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A default mode of brain function in altered states of consciousness

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ABSTRACT

Using modern brain imaging techniques, new discoveries are being made concerning the spontaneous activity of the brain when it is devoid of attention-demanding tasks. Spatially separated patches of neuronal assemblies have been found to show synchronized oscillatory activity behavior and are said to be functionally connected. One of the most robust of these is the default mode network, which is associated with intrinsic processes like mind wandering and self-projection. Furthermore, activity in this network is anticorrelated with activity in a network that is linked to attention to external stimuli. The integrity of both networks is disturbed in altered states of consciousness, like sleep, general anesthesia and hypnosis. In coma and related disorders of consciousness, encompassing the vegetative state (unresponsive wakefulness syndrome) and minimally conscious state, default mode network integrity correlates with the level of remaining consciousness, offering the possibility of using this information for diagnostic and prognostic purposes. Functional brain imaging is currently being validated as a valuable addition to the standardized behavioral assessments that are already in use.

Key words
Coma • Default mode network • Disorders of consciousness • Sleep • Anesthesia • Hypnosis • fMRI

Introduction

Consciousness is often regarded as an epiphenomenon that arises from the way in which information is processed in the brain. Although the aspect of subjective experience still evades detailed explanation, a glimpse of the neural substrate of consciousness can be obtained by using modern brain imaging technology. The concept of integration of information is incorporated in many theories that were developed to explain the observable characteristics that accompany consciousness. One of these theories, developed by Tononi et al. (2010), claims that the brain's capacity to integrate information is of crucial importance for the maintenance of consciousness. Baars et al. (1993; 2003) formulated the Global Workspace theory, in which the results of unconscious processing in different specialized areas of the brain compete with each other for conscious awareness. Both theories predict patterns of strong functional and anatomical connections between brain areas to make highly efficient integration of information possible.

Modern brain imaging techniques can indirectly examine the functional organization of the brain and can compare the brains of healthy subjects and coma patients to pinpoint the mechanisms that are likely to be important for the maintenance of consciousness. On the path to recovery, partial consciousness might be present, but the patient may not have the cognitive or motor skills to respond to questions or stimuli used in the traditional bedside behavioral tests used for

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diagnosis. Brain imaging techniques might be able to increase the sensitivity to detect residual consciousness by examining patterns in the patient's brain activity that could reflect information integration effectiveness. The discovery of robust brain activity organization in the absence of significant external stimuli presented a promising candidate in this context (Raichle et al., 2001; Damoiseaux et al., 2006).

This review will discuss the possibility of using the assessment of spontaneous brain activity for the detection of remainders of consciousness in patients with coma and related disorders of consciousness (DOC). For this purpose, patterns of spontaneous brain activity in other conditions that are associated with an altered state of consciousness, namely sleep, general anesthesia and hypnosis, will also be discussed. We will begin, however, with a description of spontaneous neuronal activity in the healthy brain as it can be measured with functional magnetic resonance imaging (fMRI).

Activity in a "resting" brain

When not involved in an attention-demanding task, the human brain switches to a 'resting mode' of activity that is thought to predominantly support a state of inner awareness (Vanhaudenhuyse et al., 2011). In the experimental setup, the resting condition is considered to be the state of lying still with closed eyes while being relaxed for some time, but not asleep, and not performing any particular task. The upcome of positron emission tomography (PET) scanning meant that scientists now had an unprecedented view of the dynamics of glucose and oxygen consumption, as well as indirect measures of regional cerebral blood flow (rCBF). Accompanying the new PET technique, which had a higher resolution and sensitivity than earlier methods (enabling examination of deep-brain structures), was a flood of paradigms that compared rCBF in task conditions to conditions in which the brain rested. The subtraction of non-task from task condition yielded areas in which rCBF, and thus likely brain activity, was higher during the task condition. However, certain areas showed a decrease in rCBF when subjects were engaged in attention-demanding tasks, and were referred to as deactivations. The fact that there are regions in the brain showing higher activity during rest than during attention-demanding tasks, combined with the finding that the attention-demanding tasks only increased global brain metabolism by no more than 10% (Raichle and Mintun, 2006), suggested that the resting brain was actually surprisingly active. An idea that was already pointed out by the alpha waves observed in electroencephalography (EEG) recordings of the resting brain by Hans Berger in the late 1920s (Chancellor, 2009), which suggested a synchronized oscillatory neuronal activity at rest.

As the resting state does not permit classical subtraction paradigms, studying the dynamics of spontaneous brain activity with fMRI has long remained challenging. Using a new approach, called resting state functional connectivity magnetic resonance imaging (resting state fMRI), it is now possible to examine these oscillating patterns reflected in the blood oxygenation level dependent (BOLD) fMRI signal. The same areas that showed a higher activity during rest in PET experiments were appearing as resting state neuronal networks in resting state fMRI.

Resting state fMRI uses temporal dynamics to group spatially separated patches of synchronously firing neuronal assemblies, thereby assuming a functional connection between them. Two main analysis methods exist within resting state fMRI: seed based and independent component analysis (for a review on advantages and pitfalls of these approaches, see Cole et al., 2010, and for their application in DOC, see Soddu et al., 2011). The seed based analysis technique uses BOLD data from a selected region of interest as the reference to search for all other regions that show similar temporal activity behavior. The more recently developed spatial independent component analysis technique (McKeown et al., 1998; Kiviniemi et al., 2003) is a completely data driven method that groups different synchronously firing patches of neurons, in a way that spontaneous activity behavior between groups is statistically independent. The advantage of this technique compared to seed based methods is that it does not require *a priori* knowledge of brain activity patterns, and BOLD activity that is not likely to represent neuronal activity is separated from neuronal activity patterns (Perlbarg and Marrelec, 2008).

Among these patterns of spontaneous activity, named resting state networks (RSNs), that can be found with resting state fMRI, are waves of spontaneous activity in the auditory, visual and sensorimotor cortices, as well as a network that displays strong activity along the frontoparietal midline of the brain; regions that showed significant task induced deactivations in initial PET scans (Shulman et al., 1997). This network has been named the default mode network (DMN), as its presence is thought to reflect a default state of brain activity vital for brain functioning and, possibly, consciousness. If the normal functioning of this network does indeed correspond to the maintenance of a normal level of consciousness, then DMN integrity could possibly act as a biomarker for the "level of consciousness" in patients with DOC. We will first discuss the evidence that links the DMN to consciousness.

The default mode network

The DMN is among the most robust networks found with resting state fMRI and encompasses the posterior cingulate cortex (PCC)/precuneus, mesiofrontal/anterior cingulate cortex, and temporoparietal cortex (Mason et al., 2007), with an oscillating frequency that lies between 0.01 and 0.1 Hz (Damoiseaux et al., 2006). Simultaneous fMRI/EEG recordings have made it possible to examine the EEG correlates of the DMN BOLD signal. Both alpha EEG rhythms, which are associated with the awake resting state when the eyes are closed, and beta EEG rhythms are strongly associated with BOLD correlates of the DMN (Jann et al., 2010). Infraslow (< 0.1 Hz) EEG oscillations have also been linked to DMN activity (Picchioni et al., 2011).

Activity in the DMN diminishes when the brain is involved in attention-demanding cognitive tasks (Raichle et al., 2001), and returns to its prominent presence when no such task is being performed. However, a subset of tasks has been shown to increase activity in parts of the DMN. These tasks include elements of introspection, theory of mind construction, and memory activation, like episodic memory retrieval (Spreng and Grady, 2010).

During certain tasks, functional connectivity is observed between DMN regions and regions that are not considered to belong to the 'core' DMN. Andrews-Hanna et al. (2010) have shown that the DMN core structures, namely the PCC/precuneus and a part of the medial prefrontal cortex, can functionally connect to two subsystems. One of these subsystems is associated with mental scene reconstruction, drawing upon memory, while the other is synchronized to DMN core behavior during the making of self-relevant decisions. These reports emphasize the possibility that the DMN consists of a mostly temporoparietal part, implicated with memory, and a frontally concentrated part, associated with self-reflection and theory of mind formation, with primary connections between them running through the PCC/precuneus hub (Ciaramelli et al., 2008; Fransson and Marrelec, 2008; van Kesteren et al., 2010). The precuneal area has a large connective repertoire that involves connections to both cortical and subcortical regions (Cavanna et al., 2007).

Interestingly, activity in the DMN is anticorrelated with activity in another resting state network, the external control network (ECN, also known as the executive control network), which is primarily located in lateral and dorsal frontoparietal brain areas and is thought to be implicated with awareness of the external environment (Boly et al., 2007; Uddin et al., 2009). Indeed, Vanhaudenhuyse, Demertzi, et al. (2010) showed that subjectively reported episodes of externally directed mental activity were strongly associated with increased ECN and decreased DMN activity. Mason et al. (2007) used a mind wandering encouraging task while measuring activity in PCC/precuneus and found that subjects who are more prone to daydreaming episodes show higher activation in the PCC/precuneus during task periods of low attentional demand then those who report a lower number of daydreaming episodes.

Network development and disturbance

The majority of DMN research has been conducted with healthy adults. However, DMN functional architecture has been shown to change during a lifetime. If DMN connectivity is necessary for the intrinsic tasks it is associated with, the network should be present at an age when these abilities develop. Some of these functions, like the ability to mentalize, form episodic memory and a theory of mind, are present in children before the age of 6 and these introspective capabilities continue to develop with age (Flavell et al., 1999). Studies have shown that a possible proto-DMN can be found in infants (Doria et al., 2010) and is likely to develop in toddlers. Their DMN functional architecture discriminates from the adult DMN in overall connective strength, especially in intrahemispheric connectivity patterns, while interhemispheric functional connections between homotopic regions are already relatively advanced (Fransson et al., 2011). DMN connectivity increases until far into adulthood and is correlated with intrinsic cognitive maturing and an increase in coherence between EEG alpha rhythms in posterior and anterior electrodes (Srinivasan, 1999). As myelination continues until early adulthood, this process is thought to be partly responsible for the establishment of stronger connectivity between distant brain regions and may reflect a summary over many years of regional simultaneous activation, resulting in Hebbian strengthening (Fair et al., 2010). In healthy elderly people, a relatively strong DMN connectivity is observed (Andrews-Hanna et al., 2007), although connectivity between anterior and posterior regions does decrease eventually (Damoiseaux et al., 2008), which has been associated with advanced age-related working memory deficiencies (Sambataro et al., 2010). Significant DMN disturbances have been found in subjects with Alzheimer's disease (Wu et al., 2011), schizophrenia (Ongur et al., 2010), epilepsy (Liao et al., 2011), attention deficit hyperactivity disorder (Uddin et al., 2008b), bipolar disorder (Ongur et al., 2010), and autism (Assaf et al., 2010), reflecting DMN's possible role in memory, integration of information, attention, and theory of mind construction. However, these disturbances, especially alterations in working task dependent PCC/precuneal deactivation, have also been linked to increased creativity (Takeuchi et al., 2011).

Functional connectivity in the DMN has been shown to greatly reflect strong, anatomical connections between the regions of the DMN (Greicius et al., 2009). The coordination of DMN activity between both brain hemispheres has long been thought to be controlled by interhemispheric commissures like the corpus collosum and the anterior and posterior commissures. Uddin et al. (2008a) examined bilateral DMN activity in a patient that did not have any intact commissures left. Applying both seed based and independent component analysis methods, they showed that bilateral DMN connectivity was relatively spared in this patient, suggesting that subcortical regions must be responsible for the residual interhemispheric coordination of DMN activity (Uddin et al., 2008a). However, the degradation of the corpus callosum and other direct interhemispheric connections does result in cognitive deficits, as interhemispheric brain regions that work together in healthy subjects become isolated. This situation leads some scientists to suspect that each hemisphere in a split brain patient possesses an independently working consciousness (Bruno et al., 2011).

As DMN activity is likely to reflect processes important for conscious awareness of the self, we expect DMN integrity to go down significantly in altered states of consciousness, like sleep and anesthesia, and possibly change during hypnosis.

Sleep, anesthesia, hypnosis, and the default mode network

EEG recordings have shown the existence of 5 sleep stages, including rapid eye movement (REM) sleep. During REM sleep, a relatively high level of consciousness is thought to exist, as it is also the period of sleep in which most dreaming occurs. During deep non-REM sleep, the lowest level of consciousness is observed. If DMN connectivity reflects the level of consciousness, lower DMN activity would be expected during episodes of deep non-REM sleep compared to REM sleep. Furthermore, early sleep stages might also show higher DMN integrity than deep non-REM sleep. PET studies have shown a sleep induced rCBF drop in the inferior and middle frontal cortex and the inferior parietal lobule, with activity in the PCC/precuneus differing clearly between sleep stages (Vogt and Laureys, 2005; Maquet et al., 2005). Two resting state fMRI studies (Horovitz et al., 2008; Larson-Prior et al., 2009) examined DMN activity in light sleep and found an intact DMN and ECN. Interestingly, Picchioni et al. (2008) actually found a transient increase in activity within DMN regions during early stage 1 sleep. In deep non-REM sleep, the PCC/precuneus and medial prefrontal cortex disconnect from the DMN (Horovitz et al., 2009; Sämann et al., 2011), while DMN connectivity with DMN subsystems in the temporal cortex also diminishes (Koike et al., 2011). During REM sleep, where high levels of consciousness are suspected, no DMN changes have been observed compared to the awake state (Koike et al., 2011).

In anesthesia studies, it is of importance to distinguish between sedation, in which consciousness still persists, and loss of consciousness. The PCC/precuneus has been found to be one of the brain areas most sensitive to anesthetics, with rCBF dropping quickly in this region in response to propofol and halothane (Vogt and Laureys, 2005). Using resting state fMRI, sedation with midazolam has been shown to reduce DMN connectivity with the PCC/precuneus (Greicius et al., 2008), while propofol sedation induced a change in the connective repertoire of the PCC/precuneus to include functional connections to motor/somatosensory cortices, the reticular activating system, and the anterior thalamic nuclei (Stamatakis et al., 2010). Martuzzi et al. (2010) found a reduction in connectivity between the PCC/precuneus and the thalamus during sevoflurane sedation, with preserved connectivity in sensory RSNs. When consciousness is lost due to anesthesia, a greater part of the DMN shows decreases in connectivity. In a study by Boveroux et al. (2010), the medial prefrontal cortex and PCC/precuneal areas were most affected during propofol induced loss of consciousness, as well as the ECN, while connectivity in visual and auditory RSNs did not alter significantly.

Hypnosis is a method that aims to deliberately lower intrusion of external stimuli, like pain, into conscious awareness. It has been described as "a procedure during which a health care professional or researcher suggests that a patient or subject experiences changes in sensations, perceptions, thoughts, or behavior" (The Executive Committee of the American Psychological Association, 1994). In most cases, the induction of hypnosis is established by using suggestions for relaxation (Faymonville et al., 2003). A combination of local anesthesia, minimal conscious sedation and hypnosis, named hypnosedation, has been used in over 6500 patients at the University Hospital of Liège since 1992 (Vanhaudenhuyse et al., 2008), as it is seen as an efficient alternative to general anesthesia during certain operations, and as a treatment for chronic pain syndrome patients (Jensen et al., 2008). Attenuation of transmission of external stimuli could in theory implicate a role for the DMN, as overall DMN activity is at its highest during internal mental processing. Although little research has been done to elucidate the neural mechanisms underlying decreased pain perception, which can be up to 50% (Faymonville et al., 2003), Maquet et al. (1999) found that hypnosis can decrease cerebral blood flow in DMN regions, especially the PCC/precuneus. Moreover, McGeown et al. (2009) found that subjects susceptible to hypnosis showed a reduction in activity in anterior regions of the DMN after induction of hypnosis, and Demertzi et al. (2011) observed a significant drop in both DMN and ECN connectivity during hypnosis. These findings suggest that hypnosis can, at least in some people, cause changes in DMN activity, which could be an explanation for decreased pain perception during hypnosis.

The observed changes in DMN connectivity during loss of consciousness and alteration of external awareness mean that DMN integrity may represent the level of consciousness. If so, this knowledge could be used for patients with coma type DOC to discriminate between different DOC states.

Default mode network activity in disorders of consciousness

Coma is defined as a condition of unarousable unresponsiveness, reflecting differences between coma and sleep, as a subject in the latter condition can be awoken, while patients in a deep coma do not respond even to noxious stimuli. On this aspect, similarities exist between pathological coma and pharmacological coma, i.e. general anesthesia. The number of coma patients is increasing every year, as medical lifesaving technologies are improving and are becoming more widely available (Laureys and Boly, 2008). The condition of coma usually does not last longer than 4 weeks, after which patients may recover or evolve to a vegetative state (VS), recently coined "unresponsive wakefulness syndrome" (UWS; Laureys et al., 2010). Some patients, classically after a focal brainstem lesion (most often caused by a stroke in the ventral pons), may evolve from a coma to a locked-in syndrome (LIS, i.e., pseudocoma). In classical LIS, patients have a fully recovered consciousness but have lost all motor control except for small eye movements, making it possible for them to answer to yes-no questions

(American Congress of Rehabilitation Medicine, 1995; Laureys et al., 2005a). Novel brain computer interfaces now enable better communication and quality of life. VS/UWS patients are not showing any behavioral sign of consciousness or response to command, but classically show sustained periods of spontaneous or stimulus induced eye opening. These patients exhibit only reflexive, "automatic" or unpurposeful motor behaviors (Laureys and Boly, 2007). VS/UWS is hence a condition in which arousal (wakefulness) exists in the absence of awareness of self and environment. VS/UWS can be a chronic condition without any behavioral signs of recovery of consciousness or patients can evolve to what is called a minimally conscious state (MCS; Giacino et al., 2002). MCS patients show signs of non-reflex behavior (such as eye tracking or oriented response to pain stimulation) or reproducible albeit inconsistent responses to command and have a better chance of recovery as compared to VS/UWS (Laureys and Boly, 2008).

The difficulty of identifying signs of consciousness with traditional, unstandardized bedside evaluation in patients that are thought to be in a VS/UWS is reflected in the high misdiagnosis rate of 40% (Schnakers et al., 2009). This number has decreased with the help of standardized behavioral scales, such as the coma recovery scale revised (Giacino et al., 2004). From both an ethical and a clinical point of view, making a correct diagnosis to discriminate between unconscious VS/UWS and partly conscious MCS has a high priority. Modern brain imaging techniques, for example, have shown relatively comparable patterns of neural activation in response to noxious stimuli in MCS brains and the brains of healthy subjects (Boly et al., 2005). This might reflect an ability to perceive pain in MCS, contrary to VS/UWS patients who do not show these patterns of activation (Laureys et al., 2002; Boly et al., 2005; 2008). Near normal brain activation patterns have also been observed in MCS brains in response to auditory stimuli with an emotional content, contrary to VS/UWS (Schiff et al., 2002; Laureys et al., 2004; Boly et al., 2005). Thus, functional brain imaging, combined with detailed standardized behavioral tests, like the coma recovery scale revised, could help decrease the rate of misdiagnosis between DOC states.

fMRI "active" paradigms (i.e., looking for command-following) have been shown to be effective for some exceptional DOC patients with enough cognitive brain capacity to demonstrate motor-independent signs of consciousness and in one unique case even enabling communication via willful modulation of brain activity (Monti et al., 2010). However, a task-free evaluation of spontaneous brain function could potentially have greater clinical usefulness given its practicability in real life clinical settings.

Historically, resting state neuroimaging has used fluorodeoxyglucose PET scanning showing 40-50% reductions in global cerebral metabolism in VS/UWS patients compared to fully conscious subjects (Laureys et al., 2005b). Possibly, recovery of consciousness could be reflected by the re-establishment of functional connections between specific brain areas (Laureys et al., 2005b), which can be examined with resting state fMRI. In this context, the DMN seems to be of particular interest, as its connectivity has been shown to decrease during loss of consciousness, and PET studies have shown an increase in neuronal activity in DMN regions (especially in the PCC/precuneus) upon recovery from VS (Laureys et al., 2006). Indeed, Vanhaudenhuyse, Noirhomme, et al. (2010) observed a correlation between the DMN integrity and the level of consciousness in non-communicative, brain damaged patients (Fig. 1). They describe a decrease in DMN integrity when descending from normal consciousness in healthy subjects and LIS patients to MCS, VS/UWS and coma. Furthermore, their results suggest that PCC/precuneus' connective strength within the DMN can be used to distinguish between VS/UWS and MCS patients. Fernández-Espejo et al. (2010) showed that restoration of DMN functioning is associated with recovery from VS/UWS. Residual DMN activity observed in some VS/UWS patients suggests that DMN connectivity may need to cross a certain threshold value to support consciousness (Boly et al., 2009b). Unsurprisingly, EEG signatures of resting state functioning are also disturbed in DOC and Babiloni et al. (2010) have shown that characteristics of resting state alpha rhythms might predict recovery in VS/UWS patients.

As the DMN consists of connections between distant brain regions, its functional integrity could be a measure of the integrity of the anatomical architecture of the brain, which in turn could be correlated to the chance of recovery. Diffusion tensor imaging is a technique that can non-invasively look at white

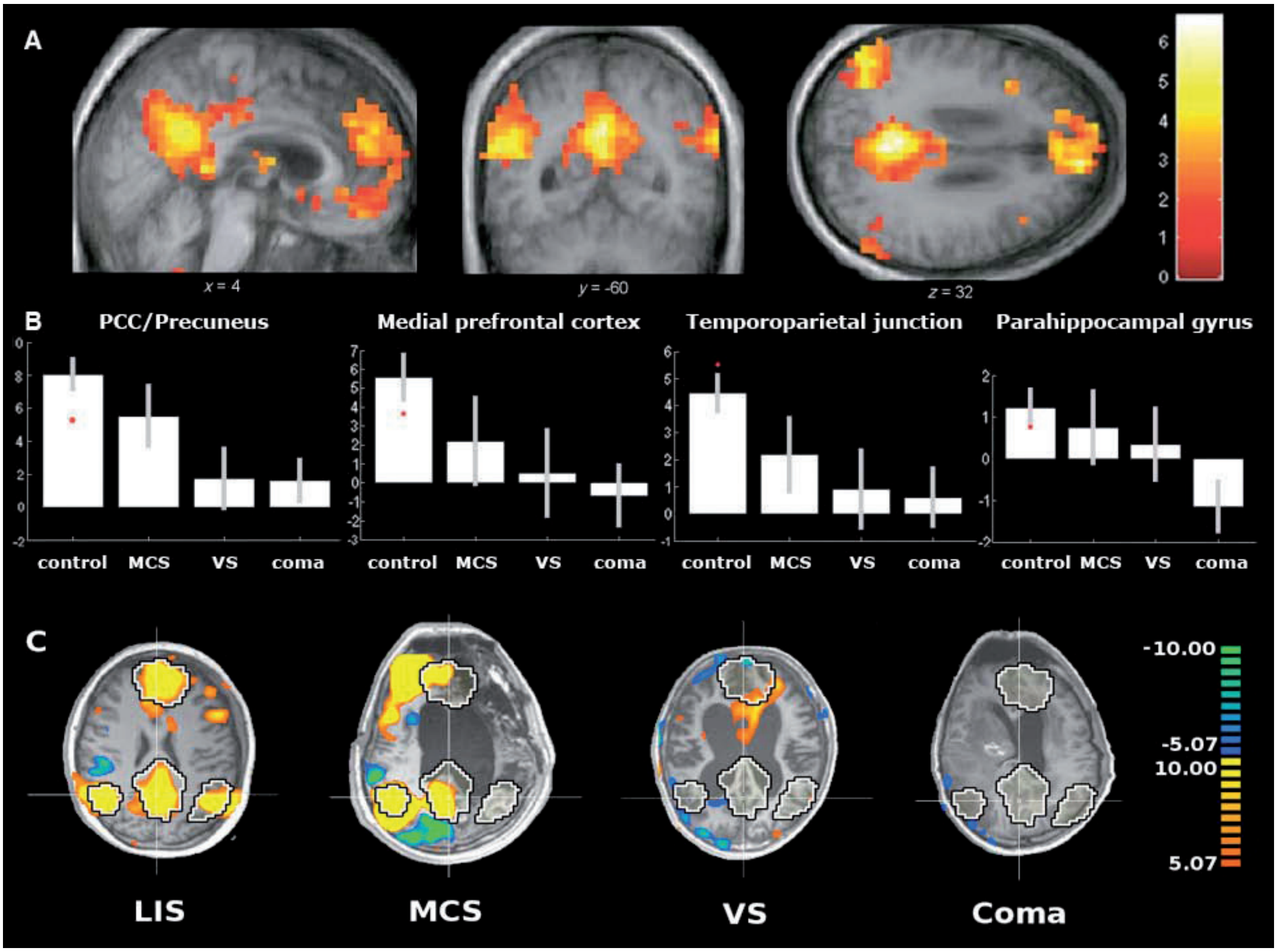

Fig. 1. - Default mode network connectivity in patients with disorders of consciousness. (A) BOLD signal of DMN regions that are correlated with the level of consciousness. (B) DMN connectivity in the PCC/precuneus, medial prefrontal cortex, temporoparietal junction, and parahippocampal gyrus in healthy controls, minimally conscious state (MCS), vegetative state (VS) and coma. (mean Z-scores and 90% confidence intervals, Z-scores from locked-in syndrome (LIS) patients are overlaid in red circles on the healthy controls) (adapted from Vanhaudenhuyse, Noirhomme et al., 2010). (C) Default mode network activity in LIS, MCS, VS and coma patients. The black and white contour was constructed from a dataset of 11 awake healthy subjects (adapted from Noirhomme et al., 2010; Vanhaudenhuyse et al., 2010; Boly et al., 2009a).

matter integrity. While no clear anatomical differences exist between the brain damage in VS/UWS and MCS patients, based on post-mortem anatomopathology (Jennett et al., 2001), a discrimination seems possible based upon mean fiber integrity in subcortical and thalamic areas as measured with diffusion tensor imaging techniques (Fernández-Espejo et al., 2011). In a case study of a 39-year-old patient who recovered from the MCS 19 years after traumatic brain injury, Voss et al. (2006) found that emergence from the MCS was associated with restoration of fiber tracts in the cuneus and precuneus; possibly reflecting axonal regrowth. The factors that contribute to this kind of neuronal regeneration remain largely unknown.

As mentioned before, the acquisition of resting state fMRI is a straightforward procedure (albeit complicated by patients' involuntary movements), but the analysis of these data, especially in DOC patients, remains challenging. Indeed the user-dependent selection of the presumed DMN component in severely brain-damaged patients introduces a potential bias. Automated software programs are being developed to choose the DMN component and calculate the strength of functional connectivity between DMN nodes (Soddu et al., 2012).

Many of these automated selection procedures only use spatial (and not temporal) characteristics. This might work with near-normal functioning brains, but problems arise when there is only degraded DMN connectivity present, as is the case in many DOC patients. Furthermore, DOC associated brain atrophy and hydrocephalus drastically reshape brain morphology, posing problems for spatial selection methods. Special spatial normalization procedures (e.g., DARTEL; Ashburner et al., 2007) could tackle this problem. The incorporation of temporal characteristics of the independent components in the selection process, as is done in 'fingerprint'-based analyses (De Martino et al., 2007), as well as information regarding DMN anticorrelated networks (i.e., ECN) or dynamic masking, could further decrease DMN selection bias (Soddu et al., 2012).

Conclusion and future directions

Interpretation of resting state fMRI data, as well as fMRI data, is complexified by the many factors that contribute to the generation of the BOLD signal. The fMRI signal is produced by oxygenated hemoglobine and is used as an indirect measurement of energy usage and neuronal activity in a specific brain area. However, the relation between neuronal activity and the supply of oxygenated hemoglobine via the blood, called neurovascular coupling, is a complex one, especially in the setting of severe traumatic or anoxic brain damage. Thus, much still needs to be understood about the relation between neuronal activity and BOLD signal in the study of DOC.

Resting state fMRI in DOC is often challenging because of movement artifacts. In many DOC patients, sedation or general anesthesia is needed, making the interpretation of resting state fMRI a complex endeavor. As discussed above, mild sedation does not seem to drastically change DMN connectivity in healthy subjects, but the effects of these sedatives and anesthetics need to be tested in the specific context of DOC. Moreover, scientific literature on DMN integrity during loss of consciousness remains scarce and results from different authors may not be easily comparable for methodological reasons.

Activity in the DMN and the ECN is anticorrelated and is thought to represent internal *versus* external awareness. Indeed, in healthy persons, internal and external awareness follow each other up about every 15 seconds during rest (Vanhaudenhuyse et al., 2011), roughly comparable with the DMN oscillation frequency. This could reflect a neural mechanism in which mental activity in the resting brain has a preference to induce external awareness when neuronal firing is highest in the ECN (the top of the oscillation) and internal awareness when neuronal firing is highest in the DMN. The DMN appears in many studies as a robust pattern of frontoparietal midline structures, with strong connections to the temporal lobe, but some experiments show different dynamics between these core nodes. Furthermore, depending on the task, subsystems like the hippocampal formation show functional connectivity with the DMN. All in all, the DMN is more complex than has been anticipated and further experiments need to be conducted to elucidate the responses of every one of these DMN core and subsystem nodes to different types of tasks. Although the DMN has attracted the attention of many research groups, few papers have yet been published that concern the dynamics of the anticorrelation between the DMN and ECN during conditions of altered consciousness, like anesthesia, sleep and hypnosis (Table I). As DMN and ECN activity are thought to be associated with internal and external awareness respectively, the ratio of anticorrelative activity between these networks is likely to be of importance for the assessment of subjects' mental state, in both health and disease.

In the last two decades, modeling of brain network connectivity has become a major field in neuroscience. The combined use of diffusion tensor imaging techniques and fMRI in DOC patients, which results in both structural and functional datasets of single subjects, offers the unique possibility of testing the correctness of these neural models, as it gives valuable insights into which neural tracts need to be intact for the maintenance of consciousness (Deco et al., 2011). A dysfunctional DMN is being associated with ever more pathological and non-pathological conditions in which memory, attention, and self-representation are affected. The strong functional and anatomical connections between distant brain areas, which themselves are likely to be integratory hubs (Buckner et al., 2009), as well as the strategic central positioning of the DMN nodes and the synchronization of oscillatory activity with subsystems following different task-driven demands, are only

Table I. - fMRI studies concerning DMN integrity in sleep, anesthesia, hypnosis and disorders of consciousness.

DMN studies	Method	Condition	Ethiology	Subjects	ECN	DMN integrity
SLEEP						
Horovitz et al., 2008	Seed based analysis	Light sleep	n./a.	14 healthy subjects (average age: 32 yrs old, age range: 21-56 yrs old)	n.a.	Intact
Picchioni et al., 2008	PCA	Stage 1 sleep	n./a.	4 healthy subjects (age: 23, 28, 38, 38 yrs old)	n.a.	Transient increase in activity in DMN areas during early stage 1 sleep
Horovitz et al., 2009	Seed based analysis	Deep non-REM sleep	n./a.	18 healthy subjects (average age: 25.3 yrs old, age range: 21-31 yrs old, SD: 2.8 yrs)	n.a.	Decoupling, especially reduced involvement of the frontal cortex. Connectivity between PCC/precuneus and IPC/AG increases
Larson-Prior et al., 2009	Seed based analysis	Light sleep	n./a.	6 healthy subjects (age range: 22-24 yrs old)	Intact	Intact
Koike et al., 2011	Seed based analysis (+ ICA movement removal method)	Non-REM, REM sleep	n./a.	12 healthy subjects (average age: 25 yrs old, age range: 22-31 yrs old)	n.a.	Core nodes: stable in all sleep stages. Deep non-REM: degraded DMN connectivity with non-core DMN subsystems
Sämann et al., 2011	ICA	Non-REM sleep	n./a.	25 healthy subjects (average age: 24.7 yrs old, SD: 2.9)	Decreases with increased sleep depth	PCC, MPFC and parahippocampal gyrus decrease involvement in DMN connectivity with increasing sleep depth
ANESTHESIA						
Greicius et al., 2008	ICA	Moderate Midazolam sedation	n./a.	9 healthy subjects (age range: 22-27 yrs old)	n.a.	PCC/precuneus connectivity in DMN decreases
Boveroux et al., 2010	Seed based analysis	Propofol, unconscious	n./a.	19 healthy subjects (average age: 22.4, age range: 18-31 yrs old, SD: 3.4 yrs, -1 subject)	Decreased	Decreased
Martuzzi et al., 2010	Seed based analysis	Sevoflurane, 0.5 MAC	n./a.	14 healthy subjects (mean age: 26.1, age range: 22-34 yrs old, SD: 3 yrs)	n.a.	No significant change in DMN connectivity, but reduced connectivity thalamus-PCC
Stamatakis et al., 2010	Seed based analysis	Low/ moderate Propofol sedation	n./a.	16 healthy subjects (average age: 34.6 yrs old, age range: 19-52 yrs old, SD: 9.1 yrs)	n.a.	Change in PCC/ precuneus connectivity, associates more with non-DMN systems: motor/somatosensory cortices, cuneus, anterior thalamus, pontine tegmentum

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Table I. - fMRI studies concerning DMN integrity in sleep, anesthesia, hypnosis and disorders of consciousness.

DMN studies	Method	Condition	Ethiology	Subjects	ECN	DMN integrity
HYPNOSIS						
McGeown et al., 2009	fMRI deactivation	Hypnosis, induction using Kirsch et al. (1993) method	n./a.	11 highly suggestible healthy subjects (mean suggestibility rating of 5.82 on the CURSS, SD: 0.87, range 5-7), 7 lowly suggestible subjects (mean suggestibility rating: 0.29, SD: 0.49, range: 0-1)	n.a.	Decrease in anterior DMN regions in highly suggestible participants
Demertzi et al., 2011	ICA	Hypnosis, induction as described in Faymonville et al. (2003)	n./a.	12 healthy subjects (average age: 21 yrs old, SD: 3.0 yrs)	Decreased	A decrease in DMN connectivity was observed, compared to normal wakefulness and mental imagery
DOC						
Boly et al., 2009b	Seed based analysis	VS	Non-traumatic	1 VS patient (48 yrs old), 6 healthy controls (average age: 41 yrs old, SD: 11 yrs, age range: 26–54 yrs old)	Decreased in VS	Partially preserved DMN; connectivity between DMN regions was significantly reduced
Vanhaudenhuyse, Noirhomme et al., 2010	ICA	DOC	2 traumatic, 12 non-traumatic	1 LIS patient, 4 MCS patients, 4 VS patients, 5 coma patients (age range: 25-77 yrs old), 14 healthy controls (age range: 28-57 yrs old)	n.a.	DMN degradation in DOC. Negative relation of activity in PCC/precuneus with severity of DOC, could differentiate between VS and MCS
Cauda et al., 2009	ICA	VS	2 traumatic, 1 mixed origin	3 VS patients (age: 19, 21, 78 yrs old), 6 healthy controls	Present in male patient	Dysfunctional DMN. Remains: Male (21yrs old): DLPFC, PP/TPJ. Female (19 yrs old): PPC, PP/TPJ. Female (78 yrs old): VMPFC and PCC/precuneus, temperal cortex areas. The worse the condition (DRS), the less DMN (and DMN subsystems) connectivity
Fernández-Espejo et al., 2010	fMRI deactivation, seed based analysis	VS → recovery	Traumatic	1 VS patient (age: 48 yrs old) GCS: 5, DRS: 24, LCF: level 2	n.a.	Before recovery: reduced pattern of task-induced deactivations in VS. After recovery: pattern looked more like a normal DMN. Especially PCC/precuneus indicative of consciousness

n./a.: not applicable, n.a.: information not available, sim.: simultaneous, fMRI: functional magnetic resonance imaging, DMN: default mode network, ECN: external control network, yrs: years, ICA: independent component analysis, PCA: principal component analysis, REM: rapid eye movement, MAC: minimal alveolar concentration, VS: vegetative state/unresponsive wakefulness syndrome, MCS: minimally conscious state, LIS: locked-in syndrome, DOC: disorders of consciousness, SD: standard deviation, GCS: Glascow coma scale, DRS = disability rating scale, LCF: level of cognitive functioning scale, CURSS: Carleton university responsiveness to suggestion scale., PCC: posterior cingulate cortex, IPC/AG: bilateral inferior parietal cortices/angular gyri, DLPFC: dorsal left prefrontal cortex, PP/TPJ: posterior parietal/temporoparietal junction, VMPFC: ventral medial prefrontal cortex.

strengthening the case of the DMN as a substrate of information integration, working memory, and consciousness. As such, imaging of DMN integrity can further aid in the diagnostic and prognostic workout of DOC patients.

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