Cognition in the Vegetative State

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Abstract

Awake but not aware: This puzzling dissociation of the two central elements of consciousness defines the vegetative state. Traditionally, this condition has been believed to imply a brain with preserved hypothalamic and brainstem autonomic functions but with no capacity for cortical cognitive processes. As is discussed in this review, over a 20-year span neuroimaging techniques have clearly demonstrated that this characterization of patients in a vegetative state is incorrect. Contrary to the initial belief, the "vegetative" brain can retain several high-level aspects of cognitive functions, across sensory modalities, including language processing and learning dynamics. Nonetheless, the residual cognitive functions observed in vegetative patients might reflect intact but functionally disconnected cortical modules that do not give rise to the subjective feeling of phenomenological awareness.

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INTRODUCTION

> Everybody knows what consciousness is: it is what vanishes every night when we fall into dreamless sleep and reappears when we wake up or when we dream. It is also all we are and all we have: lose consciousness and, as far as you are concerned, your own self and the entire world dissolve into nothingness.
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> (Tononi, 2008, p. 216)

What is consciousness? This question has long been proprietary to philosophical inquiry. Today, however, the issue of how consciousness arises from the interplay of billions of neurons is perhaps one of the most exciting and challenging frontiers of scientific inquiry. In particular, the endeavor to model and quantify the presence of consciousness in the human brain, as well as the effort to delineate how much of human cognition depends on its presence, are key to understanding some of the most mysterious conditions of the human brain: disorders of consciousness (DOC). This term refers to a set of related disorders, including coma, the vegetative state (VS), and the minimally conscious state (MCS), in which an individual's consciousness is altered in a transient or permanent fashion due to severe acquired or developed brain injury (Monti et al. 2010a). As a consequence of great progresses in intensive (and general) medical care, an increasing number of patients survive severe brain damage. Some of these patients go on to make significant recovery; others, as illustrated in **Figure 1**, enter either transiently or permanently a condition of DOC (or other associated neurological conditions).

One of the most challenging aspects of DOC is the fact that without a direct understanding of consciousness and a means to reliably assess its presence, determining whether an individual other than ourselves is conscious must necessarily rely on indirect measures (cf. Monti & Owen 2010). This constraint bears very far-reaching implications. On the one hand, despite increasingly sophisticated behavioral protocols to assess consciousness at the bedside, indirect measures have consistently been shown to be suboptimal and often prone to error (Andrews et al. 1996, Childs et al. 1993, Schnakers et al. 2009). On the other hand, the lack of a direct understanding of consciousness severely constrains our ability to develop effective interventions and treatments aimed at "reigniting" it (Elliott & Walker 2005). Similarly, our limited understanding of how much cognition is possible at the lower boundaries of consciousness (Ropper 2010) severely constrains our ability to understand the psychology of DOC. These issues ultimately lie at the heart of the unique legal and ethical challenges associated with these conditions (Fins et al. 2008, Fisher & Appelbaum 2010, Jennett 2005)—often rendered even more complicated by the use of inconsistent terminology (Jennett 2002) and incorrect media reporting (Racine et al. 2008).

The remainder of this review is organized into four sections. First, I present disorders of consciousness, one at a time, focusing on basic concepts and definitions. Second, I briefly discuss the challenges and complexities associated with assessing residual cognitive processing and awareness in patients with DOC, as well as the potential role of modern neuroimaging techniques in this context. Third, I review selected contributions to the study of cognitive processing in VS and MCS patients, focusing in particular on functional neuroimaging approaches. Finally, I briefly conclude by outlining the view that residual cortical processing in vegetative patients reflects functionally disconnected cognitive modules that are isolated from the rest of the brain and thus do not give rise to the subjective feeling of phenomenological awareness.

WHAT ARE DISORDERS OF CONSCIOUSNESS?

Consciousness is often conceptualized as encompassing two cardinal elements (Laureys 2005): wakefulness and awareness. Wakefulness refers to the level of consciousness, whereas awareness refers to its contents. Different states of the human brain, both normal and pathological, can be described with respect to these two elements. As illustrated in **Figure 2**, wakefulness and awareness generally vary together: both are absent (or low) in coma and general anesthesia, return jointly in the progression from deep sleep to light sleep and drowsiness, and are present during normal (i.e., healthy) wake. Occasionally, the two cardinal elements of consciousness dissociate, producing very puzzling conditions. The oneiric experiences that often characterize rapid eye movement (REM) sleep, for example, illustrate a scenario in which (some kind of) awareness is present in the absence of wakefulness. As I discuss below, the reverse dissociation, in which wakefulness is present in the absence of awareness, defines the vegetative state.

For convenience, in what follows I discuss impairments of consciousness as a set of discrete entities. However, it is now increasingly clear that DOC are best understood as representing a continuous spectrum (Andrews 1996, Laureys & Boly 2008).

Coma

Coma describes a transient condition of unresponsiveness in which patients present with their eyes (continuously) closed, do not respond to attempts to arouse them, and exhibit no evidence of awareness of self or of their surrounding (Posner et al. 2007). As portrayed in **Figure 2**, patients in a state of coma thus lack both awareness and wakefulness. These patients typically either recover or progress to a vegetative state within four weeks, with prolonged coma being an exceedingly rare outcome (Royal College of Physicians 1996). It should be noted that, by virtue of entering a pharmacologically induced coma, individuals undergoing general anesthesia appear to enter (transiently and reversibly) a similar condition (cf. Brown et al. 2010).

When patients "awaken" from a state of coma without recovering awareness, they are said to progress to a vegetative state (Jennett & Plum 1972). This condition of "wakefulness in the absence of awareness" is defined by three main clinical features: (*a*) alternating periods of eye opening and closing, giving the appearance of sleep-wake cycles (whether this feature actually reflects genuine circadian rhythms is currently unclear; cf. Bekinschtein et al. 2009b, Cologan et al. 2010, Landsness et al. 2011); (*b*) complete lack of any sign of awareness of the self or the environment; and (*c*) partial or complete preservation of hypothalamic and brainstem autonomic functions (Multi-Society Task Force on PVS 1994a, Royal College of Physicians 1996). According to the guidelines set by the Multi-Society Task Force on PVS in 1994, a vegetative state is considered to be persistent when it lasts longer than one month. After traumatic brain injuries, a vegetative state is considered to be permanent when it lasts longer than one year. In contrast, a vegetative state acquired following nontraumatic brain injury is considered permanent after three months (Multi-Society Task Force on PVS 1994a). Although both permanent vegetative states and persistent vegetative states are often abbreviated to PVS, it has been suggested that to avoid confusion the abbreviation should be used exclusively to indicate a permanent vegetative state (Laureys et al. 2000a).

Permanent vegetative state (PVS): a vegetative state that lasts longer than three months for nontraumatic injuries and longer than one year for traumatic injuries

Persistent vegetative state: a vegetative state that lasts longer than one month

LIS: locked-in syndrome

Vegetative State

The term vegetative state is currently the most widely used label; nonetheless, other nomenclatures have also been employed (particularly in Europe) to describe patients in a similar condition, including apallic syndrome, permanent/irreversible coma, coma vigile, postcomatose unawareness, and vegetative survival, among others (for a review, see Jennett 2002). As used by Jennett & Plum (1972), the term vegetative was chosen to describe the fact that in these patients, basic vegetative nervous functions, including thermoregulation, respiration, and sleep-wake cycles, are preserved, but in the absence of any sensation and thought. Nonetheless, because of the perceived demeaning and discriminatory subhuman connotation of the term, some have proposed alternate labels, including wakeful unconscious state (Sazbon & Groswasser 1991) and unresponsive wakefulness syndrome (Laureys et al. 2010). To avoid any potential future confusion while the clinical and scientific community evaluates the use of these alternative nomenclatures, in this review we maintain the label vegetative state.

Minimally Conscious State

Although some patients remain in a vegetative state permanently, others emerge to a minimally conscious state (MCS) (Giacino et al. 2002). As illustrated in **Figure 2**, the MCS is defined as a condition in which patients appear not only to be wakeful (like vegetative-state patients) but also exhibit inconsistent but reproducible signs of awareness of themselves or their surroundings. This state of minimal awareness is at times intermittent, alternating with periods of prolonged unresponsiveness. According to the guidelines mentioned above, once a patient is considered to be in a PVS, the chances of emerging to an MCS are exceedingly small. Nonetheless, the prognosis of irreversible unconsciousness implied in the term PVS is necessarily probabilistic in nature (cf. Multi-Society Task Force on PVS 1994b, Royal College of Physicians 1996), as confirmed by a small number of documented late recoveries (e.g., Childs & Mercer 1996). The MCS can be permanent or preface emergence to a state of severe disability (which is said to exist when a patient recovers meaningful object use or consistent communication; cf. Giacino et al. 2002).

Other Related Conditions

Finally, it is worth mentioning two additional conditions, brain death and locked-in syndrome (LIS), which, although not typically considered impairments of consciousness, are possible outcomes from the state of postinjury acute coma (see **Figure 1**). Brain death represents a condition of irreversible loss of all functions of the brain, including the brainstem (Am. Acad. Neurol. 1995), as manifested by absolute unresponsiveness to stimulation, absence of all spontaneous muscle activity and brainstem reflexes, and an isoelectric electroencephalogram for 30 minutes, in the absence of hypothermia or intoxication by central nervous system depressants. The LIS, also referred to as pseudocoma, is a condition in which patients are both awake and aware but are either unable to produce any motor response (complete LIS) or severely limited in their behavioral repertoire, typically restricted to vertical eye movements or blinking (partial LIS; Bauer et al. 1979).

ASSESSING AWARENESS AND COGNITION IN DISORDERS OF CONSCIOUSNESS

How do we ever know that someone, other than ourselves, is conscious? In the absence of a direct means of establishing or quantifying the presence of consciousness in the human brain, its assessment must necessarily rely on indirect strategies. The differential diagnosis of brain-injured patients thus relies on the detection (or failure to do so) of behavioral indicators revealing the presence of wakefulness and/or awareness (cf. Monti et al. 2009b). The return of wakefulness, for example, which marks the transition from coma to VS, is unambiguously indexed by the return of periods of eye-opening. The return of awareness, on the other hand, which marks the transition from VS and MCS, is more elusive. Currently, the assessment of awareness is mainly based on careful (albeit subjective) behavioral observation by trained personnel. Spontaneous and elicited behavior in response to multisensory stimulation is recorded in accordance with specific protocols (e.g., Glasgow Coma Scale, Teasdale & Jennett 1974; Coma Recovery Scale-Revised, Giacino et al. 2004; for an overview, see Giacino et al. 2009, Majerus et al. 2005). Regardless of the specific procedure used, the examination is focused on uncovering signs of (*a*) awareness of the self or the environment; (*b*) sustained, reproducible, purposeful or voluntary response to visual, olfactory, auditory, tactile, or noxious stimuli; and (*c*) comprehension of language or expression. If any such evidence is found, the patient is considered to be (minimally) aware (i.e., MCS). Conversely, if no evidence of awareness is found, a VS diagnosis is made.

In the past 25 years, an increasing number of studies, including retrospective clinical audits (Andrews 1996, Childs et al. 1993) as well as direct comparison of alternative clinical assessment protocols (Gill-Thwaites 1997, Schnakers et al. 2006), have shown that misdiagnosis of minimally conscious patients as being in a vegetative state might be as high as 40%. Several issues underlie this alarmingly high rate of misdiagnosis; however, most of them are expressions of a crucial flaw embedded in the logic of assessing the "lack of awareness" (Monti et al. 2009b): Absence of evidence (of awareness) is interpreted as evidence of absence (of awareness). A VS diagnosis thus ultimately relies on a null result, an approach that is prone to false negatives (Owen & Coleman 2008). What if a patient were conscious but unable to convey this fact via a clearly recognizable behavioral response? To illustrate this issue, consider **Figure 3**. The horizontal plane of the graph depicts the same two components of consciousness illustrated in **Figure 2**. On the elevation axis we add a third dimension, which captures the ability of a patient to produce voluntary motor behavior. As for the other two dimensions, we mark a conventional point along the elevation axis (highlighted by the grey plane) separating "behavioral" individuals capable of producing voluntary responses from "nonbehavioral" individuals unable to produce voluntary output. When awareness is absent (e.g., coma, anesthesia, vegetative state, and deep sleep) individuals are unable to produce voluntary output (i.e., they are nonbehavioral). Conversely, aware and awake individuals are typically able to perform voluntary responses (i.e., behavioral). Standard clinical testing based on behavioral responsiveness can thus separate these two classes of individuals. However, if any pathology impairs the ability of a patient to respond to stimulation, behavioral assessments are bound to return false-negative results and thus underestimate the patient's level of residual brain function. Physical disabilities, for example, might entirely mask the presence of residual cognition and awareness in MCS patients. In a large retrospective study, 100% of misdiagnosed patients were indeed found to suffer from motor disabilities (Andrews 1996). Sensory impairments might also have a similar effect (cf. Childs et al. 1993, Gill-Thwaites 1997), particularly if the impairment is in the visual domain (Andrews 1996). In addition, different clinical assessment protocols might be differently able to detect behaviors consistent with the presence of consciousness (Schnakers et al. 2006). Finally, the characteristic inconsistent behavior typical of MCS patients makes it difficult to interpret their responses, and their often protracted periods of unawareness makes it difficult to interpret their failure to respond (Royal College of Physicians 1996).

PET: positron emission tomography

rCBF: regional cerebral blood flow

Effectively, as illustrated in **Figure 3**, there exists a subset of aware patients (i.e., the section of MCS patients that falls below the grey plane) who are impossible to distinguish from VS patients on the basis of current clinical assessments. For this de facto category of nonresponsive MCS patients, a VS diagnosis is technically appropriate, since they show no (behavioral) sign of awareness, but it does not accurately reflect their state of (minimal) consciousness. It is in this context that noninvasive neuroimaging techniques, by observing brain responses instead of behavioral responses, might provide a crucial supplement to bedside clinical assessments (cf. Monti & Owen 2010).

COGNITION IN DISORDERS OF CONSCIOUSNESS

As classically defined, the (persistent) VS implies a uniform and chronic loss of expression of forebrain function (as assessed behaviorally; Jennett & Plum 1972) and therefore the absence of any sign of a functioning mind (Royal College of Physicians 1996). In the past 15 to 20 years, however, novel evidence has clearly shown that despite profound structural and functional damage, several aspects of cognitive processing can be preserved in VS patients. In what follows, we focus on the contribution of neuroimaging techniques to our understanding of brain function in VS and MCS patients.

A central issue that is addressed throughout the following discussion is the evaluation of what can be inferred on the basis of the existing neuroimaging data. Pragmatically, where behavior is limited or absent, neuroimaging may be the only dependent variable accessible to study cognition in this patient group. Nonetheless, assessing the presence of cognitive processes on the sole basis of brain data is an inductive (i.e., probabilistic), rather than deductive (i.e., certain), inference (Henson 2005, Poldrack 2006). Therefore, it is crucial to interpret the data with respect to the specificity of the cognitive paradigms employed (for discussion on the point, see Owen et al. 2006), the degree to which inferences reflect results expected on the basis of prior literature as opposed to posthoc explanations of "surprising" activations (Poldrack 2006), and the use of complementary models to test the inferences drawn from the experiments in this population (e.g., anesthesia, Davis et al. 2007; see Language Processing section below).

Somatosensation and Nociception

Can patients in a vegetative state perceive pain? This difficult question is at the center of many of the clinical, legal, and ethical discussions surrounding disorders of consciousness (cf. Fins et al. 2008, McQuillen 1991, Rifkinson-Mann 2003, Whyte 2008). However, as is the case for other aspects of cognitive processing in this patient population, when self-report is not available, it is difficult to make inferences about whether an individual perceives pain or experiences suffering. Furthermore, according to the Multi-Society Task Force on PVS (1994b), neither behavioral nociceptive responses, such as flexor or extensor spasms and withdrawal of extremities following painful stimulation (e.g., pinprick), nor grimacing and crying behavior necessarily imply the perception of pain. Therefore, the subjective and private nature of the experience of pain as well as our incomplete understanding of its neural substrate have long invited discussion (Klein 1997, Schnakers & Zasler 2007) and development of novel clinical tools (Schnakers et al. 2010).

Laureys et al. (2002a) employed positron emission tomography (PET) to measure changes in regional cerebral blood flow (rCBF) during high-intensity electrical stimulation of the median nerve in a set of 15 persistent VS patients. Despite the overall reduction of brain metabolism, painful stimulation activated subcortical regions, in the midbrain and thalamus, as well as primary somatosensory cortex. Nonetheless, no activation was detected in the hierarchically higher-order cortices observed in a group of healthy volunteers, including secondary somatosensory cortex, insula, anterior cingulate, and posterior parietal cortices. In addition, in the VS patients, primary somatosensory cortex appeared to be functionally disconnected from higher-order associative areas. A similar finding was reported for a group of anoxic patients fulfilling criteria for a permanent VS diagnosis by Kassubek et al. (2003). As for the patients described by Laureys and colleagues (2002a), primary sensory cortex hyperperfusion was detected in response to painful stimulation. In addition, significant responses were also observed in other regions of the pain matrix, in bilateral posterior insula and anterior cingulate, suggesting that to some extent residual cortical processing of noxious stimuli can propagate beyond the first cortical relay. Schiff et al. (2005) employed a (nonnoxious) tactile stimulation paradigm to assess the level of residual somatosensory processing available in two MCS patients. Bilateral hand stimulation elicited activations across several areas typically implicated in somatosensory processing (primary and secondary) as well as higher-level association areas (e.g., parietal and prefrontal cortices), suggesting partial preservation of distributed networks for processing of somatosensory information in patients demonstrating inconsistent signs of consciousness. Taking a step further, Boly et al. (2008) compared the rCBF response to painful median nerve stimulation of five MCS patients to that observed in the healthy volunteers and VS patients described in Laureys et al. (2002a). Overall, no significant difference was observed between MCS patients and healthy volunteers across all the regions of the pain matrix. The two groups did exhibit quantitative differences, but it is unclear whether these reflected a genuine lower-level rCBF response in MCS patients or the uneven sample sizes across the two groups (i.e., 15 versus five for healthy volunteers and MCS patients, respectively). Despite a similar sample-size imbalance, direct comparison of VS and MCS patients revealed significantly greater activations throughout the whole pain matrix for the latter group. Furthermore, the level of functional connectivity between primary somatosensory and lateral fronto-parietal cortices in the MCS group was comparable to that observed in healthy volunteers, in contrast to the lack of connectivity observed in the VS patients (Laureys et al. 2002a).

These findings suggest that the sensory-discriminative component of pain, putatively housed in primary and secondary somatosensory cortices, can be preserved beyond the boundary of unconsciousness (due to severe brain injury), perhaps subsisting as a residual cognitive module dissociated from the higher-order cortices that would be necessary to produce awareness (Schiff et al. 2002). On the other hand, the affective and motivational component of pain, supposed to rely on anterior cingulate cortex and prefrontal areas, appears to be absent in VS patients. In contrast, conscious (albeit minimally) patients demonstrate a quasi-normal metabolic response to noxious stimuli, suggesting they possess the processing resources necessary to generate the subjective feeling of pain. However, it is important to stress that the exact functional significance of activations in the so-called pain matrix, as well as their specificity to noxious stimulation, is currently debated (Mouraux et al. 2011). This uncertainty prevents interpreting activations in these areas as unequivocal evidence of pain-specific cortical processing. Overall, then, the questions of whether VS patients actually retain anything similar to the subjective experience of discomfort and pain reported by healthy volunteers remains at present outside the reach of neuroimaging studies.

Vision

From a clinical standpoint, visual processing abilities in patients surviving severe brain injury have received much attention. According to current guidelines, the ability to maintain fixation or orient gaze voluntarily (e.g., visual pursuit) is sufficient to distinguish MCS from VS patients (Giacino et al. 2002). Furthermore, visual tracking is often one of the first observable signs of recovery (Multi-Society Task Force on PVS 1994a, Shiel et al. 2000). Consequently, clinical assessment protocols that do not explicitly test for residual visual abilities suffer from higher rates of misdiagnoses fMRI: functional magnetic resonance imaging

(Schnakers et al. 2006), and patients who suffer from visual impairments are often misdiagnosed (Andrews et al. 1996). The degree of visual information processing and (neural) representation of visual information that may be available at the lower boundaries of consciousness, however, has received less attention.

In a series of pioneering PET studies, Menon et al. (1998) and Owen et al. (2002) investigated metabolic response to visual stimulation in a persistent VS patient. Surprisingly, simple visual stimuli and pictures of familiar faces elicited a metabolic response comparable to that observed in healthy volunteers (in primary visual cortex and the fusiform gyrus). In 2006, Giacino and collaborators reported significant rCBF changes in primary visual cortex in response to simple pattern flashes (as compared to no stimulation) in each of five persistent VS patients (Giacino et al. 2006). In a functional magnetic resonance imaging (fMRI) adaptation of this approach, the authors also reported significant activations in primary and higher-level visual cortices (e.g., fusiform gyrus) in response to more complex stimuli (i.e., pictures of familiar and unfamiliar faces, hands, and landscapes) for an MCS patient. In contrast to the neuroimaging result, the patient failed to show any evidence of object recognition on standardized bedside assessment of visual function. Giacino et al. (2009) employed a similar paradigm to assess the degree of cognitive function in an anoxic patient exhibiting characteristically infrequent, inconsistent, and qualitatively ambiguous signs of consciousness. Simple patterns of light stimulation, pictures of faces, and pictures of landscapes all elicited activation in the medial sections of occipital cortex. In addition, pictures of faces and landscapes selectively recruited regions of the fusiform and parahippocampal gyri, respectively, consistent with high-level processing of the stimuli.

Taken together, these results show that patients with DOC can retain some level of visual processing. Furthermore, they illustrate the wide discrepancy that may exist between observable behavior and the underlying neurophysiologic processes believed to support cognitive processing (Giacino et al. 2009). However, passive paradigms comparing brain response to different stimuli (e.g., light versus dark, pictures of faces versus scrambled versions of the same images) only allow inferring metabolic integrity of (some aspect of) neurocognitive systems. Whether patients consciously perceived the images cannot be determined (cf. Monti & Owen 2010), for it is well established that brain activation in high-level visual areas (e.g., fusiform gyrus) can be detected in the absence of any subjective conscious perception (Dehaene et al. 2006). To address this issue, Monti et al. (2011) developed a 3T fMRI hierarchical approach assessing both passive and active aspects of visual cognition (**Figure 4**). In a series of steps, they tested several levels of visual cognition, including response to light, color, motion, organized contours, and discrimination of different categories of objects (i.e., faces versus houses). In addition, at the last step of this battery, Monti et al. (2011) presented a set of figures, each consisting of a face and a house overlaid on top of each other (see **Figure 4**). During this section of the experiment, participants were prompted to alternate periods of focusing on the house to periods of focusing on the face. Importantly, each figure was presented twice, once under the instruction to focus on the face and once under the instruction to focus on the house. Consequently, any difference detected between the two periods can only be interpreted as reflecting different (voluntary) mental processes. When an MCS patient was assessed on the passive levels of the battery, brain activations were observed in the same occipital and temporal regions seen in a set of healthy volunteers. In addition, in the active level of the battery, metabolic response in the fusiform gyrus was up-regulated in the periods in which the patient was instructed to focus on the faces as compared to the periods in which the patient was required to focus on the houses (**Figure 4**). The converse pattern was observed in the parahippocampal gyrus. These results mirror the activations seen in healthy volunteers performing the same task. In contrast to the fMRI result, no evidence of object discrimination/recognition or command-following was evident during standard clinical assessments (similarly to the case described in Giacino et al. 2009). This result shows that where appropriate paradigms are employed (cf. Monti & Owen 2010), it is possible to infer not only the presence of residual (automatic) bottom-up processing, but also the presence of consciously mediated top-down processes, such as deploying visual attention in response to verbal commands.

Despite this series of intriguing results, it is important to stress that at present there is no systematic group study addressing the degree of residual bottom-up and top-down visual cognition available in VS and MCS patients and evaluating the discrepancy between the visual behavior that is observable at the bedside and that is observable with functional neuroimaging.

Audition

To date, audition has been the most exploited modality in studying residual cognitive processes in DOC patients. The advantage enjoyed by this modality rests on at least two practical/experimental considerations. First, listening to sounds through a headphone requires very little cooperation on the part of a subject, even for complex stimuli. Second, the effectiveness of auditory stimulations does not depend on anything other than integrity of the auditory system itself. Visual stimulation, in contrast, requires motor behaviors that are often compromised in these patients (e.g., maintenance of eye-opening, fixation, and pursuit) for anything more complex than light flashes.

Laureys et al. (2000b) recorded rCBF changes in response to simple auditory clicks in a sample of five persistent VS patients. In healthy volunteers and patients alike, the stimuli elicited significant activity in bilateral primary auditory cortices, including the transverse temporal and the superior temporal gyri. Healthy volunteers also exhibited activations beyond primary cortices, in the lateral sections of the superior temporal gyrus and the superior temporal sulcus contralateral to the stimulation. No such response was apparent for the patients. Furthermore, VS patients exhibited significantly less functional connectivity between cortical regions than did volunteers. Reductions in functional connectivity were apparent between the primary auditory cortex contralateral to the stimulation, its homologous region in the opposite hemisphere, and posterior temporal and parietal regions contralateral to the stimulation. A similar reduction of functional connectivity was also apparent between the superior temporal sulcus contralateral to the stimulation and areas previously associated with higher-order processing of auditory stimuli (e.g., hippocampus and cingulate cortex; see the discussion section in Laureys et al. 2000b). This finding, mirrored in other modalities (cf. Laureys et al. 2002b), suggested a limited engagement of auditory processes in VS patients confined to subcortical and primary cortical relays only. Employing the same paradigm, Boly et al. (2004) assessed rCBF changes in 15 VS and five MCS patients. All volunteers and patients exhibited bilateral responses in primary cortical areas. Activation in higher-order processing regions, however, was observed only in healthy volunteers and MCS patients. Direct comparison of activation levels for VS and MCS patients failed to show significant differences. Nonetheless, the two groups differed significantly in the degree of functional connectivity between secondary auditory regions and areas in the posterior superior temporal and middle temporal gyri as well as regions of the inferior, middle, and superior frontal gyri. These results integrate the findings of Laureys et al. (2000b) in two ways. On the one hand, they extend to a greater sample the finding of limited cortical activation and functional connectivity observed in VS patients. On the other hand, they show physiological differences mirroring the state of consciousness of patients. Due to the strong sample imbalance (five MCS versus 15 VS), it is difficult to interpret the null result, with respect to activation levels, between the two groups. Nonetheless, is noteworthy that a qualitative

EEG: electroencephalography

ERP: event-related potential

change in state (i.e., minimally conscious versus nonconscious) was clearly captured by the degree of residual connectivity between hierarchically organized cortical relays. As we discuss below, the functional disconnection of neurocognitive modules might play a key role in the failure of residual information processes to generate the subjective experience of perception (Giacino et al. 2006, Schiff et al. 2002).

A different question relates to which aspects of auditory information processing underlie the observed metabolic responses to simple sounds. Jones et al. (2000) employed electroencephalography (EEG) to assess the degree of early-stage analysis of sounds that is preserved in patients with severe brain injury. In a sample of 22 postcomatose patients, ranging from nonresponsive/VS to communicative, they recorded auditory-evoked potentials (AEPs) triggered by changes in tone pitch, timber, and in tone sequences. Surprisingly, only one patient exhibited no AEPs to any of the conditions. Twelve patients exhibited clear responses [e.g., N1 and mismatch negativity (MMN) potentials], whereas the remaining patients exhibited less-clear evidence of appropriate information processing. These findings suggest that the activations uncovered in the PET studies discussed above might entail (to a minimum) processes related to the analysis of pitch and timber as well as the comparison of incoming sounds to an image or template of the previous ones (e.g., echoic memory; Jones et al. 2000). In addition, for most patients, the level of auditory responsiveness observed with EEG matched that observed in bedside clinical testing. In four cases, however, the two sources of evidence were in disagreement, including two in which AEPs were present in the absence of behavioral responses and two exhibiting the reverse pattern. (The issue of noncorrespondence between behavioral and neuroimaging responses is discussed in the Volition section below.)

Kotchoubey et al. (2005) tested the notion that only MCS patients retain some level of information processing in higher sensory and association areas. Employing a combination of stimuli (e.g., sine waves, harmonic chords, words, sentences) and experimental procedures (e.g., oddball and MMN paradigms), Kotchoubey et al. (2005) assessed several neurophysiological indices of cortical processing [i.e., event-related potentials (ERPs)]. Importantly, different ERPs occur at different latencies from the target event, presumably reflecting increasingly deep aspects of information processing (e.g., primary undifferentiated auditory cortical responses in the 60 to 100 ms range; deep processing of high-level aspects of a stimulus in the 300 to 500 ms range). As expected, for the quasi totality of VS patients with nonpathological resting EEG slowing (i.e., background EEG activity smaller than 4 Hz), early aspects of primary undifferentiated auditory cortical responses (in the 60 to 140 ms range) were observed, together with the preattentive MMN component (cf. Jones et al. 2000). However, in contrast to the idea of limited cortical processing proposed in Laureys et al. (2000b) and Boly et al. (2004), a significant number of VS (and MCS) patients also exhibited late components, in the 400 to 600 ms interval, elicited by the semantic features of stimuli (e.g., semantic relatedness of pairs of words). Remarkably, although VS patients exhibited lower frequency of preserved higher-level information processing than did MCS patients, the difference disappeared when the two groups were matched for background EEG activity. In fact, the major differences were observed between VS patients with very severe background EEG disturbances and VS patients with moderate disturbances only. Where the resting EEG was below 4 Hz, no response was observed beyond the very early components. As discussed by Kotchoubey et al. (2005), this finding stresses the centrality of the thalamo-cortical gating system in mediating neural mechanisms of perception.

Overall, these studies (among several others) show that several complex aspects of auditory information processing can be preserved in VS patients despite not giving rise to the subjective feeling of perception.

Progressing beyond the automatic aspects of auditory processing, Bekinschtein et al. (2009a) employed a clever two-level auditory violation paradigm to assess the presence of subjective phenomenal awareness (of auditory stimuli) in a cohort of four VS and four MCS patients. In particular, they measured brain response at the scalp for "local" violations (i.e., a deviant tone following a repeating standard tone) and for "global" violations (i.e., a deviant sequence of tones following a repeating standard sequence of tones). As observed in previous studies, local violations are known to elicit automatic auditory processes (cf. Kotchoubey et al. 2005). Conversely, detection of global violations depends upon several additional cognitive processes that are believed to require the presence of consciousness. In particular, global violations require the ability to extract a rule (i.e., the standard sequence) and maintain it through time, as new sequences are delivered. As expected, the two kinds of violations elicited distinct spatio-temporal ERP patterns, with the global violation occurring significantly later in time. Crucially, the latter component was shown to disappear when individuals were distracted by a concurrent task or by simply mind-wandering, confirming the link between subjective awareness of the global structure of the task and the presence of the late ERP response. Consistent with previous findings, all MCS patients and three VS patients exhibited a significant response to local violations. No VS patient, however, exhibited a response to global violations, whereas three out of four MCS patients did, which suggests that violation of global regularities can indeed serve as a marker of conscious auditory processing.

Language Processing

The study of language processing in this population is driven by several different motivations. From a scientific standpoint, language is a central aspect of the human mind. From the clinical viewpoint, language comprehension and restored communicative ability are diagnostic milestones (implying transition from VS to MCS and emergence from MCS, respectively; cf. Giacino et al. 2002).

Pioneering the use of hierarchical experimental designs in this patient group, Owen et al. (2002, 2005b) employed PET and fMRI to assess increasingly complex levels of auditory and language processing in two VS patients. In both cases, the comparison of sound epochs to periods of silence revealed extensive rCBF increases in the bilateral superior temporal planes, consistent with previous reports (Laureys et al. 2000b). As depicted in **Figure 5**, both patients also exhibited significant rCBF changes, in the superior and middle temporal gyri, in response to hearing short sentences (as compared to an unintelligible version of the same stimuli obtained by disrupting the spectral and temporal properties of speech while preserving the duration, amplitude, and overall spectral composition of the original). This result, which closely matches the activations seen in healthy volunteers, demonstrates that in the two patients, residual auditory and linguistic processes were sufficient to discriminate patterns of sounds organized according to the rules of a natural language (i.e., English) from patterns of sound that lack this form of organization. At the top level of this hierarchy, Owen et al. (2005b) employed fMRI to compare, in one patient, brain response to sentences containing high-ambiguity words (e.g., "There were dates and pears in the fruit bowl") to sentences containing only low-ambiguity words (e.g., "There was beer and cider on the kitchen shelf"). In healthy volunteers, this subtraction has been shown to recruit left lateralized posterior sections of the inferior temporal gyrus and the inferior frontal gyrus. In the patient, however, significant activation was only detected within the posterior temporal regions. Nonetheless, these findings imply that VS patients may possess sufficiently preserved language-related processes to enable detection of speech as a specifically organized form of sound sequences and to enable detection (and presumably selection) of context-appropriate meaning.

Employing a similar approach, Schiff et al. (2005) assessed responses to simple narratives and a backward-played version of the same stimuli in two MCS patients. Intelligible and nonintelligible (i.e., backward) narratives equally recruited primary auditory areas in the transverse section of the superior temporal gyrus and in language-sensitive regions in the superior and middle temporal gyri. Although weak, some activations in response to forward narratives were also observed in inferior frontal and posterior parietal cortices, further confirming that information processing can occur beyond primary sensory areas. Extending this experimental approach to a larger cohort of patients, Fernández-Espejo et al. (2008) compared brain activity in response to sounds, specifically to speech sounds, in a cohort of three VS and three MCS patients. In four patients (two VS and two MCS), the comparison of all sounds (i.e., narratives and unintelligible narratives) versus epochs of silence revealed activations in primary auditory cortices and in the superior and middle temporal gyri. Consistent with the results of Schiff and Owen, language-specific activations (uncovered by comparing intelligible and unintelligible narratives) were also detected in middle temporal gyrus in one MCS patient and in middle and superior temporal gyri in one VS patient. The prevalence of high-level processing of sounds and speech was examined in a large cohort of patients (22 VS and 19 MCS) by Coleman and colleagues (Coleman et al. 2007, 2009). Using the hierarchical approach described in Owen et al. (2005a), 41% and 84% of patients (VS and MCS, respectively) demonstrated appropriate superior temporal activity in response to sounds. In 32% and 63% of cases, significant speech-specific activity was also detected (in superior temporal cortex). Finally, 9% of VS and 10% of MCS patients exhibited (limited) selective response in inferior frontal and/or posterior temporal regions to high-ambiguity sentences.

Do these findings imply that patients comprehended the sentences? Davis et al. (2007) addressed this very issue by assessing brain responses to nonspeech and (ambiguous and nonambiguous) speech stimuli in sedated healthy volunteers. Bilateral superior temporal activations in response to sounds (in general) and speech sounds (specifically) were detected at all levels of sedation. Conversely, light amounts of sedation were sufficient to obliterate any brain response specific to high-ambiguity sentences. Importantly, the decreased level of activation in inferior frontal and posterior temporal regions correlated significantly with postexperiment recall of the (intelligible) stimuli. This finding thus links observed brain response to actual encoding of the verbal materials and suggests that states of decreased consciousness (at least as induced by anesthetic agents) affect the higher-level processes involved in computing the meaning of sentences and encoding them into memory. Conversely, the lower-level aspects of speech processing appear to remain intact even as consciousness fades (consistent with the brain injury data; e.g., Kotchoubey et al. 2005).

Perrin et al. (2006) employed EEG to explore semantic processing of self-related stimuli (e.g., the subject's own name) in DOC patients. As expected, for all six MCS patients (as well as four LIS patients), hearing one's own name elicited a significant positive deflection (i.e., P3 wave) as compared with hearing other first names. The P3 potential is known to respond to stimulus saliency in general (e.g., acoustic rarity); however, because all names were presented with equal probability, in this circumstance it is more likely to reflect the semantic saliency of one's own name. Out of four VS patients, two exhibited a significant P3 response, consistent with other reports (e.g., Kotchoubey et al. 2005, Owen et al. 2005b). Although this response certainly entails semantic processing of the stimuli, the P3 is known to occur without conscious perception (e.g., in subliminal presentations). Indeed, the P3 response did not differentiate VS from MCS (or LIS) patients. Similar findings have also been reported with longer latency potentials [i.e., a potential with negative deflection around 400 ms (N400)] in response to sentences containing semantic anomalies (e.g., "The coffee is too hot to fly"; Schoenle & Witzke 2004).

Finally, aspects of speech prosody, including emotional prosody and affective processing, have also received some attention. These aspects of language processing are particularly interesting because they appear to be modular with respect to other components of language (e.g., semantic and syntactic interpretation; cf. Kotchoubey et al. 2009, p. 154). Furthermore, emotionally salient stimuli have been reported to increase the chances of eliciting (brain) responses in comatose patients (Signorino et al. 1995). Affective processing in a 16-year-old persistent VS patient was examined by de Jong et al. (1997). As compared to nonspeech sounds, personally relevant narratives read by the patient's mother elicited significant activation in right middle temporal cortex (the left hemisphere was heavily lesioned), as well as the anterior midline sections of the cingulate gyrus, and right precentral gyrus. Although these activations are consistent with affective processing of narratives, the use of nonwords as a baseline condition does not allow us to exclude that they reflect a more general language-specific response. This issue was controlled for in a later case report of an MCS patient (Bekinschtein et al. 2005). Using fMRI, the brain response to the voice of the patient's mother was compared with the brain response to an unfamiliar voice. As compared with silence, the latter stimulus elicited activations in superior temporal regions as well as in more anterior regions (in the insula), consistent with previous findings (e.g., Schiff et al. 2005). As compared with the unfamiliar voice, listening to the mother's voice elicited additional strong activations in the amygdala and insula, spreading to the inferior frontal gyrus (among other areas). In contrast to the de Jong et al. (1997) study, the experimental design employed by Bekinschtein and colleagues allows interpreting activations in emotion-related areas as reflecting a selective affective response to the familiar stimulus. In a larger cohort study, Kotchoubey et al. (2009) focused on a negative ERP putatively regarded as an electrophysiological marker for recognition of changes in emotional prosody (i.e., N300). Using an oddball paradigm, they contrasted the response to one (deviant) exclamation of awe interspersed among four (standard) exclamations of joy. In six out of 27 patients, significant ERPs were observed in response to the affective oddball (i.e., the sad stimulus). Although patients with a clear temporal lobe lesion exhibited a significant lower proportion of N300 responses, no difference was detected between VS and MCS patients, a finding that is in line with several previous reports demonstrating preservation of a large part of automatic processes across the boundary of (minimal) consciousness.

Taken together, these findings clearly indicate that several high-level aspects of language, including semantic and affective processing, can remain in VS patients. However, it should be stressed that these positive findings demonstrate the ability of a brain to discriminate the presence/absence of a given target feature (e.g., affective tone) but not that the patient had any conscious experience of the feature itself (e.g., the emotional content of utterances).

Learning and Memory

Kotchoubey et al. (2006) first assessed the presence of preserved cortical dynamics consistent with elementary forms of learning in a group of 33 VS patients. The design included a sequential presentation of ten simple tones at 400 ms intervals. Sequences were repeated, at 5 s intervals, in blocks of 10, and the whole block was then repeated 10 times. Across the group of VS patients, decreases in the amplitude of the negative AEP typically observed about 100 ms poststimulus (i.e., N1) support the idea of at least two forms of preserved elementary learning. On the one hand, within each single series, the N1 response decreased in amplitude from the first tone presentation to the tenth, indicating short-term habituation. On the other hand, a significant decrease in N1 amplitude was also observed across runs (i.e., from the first sequence of ten tones to the last), indicating longer-term habituation. This result suggests that in VS patients, auditory cortices can retain the ability to learn to selectively ignore repeated irrelevant stimuli. Nonetheless, the processes reflected in the N1 response are known to be automatic in nature. A higher-level form of learning, straddling the boundary between learning and consciousness, was recently explored by Bekinschtein et al. (2009c) using electromyographic recordings. In a sample of 13 VS and seven MCS patients, they employed a trace conditioning paradigm to assess the presence of learning processes. In this paradigm, two auditory tones are presented, with one of the two being associated, after a temporal delay, with an air-puff to the cornea. Crucially, as compared with classical conditioning, trace conditioning requires an active cognitive bridging of the tone (conditioned stimulus) and the air-puff (unconditioned stimulus) across a temporal delay. This bridging has been shown to require a widespread cortical and cerebellar network (including the hippocampus and prefrontal cortex) and awareness of the contingency between the two stimuli. Across healthy volunteers and patients, three different patterns were observed. Half of the volunteers (eight out of 16), two VS patients, and one MCS patient exhibited clear learning of the contingency between one of the tones and the air-puff as shown by increasing peri-ocular muscle activity following the tone paired with the air-puff. Furthermore, the muscle activity during the temporal delay increased in close proximity to the air-puff delivery. At the same time, no significant anticipatory muscle activity was recorded after the tone that was not associated with the air-puff. At a more lenient criterion, five additional controls, two VS patients, and one MCS patient also exhibited a difference between muscle activity in the late and early stages of the temporal delay. A subset of participants (one control, four VS, and three MCS) exhibited some amount of nonspecific learning. For them, significant muscle activity was observed in the late stages of the temporal delay, but for both the paired and unpaired tones. The remaining seven patients (five VS, two MCS) and three healthy volunteers failed to show any evidence of learning. Interestingly, four out of the five VS nonlearners had non-traumatic brain injury etiologies, consistent with their overall poorer prognosis (cf. Monti et al. 2010a). Groupwise, VS and MCS patients did not show significant differences, both equally exhibiting less overall learning and less specific learning in comparison with healthy volunteers. Nonetheless, for the reasons mentioned above, the finding of preserved trace-conditioning learning in patients with DOC is remarkable and is likely to index the presence of some level of consciousness. Indeed, when the same experiment was performed on a set of 12 volunteers undergoing anesthesia, only one participant exhibited some level of learning (though only when employing the more lenient test criterion). Finally, a remarkable finding of Bekinschtein and colleagues (2009c) is the close relationship between clinical improvement (within a six-month to two-year follow-up period) and the presence of trace conditioning. Clinical improvements were observed for all but three of the patients exhibiting some level of learning. Even more significant, not one of the patients failing to exhibit any sort of learning showed clinical improvements. Overall, these results can either be interpreted as demonstrating a more sensitive approach to uncovering the presence of consciousness in severely brain-injured patients or, to a minimum, as a means to detect integrity of distributed circuits that are necessary for a brain to recover at least minimal consciousness. As a footnote, it should be stressed that, in contrast to all the paradigms designed to assess the presence of awareness that I discuss in the following paragraphs, the approach of Bekinschtein et al. (2009c) has the very desirable quality of not requiring verbally mediated instructions. This feature might allow this approach to detect traces of awareness even in patients with aphasia, a condition that is likely to affect a subset of DOC patients (Majerus et al. 2009).

Executive Functions and Attention

In a modified version of the subject's own name paradigm discussed above, Schnakers et al. (2008) tested the ability of 22 patients (eight

VS and 14 MCS) to voluntarily direct attention to a target name interspersed among a set of nontarget names. During the passive component of the task, ERPs were recorded while patients listened to a series of names, including their own. In the active component of the task, patients were instructed to count, at different times, either the number of repetitions of their own name or the number of repetitions of a target unfamiliar name. Consistent with previous results, passive listening to one's own name elicited, in MCS patients and volunteers alike, a significant P3 deflection. In contrast to the results reported by Perrin et al. (2006), however, no P3 was observed for any of the VS patients. In addition, as compared to passive listening, active counting elicited significantly greater P3 waves in nine MCS patients (five in response to actively listening for their own name and four in response to actively listening for a target other name). Despite greater P3 latencies in the active condition, a likely sign of slower information processing consequent to severe brain injury, MCS patients and volunteers did not exhibit significantly different response amplitudes, which suggests that a subset of patients is able to voluntarily allocate top-down attention. Making exclusive use of nonintrinsically salient stimuli, Monti et al. (2009a) assessed global state changes correlating with the active maintenance of information through time while monitoring for incoming information. In their design, an MCS patient (as well as a set of healthy controls) was prompted to either passively listen to a set of neutral words or to count the occurrences of a randomly chosen target word (different for every block). The two conditions were matched in all perceptual respects, ensuring that any difference between the two could only reflect the process of actively holding in mind information through time, something that is considered to require conscious awareness (Dehaene & Naccache 2001). Consistent with the results of Schnakers et al. (2008), the comparison of active counting epochs and passive listening uncovered significant activity in a subset of fronto-parietal regions typically recruited by tasks requiring executive functions and considered to be a crucial component of the neural basis of consciousness (for greater discussion on the point, see Monti et al. 2009a). These two studies demonstrate the high level of executive and attentional functions that can be preserved in MCS patients. Indeed, in both approaches, differential activity across active and passive tasks is difficult to explain without assuming a conscious decision on the part of the patient to assign, in a top-down fashion, saliency to otherwise neutral words, to actively maintain a target word in working memory, and to monitor incoming stimuli. As expected, however, this kind of active cognitive process can be seen in some MCS patients but not in VS patients.

Volition and Communication

In a landmark paper, Owen et al. (2006) described the case of a persistent VS patient who, despite showing no signs of consciousness during standard clinical assessments, could unequivocally demonstrate a state of consciousness by willfully modulating her own brain activity in response to verbal commands. In this paradigm, the patient is instructed to imagine playing tennis (motor imagery), to imagine walking around the rooms of her house (spatial imagery), or simply to relax (baseline). Crucially, throughout the three conditions, no stimulation is delivered beyond a one-second verbal cue, at the beginning of each 30-second epoch, instructing the patient on what task to engage in (i.e., "tennis," "house," and "relax," for motor imagery, spatial imagery, and baseline epochs, respectively). As shown in **Figure 6**, when epochs of motor imagery were compared to rest epochs, activations were observed in the same medial frontal regions active in healthy volunteers performing the same task. Conversely, when spatial imagery epochs were compared to rest, activations were detected in the parahippocampal gyri for both the patient and healthy volunteers. This result, in stark contrast to the patient's persistent VS diagnosis, necessarily implied that she must have been, to some extent, conscious.

Could this activation reflect automatic responses to the one-second verbal cues? As discussed in Owen et al. (2007), this is unlikely for several reasons. First, each epoch of imagery (and rest) lasted 30 seconds, requiring brain responses to be protracted in time in order to reach statistical significance. The automatic responses generated by word stimuli are known to occur on a much shorter time scale (within the first few hundred milliseconds; Hauk et al. 2004) and in language-sensitive areas, not in the supplementary motor area or the parahippocampal gyri. Furthermore, when the same cues were delivered to healthy volunteers who had not been instructed to respond by engaging in mental imagery, no activation was detected. Similarly, no activation was detected when cues were replaced with more evocative sentences (ending with the cue word; e.g., "The man played tennis," "The man walked around his house"; Owen et al. 2007). The patient described by Owen et al. (2006) thus illustrates exactly the circumstance depicted in **Figure 3**: Minimally conscious patients who cannot perform sufficiently clear motor responses (i.e., the section of the MCS sphere below the grey horizontal plane) are indistinguishable from VS patients on the basis of clinical (i.e., behavioral) assessments alone. It is this very kind of patient who is at risk of being misdiagnosed and who would maximally benefit from non-muscle-dependent assessments (including fMRI, EEG, MEG, and electromyography).

In a study of 23 VS patients (among others), Monti et al. (2010b) reported four patients who produced significant responses to the imagery tasks described above. Despite the fMRI results, for two of these patients, repeated bedside clinical examinations consistently yield no observable sign of awareness. For the remaining two, thorough clinical assessments could uncover inconsistent but detectable responses. On the one hand, this finding further confirms the link between behavioral nonresponsiveness and VS misdiagnosis. On the other hand, it highlights the importance of thorough bedside assessments. Taking advantage of one patient's ability to produce brain responses to command, Monti et al. (2010b) employed the imagery paradigm as a strategy for the patient to respond to simple binary questions. The patient was asked a simple binary question (e.g., "Is your father's name Alexander?") and was instructed to engage in motor imagery to convey an affirmative response and in spatial imagery to convey a negative response. For five of the six questions, the pattern of activations detected matched the factually correct answer. (No significant activity was detected in the sixth question.) Importantly, response epochs were all cued with the neutral word "answer"; it was the patient's task to decide which imagery was to be performed to correctly respond. This small modification of the paradigm definitively puts to rest any uncertainty concerning the possibility that the activations observed in Owen et al. (2006) and here could be automatic responses triggered by the semantics of the words tennis and house.

Despite the success of active fMRI paradigms in uncovering signs of awareness in patients who appear vegetative at the bedside, negative results are typically reported in the vast majority of cases. How should these be interpreted? For some patients, negative findings might genuinely reflect a state of unconsciousness. Other patients, instead, might be conscious but lack some cognitive process necessary to comprehend a set of instructions or perform a specific task. However, in some cases the failure to detect any activation might reflect genuine false negatives. This circumstance was recently described by Bardin et al. (2011). A patient who had emerged from MCS produced no detectable activation in the imagery task described above, despite her ability to behaviorally report, outside the MRI machine, her active engagement in the task. In a second case, an LIS patient could produce significant activations in response to the imagery command but could not employ this strategy to communicate, despite being able to do so at the bedside. The reverse dissociation, with fMRI results exceeding what was observed at the bedside, was reported for an MCS patient who could communicate using a neuroimaging strategy (as in Monti et al. 2010b), but not at the bedside. Finally, for the three remaining patients, fMRI and behavioral results were in agreement.

Overall, dissociations between what is observable at the bedside and what is observable in neuroimaging tests can be as informative (where positive neuroimaging results are observed in the absence of positive behavioral results) as they are problematic (where negative neuroimaging results are observed in the presence of positive behavioral findings). Nonetheless, false negatives are a consistent problem known to occur in low-level EEG studies (e.g., Jones et al. 2000; see Audition section above) as well as in behavioral assessments (e.g., Schnakers et al. 2006).

In light of these and other factors (e.g., MRI versus EEG portability), John et al. (2011) used source localization methods to explore an EEG version of the imagery paradigm. Despite a pathological EEG profile (e.g., excesses of slow delta and theta oscillations, with markedly decreased alpha and beta activity), imagining singing and performing mental arithmetic revealed different (probable) sources of electrical activity recorded at the scalp. In particular, singing imagery elicited mostly bilateral medial and frontal activations, whereas mental calculation recruited (among others) left lateralized inferior frontal and inferior temporal regions as well as right lateralized temporo-parietal regions. Despite the fact that the activations for the two tasks were not quantitatively compared, each pattern closely matched the activations observed in a healthy control performing the same tasks. Although this is a single case report, and in fact the first report of an anoxic VS patient demonstrating awareness via brain imaging methods, this result highlights the potential of quantitative EEG measures. In a systematic large-scale study, Cruse et al. (2011) employed classification algorithms to distinguish foci of imagery-induced synchronization and desynchronization of electrical activity recorded at the scalp. In their paradigm, a set of 16 VS patients (and 12 volunteers) performed imaginary movements of their right hand and of their feet. For three out of 16 diagnosed VS patients, a support vector machine algorithm could recognize and distinguish spatio-temporal patterns in the EEG for the two tasks with significant accuracy (comparable to that observed in healthy volunteers; 61%, 71%, and 78% for each patient, respectively). Importantly, the classifier was at chance when attempting to classify precue epochs (i.e., 500 ms prior to each cue prompting the patients to engage in the imagery task), indicating that the finding is specific to the periods of imagery execution. In addition, the classifier was also at chance when attempting to classify spatio-temporal patterns observed in healthy volunteers listening to the same auditory cues but without having been instructed to engage in mental imagery. This finding discounts the possibility that the observed activations and successful classification results depended on automatic processes elicited by the semantics of the cues.

Overall, this series of studies confirms that an important share of patients with a VS diagnosis (17% and 19% in Monti et al. 2010b and Cruse et al. (2011), respectively) can be observed to respond to command, and even engage in basic communication, using neuroimaging techniques.

Self-Awareness

The presence of self-awareness in DOC patients is an important clinical milestone (cf. Giacino et al. 2002). However, assessing the presence of self-awareness and self-reflection in patients who are unable to express their thoughts is extremely challenging (Laureys et al. 2007). Nonetheless, as described above, some studies have focused on brain response to self-relevant stimuli (e.g., Perrin et al. 2006). In an fMRI version of the subject's-own-name task, Di et al. (2007) reported that five out of seven VS patients (as well as four out of four MCS patients) exhibited primary auditory activity in response to their own name. In addition, in two VS patients (and all MCS patients), activations in higher-level posterior temporal cortices were also detected. Unfortunately, it is difficult to assess the specificity of these activations to self-related processing considering that epochs of silence (or rather, scanner noise) served as a baseline comparison. Nonetheless, it is noteworthy that the two VS patients exhibiting significant activation beyond primary cortices recovered some level of consciousness by three months after the MRI session. In a similar fMRI experiment, Qin et al. (2010) reported significant activations for six out of seven VS patients in one or more of three medial prefrontal regions previously linked to processing self-related stimuli (in caudal and rostral sections of the anterior cingulate gyrus, the ACC, and the SMA; for an overview, see Laureys et al. 2007). The same regions were also found to be active in all four tested MCS patients. As for the study by Di and colleagues (2007), the lack of a baseline task prevents interpreting the findings as clear evidence of selective processing of self-related materials. However, the areas they assessed were shown in healthy volunteers to be selectively engaged by the subject's own name, and not other names, particularly when spoken by a familiar voice (see experiments I and II in Qin et al. 2010). In addition, the activation in the caudal section of the ACC was significantly different for VS and MCS patients and thus significantly correlated with behavioral measures of consciousness. Finally, the only two VS patients exhibiting significant activations in this specific area progressed to MCS by three months after the MRI session, consistent with the report by Di et al. (2007).

Overall, these initial results suggest that some aspect of self-related processing may well be preserved in MCS patients and that when markers of self-related processing are observed in VS patients they might herald some level of recovery. It is nonetheless important to stress that the selectiveness of these brain responses to self-related stimuli is still to be established in DOC patients. Similarly, it is also to be established whether they bear any substantial connection to the subjective feeling of self-awareness.

DISCUSSION: A FUNCTIONALLY DISCONNECTED BRAIN?

One of the most consistent findings in VS patients is a strong decrease of brain metabolism (typically around 40% of the values observed in healthy volunteers; De Volder et al. 1990, Laureys et al. 2002b, Levy et al. 1987, Tommasino et al. 1995). Nonetheless, it is now clear that, albeit in the absence of conscious awareness, the vegetative brain can sustain complex aspects of information processing across sensory modalities. The specific kind and extent of information processing that may be available in a given patient, however, is likely to be primarily dependent upon the specific pattern of brain injury. So far, the study of residual cognition and consciousness in this patient cohort has centered on single-case reports and central tendencies, leaving a significant amount of within-category variance (e.g., within the group of VS patients) largely untackled. In this respect, future development of truly multimodal technology, where structural analysis informs and merges with functional results, will be a necessary step toward explaining patient-specific variability.

How can we interpret the level of residual function observed in VS patients and its failure to generate phenomenological awareness? One possibility is to allow for residual information processing to extend to primary sensory cortices only (e.g., Boly et al. 2008, Laureys et al. 2002b) without it propagating to higher-level and polimodal integration areas that might be necessary for conscious experience (cf. Dehaene et al. 2006). The evidence, however, suggests that this might not be a correct characterization of the "vegetative" brain. Indeed, fMRI and EEG studies have well demonstrated the presence of activations beyond primary cortices and ERP components believed to require coordinated activity across cortical regions (e.g., P3 and N400). An alternative hypothesis is that residual cognition in VS patients might reflect isolated cognitive modules that, in the absence of global integration, do not generate conscious experience (cf. Kotchoubey et al.

2005, Schiff et al. 2002). This possibility would account for the brain responses and isolated behavioral fragments often observed in VS patients, as in the unique case of a vegetative patient who randomly produced occasional single words (Schiff & Plum 1999). VS patients might thus suffer from a functional "disconnection syndrome" (cf. Giacino et al. 2006, Laureys et al. 2000b, Schiff et al. 2002). This condition of decreased information integration might be the crucial factor underlying the absence of consciousness (Tononi 2004, 2008). Along these lines, for example, Vanhaudenhuyse et al. (2010) have shown that VS patients exhibit reduced resting-state connectivity, as compared to MCS patients and healthy volunteers, in proportion to the degree of consciousness impairment. Which specific aspect of brain circuitry underlies disrupted connectivity, however, remains unclear. In a recent report, Boly et al. (2011) demonstrated systematic differences in top-down connectivity across MCS and VS patients. In the latter group, the backward connections from frontal to superior temporal cortices were significantly impaired, implicating a specific role for top-down effective connectivity in consciousness. A second aspect of brain circuitry that has been proposed to play a central role in DOC is the thalamo-cortical axis, as shown by the case of a VS patient with relatively preserved cortico-cortical connectivity (i.e., default mode network) but impaired thalamo-cortical connectivity (Boly et al. 2009). Furthermore, Laureys et al. (2000c) reported, in a single patient, restoration of thalamo-cortical connectivity upon recovery of awareness. Indeed, both postmortem and in vivo examinations have shown that VS patients exhibit widespread thalamic damage and atrophy (Adams et al. 2000, Fernández-Espejo et al. 2010). The specific pattern of connections of the central portion of the thalami with fronto-parietal cortical systems, as well as brainstem attentional capture mechanisms, might thus be crucial to supporting the large-scale cerebral dynamics associated with goal-directed behavior and consciousness (Schiff 2008). Damage to these structures and circuits might thus effectively disconnect a structurally intact cortex and impair consciousness even in the presence of functionally intact (bottom-up) modules of information processing.

CONCLUSION: UNCONSCIOUS BUT NOT "JUST" VEGETATIVE

How vegetative is the vegetative brain? Taking stock of nearly 20 years of research, it is no longer possible to conceive of the vegetative brain as an apallic brain (i.e., *a-pallium*, "without a cortex") capable of sustaining only "vegetative" neural functions. Indeed, despite severe reductions in brain metabolism and profound structural damage, some aspects of cognitive information processing can remain. Nonetheless, residual information processing is likely to reflect functionally disconnected cognitive modules that do not give rise to phenomenological awareness.

Although unconscious, the vegetative brain is clearly not just vegetative, perhaps warranting the search for a new, scientifically updated nomenclature that may reflect not only what is observable behaviorally but also the level of residual brain function (cf. Kotchoubey 2005, Laureys et al. 2010).

SUMMARY POINTS

1. The VS is a condition of the human brain in which patients who survive severe brain injury appear to be awake but show no signs of awareness of the self or the environment.
2. The VS is traditionally believed to reflect a condition of preserved brainstem and hypothalamic functions in the absence of any cortical information processing.

3. Reliance on behavioral assessments of awareness and cognitive function might underestimate the level of residual processing available in VS patients.
4. Functional neuroimaging techniques have shown that several aspects of brain function may remain in VS patients, including auditory, visual, somatosensory, and linguistic processing.
5. Residual aspects of brain processing in these patients likely reflect functionally disconnected cognitive modules that do not generate phenomenological awareness.

FUTURE ISSUES

1. What aspects of brain processing constitute the necessary and sufficient correlates of conscious experience?
2. What is the clinical status of patients who appear to be nonresponsive (i.e., VS) during clinical/behavioral assessments but can demonstrate signs of awareness in neuroimaging studies?
3. Can sensory, pharmacological, or neuromodulatory interventions help restore consciousness after severe brain injury?
4. What role will scientific advances in neuroimaging play in routine clinical assessments?
5. To what extent can brain-computer interfaces be employed to assist patients with disorders of consciousness?

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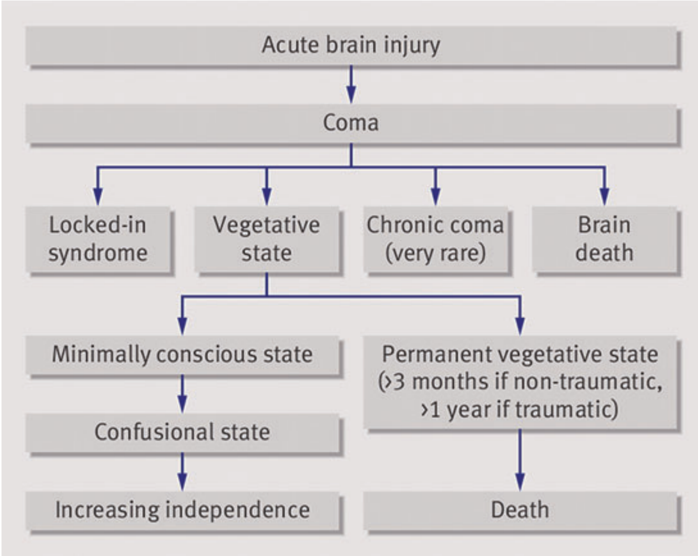

Figure 1

Flowchart of cerebral insult and coma. From Monti et al. (2010a).

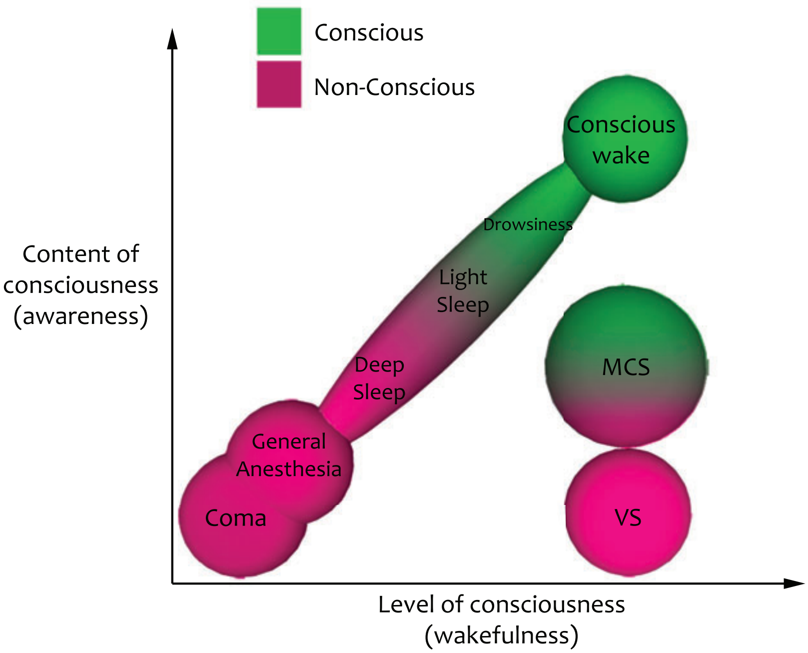

Figure 2

Illustration of the two cardinal components of consciousness, wakefulness and awareness, and how they relate to normal and pathological conditions of the human brain. Adapted from Laureys (2005).

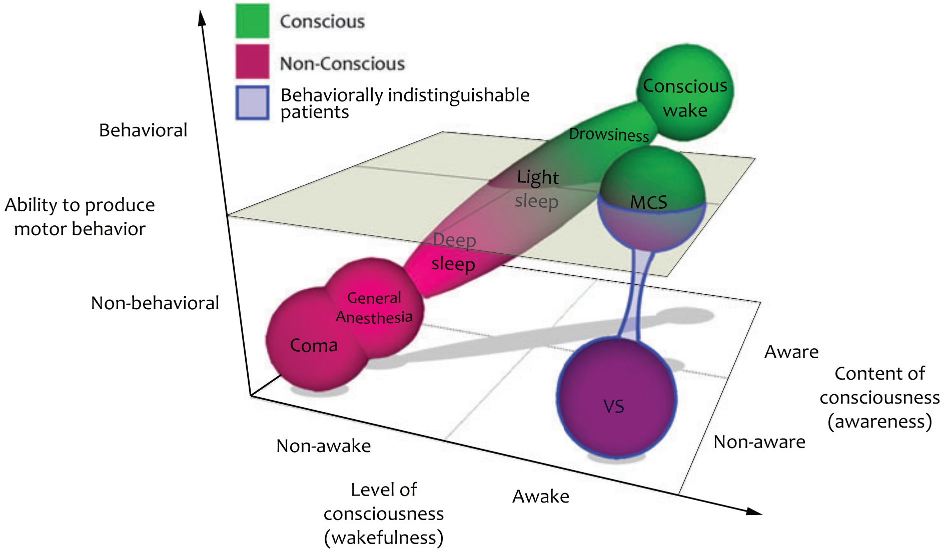

Figure 3

Illustration of the conundrum of consciousness. If a conscious patient were unable to perform voluntary motor behavior [e.g., the section of minimally conscious state (MCS) patients below the horizontal plane], it would be impossible to distinguish her from a vegetative-state (VS) patient solely on the basis of clinical (i.e., behavioral) assessments.

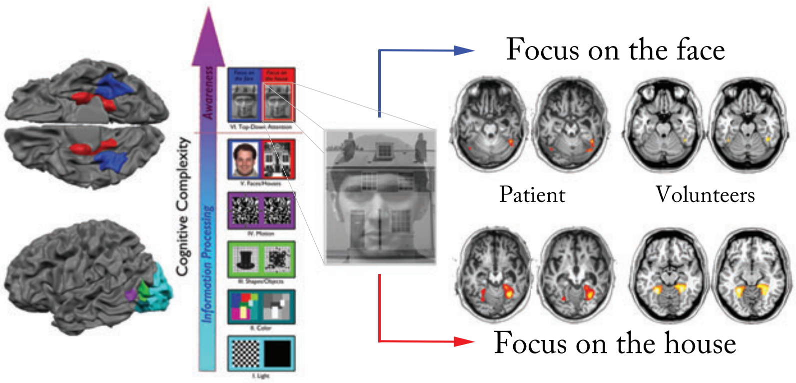

Figure 4

Hierarchical approach to assessing residual visual cognition in patients with disorders of consciousness (DOC). (*Left*) Hierarchy of increasingly complex transformation of visual information and depiction of the brain areas involved in each. (*Right*) Selective activation of the fusiform (*top*) and parahippocampal gyri (*bottom*) for an MCS patient and healthy volunteers in response to focusing on the face and on the house depicted in the ambiguous image (respectively). Adapted from Monti et al. (2011).

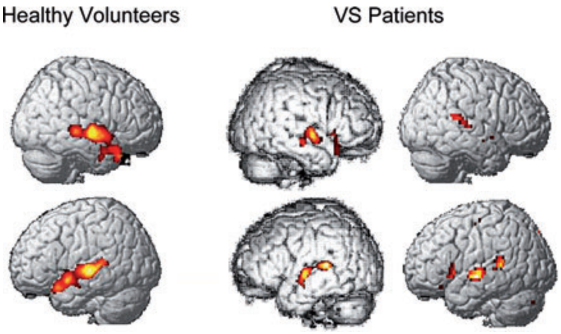

Figure 5

Areas of significant brain response in a group of healthy volunteers and the two VS patients described in Owen et al. (2002, 2005b). Adapted from Monti & Owen (2010).

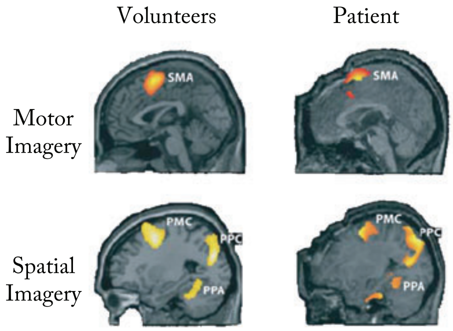

Figure 6

Brain activations for the motor and spatial imagery tasks for healthy volunteers and a patient with a VS diagnosis. From Owen et al. (2006), reprinted with permission from AAAS.