Disorders of Consciousness

MARTIN M. MONTI

Abstract

Disorders of consciousness are a spectrum of neurological disorders, encompassing coma, the vegetative state, and the minimally conscious state, in which patients acquire or develop an impairment of the two cardinal elements of consciousness–wakefulness and awareness. One of the main sources of complexity in this context is how to recognize and tell apart patients who retain some level of awareness from patients who do not. Indeed, in the absence of any direct means of assessing one's level of awareness, we are forced to indirectly infer a patient's state on the basis of their ability to perform behaviors that, appearing clearly voluntary, imply the presence of consciousness. In this contribution, we explore recent evidence showing how brain imaging can be harnessed to address the problem of consciousness in patients surviving severe brain injury. First, we focus on recent experiments demonstrating how neuroimaging can be used to detect the presence of voluntary "brain behavior" in otherwise non responsive patients, and to allow a rudimentary form of non muscle-dependent communication strategy based solely on voluntary brain activity. Second, we discuss recent findings concerning network activity at different levels of awareness, and the relationship between thalamo cortical circuits and consciousness.

INTRODUCTION

Disorders of consciousness (DOC) are a spectrum of disorders, typically acquired or developed following severe brain injury, in which an individual's consciousness is altered in a transient or permanent manner owing to severe brain injury (Monti, 2012). In this context, consciousness is (simplistically) conceived as encompassing two cardinal elements (Laureys, 2005): wakefulness and awareness. *Wakefulness* refers to the *level* of one's consciousness and includes states such as deep sleep, drowsiness, and full (normal) wake. *Awareness* refers to the *content* of consciousness, a more elusive concept relating to the degree to which an individual possesses subjective experience (of him/herself or the surrounding environment). In daily life, most people experience the two elements of consciousness as being intimately tied to each other. When asleep, for example, wakefulness and awareness are both very low and jointly return as we progress through light

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sleep and drowsiness toward awakening. In some circumstances, however, these two elements dissociate from each other. During dream sleep, for example, we commonly experience the presence of some level of (self) awareness despite the absence of wakefulness. In DOC, we are typically confronted with the reverse dissociation: wakefulness in the absence of (self) awareness.

FOUNDATIONAL RESEARCH

Definitions

Coma. Coma is a state in which patients appear to lack both elements of consciousness–they do not open their eyes even when intensely stimulated (i.e., they have low *level* of consciousness) and they do not show any evidence of awareness of themselves or of their surroundings [i.e., they have low, or no, *content* of consciousness; (Monti, Laureys, & Owen, 2010)]. This state can last from 2 to 4 weeks, with chronic coma being a rare long-term outcome.

Vegetative State (VS). While many coma patients recover within a few weeks, a subset go on to regain some *level* of consciousness (i.e., "awaken" from coma) but without regaining any *content* of consciousness (Monti, Laureys, *et al.*, 2010). This condition of "wakefulness in the absence of awareness" defines the vegetative state (VS) (The Multi-Society Task Force on PVS, 1994). VS patients appear to periodically awaken and fall asleep, as indexed by alternating periods of sustained eye-opening and eye-closing, but never show any sign of purposeful behavior or (self) awareness. When this condition lasts longer than 3 weeks, it is referred to as a *persistent* VS, after which the chances of recovery decrease with time. If this condition lasts for longer than 3 months[1] (for patients who suffered from a nontraumatic brain injury; e.g., anoxia) or 1 year (for patients who suffered from a traumatic brain injury), a prognosis of *permanent* VS is made, after which chances of recovery are typically considered to be minimal.

Until recently, the VS was believed to be a condition in which basic vegetative nervous functions (including thermoregulation, respiration, and sleep-wake cycles) are preserved, but in the complete absence of sensation or thought–a view that is well captured by the term *apallic* syndrome (from the Latin word *a-pallium*, "without a cortex"), sometimes used to describe these patients. However, taking stock of about 15 years of neuroimaging research in this cohort, employing tools such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography

1. In the United Kingdom, the threshold for a VS to be considered permanent after nontraumatic insult is set at 6 months.

(EEG), it has become increasingly clear that several aspects of cortical function, including somatosensory (Boly *et al*., 2008), nociceptive (Laureys *et al*., 2002), auditory (Kotchoubey *et al*., 2005), and semantic (Schnakers *et al*., 2008) processing, among others, can remain even in the absence of consciousness [see Monti (2012) for a recent comprehensive review].

Minimally Conscious State (MCS). Some patients remain in VS indefinitely. Other patients, however, go on to regain some degree of awareness, thereby progressing to a minimally conscious state (MCS) (Giacino *et al*., 2002). MCS patients are defined as being awake and able to show, if intermittently, reproducible signs of (self) awareness in the form of purposeful (i.e., non reflexive) behavior. An MCS patient, for example, might be able to demonstrate pursuit eye-movements toward salient stimuli in the environment, reaching for objects, or even the production of (appropriate) vocalizations or gestures in response to questions and commands. Minimally conscious patients might remain in this condition indefinitely, or might further recover, emerging from MCS, as they regain the ability to functionally/appropriately use objects or accurately communicate (verbally or gesturally).

The Conundrum of (Finding) Consciousness

The definitions above, by which we differentially diagnose patients suffering from DOCs, highlight one of the most crucial (and fascinating) questions in this field: how can we tell if an individual, other than ourselves, is conscious? Indeed, in the absence of a means to directly measure one's consciousness, the distinction between what most people would regard as "conscious" and what most people would regard as "unconscious" relies on the pragmatic principle by which the presence of voluntary (i.e., non reflexive) behavior is taken to imply the presence of consciousness (Monti, Coleman, & Owen, 2009b). This principle of *revealed consciousness* is the bedrock upon which current clinical assessments rely. If a patient can demonstrate any kind of purposeful or voluntary behavior in response to stimulation (e.g., responding to a command such as "move your foot"), an MCS diagnosis is made. Conversely, if a patient fails to demonstrate any sign of purposeful behavior, a VS diagnosis is made. This reasoning, however, is logically flawed in that it takes the absence of evidence of consciousness (e.g., absence of purposeful behavior) to be evidence of absence of consciousness (Monti *et al*., 2009b). What if a patient were conscious but unable to perform any recognizably voluntary behavior due to motor impairment? What if a patient were conscious but aphasic, and thus unable to make sense of a clinician's request to perform a certain behavior? What if a patient was conscious but did not possess sufficient residual cognitive functions to successfully comply with a clinician's instruction? In all these cases, a patient would be diagnosed as being in VS, despite retaining some level of (self) awareness. Confirming this view, several studies, including retrospective audits (Andrews, Murphy, Munday, & Littlewood, 1996; Childs, Mercer, & Childs, 1993) and comparisons of diagnostic methodologies (Schnakers *et al.*, 2006, 2009), have reported a consistent 40% misdiagnosis rate by which (minimally) conscious patients are incorrectly considered to be unconscious (i.e., vegetative). While a number of different causes might underlie the totality of these cases (e.g., lack of skill or training in specific clinical assessments, limited knowledge of this relatively rare condition, and confusion in terminology), the presence of sensory and motor impairment are well known to potentially mask the presence of consciousness by virtue of rendering the patient unable to either understand or comply with a clinician's attempt to elicit purposeful behavior (Monti, Laureys, *et al.*, 2010). In what follows, I will briefly cover the two main approaches that, today, are being developed in order to overcome this "conundrum" of consciousness (Owen & Coleman, 2008).

CUTTING-EDGE RESEARCH

Cogito Ergo Sum by Neuroimaging[2]

In 2006, a radical idea was introduced in the field as a potential solution to the conundrum of consciousness (Owen *et al.*, 2006). If some patients are (at least minimally) conscious, but unable to produce overt behavior because of motor impairments, maybe they might be able to engage in some form of recognizably voluntary "mental behavior" detectable through modern neuroimaging techniques, thereby *revealing* a state of consciousness (Monti & Owen, 2010). Consistent with this intuition, a number of patients who appeared behaviorally unresponsive in standard (behavior-based) clinical assessments were shown to be able to willfully engage in a motor and a spatial mental imagery task (i.e., imagining playing tennis and imagining walking in a familiar environment), eliciting the same neural substrate that is typically seen in healthy individuals engaging in the same task, and thereby signaling a state of consciousness (Monti, Vanhaudenhuyse, *et al.*, 2010; Owen, *et al.*, 2006).

If a patient can engage at will in (at least) two mental tasks that can be distinguished from each other on the basis of neural activity, this ability can be harnessed into a basic non motor-dependent communication strategy: a "language" made of any two possible alternatives (e.g., "yes/no" and "on/off"). In agreement with this intuition, a patient who was initially believed to be in a permanent VS was recently shown to be able to respond to autobiographical questions by engaging in one kind of imagery (e.g., playing tennis) to

2. Ropper (2010).

convey an affirmative answer and in a different kind of imagery (e.g., walking around his home) to convey a negative answer (Monti, Vanhaudenhuyse, *et al*., 2010). This finding was recently confirmed when a VS and an MCS patients were shown to be able to use selective attention (i.e., the process of focusing on a relevant stimulus while attempting to filter out irrelevant ones) to respond to binary questions (Naci & Owen, 2013). This new procedure takes the approach presented in Monti, Vanhaudenhuyse, *et al*. (2010) one step further by granting patients the ability to choose from a number of potential answers rather than constraining them to two alternatives only. In this novel procedure, patients are not asked to elicit different mental states to give a positive or negative answer, but rather are presented aurally with a number of possible answers (e.g., "yes, no, one, two, three, … ") and then asked to covertly count the number of times the answer they want to convey is repeated. The timing of the observed brain activations can then be used to infer which word (i.e., answer) a patient was focusing on.

Amidst these groundbreaking results, however, it is important to consider that the dissociation between motor and brain responsiveness can go both ways. As discussed above, some patients who appear unresponsive in clinical (motor-based) assessments can appear responsive in neuroimaging (brain-based) assessments. Conversely, some patients who appear responsive in clinical assessments can appear unresponsive in neuroimaging tests–despite being able to verbally report that they were engaging in the mental activity as instructed (Bardin *et al*., 2011), highlighting the complexities of interpreting negative findings in neuroimaging, and the need to integrate standard and neuroimaging assessments (Monti, 2013).

Toward a Neurophysiology of DOC

Despite the flourishing of research in this field, we still have a very limited understanding of the physiological mechanisms underlying the loss and (sometimes) recovery of consciousness after severe brain injury. In particular, it is unclear why patients in a VS can retain several degrees of cortical activity while failing to experience the feeling of (self) awareness.

Until recently, a prominent view held that VS patients only maintained residual information processing in primary sensory cortices (Boly *et al*., 2004; Laureys *et al*., 2002) without it propagating to higher-level and polimodal integration areas that are considered necessary for conscious experience (Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006). The evidence available to date, however, does not seem to support this idea. Indeed, neuroimaging studies have now amply shown that VS patients can exhibit information processing outside primary cortices. A recent set of studies, however, might suggest a different hypothesis accounting for the presence of extensive cortical processing in the absence of consciousness. Under this view, the VS might best be characterized as a "disconnection syndrome" (Laureys, 2005; Schiff, 2010) whereby residual brain processing in VS patients might reflect isolated cognitive modules that, in the absence of global integration, do not generate conscious experience (Monti, 2012).

Loss of Connectivity in DOC. Taking advantage of non invasive neuroimaging (and particularly task-free, or "rest," approaches) a growing amount of evidence suggests that DOC are characterized by a decrease in connectivity across frontal, parietal and temporo parietal regions. Specifically, a set of regions often referred to as the *default mode network*, show decreased connectivity in proportion to the severity of the impairment of consciousness (Vanhaudenhuyse *et al*., 2010). Similarly, it has also been shown that minimally conscious and VS patients differ significantly in the extent of "top-down" connectivity extending from prefrontal cortex to superior temporal regions (Boly *et al*., 2011), with the latter group of patients exhibiting a marked reduction. Assessing cortico cortical correlations and directional connectivity, however, does not bear much explanatory power *vis-à-vis* the question of why they are so important for the maintenance (or generation) of consciousness. To start addressing this question, and converge toward a more mechanistic understanding of the relationship between brain function and consciousness, a recent study investigated the effect of anesthetic agents on the network properties of the brain (Monti, Lutkenhoff, *et al*., 2013). Specifically, a set of healthy volunteers underwent a resting state fMRI recording at different levels of consciousness: awake, sedated, unconscious, and recovery (i.e., after having regained consciousness). Unlike the previous connectivity studies, however, brain function was not assessed on the basis of the intensity of point-to-point correlations, but rather using tools derived from a relatively recent branch of mathematics—graph theory—which allows assessing the brain as a network of nodes exchanging information (within the boundaries of the resolution offered by fMRI). In this study, the only unambiguous signature of a state of unconsciousness, with respect to how information is exchanged in brain networks, was a marked decrease in global efficiency. In other words, the unconscious (healthy) brain suffers from a global decrease in the efficiency with which information from distant parts of the brain can be integrated. One intriguing aspect of this finding, which is awaiting replication in patients, is that consciousness might best be thought of as a *how* (i.e., a mode of brain functioning) rather than a *where*–an idea that matches the view proposed by a prominent theory of consciousness [i.e., Integrated Information Theory of Consciousness; (Tononi, 2008)].

Thalamo-cortical Circuits in DOC. If indeed the loss of consciousness is related to a loss of global information integration across distant regions of cortex, the next step requires understanding the causes leading to these changes in brain function. In general, thalamus has always been considered important for the maintenance of consciousness. Indeed, post-mortem and neuroimaging examinations have revealed severe tissue death in thalamus (and hippocampus; (Adams, Graham, & Jennett, 2000)), as well as structural damage in sub cortical white matter (Fernandez-Espejo *et al.*, 2011), in this cohort of patients. Today, a number of experiments seem to indicate that specific cortico subcortical circuits—uniting, among other regions, frontal and parietal cortices, and medio dorsal thalamus–might be crucial to the integration of information across distant loci of cortex (Schiff, 2010). Indeed, a recent study has shown that, in acute severely injured patients, the degree of secondary, non mechanical, damage to thalamus, and consequential atrophy in the anterior and dorso-medial areas occurring over the first 6 months post injury, is predictive of chronic outcome (Lutkenhoff *et al.*, 2013). Consistent with this finding, chronic DOC patients have been shown to have, as a group, atrophy along the medio dorsal axis of thalamus, when compared to healthy volunteers (Fernández-Espejo *et al.*, 2010). Although this latter study reported no differences between conscious (i.e., MCS) and unconscious (i.e., VS) patients, the findings are consistent with the data observed in the acute setting. Finally, the view that thalamo cortical circuits play a key role in DOCs is also consistent with a number of case studies. First, a patient was shown to specifically recover thalamo frontal connectivity in concurrence with the reemergence of consciousness (Laureys *et al.*, 2000). Second, deep brain stimulation to the antero medial regions of thalamus have been shown to have beneficial effects in terms of improved responsiveness in DOC patients (Schiff *et al.*, 2007). Finally, it was recently shown that a patient with disrupted thalamo cortical connection was in a state of un consciousness despite the preservation of cortico cortical (i.e., "default mode network") connectivity (Boly *et al.*, 2009), thus potentially carving out very different roles, in the generation of consciousness, for thalamo cortical versus cortico cortical circuits.

KEY ISSUES FOR FUTURE RESEARCH

What Is It Like to Be in a Vegetative State?

One issue that is still to be clarified is "what is it like" to be at the lower boundaries of consciousness. More specifically, despite the flurry of recent studies demonstrating the preservation of visual processing (Monti, Pickard, & Owen, 2013), auditory and linguistic processing (Kotchoubey, *et al.*, 2005), attention (Monti, Coleman, & Owen, 2009a, Monti *et al.*, in press), and even learning (Bekinschtein *et al*., 2009), it is unclear the degree to which mental life can remain in DOC patients (Ropper, 2010), whether they can feel any pain (Schnakers, Chatelle, Demertzi, Majerus, & Laureys, 2012; Schnakers *et al*., 2010), or form lasting memories.

Harnessing BCI for Communication in Non responsive Patients

A significant portion of the research described above shows that some DOC patients can retain (a varying level of) (self) awareness even if behaviorally unresponsive. It is therefore important, for these cases, to develop methods that might, through training algorithms, harness computers as "brain-computer-interfaces" (BCI) that can be used for nonbehavioral patients to interact with their environment (Naci *et al*., 2012).

The Treatment Gap

One notable issue, in the context of DOCs, is that despite our increasing sophistication in estimating the level of residual cognition and awareness that might be retained after severe brain injury, there is today no standard treatment available for these patients [there is, however, very exciting evidence that administration of amantadine accelerates the pace of functional recovery in some post-traumatic DOC patients (Giacino *et al*., 2012)].

From Neuroscience to Clinical Practice, Law, and Ethics

Finally, it is worth considering that our theoretical and practical advances in this field bear repercussions outside the domain of science (Monti, 2013). First, what is now considered science is still in search of a practical role in medical care–a transformation that will require studies with much larger samples than those typically carried out today. Second, an increased effort in understanding the degree of mental life and cognitive processing possible in minimally responsive individuals is necessary to allow a substantial discussion concerning which rights–if any, should be recognized to the patients with respect to their participation in the medical decision making process and, ultimately, self-determination (Peterson *et al*., 2013).

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MARTIN M. MONTI SHORT BIOGRAPHY

Martin M. Monti, PhD, (http://montilab.psych.ucla.edu/people/martin-monti/MartinMMonti_CV.pdf) is Assistant Professor in the Departments of Psychology and Neurosurgery at University of California, Los Angeles. Having earned his doctoral degree at Princeton University, he moved to the MRC Cognition and Brain Sciences Unit, in Cambridge, the United Kingdom, to specialize on the study of the vegetative and minimally conscious states. Since joining the faculty at UCLA in 2011, research in Dr. Monti's laboratory (http://montilab.psych.ucla.edu) has centered on two main questions: (i) what mechanisms underlie the loss and recovery of consciousness after severe brain injury and (ii) what is the relationship (if any) between language and thought. His work has been featured in numerous international peer-reviewed journals including the New England Journal of Medicine, Brain, the Proceedings of the National Academy of Science, PLoS Computational Biology, and Psychological Science, among others. In 2013, Dr. Monti led an expert neuroimaging assessment of the late, former Israeli Prime Minister, Ariel Sharon. Research in Dr. Monti's research is supported in part by the James S. McDonnell Foundation "Scholar Award."

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