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EVENT-RELATED POTENTIAL MARKERS OF PERCEPTUAL AND CONCEPTUAL SPEECH PROCESSES IN PATIENTS WITH DISORDERS OF CONSCIOUSNESS

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by

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Abstract

Vegetative state (VS) and minimally conscious state (MCS) patients behaviorally demonstrate absent or fluctuating levels of awareness. Functional magnetic resonance imaging evidence of covert perceptual and semantic speech processing provides prognostic value for these patients. In this thesis, I examined the utility of high-density electroencephalography (EEG) in this regard. A contrast between event-related potentials (ERPs) elicited by primed and unprimed word pairs was used to isolate conceptual (semantic) processes, while ERPs elicited by signal-correlated noise were contrasted with those elicited by speech to isolate pre-semantic, perceptual aspects of speech processing. These ERP effects were found to be both temporally and spatially dissociable, indicating the contributions of not entirely overlapping regions of cortex. Four out of ten VS/MCS patients demonstrated significant perceptual effects, while no conceptual effects were observed for any patient. It is therefore possible to identify low-level stages of language processing that can now be tested for prognostic value given future follow-up studies.

Keywords

Language, N400, EEG, ERPs, speech perception, disorders of consciousness, vegetative state, minimally conscious state
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I’ve helped develop a task that works based on an individual’s covert thoughts, seen the progression of brain-computer interfaces, and witnessed a vegetative state patient not only recover - but confidently remember who I was when he woke up…

…it’s been a wild ride, and I’ll miss the passengers that shared it with me.
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1 Introduction

The ability to produce and comprehend an infinite range of expressions in language from a finite set of elements is a uniquely human skill (Hauser & Fitch, 2003). Indeed, this mode of communication allows us to express and acknowledge the self, and undeniably contributes to our understanding of human consciousness. To what degree, then, do non-communicative patients with disorders of consciousness (DOC) retain the ability to process and understand language in the same way that healthy individuals do? The answer to this question would clarify what the maintenance of these linguistic capacities means for a patient’s recovery.

Disorders of Consciousness

While the subjective definition of consciousness can vary depending on the field, the clinical perspective defines consciousness as a combination of intact arousal and awareness. Simplified, arousal is characterized by an individual’s level of wakefulness (demonstrating sleep/wake cycles), while awareness is operationalized by an individual’s ability to follow commands (eye-opening, eye tracking etc.) (Laureys, Owen, & Schiff, 2004). The degree to which these components are present is used to categorize patients into various levels of consciousness.
Healthy individuals and locked-in syndrome patients (with focal brain-stem injuries) are considered to have normal consciousness. Patients with DOCs include those in coma (no arousal, no awareness), vegetative state (high arousal, no awareness), or minimally conscious state (high arousal, fluctuated levels of awareness)(Fig.1).

The extent to which a patient demonstrates these varying degrees of arousal and awareness can be determined through the administration of various neurobehavioural scales; the most commonly used scale being the JFK Coma Recovery Scale-Revised (CRS-R, Kalmar and Giacino, 2005)(Fig.2). The CRS-R contains six measures of perceptual and cognitive functioning (auditory, visual, motor, oromotor, communication, arousal), each with a hierarchical subscale; lower scores represent reflexive capabilities, and higher scores represent cognitive mediation.
Fig 2. The CRS-R record form. Adapted from (Kalmar & Giacino, 2005).

Although, by diagnosis, vegetative state patients are said to lack awareness and be non-communicative, misdiagnosis of these patients is an on-going concern (Andrews, Murphy, Munday, & Littlewood, 1996; Childs, Mercer, & Childs, 1993; Schnakers et al., 2009). Based on a traditional clinical examination of sleep-wake cycles, response to stimuli, and motor function, 40 patients were diagnosed as in a vegetative state in one study (Andrews et al., 1996). However, those authors found that through less traditional measures like eye-blink communication and touch-sensitive buzzers, 43% of these
patients were actually misdiagnosed by traditional examination, and were capable of motor behaviors consistent with awareness. Moreover, this misdiagnosis rate has been shown to get as high as 48% with patients admitted as a result of traumatic (compared to non-traumatic) etiologies (Childs et al., 1993). With the introduction of the CRS-R, a well-established neurobehavioural rating scale was now available to pinpoint many of the misdiagnoses inherent in consensus-based diagnoses of DOC (Schnakers et al., 2009). However, signs of awareness are often minimal or inconsistent across time (CRS-R - Kalmar & Giacino, 2005) and so may still be missed in a diagnosis based solely on behavior.

This has become especially evident with functional neuroimaging. Investigations into these assertions have provided us with new tools and methods to expand our understanding towards both healthy and disordered consciousness (Cruse et al., 2011; Owen, Coleman, Boly, & Davis, 2006). Apart from increasing the reliability of clinical tools for the assessment of DOC, improved diagnostic accuracy for vegetative state and minimally conscious patients will inform the treatments made available to these populations. As it stands, the clinical diagnosis of patients as comatose, vegetative, or minimally conscious is a categorical system. While the subscales of the CRS-R help to paint DOC as more of a dimensional issue where injuries can place patients on a spectrum of varying severity, these categorical diagnoses inform access to therapy, prognosis, and end-of-life decisions. It is therefore crucial to minimize mistakes when making these clinical judgments to determine the extent of the disorder, but also to determine the extent of healthy brain activity.
Speech processing in DOC – evidence from fMRI

In several studies examining residual linguistic capacities in DOC patients, a subset of clinically diagnosed patients have indeed demonstrated some level of speech comprehension akin to healthy individuals (Coleman et al., 2009; 2007; Fernández-Espejo et al., 2008). Coleman et al., (2007) presented patients with sentences containing words of low-ambiguity (e.g., “There was ‘beer’ and ‘cider’ on the kitchen shelf”) and high-ambiguity (“There were ‘dates’ and ‘pears’ in the fruit bowl”) as well as unintelligible noise (signal-correlated noise – SCN) - a control stimulus generated by randomly switching the sign of each time-point within a speech waveform. From these stimuli, three blood-oxygenated-level-dependent (BOLD) response contrasts were assessed: low-level responses comparing auditory stimuli (both speech and SCN) to a silent baseline, mid-level responses comparing speech (both low- and high-ambiguity sentences) to unintelligible noise, and high-level responses comparing high- and low-ambiguity sentences. The lowest contrast would confirm that basic auditory processes were intact, the middle contrast would confirm intact speech-specific processing, and the highest contrast would confirm intact processing of the meaning (semantics) of speech.

Forty-three percent (three of seven) of vegetative state patients displayed both low- to mid-level speech processes, with some evidence of semantic processing in three patients.

In a follow-up conducted by Coleman et al., (2009), a larger population of patients was recruited to determine the prognostic and diagnostic value of intact speech processes in these patients. Forty-one patients (22 VS, 19 MCS) were recruited, and presented with the same hierarchal speech processing paradigm described above (Coleman et al., 2007). Nine percent of VS patients (2/22) showed significant responses
to sound only, 32% (7/22) showed significant responses to both sound and speech, and 9% (2/22) showed significant responses to semantic processing. Importantly, the level of auditory processing achieved by these patients (as evidenced by their neuroimaging data) was highly correlated with the patients’ subsequent behavioural abilities six months later (r = 0.81, p < 0.001). For example, at 6-months post-scan, seven out of eight patients who now displayed CRS-R scores consistent with progression to a minimally conscious state had shown high-level speech processes in the initial scan. Furthermore, fourteen of these patients achieved speech vs. noise effects while only four patients achieved semantic effects. This indicates that the correlation to improvement of behavioural abilities is not driven entirely by high-level semantic processes, and that lower level speech processes are worth investigating. Lower-level speech vs. noise processes may be indicative of healthy acoustic processing, speech-specific perception, or perhaps both.

Regardless of the precise mechanisms at play, these findings highlight the potential value of neuroimaging in determining the prognosis of patients with DOCs.

*Semantic processing in DOC – evidence from EEG/ERP*

Functional neuroimaging assessments of residual processes can improve our understanding of the extent to which patients with DOCs have retained low- to high-level language mechanisms. Electroencephalography (EEG) provides another means to investigate the rapid transition through low-level perceptual operations and on to higher-level semantic access during speech comprehension. Semantic processing has been studied extensively by means of the N400, a negative-going event-related potential (ERP) over centroparietal scalp that peaks around 400ms 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). Another common example of this is through the contrast of terminal-word sentences that are incongruent (“He ate the moist cake with a knife and potato”) and congruent (“He ate the moist cake with a knife and fork”; see Kutas & Federmeier, 2011, for a full review). The difference in the N400 amplitude that is produced by semantic manipulations will be referred to throughout this thesis as the ‘N400 effect’.

A number of theories of the functional significance of the N400 have been proposed, although no consensus has been reached (see Rabovsky & McRae, 2014). However, regardless of the precise mechanisms involved, the sensitivity of the N400 to manipulations of meaning indicate that, at its simplest, the N400 reflects the processing of meaning, and therefore provides a marker of the culmination of semantic processing. As such, several studies have attempted to elicit N400 effects in patient populations. However, interpretation of these studies remains difficult due to various methodological limitations.

In a study conducted by Schoenle and Witzke (2004), different subsets of DOC patients (VS, near vegetative state NEVS, and not in vegetative state NOVS) were presented with congruent and incongruent terminal-word sentences to assess preserved semantic processing. A common clinical practice in the identification of low-level evoked potentials is through visual inspection. As such, ERP waveforms were visually classified by three neurophysiologists as “no N400 present,” “emerging N400”, and “clear N400 deflection,” (for a review of clinical ERP quantification, see Duncan et al., 2009). It was
found that 39% VS, 24% NEVS, and 91% of NOVS patients produced some form of an N400, based on an agreement of these observers rather than statistical verification based on healthy controls.

Kotchoubey, (2005) and Steppacher et al., (2013) reported semantic priming effects in VS patients after a continuous wavelet transform of the ERP data. However, without a comparison to healthy controls or clarification as to why conventional statistics were not used, these results need to be interpreted with a higher degree of caution. Furthermore, while Steppacher et al., (2013) do report the presence of the semantic priming as a positive prognostic indicator for recovery, patient follow-up was conducted between 2 and 14 years post-discharge, making it unclear how useful this EEG-based prognostic information would be in a more critical time-frame.

Existing behavioural and neuroimaging evidence suggests that sentence comprehension is likely reliant on awareness (Davis et al., 2007), however, single word comprehension and associated N400 effects can persist through degraded speech as well as reduced levels of attention (Obleser & Kotz, 2011; Relander, Rämä, & Kujala, 2009). Regardless of the specific conclusions that can be made about how conscious a patient may be, the presence of an N400 effect indicates intact semantic processing, a high-order conceptual cognitive mechanism with prognostic implications (Coleman et al., 2009). Furthermore, more automatic low- to mid-level speech processes also hold positive prognostic value (Coleman et al., 2007; Fernández-Espejo et al., 2008), and are therefore also worth exploring as potential markers for prognostic and diagnostic implications using the temporal advantages of EEG to tackle the rapid nature of language processes.
In one study investigating the reliability of eliciting the N400 effect in single subjects, it was shown that both task and stimuli manipulations can affect the likelihood of observing this semantic priming effect (Cruse et al., 2014). One of the main findings of their investigation was that the sensitivity of the N400 effect diminishes as task demands decrease. Consistent with the literature, in the most passive task, where participants aren’t given any instructions beyond “pay attention”, a very weak group-level N400 effect is observed. In the most active task, a robust N400 effect was observed when participants indicated via a button box when word-pairs were related or unrelated. Interestingly, when the authors asked participants to covertly imagine saying the words “related” or “unrelated” after the presentation of each word-pair, the N400 effect was elicited in 58% (7/12) of individuals compared to 0% in the passive condition. The implications of these findings speak to the importance of giving non-communicative and behaviourally non-responsive patients a covert task, in an attempt to account for their motor deficits.

In a similar study conducted by Rohaut et al., (2015), the likelihood of eliciting N400 effects in patients with DOCs was tested. Akin to Cruse et al., (2014), the authors used normatively-associated related word-pairs (e.g., left-right – where the target word is the first word that comes to mind 81% of the time). Normatively-associated word-pairs have a more robust contrast than alternative word-pair stimuli, and an increased likelihood of producing an N400 effect at the single-subject level. At the single-subject level, 21% (6/29) of patients were observed to have a significant N400 effect. However, only one of these patients were diagnosed as VS (five MCS), indicating that the likelihood of eliciting an N400 effect in patients with DOCs is not a trivial endeavor. Finally, it should be noted the authors implemented passive task instructions, and
therefore it is possible that the sensitivity of their observed effects may have benefited from the use of covertly-based instructions.

The current investigation, then, will employ the covert task demands and associative word-pair stimuli shown to be better than alternative tasks (e.g., passive) and stimuli (e.g., semantic word-pairs, sentences) by Cruse et al., (2014). Furthermore, this investigation will introduce the use of lower-level perceptual comparisons akin to Coleman et al., (2009; 2007) given that, in the likelihood that N400 effects are too difficult for patients to achieve, more automatic processes may be able to be identified for future prognostic investigation.

Pre-semantic speech processes – evidence from functional neuroimaging

Before the meaning of speech becomes available to a listener, it is subjected to multiple levels of processing. Through both top-down (prior knowledge) and bottom-up (sensory input) predictions, multiple phonemes must be identified and combined until a match is reached within the mental lexicon, and the meaning of the utterance revealed. These processes necessarily unfold over time and are thought to be supported by a hierarchy of cortical regions (Davis & Johnsrude, 2003; Scott & Johnsrude, 2003; Scott & Wise, 2003).

Hickok (2012), for example, proposed a dual-stream model of speech processing in which early stages of speech perception – i.e., spectrotemporal access and phonological processing – occur bilaterally in auditory regions along the dorsal superior temporal gyrus (STG) and superior temporal sulcus (STS) respectively. Later stages of speech comprehension – i.e., lexical access – occur bilaterally in both anterior and posterior middle temporal gyri (MTG) and inferior temporal sulci (ITS), with a left
hemisphere dominant sensorimotor dorsal stream involving structures in the parietal junction and frontal lobes.

In one notable fMRI study, Davis et al., (2007) contrasted spoken sentences with SCN. This contrast exhibited activation within anterior and posterior regions of bilateral STG and MTG. Interestingly, the perceptual response (i.e. speech vs. noise) was observed even when participants were moderately sedated, suggesting that these perceptual aspects of speech processing are not dependent on awareness. However, the semantic response was absent even at light levels of sedation, suggesting that the conceptual level of sentence processing is more reliant on awareness.

Investigations of pre-semantic perceptual processes with ERPs, however, are relatively scarce. Some studies have employed oddball paradigms in which a rare stimulus occurs within a sequence of repeated stimuli, and observed that speech sounds and non-speech sounds produce qualitatively different patterns of mismatch negativity amplitudes, indicating speech-specific processing within the time-window of this effect (i.e. 150-250ms post-stimulus; Jaramillo, Alku, & Paavilainen, 1999; Jaramillo, Ilvonen, & Kujala, 2001).

Phonological (i.e. perceptual) processes have also been observed in a sentence terminal-word priming task (Connolly & Phillips, 1994). Specifically, participants were presented with sentences that primed both phonological and semantic expectancy. When the terminal word matched both phonological and semantic expectancy, no ERP effects were observed. However, when the terminal word fit with semantic expectancy, but differed in terms of its initial phoneme (e.g., “They left the dirty dishes in the kitchen” vs. sink), a ‘phonological mismatch negativity’ (PMN) was elicited between 200-300ms.
Moreover, when the terminal word was semantically ambiguous, but phonetically congruent (e.g., “Phil put some drops in his icicles.” vs. eyes), only an N400 effect was observed. Finally, when both phonetically and semantically incongruous (e.g., “Joan fed her baby some warm nose.” vs. milk) both PMN and N400 responses were elicited. These components provide evidence for the rapid nature of language processes unfolding over time; the low-level expectation for phonetically congruent words becomes evident even within the first phoneme, while higher-level semantic congruence is processed later on.

D’Arcy et al., (2004) also manipulated phonological and semantic expectancy of terminal words and observed a PMN that peaked at 287ms post-stimulus, and an N400 effect that peaked at 424ms. Semantically congruent but low probability sentence-endings elicited a PMN but no N400 effect, indicating dissociable perceptual processes that precede semantic processing. Topographic analyses of the two components revealed a central peak distribution for the PMN, and a centroparietal distribution for the N400 effect. Source estimation of these topographies showed PMN sources in left inferior frontal and inferior parietal lobes, and N400 sources in left-perisylvian cortex.

These approaches, however, did not isolate phonological processing itself, but rather the expression of phonological prediction errors – processes presumably downstream of the identification of phonemic information itself. In a direct examination of the earliest stages of speech-specific processing, differences were observed between spoken vowels and spectrally controlled noises within the latency of the earliest ERP components (Edmonds et al., 2010). Specifically, more positive-going P1 and P2 deflections were observed for noises, and more negative-going N1 deflections were observed for vowels, indicating that speech-specific processing can be observed in ERPs
as early as ~70ms post-stimulus. Source estimation identified primary auditory cortex as the generator of this speech-specific processing. Degradation of sentence intelligibility through the addition of noise, however, has been shown to have the opposite effect on N1 amplitudes, with more negative-going N1s for noise (Obleser & Kotz, 2011).

**Aims and hypotheses**

The aim of the current study was to investigate the sensitivity of ERPs for isolating perceptual and conceptual processing during speech comprehension in healthy and clinical populations (vegetative and minimally conscious state patients). Specifically, we employed a similar method to the fMRI studies of Davis et al. (2007) and Coleman et al., (2009; 2007) in which perceptual processes were identified through a contrast between speech and noise, and conceptual (semantic) processes through a contrast of related and unrelated word-pair targets (i.e. the N400 effect).

A more thorough understanding of how healthy language processes unfold will give us a stronger basis of support for what language processes certain patient populations have retained when tested for the preservation of these mechanisms. It is the hope of the current investigation that, while many patients with disorders of consciousness will be unlikely to possess language comprehension abilities, the presence of perceptual processes in speech may act as a positive prognostic indicator for their outcome given follow-up tests. The identification of language-specific ERPs in healthy individuals will allow the characterization of both spatially and temporally separable language processes. Neuroimaging evidence for the dissociation of these language ERPs will further our understanding of the rapid processes that underlie language comprehension, and the degree to which consciousness is required for the success of
these mechanisms.
2 Methods

2.1 Participants

2.1.1 Healthy Controls

Seventeen right handed, native English 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. One participant’s data was excluded due to a temporary equipment fault. The remaining sixteen participants ranged in age from 18 to 25 years old (median = 20) with 8 females (median = 22.5) and 8 males (median = 18.5).

All participants were compensated with one course credit per hour of participation for use towards an undergraduate Psychology course requirement, or alternatively, $15.00 per hour. The Psychology Research Ethics Board of the University of Western Ontario, Canada, granted ethical approval for this study.

2.1.2 Patients

Seventeen patients were recruited from the community and long-term care facilities in southwest Ontario. Four patients were excluded due to excessive movement artifacts in their EEG recordings, and the diagnosis for three patients recruited in Cambridge, UK, have yet to be delivered. The remaining ten patients with available diagnoses and demographic information ranged in age from 32 to 68 years old (median = 43.5) with the age of their injuries ranging from 18-65 (median = 38). Of these patients, five were diagnosed as being in the vegetative state, and five in the minimally conscious state, as per the Coma Recovery Scale-Revised (CRS-R) behavioural assessment (Appendix D).

The Health Sciences Research Ethics Board of the University of Western Ontario, and the
National Research Ethics Service (National Health Service, UK) provided approval for this study.

2.2 Stimuli

Stimuli were taken from an associative priming task reported by Cruse et al. (2014; see Experiment 2, pp 792-794). In that study, these stimuli were shown to have the highest likelihood of eliciting single-subject N400 effects relative to two other priming manipulations: semantic-priming, and high-cloze sentences. In that study, two hundred word-pairs were selected from Nelson, McEvoy, and Schreiber's (1998) associative norms. For the purposes of this study, the prime will signify the first word in each pair, the target the second. From these 200 pairs, 100 of the most strongly associated word-pairs were selected (e.g., bumble-bee) with a mean forward association of 0.81 (SD = 0.05) such that, on average, the target word was correctly identified by 81% of the participants when asked to write the first word that comes to mind that is related to the presented word. The remaining 100 word-pairs were recombined to create 100 unrelated word-pairs controlled so that phonological, semantic, or associative overlap between the target and any word associated to the prime were minimized (Nelson et al., 1998). A male, native Canadian-English speaker digitally recorded all word-pairs, and their amplitudes were normalized (mean spoken word length = 638 ms, SD = 138 ms, range = 309–980 ms). There were no significant differences between the related and unrelated pairs in the spoken length of targets ($t(198) = 1.28, p = .203$) or primes ($t(198) = 0.67, p = .505$) between the related and unrelated pairs. Due to the impact of order effects in priming studies (see Cruse et al., 2014), no words were repeated across the study. The stimuli were therefore validated by Cruse et al. (2014) to show that no significant
differences existed in the ERPs elicited by each word category in the absence of priming. These results confirm that any ERP differences found between unrelated and related targets in the experimental condition are due to priming and not other features of the stimuli.

**Fig. 3.** Experimental design. Two instances of signal-correlated noise (SCN) followed by either related or unrelated word-pairs.

Signal-correlated noise (SCN) stimuli were generated from all words according to Schroeder (1968), in order to produce a non-speech condition that matched the speech stimuli on a range of physical dimensions. One pair of SCN stimuli was presented after each word-pair (Fig. 3). Due to the potential confounding effect of bottom-up orienting effects to the first SCN stimulus of each pair, the order of presentation of the SCN stimuli was reversed – i.e. the first SCN stimulus in each pair was generated from the Targets, and the second from the Primes. This ensured that it was possible to compare Primes with their SCN counterparts without any potential attention orienting effects. In total, the
stimuli consisted of 400 words (100 related word-pairs, 100 unrelated word-pairs), and 400 signal-correlated noise stimuli.

2.3 Experimental task procedure

Participants heard all words and all noises without repetition via EARTONE® 3A Insert Headphones (E-A-R Auditory Systems). Participants are presented with the stimuli in the following repeated pattern: SCN1-SCN2-Prime-Target, where SCN1 was generated from the Target category, and SCN2 from the Prime category. Targets were either related or unrelated to the primes. The order of presentation of word-pairs and SCN-pairs were randomized independently within each participant so that SCN pairs on average were not generated from the same word pair with which they were heard. The stimulus onset asynchrony for all stimuli was 1100 milliseconds. Stimulus delivery was controlled by the Matlab Psychtoolbox (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997).

The experiment was broken up into four blocks of 100 trials (i.e. 25 SCN pairs and 25 word-pairs), after which participants were offered a break. Due to constraints in testing behaviourally non-communicative patients, the lack of sensitivity inherent in passive tasks in the production of the N400 effect (see Cruse et al., 2014), and the desire to reduce motor artifacts, a covert task procedure was implemented. All participants were instructed to judge whether each word-pair was related or unrelated by mentally ‘saying’ the word “related” or “unrelated” following the presentation of each pair. Participants were instructed to make this mental judgment quickly, firmly, and efficiently - without debate. Finally, all participants completed this task with their eyes open and fixated on a fixation cross to reduce fatigue and alpha-based artifacts in the EEG recording.
2.4 EEG recording and pre-processing procedures

EEG recordings were made using a saline-based (potassium chloride) 129-channel HydroCel™ Geodesic Sensor Net, and a dense-array high impedance amplifier by Electrical Geodesics Incorporated (EGI Inc, OR, USA). EEG data were sampled at a rate of 250Hz, referenced to the vertex, with impedances of all channels kept below 50kΩ. EEG data were digitally filtered offline between 0.5-20Hz and epochs created around each stimulus with 100ms pre-stimulus baseline, and 796ms post-stimulus. Manual artifact rejection was conducted via visual inspection to remove channels and trials with excessive amplitude variance. Bad channels were interpolated back into the data. The median number of channels interpolated from the healthy participant group was 3 (range 0–11). Independent Component Analysis (ICA) was used to remove any remaining eye blink and eye movement artifacts using EEGLAB (Delorme & Makeig, 2004). ERP amplitudes were baseline corrected. Across healthy participants, a median of 93 trials (range 84-96) contributed to the related target category, 91.5 trials (range 84-98) to the unrelated target category, and 183.5 trials (range 171-193) to the primes (related and unrelated). Overall, a median of 365 trials (range 344-384) contributed to all words and a median of 364.5 trials (range 336-390) to all the noises (SCN1: 182.5; SCN2: 182).

Across patients, a median of 82.5 trials (range 70-91) contributed to the related target category, 83.5 trials (range 74-94) to the unrelated target category, and 171 trials (range 148-185) to the primes (related and unrelated). Overall, a median of 339 trials (range 293-369) contributed to all words and a median of 328 trials (range 276-359) to all the noises (SCN1: 163; SCN2: 166). The median number of channels interpolated was 8.5 (range 1–17).
All channels were re-referenced offline to linked mastoids. All pre-processing steps were performed using MATLAB and EEGLAB (Delorme & Makeig, 2004).

2.5 ERP analyses

The FieldTrip cluster-mass procedure was used for group and single-subject statistical analyses. (Oostenveld, Fries, Maris, & Schoffelen, 2011). This procedure uses both parametric and nonparametric statistics to determine significant differences between conditions using spatiotemporal data-points. Parametric one- or two-tailed independent sample $t$-tests were conducted across every spatiotemporal point within each trial for single-subject analyses. One- or two-tailed dependent samples $t$-tests were used to compare ERP averages across conditions for within-group analyses.

Nonparametric cluster-based permutation tests were conducted to create clusters of spatiotemporally adjacent $t$-values with $p$-values <.05; these $t$-values were summated, and the largest cluster was retained. Specifically, the most minimal spatiotemporal clusters were defined as at least two statistically significant $t$-tests for temporally adjacent time-points in the waveform, occurring at the same time across at least two spatially neighbouring electrodes (within a 4cm radius). To correct for multiple comparisons, randomization tests produced 1000 Monte Carlo permutations of the above procedure to determine if the true cluster value produced were to occur above chance (Maris & Oostenveld, 2007).

The above analyses were employed to determine if significant differences existed between two comparisons: related vs. unrelated targets (the semantic N400 contrast), and primes vs. SCN2 (the perceptual contrast). The semantic contrast was one-tailed and constrained to include only data from 200ms onwards due to a priori expectations
regarding the N400 effect (Kutas & Federmeier, 2011). For the perceptual contrast, the analysis was two-tailed and not constrained to a specific time window for healthy individuals, as there were no clear hypotheses from previous investigations.

Follow up analyses were performed on the average difference waveforms from each contrast - i.e. unrelated targets minus related targets, versus Primes minus SCN2 – using the same cluster-mass based permutation tests described above to determine any differences between the two effects. The time windows of significant effects from the healthy ERP analyses were employed in the analysis of the patient data in an effort to maximize the likelihood of detecting effects.

2.6 Global field power (GFP) and Topographic dissimilarity (GD) analyses

The scalp topographies of the ERP effects were compared using the Global Dissimilarity method under the assumption that significantly different scalp distributions reflect not entirely over-lapping cortical generators (Skrandies, 1990). First, the time-windows of each effect were identified by means of a permutation test of the global field power of the difference ERPs (i.e. semantic N400 vs. perceptual speech vs. noise effects). Global field power (GFP) is calculated by taking the standard deviation of all electrode values at each time point, yielding a time-course of response potential across the scalp. Moreover, GFP is useful in scaling the data such that one can distinguish between modulations in topography and modulations in amplitude. In order to identify significant peaks of GFP in each contrast, permutation tests were performed with 1000 permutations. Specifically, trial labels in each contrast were randomly shuffled to remove any consistencies across conditions, and the GFP value at each time-point was recorded. The
true GFP value at each time-point was then compared to this surrogate distribution to create a p-value for the hypothesis that the GFP value occurred by chance. The resultant range of significant time-points were then subjected to a false-discovery rate (Benjamini & Hochberg, 1995) correction in order to correct for multiple comparisons (FDR p<.05). The boundaries of significant time-points were then used as the time-windows for the topographic dissimilarity analysis (Fig. 6).

Global dissimilarity (GD) is calculated by comparing the standard deviation between time-windows (field distributions) of interest, after the data have been scaled to the spatial standard deviation (GFP). For the current analysis, the GD was calculated between the two early and late time windows within the perceptual effect. The GD was also calculated between the early and late time windows of the two effects (N400 and speech perception) to determine if different cortical generators existed for early vs. late processing demands for these types of stimuli. The significance of the GD values was calculated via permutation test. Specifically, trial labels were shuffled randomly 1000 times and each time the GD values were recorded. The true GD value was then compared to this distribution in order to calculate a p-value that the true GD occurred by chance (p<.05).
3 Results

3.1 Healthy group ERP analyses

The ERPs elicited by unrelated targets were significantly more negative-going than those elicited by related targets from 252 to 796 ms over centroparietal scalp ($p = .005$, one-tailed; see Fig. 4). The ERPs elicited by all words were significantly more negative-going than those elicited by signal-correlated noise from 92 to 796 ms over frontocentral scalp ($p = .001$, two-tailed; see Fig. 4).

![Primes vs. SCN2 vs. Related vs. Unrelated Targets](image)

**Fig. 4.** Significant spatiotemporal clusters in the group perceptual contrast (i.e., primes vs. SCN; left) and conceptual contrast (related vs. unrelated targets; right). Upper panels represent topographic plots of significant spatiotemporal clusters, highlighting the extent to which significant electrodes reflect differences in spatial activation. Lower panels represent significant ERP grand average differences between conditions within the significant spatiotemporal clusters; light blue shading represent the temporal boundaries for which these effects are significantly different.

The comparison of the two subtraction waveforms (i.e. the semantic contrast versus the perceptual contrast) revealed two significant clusters. An early cluster with the perceptual effect being more negative than the semantic effect from 24-284ms, and a late cluster with the perceptual effect being more positive than the semantic effect between 248-668ms (Fig. 5). Therefore the perceptual contrast revealed amplitude differences...
earlier in time than those differences seen in the semantic contrast.

Fig. 5. Comparison between the perceptual and semantic contrasts revealing two significant spatiotemporal clusters of differences. Upper panels represent topographic plots of significant spatiotemporal clusters, highlighting the extent to which significant electrodes reflect differences in spatial activation. Lower panels represent significant ERP grand average differences between conditions within the significant spatiotemporal clusters; light blue shading represents the temporal boundaries for which these effects are significantly different.

3.2 Single-subject analyses

3.2.1 Healthy participants

Twelve out of sixteen participants (75%) showed significant N400 effects.

Fourteen out of sixteen participants (87.5%) showed significant speech vs. noise effects (Appendix A, B)

3.2.2 Patients

No patients showed significant N400 effects. Four out of ten patients (40%) showed significant speech vs. noise effects (3/5 VS, 1/5 MCS)(Appendix C, D).
3.3 Global field power (GFP) and topographic dissimilarity (GD) analyses

The perceptual contrast (Primes vs. SCN2) for healthy participants revealed significant GFP from 152-180ms and 380-564ms. The conceptual contrast (related vs. unrelated targets) revealed significant GFP from 332-600ms (Fig. 6). These time-windows were therefore used as time-windows of interest for the subsequent GD analysis.

![Graph showing Global Field Power (GFP) for perceptual and conceptual contrasts.](image)

**Fig. 6.** Global Field Power (GFP) of the difference ERPs from the perceptual and conceptual contrasts. Colour bars indicate time-points of significant GFP amplitudes for each contrast (FDR corrected).

The GD analysis revealed no significant differences between the early and late time windows within the perceptual contrast (GD = .034, p = .270), and no significant difference between the late time window of the perceptual contrast and the N400 effect of
the conceptual contrast (GD = .036, \( p = .137 \)). However, a significant difference was observed between the early time window of the perceptual contrast, and the N400 effect of the conceptual contrast (GD = .064, \( p < .001 \), see Fig. 7).

**Fig. 7.** Healthy participant’s scalp topographies of the perceptual effect (left; 152-180ms, speech minus noise) and the conceptual effect (right; 332-600ms, unrelated targets minus related targets).
4 Discussion

The aim of this study was to determine the sensitivity of ERPs for isolating the perceptual and semantic processing of speech for use in the identification of residual linguistic capacities in patients, and potentially the identification of neuroimaging-based biomarkers for prognostic/diagnostic measures. This was accomplished through contrasts of speech with signal-correlated noise (perceptual) and contrasts of primed and unprimed word-pair targets (semantic/conceptual). We observed speech-specific perceptual processing occurring as early as 92ms post-stimulus, and subsequent semantic processing from 252ms post-stimulus (Fig. 4). Comparisons of the scalp topographies of these effects indicated the contributions of not entirely overlapping regions of cortex to perceptual and semantic processing (Fig 7).

Our evidence for qualitatively different stages of processing is consistent with a similar contrast approach employed with sentence stimuli in fMRI by Davis et al. (2007). In that study, perceptual processing was observed in temporal regions, while semantic processing involved left frontal regions. Our data further demonstrate the temporal evolution of these processes, with perceptual processing necessarily preceding semantic processing. Indeed, the timing of the perceptual effect is consistent with previous studies of phonemic processing (Edmonds et al., 2010; Obleser & Kotz, 2011). Furthermore, consistent with over 30 years of literature on the N400 effect, our group analysis showed a robust N400 effect when comparing related and unrelated targets in word-pairs, with a centroparietal scalp topography (Fig. 4). These dissociable markers of speech processing may now provide markers for further investigations into the necessity of awareness and attention in language (Davis et al., 2007), expanding our knowledge of DOC and the
extent to which non-communicative patients can still process language comparable to that of a healthy individual.

Similar to the fMRI study conducted by Coleman et al., (2007), the current investigation served as a means to isolate language ERPs in a healthy population, and then justify whether these markers of language processes could be observed in patients with DOCs. First, our current finding of significant N400 effects in 75% of healthy participants provides a replication of the single-subject sensitivity of covert semantic judgments for the elicitation of N400 effects. In a previous study, we observed that normatively-associative word-pair stimuli and covert task instructions (attending to relatedness of word-pairs) were more sensitive on a single-subject level than other forms of priming and task requirements (Cruse et al., 2014). Second, we demonstrate that the perceptual contrast of SCN and speech revealed significant single-subject effects in 87.5% of healthy participants. Studies aimed at identifying residual cognitive abilities in patient groups, therefore, would be well-served by employing normatively associated word-pairs under covert instructions (Cruse et al., 2014).

These markers were identified in the healthy participants of our study, and akin to Coleman et al., (2009; 2007) evidence for lower-level perceptual speech processes were found in a subset of the patients tested under an EEG paradigm. Forty percent (4/10) patients with DOC (3/5 VS, 1/5 MCS) demonstrated the low-level perceptual contrast of SCN and speech, yet higher-level conceptual aspects of semantic speech processes went undiscovered in these patients. It should be noted that upon visual inspection, the patient perceptual effects are quite variable from one another with two patients displaying some high-frequency ERPs (Appendix C). Upon comparison to the healthy perceptual effects,
it becomes evident that this variability between individuals is quite normal (Appendix B). Even amongst healthy participants, some ERPs only capture an early cluster, a late cluster, and some capture both either by amalgamating the two clusters or by temporally separating them. Whatever the interpretation may be, the effects observed are very unlikely due to chance given the high level of preprocessing that went into the data analysis. Through channel and trial rejection thresholds, ICA for eye blinks, patient-specific band-pass filters for motor-movements, quality checks, and cluster stats, I can with high confidence say that the effects observed are unlikely to be false positives, but that re-tests can always help aid in the conclusion that the data are sound.

Nevertheless, now that these lower-level markers of speech processing have been identified in select patients with DOCs, a similar follow-up to that of Coleman et al., (2009) can be conducted to determine the prognostic value of these markers from the converging perspective of EEG. Furthermore, while higher-order conceptual processing indexed by the N400 may be too cognitively demanding for many patients, this does not necessarily preclude the presence of this high-level language process in others. As such, the current task allows for both low- and high-level processes to also be identified, and this data can then be used to paint a clearer picture of how a patient’s brain processes language, and whether this data will have diagnostic or prognostic implications in the future.

Consistent with predictions from both Cruse et al., (2014) and Rohaut et al., (2015) concerning the negligible probability of producing a significant N400 effect in patients with disorders of consciousness, our results show that, even under rigorous task and stimuli controls, no patient in our tested population produced this effect. This is not a
surprising finding given the decreased sensitivity in eliciting N400 effects through covert task demands, and the added difficulty with producing these effects at the single-subject level, especially in brain-injured patients. However, this caveat does not preclude the presence of an N400 effect in DOC patients that were not tested in our population, and certainly the presence of this effect would provide evidence of residual linguistic function that could aid in the diagnosis and prognosis of these non-communicative patients (Coleman et al., 2009; 2007; Owen, 2011).

The N400 effect has been reported to be present in several other studies for patients with DOCs (Hinterberger, Wilhelm, Mellinger, Kotchoubey, & Birbaumer, 2005; Kotchoubey, 2005; Rämä et al., 2010; Schoenle & Witzke, 2004; Steppacher et al., 2013), however, little control of stimuli or task demands were employed in those studies – issues shown by Cruse et al., (2014) to greatly affect the statistical verification of EEG results. From a purely methodological perspective, the parametric and nonparametric statistical algorithms that we employed (via the Matlab toolbox Fieldtrip (Oostenveld et al., 2011)) constitute a data-driven analysis that accounts for the large number of multiple-comparisons made in ERP analyses, and is therefore an empirically sound statistical analysis for ERPs; consequently, alternative methods should be used with caution in the absence of an appropriate rationale. Moreover, even through the combination of ideal task and stimulus conditions described in Cruse et al., (2014), the current investigation did not reveal N400 effects in any patients, making N400 effect findings from existing patient literature difficult to replicate. Our experiment therefore highlights the unlikelihood of observing a reliable N400 effect from vegetative-state patients using the conservative statistical algorithms employed, and attempts instead to
identify lower-level perceptual processes in lieu of this higher-order conceptual/semantic effect.

In contrast to the apparent statistical unlikelihood of observing an N400 effect in patients with disorders of consciousness (described above), several patients (40%; 4 of 10) in the tested population achieved a statistically reliable perceptual effect in our speech vs. noise contrast. Based on the rapid temporal onset of the perceptual effect in healthy individuals (92ms), it is likely that the mechanisms responsible for differentiating between words and noise is an automatic process that does not require conscious awareness (see Fig. 5). The finding then, that only a subset of our patients display this effect is an interesting one that requires some level of inference and interpretation.

It should be noted that as with any neuroscience experiment, individual differences and noise are inherent and even expected in the measured EEG. Even with regards to the healthy controls, not every single individual elicited an N400 and perceptual speech vs. noise effect (N400: 75%, perceptual effect: 87.5%); thus, while these percentages do represent a very convincing majority, the data will not always represent this truth in every individual. First, it is more likely that the N400 effect is simply not sensitive enough to be observed in every individual given one session of testing than it is that these individuals process semantic aspects of language in a fundamentally different way. Especially with existing N400 literature on patients (described above) failing to report sensitivity, and the indication from our own results that even an optimized N400 effect is not sensitive enough to be observed in 100% of healthy individuals, we were not surprised that we did not observe this effect in our patient population. Second, while the data and literature certainly do seem to indicate that
low-level perceptual processes are not reliant on conscious awareness (Davis et al., 2007), in this case, even two healthy individual’s brains ‘behaved’ differently than the ERPs represented by the group-level and majority of single-subject results. Therefore, we appropriately did not expect all patients to achieve this low-level effect, despite the assumption that consciousness is not a prerequisite.

The unfortunate reality that this low-level perceptual effect was not observed in the majority of the patients tested (69.23%) speaks to the severity of cognitive deficits these DOC patients have endured even beyond the lack of overt communication and command following prescribed by consciousness. As such, the lack of seemingly automatic and rapid cognitive mechanisms not reliant on consciousness likely indicates widespread and irreparable cortical damage. For example, damage to the bilateral STG and/or the STS auditory regions would interfere with spectrotemporal access and phonological processing in the early stages of speech perception (Hickok, 2012), likely decreasing the effectiveness of a speech vs. noise contrast. With specific regards to comparisons to SCN, damage to anterior and posterior regions of bilateral MTG (as well as the STG) would also interfere with the reliability of this low-level contrast (Davis et al., 2007). While the EEG conducted on patients in this study is not a suitable technique for determining the state of these anatomical structures, it is reasonable to assume that specific damage to these brain regions will prevent patients from demonstrating residual abilities. Interestingly, fMRI activation of these language networks accompanied with DTI evidence of an intact arcuate fasciculus has been reflected in one VS patient who recovered consciousness (Fernández-Espejo et al., 2010), calling further attention to the need for multi-modal brain imaging.
There is, however, an alternative explanation pertaining to the absence of these low-level mechanisms. While it is indeed the case that specific brain-injury would prevent VS patients from demonstrating perceptual effects despite the automaticity of the effect, many MCS patients who have retained fluctuating levels of awareness also do not display these effects. That is to say, patients we know to have some level of awareness should, theoretically, have less difficulty with these low-level contrasts. The fact that they do have greater difficulty than healthy individuals, supports the possibility that awareness can exist without this basic auditory function. For example, perhaps the patient has hearing loss through temporal lobe damage that doesn’t minimize the obvious awareness indicated through their behavioural measures (Slevc, Martin, Hamilton, & Joanisse, 2011). Depending on the time of testing, one can also not rule out the possibility that a patient’s brain has undergone functional reorganization since their injury, and we are unfamiliar with the fundamentally different way this speech process works. These are just a few examples that demonstrate the importance of converging tools when assessing patients with a DOC, and lends credibility towards behavioural measures like the CRS-R on occasions where neuroimaging evidence falls short.

What are the implications for the patients who have been discovered to retain these low-level residual capacities? It is probable that these patients are by some means better off at least to the degree that their brains are behaving in a way similar to healthy individuals to some extent. The next step then would be to use the presence of this low-level perceptual effect as a neuroimaging marker in order to determine whether or not it could serve as a positive prognostic implication for recovery. To accomplish this, a future investigation would benefit from a clinical follow-up to assess not only any changes in
the patient’s CRS-R scores, but also to re-test for language ERPs to document any changes in their neuroimaging data given a second test under the same paradigm. Improvement on the CRS-R will provide an indication of the patient’s behavioural improvement and potentially progression into a new category of DOC (VS>MCS), where their EEG will provide an indication of the patient’s neurological improvement (e.g., no effect>effect, existing effect>greater symmetry to healthy ERPs) that the CRS-R cannot account for. These measures have been proven to tell different stories (Fernández-Espejo & Owen, 2013), so data from both is necessary.

If the validity of a prognostic marker can be determined from low-level speech vs. SCN, other non-speech stimuli contrasts (speech masks, reverse speech, non-words etc.) should be investigated to develop a hierarchy of language processing (from low- to high-level semantic mechanisms) indicative of recovery. The non-speech stimuli used in our design (SCN) were chosen from several options available for investigating speech vs. non-speech effects. Signal-correlated noise (Schroeder, 1968) was created by modulating each time point in the amplitude envelope of the prime words in our speech stimuli such that the speech becomes unintelligible noise. Nevertheless, other non-speech options exist, including reverse speech or spectrally rotated speech (Scott & Mcgettigan, 2014). However, intracranial electrocorticography has demonstrated stronger activation in superior temporal cortices for reverse speech than for speech, contrary to fMRI findings, with SCN acting as the better alternative for a non-speech control stimulus in these cases (Brown et al., 2012, 2014). Furthermore, while the maintenance of the temporal and spectral complexities of speech in spectrally rotated stimuli is an advantage over SCN, adaptation to spectral rotation has been observed in participants such that partial
intelligibility of this speech can be acquired over time (Blesser, 1972; Green, Rosen, Faulkner, & Paterson, 2013). Nevertheless, we chose SCN for the current study specifically so that our results could be compared with those of the fMRI investigation of Davis et al. (2007). Future investigations may benefit from comparisons of alternative non-speech stimuli that may prove to be more sensitive at the single-subject level.

One simple rationale behind group-ERP analyses is that the increased signal to noise ratio provided by a large sample size allows one to be more confident that the observed effects are reliable given the accompanying increase in statistical power. Furthermore, group statistics imply that a sample was randomly collected, and the effect seen within this sample can be extrapolated to the greater general population. However, in patient populations where an individual patient can vary greatly in comparison to the next in terms of brain trauma (traumatic/non-traumatic) and the severity of cortical damage, group-ERP analyses are not possible. For this reason, the motivation to investigate sensitive ERP effects at the single-subject level are of crucial importance in determining the extent to which patient brains behave similarly to that of healthy individuals. It is through these types of investigations that researchers can inform clinicians about alternative practices that may aid in the understanding of these patient populations. Without neuroimaging support, diagnosis, prognosis, medical choices, caregiving, and ultimately end of life decisions would be based entirely on a flawed behavioural assessment. With regards to DOC patients, a subset of which have been shown to be able to follow commands and even communicate through neuroimaging contrary to their diagnosis (Monti et al., 2010; Owen et al., 2006), a more thorough
understanding of their language capabilities is not only necessary for the purposes of research and the acquisition of knowledge, but essential to the patient’s well-being.

Summary

Many EEG/ERP studies of speech processing in DOC do not make use of sufficient controls of stimuli, task demands, and statistical verification. I argue that this is crucial for the reliable interpretation of these data, and employ a number of methods to do so. When dealing with sensitive patient populations on which research findings may inform clinician decisions, a lack of healthy-control group and/or visual discrimination of ERP waveforms is likely to lead to false positives or false negatives. The current investigation revealed through EEG that lower-level (speech vs. noise) and high-level (semantics) language processes are temporally and spatially dissociable, and that the former is a rapid and automatic process likely not reliant on awareness, while the latter relies on higher cognitive functioning and shows the potential for awareness. The current investigation found single-subject N400 and perceptual effects in 75% and 87.5% of healthy participants respectively, and perceptual effects in 40% of patients with a DOC (three VS, one MCS). Given the available literature reviewed, and the potential tasks and stimuli sets used in a semantic priming paradigms, the current experiment represents the first known procedure to elicit sensitive single-subject effects for both low-level (as well as high-level) contrasts discussed. Regardless of whether the mechanism underlying this low-level contrast is in fact speech-perception as referred to by Davis et al., (2007) or rather, a purely acoustic-based perception, these residual abilities represent healthy brain activity. Until future investigations come forward to demonstrate better ways to increase the sensitivity of perceptual effects (perhaps through other non-speech stimuli) or
conceptual effects (perhaps through novel task and stimuli construction), the experiment in its current state represents an improvement on previous language tasks used for patient testing. Follow up investigations and assessments would need to be conducted to determine the eligibility of any observed linguistic effects described in this thesis for prognostic or diagnostic value.
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Appendix A – Single-subject N400 effects
Appendix B – Single-subject perceptual effects
Appendix C – Patients’ perceptual effects
Appendix D – Patient Information

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Thesis. Defense: July 20th. 2015

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RELATED EXPERIENCE
Disorders of Consciousness Research Assistant  University of Western Ontario  2011 - Present
- Recorded EEG measurements from healthy (~200 participants) and clinical (~30 patients) populations.

Epilepsy Research Assistant  London Health Sciences Centre, University Hospital, London, Ontario  2010/01 – 2011/09
- Ran a survey study concerning doctor’s knowledge and attitudes towards epilepsy surgery.

Language and Working Memory Research Assistant  University of Western Ontario  2010/01 – 2011/09
- Conducted school visits to assess children’s language, math, and working memory skills. Completed data entry of over 1500 children for future research.

Personality and Emotion Development Research Volunteer  University of Western Ontario  2010/09 – 2011/04
- Completed data entry for 410 children in a study examining temperamental development and to what extent genes and environment play a role in this process.
Visual Neuroscience Research Volunteer
University of Western Ontario 2010/03 - 2010/04
- Used BrainVoyager to inspect fMRI data for subject head motion for cross-referencing prior to pre-processing.

Action and Perception Research Assistant
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- Trained and supervised research participants in a variety of experiments concerned with how the brain assesses multiple targets.

Numerical Cognition Research Assistant
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Assisted undergraduate students both in and outside of the association in their pursuit of knowledge in psychology, in finding volunteer opportunities in and outside of the university, and I organized volunteer events for various charitable organizations.

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