

BRAIN COMMUNICATIONS

Applied potential of task-free event-related paradigms for assessing neurocognitive functions in disorders of consciousness

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Diagnosing patients with disorders of consciousness is immensely difficult and often results in misdiagnoses, which can have fatal consequences. Despite the severity of this well-known issue, a reliable assessment tool has not yet been developed and implemented in the clinic. The main aim of this focused review is to evaluate the various event-related potential paradigms, recorded using EEG, which may be used to improve the assessment of patients with disorders of consciousness; we also provide a brief comparison of these paradigms with other measures. Notably, most event-related potential studies on the topic have focused on testing a small set of components, or even just a single component. However, to be of practical use, we argue that an assessment should probe a range of cognitive and linguistic functions at once. We suggest a novel approach that combines a set of well-tested auditory event-related potential components: N100, mismatch negativity, P3a, N400, early left anterior negativity and lexical response enhancement. Combining these components in a single, task-free design will provide a multidimensional assessment of cognitive and linguistic processes, which may help physicians make a more precise diagnosis.

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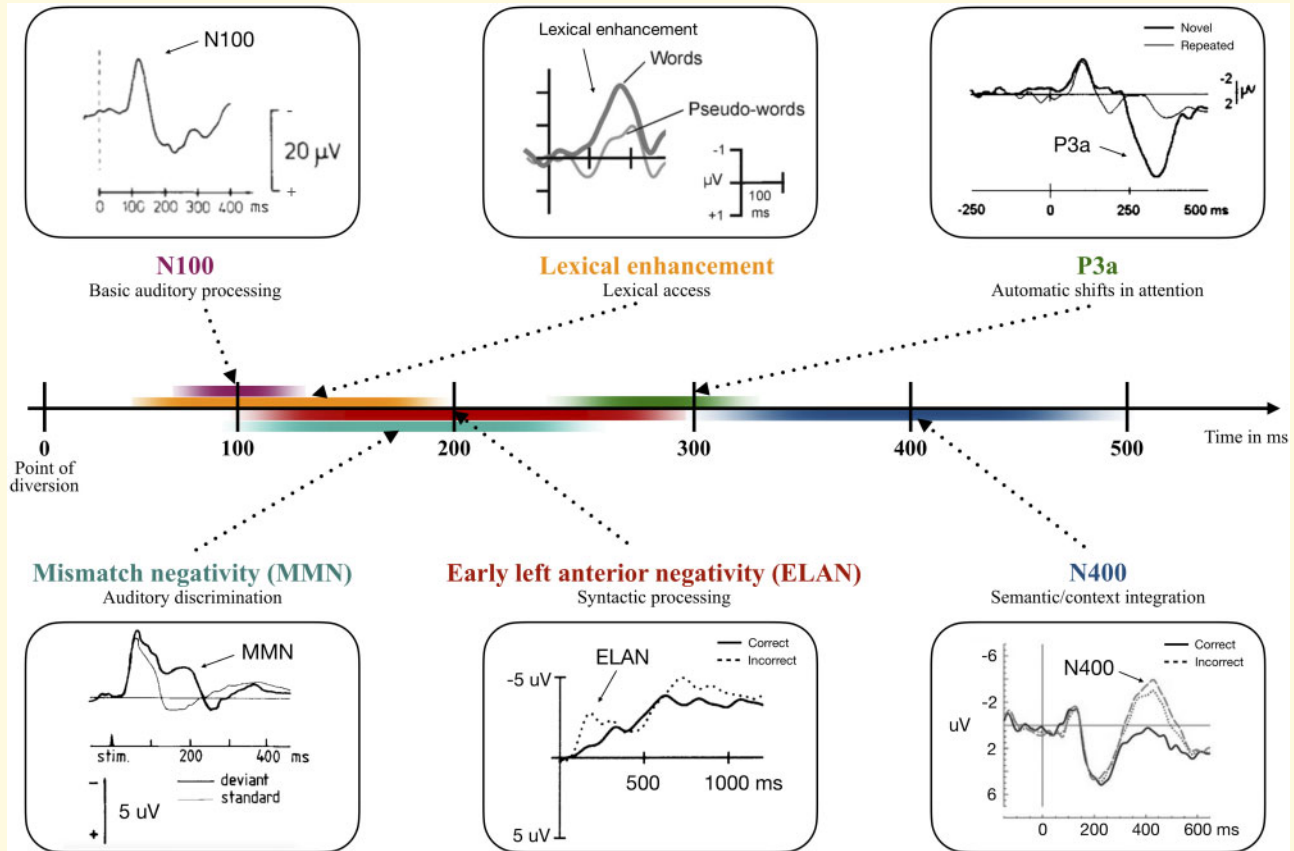
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Abbreviations: CMD = cognitive motor dissociation; DoC = disorders of consciousness; ELAN = early left anterior negativity; ERP = event-related potential; MCS = minimally conscious state; MMN = mismatch negativity; UWS = unresponsive wakefulness syndrome

Graphical Abstract



It is well accepted that a significant number of patients with disorders of consciousness (DoC) may be covertly aware despite being behaviourally non-responsive. At the same time, the rate of reported misdiagnosis, when relying on behavioural assessments, sometimes exceeds 40% (Childs *et al.*, 1993; Andrews *et al.*, 1996; Schnakers *et al.*, 2009). The high number of misdiagnoses may be explained by several factors. Patients with DoC may fluctuate in their levels of arousal, wakefulness and pain, and they may be motorically or cognitively impaired, which will affect their behavioural responses during the assessment. Examination errors can occur when, for example, assessments are not performed frequently enough to capture fluctuations in behavioural responses, or when the time given for a patient to respond to a command is too short. Furthermore, it can be very difficult to differentiate intentional behaviour from reflexive or involuntary movement. Finally, the environment can bias the assessment through poor positioning of the patient, noise, light, heat or other environmental factors that may disturb the patient during the assessment (Giacino *et al.*, 2009). Thus, there is no doubt that the process of diagnosing patients with DoC is challenging.

A misdiagnosis can have detrimental consequences for patients with DoC, as the diagnosis is used when deciding

how to manage their pain (Schnakers and Zasler, 2007; Boly *et al.*, 2008; Schnakers *et al.*, 2010; Schnakers *et al.*, 2012), whether to refer them to rehabilitation or to withdraw their life support (Fins and Shapiro, 2007; Wilkinson *et al.*, 2009; Bressman and Reidler, 2010). Behavioural assessments such as the Glasgow Coma Scale (Teasdale and Jennett, 1974) or the Coma Recovery Scale-Revised (Giacino *et al.*, 2004) are the gold standard for assessment in many hospitals (Hauger *et al.*, 2017; Gosseries *et al.*, 2019). The Glasgow Coma Scale rates patients on a scale from 3 to 15 based on the patient's motor, verbal and eye responses to pre-defined stimuli (Teasdale and Jennett, 1974). The Coma Recovery Scale-Revised takes longer to complete than the Glasgow Coma Scale, and requires a list of equipment; however, it has also been shown to have a higher diagnostic precision than the Glasgow Coma Scale (Schnakers *et al.*, 2008a; Iazeva *et al.*, 2019). It includes six sub-scales: auditory, visual, motor, oromotor, communication and arousal, and the total score ranges between 0 and 23 (Giacino *et al.*, 2004). These assessment tools can be used to divide patients with DoC into three main groups: coma, unresponsive wakefulness syndrome (UWS, previously called vegetative state) and minimally conscious state (MCS). For many patients, these states are transient, while for some patients, the states can be prolonged or even lifelong (Kondziella *et al.*, 2016; Giacino *et al.*, 2018).

Coma is an acute and temporary state characterized by the lack of both wakefulness and awareness (Young, 2009). For patients with UWS, a sleep–wake cycle is maintained, but the awareness of themselves and their surroundings is absent (Multi-Society Task Force on PVS, 1994; Adams *et al.*, 2000; Laureys *et al.*, 2010). Patients in MCS show intermittent signs of consciousness and purposeful behaviour, e.g. being able to follow commands on repeated occasions (Giacino *et al.*, 2002). The MCS can be subcategorized into MCS– and MCS+, wherein patients show either low- or high-level behavioural responses, respectively. Patients in MCS– may localize painful stimuli, pursue visual stimuli, smile or cry in emotional situations, whereas patients in MCS+ may follow commands and occasionally verbalize understandable words (Bruno *et al.*, 2011). Thus, the diagnosis of MCS depends on patients being able to produce verbal or motor responses. Some patients, however, may not be able to deliver such responses due to motor disabilities despite having some preserved cognitive functions. These patients are referred to as patients with cognitive motor dissociation (CMD; Schiff, 2015). With the current assessment tools, patients with CMD are easily confused with patients with UWS or in MCS– (Schiff, 2015; Edlow *et al.*, 2017), however; it is crucial to be able to differentiate the groups, as patients with CMD are likely to have better functional outcomes (Jöhr *et al.*, 2020). Whether to regard CMD as a clinical dimension within DoC or as a patient category of its own is still a matter of some debate (Schiff, 2015; Noel *et al.*, 2019; Pincherle *et al.*, 2019; Jöhr *et al.*, 2020), but the importance of being able to recognize patients with CMD is undisputed. The revised Motor Behaviour Tool has been suggested to help detect even very subtle signs of motor behaviour and thereby better differentiate patients with CMD from other patient categories (Pignat *et al.*, 2016; Pincherle *et al.*, 2019). Yet, even with the development of the revised Motor Behaviour Tool, all available assessment tools still rely on motor responses.

Developing an assessment tool that tests for preserved cognitive abilities more broadly and that does not rely on subjective observations of verbal and motor signals alone is essential to lower the rates of misdiagnoses and provide a more detailed description of patients with DoC or CMD. Non-invasive functional imaging and electrophysiological measures can potentially achieve these aspects. When, e.g. patients with CMD are unable to express signs of preserved cognitive functions due to motor disabilities, these alternative measures could bypass the motor disabilities and measure cognitive functions directly. Owen *et al.* (2006) famously showed that a patient with DoC, who behaviourally demonstrated no signs of consciousness, seemed to be able to modulate her brain activity similarly to healthy controls in response to verbal commands prompting her to imagine either playing tennis or walking through her home. These results have been replicated several times (e.g. Monti *et al.*, 2010; Fernandez-Espejo and Owen, 2013; Fernandez-Espejo *et al.*, 2014), which suggests that the use of linguistic stimulation in combination with non-invasive neuroimaging is potentially a reliable approach to assess which cognitive functions are preserved. The

above-mentioned studies used functional MRI; however, there are several reasons to suggest that EEG may be more advantageous when assessing patients with DoC or CMD. EEG is inexpensive, highly accessible, safe, quiet and non-invasive. Also, there is no need to move the patient to a scanner, as EEG is mobile and easy to set up at the bedside of a patient. This is beneficial for several reasons, as moving patients within and across sites requires substantial resources, may lead to fatigue in the patient, and could increase the risk of infections. Furthermore, EEG electrodes can be left on for an entire day, which allows controlling for fluctuations in patients' level of wakefulness by making repeated measurements throughout the day. Recordings in patients with DoC are subject to specific challenges, such as artefacts caused by involuntary movements such as coughing, jaw movements, and myoclonus, which are difficult to avoid. In an MR scan, these artefacts can be detrimental to scan quality, whereas in an EEG recording, the specific trials with artefacts can simply be discarded or filtered out. Finally, EEG is a direct measure of neural activity with a high temporal resolution, and is thus commonly used to test the highly dynamic linguistic processing (for a more detailed comparison of EEG and functional MRI, see Harrison and Connolly, 2013).

The present paper focuses on how EEG may help improve the diagnosis of patients with DoC, as an accurate diagnosis is essential for patients to receive the optimal course of treatment. One of the most frequently used approaches to EEG when investigating the cognitive abilities of patients with DoC is event-related potentials (ERPs), and therefore, the present paper mainly focuses on the applied potential of ERPs. Other approaches focusing on, e.g. spectral power or connectivity-related measures may similarly hold some potential in future applications; we will therefore also provide a short overview of non-ERP measures, and how they may complement the ERP paradigm for a more comprehensive picture of a patient's status. The next section provides an overview on both active (with a task) and passive (task-free) ERP paradigms.

Active and passive event-related potential paradigms

Active paradigms used for research on patients with DoC encourage patients to modulate their brain activity in a specific way to a set task, whereas passive paradigms, on the other hand, have no set task. In both paradigms, the patients' brain activity is recorded while they are presented with different stimuli, e.g. tactile, visual or auditory stimulation. The present paper focuses on the potential of assessing preserved auditory, rather than visual or tactile, processing in patients with DoC. Visual stimulation is often problematic in these patients, as many cannot maintain eye-opening and cannot fixate on visual stimuli (Monti, 2012). Tactile stimulation, on the other hand, has shown great promise for

probing residual cognitive functions in patients with DoC (Riccio *et al.*, 2012; Kaufmann *et al.*, 2013; Gibson *et al.*, 2016); however, it can be more complex to deliver, and would not allow for investigating language processing and preserved communication. Hence, the present paper's main focus is auditory paradigms.

One paradigm that is often used in both passive and active designs when probing auditory processing in patients with DoC is the so-called oddball paradigm. It presents a series of identical (standard) sounds, which can be both non-speech and speech sounds, words and word combinations. These standard sounds are occasionally interrupted by an unexpected 'deviant' sound differing in pitch, duration, location, type of word, etc. (Squires *et al.*, 1975). One frequently used addition to this design is the subject's own name paradigm that presents the subject's own name as a novel, salient stimulus embedded within standard and deviant stimuli comprised of tones or unfamiliar names (Perrin *et al.*, 2006; Fischer *et al.*, 2010). The stimuli of such paradigms generate time-locked changes in brain activity, which can be analysed as ERPs. A commonly used active task for patients with DoC is asking the patient to count the rare or novel stimuli in an oddball paradigm. This is expected to produce ERPs with significantly greater amplitudes than those obtained when passively listening to the stimuli (Schnakers *et al.*, 2008b; Kirschner *et al.*, 2015). Some studies have, indeed, found enlarged responses to active tasks in patients in MCS, and not in patients with UWS (Schnakers *et al.*, 2008b; Risetti *et al.*, 2013; Hauger *et al.*, 2015). Other studies, however, have not found such enlargements in patients with UWS or MCS despite the fact that the patients in MCS showed behavioural signs of consciousness (Kondziella *et al.*, 2016; Real *et al.*, 2016).

In 2009, Bekinschtein *et al.* developed a novel, active ERP paradigm to detect consciousness, the so-called local-global paradigm. It is similar to the oddball paradigm described above but with the variation that it contains both local and global deviants. In this approach, a local deviant is when every fifth tone differs from the preceding four tones in a train, whereas a global deviant is when every fifth train of five tones differs from the preceding four trains. The global effect is only present when participants are asked to count the global deviants, i.e. when they are actively paying attention to them, and thus it seems that the global effect is a sign that the participant is consciously aware of the stimuli (Bekinschtein *et al.*, 2009). This paradigm was tested in 49 patients with DoC, and while a local effect was present in most patients, the global effect was found more frequently in patients in MCS than in patients with UWS. The paradigm may, however, not be very sensitive, as only 4/28 of the patients with MCS presented with a significant global effect (Faugeras *et al.*, 2012). Active EEG paradigms generally have a low sensitivity due to false negatives, as they fail to classify a substantial number of patients with residual consciousness as command-following (Kondziella *et al.*, 2016). So, although active paradigms offer many

interesting opportunities, they also have their limitations. They place a high cognitive demand on patients, who may suffer from severe fatigue, fluctuations in vigilance or impaired comprehension or attention (Majerus *et al.*, 2009; Harrison and Connolly, 2013; Gibson *et al.*, 2016). Patients may be unable to understand the command, unable to keep the command in their working memory long enough to perform the task, or they may not be interested in participating if they are in pain or have impaired attention. Thus, active paradigms alone may not be optimal for a reliable assessment of patients with DoC.

Like active paradigms, passive paradigms often use an oddball design, but instead of asking patients to count certain stimuli, the stimuli are presented in a completely task-free manner. Passive paradigms do not require the patients' attention, which makes it possible to test for longer durations and thereby test more contrasts with a higher number of trials, potentially allowing for a more detailed and reliable understanding of the patients' cognitive abilities. As the patients are not able to provide overt responses to experimental tasks, both passive and active paradigms can only make indirect inferences. But, due to the limitations of active paradigms, we suggest using a passive paradigm in the first place to investigate the cognitive and linguistic functions of patients with DoC. The use of passive paradigms to assess the degree to which a patient's processing of different auditory information is preserved can provide valuable information about the patient's cognitive status. It may help researchers and doctors understand how much of a patient's low-level perceptual processing, speech recognition and semantic comprehension is functioning. Thus, in future applications, a passive paradigm may be used as a screening tool to see which patients could potentially participate in a more active assessment, e.g. the local-global paradigm.

Task-free event-related potential components in auditory cognition

Previous research has established a range of ERP components related to task-free and non-attended assessments of auditory, attentional and linguistic processes. Overall, these components can be divided into those probing generic auditory functions related to sensory, perceptual and pre-attentive processes, and those probing language-related processing. A combination of components, i.e. a multivariate approach, may improve the precision of the diagnoses of patients with DoC (Sergent *et al.*, 2017). Notably, however, most of the studies on ERPs in patients with DoC have taken a univariate approach, and thus the different ERP components will be presented individually below.

Event-related potential components related to generic auditory processes

The N100 component is an index of basic auditory processing peaking at ~100 ms (Näätänen and Picton, 1987). The component can be valuable because its presence indicates that a patient's auditory cortex is still in a functional state, which is a prerequisite for higher order linguistic communication. The component has been found in both patients with DoC and healthy controls (Kotchoubey *et al.*, 2005; Cavinato *et al.*, 2011), but more frequently, in controls and patients in MCS than in patients with UWS (Kotchoubey *et al.*, 2005; Fischer *et al.*, 2010). The amplitude of the N100 component has also been shown to be significantly different in comatose patients compared to healthy controls (Fischer *et al.*, 1999).

Another well-tested ERP component is the mismatch negativity (MMN), which is an early (100–250 ms) response obtained in oddball paradigms to an infrequent deviant stimulus within a sequence of repetitive standard stimuli (Näätänen *et al.*, 1978). The MMN is independent of attention and top-down processes, which means that it can be found in both unconscious comatose patients (Kane *et al.*, 1993; Fischer *et al.*, 1999; Naccache *et al.*, 2005) and patients with UWS (Perrin *et al.*, 2006; Wijnen *et al.*, 2007). The presence of an MMN indicates that a patient's pre-attentive ability to detect a change in a sequence of sounds, which may be linked to auditory short-term memory, is preserved. Some studies have found that MMNs are more easily obtained and have larger amplitudes in patients in MCS than in patients with UWS (Wijnen *et al.*, 2007; Faugeras *et al.*, 2012; Rossi Sebastiano *et al.*, 2015), whereas other studies have found that the presence, amplitude, and latency of the MMN are unrelated to diagnosis (Kotchoubey *et al.*, 2005; Fischer *et al.*, 2010; Risetti *et al.*, 2013; Erlbeck *et al.*, 2017). Possible explanations for such conflicting findings could be that the preservation of the automatic detection of stimulus change does not align perfectly with the UWS and MCS categories, or that the nature of the specific MMN stimuli employed in different studies, e.g. testing for pitch or duration contrasts, yields different results. Nevertheless, MMN is beneficial to include in a cognitive assessment, as its presence indicates the patient's ability to process regularities and changes in the auditory environment.

The P300 is a later (typically >250 ms) component, believed to be an index of active cognitive processing, especially attention and memory processes (Polich, 2007). It can be found in healthy participants, MCS and UWS using sine tones, words or subject's own name paradigms; however, similarly to the MMN component, the nature of the stimuli may yield different results. For example, it seems that a subject's own name paradigm is more likely to generate a P300 than the use of simple

tones (Perrin *et al.*, 2006; Schnakers *et al.*, 2008b). This may help explain why some studies have found that the P300 can be used to discriminate between patient groups, as the component appears less frequently or with a different amplitude or latency in UWS than in patients in MCS (Cavinato *et al.*, 2011; Li *et al.*, 2015; Rossi Sebastiano *et al.*, 2015; Schnakers *et al.*, 2015), whereas others have found that the P300 is unable to differentiate between patient groups (Kotchoubey *et al.*, 2005; Perrin *et al.*, 2006; Schorr *et al.*, 2015; Real *et al.*, 2016). These conflicting findings could also be due to the fact that some studies do not differentiate between the subcomponents of P300, namely the more bottom-up-related P3a and the later, top-down-related P3b (Polich, 2007). The P3b seems to be a sign of volitional engagement in an active task and is mainly found in healthy controls (Faugeras *et al.*, 2012; Chennu *et al.*, 2013; Gibson *et al.*, 2016). P3a, on the other hand, is an index of automatic shifts in attention towards novel stimuli, e.g. unexpected salient sounds (Friedman *et al.*, 2001; Simons *et al.*, 2001). Not many studies have probed auditory P3a in patients with DoC, but the evidence so far suggests that the component is found more often in patients in MCS than with UWS (Chennu *et al.*, 2013; Gao *et al.*, 2019; Wu *et al.*, 2020). Larger amplitudes have been found in response to emotional stimuli compared to neutral ones (Gao *et al.*, 2019; Wu *et al.*, 2020), and non-traumatic patients present with a more obvious frontal P3a than traumatic patients (Wu *et al.*, 2020). Thus, probing P3a specifically may be more relevant than P300, particularly as it can be elicited in task-free designs not requiring overt attention.

In sum, the N100 can be used to indicate whether a patient's auditory cortex is functionally intact, the MMN can be used to indicate which patients are able to detect regularities and irregularities in sound environment, and the P3a can be used to indicate whether a patient's involuntary attentional orientation is preserved. The presence of these ERP components could add useful information to supplement the behavioural assessment tools.

Language-related event-related potential components

The N100, the MMN and the P3a are all automatic responses that can be elicited using simple and complex tones, as well as speech sounds. Various other auditory ERP components can be linked to more language-specific processing. Language comprehension involves several processes, ranging from basic auditory perception to conscious comprehension. Previous research has shown that neurolinguistic processes may be automatized to different degrees, depending on the information type (Shtyrov, 2010). Low-level speech processing, such as the segmentation of the auditory input and feature extraction at phonetic and phonological levels, appears to be a fast and

largely automatized process, whereas higher order processes, such as comprehension of meaning of particular elements (semantics) and parsing of combinatorial relations between them (syntax and grammar), appear more complex. While early stages (<200 ms) of lexical, semantic, and syntactic access also seem to be automatic, full speech comprehension requires at least some degree of more extended controlled processing (Friederici, 2002; Shtyrov, 2010; Friederici, 2012). This hierarchy of automaticity and processing speed can thus be seen as a proxy for the complexity of the cognitive and linguistic processes under investigation. Thus, the assessment of different levels of neural speech processing in patients with DoC may potentially provide a stratified account of cognitive and linguistic processes preserved in the individual patient (Harrison and Connolly, 2013; Rohaut *et al.*, 2015).

One language-specific ERP component investigated in patients with DoC is the N400. This component occurs later (~350–500 ms) and is less automatic and more dependent on top-down processes. It is considered to be an established ERP index of semantic processing in healthy individuals, mainly occurring in response to a context-incongruent word (Kutas and Federmeier, 2011). The N400 has been found in both patients in MCS and with UWS in both active and passive paradigms (Schoenle and Witzke, 2004; Kotchoubey *et al.*, 2005; Balconi *et al.*, 2013; Steppacher *et al.*, 2013; Rohaut *et al.*, 2015). The response may be delayed (Balconi and Arangio, 2015; Rohaut *et al.*, 2015) or less common (Schoenle and Witzke, 2004; Kotchoubey, 2005) in patients with UWS compared to MCS and controls. The nature of the stimuli has been shown to have a significant influence on the probability of detecting an N400, and, in passive auditory paradigms, normatively associated word pairs have been suggested as the most optimal stimuli for eliciting it (Cruse *et al.*, 2014). Nevertheless, even with this type of stimuli, the diagnostic sensitivity of the N400 in itself is likely to be rather low due to a high number of false negatives. Using a passive paradigm with normatively associated word pairs in healthy controls, the N400 is only found in ~50% of cases (Cruse *et al.*, 2014; Rohaut *et al.*, 2015). Thus, as with many of the other ERP components, the presence of an N400 should be considered a positive sign, whereas the absence of the component is not necessarily a negative one.

Other language-specific ERP components have been well established in healthy controls using passive paradigms, but have not yet been investigated in patients with DoC. For example, syntactic processing, which is a crucial part of language comprehension, may be assessed through the early left anterior negativity (ELAN) response, which occurs 100–300 ms after a syntactic violation in phrasal stimuli (Hahne and Friederici, 1999; Friederici, 2002), as well as in the so-called syntactic MMN designs (Hasting *et al.*, 2007; Hanna *et al.*, 2014).

Unlike later syntactic responses (e.g. LAN, P600), the ELAN and the syntactic MMN do not seem to depend on attention or stimulus-directed tasks. Some authors argue that these two responses reflect the same underlying automatic syntactic parsing processes (Shtyrov *et al.*, 2003; Pulvermüller *et al.*, 2008); and while the ELAN's replicability has been questioned (Steinhauer and Drury, 2012), the syntactic MMN appears to be more reliable as long as acoustic and psycholinguistic stimulus features are controlled for. For lexical processing, during task-free paradigms, real and familiar words have been shown to elicit larger and more robust mass neuronal responses than acoustically matched pseudo words (Shtyrov *et al.*, 2010; MacGregor *et al.*, 2012; Kimppa *et al.*, 2015). This effect is generally referred to as an automatic lexical enhancement and has been found in both repetitive oddball designs and non-oddball paradigms. Such attention-independent responses that do not depend on overt tasks may therefore be of use in situations when the subject's cooperation cannot be obtained (Gansonre *et al.*, 2018; Hyder *et al.*, 2020), and thus may be of use for assessing patients with DoC or CMD. While ELAN/syntactic MMN and lexical enhancement certainly hold a promise as potential assessment tools, they have so far not been tested in DoC, which, we suggest, should be tackled in future studies.

In sum, language-related ERP components may help clinicians to assess the intactness of the semantic, syntactic and lexical processing of patients, and thereby produce a better picture of the preserved cognitive and linguistic abilities of individual patients.

Experimental design of event-related potential paradigms

The above-mentioned components may provide means for task-free electrophysiological testing of different levels of auditory and linguistic processing. The N100, the MMN, and the P3a probe relatively generic auditory processes, while the N400, the ELAN and lexical enhancement probe more language-specific mechanisms relying on higher order cognitive processes (see Fig. 1). Notably, most studies to date have focused on testing a small set of features (or even a single feature) by using just one ERP component of choice. To be of practical use, an ideal paradigm should assess a range of features. A multi-dimensional cognitive evaluation combining several cognitive markers within one test, as suggested above, could improve the evaluation and thus increase diagnostic sensitivity (Sergent *et al.*, 2017). This process would also allow for investigating whether one of the markers suffices for an accurate diagnosis or whether several are needed, and if so, which combination gives the highest

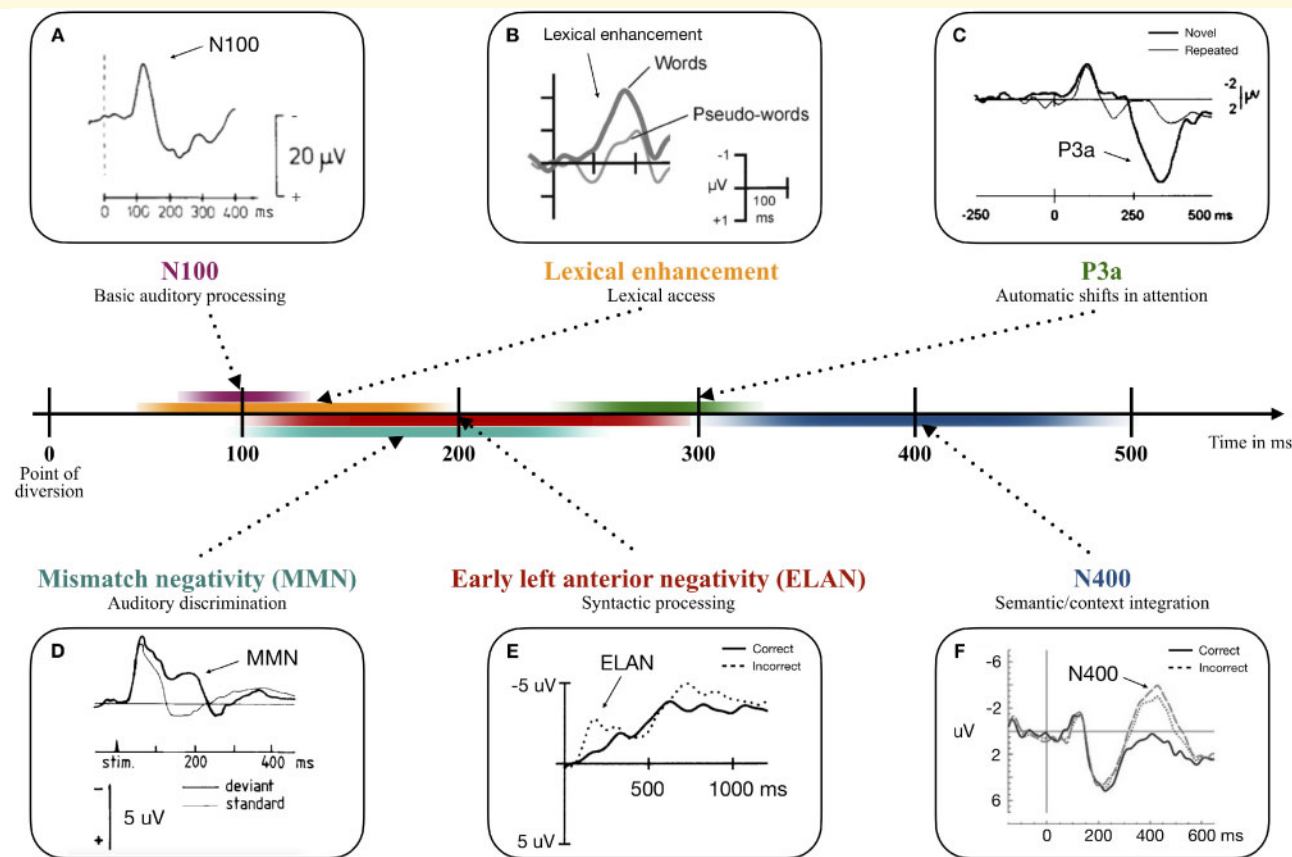


Figure 1 Overview of event-related EEG components relevant for task-free testing. Schematic overview of ERP components that may allow for task-free testing of different levels of auditory and linguistic processing in patients with DoC. (A) N100, adapted from Hari *et al.* (1982), Copyright (1982), reprinted with permission from Elsevier. (B) Lexical enhancement, adapted from Pulvermüller *et al.* (2001), Copyright (2001), reprinted with permission from American Press. (C) P3a, adapted from Haenschel *et al.* (2000), Copyright (2000), reprinted with permission from National Academy of Sciences. (D) MMN, adapted from Sams *et al.* (1985) Copyright (1985), reprinted with permission from Elsevier. (E) ELAN, adapted from Hahne and Jescheniak (2001), Copyright (2001), reprinted with permission from Elsevier. (F) N400, adapted from Hagoort *et al.* (2004), Copyright (2004), reprinted with permission from AAAS.

sensitivity. It, therefore, seems reasonable to suggest that future research should develop combined designs with multiple, yet controlled, acoustic, phonological, and psycholinguistic manipulations to elicit these components in a single task-free paradigm (see, e.g. Shtyrov *et al.*, 2012; Gansonre *et al.*, 2018) to provide a more comprehensive multidimensional test for different cognitive and linguistic processes.

In addition to being multidimensional, the optimal assessment tool may also be multimodal. In the present paper, we have only covered auditory stimulation, but it seems that some patients may only respond in the tactile or visual modality and not in the auditory (Rousseau *et al.*, 2008). Furthermore, a purely auditory assessment would exclude patients suffering from severely impaired hearing. As mentioned earlier, tactile stimulation seems promising for probing residual cognitive functions in

patients with DoC; especially interesting here is the tactile P3a (Riccio *et al.*, 2012; Kaufmann *et al.*, 2013; Gibson *et al.*, 2016). One example of combining tactile and auditory stimulation is a study by Noel *et al.* (2019), who invented a task-free multimodal ERP paradigm which allowed them to successfully differentiate patients with CMD from other patients with DoC. It is crucial to be able to distinguish patients with CMD from other patients with DoC, and thus, for the most reliable results, patients should be tested on several dimensions and modalities. Patients should also be tested on several occasions, as their vigilance can fluctuate (Schorr *et al.*, 2015; Kondziella *et al.*, 2016). Patients may drift in and out of consciousness within each EEG recording, and thus, it is important to control for levels of wakefulness during the recording; however, there is no gold standard for this. Some studies have used the Arousal Facilitation Protocol

of the Coma Recovery Scale-Revised, i.e. presenting deep pressure stimulation to different parts of the patient's body to re-establish arousal if the patient appears to be getting drowsy (Erlbeck *et al.*, 2017), while other studies have monitored patients' level of vigilance during recording by inspecting the EEG traces in real time, e.g. looking for sleep spindles or K complexes (Fingelkurts *et al.*, 2012; Risetti *et al.*, 2013).

Consequently, using a task-free paradigm to test patients on multiple dimensions, modalities, and occasions, while also controlling for their arousal level during the scan, may help give a more precise description of patients with DoC and CMD.

Other EEG measures

In order for brain response components to function as indices of residual cognitive functions in patients with DoC, they need to be reliable at the single subject level, which is not always the case with auditory ERPs (Csepe and Molnar, 1997; Bishop and Hardiman, 2010; Fischer *et al.*, 2010; Rossi Sebastiano *et al.*, 2015). So, instead of only using ERPs, recent large-scale studies on patients with DoC have used measures based on spectral properties of the recorded EEG data such as power in frequency bands or spectral entropy (Sitt *et al.*, 2014; Engemann *et al.*, 2018), or information theory measures such as weighted symbolic mutual information (King *et al.*, 2013; Sitt *et al.*, 2014; Engemann *et al.*, 2018). More specifically, Engemann *et al.* (2018) and Sitt *et al.* (2014) found that power spectrum measures in the delta (1–4 Hz), theta (4–8 Hz) and alpha (8–12 Hz) frequency bands were some of the most informative features in their analyses. Similarly, they found that connectivity measures were able to differentiate patient groups; however, great caution is recommended when interpreting the results from connectivity analyses based on EEG electrodes due to the fact that effects of current spread cannot be fully eliminated in source space (Schoffelen and Gross, 2009; Brunner *et al.*, 2016; Van de Steen *et al.*, 2019).

The above sections have been concerned with identifying data that could aid the precision of a diagnosis; however, this still leaves us with the problem of how to analyse the collected data. Traditional approaches in EEG statistics focus on group analyses, but for research on patients with DoC and CMD, we need to be able to make a diagnosis for a single individual, not for a group of patients. Arguably, one of the better statistical frameworks for this is predictive modelling, also referred to more generically as machine learning (see, e.g. Bzdok *et al.*, 2018; Bzdok and Ioannidis, 2019). Predictive modelling is designed to make predictions about out-of-sample data, e.g. data from a new patient, based on data from previous cases. Such machine learning systems have successfully been used in several large-scale studies classifying different patients with DoC (see, e.g. Tzovara *et al.*, 2013; Sitt *et al.*, 2014; Engemann *et al.*, 2018). In a recent study on 268 patients with DoC, Engemann *et al.* (2018) showed that

multivariate pattern analysis is well suited to classify states of consciousness and that using several different data features, e.g. ERPs, spectral and information theory measures, increases the ability to predict the diagnosis. The authors further showed that such models are able to generalize over different data sets, meaning that while trained on one group of patients, the model was able to predict the state of consciousness of a new patient. A similar study by Sitt *et al.* (2014) on 113 patients showed that power spectrum and information theory measures, such as weighted symbolic mutual information and Kolmogorov–Chaitin complexity, can provide information not available through traditional ERP components. Together, such studies provide evidence that machine learning models on a well-defined and understood collection of features can give hope of a very good model performance.

Conclusion

Assessments of patients with DoC or CMD could potentially benefit from a multidimensional task-free EEG paradigm probing both relatively generic auditory processes, such as those reflected by N100, MMN and P3a, and more language-specific mechanisms, indexed by, e.g. N400, ELAN and lexical ERP enhancement. Such a paradigm would also benefit from stimulation in several modalities, e.g. auditory and tactile, from repeated measures to control for fluctuations in states of consciousness, as well as from additional non-ERP types of EEG data analysis. Together with traditional neuropsychological assessments and other structural and functional neuroimaging data, such an assessment tool could give a more precise description of the patients' overall cognitive status by informing physicians of the intactness and functionality of a patient's auditory cortex, pre-attentive sensory memory, lexico-semantic processing and other neurocognitive abilities.

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The graphical abstract is based on Figure 1. Please see the legend to Figure 1 for copyright information relating to the images in the graphical abstract.

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Competing interests

The authors report no competing interests.

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