

Unresponsive wakefulness syndrome

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ABSTRACT

Recent studies providing evidence for preserved awareness in some behaviorally unresponsive patients stress the need to improve diagnosis in patients with disorders of consciousness – and stress the possible dissociation between responsiveness and preserved consciousness. Because active paradigms can only bring information in the few cases where they return positive, a major effort is needed to setup ancillary markers evaluating the brain's ability to generate consciousness without requiring the patients' collaboration – in this context, research on neural correlates of consciousness and coma science progress hand in hand.

Key words

Consciousness • Vegetative state • Responsiveness • Active paradigms

Unconsciousness or unresponsiveness?

Vegetative state (VS) is usually defined by wakefulness without any sign of awareness of self, or the environment (Laureys et al., 2004). Minimally conscious patients show non reflexive behaviors but remain unable to communicate (Giacino, et al., 2002). The presence or absence of consciousness is assessed at the patients' bedside by searching for non-reflexive behaviors in response to various types of stimulation (Seel et al., 2010). Assessing the level of consciousness of non-communicative brain-damaged patients is therefore difficult, as consciousness is a subjective first-person experience and one has necessarily to make inferences about its presence based on the patients' behavior (Laureys and Boly, 2008). However, behavioral responses of brain-damaged patients are usually limited not only by their cognitive dysfunctions, but also by their frequent motor impairment (Boly et al., 2007). The differentiation of minimally conscious state (MCS) patients from vegetative state

is also very method-sensitive and a very high rate of misdiagnosis is present in the absence of use of an appropriate clinical scale to differentiate these patients (Schnakers et al., 2009). Furthermore, clinical scales themselves are quite variable in their reliability. A recent meta-analysis revealed that the Coma Recovery Scale – Revised (CRS-R) was the best attempt to explicitly incorporate diagnostic criteria for MCS in the bedside diagnosis (Seel et al., 2010). However, the reliability of the CRS-R itself depends on examiner experience (Lovstad et al., 2010), and this scale may be time-consuming to learn and administer in a routine basis. Finally, some clinical signs are still ambiguous and difficult to interpret: for example, the significance of blink to threat (Vanhaudenhuyse et al., 2008), visual fixation (Bruno et al., 2010), or grimacing to pain (Schnakers et al., 2010) are still poorly understood. These limitations of behavior – the possible false negative due to e.g. motor, language or vigilance impairment, the reliance on assessor experience, and residual ambiguous clinical signs interpretation –

stress the need for a development of neural markers of consciousness in unresponsive patients (Laureys and Boly, 2008).

Paradigm shift: the use of active tasks in consciousness research

A first successful attempt to compensate for some limitations of behavioral assessment was to design active paradigms in order to bypass motor output when searching for a response to command in patients with disorders of consciousness (DOC) (Boly et al., 2007). The first tasks tested to be used in DOC patients were spatial navigation, and auditory imagery tasks - inspired by (Curran et al., 2004). Spatial navigation was found to be very reproducible at the individual level, while auditory imagery was less robust at the single subject level (Boly et al., 2007). Spatial navigation was then complemented by another motor imagery task – tennis playing – which was chosen to be both complex (and thus likely leading to stronger brain activation [Kuhtz-Buschbeck et al., 2003]), and easy to imagine. These two tasks, used together, allow a successful blind differentiation of rest periods, spatial and motor imagery tests in healthy awake volunteers (Boly et al., 2007). These active tasks were found to provide positive results in 50 healthy volunteers tested, but no response to only passive listening to the command words (Owen et al., 2007). They were now applied with success on a larger cohort of patients with DOC, leading to positive results in about 1/10 patients (Monti et al., 2010). It may also seem surprising that this paradigm did not seem to detect more MCS than VS, while other active paradigms did so (Schnakers et al., 2008). Other mental imagery tasks have been developed since then, also still undergoing validation process (Monti et al., 2009; Soddu et al., 2009; Sorger et al., 2009; Bardin et al., 2011). All the above cited fMRI paradigms offer the advantage that the employed block design – of typically 30 seconds – render the response unlikely to be automatic and unconscious (Boly et al., 2007) (in contrast to more transient command-following fMRI or EMG paradigms [Bekinschtein et al., 2008; 2011]). Another issue is the existence of false negative in patients that are clinically responsive (Monti et al., 2010; Bardin et al., 2011). Future studies will have to quantify the

sensitivity and specificity of the response-to-command seeking approaches, and try to develop similar paradigms that may be used at the patients' bedside, such as active paradigms using EEG/ERP or EMG (Bekinschtein et al., 2008; Schnakers et al., 2009; Cruse et al., 2011).

The consequence of the above studies is that they raised awareness on the fact that some patients clinically unresponsive, classified as in a 'vegetative state', were in fact most likely presenting some residual awareness of self and environment and were sometimes even able to communicate. This fact stresses the ethical need to be cautious about inferences on states of mind in non-communicative brain damaged patients. It led to the proposal to rename 'vegetative state' as 'unresponsive wakefulness syndrome' (Laureys et al., 2010). While most patients in a VS are unlikely to show only motor problems, but also some degree of altered cognitive functioning and decreased consciousness, caution is needed at the individual level – which is, in a clinical situation, the one that matters (Boly, 2011). Active paradigm studies probe clinicians to change the common view of patients with disorders of consciousness. They also reflect the frequent misdiagnosis that can occur in these clinical populations, as well as on the need for further research to improve diagnosis and treatment in these patients.

Back to the basics: the necessary consciousness science/coma science dialogue

To date, the gold standard for the diagnosis of VS and MCS remains the clinical assessment based on criteria described by (Giacino et al., 2002). Behavioral diagnosis is mainly based on patients' responsiveness; and, as previously mentioned, it has now been shown that a minority of totally unresponsive patients can be conscious (Owen et al., 2006; Monti et al., 2010; Bardin et al., 2011). On the other hand, the active neuroimaging paradigms used to detect these patients are also prone to false negative findings (Bardin et al., 2011). In principle, paradigms based on response to command, being clinical or neuroimaging-based, are not sufficient to systematically detect consciousness in each individual case (Boly, 2011). Indeed, it has been shown that volitional activity and consciousness can be

dissociated in many cases (Soon et al., 2008; Boly and Seth, 2012) (on another topic, see also results obtained using isolated forearm technique in anesthesia studies [Sanders et al., 2012]). In addition to these approaches, neural correlates of consciousness (NCC)-based paradigms, using the rich information already present in the literature on NCC, can provide information about the global brain function in DOC patients, and the probability that patients' residual brain function can lead to consciousness. A practical diagnostic algorithm tree would first start with behavioral assessment using standardized scales, as these remain the gold standard for diagnosis (Boly, 2011). Passive and active neuroimaging paradigms and NCC-based approaches could then usefully complement the clinical diagnosis.

Ultimately, a most accurate diagnosis of consciousness would require indentifying the mechanisms bridging conscious perception to the brain, then using for example neuroimaging techniques as a way to objectivate the presence of this mechanism. To achieve this aim, theoretical approaches attempting at describing the general mechanism for conscious perception (Tononi, 2008; Dehaene and Changeux, 2011) have a great value. However, a lot more work is needed in this field, and we are still a long way from bringing current theories to truly testable predictions (Boly et al., 2009). The aim of this issue is to promote a continuation of NCC and coma sciences dialogue, by gathering state-of-the art knowledge on clinical and neuroscientific approaches in DOC states, by leading experts in the field. In this issue, Schnakers (Schnakers, 2012) will review current approaches and challenges to the clinical diagnosis of patients with DOC. Guldemund et al. (2012) and Lehembre et al. (2012) will review the state of the art of current knowledge concerning fMRI and EEG studies of brain function in DOC patients. As a generic marker of consciousness should aim to be generalizable to different etiologies of unconsciousness, the next papers in this issue will review current knowledge concerning NCC during anesthesia (Bonhomme et al., 2012), sleep (Goupil and Bekinschtein, 2012; Massimini et al., 2012) and epileptic seizures (Bartolomei, 2012). Recent updates on some influent theoretical approaches aiming at giving a coherent account of the various results of neuroimaging studies in DOC will then be presented (Sergent and Naccache, 2012;

Tononi, 2012). Finally, NCC-based neuroimaging studies and related theoretical approaches need to be brought back to the clinical field and face the practical challenges of bringing theoretical sciences closer to the patients' bedside – the last chapter of the present issue will discuss various issues related to such a translational approach (Boly and Seth, 2012). We hope that this ground of work will provide a comprehensive review of state of the art knowledge and viewpoints concerning NCC in DOC and will stimulate insightful discussions and research in the field, in order to move further towards the challenging aims of improving both DOC patients' diagnosis and prognosis (Laureys and Schiff, 2011).

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