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Basic discriminative and semantic processing in patients in the vegetative and minimally conscious state

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ABSTRACT

Patients who survive injuries to the brain following accidents or diseases often acquire a disorder of consciousness (DOC). Assessment of the state of consciousness in these patients is difficult since they are usually incapable of reproducible motor movements. The application of event-related potentials (ERP) recorded via EEG constitutes one promising approach to complement the assessment of cognitive functions in DOC patients. For these assessments, a hierarchical approach was suggested which means that paradigms aiming at higher order ERPs are only presented if early responses were found. In this study, 19 behaviorally unresponsive or low-responsive DOC patients were presented with three auditory paradigms using passive instructions. The paradigms aimed at eliciting the Mismatch Negativity (MMN) and N400 and were applied at two time points. One oddball paradigm (MMN) and two semantic paradigms (word-pairs: N400 Words; sentences: N400 Sentences) were included. The majority of patients (n = 15) did not show any response to the stimulation. In the MMN paradigm, an MMN was identified in two patients, in the N400 Words paradigm, only an N1 was identified in one patient, and in the N400 Sentences paradigm, a late positive complex (LPC) was identified in two patients. These data contradict the hierarchical approach since the LPC was identified in patients who did not exhibit an MMN. They further support the notion that even higher information processing as addressed with the N400 paradigms is preserved in a minority of DOC patients. Thus, in this sample, around 10% of the DOC patients exhibited indicators of preserved consciousness.

1. Introduction

In the past decades, medical progress has led to an increasing number of survivals after traumatic and hypoxic brain injuries following accidents, stroke or cardio-vascular diseases. However, some surviving patients remain in altered states of consciousness and are often incapable of communication that is usually based on muscular activity. Estimating the level of consciousness in these patients is difficult and is further impeded by a lack of standardized methods independent of behavioral responses. The use of event-related potentials (ERP) measured by EEG is one promising tool to complement the clinical assessment of cognitive functions associated with attention and consciousness (Kotchoubey, 2015; Sitt et al., 2014).

Albeit being often low or non-responsive in terms of behavioral reactions, patients with disorders of consciousness (DOC) can exhibit various levels of consciousness. DOC encompass the minimally conscious state (MCS, Giacino et al., 2002), the vegetative state (VS, Jennett and Plum, 1972), coma, and brain death (Bernat, 2006). The present study focuses on MCS and VS patients. VS is defined as wakefulness without awareness meaning that these patients show signs of wakefulness like sleep-wake-cycles including phases of eye-opening but are still assumed to be unaware of themselves and their environment (Jennett and Plum, 1972). VS patients exhibit reflex movements to touch, pain, bright light, or noise. However, no reproducible reactions following commands can be observed (Laureys et al., 2010). In contrast, MCS patients do show signs of awareness such as reproducible reactions, gaze following, or yes/no gestures (Bernat, 2006). However, these behaviors are inconsistent and may occur on some days, but not on others. Thus, diagnosis of MCS is especially difficult and largely depends on the current status of the patient.

A medical condition that can easily be confused with DOC is the locked-in state (LIS). Like patients in VS, LIS patients are unable to

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move or speak, but are consciously aware of themselves and their environment (Smith and Delargy, 2005). LIS patients can be completely locked-in with no means of communication but full awareness, or incompletely locked-in with preserved movements, such as eye gaze or single fingers (Smith and Delargy, 2005). Thus, LIS patients can easily be misdiagnosed as VS or MCS or even comatose if only judged by their behavioral responses.

However, the differentiation between LIS and VS or MCS is not the only difficulty. Numerous studies have provided evidence for different degrees of awareness also in VS patients (i.e. Daltrozzo, 2006; Kotchoubey et al., 2005; Menon et al., 1998; Owen et al., 2006). The patients assessed in these studies showed preserved cognitive functioning in response to auditory stimulation that could, in some cases, also indicate preserved consciousness. Thus, patients diagnosed with these DOC are not necessarily completely unaware of their environment. High rates of misdiagnosis of patients in VS have been published repeatedly (i.e. Andrews et al., 1996; Schnakers et al., 2009). In addition, DOC patients do not remain in a constant state of consciousness for an unlimited time but experience eminent fluctuation of vigilance (Bernat, 2006). Thus, patients may be able to follow commands on one day, but not on others, complicating a correct diagnosis.

Two candidate ERPs for the assessment of the level of consciousness in DOC patients are the Mismatch Negativity (MMN) and the N400. The MMN belongs to a group of ERPs referred to as N200 (Sutton et al., 1965). MMN is associated with automatic processing irrespective of attention and is typically elicited in an oddball paradigm comprising one stimulus which occurs frequently (standard), and one that differs from this standard and occurs rarely and unpredictably (deviant). In the auditory domain, an MMN appears in response to deviants that vary in one or more stimulus features such as frequency, intensity, duration, or location (for a review, see Näätänen et al., 2007). The MMN occurs in a latency range of 100–250 ms after deviant onset and is quantified by subtracting the ERP response elicited by the standards from that elicited by the deviants (Duncan et al., 2009).

The N400 occurs as slow monophasic negativity between 200 and 600 ms and is mainly regarded as a specific response to violations of semantic expectations (Kutas and Hillyard, 1980). It occurs in response to congruent versus incongruent sentence endings (Kutas, 1987; Kutas and Hillyard, 1984), and related versus unrelated word-pairs (Bentin et al., 1985; Hagoort et al., 1996), as well as to line drawings completing a sentence (Ganis et al., 1996), incongruent endings of picture stories (West and Holcomb, 2002), and inappropriate objects in video films (Sitnikova et al., 2003).

The existence of MMN or N400 in DOC patients indicates residual information processing and the ability to discriminate between different stimuli: An MMN indicates the preserved automated recognition of deviant stimuli based on traces in sensory memory, thus representing basic processes. The existence of an N400 is a sign for complex, but partially automated linguistic information processing (Risetti et al., 2013). Elicitation of these components might be caused by preserved networks of a functional metabolism in the brain (Schiff et al., 2002). Previous studies indicated that the presence of an MMN or N400 may indicate future awakening from coma and VS (Daltrozzo et al., 2007; Faran et al., 2006; Fischer et al., 2004; Steppacher et al., 2013; Wijnen et al., 2007). N400 effects have been found to indicate preserved semantic processing in some DOC patients (Kotchoubey et al., 2005; Schoenle and Witzke, 2004).

In comparison to healthy participants, persons with closed head injuries have reduced N200 amplitudes, both visually and auditorily (Duncan et al., 2005). Other studies, however, found no differences in auditory N200 between healthy participants and patients with mild brain injuries (Potter et al., 2001; Sivák et al., 2008). Smaller auditory N400 amplitudes were found in patients with traumatic brain injuries as compared to healthy persons (Knuepffer et al., 2012). Also Münte and Heinze (1994) reported diminished and delayed auditory N400 responses after closed head injury. In their study, a clear N400 component was only identifiable in response to sentences, but not to word-primes, thus, indicating a potential benefit of sentence based stimulus material.

As a consequence, albeit playing an important role in the assessment of DOC patients, ERPs are often altered following injuries of the brain. Diminished amplitudes and prolonged latencies can complicate the identification of the relevant deflections, thus fostering the need for a comparison of ERPs within patients across different paradigms.

ERPs have long been discussed for their general benefit in the assessment of cognitive functioning in DOC patients, complementing a mere behavioral assessment. However, measurements in clinical environments are subject to several constraints, like limited attention span of the patient and limited time available for testing. Thus, a hierarchical approach for those investigations was proposed. According to this approach, the presence of simple processing mechanisms such as the N1-P2 complex is a prerequisite for more complex processes and later components like MMN and P300 as well as responses to semantic material such as N400 and P600, finally presupposing volitional decisions (Kotchoubey et al., 2005; Owen et al., 2005; Owen et al., 2006). Following this approach, recordings using complex paradigms could be skipped if no ERPs emerged in reaction to simple stimuli. Kübler and Kotchoubey (2007) suggested a five steps procedure: (1) recording of resting state EEG and auditory evoked potentials to rule out the possibility of hearing loss, (2) stimulation using passive paradigms aiming at the elicitation of MMN/P300 (oddball) and N400/P600 (semantic material), (3) stimulation with the same paradigms as in (2) with the additional task to specifically concentrate on certain stimuli, i.e. counting the odds, (4) volitional tasks, i.e. imagination of movements according to certain stimuli, and (5) decision making using brain-computer interfaces (BCI), i.e. answering yes/no questions.

In essence, the hierarchical approach postulates a procedure starting with paradigms to ensure intact hearing, slowly proceeding to more complex stimulation and terminating with the attempt to establish communication through conscious decision between different options. Following this procedure can save time and resources but presumes the absence of higher order information processing if no signs of simple discrimination abilities can be found. In a recent study, Rohaut et al. (2015) found patterns supporting this theory: The late ERP components LPC and the global effect were only found in patients who had also exhibited intact P1 and MMN responses. The global effect describes the ability to recognize global regularities within a longer series of tones consisting of standards and deviants (Bekinschtein et al., 2009).

To further establish ERPs as a means to better determine the state of consciousness in nonresponsive patients diagnosed with VS or MCS, we investigated the MMN and N400 to answer the following questions: Firstly, how many patients in VS or MCS show the respective ERPs in general? Secondly, does the pattern of arising ERPs follow the hierarchical approach, thus, do all patients exhibiting an N400 also present with an MMN? Thirdly, is there a connection between behavioral measures and emerging ERPs? Fourthly, do the paradigms differ in their potential to elicit the respective components?

It is predicted that at least some patients in VS and MCS show ERPs in response to auditory stimulation (Kotchoubey et al., 2005). Further, ERPs are expected to be altered in their physiology, i.e. latency and polarity (Perrin et al., 2006; Pokorny et al. 2013).

2. Methods and materials

2.1. Participants

EEG was recorded in 19 behaviorally unresponsive or low-responsive DOC patients (11 males) at the Clinic for Intensive Care in Schwaig and Hersbruck in Bavaria/Germany. The patients were between 31 and 69 years of age ($M = 50.74$, $SD = 13.75$ years) and all measurements were carried out at bedside. The interval between the incident and the measurement was between 3 and 141 months ($M = 72.32$, $SD = 39.81$ months). Written informed consent was provided by the legal