Measuring Consciousness in Severely Damaged Brains

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Abstract

Significant advances have been made in the behavioral assessment and clinical management of disorders of consciousness (DOC). In addition, functional neuroimaging paradigms are now available to help assess consciousness levels in this challenging patient population. The success of these neuroimaging approaches as diagnostic markers is, however, intrinsically linked to understanding the relationships between consciousness and the brain. In this context, a combined theoretical approach to neuroimaging studies is needed. The promise of such theoretically based markers is illustrated by recent findings that used a perturbational approach to assess the levels of consciousness. Further research on the contents of consciousness in DOC is also needed.

Contents

INTRODUCTION

Vegetative state (VS)/unresponsive wakefulness syndrome (UWS): patients who are aroused but not aware of themselves and their surroundings

Minimally conscious state (MCS): patients who are aroused and show fluctuating signs of awareness without being able to functionally communicate

Disorders of consciousness (DOC): refers to patients with severe acquired brain injuries in an altered state of consciousness; includes coma, VS/UWS, and MCS

EMCS: emergence of the minimally conscious state (i.e., functional communication or object use)

Clinical and neuroimaging studies have made significant progress in the differential diagnosis, treatment, and ethical management of patients in a coma, in a vegetative state/unresponsive wakefulness syndrome (VS/UWS), and in a minimally conscious state (MCS) (Giacino et al. 2014). In this review, we discuss the state of the science for clinical assessment of disorders of consciousness (DOC) and the potential use of neuroimaging to diagnose consciousness.

Following severe damage to the brain, caused by trauma, stroke, or anoxia, patients can fall into a coma. Coma is a transient state characterized by a complete absence of wakefulness and awareness (Plum & Posner 1983). The recovery of wakefulness without signs of awareness heralds a transition to VS/UWS (Laureys et al. 2010, Multi-Society Task Force on PVS 1994a). In contrast, patients in MCS show reproducible nonreflexive behaviors but remain unable to communicate (Giacino et al. 2002). The MCS entity has been divided into MCS+ and MCS−, depending on the complexity of behavioral responses (i.e., presence or absence of language functions, respectively) (Bruno et al. 2012). Emergence of MCS (EMCS) occurs when patients regain accurate communication and/or functional use of objects. Finally, locked-in syndrome (LIS) patients can be misdiagnosed as DOC despite preserved awareness because of a complete paralysis of voluntary muscles, except vertical eye movements (Bauer et al. 1979). **Table 1** summarizes diagnostic criteria for DOC and related states.

CLINICAL ASSESSMENT OF CONSCIOUSNESS

The clinical assessment of the level of consciousness is based primarily on observation of spontaneous and stimulus-evoked behaviors. Arousal is measured by eye-opening, whereas awareness is assessed by patient's command-following or the assessor's search for other nonreflexive behaviors. Misdiagnosis of unawareness is very frequent (up to 40%) when diagnosis is based solely on clinical consensus, without use of appropriate behavioral scales (Schnakers et al. 2009). The most sensitive scale to differentiate MCS from VS/UWS is, to date, the revised version of the Coma Recovery Scale (CRS-R) (Giacino et al. 2004, Seel et al. 2010). In the intensive care unit, a routine use of the Full Outline of Unresponsiveness scale, which is faster to administer, is also recommended

Table 1 Diagnostic criteria for patients with severe acquired brain injuries

Clinical entities	DOC	Definition
Coma (Plum & Posner 1983)	Yes	No wakefulness No awareness of self or environment
Vegetative state/unresponsive wakefulness syndrome (Laureys et al. 2010, Multi-Society Task Force on PVS 1994a)	Yes	Wakefulness No awareness of self or environment No sustained, reproducible, purposeful behavioral responses to external stimuli No language comprehension or expression Relatively preserved hypothalamic and brain stem autonomic functions Bowel and bladder incontinence Variably preserved cranial-nerve and spinal reflexes
Minimally conscious state (Bruno et al. 2011b, Giacino et al. 2002)	Yes	Wakefulness Fluctuating awareness with reproducible, purposeful behavioral responses to external stimuli
Minimally conscious state minus	Yes	Visual pursuit Reaching for objects Orientation to noxious stimulation Contingent behavior
Minimally conscious state plus	Yes	Following commands Intentional communication Intelligible verbalization
Emergence from minimally conscious state (Giacino et al. 2002)	No	Functional communication Functional object use
Locked-in syndrome (American Congress of Rehabilitation Medicine 1995)	No	Wakefulness Awareness Aphonia or hypophonia Quadriplegia or quadriparesis Presence of communication through the eyes Preserved cognitive abilities

DOC, disorders of consciousness.

(Wijdicks et al. 2005). Specific assessment material should also be employed to increase sensitivity (see sidebar, Clinical Assessment). On the patient side, some factors potentially causing decreased responsiveness should be noted: motor impairment, aphasia, agnosia, blindness or deafness, fluctuation of vigilance, and the presence of pain (Schnakers 2012). Other medical complications (e.g., infections) and sedating medications may also complicate the assessment of DOC (Whyte et al. 2013). These elements should be investigated. The sidebar Clinical Assessment provides our recommendations concerning clinical assessment of DOC. The sidebar Clinical Management describes how recent advances in clinical diagnosis have affected treatment, prognosis, and ethical issues in DOC.

Even if the border zone between patients in VS/UWS and MCS is, at present, well delimited, bedside assessment of consciousness is intrinsically gated by behavioral responsiveness. It is now increasingly more recognized that the absence of observed purposeful behaviors at the bedside cannot be taken as definitive proof of the absence of consciousness. If persistent doubts concerning a patient's consciousness level exist, neuroimaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG) can be useful to complement behavioral diagnosis.

Locked-in syndrome (LIS): patients who are aroused and aware but who cannot move except to make eye movements

Coma Recovery Scale-Revised (CRS-R): behavioral scale developed to assess the levels of consciousness in patients recovering from coma, and especially to differentiate conscious from unconscious patients

ACTIVE NEUROIMAGING PARADIGMS

As previously mentioned, there is a significant risk that decreased behavioral responsiveness in brain-damaged patients may be due at least partially to motor impairment. In this context, neuroimaging paradigms that identify nonreflexive brain activation patterns in response to commands, while bypassing motor output, may be helpful. A positive response to these paradigms could, in principle, be considered reasonable evidence for the presence of consciousness in a given patient.

CLINICAL ASSESSMENT

1. **What to know before starting?**
   - The **terminology** of DOC (see **Table 1**)
   - The **signs of MCS:** reproducible responses to command, visual pursuit, automatic motor response (e.g., scratching, grabbing objects), adapted emotional behavior, localization to noxious stimulation, intelligible verbalization, object recognition and localization, nonfunctional communication, resistance to eye-opening (Giacino et al. 2002, van Ommen et al. 2013)
   - The **signs of EMCS:** functional communication and object use (Giacino et al. 2002)
   - **Reflex behaviors:** auditory startle, blinking to threat, flexion withdrawal/stereotyped to pain, yawning, oral reflexes (Giacino et al. 2002)
   - **Debated behavior:** visual fixation (Bruno et al. 2010), localization to sound (Cheng et al. 2013)
2. **What to do before starting?**
   - Collect patient's past and current **medical history:** sensory deficits, cause of coma, time since onset, localized pain, sedative medication
   - Always consider the patient **conscious** even if apparently unresponsive. Explain the aim of the exam and the need for full collaboration
   - Place the patient in **sitting position**
   - All **limbs** must be **visible**
   - Ensure enough light and quiet **environment** with a period of rest before starting
   - Apply **arousal protocol** if needed (Giacino et al. 2004)
   - Perform a few minutes of **observation** of spontaneous behavior
3. **What to do during the assessment?**
   - Assess **all modalities:** audition, vision, motricity/tactile stimulation, oromotor behavior, communication, arousal
   - Use the **Coma Recovery Scale-Revised**
   - **Use specific tools:** mirror for visual pursuit (Vanhaudenhuyse et al. 2008), own name for auditory localization (Cheng et al. 2013), oral and written commands, colorful objects, meaningful/emotional stimuli
   - **Way to assess:** assess the most reactive part of the body (from medical history, spontaneous behavior), ask several command-following questions based on spontaneous behaviors, use finger for blinking to threat, evaluate visual pursuit in horizontal and vertical planes
   - Give **encouragement** to the patient
   - If signs of **fatigue:** break and/or arousal protocol
4. **Other recommendations**
   - **Repeat assessments** combining morning and afternoon evaluations, minimum 5 times total for a final diagnosis
   - **Extended evaluation time** (20–60 min) needed
   - **Qualified and trained assessor**

CLINICAL MANAGEMENT

Advances in the understanding of brain function in noncommunicative severely brain-damaged patients go hand in hand within their clinical management. There is currently no standard of care to guide clinical management of patients with DOC. Once signs of consciousness are detected at the bedside (Seel et al. 2010) or via neuroimaging (Stender et al. 2014), the next step is to find a way for these patients to communicate. Standardized protocols searching for reliable responses to commands can be used to develop a binary code (Whyte et al. 1999). Communication-enabling brain computer interfaces can also be used via active paradigms in EEG and fMRI (Chatelle et al. 2012a, Lulé et al. 2013), or even by measuring changes in pupil size (Stoll et al. 2013).

Pharmacological treatments such as amantadine (Giacino et al. 2012) and zolpidem (Thonnard et al. 2014, Whyte et al. 2014) should be systematically tried in DOC patients because they can potentially improve patients' levels of awareness (Gosseries et al. 2013). Amantadine has been correlated with an increased metabolism in the frontoparietal network in an MCS patient (Schnakers et al. 2008a), whereas Zolpidem decreased low-frequency EEG activity in several patients with DOC (Williams et al. 2013). If signs of discomfort are observed, using for instance the Nociception Coma Scale-Revised (Chatelle et al. 2012b), pain medication should be given (Schnakers & Zasler 2007). This scale has been shown to selectively capture residual activity in pain matrix regions (e.g., anterior cingulated cortex) in severely brain-damaged patients (Chatelle et al. 2014). In some cases, trials of therapeutic interventions including invasive thalamic brain stimulation (Schiff et al. 2007), spinal cord stimulation (Yamamoto et al. 2013), and noninvasive transcranial direct current stimulation are indicated (Thibaut et al. 2014).

Patients in MCS have more chance of recovery than do patients in VS/UWS (Luauté et al. 2010, Noé et al. 2012). Other prognostic factors are the CRS-R total score on admission (i.e., >6) (Estraneo et al. 2013), a young age (Howell et al. 2013), a traumatic etiology (Multi-Society Task Force on PVS 1994b), an early time since onset (Whyte et al. 2009), the presence of pupillary light reflexes (Fischer et al. 2006), the absence of medical complications (Whyte et al. 2013), and specialized early treatment (Seel et al. 2013). VS/UWS patients who show preserved fMRI activation of associative cortices also have higher chances to recover (Di et al. 2008, Vogel et al. 2013). Finally, the presence of long-latency event-related potential components in response to stimuli (Estraneo et al. 2013, Fischer et al. 2006, Steppacher et al. 2013, Xu et al. 2012) or preserved default mode network (DMN) connectivity (Norton et al. 2012) are also indicative of a better recovery.

Advances in clinical diagnosis and detection of residual cognitive function in patients with DOC also raise new ethical questions about withdrawal of nutrition and hydration in this patient population (Fernández-Espejo & Owen 2013, Kitzinger & Kitzinger 2014). Legal precedence in several countries has established the right of the medical team to withdraw artificial nutrition and hydration from patients in VS/UWS, but not those in MCS (Ferreira 2007, Manning 2012). Opinions on these end-of-life decisions vary, however, depending not only on the diagnosis of the patient, but also on the profession and the cultural background of the clinicians (Demertzi et al. 2011). Moreover, caregivers who consider that VS/UWS patients likely feel pain are more often opposed to withdrawal of life-sustaining therapy (Demertzi et al. 2009, 2013). Another ethical concern is the quality of life in chronic DOC patients. This question is difficult to address in the absence of communication with the patient. In this context, it is striking to note, however, that most LIS patients report subjective near-to-normal quality of life (Bruno et al. 2011a).

To be able to draw such strong inferences, however, these active paradigms must select only positive responses in nonreflexive brain activation patterns following task instruction. Indeed, if a reflex, involuntary brain activation led to a positive response in these paradigms, they would lose their value as a diagnostic tool for willful response to command and, hence, for the presence of consciousness in noncommunicative brain-damaged patients. Thus, validation studies should be performed to ensure that the passive listening of the instruction to perform a task cannot elicit a brain activity pattern similar to the one from a voluntary response. The most effective control

Positron emission tomography (PET): invasive neuroimaging technique that measures brain metabolism energy turnover

would be to ask subjects to listen to the task instruction while being told beforehand not to perform the task. Ideally, two different commands should also be tested and different reproducible responses should be obtained for each.

An appropriately controlled diagnostic test is the tennis imagery paradigm (Boly et al. 2007, Monti et al. 2010, Owen et al. 2006) and its variants (Bardin et al. 2011). In this fMRI paradigm, patients are instructed to repetitively alternate 30 s of motor imagery (i.e., playing tennis) or spatial navigation mental imagery (i.e., walking in your house) with 30 s of rest. To obtain a brain response to command, fMRI data are analyzed by detecting task-specific motor or spatial navigation neural activation during the periods in which the patient was instructed to perform the task, as compared with periods of rest. The 30-s imagery task duration ensures that the response assessed is not simply due to passive processing of verbal instruction. Validation studies have also been performed to verify that no activation is seen when an assessor instructs the patient not to perform the task. Moreover, comparing brain activation patterns in response to the instruction to imagine spatial navigation assesses specificity. In another recent properly controlled fMRI task, investigators used an increase in brain activation during attention to the words "yes" or "no" presented in a stream of numbers as a patient's response to a command (Naci & Owen 2013). In a separate experiment, this task was controlled for the absence of reflexive activation and, thus, for its specificity to detect only conscious responses (Naci et al. 2013). In addition, the search for a differential response to attention to "yes" or "no" ensures that brain activity patterns are specific to the question asked, which further corroborates the nonreflexivity of the response.

Functional magnetic resonance imaging (fMRI): noninvasive neuroimaging technique that measures neuronal activation based on blood-oxygen-level-dependent (BOLD) changes

Electroencephalography (EEG): noninvasive technique that allows practitioners to record electrical activity in the brain through electrodes placed on the scalp

Active paradigm: procedure that requires the subject to perform a specific task on request

Some properly designed EEG paradigms are currently available to clinicians who seek command-following without motor output in brain-damaged patients. A paradigm designed by Schnakers et al. (2008c) uses differential EEG responses during attention to names as a response to command. In this paradigm, sequences of names containing the patient's own name are presented, in both passive and active conditions. In the active condition, the patients are instructed to count her or his own name or to count another target name. The search for a difference between active and passive conditions as well as between runs with attention to the patient's own name and runs with attention to another name offers a control for both the presence of nonreflexive responses and for specificity. Finally, Cruse et al. (2011) designed an EEG paradigm to detect oscillatory changes after the instruction to imagine squeezing one's hand or moving one's feet. Here again a control experiment shows no response when the subjects are instructed not to do the task. In addition, the comparison of the EEG activity differences for the imagery of moving the hand versus that of moving the foot ensures specificity.

In all the previously cited active paradigms, a positive response can be considered as a reasonable surrogate for the presence of consciousness in brain-damaged patients. Thus, these tasks may be used as additional diagnostic tools in the clinical assessment of consciousness. In fact, these paradigms have already allowed investigators to identify behaviorally VS/UWS answering to command using brain activity (Cruse et al. 2011, Monti et al. 2010, Naci & Owen 2013, Owen et al. 2006) (see also **Figure 1**). Once identified, these patients are not to be considered unconscious anymore but should switch to a diagnostic category of functional MCS (Vogel et al. 2013) or MCS* (Gosseries et al. 2014, Stender et al. 2014).

The main limitations of the active paradigm are that negative findings occur often in DOC and that they are uninterpretable. Recent cohort studies have indeed shown that only a minority, about 20%, of DOC patients can positively respond to this approach (Monti et al. 2010, Stender et al. 2014). Negative results obtained with command-following approaches could be due not to patient unconsciousness, but to other reasons such as aphasia, apraxia, fluctuating vigilance, or simply the patient's unwillingness to collaborate. Thus, negative findings in the active paradigm can never exclude the possibility that the patient has retained awareness.

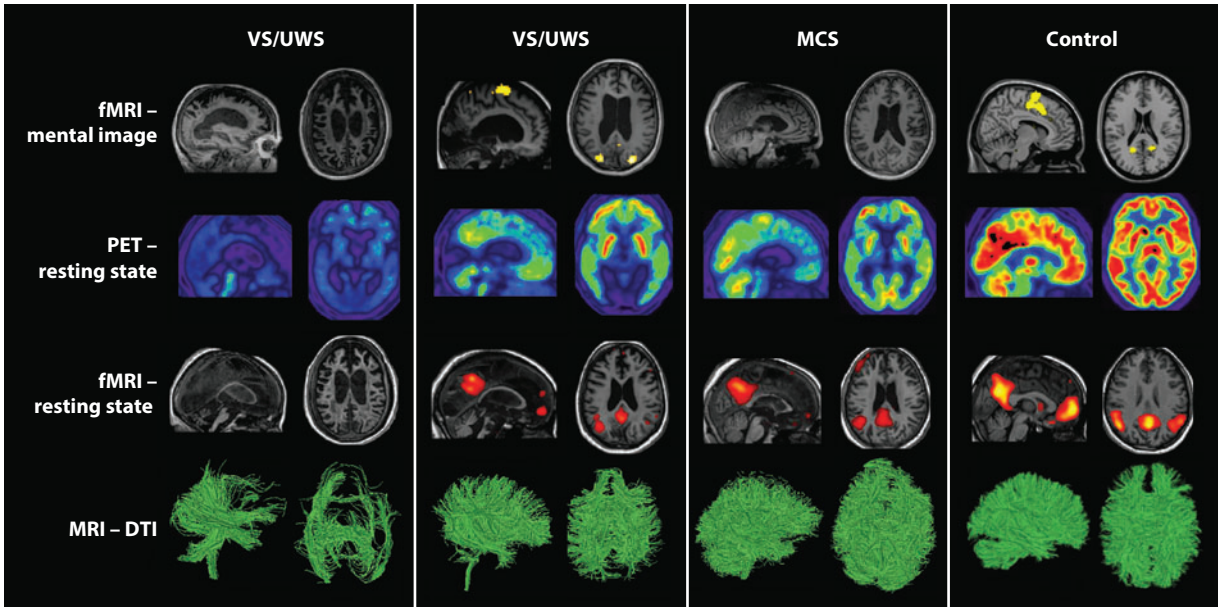

Figure 1

Multimodal diagnosis assessment in disorders of consciousness. Illustrative neuroimaging results in two vegetative state/unresponsive wakefulness syndrome (VS/UWS) patients, one minimally conscious state (MCS) patient, and one healthy control showing possible dissociations between active and passive paradigms and how they usefully complement each other in the evaluation of patients. This figure demonstrates, for example, that fMRI mental imagery tasks (motor imagery on the *left*, navigation imagery on the *right*) show positive results in the control subject and in the second VS/UWS patient. PET and fMRI resting-state results typically show a strong decrease in brain activity and anatomy [here, diffusion tensor imaging (DTI)] in the first VS/UWS patient and show partially preserved brain activity in the second VS/UWS patient as in the MCS patient. Negative responses to active paradigms in MCS patients frequently occur. Figure adapted from Gosseries et al. (2014).

Neuroimaging assessment of DOC should encompass not only active paradigm but also general measures of brain function (the so-called passive approaches). A global assessment of brain function is generally useful and can be especially helpful in the presence of negative results in active paradigms. In the next section, we review potential uses of these passive neuroimaging assessment studies for consciousness diagnosis in DOC.

NEURAL CORRELATE OF CONSCIOUSNESS

In the past few years, numerous studies identified distinct patterns of brain activity in VS/UWS as compared with MCS (Laureys & Schiff 2012). These state-of-the-art studies held to the following safeguards to ensure an accurate clinical diagnosis as well as an appropriate design to draw inferences about group-level differences in a given population study. First, clinical diagnosis should be performed using repeated CRS-R testing by trained assessors (Giacino et al. 2004, Seel et al. 2010). Second, a sufficient number of patients should be studied to obtain a representative sample of each population. It is indeed common that about 20% of patients in VS/UWS present an atypical brain activity pattern. To increase sensitivity, quantitative statistical group analyses can also be used. We now review general patterns of brain function demonstrated in recent studies of VS/UWS and MCS patient populations.

Passive paradigm: procedure without any specific instruction where the subject does not do anything in particular

Spontaneous Brain Activity

Default mode network (DMN): a network of brain regions that are active when the awake subject is at rest

There are three common ways to measure spontaneous regional brain activity using neuroimaging. PET measures regional brain metabolism, whereas fMRI and EEG quantify oscillations at the second and millisecond scales, respectively. Early PET studies identified decreased metabolism in frontoparietal cortices in VS/UWS patients as compared with controls (Beuthien-Baumann et al. 2003, Laureys et al. 1999a), resuming to normal after recovery of consciousness (Laureys et al. 1999b). In MCS patients, lateral frontoparietal area metabolism is preserved (**Figure 2*a***) (Thibaut et al. 2012). In addition, MCS+ patients show preserved metabolism in language and sensorimotor areas (Bruno et al. 2012).

EEG studies reported higher delta power in VS/UWS (Lehembre et al. 2012) and more frequent high delta power microstates in VS/UWS as compared with MCS patients (**Figure 2*c***) (Fingelkurts et al. 2012b). These results are in line with other studies that show lower bispectral index values (Schnakers et al. 2008b) and decreased spectral entropy in VS/UWS (Gosseries et al. 2011). Moreover, in contrast with MCS, VS/UWS patients do not present with preserved EEG sleep-wake patterns (Landsness et al. 2011). Finally, the amplitude of low-frequency fluctuations of resting-state fMRI signals in the precuneus is higher in MCS as compared with VS/UWS (**Figure 2*b***) (Huang et al. 2013).

Response to Stimuli

For regional spontaneous activity, brain reactivity to sensory stimuli can be evaluated with PET, fMRI, or EEG. PET studies suggest that VS/UWS patients typically activate only primary sensory cortices in response to noxious or auditory stimuli (Laureys et al. 2000a, 2002). In contrast, MCS patients show preserved higher-order areas of activation, encompassing the frontoparietal cortices (**Figure 2*d***) (Boly et al. 2005, 2004). Likewise, most VS/UWS patients display fMRI activation of only low-level cortices in response to sensory stimuli (Coleman et al. 2009, Di et al. 2007). In contrast, MCS patients typically recruit a more widespread set of associative sensory cortices. Default mode network (DMN) activation in response to self-referential stimuli is also stronger in MCS as compared with VS/UWS patients (**Figure 2*e***) (Huang et al. 2013, Qin et al. 2010). Finally, DMN deactivation is also preserved in MCS patients but is virtually absent in VS/UWS patients (Crone et al. 2011).

The mismatch negativity (MMN), an early negative waveform elicited by a deviant tone in a repetitive series, has been one of the most widely studied EEG components in patients with DOC. MMN, as with other long latency components, is found more often in individual MCS patients than in VS/UWS patients (Fischer et al. 2010, Höller et al. 2011, Qin et al. 2008). Another long-latency positive component, the P3, is also found more consistently in MCS (Bekinschtein et al. 2009, Faugeras et al. 2012), although it can be detected in some VS/UWS patients (Perrin et al. 2006). Likewise, statistical group analyses suggested that MMN and P3 amplitude are higher in MCS (Boly et al. 2011, Faugeras et al. 2012). The higher amplitude of long latency components in MCS patients as compared with VS/UWS patients could be linked to preserved function in cerebral backward connections (**Figure 2*f***) (Boly et al. 2011).

Functional Connectivity

Functional connectivity studies assess how different brain areas interact with each other. These studies have been performed with numerous conditions in healthy subjects and patient populations. They have now been successfully applied in several ways to differentiate MCS patients from VS/UWS patient populations. These studies assume that if brain areas causally

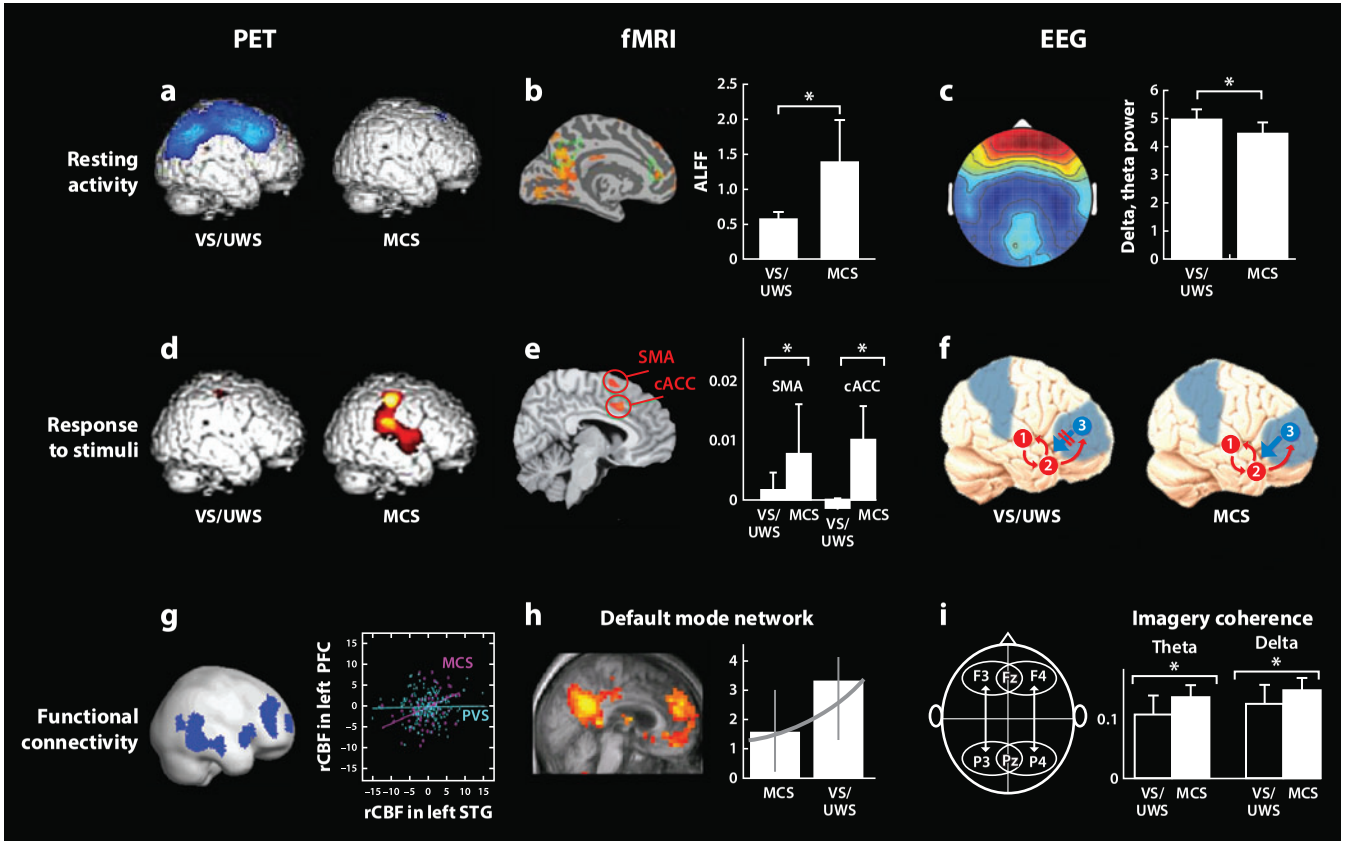

Figure 2

Neural correlates of consciousness in severely damaged brains. PET, fMRI, and EEG results using measures of spontaneous brain activity, response to stimuli, and functional connectivity in vegetative state/unresponsive wakefulness syndrome (VS/UWS) patients and minimally conscious state (MCS) patients. For example, panel *f* shows that, during auditory stimulations, patients in VS/UWS lack backward connections between inferior frontal gyrus (3) and superior temporal gyrus (2) with preserved connections of the primary auditory cortex (1) as compared to patients in MCS. Other abbreviations: ALFF, amplitude of low-frequency fluctuations; SMA, supplementary motor area; cACC, caudal anterior cingulate cortex; rCBF: regional cerebral blood flow; STG, superior temporal gyrus; PFC, prefrontal cortex; PVS, persistent vegetative state; F, frontal; P, parietal; z, central; even number (here, 4) refers to electrode position on the right hemisphere whereas odd number (here, 3) refers to those on the left hemisphere. Asterisks (*) indicate $p < 0.05$. Figure adapted from Boly et al. (2004, 2008, 2011); Fingelkurts et al. (2012b); Huang et al. (2013); Lehembre et al. (2012); Qin et al. (2010); Thibaut et al. (2012); Vanhaudenhuyse et al. (2010).

interact, the time course of their activity should be correlated. This claim usually but not always rests on the assumption of direct anatomical connectivity between the regions studied (Greicius et al. 2009). PET functional connectivity studies assess the correlation in metabolic activity between different brain areas during rest or during sensory stimulation. These studies revealed impaired frontoparietal cortico-cortical and thalamo-cortical connectivity in VS/UWS patients as compared with healthy volunteers (Laureys et al. 1999a, 2000b). As compared with VS/UWS patients, MCS patients show preserved PET functional connectivity in frontoparietal cortices (**Figure 2*g***) (Boly et al. 2004). Functional MRI resting-state connectivity studies assess correlations in blood-oxygen-level-dependent (BOLD) signal magnitude among brain regions over the course of a single task-free acquisition session. These resting-state fMRI studies identified preserved connectivity in both lateral and medial frontoparietal areas in MCS patients as compared with VS/UWS patients (**Figure 2*b***) (Huang et al. 2013; Kotchoubey et al. 2013; Ovadia-Caro et al. 2012; Soddu et al. 2011a,b; Vanhaudenhuyse et al. 2010). Finally, EEG functional connectivity studies assess similarities in signal amplitude or oscillatory phase (in given frequency bands) between scalp electrodes or between brain regions if performed in source space. Coherence and cross-approximate entropy EEG studies confirmed stronger frontoparietal connectivity in MCS patients as compared with VS/UWS patients (**Figure 2*i***) (Lehembre et al. 2012, Wu et al. 2011). The organization of oscillatory brain connectivity in interacting modules is also preserved in MCS patients as compared with VS/UWS patients (Fingelkurts et al. 2013), especially in the DMN (Fingelkurts et al. 2012a). Overall, functional connectivity studies suggest a link between preserved cerebral functional interactions and higher consciousness level (e.g., arousal and/or cognitive functions) in MCS patients as compared with VS/UWS patients.

Individual Results Analysis

As illustrated above, virtually any available neuroimaging technique can reveal different group patterns of brain function in VS/UWS and MCS patients. Even if group separation is clear, at the individual level outliers exist. The interpretation of outliers can be problematic. Combining different techniques may be helpful to better document a patient's general brain function (see **Figure 1**); however, even multimodal assessments may not provide an ultimate solution.

Let us consider this concept in more detail using an example. Suppose we use PET to assess 10 patients unambiguously diagnosed at the bedside as VS/UWS. In our experience, out of these 10 patients, 7 will show a classical frontoparietal hypometabolic PET pattern, and 3 will have preserved metabolism of PET. Among the 3 latter patients, typically only 1 will show a positive response to fMRI or EEG active paradigms. Two out of these 3 will not. What do we do then? What can we infer if the patient does not respond to the active paradigm but has a relatively normal PET? Is high PET metabolism always a definitive marker of the presence of consciousness? If a given neuroimaging measure was a definitive marker of consciousness, it should be consistent in other states of unconsciousness, such as sleep, anesthesia, or seizures. And we know that during epileptic seizures, PET metabolism can be normal, or even increased, even though subjects are unconscious (Engel et al. 1982). Preserved brain metabolism at PET is thus not necessarily definitive proof of the presence of consciousness. **Table 2** illustrates that, to date, none of the classical neuroimaging techniques mentioned above are sufficient to diagnose consciousness. To identify a definitive brain signature of consciousness, developing a theoretical framework to define the mechanisms that link consciousness and the brain is a necessary step (see sidebar, On the Nature of Consciousness, and **Figure 3**). We describe the concrete application of such a theoretical framework to the neuroimaging-based diagnosis of consciousness in the next section.

Table 2 Comparison of neuroimaging findings in different states of unconsciousness

Techniques	VS/UWS > MCS	Alike in other states	Different in other states
PET metabolism	Decrease (FP)	Propofol anesthesia (Fiset et al. 1999), sleep (Braun et al. 1997, Maquet et al. 1990)	Epilepsy (Engel et al. 1982), K complex (Picchioni et al. 2009)
fMRI: oscillation (ALFF)	Decrease (precuneus)	Isoflurane anesthesia (Wang et al. 2011)	Sleep, midazolam anesthesia (Kiviniemi et al. 2005)
EEG: oscillations (delta)	Increase	Sleep (Mascetti et al. 2011)	Epilepsy (Blumenfeld 2005)
PET: response to stimuli	Decrease	Propofol anesthesia (Bonhomme et al. 2001)	TBD
fMRI: response to stimuli	Decrease	Propofol anesthesia (Gosseries et al. 2012, Vanhaudenhuyse et al. 2012)	K complex (Dang-Vu et al. 2011)
EEG: response to stimuli	Decrease	Propofol anesthesia (Heinke et al. 2004)	Burst suppression anesthesia (Kroeger & Amzica 2007)
PET: functional connectivity	Decrease (FP)	Isoflurane, halothane anesthesia (White & Alkire 2003)	TBD
fMRI: functional connectivity	Decrease (FP)	Propofol (Boveroux et al. 2010), sevoflurane anesthesia (Martuzzi et al. 2011)	Sleep (Boly et al. 2012b, Horovitz et al. 2008)
EEG: functional connectivity	Decrease	Propofol, sevoflurane, ketamine anesthesia (Boly et al. 2012a, Lee et al. 2013)	Sleep (Langheim et al. 2011), propofol anesthesia (Barrett et al. 2012, Murphy et al. 2011)

Abbreviations: ALFF, amplitude of low-frequency fluctuations; EEG, electroencephalography; fMRI, functional magnetic resonsance imaging; FP, frontoparietal cortices; MCS, minimally conscious state; PET, positron emission tomography; TBD, to be determined; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

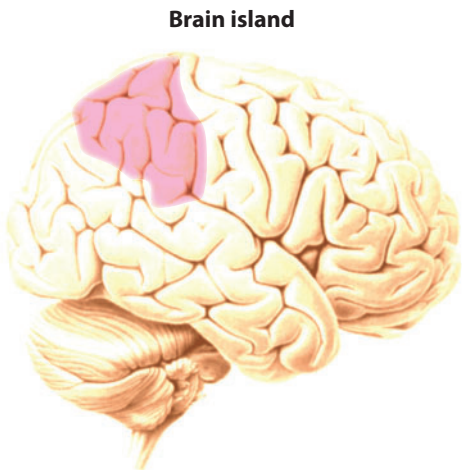

Figure 3

Brain island. See sidebar, On the Nature of Consciousness, for references.

ON THE NATURE OF CONSCIOUSNESS

To develop a mechanistic account of the relationship between consciousness and the brain, forging a comprehensive theory of consciousness is a necessary step. Developing a theory of consciousness is not only useful at a conceptual level, but would also have direct practical implications for assessing patients with DOC. A thoroughly validated theory of consciousness is ultimately the only way to make strong inferences about the presence or absence of consciousness in unresponsive brain-damaged patients where all the other approaches fail.

Let us consider a hypothetical example of an unresponsive brain-damaged patient, whose PET scan shows an island of preserved activity in the right posterior parietal cortex (**Figure 3**). The patient shows only reflexive spontaneous behavior, no behavioral response to command, and no ability to communicate. He also does not follow commands on active paradigms. Moreover, afferent pathways are damaged, impairing the recruitment of cortical areas in response to sensory stimulation. Strikingly, however, brain anatomy, resting metabolism, and fast EEG activity are well preserved in the right posterior parietal cortex.

What can we infer about the presence or absence of consciousness in such a patient? Is anybody home? Is the presence of a well-functioning parietal cortex alone enough for some amount of consciousness (even though, of course, it would be lacking some attributes)? And if so, what could we infer about the contents of consciousness? Would there be any visual, auditory, or verbal content? Would he feel any pain? Would he have any degree of self-awareness? Answering such questions exclusively on the basis of empirical data would clearly not be possible because one cannot directly ask an isolated parietal cortex if it is conscious. Instead, one needs a theory of consciousness that starts from the fundamental features of consciousness itself, provides general principles concerning the necessary and sufficient conditions for consciousness, leads to measures of consciousness that are generally applicable, and provides some guidance about how the quality of experience is determined by the neuroanatomical and neurophysiological organization of brain structures. Thus, in our view, the science of coma and the science of consciousness go hand in hand.

FROM EXPLORATORY TO EXPLANATORY NEURAL CORRELATES OF CONSCIOUSNESS

In the past two decades, several neuroscientific theories hypothesized about the relationships between the brain and consciousness (Block 2011, Dehaene & Changeux 2011, Lamme 2006, Lau & Rosenthal 2011, Tononi 2008, Tononi & Edelman 1998). Such theories can help identify brain markers of the presence or absence of consciousness using neuroimaging. We illustrate this point using the integrated information theory of consciousness (IITC) (Tononi 2012).

Transcranial magnetic stimulation (TMS): technique that allows investigators to stimulate the brain noninvasively, which induces neuronal depolarization and discharge of action potentials

NREM: non–rapid eye movement sleep

REM: rapid eye movement sleep

IITC states that consciousness is related to a system's capacity for information integration (Tononi 2008, 2012). In the case of the brain, the theory predicts that consciousness-supporting networks should present an optimal balance between functional integration and differentiation (Boly et al. 2009). This hypothesis has recently been tested using transcranial magnetic stimulation (TMS) coupled with high-density EEG. This technique allows investigators to directly measure effective connectivity responses (i.e., TMS-induced causal interactions between distant brain areas) with EEG (Massimini et al. 2009). Our group, in collaboration with Massimini (from the University of Milan) and Tononi (from the University of Wisconsin-Madison), has applied TMS-EEG to assess brain function during sleep, under anesthesia, and in brain-damaged patients. Results of these studies show clear-cut differences in TMS-EEG responses between conscious and unconscious subjects in all conditions. During non–rapid eye movement sleep (NREM), under general anesthesia (e.g., midazolam), and in VS/UWS patients, TMS typically triggers a stereotypical slow wave that stays local, which indicates a breakdown of effective connectivity (Ferrarelli et al. 2010, Massimini et al. 2005, Rosanova et al. 2012). In contrast, during normal wakefulness,

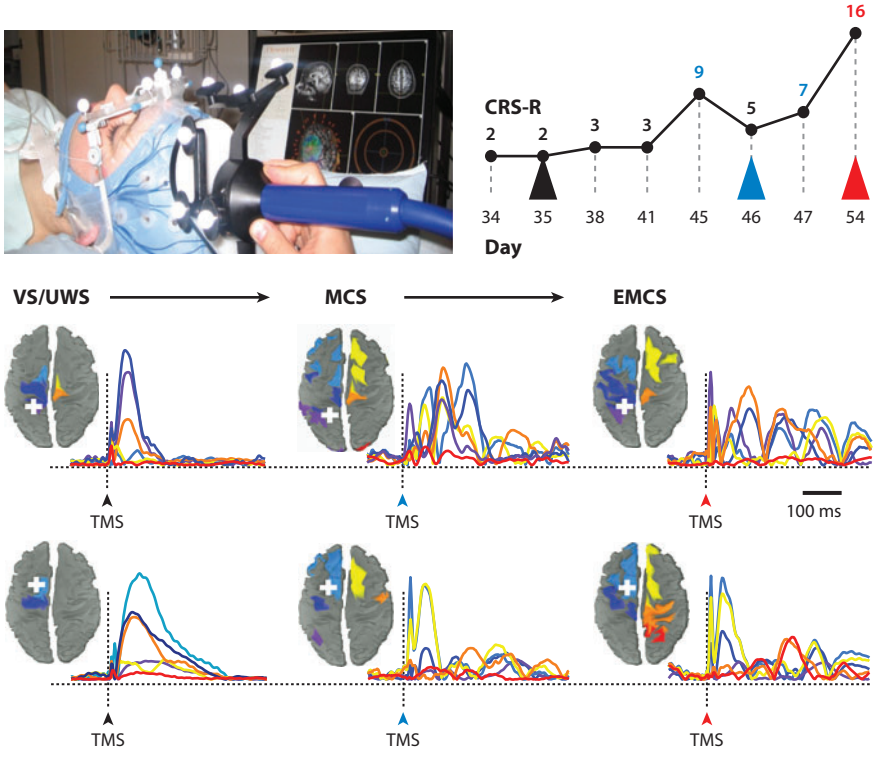

Figure 4

TMS-EEG responses during recovery from coma. TMS-EEG measurements in a patient evolving from vegetative/unresponsive wakefulness syndrome (VS/UWS, *black arrow*) to a minimally conscious state (MCS, *blue arrow*), then to emergence of MCS (EMCS, *red arrow*). The figure illustrates both the spreading and time courses of cortical currents evoked by TMS when stimulating parietal (*top*) and frontal (*bottom*) cortices (*white crosses*). In VS/UWS patients, the response stays local and stereotyped and becomes widespread and differentiated in MCS and EMCS patients. Other abbreviations: CRS-R, Coma Recovery Scale-Revised; EEG, electroencephalography; TMS, transcranial magnetic stimulation. Figure adapted from Rosanova et al. (2012).

in MCS, EMCS, and LIS patients, or during rapid eye movement (REM) sleep, brain activation patterns to TMS are always complex, i.e., widespread and differentiated (**Figure 4**) (Massimini et al. 2005, 2010; Rosanova et al. 2012).

We recently designed a new empirical measure known as the perturbational complexity index (PCI) to quantify in one number the difference in TMS-EEG responses present between states of consciousness and states of unconsciousness (Casali et al. 2013). PCI estimates both the information content and the integration of brain activations through the computation of the normalized Lempel-Ziv complexity (Lempel & Ziv 1976) of the significant EEG spatiotemporal responses to TMS. According to our current results, PCI is remarkably reliable to differentiate consciousness from unconsciousness within and across subjects and conditions: It is always high (i.e., above 0.31) in healthy awake subjects, in MCS, EMCS and LIS patients, as well as during REM sleep, but is invariably low (i.e., below 0.31) during NREM sleep, in patients in VS/UWS and under anesthesia-induced unconsciousness (using midazolam, propofol, or xenon) (**Figure 5**). PCI also allows a clear-cut differentiation between patients in VS/UWS and those who recovered

PCI: perturbational complexity index

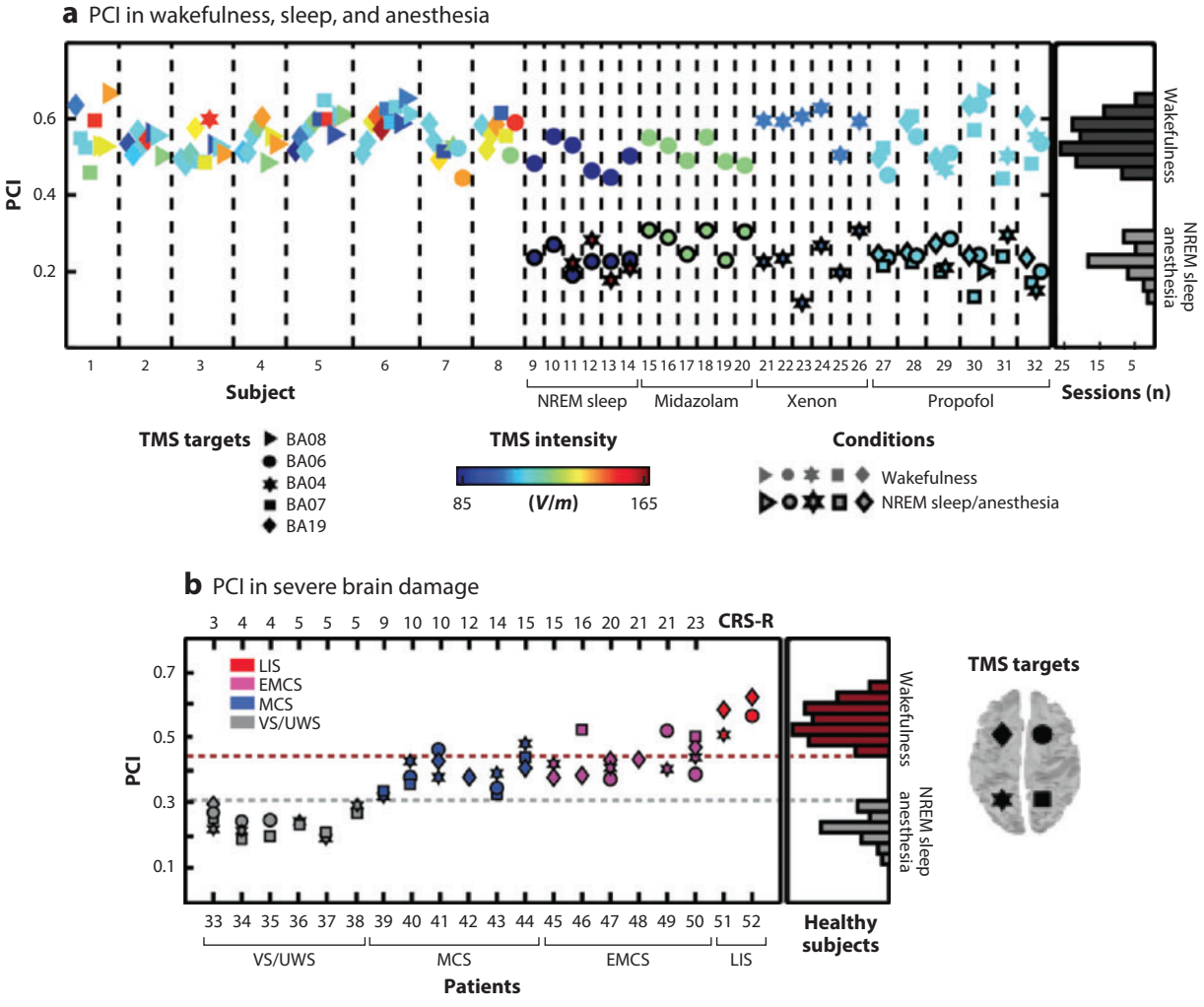

Figure 5

Perturbational complexity index (PCI) as a marker of consciousness. (*a*) PCI in wakefulness, sleep, and anesthesia. PCI calculated during wakefulness ranges between 0.44 and 0.67, whereas PCI calculated during unconsciousness [i.e., non-rapid eye movement (NREM) sleep and midazolam, xenon, or propofol anesthesia] ranges between 0.12 and 0.31. The histograms display the distributions of PCI across subjects during conscious (*dark gray bars*) and unconscious (*light gray bars*) conditions. (*b*) PCI in severe brain damage. PCI follows the level of consciousness assessed with the Coma Recovery Scale-Revised (CRS-R). It progressively increases from vegetative state/unresponsive wakefulness syndrome (VS/UWS) to minimally conscious state (MCS) and emergence of the MCS (EMCS). VS/UWS values are in the same range as those observed during NREM sleep and general anesthesia. PCI for EMCS and locked-in (LIS) patients are in the same range as healthy awake subjects. Patients in MCS show intermediate PCI values but never below the threshold of unconsciousness (*gray dashed line*, PCI = 0.31). Other abbreviation: TMS, transcranial magnetic stimulation. Figure adapted from Casali et al. (2013).

consciousness (i.e., MCS, EMCS and LIS) at the single-subject level. Further studies on larger samples should confirm these inaugural results. In sum, the highly promising aspect of this theoretically based index of consciousness levels motivates interest in a theoretical framework to help design clinically applicable diagnostic tools for consciousness.

CONTENTS OF CONSCIOUSNESS: WHAT IS IT LIKE TO BE IN AN MCS?

Previous sections discuss progress concerning the diagnosis of the level of consciousness in DOC. However, another outstanding question remains essentially unaddressed: What is the content of consciousness in MCS or in behaviorally VS/UWS patients reclassified by neuroimaging as MCS*? What is it like to be in an MCS? Contents of consciousness are usually assessed by obtaining subjects' reports. In MCS patients, no report can be obtained because no accurate communication is possible. Generalizing neural correlates of conscious content observed in healthy volunteers to interpret MCS brain findings is also problematic because of the presence of the brain lesions and the possible ensuing reorganization. Studies of cognition in MCS using EEG and fMRI active paradigms could help address this question, at least in part. Making inferences about the content of consciousness in noncommunicative patients is a question that can only be addressed fully if empirical studies are complemented by a general theoretical framework (see sidebar, On the Nature of Consciousness, above).

CONCLUSIONS

Recent years witnessed numerous advances in the diagnosis and understanding of brain function in DOC. Research combining clinical, neuroimaging, and theoretical approaches will likely lead to continued fruitful advances in the diagnosis and treatment of these patients.

We offer a few take-home messages:

1. Consciousness is tricky to diagnose clinically; consider the patient as conscious until all evidence is collected.
2. Active paradigms, when properly designed, can successfully probe evidence of the presence of consciousness in unresponsive patients; caution in interpreting negative results is needed, however.
3. Neuroimaging and electrophysiological studies have identified consistent group differences in brain activity patterns in MCS patients as compared with VS/UWS patients. Single-subject level interpretation of these results is nevertheless often limited.
4. Theoretically based neuroimaging approaches (such as PCI) are highly promising to identify reliable single-subject level markers of consciousness. Larger population studies of PCI as a consciousness meter are ongoing.
5. More research on the contents of consciousness in DOC patients is needed.

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