State of consciousness and ERP (event-related potential) measures. Diagnostic and prognostic value of electrophysiology for disorders of consciousness

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Abstract

Disorders of consciousness were amply studied in the recent years. At this regards new methodologies and technologies were applied to explore the diagnostic and prognostic criteria that may be applied to the patients. Specifically electrophysiological measures were used to verify the degree of awareness and responsiveness in coma, vegetative states (VS), minimal consciousness state (MC), and locked-in syndrome (LI). Recently, ERPs (event-related potentials) were adopted to integrate the classical neuroimaging measures. Between the others, MMN (mismatch negativity) and P300 deflections were found to represent a consistent index of the present state of consciousness and to be predictive of successive modifications of this state. Also frequency-based EEG measures, such as brain oscillations, were revealed to be relevant marker of consciousness and awareness, able to predict the future evolution of pathology.

Keywords: Consciousness; ERPs; MMN; P300; Brain oscillations; Electrophysiology

1. Some preliminary remarks on consciousness states

An increasing number of studies have focused their attention to disorders of consciousness (Giacino et al., 2009). These disorders were classified in terms of awareness and wakefulness (Balconi, 2006; Gawryluk et al., 2010). Awareness refers to a state in which people have complete experiences such as thoughts, memories and emotions. Wakefulness refers to the state in which people can open their eyes and presents motor responsiveness. Three different typologies of distinct disorders of consciousness can be defined based on these two states: coma (C), where patients show absence of both awareness and wakefulness; persistent vegetative state (VS), where there is wakefulness without awareness; locked-in syndrome (LI), where there are both awareness and wakefulness. An adjunctive condition was reported by recent contributions, that is the minimally conscious state (MC) (Giacino et al., 2002). In this case people show wakefulness, but in contrast to patients in vegetative state, they also reveal inconsistent but discernible evidence of awareness. For example they may reach for objects or speak a word or gesture in response to a command (Figure 1).

The European Task Force on Disorders of Consciousness recently proposed an alternative name to represent VS, that is Unresponsive wakefulness syndrome (UWS) (Laureys, Celesia & Cohadon, 2010), where patients show a number of clinical signs of unresponsiveness (without response to commands or oriented voluntary movements) in the presence of wakefulness. In contrast to coma, which is an acute condition lasting no more than some days or weeks, VS/UWS can be a chronic condition lasting years or remain permanent.

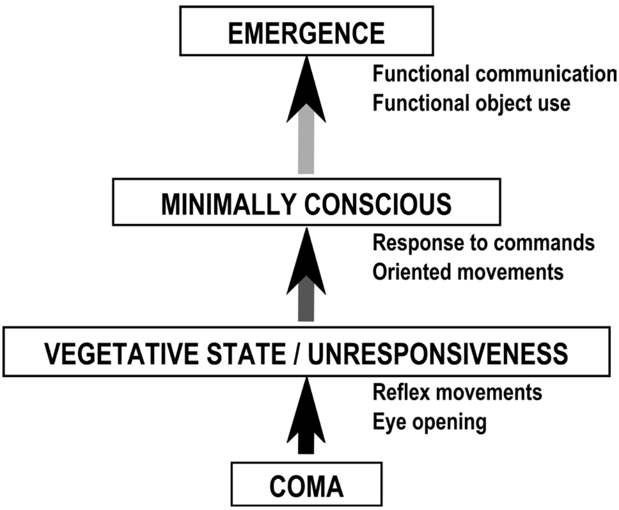

Figure 1. See Bruno et al., 2011, p. 147

These different profiles generally follow from specific brain damages, that is coma typically follows either brainstem injury or bilateral hemispheric damage (Bateman, 2001). Contrarily, VS occurs when the brainstem is intact but the cortex is extensively damaged, although also thalamic lesions are sometimes reported in this state (Laureys, Owen & Schiff, 2004). The MC generally consists of an evolution of the VS, that can persist indefinitely or progress to full consciousness (Giacino et al., 2002). Finally LI is a condition associated with injury to the ventral pons. A diagnosis of VS or MC is difficult to provide, because clinical examination is limited in these unresponsive patients. It is commonly agreed that VS and MC patients are frequently misdiagnosed. Clinical tests rely on a patient demonstrating awareness by means of overt motor actions, as does the Glasgow Coma Score, which includes measures such as count of eye opening, as well as the best verbal and motor responses (for this topic see also in the present Issue). However, the ability to perform these overt behaviors is often decoupled from consciousness as a direct outcome of the brain injury.

It is therefore important to obtain additional means of evaluating brain functions in these patients with reference to control (healthy) subjects. Functional brain imaging like positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) as well as electrophysiological examination through event-related potentials (ERPs) may furnish this possibility.

Both brain imaging and ERPs have been applied in VS. The first PET studies indicating that the brain of such patients can respond to very complex aspects of stimulation were single-case reports (de Jong et al., 1997; Menon et al., 1998), but very soon it was shown that brain metabolic responses in VS are not limited to exceptional cases (Schiff et al., 2005). Moreover, the first ERP study indicated electrophysiological signs of profound stimulus processing, such as P300 effect to rare stimuli (Reuter et al., 1989). Nevertheless, only recently it was evaluated the relevance of different ERP components in large sample of VS and MS (Kotchoubey et al., 2005). Based on previous evidences, there is no doubt that the brain of many patients with disorder of consciousness can perform very complex information processing operations.

About the relationship between the physiological findings and the behavioural signs of conscious awareness, three types of approach can be distinguished. The first adopts the clinical diagnosis to introduce specific distinctions (such as VS and MC). However, we know that the rate of diagnostic errors in VS is up to 40%: thus we cannot rely upon the clinical assessment as a solid base. A second approach considers as prominent the physiological criteriom. For example the occurrence of various cognitive ERP components in VS with a predominant alpha- or theta-rhythm in the EEG was the same as in MC, but that this occurrence was almost zero in VS with predominant slow wave activity. The EEG criterion appeared to be more important than the diagnosis. A third approach showed a concomitant variation of diagnosis of consciousness state modification and neuroimaging data. To activate the corresponding brain areas the patients have to understand the specific task (for example a verbal task) and to follow them under a limited time interval. In this case we may state that the approach is much too conservative, since the patients would show clear awareness and not only a rudimentary consciousness. Thus, this method is highly appropriate to uncover main diagnostic errors but it cannot be applied for finding out basic forms of daily experience (Owen et al., 2006).

2. Measure of consciousness

To measure the state of consciousness the structural an functional imaging technique (CT, MRI, fMRI etc.) and behavioral assessment (such as Glasgow Coma Scale, JFK Coma recovery Scale, for this and other measures see the contribution of in the present issue) that are commonly used are inadequate. Thus many of these tests rely on the observation of behaviors (motor and communicative indexes) that, as we have previously observed, may be impaired in brain injured subjects.

The seriousness of the consciousness assessment problem is demonstrated by the situation in which almost half of the cases are misdiagnosed. Specifically, examination of the failings of conventional diagnostic approaches has yielded a misdiagnosis rate as high as 40-50% (Andrews, Murphy & Munday, 1996; Schnakers et al., 2009). The Glasgow Coma Scale remains the "goal standard" for routine assessment of consciousness, but relies exclusively on behavioural responses. Although other measures of consciousness exist, all are based on behavioral signs of consciousness that are subjectively observed. The search for objective physiological measures yielded electrophysiological approaches, which were soon followed by functional imaging approaches. While both approaches can provide valuable information, the current contribution focuses on electrophysiology as this measure is readily available across a range of clinical settings and thus provides an important tool for the consciousness assessment problem (Gawryluk et al., 2010).

Functional imaging was used to assess brain functions from a physiological perspective. By using fMRI, for example, it is possible to track fluctuations in blood oxygenation to examine activation differences between normal speech and reverse speech conditions. Nevertheless, there is a critical need to improve the clinical evaluation of consciousness state using alternative measures, that is physiological measure (Balconi & Mazza, 2009) such as electrophysiological indexes which may introduce important evidences on the functional responsiveness of the injured brain. Specifically, event-related potentials (ERPs) provide useful clinical tool to assess consciousness, providing an on-line monitoring of information processing in the brain. Such electrophysiological markers have emerged from both diagnostic and prognostic levels of analysis, pointing out the possible interplay of these two clinical aspects (Bruno et al., 2011).

Thus, when used in conjunction with functional imaging modalities (such as fMRI and PET) electrophysiological evaluations have demonstrated value in determining differential diagnosis, residual functions, and prognosis. Moreover, EEG-based paradigms have many advantages over fMRI for monitoring patients with altered consciousness for some main reasons: the millisecond-range resolution; the non invasiveness of the technique; the possibility of designing dedicated systems for clinical use.

We may distinguish different planes of analysis related to ERP profile. Sensory ERPs, generally appearing in response to perceptual features of a stimulus (exogenous potentials), are used for clinical assessment of basic sensory functions. For example, brainstem auditory evoked potentials (BAEPs) occurring in the 10 ms post-stimulus processing, are used in the assessment of coma, since the absence of an intact brainstem response is indicative of a negative prognosis for recovery (Daltrozzo et al., 2007). Also somatosensory evoked potentials (SEPS), middle-latency auditory evoked potentials (MLAEPs), and visual potentials (VEPs) are employed to evaluate primary sensory cortices.

Contrarily, cognitive ERPs are used to evaluate higher level functions like attention, memory, and language. These long-latency potentials are considered well-suited to assess functions of consciousness. Four specific components were considered focusing on the analysis of conscious awareness, that is N100, the mismatch negative (MMN), the P300, and the N400 (Schoenle & Witzke, 2004). The N100 indexes perceptual functions during visual, auditory and somatosensory processing. The MMN, a negative deflection occurring around 150-250 sec. post-stimulus, was linked to processing of deviant auditory stimuli that occur below the level of consciousness. It is regarded as an automatic response of the brain to stimulus deviation from preceding repetitive auditory stimuli and requires fully processed physical features of the auditory stimuli (Näätänen, 1990). The P300 generally occurs to deviant or oddball stimuli and is thought to reflect higher level processing. It was considered the most appropriate candidate as an indicator of conscious awareness. A vast amount of studies have confirmed the utility of P300 to predict awakening and favourable outcome from coma and VS (Kotchoubey, 2005). Finally, the N400 deflection is observed following sentences that end with semantically inappropriate words or, more generally, significant stimuli (Balconi & Pozzoli, 2003; 2005). In this case the semantic violation may be used to assess language comprehension.

3. ERP applications to the evaluation of consciousness across the different states

Different ERP correlates were used to assess consciousness state across the spectrum of pathologies associated with disorders of consciousness.

Specifically, in case of coma state the absence of response BAEPs, SEPs and MLAEPs-related is generally indicative of a poor prognosis. Additionally, cognitive ERPs have shown proficiency in determining prognosis (Gawryluk et al., 2010). Recent research found that MMN response was the stronger predictor of functional recovery, since this negative ERP deflection can predict progression towards improved levels of consciousness. Moreover, MMN and P300 were found to be more accurate than the N100 at predicting a progressive awake state. An interesting study demonstrated that P300 elicited by the subjects own name can be used to enhance the sensitivity of assessment with the MMN, increasing prognostic utility of ERP measure (Fischer, Luaute & Morlet, 2010).

In the case of vegetative state it was shown larger MMN components were associated with increased signs of consciousness. Also linguistic marker such as N400 effect may be used to test the preserved abilities to respond to linguistic stimuli. In some cases misdiagnosis occurs for patients who are considered in vegetative state and that instead could be more correctly classified as minimally conscious, by adopting ERP measures (and specifically N400 index). Thus these markers highlight the ability to evaluate intent, which is a critical component of awareness. About the minimally conscious state a significant amount of data confirmed the presence of some cognitive functions, such as it was shown by analysis on P300 and N400 ERP deflections (Fischer et al., 2010). Finally, locked-in syndrome can be analyzed by adopting cognitive ERPs, by diagnosing this state at an early time point. Some recent results indicate that P300 waveform could be reliably detected in locked-in patients, since finding of residual cognitive functions may support the diagnosis of locked-in syndrome as opposed to vegetative state.

4. The specificity of P300 oddball paradigm and MMN for consciousness studies

The adoption of P300 oddball paradigm was integrated by the use of complex salient stimuli, such as those adopted by recent research (Fischer et al., 2010; Laureys et al., 2004; Perrin et al., 2006) who included in their studies the subject's own name as salient stimulus. Comparing the responses to SON (subject own name) in patients in VS and patients in MC it was found the presence of a P300 in both the categories. Thus it may be concluded that some semantic processes are preserved in VS.

More recently Cavinato and coll. (2011) found that in VS a reliable P300 component could be observed. The presence of a reproducible ERPs in non-conscious patients may indicate the ability of severely damaged brains to execute spared modular cognitive functions. In general the morphology of the P300 wave, specifically its latency, is affected by stimulus relevance and increases systematically with the complexity of the semantic categorization (Picton, 1992). It was suggested that the P300 latency is an index of stimulus evaluation time and classification speed and is sensitive to the complexity of the semantic categorization. Thus, the presence of an analogous latency for the P300 effect in controls and MC patients may suggest a similar responsiveness to the complexity of the stimulus in different states of consciousness. Nevertheless, VS patients do not produce clear variation of P300 latency parameters, fact that may be explained by an impairment of higher cognitive resources that involve semantic processes and language comprehension, which instead are partially preserved in the MC.

More generally, previous studies on the role the P300 has for the analysis of different states of consciousness confirmed this component may be generated even when no externally observable behaviours are expressed by patients. The endogenous processes manifested and reflected in P300 should be associated with stimulus evaluation rather when with response selection. In other words, patients in whom P300 is present were likely able to respond consciously or non-consciously to novel stimuli.

To summarize, novelty detection mechanisms require incoming information to be compared with a relevant memory template. This ERP deflection represents an automatic brain process related to the detection of stimulus novelty and salience. The presence of novelty processing in unresponsive patients represents the ability for their brain to detect novel events and it may prove that some cognitive activity is preserved. Thus we may conclude some VS and MC patients are able to unconsciously process sound deviance and novel sounds. It was largely discussed that the frontal aspect of the novelty P300 reflects processes related to orienting and that its posterior aspect reflects a categorization process (Friedman et al., 2001). Since the P300 component is associated with high-order functions such as decision-making and memory processing (Polich, 2007), then it may be inferred that some VS and MC patients are able to put certain awareness marker processes to work.

About the MMN, it also seems to have potential value in predicting clinical improvement in patient chronic disturb of consciousness. Although it may reflect a pre-attentive process, the MMN can be modulated by attention. That is, assessment of MMN in patients with disorder of consciousness might be useful for detecting attentional abilities that are related to conscious functioning.

Thus, it is suited to the examination of discriminatory functions and attentional mechanisms in non-responsive patients because it is elicited irrespective of the patient's direction of attention. Prognostic validity was revealed in many studies, for prediction of recovery from coma. Detection of MMN after coma was found to predict the return of consciousness with high accuracy (Fischer et al., 1999; Wijnen et al., 2007). Similarly, preserved MMN in VS of MC is related to clinical improvement (Kotchoubey et al., 2005). This negative deflection was found to be useful to for monitoring the patient's state in the weeks after coma onset, as MMN was observed to increase over the course of regaining consciousness. Nevertheless we may state that MMN reflects attentional processes and it is not clear how these are related to consciousness. In other words no causal relationship between consciousness and automatic redirection of attention may be established a priori.

Whereas MMN evoked by non-self-related stimuli is shown to be able to predict awakening state changes, the prognostic value of MMN evoked by self-referential stimuli has not been previously evaluated. A recent study explored this topic, by pointing out the effect the subject's own name has on the brain activity (Pengmin et al., 2008) (for this paradigm see also previous consideration on P300 effect). The authors revealed a high prognostic value of MMN-name related, since it may mark the future transition from VS to MC. These results were also in line with some previous fMRI results showing that brain activation evoked by subject's own name could predict the outcome of patient with disturb of consciousness (Di et al., 2007).

5. New evidences on brain oscillations for consciousness monitoring

Recently it was shown that the analysis of event-related brain activity by time-frequency decomposition can increase the detectability of relevant responses. In fact recent empirical evidences showed that time-frequency analysis is more sensitive than ERPs for revealing differential reactivity. Interest in the oscillatory characteristics of patients with disorders of consciousness is arisen. Research on the resting EEG has found lower magnitudes with higher frequencies for patients in MC compared to patients with severe neurocognitive but intact consciousness. Similarly the delta-alpha ratio correlates with the level of recovery after neurorehabilitation (Leon-Carrion et al., 2009). As the alpha rhythm (8-12 Hz) is considered to be strongly related to attention and alertness, differential responses in the alpha range to deviant stimuli can be expected. An interesting relationship between MMN and alpha oscillations was found by Nashida et al. (2000). It was reported that patients with disorders of consciousness have predominant oscillatory activity in the delta range that might disturb MMN detectability. Thus, time-frequency analysis could detect residual, non phase-locked reactivity, that is possibly related to the level of consciousness. However, future research should explore the entire range of brain oscillations, by pointing out the direct (or indirect) relationship between specific disturbs of consciousness and frequency band modulation, intended as a brain marker of modifications of the consciousness states.

6. To conclude

Relationships between neurophysiological markers, behavioural states, and state of consciousness are like a system of two linear equations with three unknowns: when you fix one of them, you can find the other two. For example, if we know that the P300 reflects conscious information processing, we can distinguish between states with and without elements of conscious awareness. Conversely, if we were sure that no conscious processing is possible in a given state, we could split up ERP into the components related vs. unrelated to conscious experience. Unfortunately, we do not know for sure whether our VS subjects could not shortly perceive some of the stimuli presented. We have not direct possibility to distinguish responses to occasionally perceived stimuli in coma or VS, but we cannot rule out that at least some stimuli in some patients do attain the level of awareness despite the lack of a behavioural response.

Nevertheless, current methods for evaluating altered levels of consciousness are highly reliant on either behavioural measures or anatomical imaging. While these methods have some utility, estimates of misdiagnosis are worrisome, clearly this is a major clinical problem: the solution should involve objective, physiologically based measures that enable better evaluation of consciousness states (come, VS, MC, and LI). Based on the evidence to-date, electroencephalographic assessments of consciousness provide valuable information for evaluation of residual function, formation of differential diagnoses, and estimation of prognosis.

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