

CHAPTER 18

# Reaching across the abyss: recent advances in functional magnetic resonance imaging and their potential relevance to disorders of consciousness

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**Abstract:** Disorders of consciousness (DOC) raise profound scientific, clinical, ethical, and philosophical issues. Growing knowledge on fundamental principles of brain organization in healthy individuals offers new opportunities for a better understanding of residual brain function in DOCs. We here discuss new perspectives derived from a recently proposed scheme of brain organization underlying consciousness in healthy individuals. In this scheme, thalamo-cortical networks can be divided into two, often antagonistic, global systems: (i) a system of externally oriented, sensory-motor networks (the “extrinsic” system); and (ii) a system of inward-oriented networks (the “intrinsic” or default system). According to this framework, four distinct mental states would be possible that could be relevant for understanding DOCs. In normal healthy volunteers and locked-in syndrome patients, a state of high functionality of both the extrinsic and intrinsic or default systems is expected — associated with full awareness of environment and self. In this case, mental imagery tasks combined with fMRI can be used to detect covert awareness in patients that are unable to communicate. According to the framework, two complementary states of system imbalance are also possible, in which one system is in a hyperfunctional state, while the other is hypoactive. Extrinsic system hyperfunction is expected to lead to a state of total sensory-motor “absorption” or “lost self.” In contrast, intrinsic or default system hyperfunction is expected to lead to a state of complete detachment from the external world. A state where both extrinsic and intrinsic systems are hypofunctional is predicted to lead to markedly impaired consciousness as seen in DOCs. Finally, we review the potential use of ultra-slow fluctuations in BOLD signal as a tool for assessing the functional integrity of extrinsic and intrinsic systems during “resting state” fMRI acquisitions. In particular, we

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discuss the potential provided by assessment of these slow spontaneous BOLD fluctuations as a novel tool in assessing the cognitive state and chances of recovery from brain pathologies underlying DOCs.

**Keywords:** coma; consciousness; resting state; spontaneous activity; imagery; functional magnetic resonance imaging; default network

## Introduction

Disorders of consciousness (DOC) are a devastating spectrum of clinical conditions involving profound disruption in global conscious states due to massive brain lesions (Bernat, 2006; Giacino et al., 2002; Laureys et al., 2004; Plum and Posner, 1972; Schiff, 2006b). Clinical characterization of the different DOCs is based on two main distinct components of human consciousness: arousal and awareness (Plum and Posner, 1972). If arousal refers to the behavioral alternation of sleep and wakefulness, awareness refers to the collective thoughts and feelings of an individual (Laureys, 2005). Coma is characterized by the absence of arousal and hence of awareness. Vegetative-state patients are aroused but unaware of environment and self (Jennett and Plum, 1972). Minimally conscious state patients are unable to reliably communicate but show reproducible behavioral evidence of awareness of environment or self (Giacino et al., 2002, 2004; Majerus et al., 2005). Locked-in syndrome patients (Plum and Posner, 1972) are fully conscious but have no means of producing speech, limb, or facial movements, except for small movements of the eyes or eyelids.

While progress has been made in describing DOCs from the clinical perspective (Giacino et al., 2004), we focus in the present review on examining DOCs from the point of view of recent developments and understandings derived from the healthy human brain. We argue that recent insights obtained through functional magnetic resonance imaging (fMRI) are relevant to a better understanding of DOCs and have the potential of allowing a better diagnosis and treatment (Giacino et al., 2006; Laureys et al., 2006; Schiff, 2006a, b). Specifically, we will focus on assessing brain function in a set of areas, termed the “default” network (Raichle et al., 2001; Raichle

and Snyder, 2007), characterized by higher activity at rest than during externally oriented sensory-motor or cognitive tasks. This network appears to show antagonistic behavior to sensory-motor areas, which show increased fMRI signal under such tasks. Importantly, areas belonging to the default network also show a tendency for coherent fluctuations both during rest (Greicius et al., 2003; Nir et al., 2006) and during visual activation (Hasson et al., 2004) further supporting their association within a common functional system.

Based on the functional antagonistic profile of the sensory-motor cortex on the one hand and the default system on the other, as well as their complementary neuroanatomical organization (Boly et al., 2007a; Fox et al., 2005, 2009; Golland et al., 2007, 2008; Tian et al., 2007; see Fig. 1) we have proposed (Boly et al., 2008a, b; Golland et al., 2008) a fundamental “dual” subdivision of the human cortex into two basic — “extrinsic” versus “intrinsic” — functionalities. More specifically, we hypothesize that the cerebral cortex can be subdivided according to two basic functional orientations — an “extrinsic” orientation, which engages sensory-motor cortices, and an “intrinsic” orientation, which engages the default system. Sensory-motor cortices are involved in the processing of information immediately incoming from the external world, while the complementary “intrinsic” or default system appears to be involved in self-representations, episodic memory, mind wandering, and stimulus-independent thoughts (e.g., see Goldberg et al., 2006; Mason et al., 2007; D’Argembeau et al., 2005; Laureys et al., 2007).

We here will address the study of residual brain function in DOCs from the perspective of this “extrinsic” versus “intrinsic” functional subdivision and propose a conceptual framework around which to organize our knowledge and hypotheses concerning DOCs. Specifically we will consider

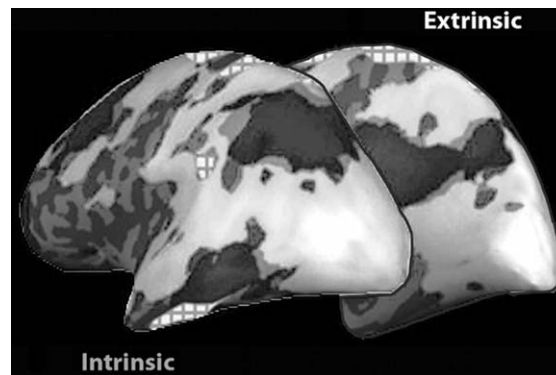


Fig. 1. An illustration of the proposed fundamental specialization of the human cortex showing the “extrinsic” sensory motor system and the “intrinsic” or default networks. It is hypothesized that the extrinsic system specializes in processing incoming information from the external environment, while the more enigmatic intrinsic or default system is specialized in internally oriented functions. Note the complementary nature of the “extrinsic” and “intrinsic” or default networks. Adapted from Golland et al. (2007).

four different mental states associated with different extrinsic–intrinsic organizations, as predicted by our framework.

### High extrinsic and intrinsic functionality: the “locked-in” syndrome

The first case to consider is the situation in which both the extrinsic and intrinsic systems are highly functional yet the patient is unable to communicate or report in an effective manner about her or his mental state. In the case of locked-in syndrome this situation of disconnection between internal states and verbal or nonverbal report is due to quadriplegia and anarthria, classically caused by a ventral pontine lesion, disrupting the corticospinal and corticobulbar pathways (Plum and Posner, 1972; Smart et al., 2008). In the case of fully conscious but completely paralyzed patients (i.e., complete locked-in syndrome; Schnakers et al., 2009), fMRI may be able to detect response to command using brain activation in the absence of any overt motor response. fMRI activation paradigms offer the opportunity to directly communicate with locked-in syndrome patients by assessing responses from their brains without dependence on motor output (Birbaumer et al., 2008, 2006; Sorger et al., 2009). A demonstration that this method could effectively

work was provided in recent years by the successful use of mental imagery tasks and fMRI imaging to uncover awareness in a patient clinically assessed as vegetative (Boly et al., 2007b; Owen et al., 2006). Two important methodological considerations have to be taken into account while developing fMRI activation paradigms. First, we need to find tasks that produce the most reliable and robust activation pattern in a single subject. Second, we need to be cautious in designing the fMRI paradigms, in order to avoid brain activations which could occur passively, in the absence of any willful mental effort. To address these two issues, we conducted two fMRI experiments in healthy individuals.

In the first experiment, six healthy subjects were scanned in a 3 T MRI scanner during: (i) passive listening to verbal commands and (ii) active mental imagery in response to the same instructions. Mental imagery tasks included: (1) imagining opening and closing the left hand, (2) mental calculation (counting down), (3) imagining preparing luggage, (4) imagining walking from home to work, (5) covertly describing a face, (6) imagining filling in a check, and (7) covertly describing ones own thoughts. An eighth condition of rest (eyes closed) was used as a baseline. In the second experiment, we compared visual mental imagery (eyes closed) with passive visual stimulation (Farah, 1989; Ganis et al., 2004). Here, eight healthy subjects were

scanned in four different conditions: (i) visual, (ii) imagery, (iii) visual and verbal description (covert), and (iv) imagery and verbal description (covert). The tasks (lasting 12s) included viewing or imaging: (a) walking from home to work, (b) filling a check, (c) observing the own face, and (d) preparing a luggage. A fifth condition of rest (blank screen for visual and keeping the eyes closed for imagery) was used as reference “base-line” activity. A common finding for all active tasks in the first experiment (Fig. 2) was a widespread activation encompassing bilateral intraparietal sulcus, primary sensory-motor areas, supplementary motor area, parahippocampal gyrus, inferior and middle temporal gyri, language-related and inferior frontal areas. Together with the activation pattern, there was also a consistent activity reduction in the intrinsic or default network during performance of the tasks. In Fig. 2, the superimposed contour map show the intrinsic or default network (identified using independent component analysis from a group of seven healthy volunteers scanned during 10 min “eyes-closed resting state”) encompassing precuneus and adjacent posterior cingulate cortex, mesiofrontal cortex and adjacent anterior cingulate

cortex, and bilateral temporoparietal junctions areas. The combined increased activation of the extrinsic network and the deactivation of the intrinsic system suggest that mental imagery tasks have a preferentially extrinsic component, likely due to a process of “replay” of extrinsic sensory-motor activations (Gelbard-Sagiv et al., 2008). These activations were consistent across individual subjects. Table 1 shows identified areas for the seven different mental imagery tasks. In line with previous studies (e.g., Boly et al., 2007b), the spatial navigation task (imagining walking from home to work) was among the tasks showing the most consistent activity across subjects (together with imagery tasks of writing a check and preparing a luggage). Figure 3 shows the activation patterns during two different sessions for the active mental imagery task (spatial navigation) compared to activation induced by passive listening to the same task instructions. While passive listening did not elicit activation, both active imagery tasks elicited activation of parahippocampal areas, well known to be involved in spatial navigation tasks (Epstein et al., 1999; Epstein and Kanwisher, 1998). This differential activation in active

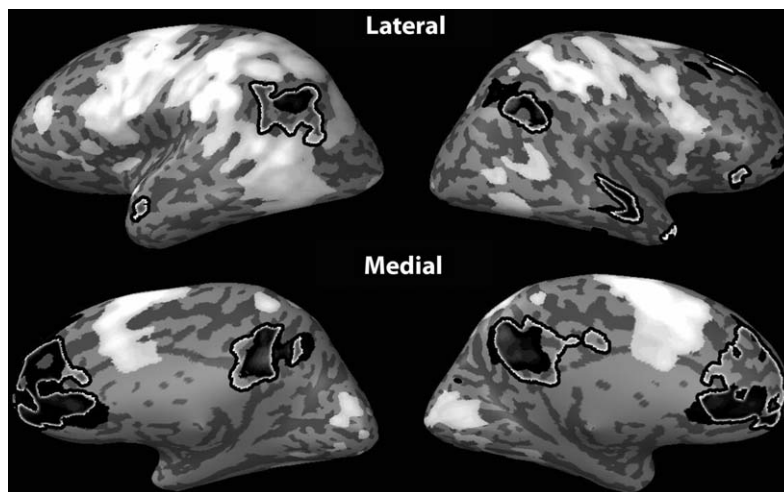


Fig. 2. Common activation and deactivation patterns (as compared to eyes-closed resting) observed during seven mental imagery tasks (i.e., imagining opening and closing the left hand; mental calculation; imaging preparing luggage; imaging walking from home to work; covertly describing ones own face; imaging filling in a check and covertly describing ones own thoughts). Fixed effects group analysis thresholded at false discovery rate corrected  $p < 0.05$ . The contours of the independently identified default mode network are contoured in black. Note the robust imagery-related activation overlapping with regions associated with the extrinsic system (see text for details).

Table 1. Random effect group analyses identifying areas activating during the seven mental imagery tasks as compared to eyes-closed resting state

Imagery task	Region	X	Y	Z	T-value	p-value
Imagining opening and closing the left hand	Superior parietal lobe	-36	-35	40	9.3	<0.001
	Supplementary motor area	2	7	50	6.5	<0.001
	Middle temporal gyrus	-50	-52	3	6.4	<0.001
Counting down	Superior parietal lobe	-42	-33	40	5.7	<0.001
	Precentral gyrus	-53	2	23	5.5	<0.001
	Supplementary motor area	-1	4	51	5.2	<0.001
Imaging preparing luggage	Superior parietal lobe	-35	-34	42	6.2	<0.001
	Parieto-occipital sulcus	-18	-59	44	5.4	<0.001
	Supplementary motor area	-5	5	48	5.3	<0.001
Imaging walking from home to work	Parahippocampal gyrus	-13	-56	10	7.1	<0.001
	Superior parietal lobe	-35	-34	38	6.6	<0.001
	Medial occipitotemporal gyrus	-24	-36	-7	5.7	<0.001
Describing a face	Superior parietal lobe	-44	-30	38	7.9	<0.001
	Supplementary motor area	-5	5	50	5.9	<0.001
	Lateral occipitotemporal gyrus	-40	-54	-14	5.3	<0.001
Imaging filling a check	Superior parietal lobe	-48	-29	42	6.7	<0.001
	Superior parietal lobe	-33	-35	40	6.4	<0.001
	Middle temporal gyrus	-44	-45	-4	6.2	<0.001
Describing own thoughts	Middle frontal gyrus	-44	-1	51	4.9	<0.001
	Superior parietal lobe	-46	-33	41	4.6	<0.001
	Superior temporal gyrus	-61	-39	10	4.3	<0.001

compared to passive conditions strengthens the hypothesis that observed brain responses are indeed associated with intentional mental effort and are not merely induced by passive listening to the task instructions. Finally, Fig. 4 illustrates brain activation patterns when one sees a video of oneself walking (visual) compared to imagining oneself walking, and when the visual imagery process is accompanied by a covert description. The activation of Broca's area both in the "imagining" and "imagining and verbal description" conditions suggests that even when subjects were asked to perform the mental imagery tasks using only visualization strategies they could not avoid adding a verbal component to the visual imagery aspect.

Overall, three conclusions can be drawn from these results. First, robust brain activations can be elicited and measured with fMRI without the subjects performing any overt responses. This brain activation seems particularly robust in tasks involving action planning, while recognition tasks such as imagining faces seemed less effective. Second, the obtained activations could be

differentiated in a reproducible manner from the passive conditions in which subjects did not engage in any active mental imagery. Finally, requiring a verbal description of the cognitive action while performing mental imaging tasks increases the neural activation intensity and extent. These results are encouraging in showing that a consistently detected increase in fMRI signal can be obtained when subjects are engaged in active mental imagery, and that this activation pattern can be reliably differentiated from the more automatic neural responses to presentation of the task instructions. On the other hand, for communication purposes, it appears that relying only on the patterns of activations associated with different mental imagery tasks may not be an effective solution as in the above-reported study many patterns of activations were rather similar between tasks. In this context, it is useful to also collect information on the timing of the fMRI response to a given task (i.e., starting time and latency of the subject's BOLD response) in order to better segregate the activation patterns elicited by different mental imagery tasks (see Sorger et al., 2009).



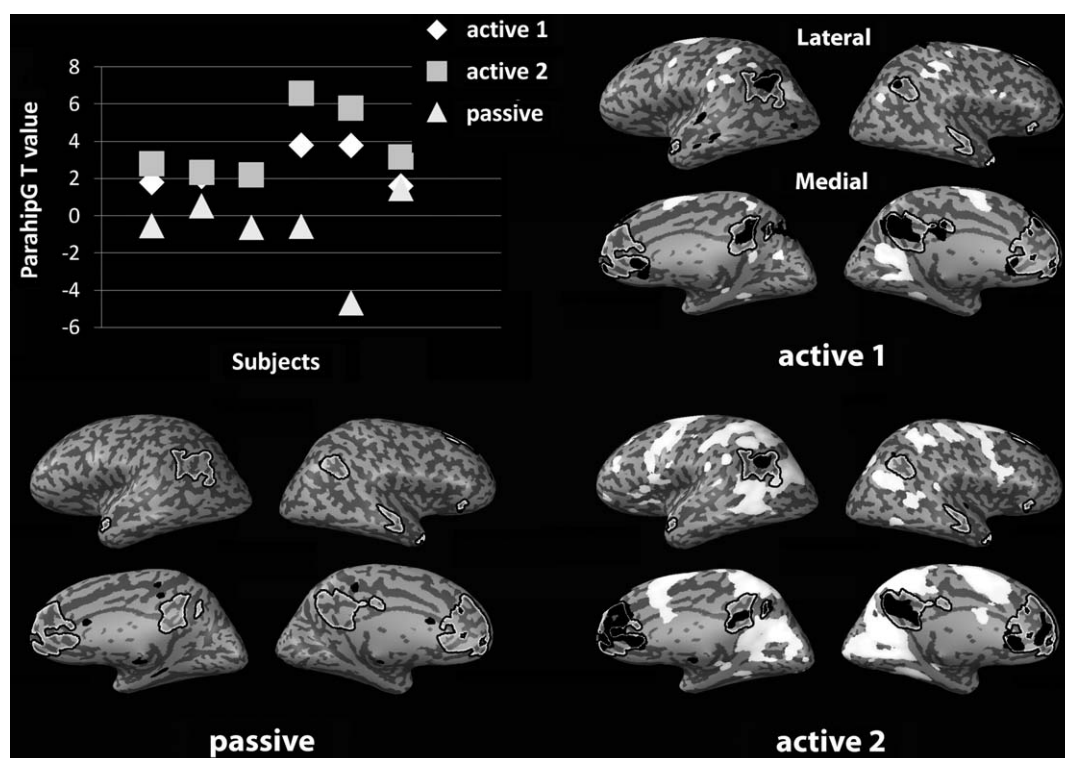


Fig. 3. Activation patterns observed during two different sessions of active mental imagery (spatial navigation) compared to activation induced by passive listening to the same task instructions. Fixed effects group analysis thresholded at false discovery rate corrected  $p < 0.05$ . Superimposed are the contours of the default mode network as in Fig. 2. Parahippocampal gyrus activity (Talairach coordinates  $X = -13$ ,  $Y = -15$ ,  $Z = 10$  mm) is shown for each of the six healthy volunteers for the three acquisitions. Note the consistently higher activation during active imagery compared to passive listening.

We described here the first condition predicted by the framework, that is, full consciousness with preserved functionality of both extrinsic and intrinsic networks, and the use of mental imagery tasks to detect this condition in brain-damaged patients. We will now consider two hypothetical situations in which there is an imbalance between the extrinsic and intrinsic systems.

#### **“Losing the self”: hypoactivity of the intrinsic system**

Perhaps the most robust fMRI finding which concerns the functionality of the intrinsic or default system is the consistent reduction of activity in this network during performance of cognitively demanding externally oriented tasks

such as visual recognition and motor planning (Gusnard et al., 2001). In contrast, the intrinsic system shows increased fMRI activity during no-task “resting” conditions, leading to the notion that this network might be a “task-negative” system (Fox et al., 2005, 2009) or be engaged in a “default” function during resting conditions (Raichle et al., 2001; Raichle and Snyder, 2007). It has been proposed that this reduced activity may be attributed to the fact that during an intense externally oriented task, the performing subject is fully attentive to the external world, and metaphorically speaking “loses itself” in the act (Goldberg et al., 2006; Golland et al., 2007). What then could be the outcome of a permanent reduction in the intrinsic system activity due to brain abnormality? Since no direct data are available, yet from DOCs one can only

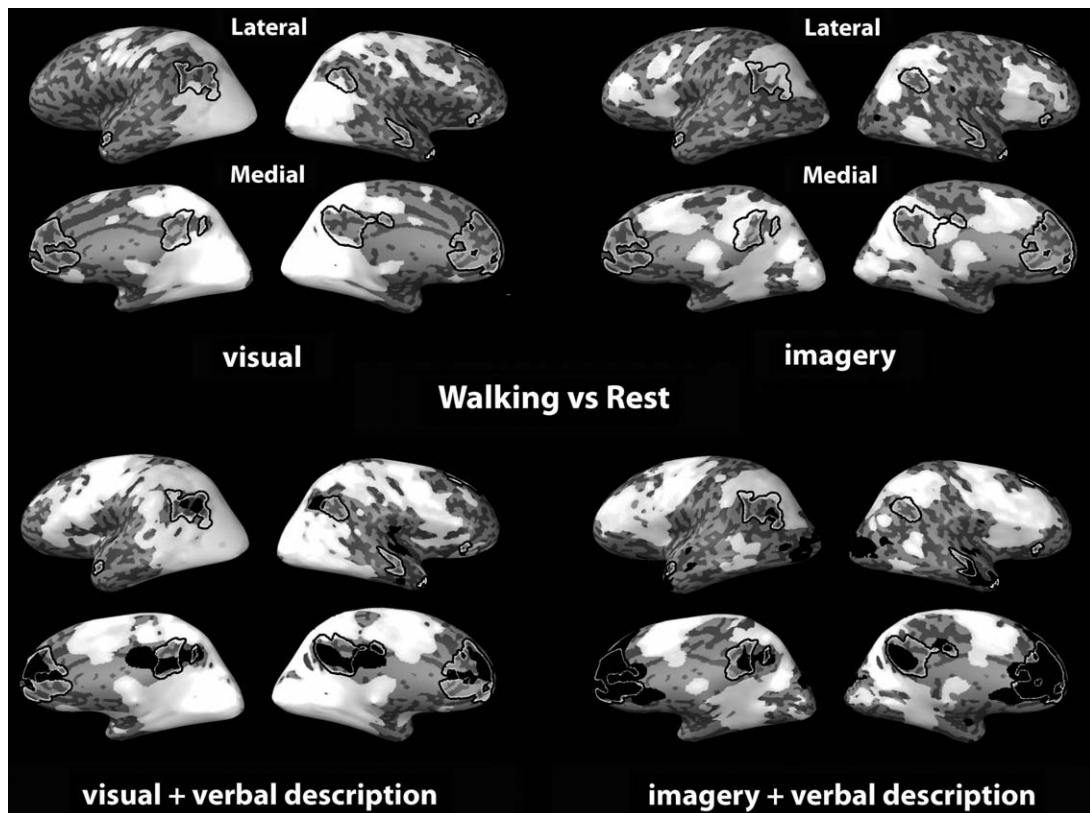


Fig. 4. Activation patterns induced by passively seeing a video of oneself walking (visual); imagining oneself walking (imagery), covert verbal description during the visual stimulation, and covert verbal description during the mental visual imagery task. Fixed effects group analysis thresholded at false discovery rate corrected  $p < 0.01$ . Superimposed are the contours of the default mode network. Note the substantial overlap of activity patterns between all four conditions, and the enhancement in neural activation associated with verbal descriptions.

extrapolate from studies in healthy individuals. It appears that some aspect of the intrinsic system function may be associated with voluntary decisions and action initiation (Goldberg et al., 2008). Extrapolating from such findings leads to the conjecture that a possible consequence of a pathological damage to this system might be a condition akin to catatonic or akinetic mutism (Naccache et al., 2004) in which the patient is unable to voluntarily initiate a motor action — in De Tieg et al. (2003) akinetic mutism was indeed linked to medial prefrontal dysfunction. Note that such a condition, associated with lack of movement, could in principle masquerade as a DOC since the patient may not initiate any response or communication.

### “Self-centered absorption”

The third condition predicted by the framework, in which the extrinsic system is hypofunctional, would be reflected by the disengagement of the subjects from the external environment. Few hints associate such conditions with “mind wandering,” where typically high default network activity is observed (Christoff et al., 2009; Gilbert et al., 2007; Mason et al., 2007; Wang et al., 2009). While these notions fit the conceptual framework of an antagonistic relationship between the extrinsic and intrinsic networks — that is, an enhancement in intrinsic activity comes at the expense of processing of the extrinsic information, the relevant data are too scant as yet. Nevertheless,

it is tempting to speculate how a pathological imbalance in which the extrinsic system is largely inactive should be reflected in the mental state of DOCs. From our conceptual framework we anticipate that such an imbalance would manifest itself again in a severe motor inaction, but also in a reduced sensory responsivity (since the patient is detached and self-absorbed and is incapable of orienting to the external world) either in terms of receiving sensory signals, or emitting motor actions. Behaviorally, then, the two conditions (“lost self” and “self-centered absorption”) could paradoxically lead to similar behavioral manifestations. Again, brain imaging, and particularly the study of spontaneous cerebral BOLD fluctuations by means of fMRI, might provide useful clues in diagnosing these hypothetical conditions — as will be discussed later. Finally, we consider the possibility that both systems are abnormally hypofunctional. In this case, we predict a deep DOC in which the patient does not respond and is also incapable of initiating any voluntary communication. In such severe and widespread brain abnormalities we expect a greatly reduced brain metabolism and a general reduction in neuronal activity.

### **Spontaneous fMRI activity patterns as a diagnostic tool in DOCs**

Although the above discussions of possible abnormalities associated with the new framework of brain organization are largely hypothetical and speculative, they do illustrate the complexity of brain abnormalities that could produce behavioral symptoms which may deceptively appear identical at the behavioral level. Here, the potentially powerful approach of functional brain imaging (Hirsch, 2005; Laureys et al., 2000, 1999a, b; Schiff et al., 2005) and particularly of fMRI may come as a useful and incisive tool. It may be argued that functional neuroimaging, if using active paradigms (Boly et al., 2007b; Owen et al., 2006, 2007) will be useful only in those limited “pseudo locked-in” cases where the patient behaviorally looks unconscious but in reality is fully aware and can initiate complex voluntary

mental activity. Recent progress in studying spontaneous brain activity (Biswal et al., 1995; Cordes et al., 2000; Damoiseaux et al., 2006; Fox and Raichle, 2007; Fox et al., 2005; Greicius et al., 2003; Lowe et al., 1998; Mitra et al., 1997; Nir et al., 2006; Vincent et al., 2007; Xiong et al., 1999) demonstrating activity patterns that emerge without any task or sensory stimulation, promise for studying higher-order associative network functionality and revealing their potential abnormalities in the absence of the patients’ collaboration (Boly et al., 2009b; Greicius et al., 2004; Rombouts et al., 2009).

The functional significance of low-frequency fMRI activity fluctuations remains yet poorly understood. A demonstration that such spontaneous activity occurs in primary sensory systems is of particular importance in this context. Indeed, the spontaneous nature of brain activity can be ascertained in such systems, if the sensory stimuli are completely blocked, and careful controls for imagery and attention are used (Nir et al., 2006, 2008). Recent research using intracranial recordings have revealed a putative electrophysiological correlate of such fMRI spontaneous activity in the neuronal responses of human cortex (He et al., 2008; Nir et al., 2008). More specifically, during resting-state conditions the human cortex manifests ultra-slow modulations of neuronal activity reflected both in firing rate modulations of individually isolated cortical neurons, as well as in modulation of high-frequency gamma power of local field potentials. These ultra-slow fluctuations show a remarkable coherence across functionally similar sites, and interestingly, are greatly accentuated during different sleep stages. Figure 5 depicts an example of such spontaneous activity recorded bilaterally from human auditory cortex during quiet rest (stage II sleep), showing a remarkable coherence of the activity in auditory cortices of both hemispheres. Although these activity patterns have a much slower dynamics than task-related activations (Nir et al., 2008), their widespread nature and remarkable reproducibility among subjects (Damoiseaux et al., 2006) makes them a potential tool for assessing the viability and functionality of cortical networks.



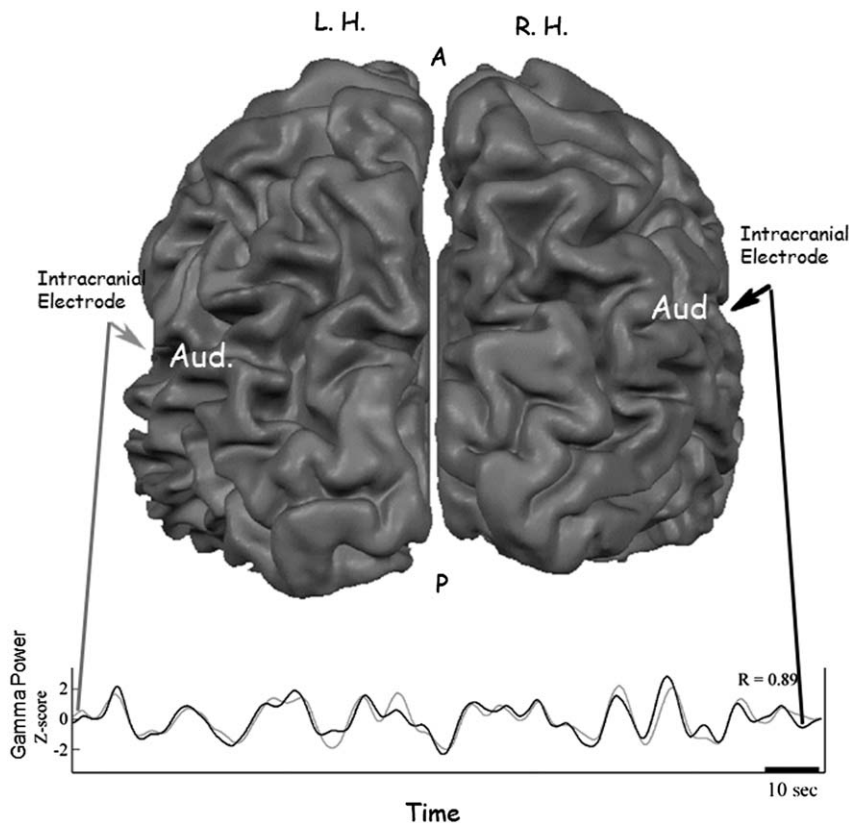


Fig. 5. Intracranial recordings obtained from bilateral auditory cortex depicting gamma power modulations in the local field potentials. Note the ultra-slow, spontaneous fluctuations and their remarkable correlation across the two hemispheres. Adapted from Nir et al. (2008).

Data-driven approaches such as independent component analysis (Hyvärinen, 1999) or *k*-clustering (Golland et al., 2008) applied to spontaneous activity, could reveal a full set of independent networks with a particular spatial distribution and a characteristic frequency power spectrum (Beckmann et al., 2005; De Luca et al., 2006; Esposito et al., 2008, 2006, 2005; Mantini et al., 2007; McKeown et al., 1998; Perlberg and Marrelec, 2008). The advantage of studying these activity patterns is that they nicely correspond to the functional organization of global brain systems (Bullmore and Sporns, 2009; Hagmann et al., 2008; Honey et al., 2009). Thus, cortical systems, which are functionally coupled during task performance, also show a similar coupling of spontaneous activity. Consequently, these spontaneous activations offer a tool in assessing cortical functional

abnormalities in patients that cannot cooperate. Indeed, a recent report has presented important evidence that such spontaneous activity can provide a sensitive marker for detecting cortical abnormalities in neurodegenerative disorders (Seeley et al., 2009). More specific to DOCs, we have recently demonstrated that default network connectivity was decreased in severely brain-damaged patients in proportion to their degree of consciousness impairment Boly et al., (2009); Vanhaudenhuyse et al. (submitted), Boly et al., (2009), demonstrated absent cortico-thalamic BOLD functional connectivity (i.e., cross-correlation between precuneal areas and medial thalamus) but partially preserved cortico-cortical connectivity within the default network in a vegetative-state patient studied 2.5 years following cardio-respiratory arrest (see Fig. 6). In a more comprehensive

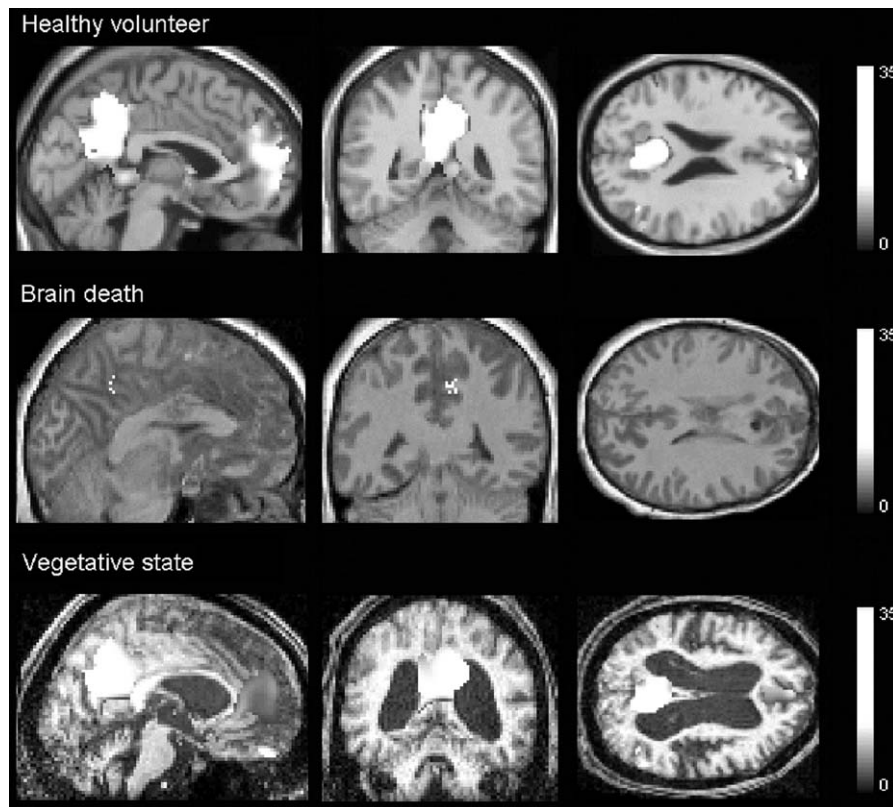


Fig. 6. Positive correlations with precuneal and posterior cingulate activity in a healthy volunteer, a patient in brain death and a patient in a vegetative state. Results are thresholded at false discovery rate corrected  $p < 0.001$ . Note that there is no residual long-range functional connectivity in brain death. In the vegetative state, despite the presence of residual functional connectivity within the default network, the observed activity is reduced compared to healthy controls. Adapted from Boly et al. (2009).

study (Vanhaudenhuyse et al. (submitted)) 14 noncommunicative brain-damaged patients and 14 healthy controls participated in a resting-state fMRI protocol. Connectivity was investigated using probabilistic-independent component analysis and an automated template-matching component selection approach. Connectivity in all default network areas was found to be linearly correlated with the degree of consciousness, ranging from healthy volunteers and locked-in syndrome to minimally conscious, vegetative, and comatose patients. Furthermore, precuneus connectivity was found to be significantly stronger in minimally conscious patients compared to vegetative-state patients. Locked-in syndrome patients' default network connectivity was shown not to be significantly different from healthy control subjects.

A remaining issue in the study of spontaneous BOLD signal fluctuations, especially for patients that show a significantly reduced neuronal activity, is the possible contamination by noise sources (Birn et al., 2006; Chuang and Chen, 2001; Cordes et al., 2000). Different strategies have been adopted based on two major defining characteristics of spontaneous brain activity as reported also by fMRI studies: (i) their tendency to be correlated across hemispheres (Biswal et al., 1995; Cordes et al., 2000; Damoiseaux et al., 2006; Fox and Raichle, 2007; Fox et al., 2005; Golland et al., 2007; Greicius et al., 2003; Lowe et al., 1998; Nir et al., 2006; Vincent et al., 2007; Xiong et al., 1999) and (ii) their neuroanatomical selectivity, that is, such fluctuations are not global, and distinct functional systems are often decorrelated (Biswal

et al., 1995; Cordes et al., 2000; Damoiseaux et al., 2006; Fox and Raichle, 2007; Fox et al., 2005; Golland et al., 2007; Greicius et al., 2003; Lowe et al., 1998; Nir et al., 2006; Vincent et al., 2007; Xiong et al., 1999). Data-driven approaches like independent component analysis offer the advantage to better isolate physiological artifacts from the neuronal components and are now being commonly adopted in this field (Beall and Lowe, 2007; Birn et al., 2008; Perlberg et al., 2007).

In conclusion, the integration and cross-referencing from recent advances in studying the healthy human brain provide new conceptual frameworks and methodological approaches that could help better diagnosing and understanding DOC. We here emphasized two perspectives for such integration: (i) from a neuroanatomical point of view (i.e., the subdivision of the human cortex according to a fundamental extrinsic versus intrinsic specialization reflected in two global and complementary cortico-thalamic systems); and (ii) from a functional point of view (i.e., the discovery of spontaneous ultra-slow and coherent activity patterns). Both perspectives are likely to provide important advances in our attempts to reach across the abyss and gain further insight in the neural correlates of human consciousness.

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