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A hierarchy of event-related potential markers of auditory processing in disorders of consciousness

Steve Beukema[a,b], Laura E. Gonzalez-Lara[a], Paola Finoia[c], Evelyn Kamau[c], Judith Allanson[c], Srivas Chennu[d,e], Raechelle M. Gibson[a], John D. Pickard[c], Adrian M. Owen[a], Damian Cruse[f,*]

[a]The Brain and Mind Institute, University of Western Ontario, London, ON, Canada
[b]McGill Vision Research, Department of Ophthalmology, McGill University, Montreal, Canada
[c]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[d]School of Computing, University of Kent, Chatham Maritime, UK
[e]Department of Clinical Neurosciences, The University of Cambridge, Cambridge, UK
[f]School of Psychology, University of Birmingham, Birmingham, UK

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ABSTRACT

Functional neuroimaging of covert perceptual and cognitive processes can inform the diagnoses and prognoses of patients with disorders of consciousness, such as the vegetative and minimally conscious states (VS;MCS). Here we report an event-related potential (ERP) paradigm for detecting a hierarchy of auditory processes in a group of healthy individuals and patients with disorders of consciousness. Simple cortical responses to sounds were observed in all 16 patients; 7/16 (44%) patients exhibited markers of the differential processing of speech and noise; and 1 patient produced evidence of the semantic processing of speech (i.e. the N400 effect). In several patients, the level of auditory processing that was evident from ERPs was higher than the abilities that were evident from behavioural assessment, indicating a greater sensitivity of ERPs in some cases. However, there were no differences in auditory processing between VS and MCS patient groups, indicating a lack of diagnostic specificity for this paradigm. Reliably detecting semantic processing by means of the N400 effect in passively listening single-subjects is a challenge. Multiple assessment methods are needed in order to fully characterise the abilities of patients with disorders of consciousness.

1. Introduction

The vegetative state (VS; also referred to as unresponsive wakefulness syndrome, Laureys et al., 2010) and minimally conscious state (MCS) are chronic disorders of consciousness that can follow from a severe brain injury. A diagnosis of VS occurs when a patient is considered to be 'wakeful without awareness', defined by four broad criteria (Jennett and Plum, 1972; Royal College of Physicians, 2003): 1) evidence for preserved sleep-wake cycles; 2) no evidence of awareness of the self or the environment; 3) no evidence of sustained, reproducible, purposeful, or voluntary response to auditory, tactile, or noxious stimuli; 4) no evidence of language comprehension or expression. A diagnosis of MCS, on the other hand, occurs when minimal but reproducible evidence of awareness is observed.

Clinical judgments of the relative fulfilment of these criteria are currently based on behavioural observations. However, the insensitivity of behavioural assessments of consciousness is well documented, with an estimated misdiagnosis rate of 40% for VS (Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2009). Furthermore, in recent years, it has become evident that functional neuroimaging can sometimes provide a clearer picture of the extent to which a given patient fulfils these criteria. Indeed, many examples of covert cognition and consciousness have been reported in patients whose behaviour is nevertheless consistent with the VS (Fernandez-Espejo and Owen, 2013; Stender et al., 2014). In this manuscript, we focus on the fourth criterion above, namely the evidence for the absence of language comprehension.

In two early functional magnetic resonance imaging (fMRI) studies, Coleman et al. (2009, 2007) endeavoured to place patients on a hierarchy of auditory processing abilities: from low-level audition, through speech perceptual processes, to the extraction of meaning (semantics). To accomplish this, patients were presented with sentences containing words that were either semantically ambiguous (e.g. "There were *dates* and *pears* in the fruit bowl") or relatively less ambiguous (e.g., "There was *beer* and *cider* on the kitchen shelf"). Because resolving this semantic ambiguity required comprehension of the sentence as a whole, the contrast between high and low-ambiguity sentences was considered to index speech *comprehension*, or at least the processing of the meaning of the words. A further contrast was performed between all speech stimuli and a non-speech control stimulus - signal-correlated noise

* Corresponding author.
E-mail address: d.cruse@bham.ac.uk (D. Cruse).

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(SCN) - in order to identify what the authors considered to be speech-specific *perceptual* processing of speech. Finally, a contrast of all stimuli to silence was performed to identify early auditory processing. Sixty percent of VS patients (13/22) demonstrated no fMRI activity in any of the contrasts. Nine percent (2/22) showed significant auditory responses, 32% (7/22) showed appropriate activity in the perceptual contrast, and 9% (2/22) in the semantic contrast. Interestingly, the level of auditory processing possessed by these patients (as indexed by the neuroimaging data) was correlated with the patients' behavioural abilities at six-months follow-up ($r = 0.81$), suggesting a potential prognostic value to neural markers of speech processing.

However, few patients can have their language comprehension abilities assessed in this way due to the high cost of MRI, poor scanner availability, and clinical contraindications. Electroencephalography (EEG), however, can reach a greater number of patients than fMRI because it is relatively less expensive and can be performed at the bedside. Moreover, EEG provides a well-studied index of semantic processing in healthy individuals, known as the N400 event-related potential (ERP) - a negative-going potential over centroparietal scalp that peaks around 400 ms post-stimulus. The amplitude of the N400 is primarily sensitive to the context in which a meaningful stimulus occurs. For example, when words are presented in pairs, the second word of the pair (i.e. the target) elicits a larger N400 when the words in the pair are unrelated than when they are related (e.g., cat–*chair* versus table–*chair*). Similarly, when a word is incongruent with a sentence context, it elicits a larger N400 (e.g. "He ate the moist cake with a knife and *potato*/*fork*"; see Kutas and Federmeier, 2011, for a full review). The difference in the N400 amplitude that is produced by such priming manipulations will be referred to here as the 'N400 effect'.

While the exact linguistic processes indexed by the N400 are still a matter of debate, the sensitivity of the N400 to manipulations of meaning indicate that, at its simplest, the N400 effect reflects the processing of meaning, and therefore provides a neural marker of semantic processing that may not be evident from behaviour. As a result, a number of studies have sought evidence of N400 effects in disorders of consciousness.

Schoenle and Witzke (2004) visually inspected the ERPs elicited by semantically incongruent and congruent sentence-endings and reported evidence of an N400-like deflection in 39% of VS patients. Steppacher et al. (2013; see also Kotchoubey et al., 2005) also reported N400-like effects in continuous wavelet transformed ERP data of 32% of a group of 48 VS patients. Furthermore, the presence of N400-like effects was also correlated with behavioural improvement at long-term follow-up (2–14 years). Rohaut et al. (2015) also observed significant N400 ERP effects in 1/15 VS patients and 5/14 MCS patients, contributing to the evidence that some patients with disorders of consciousness are capable of processing the meaning of speech.

Cruse et al. (2014a) recently demonstrated the importance of the stimuli used to detect statistically significant N400 effects in single-subjects. Specifically, they found that word-pairs taken from associations norms - i.e. pairs in which the target is the word most often produced by a group of healthy participants during free association of a prime - were more likely to lead to reliable single-subject N400 effects when compared with two other common N400 approaches - semantically related word-pairs, and high-cloze sentences. Furthermore, Cruse et al. (2014a) found that repeating words within an assessment - a common practice in N400 studies – altered the observed N400 effects. However, even with a high level of stimulus control, Cruse et al. (2014a) could only detect a statistically reliable N400 effect in 50% of healthy individuals during passive listening. Similarly, Rohaut et al. (2015) employed normatively associated word-pairs and found significant N400 effects in only 42% of healthy controls during passive listening.

Together these results suggest that tests of semantic processing that rely on the priming N400 effect do not have sufficient sensitivity for regular clinical use. Indeed, Cruse et al. (2014a) found that instructing healthy participants to make judgments on the relatedness of the words in each pair led to an increase in the probability of detecting a significant N400 effect relative to when participants were only instructed to passively listen to the stimuli. This is somewhat unsurprising as relatedness judgments require the participants to attend to the meaning of the stimuli - a manipulation known to increase group-level N400 effects (Bentin et al., 1993). Therefore, even though passive listening to word-pairs does elicit a group level N400 effect, the size of the signal is reduced and therefore is more difficult to detect in single-subjects.

It is plausible, then, that some patients are able to process the meaning of speech, but are unable to complete the demanding task necessary for them to produce positive evidence of an N400 effect. Indeed, patients in the VS are by definition unable to follow commands. It may therefore not be possible to reliably separate semantic processing from an ability to follow commands using an N400 priming paradigm - at least not to the level of sensitivity necessary for its use as a clinical tool.

As a result of the apparent single-subject insensitivity of the priming N400 effect, we sought to identify complementary ERP markers of related speech processes. We employed an approach similar to the fMRI paradigm of Coleman et al. (2009, 2007; Davis et al., 2007) in which a three level hierarchy of auditory processes were investigated. Specifically, we presented participants with speech stimuli taken from the normative-association word-pair task of Cruse et al. (2014a) alongside non-speech noise stimuli (signal-correlated noise). This allowed us to identify 1) *semantic processing* through the (albeit poorly sensitive) classic N400 contrast of related and unrelated targets; 2) speech *perceptual processing* through the contrasts of speech and noise; and 3) *auditory processing* through evidence of auditory evoked potentials.

While there are decades of studies of semantic processing with ERPs, investigations of pre-semantic speech processes (i.e. speech versus noise) are relatively scarce. Within oddball paradigms, in which a rare stimulus occurs within a sequence of repeated stimuli, speech sounds and non-speech sounds have been shown to produce different patterns of mismatch negativity amplitudes, indicating ERP markers of the differential processing of speech and non-speech within 150-250 ms post-stimulus (Jaramillo et al., 1999, 2001). Furthermore, relative to speech sounds (vowels), more positive-going P1 and P2 deflections (~100 and ~200 ms post-stimulus respectively) have been reported in response to noises, while N1 deflections (~70 ms post-stimulus) are more negative-going for vowels relative to noises with primary auditory cortex implicated as the generator of this speech-specific processing (Edmonds et al., 2010). To our knowledge, the exact contrast employed by Coleman et al. (2009, 2007) with fMRI has not been reported with ERPs - i.e. speech versus signal-correlated noise. Nevertheless, we would expect the ERPs elicited by speech to deviate from those elicited by noise early in the epoch, followed by a later deviation according to the meaning of the speech (i.e. the N400 effect).

As this type of speech paradigm has been shown to have potential clinical utility in fMRI (Coleman et al., 2009), here we investigated the potential for ERPs to provide a similar hierarchical assessment of auditory processing in a group of 16 healthy control participants. As a proof of concept, we subsequently applied this method to a group of 16 patients with chronic disorders of consciousness (8 VS, 8 MCS).

2. Materials and methods

2.1. Control participants

Seventeen right-handed, native Canadian English speaking participants were recruited from the Psychology Department's participant resource pool at The University of Western Ontario, or via posters distributed around the University campus. Data from one participant were excluded due to an equipment fault. The remaining sixteen participants ranged in age from 18 to 25 years old (median = 20; 8 female). All participants were compensated with one credit per hour of participation for use towards an undergraduate course requirement, or