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Chapter 13

Acute loss of consciousness

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INTRODUCTION

Consciousness has long been a fascinating subject to both philosophers and scientists, yet it was not until recently that neuroscientists started paying attention to consciousness as a topic for research. Comprising two distinct sets of processes, namely, wakefulness and awareness, consciousness may be altered as a result of different neurologic conditions that affect the brain systems supporting each of these two components. It has been suggested that the brainstem's ascending reticular formation system and its thalamic projections support alertness and the sleep–wake cycle, which are key elements of wakefulness; instead, conscious awareness appears to rely on a functional thalamocortical and corticocortical system (Bekinschtein et al., 2009). The widely distributed network that evidently gives rise to consciousness as we know it is naturally prone to being disrupted in a variety of clinical contexts (Zeman, 2008). Here, we begin by briefly delineating the framework we will use to approach altered states of consciousness and introducing some models of acute loss of consciousness that can and have been employed in the scientific literature to further our understanding of conscious and unconscious states. We will then explore the different disorders of consciousness that can result from acute brain injury and techniques used in the acute phase to predict clinical outcome in different patient populations. Finally, we will delve into post-traumatic amnesia as a model to predict cognitive sequels following acute loss of consciousness. We attempt to provide a comprehensive approach to acute loss of consciousness that integrates theoretical and clinical perspectives.

ETIOLOGY OF ACUTE LOSS OF CONSCIOUSNESS: NATURAL, INDUCED, AND ACQUIRED MODELS

Disorders of consciousness mostly stem from acute brain insults, which may be caused by hypoxic/ischemic neural injury or traumatic brain injury. Traumatic brain injury (TBI) is currently the most common neurologic cause leading to loss of consciousness that lasts over a day. Nontraumatic causes of disorders of consciousness include stroke, cardiopulmonary arrest, meningoencephalitis, and the final stages of certain neurodegenerative conditions, including Parkinson dementia, Alzheimer's disease, and Huntington's disease (Bekinschtein and Manes, 2008; Monti et al., 2010a). Unconsciousness may of course result from drugs depressing the central nervous system (CNS), severe fatigue, sleep, hypnosis, and epileptic seizures or simply fainting. These conditions, however, tend to be associated with more easily reversible states and, in principle, do not lead to persistent loss of consciousness. Though these causes may be all different from a physiopathologic viewpoint, they all share a common behavioral core: they show complete or near complete lack of responsiveness to simple commands and/or other environmental stimuli. If all these states are characterized by lack of responsiveness what then are their behavioral differences?

The simplest, albeit very powerful framework to conceptualize this issue was introduced by Jennett and Plum

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(1972) when they first defined the vegetative state. They endeavored to divide consciousness into two core aspects: wakefulness and awareness. Wakefulness refers to the alternation between periods of eyes-opened and eyes-closed. Awareness instead implies a more complex set of processes that grant us the capacity to integrate information, process it, and act volitionally towards a target. For a person to become unconscious he/she must lose their awareness. As defined in the authors' seminal work, the vegetative state (also more appropriately called unresponsive wakefulness syndrome), regardless of the cause, is a condition where the patient exhibits a dissociation between wakefulness and awareness: patients in the vegetative state have their awareness completely abolished while wakefulness is spared (Multi-Society Task Force on PVS, 1994). This leads to an important conclusion in the medical approach of loss of consciousness: unconsciousness may occur with preserved wakefulness.

Under this framework, unconscious states can be reclassified by specifying which aspects of wakefulness are affected. For instance, in the cases of hypnotics and anesthetics, it is clear that – depending on the drug or combination of drugs used – awareness, but not wakefulness, may be affected, as it occurs when administering low doses of ketamine, which preferentially inhibits N-methyl-D-aspartate (NMDA)-mediated glutamatergic inputs, thus leading to aberrant excitatory activity in the cortex but mostly sparing brainstem activity (Seamans, 2008). Most anesthetics modulate brain networks that are responsible for different aspects of wakefulness, and are usually employed in the medical field for varying degrees of anesthesia depending on the procedure to be carried out. One of the most commonly used anesthetics, propofol, a $GABA_{\alpha}$-antagonist (Nelson, 2002) administered in bolus dose, quickly modulates arousal centers in the brainstem, triggering a loss of consciousness (Andrada et al., 2012), together with an effect at multiple sites in the cerebral cortex and some key cortico-subcortical pathways (for a review see Brown et al., 2010). The effect of propofol on these circuits can be assessed behaviorally by asking the patient to follow the anesthetist's finger or to follow simple commands, and to respond to his/her name using several behavioral scales (reviewed by Sessler et al., 2008 and Schnakers et al., 2009). To further test the effect of the anesthetic on the brainstem, the loss of oculocephalic and corneal reflexes are assessed. The drug is known to affect the oculomotor, trochlear, trigeminal, and facial nuclei in the midbrain and pons (Posner et al., 2007), and can thus be thought of as a model for *induced* acute loss of consciousness.

Sleep is a different state of unconsciousness, and a model for *natural* and *nondangerous* acute loss of consciousness. It is defined by low arousal and stereotyped electroencephalogram (EEG) markers, constituting a self-reversible state (Murphy et al., 2011; Goupil and Bekinschtein, 2012). Sleep happens as a consequence of sleep pressure (the amount of hours awake) and the circadian rhythm (as determined by the brain's internal clock). Every normal human being can fall asleep, go unconscious, and regain awareness without the need of external stimulation. Sleep is triggered by the circadian system and it has been shown that the pons and the reticular activation system change their pattern of firing first, followed by the thalamus and the cerebral cortex (Magnin et al., 2010). There is evidence that sleep also dissociates wakefulness from awareness in a manner opposite to the vegetative state, specifically during rapid eye movement (REM) periods. It is generally thought that, when dreaming, the subject is aware of his/her contents of consciousness, aware of an internal context, yet not awake and therefore unconscious in terms of low arousal, low responsiveness (Pace-Schott and Hobson, 2002). Following this logic, patients in a vegetative, who are awake but not aware, should not dream and should not have REM periods of sleep. This idea has in fact been supported by polysomnographic evidence of overnight recordings in patients with disorders of consciousness (Landsness et al., 2011), although some evidence suggests otherwise (Oksenberg et al., 2001; Cologan et al., 2013). Despite the fact that currently dreaming cannot be assessed in minimally conscious state patients (see below), the general assumption is that if the patient shows sleep cycles, even if inconsistent in structure, they might coexist with the contents of consciousness during REM or deep sleep. Unlike all other loss of consciousness states, during sleep a perturbation of the system can wake the person up, restoring both wakefulness and full awareness, and hence becoming responsive and interactive. This is not the case during sedation with drugs, as discussed above, because while the subject may be arousable, the effect of the drug makes him/her respond only briefly, if at all, and if the intensity of the stimulation is not maintained the subject goes back into a state of unconsciousness.

Brain injury patients have also served as fruitful models to study acute loss of consciousness. As we will discuss in the next section, these patients are in consciousness states that can make them barely arousable. The distinct characteristics of each of the conditions clustered under the category of *acquired* acute loss of consciousness can shed light on the underpinnings of conscious processes in the brain. As such, stimulation produces a different outcome depending on the level of unconsciousness: If comatose, no response changes should be observed; if in the vegetative state, stimulation should only induce a change in wakefulness or vigilance, but not in awareness. In other, more infrequent cases

the patient may appear unresponsive to commands, thus suggesting a diagnosis of vegetative state, yet after a vigorous wakefulness protocol the otherwise hidden conscious state of the patient may emerge, thus unveiling awareness from the mists of low arousal (Elliott et al., 2005; Schiff et al., 2007; Bekinschtein et al., 2009), placing them in the category of the so-called minimally conscious state. Often, however, the acute phase of brain injury demands that physicians administer sedatives to unconscious patients, which, as discussed above, can modulate both awareness and wakefulness. Hence studies in the acute phase of acquired loss of consciousness states need to be analyzed with caution. Sedatives can act as powerful masking agents for behavioral signs, significantly diminishing the diagnostic capacity of the behavioral clinical tests.

CLASSIFICATION OF THE DISORDERS OF CONSCIOUSNESS

Disorders of consciousness mainly comprise three states: the comatose state, the vegetative state, and the minimally conscious state (MCS). Coma is a condition of almost complete unresponsiveness in which the patient lies with eyes closed, very limited reflexes, no cyclical wakefulness, and, above all, no signs of awareness. Coma is normally attained after an acute brain insult and may last for about 2 weeks, although chronic coma cases have been described, and are usually caused by either temporary or permanent damage to the reticular system (Laureys et al., 2010).

Following coma, some patients may enter the vegetative state, which involves a complete absence of consciousness of one's environment (i.e., awareness) but with preserved sleep-wake cycles and autonomic functions (i.e., wakefulness), although we have challenged this notion (Bekinschtein et al., 2009). The vegetative state is easily differentiated from brain death, in which the EEG shows no brain wave or activity. Brain death is the irreversible end of all brain activity and should not be confused with a vegetative state. Again, the vegetative state is a condition of (relative) wakefulness without awareness in which the patient exhibits a partially preserved sleep–wake cycle (mainly arousal alternations without true sleep) (Landsness et al., 2011) and a variable array of reflexes and/or spontaneous nonvolitional behaviors. A patient who has been in a vegetative state for a period longer than a month, with no improvements, is often said to be in a *persistent* vegetative state. The term *permanent* vegetative state is frequently used when the vegetative state persists for over 3 months after a nontraumatic insult, such as cardiac arrest, or for longer than a year after a traumatic brain injury, and implies an irreversible state (Multi-Society Task Force on PVS, 1994); nevertheless, these notions are currently under revision (Laureys et al., 2010).

Some patients in a vegetative state may start to recover by entering a minimally conscious state, where conscious awareness is evident despite profound physical and cognitive impairment. Although communication capabilities are absent (which would hence signal emergence from this state), cognitively mediated (or voluntary) behavior occurs in the minimally conscious state, which may be inconsistent but reproducible enough to be differentiated from reflexive behavior. For example, patients may occasionally be able to smile when asked to do so or follow an object with their eyes. In the minimally conscious state, patients show the basic array of behaviors seen in the vegetative state along with islands of presumably conscious processing, such as inconsistent responses to simple commands and sustained visual pursuit (Vanhaudenhuyse et al., 2008). As such, it can be inferred that the integrity of the neural circuitry feeding consciousness among patients in a minimally conscious state is superior to that of patients in vegetative state and thus the former have a better prognosis. From a clinical perspective, it is important to differentiate a patient in a vegetative state from a patient in a minimally conscious state, as the latter group has a much higher chance of a favorable outcome. Evaluation of cerebral metabolism and imaging studies, both structural and functional, when available, can provide clues to brain function (Owen and Coleman, 2008; Owen, 2013).

Another condition that is often confounded with vegetative or minimally conscious states is the locked-in syndrome, which is characterized by complete paralysis of voluntary muscles in all parts of the body except those controlling eye movements (Schnakers et al., 2008). Individuals with locked-in syndrome are conscious and can think and reason, but they are unable to speak or move. The disorder confines the patient to paralysis and a mute state. Communication may be possible with blinking eye movements (Bruno et al., 2008) or brain computer interfaces (Lulé et al., 2013).

THE ACUTE PHASE FOLLOWING TRAUMATIC BRAIN INJURY

As stated earlier, TBI continues to be a major cause of acute loss of consciousness. During the early stages that follow TBI, a small proportion of patients will be unconscious due to the injury itself for more than a few minutes (Salazar et al., 1986; Chesnut et al., 2013), but most of them will be initially sedated upon hospitalization in order to be clinically and systemically (e.g., intracranial pressure, mechanical ventilation) stabilized. The administration of sedatives that modulate both

awareness and wakefulness provide analgesia and serve as anxiolytics while the patient's vital signs are stabilized. Furthermore, sedation helps to prevent intracranial pressure increase related to muscular activity and allows for the optimization of the brain's blood flow, oxygen and substrates delivery. Depending on the severity of the injury and its resulting complications, as well as complications that may arise at the hospital, the withdrawal of sedation may last from a few hours to several days, after which one of three main outcomes is expected. The first is the awakening from the state of unconsciousness, as if the patient had been asleep for a prolonged period of time. This is possible when the core basic networks underlying consciousness were spared from injury, and thus able to switch back to wakefulness (and awareness) after the drug starts to wash out. Among these patients, awareness is recovered with wakefulness when the drug is removed, or shortly after, as a result of the system's ability to re-establish full consciousness; good recovery is highest in this group, albeit cognitive functioning may nonetheless remain affected, depending on the type, extent, and location of the lesion that originally triggered the acute loss of consciousness.

A second possibility, as previously discussed for all comatose patients, is for the patient to transition from being sedated to the vegetative state. These patients are at the other end of the spectrum: once the drug washes out, they open their eyes spontaneously and recover part or full reflexes, but display no signs of behaviors consistent with conscious awareness. This is particularly characteristic of the earlier stages of vegetative state, that is, acute unconsciousness due to wakefulness without awareness. This group does not have a good prognosis, in particular after a hypoxic or anoxic event.

The third case involves a slow transition (or oscillation) from full unconsciousness to full conscious awareness. Patients may start waking up from a drug-induced coma by initially showing some higher reflex responses. In the course of a few hours to days, automatic, stereotyped and complex reflexes may re-emerge, while patients start to show signs of being in the minimally conscious state as they go from visual fixation, to visual smooth pursuit of a bright object or a mirror (Vanhaudenhuyse et al., 2008), to following simple motor commands, even if inconsistently. Some of these patients may progress to a severely disabled state and remain in the blurry frontier of consciousness/unconsciousness for long periods of time; some of them may even go back to the vegetative state, displaying cycles of wakefulness in the absence of awareness; and others may indeed start to recover and progress to higher levels of awareness. These are difficult patients from a clinical perspective, who are behaviorally unreliable, neuroanatomically difficult to define, and neurophysiologically "noisy."

DEFINING THE LEVEL OF CONSCIOUSNESS

Semiology

With the advancement of technology, it is sometimes easy for both neuroscientists and physicians alike to forget that conventional clinical assessment of patients remains a rich and very powerful source of information. A detailed behavioral evaluation of a patient remains extremely informative, and can even inspire new research questions to be answered with more advanced techniques. The assessment of reflexes, automatic behaviors, and command following are still widely accepted as reliable measures, and if performed systematically and consistently in protocols dealing with disorders of consciousness, the rate of misdiagnosis would not be as high as reported in the literature (Schnakers et al., 2009). In previous years, decisions were made based on brainstem behavioral assessment, such as the absence of corneal, pupillary light, and oculocephalic reflexes, in agreement with spontaneous eye movements and spontaneous or evoked movements. All of these signs can be masked by edema and/or sedation or muscle blockage, posing a major problem to be faced by intensive care unit (ICU) professionals. For this reason, it is crucial that patients be assessed continuously and repeatedly at different stages of their progress (Bekinschtein et al., 2009).

Given the challenge posed by patients following acute loss of consciousness, the employment of certain techniques can provide rich information, helpful in deciding what the current state of unconsciousness is and contributing to the prediction of clinical outcome. A few techniques have proved particularly useful in assessing neural function in disorders of consciousness following an acute injury, especially functional magnetic resonance imaging (fMRI), EEG, and evoked response potentials. Their use in combination is essential, mainly because EEG is a direct brain measure but has little spatial resolution, so conclusions regarding localized brain activity demand the use of fMRI, which in turn is an indirect measure and has very little temporal resolution. This latter technique relies on voxel intensity changes to measure the rate of oxygen consumption during brain activity, and while it is not yet mature enough as a clinical tool – mostly because it is not widely used in hospitals around the world in everyday practice – the analysis of fMRI data is becoming more accessible to clinical doctors. A series of protocols to test conscious awareness have been proposed and they are starting to be implement in clinical settings towards its regular clinical use in the future (Monti et al., 2010b; Naci et al., 2013). See Chapter 32 for a discussion on self-awareness deficits after TBI.

EEG

EEG is a well-established method to look at brain activity in a direct manner, as it measures the combined activity of neural discharges through the scalp. EEG has been used to monitor acute disorders of consciousness for many years, but the systematization of diagnostic or prognostic biomarkers has been difficult due to variability in the patients' signal and varying protocols and technologies across the globe. This is certainly expected given that comatose, vegetative states and minimally conscious states are defined behaviorally. Recovery after coma due to severe brain insult (global anoxia/hypoxia or traumatic brain injury) varies between 10% and 70% in the literature; information to know whom to treat in the ICU is key due to limited resources. Despite great disagreement, EEG gives a fair initial indication of clinical status when no other methods are available (Kaplan et al., 2000; Kaplan, 2004). EEG is relatively cheap and easy to perform; however, a very well trained electrophysiologist is needed to read and interpret the signal. There is general agreement in the main EEG pathologic markers, yet a high proportion of patients are often in the gray interpretative zone and do not show clear signs of irreversible brain damage (Guérit, 2000). Shortly after resuscitation, the EEG appears silent in some cases and it should not be misdiagnosed as brain death or brainstem death since some brain rhythms return after a few hours and develop into specific patterns that may guide prognosis. In fact, the level of consciousness of patients with these conditions may vary with cause of injury, drugs employed to maintain sedation, and degree and location of the lesion, together with the resulting inflammatory process from acute injury. Standard EEG has been used successfully to predict the cognitive outcome of patients with altered consciousness states following coma due to traumatic acute brain injury. This technique correlates well with the variation of the level of consciousness after 3 months, as determined by the difference between the level of cognitive functioning after 3 months and basal scores and with the level of consciousness at admission (i.e., the basal score) using Synek's classification (Synek, 1988; Bagnato and Boccagni, 2010). In particular, α and θ coma patterns have a poor prognosis, while spindle coma has a better prognosis, especially if associated with patient reactivity to stimuli available (Kaplan et al., 2000; Kaplan, 2004). In severe traumatic coma patients, δ patterns in the EEG have been associated with deep coma states and predict a poor functional outcome within the month. EEG-R (reactivity) is a good positive factor for the prognosis of recovery of consciousness in the postacute phase of brain injury, with a high specificity (about 90%). Nevertheless, its absence is not invariably associated with a poor prognosis (Logi and Pasqualetti, 2011). More specifically, the occurrence of mostly δ and slow-θ oscillations alone or in combination were found during the first assessment for patients who showed a bad outcome (i.e., died) 6 months after the brain injury compared to patients who survived. At the same time, patients who were alive 6 months after brain injury showed more frequently fast- θ and α oscillations alone or their combinations during the first assessment, when compared to patients who died 6 months after the brain injury.

It seems then that brain activity during the first month following an acute brain injury recorded with EEG can provide potentially prognostic, valuable information on the patient's outcome (survival or death) 6 months later, at least at the group level. In a study in postacute and chronic patients, Cruse and collaborators (2012) further employed EEG to study the relationship between brain injury etiology (i.e., traumatic versus nontraumatic) and cognitive skills in patients with the minimally conscious state (EEG reflection of the capacity to imagine actions). The authors found that there may be high level cognitive activity in the brains of patients with injuries resulting from traumatic causes, which go otherwise unnoticed when employing behavioral scales such as the Coma Recovery Scale – Revised. However, none of the nontraumatic patients showed any sign of EEG-related cognitive skills.

There is general agreement that reactivity to external responses is more informative than underlying EEG rhythms on their own. Responses to auditory, noxious, and visual stimuli must be examined, looking for changes in the underlying pattern of steady state EEG. As mentioned before, the enhancement of fast rhythms and the diminution of slow waves are classic markers of reactivity and hence markers for better prognosis in those acute stages (Howard et al., 2011). Electrical silence, a generalized voltage suppression (less than 12 μV) indicates thalamic damage or damaged connections to the cortex. If any of these patterns is present in a nonsedated patient, chances of recovery decrease significantly. It is actually regarded as a fatal outcome of the acute phase, facing similar prognostic values as myoclonic or nonconvulsive status epilepticus. Nevertheless, there is some agreement that if reactivity is preserved, the decision of treatment should be reinstated since there are well described cases of these mixed patterns that have shown recovery of consciousness in the past (Guérit, 2000; Brown et al., 2010).

Somatosensory evoked potentials

Several studies have demonstrated the prognostic value of somatosensory evoked potentials (SEPs) during the acute phase of loss of consciousness following TBI.

One such study (Houlden and Taylor, 2010) revealed a strong association between SEPs recorded 3 days after injury and cognitive performance assessed a year after the TBI had occurred. Indeed, SEPs in these acute phases predicted processing speed, working memory, and attention, thus providing a reliable tool for functional and cognitive prognosis. The authors found that SEPs assessed on day 1 followed by improvement by day 3 postinjury predicted better functional outcomes. Conversely, absent SEPs have been shown to be associated with unfavorable outcome in anoxic-ischemic coma patients (Rothstein, 2009).

Neuroimaging

Given that our clinical measurement of consciousness can be severely compromised when a patient lacks motor responsiveness, functional neuroimaging in principle offers a more direct and objective tool to measure residual cognition in severely brain-damaged patients (Owen, 2013). fMRI evaluation in cases where the patient is unresponsive or sedated is limited to passive stimulation paradigms; further cognitive assessment is not possible without direct patient interaction for tests such as expressive language or memory function. Moritz and Rowley (2001) introduced the first reported case of fMRI to predict brain function in a comatose head-injured patient. Whole-brain fMRI was performed utilizing visual, somatosensory, and auditory stimulation paradigms during the acute state of traumatic severe brain injury. Results demonstrated intact task-correlated sensory and cognitive blood oxygen level dependent (BOLD) hemodynamic response to stimuli. At 3 months post-trauma the patient had recovered many cognitive and sensorimotor functions, accurately reflecting the prognostic value of this fMRI evaluation. These results suggested that fMRI examinations may provide a useful evaluation for brain function in nonresponsive brain trauma patients. The follow-up electrodiagnostic studies and the patient's clinical improvement showed that significant brain function and potential for recovery were correctly identified using fMRI. Previous work, pioneering the use of fMRI in subacute and chronic patients by the Cambridge and Liege Groups (Menon et al., 1998; Laureys et al., 1999) established the bases for initial use of these techniques demonstrating that there was use in both single subject and group analysis of functional imaging in disorders of consciousness patients. Insights such as this can have important implications in decisions of whether or not aggressive therapy is warranted to a patient with a disorder of consciousness. Coleman and Davis (2009) later described the functional brain imaging findings from a group of 41 patients with disorders of consciousness (traumatic and nontraumatic etiology), who undertook a hierarchical speech processing task. The authors found, contrary to the clinical impression of a specialist team using behavioral assessment tools, that two patients referred to the study with a diagnosis of vegetative state did in fact demonstrate neural correlates of speech comprehension when assessed using functional brain imaging. The level of auditory processing revealed by functional brain imaging, correlated strongly with the patient's subsequent behavioral recovery, 6 months after the scan, suggesting that brain imaging may also provide valuable prognostic information despite the fact that speech processing it is not considered a direct test for conscious awareness.

Functional neuroimaging has also allowed objective measurement of brain responsiveness to external stimuli in the vegetative state (Di et al., 2008). The patterns of activation observed when using fMRI and positron emission tomography (PET) can be classified into one of two patterns: absent cortical activation or "typical" activation of "low level" primary sensory cortices on the one hand, and "atypical" activation spreading to "higher level" associative cortices, on the other. Such atypical activation patterns seem to herald recovery from the vegetative state with a 93% specificity and 69% sensitivity. Contrary to passive neuroimaging paradigms measuring basal activity, Owen and collaborators (Owen et al., 2006; Monti et al., 2010b) used an fMRI paradigm asking noncommunicative patients to perform mental imagery tasks at specific points during brain scanning. This novel approach provided strong evidence for the presence of consciousness, particularly awareness, in a patient otherwise clinically diagnosed as vegetative. So can fMRI be incorporated in the clinical practice of disorders of consciousness? Functional MRI has gone from a tool used in a few laboratories around the world in the 1990s to a well-established technique for studying human neuroscience in the 21st century. At a group level, it has become a useful tool for clinical neuroscience and it is now used in clinical trials as a measure of trial end points, especially in chronic disorders. Its employment in acute loss of consciousness has the potential to provide rich clinical information critical for patient care. See Chapter 18 for an overview on fMRI in disorders of consciousness.

As we stated above, especially during the acute phase, patients may be comatose due to the injury and/or as a result of drugs, as a result of which their general cerebral metabolic rate might be severely diminished. Such reduced metabolism makes PET and single-photon emission computed tomography (SPECT) results very limited in the value for diagnosis and prognosis (Bergsneider et al., 2001). This metabolic hypoactivity in the acute phase seems to resolve itself within a few weeks of

injury, but this restoration is extremely variable and does not correlate between acute and postacute phases. Initial studies in acute head injury patients showed a clear separation between patients in acute phase with GCS 3–4 and very low cerebral metabolic rates, as compared to GCS 5–10 patients, who had significantly higher cerebral metabolic rates (Obrist et al., 1984); unfortunately, these results were not supported by previous (Bruce et al., 1973) or later findings. Given the clinical complexity of the acute phase, the lack of correlation between general metabolic rate and behavioral measures comes as no surprise. Initial hopes from the early clinical imaging community were to find general physiologic markers, independent from behavioral measures that would be resistant to the difficulties of the acute stage. They are not. Nevertheless, some authors argue that combined PET ^{18}F-fluordeoxyglucose (FDG) and ^{11}C-Flumazenil (FMZ, a measure of density of benzodiazepine receptors and neuronal integrity) may provide a more global picture, since the combination of information of metabolic consumption and tissue integrity can potentially be stronger in prognostic value (Heiss, 2012).

With new advances in MRI, comatose patients may benefit more from a full structural and functional MRI, including high-resolution structural T1 and T2/PD, and FLAIR, white matter tractography (DTI) and resting state fMRI. In particular, resting state fMRI, the collection of EPI images without instructions or stimulation in the scanner, can potentially replace PET as a measure of metabolic activity. Resting state is based on the spontaneous brain fluctuations in blood oxygen dependent signal (BOLD) picked by the MRI, and is based on the concept coined by Raichle and collaborators (2001): the default mode network (DMN). The idea is related to a series of areas such as the precuneus, bilateral temporoparietal junctions and medial prefrontal cortex, all of which have been shown to be more active at rest than when the subjects were involved in an attention-demanding cognitive task. The hypothesis states that these spontaneous fluctuations constitute the bases of the brain processes needed for normal conscious awareness (Boly et al., 2008). So far, there have been a few studies in vegetative state and minimally conscious state patients (Vanhaudenhuyse et al., 2010; Crone et al., 2011), but only one in the acute states (Norton et al., 2012). This study revealed that DMN connectivity was present in patients who regained consciousness, and disrupted in those who either died, stayed comatose, or progressed only to a vegetative state. In short, PET and resting state fMRI are potentially useful in acute stages postinjury, but the evidence is scarce and variable in its prognostic value.

POST-TRAUMATIC AMNESIA

Patients who have suffered an episode of acute loss of consciousness due to traumatic events and who survive and evolve out of unconsciousness may suffer a variety of sequelae, many of which are the direct result of brain injury, rather than the loss of consciousness *per se*. Amnesia is one such negative outcome, which has been matter of controversy in the field of clinical neurology, chiefly due to diverse definitions, the use of different and inconsistent methods across studies, and the difficulty in assessing amnesia in some of these patients (Chadwick et al., 1981; McMillan and Glucksman, 1987; Dikmen et al., 2001; Ropacki and Elias, 2003). One definition of post-traumatic amnesia (PTA) that is widely accepted refers to the period from injury until resumption of the ability to store new memories early after TBI. During such a period, usually described as a confusional state, patients exhibit impaired performance on attentional tasks that impacts on their ability to form new explicit memories (Russell, 1932; Russell and Nathan, 1946; Russell and Smith, 1961). Remarkably, both outcome (Cattelani et al., 2002; Williamse-van Son et al., 2007) and the extent of atrophy after TBI (Wilde et al., 2006) are better predicted by the duration of PTA than by other early injury markers typically used in the ICU, such as the GCS.

Once anterograde amnesia and/or orientation are recovered, one can determine PTA duration by considering the time of injury and these recovered cognitive skills. In a recent meta-analysis (Königs et al., 2012) looking at the impact of TBI on intelligence, injury severity was classified based on the duration of the PTA into mild (PTA duration 1–24 h), moderate (PTA duration 1–7 days) and severe TBI (PTA duration $>$ 7 days). The authors found that longer PTA duration was strongly predictive of intelligence deficits, as measured by the widely used Wechsler intelligence scales. Because these measures of intelligence rely on global cognitive functioning, for which memory is essential, understanding the relationship between cognitive decline after TBI and duration of PTA may be essential. Overall, it appears that PTA duration is gaining strength as a clinically valuable predictor of intelligence impairment and other cognitive outcomes and determining the duration of PTA in everyday practice of TBI patients with acute loss of consciousness should be encouraged in all ICUs. Naturally, for this to occur, trained neuropsychologists able to assess memory and attention recovery must be available. This is not always possible and it may constitute a major limitation for outcome prediction. For this reason, we encourage future research studies to determine the ability of brief yet reliable neuropsychological screening tools, such as the Addenbrooke's Cognitive

Examination – Revised (Mioshi et al., 2006; Torralva et al., 2011) or the INECO Frontal Screening (Torralva et al., 2009; Gleichgerrcht et al., 2011) to detect recovery of these functions in order to provide clinicians with easy-to-administer cognitive tests that may assist in evaluating PTA when human resources are scarce. As well, incorporating measures of health-related quality-of-life designed specifically for neurologic disorders, such as the Neuro-QOL commissioned by the National Institute of Neurological Disorders and Stroke (Cella et al., 2011).

CONCLUSIONS

The time has come for clinicians in acute care centers to incorporate new measurements and techniques to assess their patients with loss of consciousness. Immediately following their administration of classic coma scales in unresponsive patients, more sophisticated methodologies should be implemented to assess not only reflexive and intentional behaviors, but also patients' physiologic and cognitive profiles. The combination of behavior and electrophysiology is the most promising strategy for the years to come, as they make use of the equipment already available in the ICU and they only require training. The information that could be garnered by this more comprehensive approach may help establish consensus criteria leading to more accurate diagnoses of a patient's disorder of consciousness, therefore providing better prospects for their prognosis, guiding longer term rehabilitation and care, and even facilitating communication in patients with pathologies of consciousness.

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