsychological examination, selected laboratory studies, and neuroimaging investigations, the latter being particularly relevant for consciousness studies.

The main clinical application of neuroimaging is the differential diagnosis between the structural and physiological modifications of normal brain aging and the pathological patterns associated with dementia. Hypoperfusion in the temporal and parietal lobes is characteristic of AD. A single brain computed tomography (CT) scan is often sufficient to diagnose AD and exclude other neurological disorders. Magnetic resonance imaging (MRI) can also show small subcortical lacunae and mesial temporal lobe atrophy (Knopman et al. 2001), while functional MRI (fMRI) is commonly employed to evaluate the functional modifications of brain networks in AD and vascular dementia (Iacoboni et al. 1999). Single photon emission computed tomography (SPECT) can also help to correctly diagnose atypical or early cases of AD (Richards and Hendrie 1999; Talbot et al. 1998).

13.2.2 Frontotemporal Dementia

Frontotemporal dementia (FTD) is related to a focal and often asymmetric degeneration of the frontal and temporal lobes, accounting for about 10–15 % of all cases of dementia (Neary et al. 1998; Johnson et al. 2005). The initial manifestation of FTD is subtle and characterized by personality changes, emotional disturbances, and behavioral problems. The clinical evolution can show frontal signs (patients appear apathetic, socially withdrawn, disinhibited) and/or temporal lobe syndromes (e.g., Kluver-Bucy-like syndrome), plus extrapyramidal signs. In particular, the behavioral variant of FTD (bvFTD) is characterized by a disruption of complex social-emotional functions that rely on anterior peri-allocortical structures, including anterior cingulate cortex and frontoinsula, as well as amygdala and striatum (Rosen et al. 2002; Boccardi et al. 2005). The onset usually occurs among the fifth and the seventh decade of life. The neuropathological changes seen in FTD are not specific (McKhann et al. 2001). It is possible to find Pick bodies in 20 % of patients with FTD. Overall, the clinical phenotype exhibits the anatomo-pathological distribution of the neurodegeneration rather than a distinctive pathological progression.

Within FTD, primary progressive dysphasia (Amici et al. 2006) is a progressive decline in language production that occurs with a relative absence of other psychological deficits. Speech is nonfluent, difficult, and lacking in prosody. Articulation is disturbed, intermingled with word-finding pauses, and syntactic errors are frequent. Communication difficulties are evident to both the patient and the observer. Repetition and reading aloud are impaired, and anomia is pronounced. Progressively, speech becomes unintelligible. In contrast, comprehension is relatively preserved. Neuroradiological examinations show a perisylvian atrophy of the dominant hemisphere. Primary progressive dysphasia has a presenile onset, a low prevalence, and a high familiarity.

A distinctive variety of FTD is semantic dementia, in which patients display increasingly empty and circumlocutory speech, indicating profound loss of semantic knowledge (Knibb and Hodges 2005). The fluent dysphasia observed in these patients is associated with anomia and reduced vocabulary. Notably, patients tend to complain about their condition: these complaints may reflect the frustration of not remembering the names of things along with the lack of knowledge as to their cognitive decline in word comprehension.

13.2.3 Dementia with Lewy Bodies

Lewy bodies are neuronal cytoplasmic inclusions (phosphorylated neurofilament proteins aggregated with ubiquitin) accumulating in brainstem nuclei and paralimbic and neocortical areas. The clinical phenotype of dementia with Lewy body (DLB) involves visual hallucinations, parkinsonism, and fluctuating attention and alertness with intervals of lucidity (McKeith et al. 1996). Typically, visual hallucinations are well formed and detailed. The cognitive profile is affected by a combination of cortical and subcortical degeneration. Bradyphrenia occurs with impairment of frontal executive functions and attention, while degeneration in parieto-occipital areas leads to visuospatial and memory problems. DLB is also related to repeated falls and episodes of transient loss of consciousness. Cognitive impairment can develop before and/or after parkinsonian features, such as akinesia, rigidity, and tremor. DLB can present with two different pathological patterns: pure DLB and AD with cortical Lewy bodies. Notably, Lewy bodies are present in 80 % of patients with Parkinson's disease, even if in these cases dementia follows the rigid-akinetic syndrome.

13.2.4 Mild Cognitive Impairment

Mild cognitive impairment (MCI) is a clinical condition formerly defined as *benign forgetfulness senescence* (Kral 1962). It is diagnosed in patients with significant memory loss in the absence of other cognitive impairment and patients with minor impairments in various cognitive domains but no functional impairment in their working or familiar environment. MCI diagnosis is based on the following criteria

(Petersen 2004): (1) report of memory loss (by the patient or an informant), (2) abnormal memory performance compared to age and scholarity, (3) normal general cognition, (4) normal activities of daily living, and (5) criteria for dementia not met. MRI investigations have shown that hippocampal atrophy, observed in both AD and FTD, is also a typical feature of MCI patients so that it seems to be a potential predictive index of a progression to dementia (Blass et al. 2004).

13.3 The Neural Correlates of Reflective Consciousness in Patients with Dementia

The exact nature of the "self" is one of the major conundrums for thinkers of all times, as it lies at the center of any theoretical understanding of what it is like to be human. The capacity of self-reflection, in fact, allows man to ask the essential questions about life and death and thereby to give meaning to actions and events. Over the last decades, considerable progress in scientific research methodology and technology made it possible to place the concept of "self" within the scope of neuroscientific investigation (Miller et al. 2001). In fact, the clinical pictures of patients with AD or other types of dementia often raise the fundamental question of the degree of impairment in self-consciousness (Gil et al. 2001). In particular, the faculty of memory, which is intimately connected with the sense of self, is profoundly impaired in AD and other types of dementia. Memory alterations, in turn, may lead to difficulties in the awareness of body and perceptions. Specifically, patients with AD can present with an intrinsic degree of anosognosia or "loss of insight," i.e., the lack of awareness of their pathological condition (Ott et al. 1996). Intriguingly, this "loss of insight" in patients with AD may affect the ability to see themselves from a third-person perspective, i.e., to imagine themselves as other people see them.

As shown in Chap. 1, the default-mode network (DMN) appears to play a central role in promoting consciousness and especially self-reflection or self-oriented cognition. Although AD is associated with a large-scale alteration of functional brain networks (Agosta et al. 2012), neuroimaging studies of abnormalities in the DMN may offer useful insights into alterations of self-awareness in this condition. In fact, specific DMN regions have been found to be vulnerable to structural and functional change in both AD and MCI (Morris and Price 2001; Ries et al. 2008). Over the last few years, a number of neuroimaging studies have provided evidence for alterations in the resting-state functional connectivity of DMN in AD. Decreased activity has consistently been detected in the posterior cingulate cortex, medial prefrontal cortex, inferior parietal cortex, inferior temporal cortex, and hippocampus (Wu et al. 2011). The hippocampus, in particular, is characterized by marked volume loss (Bottino et al. 2002; Wolf et al. 2004), while the posterior cingulate and precuneus show a pattern of early decreased metabolic activity which has been considered a hallmark of early-stage AD (Friedland et al. 1983; Minoshima et al. 1997). These areas are also very sensitive to amyloid β-protein deposition, which correlates with neural dysfunction. In addition, high levels of amyloid deposition, similar to the

patterns reported in AD, have been associated with abnormal DMN functioning in asymptomatic and minimally impaired older individuals (Sperling et al. 2009). These findings support the hypothesis that evidence of amyloid pathology in elderly people with relatively cognitive intact abilities may be predictive of AD. Consequently, abnormal connectivity patterns and alterations of default-mode activity may be important in the clinical etiology of AD and other age-related brain diseases (Van Horn 2004). Moreover, in individuals at risk for AD, selective changes in the functional connectivity of DMN might represent the early signs of ongoing neurodegeneration (Sorg et al. 2007).

MRI studies have also suggested that DMN resting-state functional connectivity is decreased in normal aging but much more so in patients diagnosed with dementia (Lustig et al. 2003; Greicius et al. 2004). Neuroimaging techniques, therefore, provide an invaluable tool, along with clinical examination, to validate the diagnosis of AD and other forms of dementia. In particular, it has been suggested that neuroimaging investigations of DMN and another resting-state functional network called *salience network* (SN) can help differentiate AD from bvFTD. The SN is a distributed anterior network that has been associated with social-emotional and visceroautonomic processing (Seeley et al. 2007; Taylor et al. 2009). Patients with bvFTD present decreased SN connectivity in the right frontoinsula, left dorsal anterior insula, right superior temporal pole, and bilateral mid-cingulate cortices. Moreover, these patients can show disrupted SN connectivity patterns in subcortical, limbic, and brainstem structures, along with increased connectivity in posterior DMN regions, which has been related to episodic memory and visuospatial imagery (Buckner et al. 2005; Cavanna and Trimble 2006). Patients with AD, in contrast, seem to have a divergent pattern: reduced DMN connectivity in posterior hippocampus, medial cingulo-parieto-occipital regions, and dorsal raphe nucleus, coupled with increased SN connectivity (Fig. 13.2). Intriguingly, increased SN functional connectivity may account for the shift from sensitive to oversensitive emotional responses, resulting in states of overflowing anxiety and agitation, often seen in patients with advanced AD. On the other hand, in bvFTD complex social-emotional functions, including self-conscious emotion (Sturm et al. 2008), theory of mind (Lough et al. 2006), empathy (Rankin et al. 2005), and morality (Mendez and Shapira 2009), seem to be disrupted in parallel with consistent and progressive atrophy of SN areas (Brambati et al. 2007; Schroeter et al. 2008).

Overall, FTD has long been known to selectively affect anterior frontal and temporal regions, particularly in the right hemisphere (Miller et al. 2001), suggesting that asymmetry itself could play an important role in the progressive loss of the self. In other words, it seems that a normal activity in the nondominant frontal lobe – connecting the *ego* to emotionally relevant past experiences and memories underlying self-agency – may be crucial for maintaining a coherent sense of self.

Our understanding of the neural correlates of the progressive deterioration of self-awareness and higher-order self-reflection is far from being complete. It is plausible, however, that the combined use of more refined clinical assessment measures and sophisticated brain imaging techniques will shed further light on the various and complex neural mechanisms that lie at the root of our human nature.

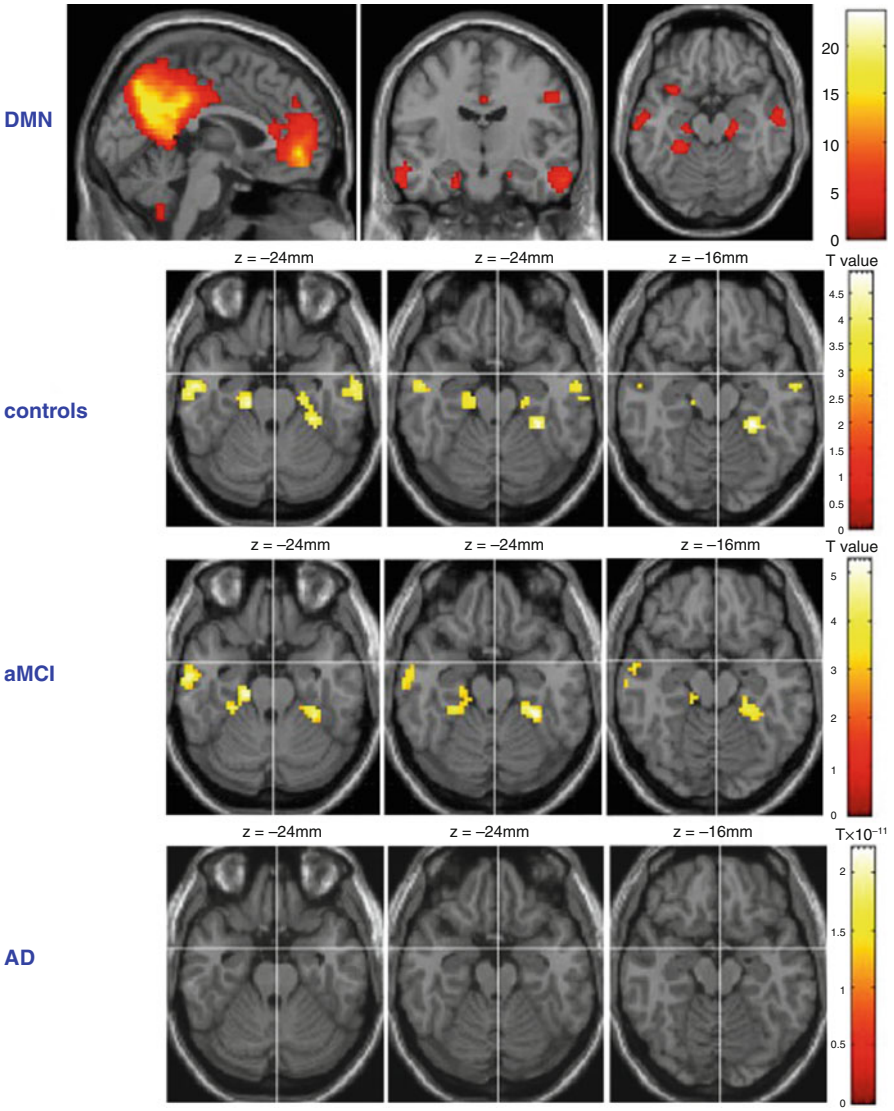

Fig. 13.2 Differences in default-mode network (*DMN*) spatial map obtained from the 1-sample *t*-test across the entire group from the study by Agosta et al. (2012). *Rows 2–4*: axial slices showing the behavior of the DMN in the temporal regions in the three groups of subjects. The medial and lateral temporal lobe resting-state fMRI signal was found in healthy controls and patients with amnestic mild cognitive impairment (*aMCI*), but not in those with Alzheimer's disease (*AD*)

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