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Information processing in patients in vegetative and minimally conscious states

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HIGHLIGHTS

- Rates of misdiagnoses in patients with disorders of consciousness (DOC) are high.
- The auditory P300 was more prevalent in healthy participants than in DOC patients.
- P300 prevalence did not differentiate between VS and MCS patients.

ABSTRACT

Objective: Evaluation of a short two-tone oddball paradigm to discriminate between the vegetative state (VS) and minimal consciousness state (MCS) in a sample of patients with severe disorders of consciousness (DOC).
Method: EEG was recorded from 45 DOC patients and 14 healthy participants while listening to an auditory oddball paradigm presented in a passive – just listen – and an active – count the odd tones – condition. In patients, the experiment was repeated after a minimum of one week.
Results: Prevalence of the P300 was higher in healthy participants (71%) than in patients, but did not discriminate between VS (T1: ~10%; T2: ~11%) and MCS (T1: ~13%; T2: 25%) patients.
Conclusion: Results cast doubt on whether this simple auditory stimulation paradigm, which requires cognitive action from the listener, is sensitive enough to discriminate between patients with DOC.
Significance: The sensitivity of the P300 ERP obtained in a short two-tone oddball paradigm presented in a passive and an active condition appears to be too low for routine application in a clinical setting aiming at distinguishing between VS and MCS patients.

1. Introduction

Disorders of consciousness (DOC) challenge routine diagnostic and clinical practice. After a period of coma, patients may become awake yet still not show behavioural signs of awareness. These patients are assigned the diagnosis "vegetative state" (VS; Plum and Posner, 1972), more recently termed "unresponsive wakefulness syndrome" (Laureys et al., 2010). Later, some of these patients may start to show non-reflexive behaviour, albeit inconsistently, e.g. gaze following, orienting responses or command following. These patients are then diagnosed as minimally conscious (MCS; Giacino et al., 2002). Clinically, correctly diagnosing these patients is difficult, as evidenced by high rates of misdiagnoses (Schnakers et al., 2009).

Originally, the term VS was meant to indicate a complete lack of cortical functioning. However, neuroscientific evidence from passive techniques such as stimulation (e.g. Kotchoubey et al., 2005) or connectivity studies (c.f. Gantner et al., 2013) suggests that some VS patients possess at least some intact cognitive functions, e.g. pitch discrimination, or recognition of nonsensical sentence endings (c.f. Harrison and Connolly, 2013; Monti, 2012; Steppacher et al., 2013). Unfortunately, these studies cannot

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answer the question of whether these patterns of activation reflect conscious awareness. Studies using active paradigms, i.e. paradigms requiring the wilful modulation of brain activity, suggest that at least some VS patients do show signs of awareness and volitional control in various paradigms using functional MRI (fMRI; Bardin et al., 2011; Owen et al., 2006), or electroencephalography (EEG; Cruse et al., 2011, but see Cruse et al., 2013; Goldfine et al., 2013). Thus, on a purely functional, but not behavioural basis, at least some of these patients might be more appropriately classified as MCS (Monti, 2012), or even completely locked-in (Lulé et al., 2013).

Yet, these paradigms are restricted to experimental research and have yet to be transferred into routine clinical practice (Harrison and Connolly, 2013). To promote application of psychophysiological paradigms in supporting the clinical assessment of the state of consciousness we developed a short (2×6.8 min) two-tone auditory oddball paradigm, and analysed its performance in a large sample of DOC patients. In the EEG, randomly occurring odd tones within a series of frequent tones are associated with a marked centro-parietal positivity, occurring approximately 300 ms after onset of the odd tone (event-related potential, ERP, P300). Apart from physiological factors, such as arousal (Polich and Kok, 1995), the amplitude of the P300 was shown to be sensitive to shifts of attention. Instructions designed to shift attention towards the odd tones, such as asking participants to count how often such a tone occurs, lead to an increased P300 amplitude (Polich, 1986a,b) as compared to a passive listening condition. Conversely, an increased P300 following an instruction to count the odd tones may be taken as evidence, that the participant successfully followed the instruction which is only possible if he or she is consciously aware during testing.

Passive stimulation paradigms appear not to discriminate between VS and MCS patients (Harrison and Connolly, 2013; Kotchoubey et al., 2005). Thus, in this study we investigated whether a direct comparison of the same paradigm between a passive and an active condition would be able to do so. Specifically, we hypothesised that at least some VS but more MCS would show, (1) undifferentiated cortical activation in relation to the sole presence of tones (N100–P200), (2) differential activation between frequent and odd tones in the passive and active conditions (Kotchoubey et al., 2005), (3) an increased P300 following the odd tones in the active as compared to the passive condition (difference P300). Further, presence/absence of ERPs should be stable across time. In addition, we analysed several possible predictors. Firstly, we hypothesised that the presence of the P300 component (in either condition) would be predicted by the early N100–(P200) complex (Harrison and Connolly, 2013; Kotchoubey et al., 2005). Secondly, we assumed that the time since the incident would predict presence of a P300 since this parameter is known to be an important predictor of recovery (The Multi-Society Task Force on PVS, 1994). Finally, we investigated the role of aetiology, hypothesising that ERPs would be less frequent in patients with hypoxia, in whom cortical injuries are more diffuse, as compared to traumatic patients who present with more focal injuries (Daltrozzo et al., 2007; Kotchoubey, 2005; Kotchoubey et al., 2005).

2. Methods

2.1. Samples

The study was conducted at three clinics specialised in the care for patients with chronic and severe disorders of consciousness between September 2011 and May 2012. We recruited $N = 61$ adult patients who met the definition of VS or MCS according to the revised Coma Recovery Scale (CRS-R; Giacino et al., 2004; see Table 1 and Supplementary Table S1). Exclusion criteria were psychomotor agitation, use of drugs affecting vigilance, infectious diseases, and a history of auditory impairment. Information about their medical histories was obtained from the patients' files. Informed consent was obtained from the legal guardians. In addition, data from $N = 14$ healthy adult participants (5 male, 9 female, mean age = 27.6, $SD = 9.5$) was collected at the psychophysiological laboratories of the Institute of Psychology, University of Würzburg, and the Institute for Medical Psychology and Behavioural Neurobiology, University of Tübingen. In patients, the study was conducted at two time points (T1 and T2) separated by at least one week. The study was approved by the local Ethical Review Boards of the institutions involved (Fondazione Santa Lucia, Rome, Italy; University of Tübingen, and University of Würzburg, both Germany) and conformed to the Declaration of Helsinki (World Medical Association, 2008).

Diagnoses (as per CRS-R) were stable between T1 and T2 in 48 patients, but changed in three patients (from VS to MCS: one patient; from MCS to VS: two patients). CRS-R scores were significantly higher in MCS than in VS patients ($t = 8.49$, $DF = 43$, $p < .001$). VS and MCS patients did not differ in age ($t = 0.15$, $DF = 43$, $p = .88$), time since onset ($t = -0.54$, $DF = 43$, $p = .59$), and aetiology (Fisher's Exact Test, $p = .846$).

2.2. Procedure

Prior to EEG recording, each patient was assessed using the CRS-R. If, during the course of the experiment, patients appeared to be drowsy, recordings were aborted, the Arousal Facilitation Protocol of the CRS-R administered, and the recording restarted. Via in-ear headphones (E-A-RTONE Gold, Auditory Systems, Indianapolis, Indiana), participants were then presented with a binaural stream of 420 short complex (Kotchoubey et al., 2005) high (440 + 880 + 1760 Hz) tones into which 60 short complex low (247 + 494 + 988 Hz) tones were pseudo-randomly interspersed. Stimulus duration was 50 ms, linear rise/fall time was 5 ms, intensity was 70 dB (Polich, 1986b), and ISI was 850 ms. This paradigm was designed to detect the early auditory cortical responses expressed in components N100 (defined as the most negative deflection within 50–200 ms post onset of a tone; Näätänen and Picton, 1987), and P200 (most positive deflection between 100 and 250; Crowley and Colrain, 2004), and – as an indicator of deeper differentiation – the P300 (most positive deflection between 250 and 500 ms; Polich, 2007; in patients the interval was chosen between 300 and 700 ms, to compensate for the delayed latencies of cognitive ERPs in patients with acquired brain damage; Guérit et al., 1999). Tone streams were presented twice, once in a passive (always presented first) and once in an active condition. In the passive condition, participants were told that they were going to listen to a series of tones and that they would just have to listen to the

Table 1
Description of patient sample.

	VS ($n = 29$)	MCS ($n = 16$)
Males/females	19/10	9/7
Age (mean, *SD*)	49.72 (13.58)	50.38 (16.64)
Time since incident, months (mean, *SD*)	36.73 (44.94)	29.46 (39.02)
CRS-R (mean, *SD*)	4.86 (2.1)	11.69 (3.3)
Aetiology (*n*)		
Haemorrhage	4	3
Hypoxia	13	6
TBI	10	5
Other[a]	2	2
Second measurement available (*n*)	28	12

[a] Anaphylactic shock, Guillain–Barre, Aneurism A. Cerebri media, central pontine myelinolysis.