Finding a way in: A review and practical evaluation of fMRI and EEG for detection and assessment in disorders of consciousness

Harrison, A. H.[a], & Connolly, J. F. [a,b,c,*]

[a]McMaster Integrative Neuroscience Discovery and Study (MiNDS), McMaster University, 1280 Main St. W., Hamilton, Ontario, Canada L8S 4L8

[b]Department of Linguistics and Languages, McMaster University, 1280 Main St. W., Hamilton, Ontario L8S 4L8, Canada

[c]Department of Medicine, Division of Physical Medicine and Rehabilitation, McMaster University, 1280 Main St. W., Hamilton, Ontario L8S 4L8, Canada

[*]Corresponding author at: McMaster University, Department of Linguistics and Languages, Language, Memory, and Brain Laboratories, 613 Togo Salmon Hall, 1280 Main St. W., Hamilton, Ontario, Canada L8S 4M2. Tel.: +1 905 525 9140x27095. E-mail address: jconnol@mcmaster.ca (J.F. Connolly).

Abstract
Diagnoses and assessments of cognitive function in disorders of consciousness (DOC) are notoriously prone to error due to their reliance on behavioural measures. As a result, researchers have turned to functional neuroimaging and electrophysiological techniques with the goal of developing more effective methods of detecting awareness and assessing cognition in these patients. This article reviews functional magnetic resonance imaging (fMRI) and electroenchphalography (EEG)-based studies of cognition and consciousness in DOC, including assessment of basic sensory, perceptual, language, and emotional processing; studies for detection of conscious awareness; paradigms for the establishment of communication in the absence of behaviour; and functional connectivity studies. The advantages and limitations of fMRI and EEG-based measures are examined as research and clinical tools in this population and an explanation offered for the rediscovery of the unique advantages of EEG in the study of DOC.

Keywords
Disorders of consciousness; Functional magnetic resonance imaging (fMRI); Electroencephalography (EEG); Vegetative state; Minimally conscious state; Unresponsive wakefulness syndrome; Event-related potentials (ERP); Consciousness; Cognition

1. Introduction: Disorders of consciousness, diagnostic difficulties, and the importance of accurate assessment

Over the past few decades, improvements in emergency and intensive care medicine have resulted in an increasing number of patients who survive severe brain injury. While some patients recover well once they emerge from coma, others may remain in a vegetative or minimally conscious state. Together, coma, vegetative state (VS)[1], and minimally conscious state (MCS) are known as 'disorders of consciousness' (DOC). These are not to be confused with brain death, which is a complete and irreversible loss of all brain function (Medical Consultants on the Diagnosis of Death, 1981). Coma is a state of profound unresponsiveness in which the patient has their eyes closed and cannot be aroused with any amount of stimulation. Coma rarely lasts more than 10–30 days, after which time itis replaced by vegetative behaviour (Posner et al., 2007). The vegetative state (Jennett and Plum, 1972) is defined by a state of "wakefulness without awareness", meaning that patients have some form of sleep–wake cycling, but exhibit no evidence of awareness of self or the environment (Royal College of Physicians Working Group, 2003; The Multi-Society Task Force on PVS, 1994). Diagnosis is upgraded to minimally conscious state when a patient demonstrates inconsistent, but reproducible, evidence of purposeful behaviour, usually in the form of command following (Giacino et al., 2002). Another diagnosis that is frequently included with DOC is locked-in syndrome (LIS). Patients with locked-in syndrome are conscious and have near-normal cognition, but are completely unable to move or speak (American Congress of Rehabilitation Medicine, 1995). LIS is often misdiagnosed as VS because, in its complete form, the behavioural presentation is exactly the same. The current taxonomy does not include LIS as a DOC, since consciousness is not impaired in LIS. However, the distinction between LIS and DOC is not always clear, since LIS can be a stage in recovery from DOC (Formisano et al., 2011). Locked-in syndrome presents a unique and fascinating set of issues for discussion, but the present paper focuses on diagnostic issues surrounding disorders of consciousness, specifically the vegetative and minimally conscious states. Table 1 contains a summary of the key diagnostic distinctions between DOC, brain death, and coma.

The fundamental distinction between VS and MCS lies in the assumptions about the underlying level of mental function in each case. A diagnosis of MCS implies that a patient has some level of conscious awareness – albeit fluctuating and inconsistent – but a diagnosis of VS carries with it the assumption that the patient is not conscious and therefore has no mental life. The definition of consciousness is a contentious, philosophical issue that has been debated for centuries. For our purposes, we make use of the 'two-component' definition widely accepted in medicine in which consciousness is composed of arousal (i.e., wakefulness) and of awareness (i.e., subjective experiences of self and environment) (Posner et al., 2007). Arousal is easily measured by the presence of eye opening, but awareness is fundamentally a subjective experience; therefore, we can unequivocally establish that a person is conscious only if they can indicate, by some verbal or behavioural sign, that this is the case (see Connolly, 2012; Stins, 2009; Stins and Laureys, 2009). This becomes complicated when a person loses the ability to produce behavioural output, as in the case of DOC. A number of assessment scales exist for disorders of consciousness, some more precise than others (Seel et al., 2010), but all currently accepted methods have in common their reliance on bedside observations of behavioural signs of consciousness: a diagnosis of MCS depends on a patient's ability to generate verbal or motor responses to commands, whereas a

[1] Recently, the term "unresponsive wakefulness syndrome" has been proposed as an updated alternative name for vegetative state (Bruno et al., 2011; Gosseries et al., 2011; Laureys et al., 2010) We do not disagree with the adoption of an alternative to "vegetative state", which has unintentionally acquired a pejorative connotation, however, in this review we will use VS for the sake of consistency with the majority of the studies cited here, which were published before the term UWS was proposed.

diagnosis of VS depends on the absence of such evidence (Royal College of Physicians Working Group, 1996). In this case, the absence of evidence is necessarily taken as evidence of absence—a logic that is fundamentally flawed. A person may be conscious but unable to produce any verbal or behavioural signals (e.g., Connolly et al., 1999; Owen et al., 2006), as is the case in complete locked-in syndrome and advanced neuromuscular diseases such as amyotrophic lateral sclerosis (ALS; Hayashi and Kato, 1989; Hayashi et al., 1991). A patient with a DOC may have some conscious awareness, but be unable to respond due to sensory or perceptual impairments, aphasia, motor impairments, subclinical seizure activity, pain, fluctuating arousal, fatigue, and a range of other problems (Giacino et al., 2009). With conventional assessment tools such a patient would receive an inaccurate diagnosis of VS. This scenario is far from uncommon; in fact, misdiagnosis rates for VS are consistently estimated at about 40%(Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2009a,b).

The importance of accurately making the diagnostic distinction between VS and MCS is thrown into sharp relief when one considers the many decisions about patient care that are made based on the diagnosis. MCS typically carries a better prognosis than VS (e.g., Giacino and Kalmar, 2005); long-term care support is funded partly on the basis of diagnosis, and referrals for rehabilitation are often not made if it is believed that the patient does not have the mental function necessary to benefit from it. Additionally, diagnosis has ethical and legal implications for end-of-life decisions concerning withdrawal of nutrition and hydration (Bressman and Reidler, 2010; Fins and Shapiro, 2007; Wilkinson et al., 2009), and pain management (Boly et al., 2008; Schnakers et al., 2010, 2012; Schnakers and Zasler, 2007). Not least of all is the potential emotional harm inflicted upon a covertly aware patient by careless bedside discussions of the patient's condition and prognosis.

New assessment tools that circumvent the reliance on behavioural output are necessary. A growing body of research seeks to address this issue by examining a patient's brain activity under various conditions, using functional neuroimaging and electrophysiological measures. These studies can be divided into three types, based on the experimental paradigms they employ: passive stimulation paradigms, active paradigms, and resting state or connectivity studies. In passive stimulation paradigms, subjects are presented with various stimuli and their brain responses are monitored for characteristic patterns indicative of normal cognitive processing. These paradigms do not require any intentional interaction—physical or mental—on the part of the patient. The question that inevitably arises from studies that employ passive paradigms in patients with DOC is whether the presence of typical patterns of activation to sensory and cognitive stimuli necessarily implies that they reflect conscious awareness. While normal brain responses to semantic ambiguity, for example, in a patient diagnosed as vegetative is an encouraging finding (Coleman et al., 2009), it is not sufficient evidence to conclude that a patient is consciously aware (Stins, 2009; Stins and Laureys, 2009). Many brain responses to stimuli are automatic, meaning that a person need not willfully process the information in order for a typical brain response to occur. For example, one cannot choose not to recognize a familiar face, or not to understand speech in one's native language. Indeed we know from studies of priming (Dehaene et al., 1998), sleep (Perrin et al., 1999; Portas et al., 2000) and anaesthesia (Davis et al., 2007) that some cognitive functions do occur in the absence of full conscious awareness. Therefore, in order to demonstrate that a patient is truly aware of self and environment, one must demonstrate willful modulation of brain activity; activation that would not appear unless the patient were intentionally performing the cognitive task in question. This is where active paradigms become relevant. Active paradigms involve some sort of instruction to the subject, either with or without accompanying stimulation. Brain responses are monitored for patterns of activation that could only occur if the subject has understood the instruction and has actively engaged in the mental task. Thus, mental imagery paradigms – for example imagination of physical activity or navigation – requiring the active involvement of participants have become a common method of tapping into consciousness in the absence of behaviour.

Very recently, a third avenue of investigation into neural correlates of consciousness has expanded rapidly, in part due to concerns over the high cognitive demands that active paradigms place on severely injured patients. In the same way as a patient may not be able to produce behavioural output as a result of their injury, a variety of factors may also prevent them from performing or sustaining the complex coordination of cognitive systems required to generate differential patterns of brain activity in an active paradigm such as a mental imagery task. Several groups have recently begun to use fMRI to investigate functional and effective connectivity between brain regions as a measure of consciousness, based on earlier positron emission tomographic (PET) findings that while 'islands' of cognitive function may be preserved, DOC are characterized by widespread functional network disconnection (Boly et al., 2004; Laureys et al., 1999, 2000; Schiff et al., 2002).

In this article, we will review fMRI and EEG-based findings relating to the assessment of mental status in patients with disorders of consciousness, beginning with passive stimulation paradigms for the assessment of specific cognitive functions followed by active paradigms for the detection of awareness and the establishment of communication, and connectivity studies for the classification of DOCs. Note that we have included sample sizes for each study discussed for the information of the reader. A large majority of published studies in the field of DOC have very small sample sizes, and as a result cannot be generalized to larger patient populations. However, much can still be gained by examining small samples at the individual subject level. It quickly becomes apparent that current diagnostic criteria leave much to be desired. General patterns of performance emerge within diagnostic categories, but there are invariably exceptions—be it a VS patient who shows neuroimaging evidence of command following, or an MCS patient who can communicate at bedside but does not show corresponding neuroimaging markers of cognitive function. Thus, it is important to consider not only statistically powerful large group studies, but also individual patient results.

The literature review will be followed by a discussion of the relative advantages and limitations of fMRI and EEG as assessment tools in patients with DOC in the context of future research directions and the development of practical clinical tools.

2. Literature review: Assessing cognition and consciousness with fMRI and EEG

The literature review in the following sections is summarized in Table 2.

2.1 Passive stimulation paradigms

Many cognitive functions are associated with reliable event related potentials (ERP) and oscillatory patterns in EEG recordings, and with blood-oxygen level dependent(BOLD) activation patterns in fMRI studies. If these responses can be elicited in patients with DOC under the same conditions as in healthy controls, then inferences might be drawn reasonably about the cognitive functions that remain intact. The abundance of basic fMRI and EEG-based research on cognitive processes has enabled brain-injury researchers to select cognitive tasks that have robust activation patterns associated with them and adapt them for the purpose of assessing these specific processes in patients, from low-level sensory and perceptual processing, to emotion-modulated responses, to speech recognition and semantic comprehension. The following sections provide an overview of the use of fMRI and EEG-based measures in the assessment of cognitive functions in patients with disorders of consciousness.

2.1.1. Sensory, perceptual and pre-attentive processing

Many functional neuroimaging studies in vegetative and minimally conscious patients have focused on basic sensory and perceptual processing. These studies do not, in and of themselves, allow inferences to be made about a patient's level of awareness or cognitive ability, but they are crucial in the interpretation of findings from tasks that require higher-order cognitive processing, particularly negative findings. For example, in order to assess whether a patient can discriminate speech sounds from other auditory signals, we must first establish that the auditory cortex is intact functionally and shows activation to sound. Establishing this level of functioning provides some reassurance that a lack of activation to speech sounds is not simply due to a damaged auditory system that is equally unresponsive to all acoustic stimuli. Likewise, there is little to be gained by searching for responses to images of familiar faces without establishing that there is a functioning visual system. The pivotal role of establishing the integrity of a key element of the communication system is central to any assessment of cognitive function in the circumstances being discussed (see Connolly, 2012). Establishing the integrity of sensory systems with EEG is a well-established practice and has been performed as a routine part of brain injury assessments for decades (Chiappa, 1997). Evoked potentials are short-latency, time-locked EEG responses to sensory stimuli. Brainstem auditory evoked potentials (BAEPs) and middle-latency auditory evoked potentials (MLAEPs) are elicited by the presentation of auditory stimuli, and reflect the integrity of the auditory pathways and primary auditory cortex, respectively. Somatosensory evoked potentials (SEP) are elicited by electrical stimulation of the median nerve, and reflect integrity of the ascending somatosensory tracts and primary somatosensory cortex. Visual evoked potentials (VEP) are usually elicited by a rapidly reversing checkerboard or grating pattern and reflect the integrity of visual input pathways and primary visual cortex (Schomer and Lopes da Silva, 2010).

One of the first studies to apply fMRI to DOC investigated BOLD responses to basic auditory, visual, and tactile stimulation in a single vegetative patient (Moritz et al., 2001). The patient demonstrated activation in the superior temporal gyrus bilaterally, as well as in the angular gyrus and middle and inferior frontal gyri of the left hemisphere in response to narrated text versus rest; in the posterior occipital pole bilaterally in response to flashing light versus rest; and in the central sulcus bilaterally in response to tactile stimulation of both hands–all responses that are typical in healthy subjects. However, this was a single case study, and evidence from subsequent studies shows that "normal" activation in patients with DOC is certainly not typical of this group. Rousseau et al.(2008) used a similar tri-modal stimulation paradigm in 4 VS patients with variable results. One patient showed no observable activation to any of the stimuli; another showed extensive activation in expected locations to all stimuli; a third patient showed appropriate activation to tactile stimulation but not to auditory or visual stimuli; and, the fourth showed very slight activation to tactile and visual stimuli but not to auditory. This study illustrates the importance of multi-sensory paradigms in neuroimaging assessments of patients with DOC—a patient may show no response in one modality, but given a different type of stimulation may show normal responses (e.g., Connolly et al., 2000). However, most studies in this area are still conducted primarily in the auditory modality, for a number of reasons. Firstly, auditory stimuli are by their very nature relatively impossible for a patient/participant to avoid. Patients in VS and MCS frequently have difficulty maintaining eye-opening and fixation for visual stimulation (e.g., Zhu et al., 2009); and tactile stimuli are generally more complex to deliver. Secondly, the integrity of the various components of the auditory system is easily established outside of the scanner using auditory evoked potentials. Absent or abnormal auditory evoked potentials can be used as exclusion criteria for auditory fMRI studies (e.g., Bekinschtein et al., 2011). Visual evoked potentials can also be measured in a similar fashion, but are less straightforward to interpret and can tell us very little about a patient's visual acuity over and above the basic function of visual pathways (Evans and Boggs, 2012). And finally, perhaps the most intuitive reason that functional neuroimaging studies of DOC focus on auditory stimuli is that speech is our primary method of communication and most fundamental form of interaction.

While auditory stimuli have advantages over other modalities in principle, using them in combination with fMRI presents several difficulties (see Section 3.2.1) that limit the practicality of using fMRI in patients with DOC. ERPs do not suffer from these same limitations, making EEG a much more practical methodology for this purpose. The auditory 'oddball' is a very common paradigm widely used to investigate basic auditory discrimination and pre-attentive orienting responses. In its most basic form, a series of standard tones are presented, with the occasional deviant tone, which may differ from the standard tones in pitch, intensity, or duration. The deviant tone elicits a negativity at fronto-central electrode sites around 150–250 ms post stimulus called the mismatch negativity (MMN) (Näätänen et al., 2007). The MMN reflects pre-attentive auditory discrimination processes.

The same type of stimulus sequence can elicit an entirely different response called the P300 if the subject is actively attending to the stimulus (Polich, 2012). However, the P300 has proved particularly interesting in response to more complex stimulus environments than the simple oddball paradigm. One P300 variant (referred to as the P3a) is related to novelty detection and orienting behaviour while another variant (the P3b) is widely regarded as a measure of memory function and active information processing. The P3a shows a more frontal topography and a more restricted temporal nature occurring between about 250 and 350 ms. In contrast, the P3b exhibits a parietal distribution and varies in time (typically between about 250 and 500 ms) depending on stimulus complexity. For example, one paradigm that will figure prominently in the discussion below involves the presentation (typically aurally) of lists of names (e.g., John, James, Amy) within which is also presented the subject's name (unsurprisingly known as the Subject's Own Name, SON, paradigm). The subject's own name enhances the P300 amplitude compared to other names and delays its latency compared to less complex stimuli (e.g., deviant tones in an oddball sequence) (Holeckova et al., 2008).

The MMN can be elicited in both VS and MCS patients, with a frequency ranging from about 13–50% with no significant difference in occurrence between patient groups (Fischer et al., 2010; Höller et al., 2011; Kotchoubey et al., 2005; Qin et al., 2008). Kotchoubey et al. (2003) demonstrated that the MMN is elicited more frequently and with greater amplitude by complex tones than by simple sine tones in patients with DOC—an important finding given that the MMN is one of the most useful components in predicting outcome in DOC (Daltrozzo et al., 2007; Fischer et al., 2000, 2010). Several studies have also investigated the P300 as an indicator of pre-attentional orienting and working memory updating on DOC patients, with equally variable results. Hinterberger et al. (2005) did not observe a P300 response to deviant tones in any of their 5 VS patients, while Cavinato et al. (2009) observed a P300 to the SON vs. tones in68%oftheirVS sample (N = 34). Perrinet al. (2006) observed a P300 response in all members of a sample of LIS (N = 4) and MCS (N = 6) patients and in 60% of VS patients (N = 5). Other studies lie in between these two extremes: Kotchoubey and colleagues consistently report a P300 in about 30% of their VS and MCS patients (Kotchoubey, 2005, 50 VS patients; Kotchoubey et al., 2005, 50 VS patients and 38 MCS patients), with no differences between the two groups (Kotchoubey et al., 2005); Cavinato et al. (2011) observed P3 in all of their 6 MCS patients, and 6/11 VS patients. The variability in these results is attributable to many of the same factors as variability in fMRI results among patients with DOC, such as aetiology, diagnostic criteria, level of arousal–but also to the type of stimuli used to elicit the P3. Studies that used different levels of stimulus complexity to elicit the P3 (e.g., 3-component chords, vowel sounds (Kotchoubey et al., 2005), or SON (Cavinato et al., 2011) found greater P300 responses, both in number and in amplitude, to the complex stimuli than to sine tones.

2.1.2. Speech and language processing

One of the most common questions regarding patients with DOC is "Can they understand us?" The majority of ERP and fMRI studies in these patients seeks to answer just that question, not only in individual cases but also at the level of diagnostic category. The clinical diagnosis of MCS implies some level of speech comprehension indicated by reproducible responses to command, whereas the diagnosis of VS is based on the absence of such evidence. Many fMRI and EEG studies of DOC have investigated whether neuroimaging markers of language processing support these assumptions.

FMRI studies of spoken language function in VS and MCS patients typically focus on two main processes: speech recognition and semantic comprehension. The speech recognition paradigms have typically used narratives and signal-correlated noise or narratives played in reverse along with stimulus free periods to determine whether a patient is processing speech as speech or merely as general auditory input. Schiff et al. (2005) were the first to publish findings using this type of paradigm in patients with DOC. The study reports fMRI results from 2 MCS cases and 7 healthy controls who listened to narratives of familiar events read by familiar voices, or heard those same narratives played in reverse. In the forward narrative condition, both patients showed activation patterns similar to controls in the superior and middle temporal gyri. Interestingly, in the reversed narrative condition, controls showed similar patterns of activation as to the forward narrative condition; results interpreted as indicating that they recognized the narrative as speech, but simply meaningless speech. However, both patients showed severely reduced activation in this condition reflecting reduced processing of linguistically meaningless stimuli. While the results of the patients differ from those of the control group for the reverse-narrative condition, the results are still suggestive that the patients are processing speech signal as distinct from acoustically identical non-linguistic sound. Fernández-Espejo et al. (2008) used a similar paradigm in a group of 3 VS and 3 MCS patients compared to 19 healthy controls, and subsequently in another single VS patient (Fernández-Espejo et al., 2010). The results suggested that there is not a clear distinction between VS and MCS patients in terms of fMRI markers of speech recognition. When both narrative conditions (forward and backward combined) were contrasted with a silent baseline 3 VS and 2 MCS patients showed activation in superior temporal regions comparable to controls, reflecting intact auditory processing of complex sound. Of these 5 patients, 1 MCS and 1 VS patient also showed appropriate temporal and inferior frontal activation in the forward narrative condition compared to the backward narrative condition, reflecting language-specific processing. The remaining 1 MCS and 1 VS patient showed no significant activation in either contrast.

The studies reported above demonstrate that some patients with diagnoses of VS or MCS process speech as distinct from other auditory signals. However, these studies provide no indication of 1410 A.H. Harrison, J.F. Connolly / Neuroscience and Biobehavioral Reviews 37 (2013) 1403–1419 whether the speech stimuli are processed at a semantic level. A long history of ERP studies has provided a widely used and reliable marker of semantic processing, well-suited to this purpose. The N400 component is observed in response to a word that is incongruent with its semantic context and is indisputably linked to processes related to semantic comprehension (Kutas and Federmeier, 2011).

Connolly et al.(1999) were the first to employ the N400 to investigate semantic processing in a patient with a DOC.[2] They used a series of simple sentences whose terminal word was either congruent(e.g., "Father carved the turkey with a knife.") or incongruent (e.g., "The

[2] Strictly speaking, Witzke and Schönle (1996) were the first do so, however their identification of the presence/absence of the N400 component was questionable. Additionally, the findings were published in German. Since this review was restricted to English-language articles, we cite Connolly et al. (1999) as the first.

winter was harsh this allowance.") with the context of the sentence. Sentences were presented aurally and visually, in separate sessions. The patient's auditory N400 response demonstrated intact semantic processing, while the visual N400 did not, consistent with the patient's injury-related deficits. Kotchoubey (2005) and Kotchoubey et al. (2005) used two different N400 paradigms to assess semantic processing in large samples of DOC patients: word pairs that were semantically related or unrelated, and sentences similar to those used by Connolly et al. (1999). Both studies observed evidence of semantic differentiation in the form of the N400 in approximately 25% of the 100 total VS and 38 MCS patients studied, with no significant differences between the groups in terms of the frequency of an observed N400. Schoenle and Witzke (2004) observed higher rates of N400 response to semantically incongruent sentences– about 38% of VS patients (N = 43) and 77% of their "near VS" patient group (N = 23, who would fall in the MCS(-) category according to the Aspen Workgroup criteria). The differences in occurrence of the N400 between studies are attributable, at least in part, to the use of different criteria for identifying the component, illustrating the need for guidelines in quantifying ERPs in patient populations (Duncan et al., 2009). Schabus et al. (2011) took a different approach by examining oscillatory responses to semantic incongruity. They calculated event-related synchronization/desynchronizations (ERS/D) to antonym sentences (e.g., "The opposite of black is white/yellow/nice.") in 10 VS patients and 4 MCS. They did not report individual-level results, but observed significant group-level differences in ERS/D between VS, MCS and healthy controls: VS patients showed no significant ERS/D, while MCS patients show an ERS to unrelated words and an ERD to antonyms in the upper alpha band, compared to the opposite response in controls (ERD to unrelated words and ERS to antonyms). The authors attribute this reversal to a difference in processing strategy in MCS patients vs. controls, wherein MCS patients do not anticipate the terminal word as controls do, but rather perform semantic integration in a post hoc, bottom up manner.

A slightly different paradigm has been used to investigate semantic processing with fMRI. Semantically ambiguous sentences containing words that have homonyms (same spelling, different meaning) or homophones (same pronunciation, different spelling and meaning) are compared to unambiguous sentences which contain no such words. In a large group study (which included patients reported separately in Owen et al., 2005, 2006; and Coleman et al., 2007), Coleman et al. (2009) investigated semantic comprehension in a total of 22 VS and 19 MCS patients. 2 VS and 2 MCS patients showed some evidence of semantic processing in the form of temporal and/or frontal activation in the same areas as controls in response to semantically ambiguous vs. unambiguous sentences. 7 VS and 12 MCS showed temporal lobe responses to speech versus noise; 2 VS and 4 MCS patients showed activation to sounds vs. silence only; and 13 VS and 3 MCS showed no significant activation to any of the conditions, although some showed activation in appropriate areas below the threshold for statistical significance.

2.1.3. Familiarity and emotion

An area of particular interest and importance for both clinician and families of DOC patients is emotion and sense of familiarity. Families of patients with DOC are frequently concerned about whether their loved one recognizes their voices, faces, or names. Familiar or emotional stimuli are especially salient and can evoke stronger responses than similar stimuli lacking the elements of familiarity or emotion (Holeckova et al., 2008). For this reason, such stimuli are well-suited to ERP and fMRI assessments, although few studies have employed them. Two common strategies to elicit responses related to familiarity are to compare responses to the subject's own name (SON) compared to other names (see Section 2.1.1); and responses to familiar voices (usually the mother's) compared to unfamiliar voices. Laureys et al. (2004) report a single MCS patient who showed a P300 to his own name compared to other names. This finding was replicated by Perrin et al. (2006) in 3 out of 5 VS patients, all 6 MCS patients, 4 LIS patients, and 5 healthy controls. Machado et al. (2007) observed oscillatory changes in the gamma band in a boy in VS when he listened to his mother's voice, but not when the same words were spoken by unfamiliar women. In the only substantial group study of emotion in DOC, Kotchoubey et al. (2009) examined patients' ERP responses to woeful exclamations as oddball stimuli in a series of joyful stimuli (single words in which only the prosody determined the emotion). They observed a broadly distributed negativity occurring at around 150 ms in response to the emotional oddball in all healthy controls, and in 6 of the 27 VS and MCS patients studied. Staffen et al. (2006) reported a single VS patient who showed selective BOLD activation in the medial prefrontal cortex (similar to controls) to his own first name compared to other first names. Qin et al. (2010) observed BOLD activation in regions of interest related to self-reference processing (based on a more complex manipulation of degree of self-relatedness of name stimuli in 17 healthy controls) in response to the subject's own name spoken by a familiar voice in 6 of 7 VS patients and all 4 MCS patients. However, caution must be used in interpreting these findings. Although analyses were carried out in regions established in healthy controls to be relevant to self-referential processing, they did not employ an adequate control condition in the patient experiment: the self-referential stimuli were contrasted to a resting baseline only, and not to an equally complex, but non-self-referential stimulus. In an fMRI investigation of a rare long-term comatose patient (eyes remained closed at 35 months post-injury), Eickhoff et al. (2008) reported a particularly surprising finding. Not only did the patient show robust and appropriate activation to tactile and visual stimulation (with eyes taped open) but she also showed appropriate primary and associative auditory activation and left inferior frontal gyrus (Broca's area) activation to spoken words. Moreover, when the speech was directed to the subject by name, additional activation was observed in the left amygdala and right anterior superior temporal sulcus, and this activation was modulated by the familiarity of the speaker, i.e., the patient's children evoked the strongest response, followed by friends, with significantly weaker responses to unknown voices. In a related finding, Bekinschtein et al. (2004) reported an MCS patient who showed appropriate auditory activation when listening to a story read by an unfamiliar voice, but showed additional activation in the amygdala and insula when the story was read by the patient's mother. Although, as mentioned above, studies in the visual domain are rare in patients with disorders of consciousness, Zhu et al. (2009) have reported increased activation of visual association areas in MCS patients A.H. Harrison, J.F. Connolly / Neuroscience and Biobehavioral Reviews 37 (2013) 1403–1419 1411 in response to historically familiar photos compared to unfamiliar ones.

2.2. Active paradigms

2.2.1. Detection of awareness

While demonstrations of intact perceptual, language, and emotional processing are essential to a complete assessment of a patient's cognitive status, they give us little insight into the patient's level of conscious awareness. We cannot know, without some form of report from the individual, whether they have any conscious experience of the stimuli they are processing. In order to conclude, in the absence of behaviour, that an individual is consciously aware, we must observe patterns of brain activity that could only occur if this were the case. Take for example the case reported in 2006, and since widely publicized, by Owen and colleagues of a young woman who had been diagnosed as being in a vegetative state (although the patient may have been exhibiting visual fixation indicative of transition to MCS (Posner et al., 2007, Chapter 9; Schnakers et al., 2008)). The authors employed an active mental imagery paradigm developed by Boly et al. (2007). While undergoing fMRI scanning, the patient was instructed to perform two mental imagery tasks: to imagine playing tennis, and to imagine navigating from room to room around her home. These tasks had previously been shown to elicit different and robust patterns of activation in healthy volunteers, particularly in the supplementary motor area for tennis imagery and in the parahippocampal gyrus, posterior parietal cortex, and lateral premotor cortex for navigation imagery (Boly et al., 2007). The patient's activation patterns were virtually indistinguishable from those of controls. This finding confirmed that she was able to understand the instructions given to her, and to respond to them by willfully performing the mental imagery task in the absence of any external stimulation, which in turn produced a typical pattern of fMRI activation, despite her inability to respond behaviourally. The authors therefore concluded that the patient was in fact consciously aware (see Greenberg, 2007; Nachev and Husain, 2007; Owen et al., 2007; Stins, 2009; Stins and Laureys, 2009 for further discussion of this case).

Though rare, the patient described by Owen et al. (2006) is not a one-of-a-kind case; the results have since been replicated. In the largest fMRI study of patients with DOC published to date (Monti et al., 2010), 23 VS and 31 MCS patients underwent fMRI scanning while being instructed to imagine playing tennis or navigating a familiar environment. Of this sample, 5 patients (4 VS patients and 1 MCS patient) were identified whose brain activity indicated that they were successfully performing the mental imagery tasks. Goldfine et al. (2011) used a similar task while recording EEG from 5 healthy controls, 1 LIS patient, and 2 MCS patients. They compared power spectra during imagery of swimming or navigation to resting baseline. The LIS patient and 1 MCS patient showed evidence of motor imagery task performance, as measured by the consistency of each patient's signal pattern changes across runs, rather than in comparison to healthy subjects' patterns. Similarly, Owen and colleagues (Cruse et al., 2011) observed command-following in the form of appropriate event-related synchronizations/desynchronizations (ERS/D) to motor imagery instructions in 3 out of 16 VS patients. The motor imagery task they employed, which the authors claim to have developed as 'novel', involves imagination of hand and foot movement and has in fact been used for over two decades in both basic research and in clinical research involving brain-computer interfaces in patients with motor and neuromuscular disorders (Kalcher et al., 1996; McFarland et al., 1997, 2000; Müller-Putz et al., 2005; Neuper et al., 2003; Penny et al., 2000; Pfurtscheller and Neuper, 1997; Pfurtscheller et al., 1993, 1997, 2000; Scherer et al., 2004; Wolpaw et al., 1991; for reviews see e.g., Neuper and Pfurtscheller, 1999; Neuper et al., 2006a,b; Wolpaw et al., 2002). Recently, a debate has arisen over the statistical methods employed by Cruse et al. in a re-analysis of the study's data by Goldfine et al. (2013) which suggests that Cruse et al.'s methods violate statistical assumptions and are biased towards falsely identifying awareness in VS patients. However Cruse et al.'s (2013) rebuttal argues that Goldfine and colleagues' methods are unsuitable for the data and equally error-prone in the opposite direction, making detection of awareness unlikely not only in patients, but also in a majority of healthy controls. They also point out that even with Goldfine et al.'s stringent statistical criteria two of the three patients in whom they detected awareness were pushed only slightly below accepted statistical thresholds, while the third remained significant. It is clear that the application of this technique for the detection of awareness is still in its infancy, and much further study is needed before its reliability as a clinical tool can be established. A cautious and critical eye must be employed when evaluating findings, and an attitude of open data sharing and scientific debate such as that demonstrated by Cruse and Goldfine and their colleagues will be essential to the development of a useful and reliable method of detecting awareness in patients with DOC.

The cognitive control required to generate statistically significant brain activation to complex mental imagery tasks is considerable. It must be noted that a subset of patients may be consciously aware, but unable to perform those specific tasks, for any number of reasons including impaired attention, fluctuating arousal, fatigue, selective damage to networks involved, misunderstood instructions, and so on. Other studies have attempted to compensate for some of these potential difficulties by using tasks that are somewhat less cognitively demanding, but still require willful processing on the part of the patient. Schnakers et al. (2008) developed an active ERP paradigm based on the commonly used "subject's own name" (SON) paradigm (e.g., Perrin et al., 2006) with the modification that subjects were asked to count the instances of their own name. The SON in the active (counting) condition elicits a larger P300 than in the passive condition in healthy subjects. Schnakers et al. (2008) observed P300 responses similar to controls in 9 out of 14 MCS patients. Conversely, none of the 8 VS patients showed a P300 in either the passive or active conditions. The same group detected a case of total locked-in syndrome using the same paradigm in a patient who would have been behaviourally diagnosed as comatose (Schnakers et al., 2009a,b). Following suit, Monti et al. (2009) reported a single MCS patient who was asked to listen to a series of words passively, or to listen to the same series of words and count the occurrences of a target word while undergoing fMRI. In 20 healthy controls, the target-counting task, compared to the passive listening task, elicited activation in a widespread network involving frontal, temporal, parietal, and cerebellar regions. The MCS patient showed activation of the same network to an extent that fell within the range of normal subject variability, suggesting that the patient successfully performed the target-counting task.

Bekinschtein et al. (2009) developed a novel ERP task based on the classic mismatch negativity (MMN) to detect awareness. A series of tones were presented which included both local deviants (every fifth tone) and global deviants (every fifth group of five tones had the same or different structure than the preceding four). In healthy subjects, the local deviant elicited an MMN and a P3a, and the global deviant elicited an additional but later P3b. However, the global effect was only observed when the participants were actively counting the global deviants and disappeared when they were mind-wandering or engaged in a visual interference task. The authors concluded that the global ERP effect required conscious awareness of the stimuli, and this was upheld by participant reports. The paradigm was subsequently tested on a group of 4 VS and 4 MCS patients. Three of the VS patients showed the local effect, but none of them showed the global effect. In contrast, all MCS patients showed the local effect and 3 out of 4 showed the global effect. This finding was extended in 2 further publications, the second encompassing the findings of the first: Faugeras et al. (2012) tested the same paradigm on 100 patients (including those reported in Faugeras et al., 2011), some of which were tested on several occasions. Sixty-five datasets were retained from 49 patients, the rest being excluded due to excessive artifact. Of these 49 patients, 24 were in VS, 28 in MCS, and 13 were conscious. The global effect was observed in all of the 8 healthy controls that were included in the analysis, in 54% of the conscious patients, 14% of the MCS patients, and in 8% of the VS patients. These patient results illustrate both the utility of ERPs for detecting conscious processing in DOC patients, and also the caution that must be used in interpreting negative results, since only half of the patients who were clinically assessed as conscious showed the ERP results indicative of consciousness in this paradigm.

Bekinschtein et al. (2011) used motor preparatory BOLD activity as a marker of purposeful behaviour in a sample of 5 VS patients who showed intact auditory evoked potentials and word-related fMRI activation, out of an original sample of 24 VS patients. Subjects simply received instructions to move their left or right hand. Only the control subjects were able to actually move their hands, but two of the 5 VS patients showed movement preparatory activity in the left premotor cortex to the right hand command. None showed activation to the left hand command, possibly due to lesions selectively affecting the right hemisphere.

Only one study has investigated volitional cognition in the visual domain. Rodriguez Moreno et al. (2010) used a picture-naming task to probe consciousness in 5 MCS, 3 VS, 1 patient who had emerged from MCS (EMCS) and 1 LIS patient. Subjects were asked to silently name drawings of objects as they were presented. Control subjects activated a language-related network, outside of the visual network, known to be selectively activated by picture naming versus passive viewing. The locked-in, EMCS, 2 MCS and 1 VS patient activated the complete network, 3 MCS patients and 1 VS activated a partial network, and 1 VS patient did not show activation in the naming network.

The results of the studies reviewed so far illustrate the incongruity between clinical diagnoses and neuroimaging assessments of cognitive function. Some patients with a diagnosis of vegetative state showed evidence of high-level cognition and even awareness; whereas some diagnosed MCS patients – who showed behavioural evidence of purposeful behaviour and therefore some level of conscious awareness – failed to show activation even at the level of primary auditory cortex (Coleman et al., 2009). The implication for vegetative patients is clear: some patients who have received a diagnosis of vegetative state may actually be misdiagnosed cases of MCS, or even locked-in syndrome. However, negative findings in MCS patients are somewhat more puzzling, but could be attributed to damage to auditory pathways (in cases where subjects have not been pre-screened with auditory evoked potentials), to fluctuating levels of arousal, to cortical responses too weak or variable to reach statistical significance, or to alterations in neurovascular coupling (see Section 3.3.1). Add to this already complex issue the diagnostic disagreements between different behavioural assessment methods and there is little wonder that fMRI and EEG findings appear to be at odds with diagnosis on occasion, again underscoring the need for comprehensive, multimodal, hierarchical assessments to gather evidence about a patient's true mental status.

2.2.2. Communication

Once it has been established that a patient who has been diagnosed as vegetative is indeed conscious despite outward appearances, the question becomes "What can be done for this patient?" Aside from intensifying rehabilitation efforts, all attempts must be made to establish some form of communication. When the patient does not have the physical capacity to make behavioural responses, we must again turn to their brain responses. A vast literature exists on the use of electrophysiological measures as means of communication with and control of devices (known as brain computer interfaces, BCI) in physically disabled populations (see e.g., Birbaumer et al., 2006; Curran and Stokes, 2003; Daly and Wolpaw, 2008; Neuper et al., 2006a,b; Nicolas-Alonso & GomezGil, 2012; Wolpaw et al., 2002). These systems make use of various EEG signals, including slow cortical potentials (e.g., Birbaumer et al., 2000),the 'oddball' P300 ERP (e.g., Donchin et al., 2000), and sensorimotor ERS/D (e.g., Pfurtscheller et al., 1993; Wolpaw et al., 1991), which are translated into various outputs like cursor movement, spelling, or prosthesis control. These devices have been developed primarily for application in ALS, but the potential application to DOC is obvious (Chatelle et al., 2012; Kübler & Kotchoubey, 2007; Kübler, 2009; Naci et al., 2012). This vast body of existing knowledge on EEG-based BCI had not been applied in DOC until very recently, and it had rarely been cited in the DOC literature, even when the techniques developed by BCI researchers were being employed directly, as in Cruse et al. (2011). Until very recently, the field has overwhelmingly remained focused on fMRI as the technique of choice for detecting awareness and establishing communication in patients with DOC.

Using the same strategy as many BCIs, Monti et al. (2010) explored the use of mental imagery conditions in fMRI for basic communication (e.g., yes/no questions) in patients with disorders of consciousness. From the 5 patients who showed modulation of BOLD activation in the mental imagery tasks discussed in Section 2.2.1 above, 1 VS patient with reliable responses was chosen to undergo the communication experiment. The patient was posed a series of autobiographical questions and asked to respond by using one of the imagery conditions (i.e., playing tennis or navigating) for "yes" and the other for "no". In 16 healthy control subjects, a blinded experimenter was able to determine the answers to the questions based on activation patterns in individual subjects with 100% accuracy. In the patient the answers to 5 out of 6 questions were correctly determined based on the mental imagery responses (the 6th question showed virtually no activation in the regions of interest for either imagery condition).

Bardin et al. (2011) used a modified version of the Monti et al. (2010) paradigm to attempt simple communication with 5 MCS patients and 1 patient with locked-in syndrome. They simplified the imagery task slightly by using only one imagery condition (physical activity imagery, expanded to other activities like swimming) and a rest condition in place of the second imagery task. They first investigated whether the expected activations could be reliably elicited to command. Appropriate activation to the imagery task was observed in all 14 healthy controls, 2 MCS patients and the locked-in patient, with no activation observed in the other 3 MCS patients. Control subjects and 4 patients then underwent 2 communication scans: a binary choice and a multiple choice. In the binary choice task, subjects were asked a yes/no question and asked to perform the physical activity imagery for “yes” and do nothing for “no”. In the multiple-choice task, subjects were shown a face card from a deck of playing cards and asked to remember it. During the scan the four possible suits and four possible faces were presented verbally and subjects were asked to respond using the imagery task when they heard the options that corresponded to their cards. In both the binary and multiple-choice conditions, blinded experimenters were able to determine the healthy volunteers’ answers with 100% accuracy. However, only one patient(MCS) showed observable activation in the multiple choice condition, with no successful data in the binary condition, a result which is especially puzzling because 2 of the 3 patients who failed to produce BOLD responses were in fact able to communicate at the bedside. This result speaks directly to the preliminary nature of these methods and the need for much more research before this technique can be considered a reliable clinical tool. It also reiterates the degree of caution required in interpreting negative BOLD findings (see section 3.3.1 below).

Lulé et al. (2013) attempted to apply an auditory oddball EEG based BCI paradigm to probe command following and establish communication in 2 LIS, 13 MCS, and 3 VS patients. One LIS patient was able to demonstrate command following and use the BCI for communication. One MCS showed some evidence of command following, but none of the MCS or VS patients were able to use the BCI for communication. EEG-based BCIs hold obvious potential for patients with DOC but clearly much work has yet to be done to optimize both the input and the classification algorithms for this population.

2.3. Resting state activity and functional connectivity

Research into resting state activity and connectivity is arguably the fastest growing area in the field of neuroimaging in DOC. Part of the rationale for these studies is that the types of paradigms used in the studies reviewed above require at a minimum intact sensory pathways, and at a maximum highly coordinated cognitive function, and that these methods should be complemented by tools that do not depend on sensory integrity or a patient’s ability to understand instructions. Earlier PET studies provided evidence that islands of cognition may remain intact in patients with DOC, and that reduced cortico-cortical and thalamocortical connectivity may lie at the heart of impaired consciousness (see Laureys and Schiff, 2012 for discussion and an eloquent model of consciousness as an emergent property of frontoparietal connectivity). As a result, more and more studies are investigating the nature of resting-state activity and connectivity using both fMRI and EEG.

The default mode network (DMN, Raichle et al., 2001) has been a particular area of focus for fMRI connectivity studies in DOC. The DMN encompasses the posterior cingulate cortex/precuneus, medial prefrontal cortex, and temporoparietal junctions and is particularly intriguing because it is more active at rest than during an attention-demanding task (Raichle et al., 2001). Recent research in DOC suggests that an intact default mode network may be a prerequisite for consciousness, and may therefore serve as a potentially useful marker in diagnosis. Boly et al. (2009) found reduced functional connectivity in the DMN of a vegetative patient compared to 6 healthy controls; and absent DMN functional connectivity in a brain dead patient. Cauda et al. (2009) also found impaired default mode networks in 3 VS patients, and observed a qualitative correspondence between a behavioural measure of function and DMN impairment. Vanhaudenhuyse et al. (2010) studied DMN connectivity in 4 VS, 4 MCS, 1 locked-in, and 5 coma patients and observed an exponential correlation between DMN connectivity and clinical level of consciousness that was particularly pronounced in the precuneus/PCC region. Similarly, Soddu et al. (2011) observed fewer connections in their 8 VS patients than in controls; but connectivity comparable to controls in their 2 locked-in patients. Ovadia-Caro et al. (2012) investigated interhemispheric functional connectivity between homologous regions, not in the DMN, but rather in the opposing, "extrinsic" task-positive network. They observed reduced connectivity in DOC patients compared with controls, and also a correlation between the clinical level of consciousness and the degree of interhemispheric connectivity. Several very recent studies have also investigated connectivity using EEG power spectra, with similar findings. Lehembre et al. (2012) analyzed power spectra in 10 VS and 18 MCS patients, and observed increased delta power and decreased alpha power in the VS group compared to the MCS group. They also observed lower connectivity in the alpha and theta bands in the VS group than in the MCS group. León-Carrión et al. (2012) found stronger connectivity between anterior and posterior brain regions in a group of 9 patients with severe neurocognitive disorders compared to a group of 7 MCS patients, who showed a disconnection particularly between frontal cortex and other brain regions. Fingelkurts et al. (2012) studied EEG microstates in 14 VS and 7 MCS patients compared to 5 healthy volunteers and observed that the DOC patients had fewer microstates than healthy controls. They also found that microstates characterized by fast alpha oscillations were positively related to the clinical level of consciousness, whereas microstates characterized by delta, theta, or slow alpha oscillations were negatively related to clinical level of consciousness.

Resting state functional connectivity appears to have a relationship to level of consciousness, and holds the advantage of not relying on potentially damaged sensory, perceptual, and cognitive systems. However, even more insight could be gained by studying functional connectivity under task conditions. To our knowledge, only two studies have investigated functional connectivity under cognitive stimulation. Boly et al. (2011) employed dynamic causal modelling to ERP responses during an MMN task to examine not only functional connectivity but also effective connectivity, that is, directional, causal connections between brain regions. They found that while VS patients were still able to generate an MMN response, they lacked a top-down connection from frontal to superior temporal cortex. This connection was preserved in MCS patients, who did not differ significantly from controls. This finding lends further support to the notion that isolated cognitive processes may be preserved in VS, but that deficient connectivity is at the heart of decreased consciousness. Kotchoubey et al. (2013) studied global functional connectivity under emotional load in 6 VS and 6 MCS patients who listened to recorded human pain cries compared to non-emotional vocalizations. While they observed no significant stimulus-related activation in either group in a typical GLM analysis, a whole brain functional connectivity analysis revealed stronger connectivity in the MCS than in VS patients, in emotion-related networks similar to those observed in healthy controls.

The studies in this section support a link between functional connectivity and consciousness; however caution must be used when interpreting these findings at the individual subject level, as they are based on a tautology. The problem lies in the fact that these studies have used behavioural measures as the independent variable 'level of consciousness'. While the level of functional connectivity appears to be related to the patient's behaviour, we know from the body of research discussed in earlier sections of this review that behavioural measures are not always reliable indicators of conscious awareness. Developing and validating an objective neural marker of consciousness in non-communicating patients therefore presents a formidable task, since in this patient group we necessarily have no absolute reference to assess the accuracy of any determination of the presence or absence of consciousness. Consider the impact of a patient behaviourally diagnosed as vegetative, but who is in fact covertly conscious on the results of a group level connectivity study: if this patient showed intact functional connectivity, correctly indicating awareness, it would statistically weaken the link between consciousness (determined behaviourally) and functional connectivity, rather than highlighting the potential utility of the technique in detecting awareness. Connectivity studies undoubtedly do and will continue to be instrumental in our understanding of the neural substrates of disorders of consciousness, and they have the unique advantage of not relying on the integrity of sensory pathways or a patient's ability to understand instructions or actively participate in cognitively demanding tasks. However, their utility as diagnostic tools is currently limited by the circularity of their reference to behavioural measures. It is completely circular logic to develop tools aimed at reducing misdiagnosis while using the current diagnosis as a gauge for the accuracy of the new tools.

1. *Advantages and limitations of fMRI and EEG for the study of DOC*

Since fMRI was introduced in the early 1990s, it has had an immense impact on cognitive neuroscience research, and its use has grown exponentially, from 4 peer-reviewed fMRI publications in 1992, to about 13 per day in 2011 (using the same database and search terms as Logothetis, 2008). It has become a very "fashionable" technique and there are occasions when it appears to have been chosen as a research method for this reason, rather than for its suitability to a particular research question or population. This is not to minimize its importance or its contribution to cognitive neuroscience and other fields, but merely to point out that it is not the answer to every question (Logothetis, 2008). While fMRI has contributed immensely to our understanding of disorders of consciousness, and highlighted the need for brain-based tools to assess cognition and awareness in patients with DOC, it is itself clearly not the most practical solution to the problem. In order for an assessment technique to be readily adopted into standard clinical practice, it must be inexpensive, easily accessible, have few limitations in terms of patient compatibility, and be relatively simple to administer whether at the bedside, in the patient's home or care facility or in a research laboratory. fMRI and patients with severe brain injuries rarely combine to meet these criteria. Conversely, EEG is widely available, inexpensive, easy to administer at the bedside, is fairly robust to many artifacts that can cause fMRI data to be unusable, and has virtually no restrictions with regard to patient compatibility and safety. EEG is more easily validated on large groups of subjects and data acquisition times are generally shorter, making it not only more suited for clinical applications but also for the basic research required prior to applications in patients.

The potential implications for patients with disorders of consciousness, their families, and care teams of the fMRI research described above are profound. Unfortunately, there are many, significant logistical and methodological considerations that will prevent fMRI from becoming a part of routine diagnostic assessments in standard clinical practice. The following sections will review these issues and discuss the advantages and disadvantages of employing EEG as an alternative methodology (see Table 3 for a summary).

1.1. *Patient safety and monitoring*

Many of the limitations of performing fMRI in patients with DOC are safety issues that apply to any MRI procedure in any population, but require special consideration in patients. Of particular concern for brain injury patients are implanted devices such as neurostimulators, CSF shunts, aneurysm clips, and bone flap fixation wires and clamps. Many of these devices have now been tested and deemed MR-safe at specific fields, but many are still contra-indicated or restricted (see Shellock, 2011). Some aneurysm clips are ferromagnetic and may displace and cause serious injury or death. A number of shunt valves use magnetic components and exposure to the MRI's magnetic field may change the valve settings and lead to increase intracranial CSF pressure. Some neurostimulators may malfunction, overheat, or be displaced causing injury or death. Any implanted devices and any other surgical hardware must have documented evidence of MRI compatibility for the specific model and manufacturer at the field strength of the scanner to be employed. Also, as a routine part of general MRI screening, patient background regarding previous surgeries, implants, as well as possible embedded metal such as shrapnel or bullets is required. In the case of non-communicative patients, this essential information may not be available and other, preliminary diagnostic procedures (e.g., computerized tomography, CT) may be required to rule out safety hazards prior to MRI scanning. Conversely, there are virtually no contraindications to recording EEG from the scalp surface.

The Safety Committee of the Society for Magnetic Resonance Imaging recommends that all patients who are unable to communicate should be physiologically monitored while in the scanner (Kanal and Shellock, 1992). This requires that the MR unit be equipped with specialized, MR-compatible monitoring equipment. While clinical-use MRI facilities have such equipment available, research-dedicated MRI facilities are frequently not equipped for sophisticated physiological monitoring. Monitoring is required not only for the patient's medical safety, but also for their emotional well-being. Up to 20% of patients undergoing MRI experience a claustrophobic or other distress reaction (Shellock, 2011), and may elect to terminate the scan as a result. Non-communicative patients, however, would be unable to signal such a reaction, and so should be monitored for physiological changes that might indicate distress (e.g., increased heart rate, respiration). EEG does not induce claustrophobic reactions, and requires no special monitoring.

Periods of low arousal and sleep are very common in patients with disorders of consciousness. As a quality control measure, arousal should be monitored, ideally with EEG, during fMRI scanning to avoid collecting data when the patient is least likely to show activation (Laureys et al., 2004). While simultaneous EEG and fMRI recording is possible with specialized EEG equipment, it introduces a whole new set of safety concerns (see Allen, 2010 for a review), and extra analysis steps to remove gradient and ballistocardiogram artifact from the EEG data (Benar et al., 2003). When recorded in isolation, EEG easily identifies periods of sleep, low arousal, or seizure activity, so that data can be recorded during periods of arousal, and contaminated data can easily be eliminated.

1.2. Data acquisition

Once a patient has passed through all the necessary safety screening steps, there are still many hurdles to collecting fMRI data. Patients are often recruited from the hospital-based treatment or rehabilitation programs with which the researchers are affiliated, and scanned at the same facility. However, in cases where patients are not housed in the same facility as the scanner, specialized transport and accompanying support staff are required. Once at the scanning facility, many difficulties may be encountered in physically positioning the patient in the scanner due to muscle contractures or injuries that prevent them from lying flat and still. Though rarely mentioned in fMRI studies, data loss due to transport and positioning issues is high, which raises questions about validity of population data due to subject selection bias. EEG equipment, on the other hand, is highly portable, and patient positioning is rarely an issue making it applicable to a much wider sample of patients, even to those who are not medically stable enough to be transported or to undergo MRI scanning. In either case, we believe that it is important for studies to report the original number of candidate patients from which the final sample were drawn, and details of the reasons for excluding patients – such as transportation issues, positioning difficulties, artifact, MRI-incompatibility, etc. – so that readers can get a more accurate sense of the representativeness of the study's final sample.

1.2.1. Stimulus delivery

Most fMRI studies in patients with DOC are conducted in the auditory modality since patients with DOC frequently have difficulty keeping their eyes open, and VS patients by definition cannot fixate on a visual stimulus. However, auditory stimulation in the very noisy scanner environment presents its own set of challenges. If data are sampled in a standard, continuous fashion, the scanner noise may interfere with the auditory stimuli, or even drown them out completely if they are not carefully titrated. The presence of scanner noise may also complicate the interpretation of results, particularly negative ones. For example, if basic auditory processing were investigated through a simple stimulus vs. rest comparison, but the stimulus generated only weak or no activation on top of the primary auditory activation elicited by the scanner noise, the resulting map (computed by subtracting the rest activation from the stimulus activation) would appear as though the primary auditory cortex was not functioning. For this reason, many investigators opt to employ a sparse sampling procedure (Hall et al., 1999) in which images are acquired immediately following (not during) stimulus delivery, in the period where the haemodynamic response is near its peak. Stimulus-related activation is still captured, but not contaminated by the noisy gradient switching. This technique yields better estimates of stimulus-related auditory activation but results in smaller datasets (and consequently lower statistical power) and/or considerably longer scan times, which are undesirable especially in patient groups. EEG, on the other hand, can easily be recorded during virtually any type of stimulus delivery.

1.2.2. Artifact

Undoubtedly the most problematic source of artifact in patients with DOC is motion. In almost every published group study in DOC patients, subjects have been excluded from analyses due to excessive motion artifacts. Data loss due to motion in patients with DOC is estimated at more than 25% (Adrian Owen, personal communication, 2009). Large, involuntary movements of the head or body are common, and while cushioning and light restraint may be used, movements cannot be entirely prevented from occurring in the scanner. Very small movements can be corrected during preprocessing of fMRI data, but movements of even a few millimeters can make an entire dataset unusable. Another source of artifact in brain injured patients comes from devices implanted in the head, such as the aforementioned aneurysm clips, shunts, and neurostimulators. Even when these devices have been deemed non-ferromagnetic and completely MRI-safe, they are still foreign, usually metallic objects with different magnetic susceptibility than the surrounding brain tissue. They can create significant artifacts, loss of signal, and/or distortion of the image surrounding the object (Shellock, 2011).

EEG is also prone to certain artifacts, however these are generally correctable with little difficulty. Like fMRI, EEG is sensitive to motion, but unlike fMRI, only data recorded during the actual motion are affected. If motion is constant it becomes problematic, but occasional movements of any magnitude can easily be removed from the data without having to discard the entire dataset. EEG is also prone to EMG artifacts generated by muscles in the face and neck, for example by squinting of the eyes, grimacing, teeth-clenching, swallowing, or chewing motions. However, EMG has distinct characteristics particularly in the frequency domain and can be removed successfully, leaving the underlying EEG intact.

3.3 Analysis

Several issues arise when analyzing both structural and functional MRI data from patients with severe brain injuries. Most obvious is the issue of spatial normalization. Patients with DOC may have abnormal or deformed brain structures as a result of many factors including focal haemorrhages, hydrocephalus, shifting, craniotomy, swelling, dilated ventricles, and atrophy. This complicates co-registration of functional data to anatomical data, as well as transformation into stereotaxic space (e.g., Talairach space or MNI space) for group analyses or comparisons of individual patients to control subjects. The heterogeneity of injuries and their aetiologies also complicates any between-subjects comparisons. Even if normalization can be performed, it must be considered that, depending on the injury, an indeterminate amount of functional remapping may have taken place, so that functional areas may no longer correspond to the coordinates of the same functional areas in healthy controls or other patients. Given that most fMRI studies use a region-of-interest (ROI) approach to compare activations in patients to those observed in control subjects under the same conditions, the issues of normalization and functional remapping present a significant hurdle for the use of fMRI in DOC.

While EEG circumvents nearly all of the safety and data acquisition issues of fMRI, it is also prone to some of the same analysis problems as fMRI. While EEG does not require spatial normalization, functional remapping will alter the spatial distribution of signals. Temporal characteristics of EEG are also affected, often resulting in significantly delayed ERP latencies. These ERP latency shifts and unusual topographies can lead to problems in identification of ERP components. For example, the P3a and P3b components discussed in Section 2.1.1 can overlap temporally, and therefore the identification of these two components relies heavily on their topographical distributions. Since both the latencies and topographies of ERPs can be altered in severe brain injury, the identification of relevant components becomes problematic. However, a set of guidelines for the recording and analysis of ERPs in clinical populations has been advanced with the goal of eliminating experimenter bias (Duncan et al., 2009). Additionally, brain injuries are often associated with marked changes in oscillatory activity, particularly in the delta and theta ranges (see Schomer and Lopes da Silva, 2010), which may complicate the interpretation of data in the frequency and time domains when comparing patients to healthy controls.

3.3.1 Interpretation

It is imperative to remember that the BOLD signal on which fMRI is based is a measure of haemodynamic response, and not a direct measure of neural activity. Neurovascular coupling is the relationship between neural activity and the haemodynamic response reflected by the BOLD signal. It is dependent upon intact signalling between neurons and blood vessels, and on the various components of vascular reactivity. Any changes to metabolic or neurotransmitter signalling, vascular tone, cerebral blood volume, blood flow, blood oxygenation, or oxygen consumption can affect the BOLD signal (Iannetti and Wise, 2007). A growing body of evidence shows that many diseases and pathologies – including brain injuries – alter neurovascular coupling and change BOLD signal without necessarily affecting neuronal function (Füchtemeier et al., 2010; Gsell et al., 2000; Krainik et al., 2005; Lindauer et al., 2010; Sakatani et al., 2003, 2007). In the same vein, we must also consider that patients with severe brain injuries are usually on several medications, which can also influence neurovascular coupling (Bruhn et al., 2001; Luchtmann et al., 2010; Pattinson et al., 2007; Reinhard et al., 2010). We can attribute changes in BOLD signal to changes in neural activity if and only if signalling and vascular reactivity are not altered; and we can compare between groups (e.g., patients and controls) only if these properties are the same in both groups. Therefore, the utmost caution must be used when interpreting BOLD signal in brain-injured patients, and the potential confounds in the intermediate steps of neurovascular coupling must be considered.

Conversely, EEG is a direct measure of neural activity. Currents generated by local field potentials must pass through, and are attenuated by the skull and scalp before reaching sensors on the scalp surface but the signal recorded directly reflects the brain's electrical activity, and is not dependent upon the many components of neurovascular coupling. Therefore, the degree of inference required to interpret EEG-based measures is substantially reduced compared to fMRI. Naturally, the effects of medication must also be considered with EEG, however only drugs that act on the CNS are of major concern since neurovascular coupling is not a factor in EEG.

3.4 Prognostic value

Findings from fMRI studies of cognition and consciousness all have one thing in common. There is enormous variability in the type and amount of activation that patients show under the same conditions, even within the same diagnostic category. The question becomes whether there is some significance to this variability in terms of the patients' likely outcome. Clinically, this would be one of the most useful pieces of information that could be extracted from fMRI. Most studies state prognosis as one of the main goals of brain research in disorders of consciousness, however only two fMRI studies have systematically examined it. In 2008, Di et al. systematically reviewed 15 fMRI and PET studies that included a total of 48 VS patients. They classified the results from all patients according to whether they showed no activation; typical, low-level activation of primary sensory cortices; or higher-level activation of associative cortices that is 'atypical' for VS. They observed that atypical, higher-level associative cortex activation predicted recovery of consciousness in the cases they analyzed with 93% specificity and 69% sensitivity. Coleman et al. (2009) found an equally encouraging result when they examined the correspondence between level of auditory processing in their 22 VS and 19 MCS patients (study described above in Section 2.1.2). They classified the level of activation observed in each patient as 1: no response to sound, 2: low-level response to sound only, 3: mid-level response to speech stimuli, and 4: high-level response to semantic aspects of speech. This score was compared to each patient's score on the Coma Recovery Scale–Revised (Giacino et al., 2004) that was measured at the time of testing and 6 months later. The analysis revealed a strong correlation ($r = 0.81$) between the level of auditory activation and the CRS-R score 6 months post-testing—despite a non-significant correlation between auditory activation and CRS-R at time of testing. These two studies provide strong evidence that fMRI could offer valuable prognostic information, however the selection bias inherent in fMRI studies of DOC (see Section 3) limits the generalizability of such findings.

A considerable body of literature exists on the predictive value of evoked potentials and ERPs in coma. A full review is beyond the scope of this paper, but a meta-analysis found that the N100, the MMN, and the P300 are all significant predictors of outcome following severe brain injury (Daltrozzo et al., 2007). The interested reader is referred to recent reviews (Duncan et al., 2011; Folmer et al., 2011; Guérit et al., 2009; Vanhaudenhuyse et al., 2008). However, only a few studies have produced preliminary prognostic data for VS and MCS. Kotchoubey et al. (2005) found that the presence of an MMN was related to better outcome in VS patients, and Cavinato et al. (2009) observed a positive relationship between the P300 and outcome from VS.

4 Conclusion

Over the past decade or so, fMRI has lent new insight into disorders of consciousness, and together with EEG has revealed that a small proportion of patients diagnosed as vegetative or minimally conscious have a much greater conscious awareness than they are able to indicate through behaviour. fMRI has helped to highlight the inadequacies of current diagnostic tools, and set the stage for the further development of brain-based, behaviour-independent measures of cognition and consciousness. However, it is difficult to argue that fMRI is well suited for use in this population. The logistics of simply putting these patients in an MRI scanner are prohibitive, before even discussing issues of data quality and interpretation. Ultimately, the goal of using technology like fMRI in this context is to reliably detect those cases where the patient possesses conscious awareness that cannot be detected through behavioural measures, and to facilitate some form of communication. Identifying patients with signs of conscious awareness is critically important because it opens the door to existing and highly effective rehabilitation interventions for a group of people who historically have been judged as incapable of benefitting from such interventions. However, if the technology we have chosen to use can only be applied to a small subset of MRI-compatible and cooperative patients, we are not much closer to having a practical clinical tool. While researchers should always carefully consider which methodology is best suited to address their specific research questions, EEG is overall a more widely applicable, less expensive, more readily available, and more practical technique for application in patients with DOC, and research in the field is quickly evolving away from fMRI and back to EEG-based measures.

Acknowledgements

This article was written while AH was supported by a doctoral scholarship from the Canadian Institutes of Health Research, and JFC was supported by grants from the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation, and McMaster University.

This article is dedicated to the memory of Dr. Jane Gillett.

References

Allen, P.J., 2010. EEG instrumentation and safety. In: Mulert, C., Lemieux, L. (Eds.), EEG-fMRI: Physiological Basis, Technique, and Applications. Springer, Heidelberg, pp. 115–134.

American Congress of Rehabilitation Medicine, 1995. Recommendations for use of uniform nomenclature pertinent to patients with severe alterations in consciousness. Arch. Phys. Med. Rehabil. 76 (2), 205–209

Andrews, K., Murphy, L., Munday, R., Littlewood, C., 1996. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. BMJ 313, 13–16.

Bardin, J.C., Fins, J.J., Katz, D.I., Hersh, J., Heier, L.A., Tabelow, K., Dyke, J.P., et al., 2011. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. Brain 134, 769–782.

Bekinschtein, T.A., Dehaene, S., Rohaut, B., Tadel, F., Cohen, L., Naccache, L., 2009. Neural signature of the conscious processing of auditory regularities. Proc. Natl. Acad. Sci. U.S.A. 106 (5), 1672–1677.

Bekinschtein, T.A., Manes, F.F., Villarreal, M., Owen, A.M., Della-Maggiore, V., 2011. Functional imaging reveals movement preparatory activity in the vegetative state. Front. Hum. Neurosci. 5, 5, http://dx.doi.org/10.3389/fnhum.2011.00005.

Bekinschtein, T.A., Niklison, J., Sigman, L., Manes, F., Leiguarda, R.,Armony, J.L., Owen, A.M., et al., 2004. Emotion processing in the minimally conscious state. J. Neurol., Neurosurg. Psychiatry 75 (5), 788.

Benar, C., Aghakhani, Y., Wang, Y., Izenberg, A., Alasmi, A., Dubeau, F., Gotman, J., 2003. Quality of EEG in simultaneous EEG-fMRI for epilepsy. Clin. Neurophysiol. 114 (3), 569–580.

Birbaumer, N., Kübler, A., Ghanayim, N., 2000. The thought translation device (TTD) for completely paralyzed patients. Rehabilitation (Stuttg.) 8 (2), 190–193.

Birbaumer, N., Weber, C., Neuper, C., Buch, E., Haapen, K., Cohen, L., 2006. Physiological regulation of thinking: brain-computer interface (BCI) research. Prog. Brain Res. 159, 369–391.

Boly, M., Coleman, M.R., Davis, M.H., Hampshire, A., Bor, D., Moonen, G., Maquet, P., et al., 2007. When thoughts become action: an fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. Neuroimage 36 (3), 979–992.

Boly, M., Faymonville, M.-E., Peigneux, P., Lambermont, B., Damas, P., Del Fiore, G., Degueldre, C., et al., 2004. Auditory processing in severely brain injured patients. Arch. Neurol. 61, 233–238.

Boly, M., Faymonville, M.-E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., Lancellotti, P., et al., 2008. Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol. 7 (11), 1013–1020.

Boly, M., Garrido, M.I., Gosseries, O., Bruno, M.-a., Boveroux, P., Schnakers, C., Massimini, M., et al., 2011. Preserved feedforward but impaired top-down processes in the vegetative state. Science 332, 858–862.

Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D., Boveroux, P., et al., 2009. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. Hum. Brain Mapp. 30 (8), 2393–2400.

Bressman, J.O., Reidler, J.S., 2010. Willful modulation of brain activity in disorders of consciousness: legal and ethical ramifications. J. Law Med. Ethics 38 (3), 713–716.

Bruhn, H., Fransson, P., Frahm, J., 2001. Modulation of cerebral blood oxygenation by indomethacin: MRI at rest and functional brain activation. J. Magn. Reson. Imag. 13 (3), 325–334.

Bruno, M.-A., Vanhaudenhuyse, A., Thibaut, A., Moonen, G., Laureys, S., 2011. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J. Neurol. 258 (7), 1373–1384.

Cauda, F.,Micon,B.M., Sacco,K., Duca, S., D'Agata, F., Geminiani, G.,Canavero, S., 2009. Disrupted intrinsic functional connectivity in the vegetative state. J. Neurol., Neurosurg. Psychiatry 80 (4), 429–431.

Cavinato, M., Volpato, C., Silvoni, S., Sacchetto, M., Merico, A., Piccione, F., 2011. Event-related brain potential modulation in patients with severe brain damage. Clin. Neurophysiol. 122 (4), 719–724.

Cavinato, M., Freo, U., Ori, C., Zorzi, M., Tonin, P., Piccione, F., Merico, A., 2009. Postacute P300 predicts recovery of consciousness from traumatic vegetative state. Brain Inj. 23 (12), 973–980.

Chatelle, C., Chennu, S., Noirhomme, Q., Cruse, D., Owen, A.M., Laureys, S., 2012. Brain-computer interfacing in disorders of consciousness. Brain Inj. 26 (12), 1510–1522.

Chiappa, K.H. (Ed.), 1997. Evoked Potentials in Clinical Medicine. , third ed. Lippincott-Raven, Philadelphia.

Childs, N.L., Mercer, W.N., Childs, H.W., 1993. Accuracy of diagnosis of persistent vegetative state. Neurology 43 (8), 1465–1467.

Coleman, M.R., Davis, M.H., Rodd, J.M., Robson, T., Ali, A., Owen, A.M., Pickard, J.D., 2009. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. Brain 132, 2541–2552.

Coleman, M.R., Rodd, J.M., Davis, M.H., Johnsrude, I.S., Menon, D.K., Pickard, J.D., Owen, A.M., 2007. Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. Brain 130, 2494–2507.

Connolly, J.F., 2012. Communicating with the non-communicative: assessing the mental life of non-verbal individuals using neurophysiological techniques. In: jima, S., Otsu, Y., Connolly, J.F., Thierry, G. (Eds.), Future Trends in the Biology of Language. Keio University Press, Tokyo, pp. 153–172.

Connolly, J.F., D'Arcy, R.C.N., Newmann, R.L., Kemps, R., 2000. The application of cognitive event-related brain potentials (ERPs) in language-impaired individuals: review and case studies. Int. J. Psychophysiol. 38 (1), 55–70.

Connolly,J.F.,Mate-Kole,C.C.,Joyce,B.M., 1999. Global aphasia: aninnovative assessment approach. Arch. Phys. Med. Rehabil. 80 (10), 1309–1315.

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T.A., 2011. Bedside detection of awareness in the vegetative state: a cohort study. Lancet 378 (9809), 2088–2094.

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T.A., Fernández-Espejo, D., Pickard, J.D., Laureys, S., et al., 2013. Authors' reply. Lancet 381, 291–292.

Curran, E.A., Stokes, M.J., 2003. Learning to control brain activity: a review of the production and control of EEG components for driving brain-computer interface (BCI) systems. Brain Cogn. 51 (3), 326–336.

Daly, J.J., Wolpaw, J.R., 2008. Brain-computer interfaces in neurological rehabilitation. Lancet Neurol. 7 (11), 1032–1043.

Daltrozzo, J., Wioland, N., Mutschler, V., Kotchoubey, B., 2007. Predicting coma and other low responsive patients outcome using event-related brain potentials: a meta-analysis. Clin. Neurophysiol. 118 (3), 606–614.

Davis, M.H., Coleman, M.R., Absalom, A.R., Rodd, J.M., Johnsrude, I.S., Matta, B.F., Owen, A.M., et al., 2007. Dissociating speech perception and comprehension at reduced levels of awareness. Proc. Natl. Acad. Sci. U.S.A. 104 (41), 16032–16037.

Dehaene, S., Naccache, L., Le Clec'H., G., Koechlin, E., Mueller, M., Dehaene-Lambertz, G., Van de Moortele, P.F., et al., 1998. Imaging unconscious semantic priming. Nature 395 (6702), 597–600.

Di, H., Boly, M., Weng, X., Ledoux, D., Laureys, S., 2008. Neuroimaging activation studies in the vegetative state: predictors of recovery? Clin. Med. 8 (5), 502–507.

Donchin, E., Spencer, K.M., Wiejesinghe, R., 2000. The mental prosthesis: assessing the speed of a P300-based brain-computer interface. IEEE Trans. Rehabil. Eng. 8 (2), 174–179.

Duncan, C.C., Barry, R.J., Connolly, J.F., Fischer, C., Michie, P.T., Näätänen, R., Polich, J., et al., 2009. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clin. Neurophysiol. 120 (11), 1883–1908.

Duncan, C.C., Summers, A.C., Perla, E.J., Coburn, K.L., Mirsky, A.F., 2011. Evaluation of traumatic brain injury: brain potentials in diagnosis, function, and prognosis. Int. J. Psychophysiol. 82 (1), 24–40.

Eickhoff, S.B., Dafotakis, M., Grefkes, C., Stöcker, T., Shah, N.J., Schnitzler, a, Zilles, K., et al., 2008. fMRI reveals cognitive and emotional processing in a long-term comatose patient. Exp. Neurol. 214 (2), 240–246.

Evans, A.B., Boggs, J.G., 2012. Visual evoked potential. In: Benbadis, S.R. (Ed.), Clinical Utility of Evoked Potentials. , Retrieved from http://emedicine. medscape.com/article/1137451-overview#aw2aab6b3

Faugeras, F., Rohaut, B., Weiss, N., Bekinschtein, T.A., Galanaud, D., Puybasset, L., Bolgert, F., et al., 2011. Probing consciousness with event-related potentials in the vegetative state. Neurology 77 (3), 264–268.

Faugeras, F., Rohaut, B., Weiss, N., Bekinschtein, T.A., Galanaud, D., Puybasset, L., Bolgert, F., et al., 2012. Event related potentials elicited by violations of auditory regularities in patients with impaired consciousness. Neuropsychologia 50 (3), 403–418.

Fernández-Espejo, D., Junque, C., Cruse, D., Bernabeu, M., Roig-Rovira, T., Fábregas, N., Rivas, E., et al., 2010. Combination of diffusion tensor and functional magnetic resonance imaging during recovery from the vegetative state. BMC Neurol. 10, 77.

Fernández-Espejo, D., Junqué, C., Vendrell, P., Bernabeu, M., Roig, T., Bargalló, N., Mercader, J.M., 2008. Cerebral response to speech in vegetative and minimally conscious states after traumatic brain injury. Brain Inj. 22 (11), 882–890.

Fingelkurts, A., Fingelkurts, A., Bagnato, S., Boccagni, C., Galardi, G., 2012. EEG oscillatory states as neuro-phenomenology of consciousness as revealed from patients in vegetative and minimally conscious states. Consciousness Cogn. 21 (1), 149–169.

Fins, J.J., Shapiro, Z.E., 2007. Neuroimaging and neuroethics: clinical and policy considerations. Curr. Opin. Neurol. 20 (6), 650–654.

Fischer, C., Luauté, J., Morlet, D., 2010. Event-related potentials (MMN and novelty P3) in permanent vegetative or minimally conscious states. Clin. Neurophysiol. 121 (7), 1032–1042.

Fischer, C., Morlet, D., Giard, M.-H., 2000. Mismatch negativity and N100 in comatose patients. Audiol. Neurootol. 5, 192–197.

Folmer, R.L., Billings, C.J., Diedesch-Rouse, A.C., Gallun, F.J., Lew, H.L., 2011. Electrophysiological assessments of cognition and sensory processing in TBI: applications for diagnosis, prognosis and rehabilitation. Int. J. Psychophysiol. 82 (1), 4–15.

Formisano, R., Pistoia, F., Sarà, M., 2011. Disorders of consciousness: a taxonomy to be changed? Brain Inj. 25 (6), 638–639.

Füchtemeier, M., Leithner, C., Offenhauser, N., Foddis, M., Kohl-Bareis, M., Dirnagl, U., Lindauer, U., et al., 2010. Elevating intracranial pressure reverses the decrease in deoxygenated hemoglobin and abolishes the post-stimulus overshoot upon somatosensory activation in rats. Neuroimage 52 (2), 445–454.

Giacino, J.T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D.I., Kelly, J.P., et al., 2002. The minimally conscious state: definition and diagnostic criteria. Neurology 58 (3), 349–353.

Giacino, J.T., Kalmar, K., 2005. Diagnostic and prognostic guidelines for the vegetative and minimally conscious states. Neuropsychol. Rehabil. 15 (3–4), 166–174.

Giacino, J.T., Kalmar, K., Whyte, J., 2004. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility.Arch. Phys.Med.Rehabil. 85 (12), 2020–2029.

Giacino, J.T., Schnakers, C., Rodriguez-moreno, D., Kalmar, K., Schiff, N., Hirsch, J., 2009. Behavioral assessment in patients with disorders of consciousness: gold standard or fool's gold? Prog. Brain Res. 177, 33–48.

Goldfine, A., Bardin, J., Noirhomme, Q., Fins, J.J., Schiff, N.D., Victor, J.D., 2013. Reanalysis of Bedside detection of awareness in the vegetative state: a cohort study. Lancet 381, 289–292.

Goldfine, A.M., Victor, J.D., Conte, M.M., Bardin, J.C., Schiff, N.D., 2011. Determination of awareness in patients with severe brain injury using EEG power spectral analysis. Clin. Neurophysiol. 122 (11), 2157–2168.

Gosseries, O., Bruno, M.-A., Chatelle, C., Vanhaudenhuyse, A., Schnakers, C., Soddu, A., Laureys, S., 2011. Disorders of consciousness: what's in a name? NeuroRehabilitation 28 (1), 3–14.

Greenberg, D.L., 2007. Comment on detecting awareness in the vegetative state. Science 315 (5816), 1221.

Gsell, W., De Sadeleer, C., Marchalant, Y., MacKenzie, E.T., Schumann, P., Dauphin, F., 2000. The use of cerebral blood flow as an index of neuronal activity in functional neuroimaging: experimental and pathophysiological considerations. J. Chem. Neuroanat. 20 (3–4), 215–224.

Guérit, J.-M., Amantini, A., Amodio, P., Andersen, K.V., Butler, S., De Weerd, A., Facco, E., et al., 2009. Consensus on the use of neurophysiological tests in the intensive care unit (ICU): electroencephalogram (EEG), evoked potentials (EP), and electroneuromyography (ENMG). Clin. Neurophysiol. 39 (2), 71–83.

Hall, D.A., Haggard, M.P., Akeroyd, M.A., Palmer, A.R., Summerfield, A.Q., Elliott, M.R., Gurney, E.M., et al., 1999. Sparse temporal sampling in auditory fMRI. Hum. Brain Mapp. 7 (3), 213–223.

Hayashi, H., Kato, S., 1989. Total manifestations of amyotrophic lateral sclerosis. ALS in the totally locked-in state. J. Neurol. Sci. 93 (1), 19–35.

Hayashi, H., Kato, S., Kawada, A., 1991. Amyotrophic lateral sclerosis patients living beyond respiratory failure. J. Neurol. Sci. 105 (1), 73–78.

Hinterberger, T., Wilhelm, B., Mellinger, J., Kotchoubey, B., Birbaumer, N., 2005. A device for the detection of cognitive brain functions in completely paralyzed or unresponsive patients. IEEE Trans. Bio-med. Eng. 52 (2), 211–220.

Holeckova, I., Fischer, C., Morlet, D., Delpuech, C., Costes, N., Mauguière, F., 2008. Subject's own name as a novel in a MMN design: a combined ERP and PET study. Brain Res. 1189, 152–165.

Höller, Y., Bergmann, J., Kronbichler, M., Crone, J.S., Schmid, E.V., Golaszewski, S., Ladurner, G., 2011. Preserved oscillatory response but lack of mismatch negativity in patients with disorders of consciousness. Clin. Neurophysiol. 122 (9), 1744–1754.

Iannetti, G.D., Wise, R.G., 2007. BOLD functional MRI in disease and pharmacological studies: room for improvement? Magn. Reson. Imag. 25 (6), 978–988.

Jennett, B., Plum, F., 1972. Persistent vegetative state after brain damage.Asyndrome in search of a name. Lancet 1 (7753), 734–737.

Kalcher, J., Flotzinger, D., Neuper, C., Gölly, S., Pfurtscheller, G., 1996. Graz braincomputer interface II:towards communication between humans and computers based on online classification of three different EEG patterns. Med. Biol. Eng. Comput. 34 (5), 382–388.

Kanal, E., Shellock, F.G., 1992. Policies, guidelines, and recommendations for MR imaging safety and patient management. SMRI Safety Committee. J. Magn. Reson. Imag. 2 (2), 247–248.

Kotchoubey, B., 2005. Apallic syndrome is not apallic: is vegetative state vegetative? Neuropsychol. Rehabil. 15, 333–356.

Kotchoubey, B., Kaiser, J., Bostanov, V., Lutzenberger,W., Birbaumer, N., 2009. Recognition of affective prosody in brain-damaged patients and healthy controls: a neurophysiological study using EEG and whole-headMEG. Cognit.,Affect. Behav. Neurosci. 9 (2), 153–167.

Kotchoubey, B., Lang, S., Herb, E., Maurer, P., Schmalor, D., Bostanov, V., Birbaumer, N., 2003. Stimulus complexity enhances auditory discrimination in patients with extremely severe brain injuries. Neurosci. Lett. 352, 129–132.

Kotchoubey, B., Lang, S., Mezger, G., Schmalohr, D., Schneck, M., Semmler, a, Bostanov, V., et al., 2005. Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. Clin. Neurophysiol. 116 (10), 2441–2453.

Kotchoubey, B., Merz, S., Lang, S., Markl, A., Müller, F., Yu, T., Schwarzbauer, C., 2013. Globalfunctional connectivity reveals highly significant differences between the vegetative and the minimally conscious state. J. Neurol. 260 (4), 975–983.

Krainik, A., Hund-Georgiadis, M., Zysset, S., Von Cramon, D.Y., 2005. Regional impairment of cerebrovascular reactivity and BOLD signal in adults after stroke. Stroke 36 (6), 1146–1152.

Kübler, A., 2009. Brain-computer interfaces for communication in paralysed patients and implications for disorders of consciousness. In: Laureys, S., Tononi, G. (Eds.), The Neurology of Consciousness. Elsevier, London, pp. 217–233.

Kübler, A., Kotchoubey, B., 2007. Brain-computer interfaces in the continuum of consciousness. Curr. Opin. Neurol. 20 (6), 643–649.

Kutas, M., Federmeier, K.D., 2011. Thirty years and counting: finding meaning in the N400 component of the event-related brain potential (ERP). Ann. Rev. Psychol. 62, 621–647.

Laureys, S., Celesia, G.G., Cohadon, F., Lavrijsen, J., León-Carrión, J., Sannita, W.G., Sazbon, L., et al., 2010. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med. 8 (1), 68.

Laureys, S., Faymonville, M.E., Degueldre, C., Fiore, G.D., Damas, P., Lambermont, B., Janssens, N., et al., 2000. Auditory processing in the vegetative state. Brain 123, 1589–1601.

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A., Franck, G., et al., 1999. Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. Neuroimage 9 (4), 377–382.

Laureys, S., Perrin, F., Faymonville, M.-E., Schnakers, C., Boly, M., Bartsch, V., Majerus, S., et al., 2004. Cerebral processing in the minimally conscious state. Neurology 63 (5), 916–918.

Laureys, Steven, Schiff, N.D., 2012. Coma and consciousness: paradigms (re)framed by neuroimaging. Neuroimage 61 (2), 478–491.

Lehembre,R.,Bruno,M.-A.,Vanhaudenhuyse,A.,Chatelle,C.,Cologan,V., LeClercq,Y., Soddu,A., et al., 2012. Resting-state EEG study of comatose patients: a connectivity and frequency analysis to find differences between vegetative and minimally conscious states. Funct. Neurol. 27 (1), 41–47.

León-Carrión, J., Leon-Dominguez, U., Pollonini, L., Wu, M.-H., Frye, R.E., DominguezMorales, M.R., Zouridakis, G., 2012. Synchronization between the anterior and posterior cortex determines consciousness level in patients with traumatic brain injury (TBI). Brain Res. 1476, 22–30.

Lindauer, U., Dirnagl, U., Füchtemeier, M., Böttiger, C., Offenhauser, N., Leithner, C., Royl, G., 2010. Pathophysiological interference with neurovascular coupling – when imaging based on hemoglobin might go blind. Front. Neuroenerget. 2, 25.

Logothetis, N.K., 2008. What we can do and what we cannot do with fMRI. Nature 453 (7197), 869–878.

Luchtmann, M., Jachau, K., Tempelmann, C., Bernarding, J., 2010. Alcohol induced region-dependent alterations of hemodynamic response: implications for the statistical interpretation of pharmacological fMRI studies. Exp. Brain Res. 204 (1), 1–10.

Lulé, D., Noirhomme, Q., Kleih, S., Chatelle, C., Halder, S., Demertzi, A., et al., 2013. Probing command following in patients with disorders of consciousness using a brain-computer interface. Clin. Neurophysiol. 124, 101–106.

Machado, C., Korein, J., Aubert, E., 2007. Recognizing a mother's voice in the persistent vegetative state. Clin. EEG Neurosci. 38 (3), 124–126.

McFarland, D.J., McCane, L.M., David, S.V., Wolpaw, J.R., 1997. Spatial filter selection for EEG-based communication. Electroencephalogr. Clin. Neurophysiol. 103 (3), 386–394.

McFarland, D.J., Miner, L.A., Vaughan, T.M., Wolpaw, J.R., 2000. Mu and beta rhythm topographies during motor imagery and actual movements. Brain Topogr. 12 (3), 177–186.

Medical Consusltants on the Diagnosis of Death, 1981. Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. J. Am. Med. Assoc. 246 (19), 2184–2186.

Monti, M.M., Coleman, M.R., Owen, A.M., 2009. Executive functions in the absence of behavior: functional imaging of the minimally conscious state. Prog. Brain Res. 177, 249–260.

Monti, M.M., Vanhaudenhuyse, A., Coleman, M.R., Boly, M., Pickard, J.D., Tshibanda, J.-F., Owen, A.M., et al., 2010. Willful modulation of brain activity in disorders of consciousness. N. Engl. J. Med. 362 (7), 579–589.

Moritz, C.H., Rowley, H.A., Haughton, V.M., Swartz, K.R., Jones, J., Badie, B., 2001. Functional MR imaging assessment of a non-responsive brain injured patient. Magn. Reson. Imag. 19 (8), 1129–1132.

Müller-Putz, G.R., Scherer, R., Pfurtscheller, G., Rupp, R., 2005. EEG-based neuroprosthesis control: a step towards clinical practice. Neurosci. Lett. 382 (1–2), 169–174.

Näätänen, R., Paavilainen, P., Rinne, T., Alho, K., 2007. The mismatch negativity (MMN) in basic research of central auditory processing: a review. Clin. Neurophysiol. 118 (12), 2544–2590.

Nachev, P., Husain, M., 2007. Comment on detecting awareness in the vegetative state. Science 315 (5816), 1221.

Naci, L., Monti, M.M., Cruse, D., Kübler, A., Sorger, B., Goebel, R., Kotchoubey, B., et al., 2012. Brain-computer interfaces for communication with nonresponsive patients. Ann. Neurol. 72 (3), 312–323.

Neuper, C., Müller, G.R., Kübler, A., Birbaumer, N., Pfurtscheller, G., 2003. Clinical application of an EEG-based brain-computer interface: a case study in a patient with severe motor impairment. Clin. Neurophysiol. 114 (3), 399–409.

Neuper, C., Müller-Putz, G.R., Scherer, R., Pfurtscheller, G., 2006a. Motor imagery and EEG-based control of spelling devices and neuroprostheses. Prog. Brain Res. 159, 393–409.

Neuper, C., Pfurtscheller, G., 1999. Motor imagery and ERD. In: Pfurtscheller, G., Lopes da Silva, F.H. (Eds.), Handbook of Electroencephalography and Clinical Neurophysiology. Elsevier, Amsterdam, pp. 203–325.

Neuper, C., Wörtz, M., Pfurtscheller, G., 2006b. ERS/D patterns reflecting sensorimotor activation and deactivation. Prog. Brain Res. 159, 211–222.

Nicolas-Alonso, L.F., Gomez-Gil,J., 2012.Braincomputer interfaces, a review. Sensors 12 (2), 1211–1279.

Ovadia-Caro, S., Nir, Y., Soddu, A., Ramot, M., Hesselmann, G., Vanhaudenhuyse, A., Dinstein, I., et al., 2012. Reduction in inter-hemispheric connectivity in disorders of consciousness. PloS One 7 (5), e37238.

Owen, A.M., Coleman, M.R., Boly, M., Davis, M.H., Laureys, S., Pickard, J.D., 2006. Detecting awareness in the vegetative state. Science 313, 1402.

Owen, A.M., Coleman, M.R., Boly, M., Davis, M.H., Laureys, S., Pickard, J.D., 2007. Using functional magnetic resonance imaging to detect covert awareness in the vegetative state. Arch. Neurol. 64 (8), 1098–1102.

Owen, A.M., Coleman, M.R., Menon, D.K., Johnsrude, I.S., Rodd, J.M., Davis, M.H., Taylor, K., et al., 2005. Residual auditory function in persistent vegetative state: a combined PET and fMRI study. Neuropsychol. Rehabil. 15 (3/4), 290–306.

Pattinson, K.T.S., Rogers, R., Mayhew, S.D., Tracey, I., Wise, R.G., 2007. Pharmacological FMRI: measuring opioid effects on the BOLD response to hypercapnia. J. Cerebr. Blood Flow Metab. 27 (2), 414–423.

Penny,W.D., Roberts, S.J., Curran, E.A., Stokes, M.J., 2000. EEG-based communication: a pattern recognition approach. IEEE Trans. Rehabil. Eng. 8, 214–215.

Perrin, F., Garcia-Larrea, L., Maugiere, F., Bastuji, H., Mauguière, F., 1999. A differential brain response to the subject's own name persists during sleep. Clin. Neurophysiol. 110 (12), 2153–2164.

Perrin, F., Schnakers, C., Schabus, M., Degueldre, C., Goldman, S., Brédart, S., Faymonville, M.-E., et al., 2006. Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. Arch. Neurol. 63 (4), 562–569.

Pfurtscheller, G., Flotzinger, D., Kalcher, J., 1993. Brain-computer interface—a new communication device for handicapped persons. J. Microcomput. Appl. 16, 293–299.

Pfurtscheller, G., Neuper, C., 1997. Motor imagery activates primary sensorimotor area in humans. Neurosci. Lett. 239 (2–3), 65–68.

Pfurtscheller, G., Neuper, C., Flotzinger, D., Pregenzer, M., 1997. EEG-based discrimination between imagination of right and left hand movement. Electroencephalogr. Clin. Neurophysiol. 103 (6), 642–651.

Pfurtscheller, G., Neuper, C., Guger, C., Harkam, W., Ramoser, H., Schlögl, A., Obermaier, B., Pregenzer, M., 2000. Current trends in Graz brain-computer interface (BCI) research. IEEE Trans. Rehabil. Eng. 8 (2), 216–219.

Polich, J., 2012. Neuropsychology of P300. In: Luck, S.J., Kappenman, E.S. (Eds.), The Oxford Handbook of Event-related Potential Components. Oxford University Press, New York, pp. 159–188.

Portas, C.M., Krakow, K., Allen, P., Josephs, O., Armony, J.L., Frith, C.D., 2000. Auditory processing across the sleep-wake cycle: simultaneous EEG and fMRI monitoring in humans. Neuron 28 (3), 991–999.

Posner, J.B., Saper, C.B., Schiff, N.D., Plum, F., 2007. Plum and Posner's Diagnosis of Stupor and Coma, Fourth ed. Oxford University Press.

Qin, P., Di, H., Liu, Y., Yu, S., Gong, Q., Duncan, N., Weng, X., et al., 2010. Anterior cingulate activity and the self in disorders of consciousness. Hum. Brain Mapp. 31 (12), 1993–2002.

Qin, P., Di, H., Yan, X., Yu, S., Yu, D., Laureys, S., Weng, X., 2008. Mismatch negativity to the patient's own name in chronic disorders of consciousness. Neurosci. Lett. 448 (1), 24–28.

Raichle, M.E., MacLeod, a.M., Snyder, a.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U.S.A. 98 (2), 676–682.

Reinhard, M., Rosengarten, B., Kirchhoff, L., Hetzel, A., Rauer, S., 2010. Natalizumab and regulation of cerebral blood flow: results from an observational study. Eur. Neurol. 64 (2), 124–128.

Rodriguez Moreno, D., Schiff, N.D., Giacino, J., Kalmar, K., Hirsch, J., 2010. A network approach to assessing cognition in disorders of consciousness. Neurology 75 (21), 1871–1878.

Rousseau, M.C., Confort-Gouny, S., Catala, a, Graperon, J., Blaya, J., Soulier, E., Viout, P., et al., 2008. A MRS-MRI-fMRI exploration of the brain. Impact of long-lasting persistent vegetative state. Brain Inj. 22 (2), 123–134.

Royal College of Physicians Working Group, 1996. The permanent vegetative state. J. R. Coll. Physic. Lond. 30 (2), 119–121.

Royal College of Physicians Working Group, 2003. The vegetative state: guidance on diagnosis and management. Clin. Med. 3 (3), 249–254.

Sakatani, K., Murata, Y., Fukaya, C., Yamamoto, T., Katayama, Y., 2003. BOLD functional MRI may overlook activation areas in the damaged brain. Acta Neurochirurg. 87 (Supplement), 59–62.

Sakatani, Kaoru, Murata, Y., Fujiwara, N., Hoshino, T., Nakamura, S., Kano, T., Katayama, Y., 2007. Comparison of blood-oxygen-level-dependent functional magnetic resonance imaging and near-infrared spectroscopy recording during functional brain activation in patients with stroke and brain tumors. J. Biomed. Opt. 12 (6), 062110.

Schabus, M., Pelikan, C., Chwala-Schlegel, N., Weilhart, K., Roehm, D., Donis, J., Michitsch, G., et al., 2011. Oscillatory brain activity in vegetative and minimally conscious state during a sentence comprehension task. Funct. Neurol. 26 (1), 31–36.

Scherer, R., Müller, G.R., Neuper, C., Graiman, B., Pfurtscheller, G., 2004. An asynchronously controlled EEG-based virtual keyboard:improvement ofthe spelling rate. IEEE Trans. Biomed. Eng. 51 (6), 979–984.

Schiff, N.D., Rodriguez-Moreno, D.,Kamal, a,Kim,K.H.S., Giacino, J.T., Plum, F., Hirsch, J., 2005. fMRI reveals large-scale network activation in minimally conscious patients. Neurology 64 (3), 514–523.

Schiff, N.D., Ribary, U., Moreno, D.R., Beattie, B., Kronberg, E., Blasberg, R., Giacino, J., et al., 2002. Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. Brain 125, 1034–1210.

Schnakers, C., Chatelle, C., Demertzi, a, Majerus, S., Laureys, S., 2012. What about pain in disorders of consciousness? AAPS J. 14 (3), 437–444.

Schnakers, C., Chatelle, C., Majerus, S., Gosseries, O., De Val, M., Laureys, S., 2010. Assessment and detection of pani in noncommunicative severely brain-injured patients. Exp. Rev. Neurother. 10 (11), 1725–1731.

Schnakers, C., Perrin, F., Schabus, M., Hustinx, R., Majerus, S., Moonen, G., Boly, M., et al., 2009a. Detecting consciousness in a total locked-in syndrome: an active event-related paradigm. Neurocase 15 (4), 271–277.

Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., Boly, M., et al., 2008. Voluntary brain processing in disorders of consciousness. Neurology 71 (20), 1614–1620.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J.T., Ventura, M., Boly, M., Majerus, S., Moonen, G., et al., 2009b. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol. 9, 35.

Schnakers, C., Zasler, N.D., 2007. Pain assessment and management in disorders of consciousness. Curr. Opin. Neurol. 20 (6), 620–626.

Schoenle, P.W., Witzke, W., 2004. How vegetative is the vegetative state? Preserved semantic processing in VS patients—evidence from N 400 event-related potentials. NeuroRehabilitation 19 (4), 329–334.

Schomer, D.L., Lopes da Silva, F. (Eds.), 2010. Niedermeyer's Electroencephalography: Basic Principles, Clinical Applications, and Related Fields. , sixth ed. Lippincott, Williams & Wilkins, Philadelphia.

Seel, R.T., Sherer, M., Whyte, J., Katz, D.I., Giacino, J.T., Rosenbaum, A.M., Hammond, F.M., et al., 2010. Assessment scales for disorders of consciousness: evidencebased recommendations for clinical practice and research. Arch. Phys. Med. Rehabil. 91 (12), 1795–1813.

Shellock, F., 2011. Saf. Inform. www.mrisafety.com (Accessed July 19, 2011).

Soddu, A., Vanhaudenhuyse, A., Demertzi, A., Marie-Aurélie, B., Tshibanda, J.-F., Di, H., Mélanie, B., et al., 2011. Resting state activity in patients with disorders of consciousness. Funct. Neurol. 36 (1), 37–43.

Staffen, W., Kronbichler, M., Aichorn, M., Mair, A.G.L., 2006. Selective brain activity in response to one's own name in the persistent vegetative state. J. Neurol., Neurosurg. Psychiatry 77 (12), 1383–1384.

Stins, J.F., 2009. Establishing consciousness in non-communicative patients: a modern-day version of the Turing test. Consciousness Cogn. 18 (1), 187–192.

Stins, J.F., Laureys, S., 2009. Thought translation, tennis and Turing tests in the vegetative state. Phenomenol. Cogn. Sci. 8 (3), 361–370.

The Multi-Society Task Force on PVS, 1994. Medical aspects of the persistent vegetative state (1). N. Engl. J. Med. 330 (21), 1499–1508.

Vanhaudenhuyse, A., Laureys, S., Perrin, F., 2008. Cognitive event-related potentials in comatose and post-comatose states. Neurocrit. Care 8 (2), 262–270.

Vanhaudenhuyse, A., Noirhomme, Q., Tshibanda, J.-F., Bruno, M.-A., Boveroux, P., Schnakers, C., Soddu, A., et al., 2010. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain 133, 161–171.

Witzke, W., Schönle, P.W., 1996. Ereigniskorrelierte Potentiale als diagnostisches Mittel in der neurologischen Frührehabilitation. Neurologische Rehabilitation 2, 68–80.

Wilkinson, D.J., Kahane, G., Horne, M., Savulescu, J., 2009. Functional neuroimaging and withdrawal of life-sustaining treatment from vegetative patients. J. Med. Ethics 35 (8), 508–511.

Wolpaw, J.R., Birbaumer, N., McFarland, D.J., Pfurtscheller, G., Vaughan, T.M., 2002. Brain-computer interfaces for communication and control. Clin. Neurophysiol. 113 (6), 767–791.

Wolpaw, J.R., McFarland, D.J., Neat, G.W., Forneris, C.A., 1991. An EEG-based braincomputer interface for cursor control. Electroencephalogr. Clin. Neurophysiol. 78, 252–259.

Zhu, J., Wu, X., Gao, L., Mao, Y., Zhong, P., Tang, W., Zhou, L., 2009. Cortical activity after emotional visual stimulation in minimally conscious state patients. J. Neurotrauma 26 (5), 677–688.

Table 1
Diagnostic features of brain death, disorders of consciousness, and locked-in syndrome
Adapted from Giacino et al. (2009)

Diagnosis	Eye opening	Brainstem reflexes	Autonomic function	Behaviour	Communication	Cognition	Awareness
Brain Death	Absent	Absent	Absent	None	None	None	No
Coma	Absent	Impaired	Impaired	None	None	Low-level	No
Vegetative state	Spontaneous or stimulus-induced	Preserved	Preserved	Non-purposeful	None	Low-level	No
Minimally conscious state	Present	Preserved	Preserved	Fluctuating but reproducible purposeful	Unreliable but intentional	Understand commands, environmentally contingent emotion	Partial
Locked-in syndrome	Present	Preserved	Preserved	Vertical eye gaze	Vertical eye gaze	Normal	Yes