Disorders of Consciousness

ADRIAN M. OWEN

MRC Cognition and Brain Sciences Unit, Cambridge, United Kingdom

The vegetative state and other so-called disorders of consciousness present some of the most significant practical and ethical challenges in modern medicine. It is extremely difficult to assess residual cognitive function in these patients because their movements may be minimal or inconsistent, or because no cognitive output may be possible. In recent years, behavioral and neuroimaging techniques developed within the cognitive neurosciences have provided a number of new approaches for investigating these disorders, leading to significant advances in current understanding. In several cases, residual cognitive function and even conscious awareness have been demonstrated in patients who are assumed to be vegetative yet retain cognitive abilities that have evaded detection using standard clinical methods. In this article, I review these data, focusing primarily on the vegetative and minimally conscious states.

Key words: **vegetative state; fMRI; minimally conscious state; locked-in syndrome; coma; imaging; consciousness; awareness**

Introduction

In recent years, improvements in intensive care have increased the number of patients who survive severe acute brain injuries. Although some of these patients go on to make a good recovery, many do not and remain in one of several states now known collectively as "disorders of consciousness" (Bernat 2006). These include the vegetative state, the minimally conscious state, the minimally conscious state, and coma. The assessment of such patients is extremely difficult and depends frequently on subjective interpretations of the observed spontaneous and volitional behavior. This difficulty is reflected in frequent misdiagnoses between these conditions and confusion about precise definitions (Andrews et al. 1996; Childs et al. 1993). For those patients who retain peripheral motor function, rigorous behavioral assessment supported by structural imaging and electrophysiology is usually sufficient to establish a patient's level of wakefulness and awareness. However, it is becoming increasingly apparent that, in some patients, damage to the peripheral motor system may prevent overt responses to command, even though the cognitive ability to perceive and understand such commands may remain intact.

Recent advances in functional neuroimaging suggest a novel solution to this problem; so-called activation studies can be used to assess cognitive functions in altered states of consciousness without the need for any overt response on the part of the patient. For example, this approach has been used to identify residual brain functions in patients who behaviorally meet all of the standard clinical criteria for the vegetative state yet retain cognitive abilities that have evaded detection using standard clinical methods. Similarly, in some patients diagnosed as minimally conscious, functional neuroimaging has been used to demonstrate residual cognitive capabilities even when there is no clear and consistent external behavioral evidence to support this conclusion. Such studies have led several leading groups in this area to suggest that the future integration of emerging functional neuroimaging techniques with existing clinical and behavioral methods of assessment will be essential for improving our ability to reduce diagnostic errors between these related conditions (Laureys et al. 2006; Schiff et al. 2006). Moreover, such efforts may provide important new prognostic indicators, helping to disentangle differences in outcome on the basis of a greater understanding of the underlying mechanisms responsible and thus improve therapeutic choices in these challenging populations (Laureys et al. 2006). Finally, the use of functional neuroimaging in this context will undoubtedly contribute to our understanding of concepts such as awareness, arousal, volition, and even consciousness itself.

Disorders of Consciousness: Descriptions and Definitions

Although the term "disorders of consciousness" provides a useful short hand for referring to a group

---

Address for correspondence: Adrian M. Owen Ph.D., MRC Cognition and Brain Sciences Unit, Cambridge, CB2 7EF, UK. Voice: +44 1223 355294 ext 511; fax: +44 1223 359062.
adrian.owen@mrc-cbu.cam.ac.uk

Ann. N.Y. Acad. Sci. 1124: 225–238 (2008). © 2008 New York Academy of Sciences.
doi: 10.1196/annals.1440.013

of related disorders, it is also problematic because it implies that they are all linked by disruption to some common, underlying, clearly defined system known as consciousness. Unfortunately, there is, as yet, no universally agreed definition of *consciousness*. Widely accepted definitions often refer to *awareness* of the self and the environment (Plum & Posner 1966); and, accordingly, patients with disorders of consciousness (e.g., the vegetative state) are often described as lacking awareness of self or environment. Such descriptions inevitably provoke further questions, including what constitutes *awareness* and what level of awareness is sufficient for a patient to be described as *consciously aware*. On the other hand, Koch (2007) recently stated that the distinction between consciousness and awareness is a largely one of social convention, there being no clear distinction between them. It is far beyond the remit of this article to provide even a brief summary of the consciousness literature. Indeed, the central problem in the investigation of disorders of consciousness is not in understanding the nature of consciousness itself, but rather in defining where the transition point lies between what most people would agree is an unconscious or unaware state and what most would agree is a conscious or aware state. This transition point is not always easily recognized in people with severe brain damage, particularly in patients whose neurological course (improvement or deterioration) is evolving slowly. Accordingly, for the purposes of this review, “consciousness,” “awareness,” and the combined term “conscious awareness,” which is often heard in common parlance, will be used interchangeably.

The Vegetative State

The clinical features of the vegetative state were formally introduced into the literature by Jennett and Plum (1972) and later clarified and refined by the Multi-Society Task Force on Persistent Vegetative State (1994a, b) and the Royal College of Physicians (1996). Etiology is variable, although the condition may arise as a result of road traffic accident, stroke, hypoxia (oxygen deficiency), encephalitis, or viral infection. After stroke or hypoxia, the damage is usually cell death in the cortex, almost always associated with thalamic damage, although occasionally the cortex is relatively spared (Jennett 2002). After traumatic brain injury, the dominant lesion is diffuse damage to the subcortical white matter, often referred to as diffuse axonal injury (DAI), although the degree and extent of this damage is highly variable. A diagnosis of vegetative state is only made after repeated examinations that have yielded *no evidence whatsoever* of sustained, reproducible, purposeful, or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli. There must also be no evidence of language comprehension or expression, although there is generally sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival with medical care. Unlike patients in coma, the vegetative state is characterized by cycles of eye closure and eye opening giving the appearance of a sleep/wake cycle. It is this waking pattern, combined with the wide range of reflexive responses that are often observed in vegetative patients, that can result in this activity being misinterpreted as evidence of volitional behavior and even the return of conscious awareness. However, although these patients will often appear to be awake and will make nonpurposeful movements, rigorous observation reveals no consistent activities that are voluntary or learned and no responses to command or mimicry (Jennett 2002). In short, these patients show no signs of being aware of themselves or of their environment (Schnakers et al. 2006; Tresch et al. 1991).

The term *persistent* vegetative state has been used arbitrarily to denote that the vegetative state has persisted for more than one month after brain injury. However, because it is often confused with the term *permanent* vegetative state its use in the first few months is now discouraged in favor of simply the vegetative state. The Multi-Society Task Force (1994a, b) on the vegetative state recommended that six months following a nontraumatic brain injury and twelve months following a traumatic brain injury the condition should be regarded as a permanent vegetative state. Although the chances of recovery at this stage are diminishingly small, some exceptional patients may begin to show signs of limited recovery even after very long delays.

Minimally Conscious State

The minimally conscious state is a relatively new diagnostic category (Giacino et al. 2002) and describes patients who show limited but clear evidence of awareness. Some vegetative patients pass through the minimally conscious state on the road to further recovery, while others remain minimally conscious indefinitely. Like vegetative patients, cycles of eye closure and eye opening give the appearance of a sleep/wake cycle and reflexive and nonpurposeful movements are commonly observed. However, unlike vegetative patients, at least one of the following behaviors must also be observed on a reproducible or sustained basis: simple command following (e.g., “move your right hand”), verbal or gestural yes/no responses, intelligible speech, nonreflexive purposeful movements. A patient is considered to have progressed beyond the minimally conscious state when there is consistent functional interactive communication and/or the functional use of more than one object. Because the minimally conscious state is characterized by *inconsistent* responses, such patients can be difficult to distinguish from vegetative patients, particularly in the initial stages. Given the strong relationship between the vegetative and minimally conscious states, similar pathophysiological changes are likely to underlie the two conditions (i.e., multifocal or diffuse cortical and/or thalamic damage or very severe DAI). However, the clear behavioral distinction between the two conditions suggests a difference in the extent of cortical dysfunction such that minimally conscious patients are likely to have resumed some associative cortical activity.

Locked-in Syndrome

Another group of patients who may be mistaken for vegetative are those in what has been termed the "locked-in syndrome" (Plum & Posner 1966). Patients who are locked in are unable to speak or move, although limited eye movements and blinks are usually possible. This condition arises when a lesion of the pons disrupts the descending motor pathways, leaving sensation and consciousness entirely intact, while disrupting almost all forms of motoric behavior.

Coma

In contrast to the vegetative state, coma is characterized by a complete absence of arousal (Laureys et al. 2004). Thus, comatose patients lie, completely unresponsive, with their eyes closed. Unlike the vegetative state, there are no periods of wakefulness. Stimulation does not lead to arousal, and it is widely assumed that such patients have no awareness of themselves or their surroundings. Reflexes frequently remain, but unlike in the vegetative and minimally conscious states, sleep/wake cycles are absent. Of those that survive, most comatose patients begin to recover within 2–4 weeks, although many will not recover beyond the vegetative or minimally conscious state. A comatose state may arise as a result of diffuse cortical or white-matter damage following neuronal or axonal injury, or from a focal brain-stem lesion affecting the pontomesencephalic tegmentum or paramedian thalami, bilaterally.

Functional Neuroimaging in Disorders of Consciousness

Until recently, the majority of neuroimaging studies in disorders of consciousness used either flurodeoxyglucose (FDG) positron emission tomography (PET), or single photon emission computed tomography (SPECT) to measure resting cerebral blood flow and glucose metabolism (e.g., Beuthien-Baumann et al. 2003; De Volder et al. 1990; Laureys et al. 1999a, b; Levy et al. 1987; Momose et al. 1989; Rudolf et al. 1999; Schiff et al. 2002; Tommasino et al. 1995). Typically, widespread reductions in metabolic activity of up to 50% have been reported in the vegetative state, although in a few cases normal cerebral metabolism (Schiff et al. 2002) and blood flow (Agardh et al. 1983) have been found in such patients. In some cases isolated islands of metabolism have been identified in circumscribed regions of cortex, suggesting the potential for cognitive processing in a subset of patients (Schiff et al. 2002). PET studies have shown significantly higher metabolic levels in the brains of patients diagnosed as locked-in syndrome compared to patients diagnosed as vegetative state (Levy et al. 1987). Indeed, several reports have suggested that no grey matter areas show metabolic signs of reduced function in acute or chronic locked-in patients compared to age-matched healthy controls (e.g., Laureys et al. 2004). In one recent and remarkable case of late recovery from minimally conscious state, longitudinal PET examinations revealed increases in resting metabolism coincident with marked clinical improvements in motor function (Voss et al. 2006). While metabolic studies are useful in this regard, they can only identify functionality at the most general level; that is, mapping cortical and subcortical regions that are *potentially* recruitable, rather than relating neural activity within such regions to specific cognitive processes. On the other hand, methods such as $H_2{}^{15}O$ PET and functional magnetic resonance imaging (fMRI) can be used to link distinct and specific physiological responses (changes in regional cerebral blood flow or changes in regional cerebral hemodynamics) to specific cognitive processes in the absence of any overt response (e.g., a motor action or a verbal response) on the part of the patient.

Early activation studies in patients with disorders of consciousness used $H_2{}^{15}O$ PET, in part because the technique was more widely available and in part because the multiple logistic difficulties of scanning critically ill patients in the strong magnetic field that is integral to fMRI studies had yet to be resolved. In the first of such studies, $H_2{}^{15}O$ PET was used to measure regional cerebral blood flow in a posttraumatic vegetative patient during an auditorily presented story told by his mother (de Jong et al. 1997). Compared to nonword sounds, activation was observed in the anterior cingulate and temporal cortices, possibly reflecting emotional processing of the contents, or tone, of the mother's speech. In another patient diagnosed as vegetative, Menon et al. (1998) used PET to study covert visual processing in response to familiar faces. When the patient was presented with pictures of the faces of family and close friends, robust activity was observed in the right fusiform gyrus, the so-called human face area. Importantly, both of these studies involved single, well-documented cases; in cohort PET studies of patients unequivocally meeting the clinical diagnosis of the vegetative state, normal brain activity in response to external stimulation has generally been the exception rather than the rule. For example, in one PET study of 15 vegetative patients, high-intensity noxious electrical stimulation activated midbrain, contralateral thalamus, and primary somatosensory cortex in every patient (Laureys et al. 2002). However, unlike control subjects, the patients did not activate secondary somatosensory, insular, posterior parietal, or anterior cingulate cortices.

$H_2{}^{15}O$ PET studies are limited by issues of radiation burden which may preclude essential longitudinal or follow-up studies in many patients or even a comprehensive examination of multiple cognitive processes within any one session. The power of PET studies to detect statistically significant responses is also low, and group studies are often needed to satisfy standard statistical criteria. Given the heterogeneous nature of disorders of consciousness and the clinical need to define individuals in terms of their individual diagnosis, residual functions, and potential for recovery, such limitations are of paramount importance in the evaluation of these patients.

A significant development in this rapidly evolving field has been the relative shift of emphasis from PET activation studies using $H_2{}^{15}O$ methodology, to fMRI. Not only is MRI more widely available than PET, it offers increased statistical power, improved spatial and temporal resolution, and has no associated radiation burden. Recently, Di and colleagues (2007) used event-related fMRI to measure brain activation in seven vegetative patients and four minimally conscious patients in response to the patient's own name spoken by a familiar voice. Two of the vegetative patients exhibited no significant activity at all, three patients exhibited activation in primary auditory areas, and two vegetative patients and four minimally patients exhibited activity in higher-order associative temporal-lobe areas. Although this result is encouraging (particularly because the two vegetative patients who showed the most widespread activation subsequently improved to the minimally conscious state in the following months), it lacks cognitive specificity; that is to say, responses to the patient's own name spoken by a familiar voice were compared only to responses to the attenuated noise of the MRI scanner. Therefore, the activation observed may have reflected a specific response to one's own name, but it is equally possible that it reflected a low-level orienting response to speech in general, an emotional response to the speaker (see Bekinschtein et al. 2004), or any one of a number of possible cognitive processes relating to the unmatched auditory stimuli. As a result, the interpretation hinges on a reverse inference, an unfortunately common practice in neuroimaging by which the engagement of a given cognitive process is inferred solely from the observed activation in a particular brain region (Poldrack 2006; Christoff & Owen 2006). Thus, in the study by Di and colleagues (2007), conclusions about higher-order cognitive processing were derived on the basis of activation in associative temporal-lobe areas, without any evidence that those processes are actually recruited by the task.

Staffen et al. (2006) have recently used event-related fMRI to compare sentences containing the patient's own name (e.g., "James, hello James"), spoken by a variety of unfamiliar voices, with sentences containing another first name, in a patient who had been vegetative for 10 months at the time of the scan. In this case, because identical speech stimuli were used which differed only with respect to the name itself, activations can be confidently attributed to cognitive processing that is specifically related to the patient's own name. Differential cortical processing was observed to the patient's own name in a region of the medial prefrontal cortex, similar to that observed in three healthy volunteers. These findings concur closely with a recent electrophysiological study that has shown differential P3 responses to patient's own names (compared to other names) in locked-in, minimally conscious, and some vegetative patients (Perrin et al. 2006). Selective cortical processing of one's own name (when it is compared directly with another name) requires the ability to perceive and access the meaning of words and may imply some level of comprehension on the part of this patient. However, as the authors point out (Staffen et al. 2006), a response to one's own name is one of the most basic forms of language, is elicited automatically (you cannot choose to *not* orient to your own name), and may not depend on the higher-level linguistic processes that are assumed to underpin comprehension.

A Hierarchical Approach to Studying Disorders of Consciousness

It has recently been argued that fMRI studies in patients in the vegetative state and other disorders of consciousness should be conducted hierarchically (Owen et al. 2005a, b) beginning with the simplest form of processing within a particular domain (e.g., auditory) and then progressing sequentially through more complex cognitive functions. Many patients with disorders of consciousness suffer serious damage to auditory and/or visual input systems, which may impede performance of any higher cognitive functions (e.g., voice discrimination), which place demands on these lower sensory systems (e.g., hearing). This is particularly crucial for functional neuroimaging studies in this patient group because, unlike the majority of studies in healthy volunteers, the participants are unlikely to be able to verify that stimuli have been perceived as they were intended by the experimenter. By way of example, a series of auditory paradigms were described that have all been successfully employed in functional neuroimaging studies of vegetative patients (Coleman et al. 2007). These paradigms increase in complexity systematically from basic acoustic processing to more complex aspects of language comprehension and semantics.

Acoustic Processing

At the most basic level, it is important to establish normal or near-normal sensory perception in any candidate patient for functional neuroimaging studies of higher cognitive functions (e.g., language processing). For the most part, functional neuroimaging is not necessary in this regard; that is to say, the measurement of auditory or visual evoked potentials are usually sufficient to establish that the respective neural pathways are intact. The integrity of the auditory neural axis can be assessed using a number of tests including the brain-stem auditory evoked response (BAER) and passive mismatch negativity (MMN). The MMN is widely thought to reflect a precognitive response generated from a comparison between the deviant input and a neural memory trace encoding the physical features of the repetitive sound (Naatanen 2003). The MMN has been successfully applied to the assessment of vegetative patients, although with considerable variability in results (Jones et al. 2000; Kotchoubey et al. 2001).

Speech Perception

Once basic neural responses to sounds have been established, it becomes possible to investigate whether the damaged brain is able to discriminate between different categories of sound. Speech perception in healthy volunteers has been widely investigated within the functional neuroimaging literature, and the findings have obvious clinical and therapeutic relevance for the investigation of preserved cognitive function in patients with disorders of consciousness. Most often, studies of speech perception involve volunteers being scanned during an experimental condition (e.g., while listening to binaurally presented spoken words) and an acoustic control condition (e.g., while listening to sounds that have the same duration, spectral profile, and amplitude envelope as the original speech, but are entirely unintelligible because all spectral detail has been replaced with noise, commonly referred to as signal correlated noise) or a silence condition (no auditory stimulus at all). For example, Mummery et al. (1999) scanned six neurologically normal volunteers while they listened to concrete nouns or signal correlated noise at a rate of 30 items per minute. The task instruction was to pay attention to the stimuli without responding. When speech was compared to signal correlated noise, they found a broad swathe of activation along both superior temporal gyri, extending ventrolaterally into the superior temporal sulcus (see Fig. 1A).

The same paradigm, or variants of it, has been applied recently to groups of patients meeting the clinical criteria for the vegetative state or the minimally conscious state (Owen et al. 2002, 2005b; Coleman et al. 2007). For example, Owen and colleagues (2002), described one case of a 30-year-old female bank manager who suffered severe head injuries during a road traffic accident involving a head-on collision with another vehicle. Over several weeks, the patient developed a withdrawal to pain but showed no consistent evidence of volitional activity and was diagnosed as vegetative. The decision to use an auditory speech task was made largely on the basis of the partially intact BAERs. The patient was scanned while being presented with spoken words, matched signal-correlated noise bursts, or silence. The comparison of noise bursts with rest revealed significant foci of activation bilaterally in the auditory region, confirming the BAER results suggesting that basic auditory processes were at least somewhat functional. More remarkably, the comparison of speech sounds with matched noise bursts revealed significant activity on the superior temporal plane bilaterally and posterior to auditory cortex, in the region of the planum temporale, in the left hemisphere only (see Fig. 1B). These findings correspond extremely closely with previous results in healthy volunteers (Mummery et al. 1999, see Fig. 1A), suggesting that this patient's brain processed speech in a way that was indistinguishable from controls. Similar findings were described in a second patient who also met the clinical criteria for the vegetative state (Owen et al. 2005b). In that study, a similar contrast between speech stimuli and signal-correlated noise yielded an almost identical pattern of activity in the vegetative patient and in a group of healthy volunteers (Fig. 1C).

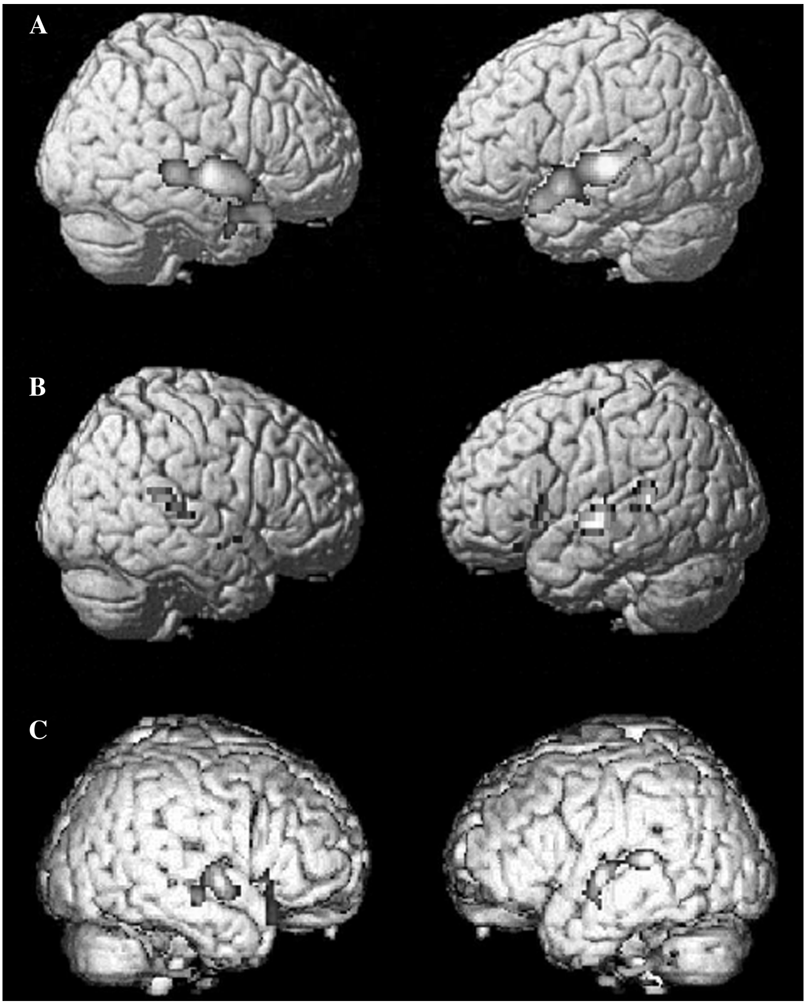

FIGURE 1. Brain activity when speech is compared with signal-correlated noise in healthy volunteers **(A)** and in two patients **(B, C)** meeting the clinical criteria for vegetative state. The speech-specific bilateral superior temporal-lobe activity observed in the two patients is similar to that observed in controls. Adapted from Owen et al. (2005a).

These preliminary findings in individual case studies have been extended recently using fMRI in a mixed group of 12 vegetative and minimally conscious patients (Coleman et al. 2007). Three of seven vegetative patients and two of five minimally conscious patients demonstrated some evidence of preserved speech processing, while four patients showed no significant activity at all, even when responses to any sound were compared to silence.

In short, simple perceptual tasks that compare speech with psycho-acoustically matched auditory stimuli can be used to demonstrate normal patterns of brain activity in some patients diagnosed with disorders of consciousness. Of course, recognizing speech as speech does not imply anything about comprehension; that is, whether the content of the speech is understood or not (consider the experience of listening to speech in a language of which you have no prior experience). To assess speech comprehension in disorders of consciousness it is necessary to employ more complex experiment designs that tap aspects of phonological processing.

Phonological Processing

Although the results from studies of speech processing in disorders of consciousness (e.g., Boly et al. 2004; Owen et al. 2002, 2005a, b; Coleman et al. 2007), have suggested that some level of covert linguistic functioning may be preserved, such tasks do not allow any conclusions to be drawn about comprehension; that is, whether speech is processed beyond the point at which it is identified as speech. One approach to this problem, which has met with some success, is to document responses to a set of stimuli of graded complexity. Davis and Johnsrude (2003) have developed such a task using graded intelligibility as a measure of speech comprehension. During the task, volunteers listen passively to sentences that have been distorted by adding noise such that they produce a range of six levels of intelligibility (as measured by subsequent word report scores). In a parallel fMRI study, intelligibility (operationalized as "the amount of a sentence that is understood") was found to correlate with activation in a region of the left anterior and superior temporal lobe; as intelligibility increased, so did signal intensity in this region (Davis & Johnsrude 2003). This increase was also significantly positively correlated with word report scores; signal intensity increasing linearly as the subjects reported more words as being understood correctly. These findings in healthy volunteers suggest that activity in the left anterior and superior temporal lobe reflects processing of the linguistic content of spoken sentences (words and meanings), rather than their more general acoustic properties.

This auditory comprehension paradigm has been adapted for use in patients with disorders of consciousness (Owen et al. 2005b). In one case, a 30-year-old male was diagnosed as vegetative following a basilar thrombosis and posterior circulation infarction. Four months after his brain injury, the auditory comprehension task described above was administered; the comparison of speech (collapsed across three levels of intelligibility) with a silence baseline condition revealed significant foci of activation over the left and right superior temporal planes confirming preliminary BAER and MMN findings suggesting that basic auditory processes were probably functional. Moreover, when low intelligibility sentences were compared with high intelligibility sentences in order to isolate any residual activity related specifically to the comprehension of spoken language, two peaks were observed in the superior and middle temporal gyri of the left hemisphere that were extremely similar to the pattern of results reported previously in healthy volunteers (Davis & Johnsrude 2003).

These results suggest that a test of graded intelligibility may be a useful indicator of some level of speech comprehension in patients with disorders of consciousness. Thus, while the left superior temporal sulcus responds to the presence of phonetic information in general, its anterior part (which was similarly activated in the patient and in healthy volunteers) appears to respond only when the stimuli become intelligible (Scott et al. 2000). However, whether the responses observed reflect speech comprehension per se (i.e., understanding the contents of spoken language) or a more basic response to the acoustic properties of intelligible speech that distinguish it from less intelligible speech can not be determined on the basis of these data alone.

Semantic Processing

Understanding natural speech is ordinarily so effortless that we often overlook the complex computations that are necessary to make sense of what someone is saying. Not only must we identify all the individual words on the basis of the acoustic input, we must also retrieve the meanings of these words and appropriately combine them to construct a representation of the whole sentence's meaning. When words have more than one meaning, contextual information must be used to identify the appropriate meaning. For example, given the sentence "The boy was frightened by the loud bark," the listener must work out that the ambiguous word "bark" refers to the sound made by a dog and not the outer covering of a tree. This process of selecting appropriate word meanings is important because the majority of English words have more than one meaning and are therefore ambiguous (Rodd et al. 2005). Selecting appropriate word meanings is likely to place a substantial load on the neural systems involved in computing sentence meanings.

Recently, an fMRI study in healthy volunteers has used semantic ambiguity to identify the brain regions that are specifically involved in speech comprehension and in particular in the processes of activating, selecting, and integrating contextually appropriate word meanings (Rodd et al. 2005). During the fMRI scan, the volunteers were played sentences containing two or more ambiguous words (e.g., "the *creak/creek* came from a *beam* in the *ceiling/sealing*") and well-matched, low-ambiguity sentences (e.g., "her secrets were written in her diary"). The ambiguous words were either homonyms (the two meanings have the same spelling and pronunciation; e.g., *beam*), or homophones (the two meanings that have the same pronunciation but different spellings; e.g., *creak/creek*). While the two types of sentences have similar acoustic, phonological, syntactic, and prosodic properties (and are rated as being equally natural), the high-ambiguity sentences require additional processing to identify and select contextually appropriate word meanings. Relative to low-ambiguity sentences, high-ambiguity stimuli produced increases in signal intensity in the left posterior inferior temporal cortex and inferior frontal gyri bilaterally (FIG. 2B).

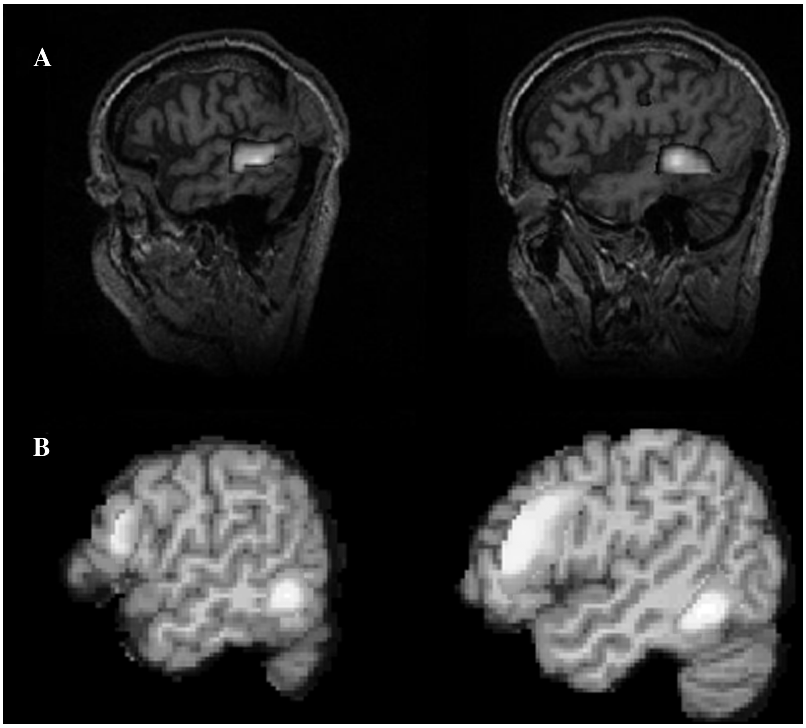

FIGURE 2. fMRI data for the ambiguous sentences versus unambiguous sentences comparison. Like healthy volunteers (**B**; adapted from Rodd et al. 2005), this patient **(A)** exhibited significant signal intensity changes in the left posterior inferior temporal cortex, suggesting that some of the processes involved in activating, selecting, and integrating contextually appropriate word meanings may be intact, despite the clinical diagnoses.

The results of this study demonstrate that a key aspect of spoken language comprehension—the resolution of semantic ambiguity—can be used to identify the brain regions involved in the semantic aspects of speech comprehension (e.g., activating, selecting, and integrating word meanings). Moreover, they support models of speech comprehension in which posterior inferior temporal regions are involved in semantic processing (Hickok & Poeppel 2000), and they demonstrate that the lateral inferior frontal gyrus, which has long been known to be important in syntactic processing of sentences and the semantic properties of single words, also plays an important role in processing the meanings of words in sentences.

Two recent studies have explored the utility of this approach in identifying residual comprehension in disorders of consciousness (Owen et al. 2005b; Coleman et al. 2007). In the more recent study, seven vegetative state and five minimally conscious patients were scanned during the semantic paradigm developed by Rodd et al. (2005). Two of the vegetative patients showed a significant response in the semantic ambiguity contrast, consistent with high-level comprehension of the semantic aspects of speech. These results provide compelling evidence for high-level residual linguistic processing in some patients meeting the clinical criteria for vegetative state and suggest that some of the processes involved in activating, selecting and integrating contextually appropriate word meanings may be intact, despite their clinical diagnoses.

Conscious Awareness

A question that is often asked, however, is whether the presence of normal brain activation in patients with disorders of consciousness (e.g., de Jong et al. 1997; Menon et al. 1998; Laureys et al. 2002; Owen et al. 2002; Boly et al. 2004; Owen et al. 2005a, b; Coleman et al. 2007), indicates a level of awareness, perhaps even similar to that which exists in healthy volunteers when performing the same tasks. Many types of stimuli, including faces, speech, and pain will elicit relatively automatic responses from the brain; that is to say, they will occur without the need for active intervention on the part of the participant (e.g., you can not choose to *not* recognize a face, or to *not* understand speech that is presented clearly in your native language). In addition, there is a wealth of data in healthy volunteers, from studies of implicit learning and the effects of priming (e.g., see Schacter 1994 for review), to studies of learning and speech perception during anesthesia (e.g., Bonebakker et al. 1996; Davis et al. 2007) that have demonstrated that many aspects of human cognition can go on in the absence of awareness. Even the semantic content of masked information can be primed to affect subsequent behavior without the explicit knowledge of the participant, suggesting that some aspects of semantic processing may occur without conscious awareness (Dehaene et al. 1998). By the same argument, normal neural responses in patients who are diagnosed with disorders of consciousness do not necessarily indicate that these patients have any conscious experience associated with processing those same types of stimuli. Thus, such patients may retain discreet islands of subconscious cognitive function, which exist in the absence of awareness.

The logic described above exposes a central conundrum in the study of conscious awareness and, in particular, how it relates to disorders of consciousness. As noted above, there is, as yet, no universally agreed definition of consciousness and even less so self-consciousness or sense of self/being (Laureys et al. 2007). Deeper philosophical considerations notwithstanding, the only reliable method that we have for determining if another being is consciously aware is to ask him/her. The answer may take the form of a spoken response or a nonverbal signal (which may be as simple as the blink of an eye, as documented cases of the locked-in syndrome have demonstrated), but it is this answer, and only this answer, that allows us to infer conscious awareness. In short, our ability to know unequivocally that another being is consciously aware is ultimately determined, not by whether they are aware or not, but by their ability to communicate that fact through a recognized behavioral response. But what if the ability to blink an eye or move a hand is lost, yet conscious awareness remains? Much of the debate about the vegetative state revolves around what behaviors reflect cortical activity and whether signs of activity in the cortex necessarily indicate conscious awareness. Yet the crux of the diagnosis is that the patient displays no evidence of awareness or self or surroundings. Thus, by definition, patients who are diagnosed as vegetative are not able to elicit any behavioral responses. Following the logic of this argument then, even if such a patient *were* consciously aware, he/she would have no means for conveying that information to the outside world.

A novel approach to this conundrum has recently been described, using fMRI, to demonstrate preserved conscious awareness in a patient fulfilling the criteria for a diagnosis of vegetative state (Owen et al. 2006). Between the time of the accident and the fMRI scan in early January 2006, the patient was assessed by a multidisciplinary team employing repeated standardized assessments consistent with the procedure described by Bates (2005). Throughout this period the patient's behavior was consistent with accepted guidelines defining the vegetative state. She would open her eyes spontaneously, exhibited sleep/wake cycles, and had preserved, but inconsistent, reflexive behavior (startle, noxious, threat, tactile, olfactory). No elaborated motor behaviors (regarded as voluntary or willed responses) were observed from the upper or lower limbs. There was no evidence of orientation, fixation greater than 5 seconds, or tracking to visual or auditory stimuli. No overt motor responses to command were observed.

Prior to the fMRI scan, the patient was instructed to perform two mental imagery tasks when cued by the instructions "imagine playing tennis" or "imagine visiting the rooms in your home." Importantly, these particular tasks were chosen, not because they involve a set of fundamental cognitive processes that are known to reflect conscious awareness, but because imagining playing tennis and imagining moving around the house elicit extremely reliable, robust, and statistically distinguishable patterns of activation in specific regions of the brain (Boly et al. 2007). For example, in a series of studies in healthy volunteers (Boly et al. 2007; Owen et al. 2006) imagining playing tennis has been shown to elicit activity in the supplementary motor area, a region known to be involved in imagining (as well as actually performing) coordinated movements, in each and every one of 34 participants scanned. In contrast, imagining moving from room to room in a house commonly activates the parahippocampal cortices, the posterior parietal lobe, and the lateral premotor cortices, all regions that have been shown to contribute to imaginary, or real, spatial navigation (FIG. 3A).

Given the reliability of these responses across individuals, activation in these regions in patients with disorders of consciousness can be used as a neural marker, confirming that the patient retains the ability to understand instructions, to carry out different mental tasks in response to those instructions, and, therefore, is able to exhibit willed, voluntary behavior in the absence of any overt action. Thus, they permit the identification of volitional brain activity (and thus of consciousness) at the single-subject level, without the need for any motor response (Boly et al. 2007).

During the periods that the vegetative patient was asked to imagine playing tennis, significant activity was observed in the supplementary motor area (Owen

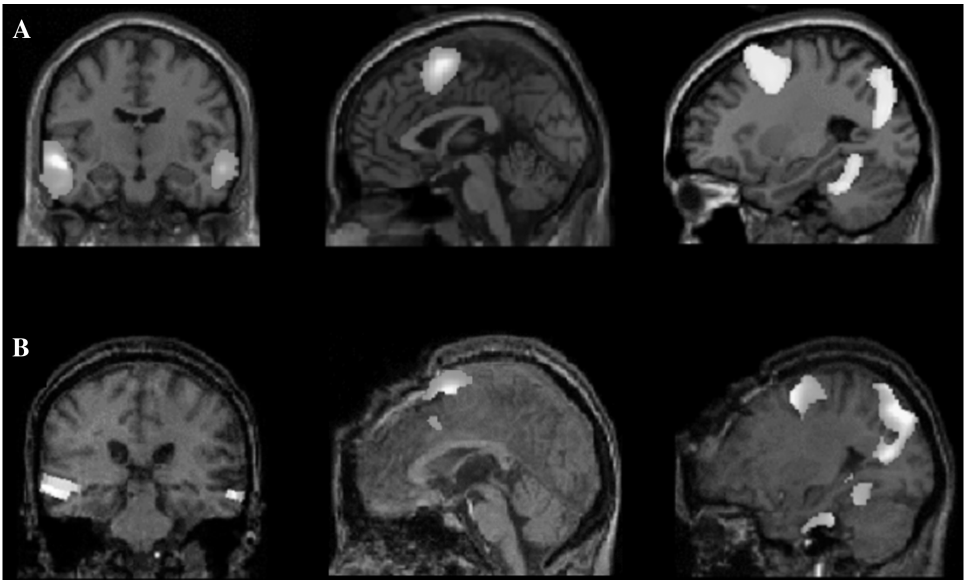

FIGURE 3. Indistinguishable fMRI activity in healthy controls **(A)** and in a vegetative patient **(B)** while listening to speech versus signal-correlated white noise (left column), while imagining playing tennis (middle column), or while imagining walking around the house (right column). Adapted from Owen et al. (2006).

et al. 2006; Fig. 3B). In contrast, when she was asked to imagine walking through her home, significant activity was observed in the parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex (Fig. 3B). Her neural responses were indistinguishable from those observed in healthy volunteers performing the same imagery tasks in the scanner (Boly et al. 2007; Owen et al. 2006; Fig. 4A). It was concluded that, despite fulfilling all the clinical criteria for a diagnosis of vegetative state, this patient retained the ability to understand spoken commands and to respond to them through her brain activity, rather than through speech or movement, confirming beyond any doubt that she was consciously aware of herself and her surroundings.

Of course, skeptics may argue that the words "tennis" and "house" could have automatically triggered the patterns of activation observed in the supplementary motor area, the parahippocampal gyrus, the posterior parietal lobe, and the lateral premotor cortex in this patient in the absence of conscious awareness. However, no data exist supporting the inference that such stimuli can unconsciously elicit sustained hemodynamic responses in these regions of the brain. Indeed, considerable data exist to suggest such words do not elicit the responses that were observed. For example, although it is well-documented that some words can, under certain circumstances, elicit wholly automatic neural responses in the absence of conscious awareness, such responses are typically transient (i.e., lasting for a few seconds) and, unsurprisingly, occur in regions of the brain that are associated with word processing. In the patient described by Owen et al. (2006, 2007a, b), the observed activity was not transient but persisted for the full 30 seconds of each imagery task, that is, far longer than would be expected, even given the hemodynamics of the fMRI response (Fig. 4B). In fact, these task-specific changes persisted until the patient was cued with another stimulus indicating that she should rest (Owen et al 2007b). Such responses are impossible to explain in terms of automatic brain processes. In addition, the activation observed in the patient was not in brain regions that are known to be involved in word processing, but rather in regions that are known to be involved in the two imagery tasks that she was asked to carry out. Again, sustained activity in these regions of the brain is impossible to explain in terms of unconscious responses to either single key words or to short sentences containing those words. In fact, in a supplementary study (Owen et al. 2007a), noninstructive sentences containing the same key words as those used with the patient (e.g., "The man enjoyed playing tennis") were shown to produce no sustained activity in any of these brain regions in healthy volunteers.

The most parsimonious explanation is, therefore, that this patient was consciously aware and actively following the instructions given to her, despite her diagnosis of vegetative state.

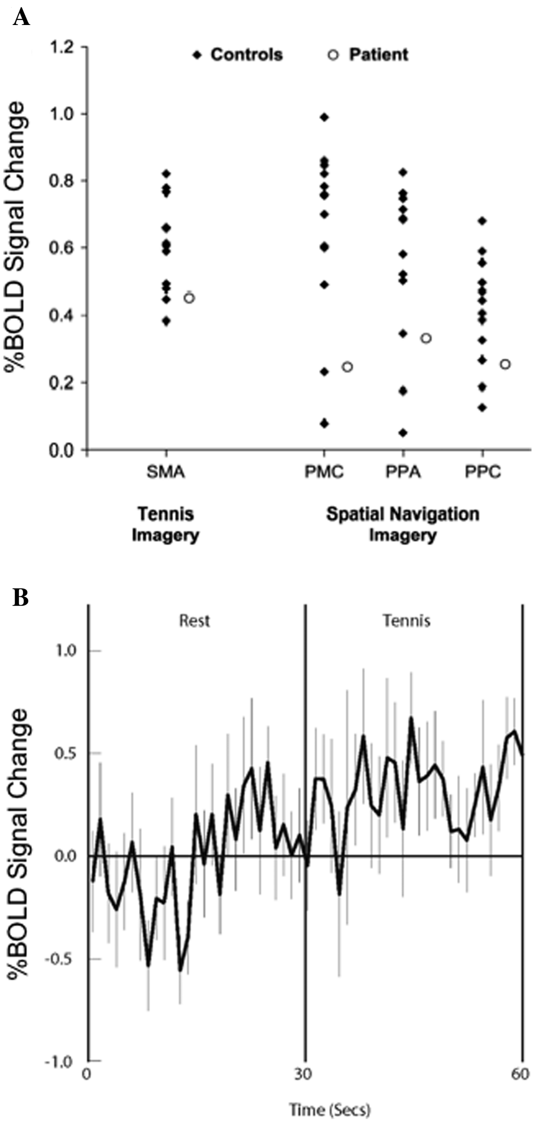

FIGURE 4. (A) Signal intensity changes in the vegetative patient described by Owen et al. (2006) plotted against 12 healthy volunteers while imagining playing tennis or while imagining moving around their own house. SMA, supplementary motor area; PMC, lateral premotor cortex; PPA, parahippocampal gyrus; PPC, posterior parietal cortex. Signal intensity changes for the patient are all within the normal range. **(B)** Mean signal intensity changes in the patient over two 30s epochs of the imaginary tennis playing task. A sustained 30s fMRI response in the supplementary motor cortex was observed when the vegetative patient was asked to imagine playing tennis relative to rest.

Limitations

This work raises a number of important issues regarding the use of fMRI in the assessment of patients with disorders of consciousness. First, although this technique provides a new means for detecting conscious awareness when standard clinical approaches are unable to provide that information, the method will not be applicable to all vegetative patients. For example, after 5 months (as was the case in the patient described by Owen et al. 2006, 2007a) the incidence of recovery of consciousness following a traumatic brain injury remains at nearly 20%, with a quarter of those recovering moving on to some level of social independence. Nontraumatic injuries are considered to have a much poorer prognosis. Similarly, the likelihood of recovery is much lower in patients who meet the diagnostic criteria for the permanent vegetative state. International guidelines, including those of the Royal College of Physicians in the U.K. and the Multi-Society Task Force, representing five major medical societies in the United States, suggest that a diagnosis of permanent vegetative state should not be made in cases of traumatic brain injury until 12 months postinjury and 6 months postinjury for cases of anoxic brain injury. In many of these cases, standard clinical techniques, including structural MRI, may be sufficient to rule out any potential for normal activation, without the need for fMRI.

More generally, the acquisition, analysis, and interpretation of fMRI data from patients with severe brain damage are also complex (Giacino et al. 2006). For example, the coupling of neuronal activity and local hemodynamics, essential for fMRI activation measurements, is likely to be different from that in healthy controls (Gsell et al. 2000; Hamzei et al. 2003; Rossini et al. 2004; Sakatani et al. 2003), making interpretation of such data sets extremely difficult. Notwithstanding this basic methodological concern, the choice of the study design is also crucial. For example, if brain-stem auditory evoked responses are abnormal, auditory stimuli may be inappropriate and alternatives (e.g., visual stimuli) should be considered. The investigation should also be complex enough that the cognitive processes of interest will be studied (i.e., preferably beyond stimulus perception), yet not so complex that the tasks could easily overload the cognitive capacities of a tired or inattentive patient. Many studies also suffer from the reverse inference problem described above (Christoff & Owen 2006; Poldrack 2006). For example, activity in the amygdala is not sufficient evidence for an emotional response unless well-documented studies in healthy volunteers have established previously that the task in question produces such a response, accompanied by an anatomically specific, robust, and reproducible activation pattern in this brain region. In vegetative state, minimally conscious state, and locked-in syndrome, episodes of low arousal and sleep are common and close patient monitoring—preferably through EEG recording—during activation scans is essential so that these periods can be avoided. Spontaneous movements during the scan itself may also compromise the interpretation of functional neuroimaging data, particularly with fMRI scans. Processing of functional neuroimaging data may also present challenging problems in this patient group. For example, the presence of gross hydrocephalus or focal pathology may complicate the fitting of functional imaging data to structural imaging data, and the normalization of these images through reference to a healthy brain. Under these circumstances, statistical assessment of activation patterns is complex and interpretation of activation foci with standard stereotaxic coordinates may be impossible.

Finally and most importantly, negative fMRI findings in patients with disorders of consciousness should never be used as evidence for impaired cognitive function or lack of awareness. For example, a patient may fall asleep during the scan or may not have properly heard or understood the task instructions, leading to so-called false negative results. False negative findings in functional neuroimaging studies are common, even in healthy volunteers. Whether this will ultimately limit the practical application that functional neuroimaging might have for distinguishing between those patients who are likely to recover and those who are not will only be determined when the technique has been applied to many more patients who have been followed longitudinally. Nevertheless, positive findings, when they occur and can be verified by careful statistical comparison with data from healthy volunteers, can be used to detect conscious awareness in patients, without the need for conventional methods of communication such as movement or speech.

Conclusions

In the last two decades, rapid technological developments in the field of neuroimaging have produced a cornucopia of new techniques for examining both the structure and function of the human brain *in vivo*. Detailed anatomical images, acquired through computerized tomography (CT) and magnetic resonance imaging (MRI), can now be combined with PET, fMRI, quantitative electroencephalography (EEG), and magnetoencephalography (MEG) to produce a cohesive picture of normal and abnormal brain function. As a result, functional neuroimaging has become the technique of choice for neuropsychologists, cognitive neuroscientists, and many others in the wider neuroscientific community with an interest in the relationship between brain and behavior. Until recently, these new methods of investigation have been used primarily as a correlational tool to map the cerebral changes that are associated with a particular cognitive process or function, be it an action, a reaction (e.g., to some kind of external stimulation), or a thought. But recent advances in imaging technology, and in particular the ability of fMRI to detect reliable neural responses in individual participants in real time, are beginning to reveal a participant's thoughts, actions, or intentions based solely on the pattern of activity that is observed in their brain. The case of the vegetative patient described above provides a clear example of such an application (Owen et al. 2006, 2007a). In the absence of any overt action on her part, the fact that she was consciously aware was evident only by examination of her time-locked and sustained fMRI responses following instructions to perform specific mental tasks. On this basis, it was possible to infer not only that she was thinking, but what she was thinking at any given point in time (within the constraints of the tasks given to her). Similarly, Boly et al. (2007) have demonstrated that when healthy volunteers are instructed to choose to imagine either playing tennis or navigating around their homes (without informing the investigators of their choice), it is possible to determine, with 100% accuracy, which task is being imagined by each and every participant based solely on their brain activity. Finally, in another recent fMRI study, participants were asked to freely decide which of two different tasks to perform and to covertly hold onto that intention during a variable delay (Haynes et al. 2007). During the delay, it was possible to decode from activity in the prefrontal cortex which of the two tasks the participants were covertly intending to perform.

Such feats of rudimentary "mind-reading" using fMRI pave the way for new and innovative applications of functional neuroimaging, both in basic neuroscience and in clinical practice. For example, the presence of reproducible and robust task-dependent fMRI responses to command without the need for any practice or training (Owen et al. 2006, 2007a) suggests a novel method by which both healthy participants and patients with disorders of consciousness may be able to communicate their thoughts to those around them by simply modulating their own neural activity. The use of functional neuroimaging in this context will clearly continue to present innumerable logistic, theoretical, and ethical problems. However, its clinical and scientific implications are so major that such efforts are clearly justified.

Acknowledgments

I thank M. Coleman, M. Davis, J. D. Pickard, J. Rodd, D. Menon, I. Johnsrude, M. Boly, S. Laureys, and the Cambridge Impaired Consciousness Research Group for their contributions to work discussed in this review.

Conflict of Interest

The author declares no conflicts of interest.

References

Agardh, C. D., Rosen, I., & Ryding, E. (1983). Persistent vegetative state with high cerebral blood flow following profound hypoglycemia. *Ann. Neurol.*, *14*(4), 482–486.

Andrews, K., Murphy, L., Munday, R., et al. (1996). Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. *BMJ*, *313*, 13–16.

Bates, D. (2005). Incidence and prevalence of the vegetative and minimally conscious states. *Neuropsychol Rehabil*, *15*, 175.

Bekinschtein, T., Leiguarda, R., Armony, J., et al. (2004). Emotional processing in the minimally conscious state. *Journal of Neurosurgery, Neurology and Psychiatry*, *75*, 788.

Bernat, J. L. (2006). Chronic disorders of consciousness. *Lancet*, *367*, 1181–1192.

Beuthien-Baumann, B., Handrick, W., Schmidt, T., et al. (2003). Persistent vegetative state: evaluation of brain metabolism and brain perfusion with PET and SPECT. *Nucl Med Commun*, *24*(6), 643–639.

Boly, M., Faymonville, M. E., Peigneux, P., et al. (2004). Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. *Arch Neurol*, *61*(2), 233–238.

Boly, M., Coleman, M. R., Davis, M. H., et al. (2007). When thoughts become action: an fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. *Neuroimage*, *36*, 979–992.

Bonebakker, A., Bonke, B., Klein, J., Wolters, G., Stijnen, T., Passchier, J., et al. (1996). Information processing during general anaesthesia: Evidence for unconscious memory. In B. Bonke, J.G.W. Bovill, & N. Moerman (Eds.), *Memory and Awareness in Anaesthesia* (pp. 101–109). Lisse, Amsterdam: Swets and Zeitlinger.

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

Christoff, K., & Owen, A. M. (2006). Improving reverse neuroimaging inference: cognitive domain versus cognitive complexity. *Trends Cogn. Sci.*, *10*(8), 352–353.

Coleman, M. R., Rodd, J. M., Davis, M. H., et al. (2007). Do vegetative patients retain aspects of language Evidence from fMRI. *Brain*, *130*, 2494–2507.

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

Davis, M. H., & Johnsrude, I. S. (2003). Hierarchical processing in spoken language comprehension. *J Neurosc Sci*, *23*(8), 3423–3431.

de Jong, B., Willemsen, A. T., & Paans, A. M. (1997). Regional cerebral blood flow changes related to affective speech presentation in persistent vegetative state. *Clin. Neurol. Neurosurg.*, *99*(3), 213–216.

De Volder, A. G., Goffinet, A. M., Bol, A., et al. (1990). Brain glucose metabolism in postanoxic syndrome. Positron emission tomographic study. *Arch. Neurol.*, *47*(2), 197–204.

Dehaene, S., Naccache, L., Le Clec'h, G., Koechlin, E., Mueller, M., Dehaene-Lambertz, G., et al. (1998). Imaging unconscious semantic priming. *Nature*, *395*, 597–600.

Di, H. B., Yu, S. M., Weng, X. C., et al. (2007). Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology*, *68*, 895–899.

Giacino, J., Hirsch, J., Schiff, N., et al. (2006). Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. *Arch Phys Med Rehabil*, *87*, 67–76.

Gsell, W., De Sadeleer, C., Marchalant, Y., et al. (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.

Giacino, J. T., Ashwal, S., Childs, N., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*(3), 349–353.

Hamzei, F., Knab, R., Weiller, C., et al. (2003). The influence of extra- and intracranial artery disease on the BOLD signal in FMRI. *Neuroimage*, *20*(2), 1393–1399.

Haynes, J. D., Sakai, K., Rees, G., et al. (2007). Hidden intentions in the human brain. *Curr. Biol.*, *10*, 1016.

Hickok, G., & Poeppel, D. (2000). Towards a functional neuroanatomy of speech perception. *Trends Cogn Sci*, *4*, 131–138.

Jennett, B. (2002). *The Vegetative State. Medical Facts, Ethical and Legal Dilemmas*. Cambridge: Cambridge University Press.

Jones, S. J., Vaz Pato, M., Sprague, L., Stokes, M., Munday, R., & Haque, N. (2000). Auditory evoked potentials to spectro-temporal modulation of complex tones in normal subjects and patients with severe brain injury. *Brain*, *123*, 1007–1016.

Koch, C. (2007). *The quest for consciousness: A neurobiological approach*. Englewood, CO: Roberts and Company.

Kotchoubey, B., Lang, S., Baales, R., Herb, E., Maurer, P., Mezger, G., et al. (2001). Brain potentials in human patients with extremely severe diffuse brain damage. *Neurosci Lett*, *301*, 37–40.

Jennett, B., & Plum, F. (1972). Persistent vegetative state after brain damage. *Lancet*, *1*, 734–737.

Laureys, S., Faymonville, M. E., Peigneux, P., et al. (2002). Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage*, *17*(2), 732–741.

Laureys, S., Giacino, J. T., Schiff, N. D., et al. (2006). How should functional imaging of patients with disorders of consciousness contribute to their clinical rehabilitation needs? *Curr Opin Neurol*, *19*(6), 520–527.

Laureys, S., Goldman, S., Phillips, C., et al. (1999a). Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. *Neuroimage*, *9*(4), 377–382.

Laureys, S., Lemaire, C., Maquet, P., et al. (1999b). Cerebral metabolism during vegetative state and after recovery to consciousness. *J. Neurol. Neurosurg. Psychiatry*, *67*, 121.

Laureys, S., Owen, A. M., & Schiff, N. (2004). Brain function in coma, vegetative state, and related disorders. *The Lancet Neurology*, *3*(9), 537–546.

Laureys, S., Perrin, F., & Brédart, S. (2007). Self-consciousness in non-communicative patients. *Conscious Cogn. 16*, 722–741.

Levy, D. E., Sidtis, J. J., Rottenberg, D. A., et al. (1987). Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. *Ann. Neurol.*, *22*(6), 673–682.

Menon, D. K., Owen, A. M., Williams, E. J., et al. (1998). Cortical processing in persistent vegetative state. *Lancet*, *352*(9123), 200.

Momose, T., Matsui, T., & Kosaka, N. (1989). Effect of cervical spinal cord stimulation (cSCS) on cerebral glucose metabolism and blood flow in a vegetative patient assessed by positron emission tomography (PET) and single photon emission computed tomography (SPECT). *Radiat. Med.*, *7*(7), 243–246.

Multi-Society Task Force on PVS. (1994a). Medical aspects of the persistent vegetative state (first part). *N Eng J Med*, *330*, 1400–1508.

Multi-Society Task Force on PVS (1994b). Medical aspects of the persistent vegetative state (second part). *N Eng J Med*, *330*, 1572–1579.

Mummery, C. J., Ashburner, J., Scott, S. K., & Wise, R. J. S. (1999). Functional neuroimaging of speech perception in six normal and two aphasic subjects. *Journal of the Acoustical Society of America*, *106*, 449–456.

Naatanen, R. (2003). Mismatch negativity: clinical research and possible applications. *International Journal of Psychophysiology*, *48*, 179–188.

Owen, A. M., Menon, D. K., Johnsrude, I. S., Bor, D., Scott, S. K., Manly, T., et al. (2002). Detecting residual cognitive function in persistent vegetative state. *Neurocase*, *8*, 394–403.

Owen, A. M., Coleman, M. R., Menon, D. K., et al. (2005a). Using a heirarchical approach to investigate residual auditory cognition in persistent vegetative state. In S. Laureys (Ed.), *The Boundaries of Consciousness: Neurobiology and Neuropathology. Progress in Brain Research* (Vol. 150, pp. 461–476). London: Elsevier.

Owen, A. M., Coleman, M. R., Menon, D. K., et al. (2005b). Residual auditory function in persistent vegetative state: A combined PET and fMRI study. *Neuropsychological Rehabilitation*, *15*(3–4), 290–306.

Owen, A. M., Coleman, M. R., Davis, M. H., et al. (2006). Detecting awareness in the vegetative state. *Science*, *313*, 1402.

Owen, A. M., Coleman, M. R., Davis, M. H., et al. (2007a). Response to Comments on "Detecting awareness in the vegetative state". *Science*, *315*, 1221c.

Owen, A. M., Coleman, M. R., Davis, M. H., et al. (2007b). Using fMRI to detect awareness in the vegetative state. *Archives of Neurology*, *64*, 1098–1102.

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

Plum, F., & Posner, J. B. (1966). *The Diagnosis of Stupor and Coma*. Philadelphia, PA: F.A. Davis Co.

Poldrack, R. A. (2006). Can cognitive processes be inferred from neuroimaging data? *Trends Cogn. Sci.*, *10*, 59–63.

Rossini, P. M., Altamura, C., Ferretti, A., et al. (2004). Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? *Brain*, *127*(Pt 1), 99–110.

Rudolf, J., Ghaemi, M., Haupt, W. F., et al. (1999). Cerebral glucose metabolism in acute and persistent vegetative state. *J. Neurosurg. Anesthesiol.*, *11*(1), 17–24.

Rodd, J. M., Davis, M. H., & Johnsrude, I. S. (2005). The neural mechanisms of speech comprehension: fMRI studies of semantic ambiguity. *Cereb. Cortex*, *15*, 1261.

Royal College of Physicians Working Group (1996). The permanent vegetative state. *Journal of the Royal College of Physicians of London*, *30*, 119–121.

Schacter, D. L. (1994). Priming and multiple memory systems: Perceptual mechanisms of implicit memory. In D.L. Schacter & E. Tulving (Eds.), *Memory Systems* (pp. 233–268). Cambridge, MA: MIT Press.

Sakatani, K., Murata, Y., Fukaya, C., et al. (2003). BOLD functional MRI may overlook activation areas in the damaged brain. *Acta Neurochir Suppl*, *87*, 59–62.

Schiff, N. D. (2006). Multimodal Neuroimaging Approaches to Disorders of Consciousness. *Journal of Head Trauma Rehabilitation*, *21*(5), 388–397.

Schiff, N. D., Ribary, U., Moreno, D. R., et al. (2002). Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain*, *125*(Pt 6), 1210–1234.

Schnakers, C., Giacino, J., Kaknar, K., et al. (2006). Does the FOUR score correctly diagnose the vegetative and minimally conscious states? *Ann Neurol*, *60*, 744–745.

Scott, S. K., Blank, C., Rosen, S., & Wise, R. J. S. (2000). Identification of a pathway for intelligible speech in the left temporal lobe. *Brain*, *123*, 2400–2406.

Staffen, W., Kronbichler, M., Aichhorn, M., et al. (2006). Selective brain activity in response to one's own name in the persistent vegetative state. *J Neurol Neurosurg Psychiatry*, *77*, 1383–1384.

Tommasino, C., Grana, C., & Lucignani, G. (1995). Regional cerebral metabolism of glucose in comatose and vegetative state patients. *J. Neurosurg. Anesthesiol.*, *7*(2), 109–116.

Tresch, D. D., Sims, F. H., & Duthie, E. H. (1991). Clinical characteristics of patients in the persistent vegetative state. *Arch Intern Med*, *151*, 930–912.

Voss, H. U., Uluc, A. M., & Dyke, J. P. (2006). Possible axonal regrowth in late recovery from the minimally conscious state. *J Clin Invest*, *116*, 2005–2011.