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ORIGINAL ARTICLE

Positive Prognostication from Median-Nerve Somatosensory Evoked Cortical Potentials

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Abstract
Background The bilateral absence of the cortical N20 median-nerve somatosensory evoked potential (SSEP) is a strong predictor of poor outcome from coma. However, when N20s are present, accurate prognostication is challenging. Here, we investigated the potential for later SSEP components to help disambiguate outcome in these cases.
Methods In a retrospective review of data from two intensive care units, the amplitudes and latencies of the N20, P25, and N35 components of 28 patients in coma were quantified and related to outcome at discharge from primary care (average 1-month post-injury). Only patients who had survived primary care were included in order to avoid self-fulfilling prophecies, and to focus outcome prediction on those patients with relatively present SSEPs.
Results The amplitudes of the N20 and N35 components (averaged across hemispheres) significantly predicted the range of outcomes beyond death. Abnormal amplitudes of the N20 and N35—as derived from a healthy control group—were significantly associated with poor outcome. The relative latencies of the cortical components were not related to outcome.
Conclusions While it is well documented that absent SSEPs are highly predictive of poor outcome, the current data indicate that the relative preservation (absolute amplitude) of "present" N20 and N35 SSEP components can also provide predictive value and thereby inform clinicians and families with decision-making in coma. Further prospective study will elucidate the relative contributions of etiology to the predictive power of these SSEP measures.

Keywords Coma · Somatosensory evoked potentials · Prognosis

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Introduction

In order to make informed decisions regarding treatment options, it is crucial for the families and caregivers of severely brain-injured patients to be provided with accurate prognostic information. One recommended approach to prognostication from coma is the administration of a median-nerve somatosensory evoked potential (SSEP) assessment [1].

Upon stimulation of the median nerve, a series of electrophysiological components are evident over the contralateral cortex in healthy individuals (see Fig. 1). When referenced to the frontal scalp, two negative-going peaks are typically observed with latencies of ~20 ms (N20) and ~35 ms (N35), separated by a positive-going peak at ~25 ms (P25). The generators of these potentials are considered to be located in primary somatosensory cortex; the earlier potential (N20) generated in the posterior bank of the central sulcus, and the later potentials (P25, N35) generated somewhat more anteriorly in peri-central cortex [2].

The bilateral absence of the N20 component in the first week following a severe brain injury is strongly associated with poor outcome—death or vegetative state—with an estimated false negative rate below 2 % following anoxic-ischemic injury [3]. Similar levels of negative predictive

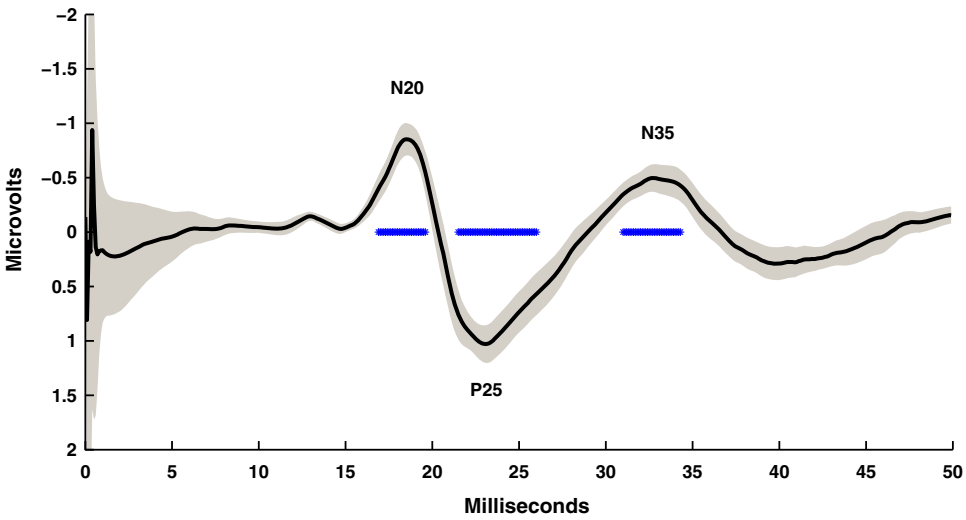

Fig. 1 Grand average cortical SSEPs from 20 healthy subjects. Standard error is shaded in gray. *Blue shading marks* time-points at which SSEP amplitude was significantly different from zero across participants (*t* tests, $p < .05$, two-tailed, False Discovery Rate corrected between 15 and 50 ms) (Color figure online)

power have also been found for patients with traumatic injuries [4, 5] and those undergoing hypothermia [6]. The N20 component, however, has low positive predictive value, with bilaterally present N20s contributing very little to prognostication [5, 7, 8]. Indeed, in one study, 66 % of post-cardiac patients who exhibited present N20s died during hospitalization [6].

Due to the prognostic ambiguity of present N20s, efforts have been made to investigate the predictive value of other aspects of the SSEP. Abnormal amplitudes or latencies of the N70 component have been shown to predict poor outcome in post-anoxic patients with normal N20s [8]. However, this approach similarly contributes little to positive predictions, with good outcome only achieved by 28 % of patients who exhibited both normal N20s and normal N70s [8]. Following traumatic brain injury, P25 amplitudes and N13–N20 inter-peak latencies that fall within the normal range have been found to predict good recovery [9, 10]. However, when these measures are present but of an abnormal amplitude or latency, their predictive value is poor, with outcomes ranging from vegetative state to good recovery [9, 10].

The wide range of outcomes associated with present SSEP components raises the question of whether other aspects of the SSEP waveform may provide further prognostic information, and thereby disambiguate outcome in these cases. At our hospitals, median-nerve SSEP recordings are performed for many coma patients in order to inform withdrawal-of-care decisions. We, therefore, performed a retrospective review of the SSEP recordings made between 2007 and 2013 in order to investigate the potential for accurate prognostication. As the outcome of the SSEP assessments would have contributed to end-of-life decisions at the time, all patients who died were excluded from our analyses. This allowed us to remove the confounding effect of self-fulfilling prophecies—i.e., those patients who died as a result of care withdrawals that were informed by absent SSEP results. We were, therefore, able to focus our analyses on identifying the prognostic utility of "present" SSEP components. Our exploratory aim was to investigate the relationships between patient outcome and the relative latencies and absolute amplitudes of the three cortical components recorded in our stimulation protocol—the N20, P25, and N35.

Materials and Methods

Patients

A retrospective review was undertaken of the SSEP recordings of 189 patients admitted to the intensive care units at the University and Victoria Hospitals, London, Ontario, between 2007 and 2013. Ethical approval was provided by the Health Sciences Research Ethics Board of Western University. When multiple SSEP recordings existed for any patient, the first clean recording was always chosen for analysis. Data from 76 patients were excluded due to incomplete data (i.e., only unilateral recordings), absent cervical spine potentials (N13), outlying time-points of SSEP assessment, or discharge from primary care (i.e., >2.5 standard-deviations above the mean), or inadequate data quality. Of the remaining 113 patients, 85 died. As described above, all patients who died were excluded in order to control for self-fulfilling prophecies—i.e., patients who died as a result of withdrawal-of-care that would have been informed by the outcome of the SSEP test. No patients were being treated with etomidate, known to increase SSEP amplitudes, at the time of assessment.

Across the remaining 28 patients (median age 50.5-years, range 17–77), coma was caused by traumatic injury (8 patients), cardiac arrest (16 patients), hypoxia (2

patients), and hepatic encephalopathy (2 patients). Two patients progressed to the vegetative state, 7 to severe disability, 13 to moderate disability, and 6 to good recovery (see "Outcome Measure" section, below). All cardiac arrest patients were treated with hypothermia upon admission and had returned to normothermia for at least 24-h before SSEP assessment. The median number of days post-injury at which the SSEP assessment was performed was 5 (range 2–22). Discharge from primary care occurred at a median of 31 days post-injury (range 12–90). None of the patients presented with bilaterally absent cortical SSEPs. At the time of assessment, all patients were non-responsive to verbal stimuli and scored 10 or less on the Glasgow coma scale ([11] median 6, range 3–10). All patients were intubated and therefore scored 1 on the verbal subscale of the Glasgow coma scale.

Healthy Controls

The retrospective review included data from 20 healthy control participants who had been tested in order to calibrate the SSEP system (median age 37.5-years, range 27–61).

Outcome Measure

The primary care discharge report of each patient was reviewed in order to estimate a score on the Glasgow outcome scale (GOS [12]) with possible values of: death (1), vegetative state (2), severe disability (3), moderate disability (4), or good recovery (5).

SSEP Stimulation and Recording Procedure

At the time of testing, SSEPs were obtained using a VikingQuest system (Viasys/Nicolet). The median nerves were alternately stimulated by surface electrodes (S403 electrical stimulator probe) at each wrist with a stimulus intensity necessary to evoke a visible thenar muscle twitch. The stimulus pulse duration was .1 ms, and the stimulus rate was 4.7 Hz. SSEP recordings were obtained from electrodes placed on the surface of the skin using EEG disk electrodes (Grass Instruments) on the scalp. Skin/electrode impedance was kept below 5 kΩ. The locations of the five recording electrode pairs were: (1) ipsilateral Erb's point (EP)—frontal pole electrode (Fz); (2) the C2 spinous process (Cv2)—Fz; and (3) the scalp overlying the contralateral somatosensory cortex (C3′ or C4′)—Fz. and (4) linked contralateral EP—ipsilateral EP (EP1–EP2). SSEP waveforms were the averaged results of at least 500 stimulus presentations. The amplifier gain was 20 μV/division, and the recording bandpass was 30–3,000 Hz. The sweep time was 50 ms bilaterally. Two SSEPs from each limb were superimposed in order to confirm waveform reproducibility.

SSEP Component Analyses

The latencies and amplitudes of the N20, P25, and N35 components were recorded using a combination of visual inspection and MATLAB (Mathworks Inc.). All correlation and regression analyses were non-parametric due to the categorical nature of the outcome measure and were performed using MATLAB.

Outcome Prediction

Ordinal multinomial regression analyses were used to fit predictor variables to outcome (MATLAB function "mnrfit"). For the single-patient outcome prediction, a leave-one out cross-validation approach was employed. Specifically, the data from one patient were removed (test patient), and a regression model was trained on the data from all other patients (training patients). This model was then used to predict the outcome of the test patient (MATLAB function "mnrval"). This process was repeated once for each patient, with a different patient tested each time, resulting in a predicted outcome score for each patient. These predictions were then compared with the true outcome score in order to calculate the overall single-patient accuracy of the model.

The statistical significance of this single-patient accuracy was subsequently determined using randomization testing. Specifically, the outcome scores of the patients were randomly shuffled in order to destroy the relationship between outcome and the predictor variables. The above cross-validation procedure was then performed using the shuffled outcomes. This was repeated 1,000 times with the outcome scores randomly shuffled each time. The prediction accuracies returned by each of these repetitions were used to form a surrogate distribution describing the null hypothesis that the single-subject prediction accuracy came about by chance. The p value of the original single-patient accuracy was defined as the proportion of prediction accuracies from the surrogate distribution that exceeded it.

Results

SSEP Component Analyses

There were no significant correlations with outcome for the absolute differences in latencies or amplitudes for the N20, P25, or N35 components between hemispheres (all ps $>$ .10). In order to reduce the dimensionality of the data, this result was taken as justification for conducting

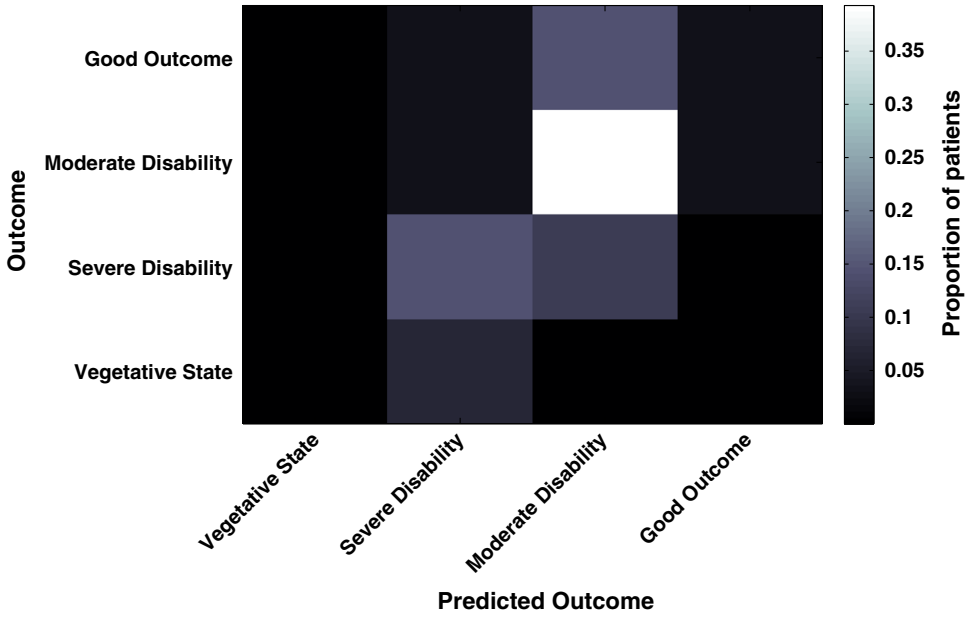

Fig. 2 Observed outcome versus that predicted by the full regression model (N20, P25, N35). *Shading* indicates the proportions of patients within each cell

subsequent analyses on the average of the SSEP waveforms from both hemispheres.

The amplitudes of the bilateral mean N20, P25, and N35 all significantly correlated with outcome (N20: $\rho = -.39$, $p = .021$; P25: $\rho = .377$, $p = .024$; N35: $\rho = -.46$, $p = .007$; all one-tailed). Pairwise partial correlations revealed significant correlations with outcome for the N20 and N35 components when taking into account the amplitudes of the other two components (N20: partial $\rho = -.39$, $p = .023$; N35: partial $\rho = -.44$, $p = .013$; all one-tailed). None of the pairwise inter-peak latencies were significantly correlated with outcome (N20–P25: $\rho = -.092$, $p = .321$; N20–N35: $\rho = .080$, $p = .658$; P25–N35: $\rho = -.196$, $p = .160$; all one-tailed).

Outcome Prediction

An ordinal multinomial regression analysis, using N20, P25, and N35 amplitudes as predictors, retained only N20 and N35 amplitudes as significant predictors of outcome [N20: $\exp(\beta) = 1.23$ (95 % CI [1.02 1.49]); N35: $\exp(\beta) = 1.56$ (95 % CI [1.06 2.28])] with the model performing significantly better than a null model ($\chi^2 = 12.78$, $p < .001$). The predictions of this model are shown in Fig. 2.

A follow-up ordinal multinomial regression analysis using only those significant predictors from the above full model (N20 and N35 amplitudes) retained only the N35 amplitude as a significant predictor [$\exp(\beta) = 1.30$ (95 % CI [1.01 1.68])]. This model performed significantly better than the null model ($\chi^2 = 11.00$, $p < .001$) but did not perform significantly better than the full model ($\chi^2 = 3.21$, $p = 1$). The predictions of this model are shown in Fig. 3.

Using the leave-one-out prediction approach described in the "Materials and Methods" section, outcome (GOS 2–5) could be accurately predicted above chance using the full model (accuracy = 50 %; chance = 25 %; $p = .011$) and the N20/N35 model (accuracy = 46 %; chance = 25 %; $p = .041$).

Comparison with Healthy SSEPs

Due to the predictive value of the amplitudes of the bilateral mean N20 and N35 components in the patient group, the averaged SSEPs of the healthy participant group were investigated in order to determine normative limits (see Fig. 1). The amplitudes were log-transformed before an upper limit of 2.5 standard deviations above the mean of the healthy control group was determined. These cut-offs were then converted back into amplitude values (i.e., no longer log-transformed). Patient component amplitudes that were less negative than this value (N20: −.2838 μV; N35: −.2626 μV) were considered "abnormal." Outcome was significantly correlated with the abnormal/normal dichotomy of the amplitudes of the N35 (Pearson's $\rho = .36$, $p = .028$, one-tailed) and the N20 (Pearson's $\rho = .34$, $p = .039$, one-tailed).

Discussion

Absent cortical SSEPs are known to be strongly predictive of poor outcome [3–6]. In the current retrospective review of 28 SSEP recordings made between 2007 and 2013, we have identified a statistically significant relationship

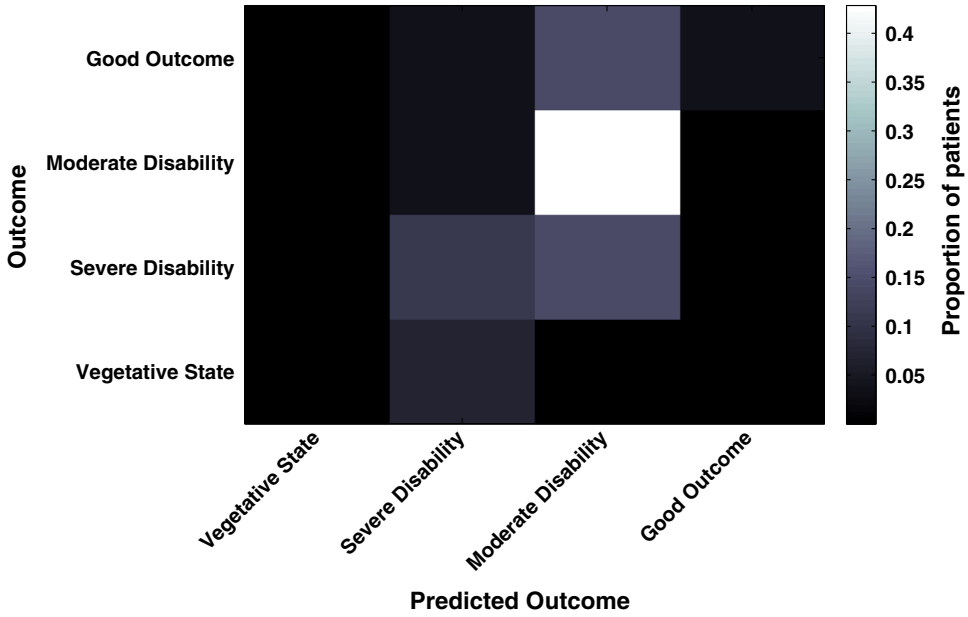

Fig. 3 Observed outcome versus that predicted by the N20/N35 regression. *Shading* indicates the proportions of patients within each cell

between patient outcome and the absolute magnitudes of the N20 and the N35 components. This result highlights the potential for both absent and present SSEPs to contribute to prognostication in coma.

As the full model regression output indicates, for every .1-μV increase in the amplitude of the bilateral mean N35, there was a 56 % increase in the log odds that a patient would achieve a better outcome than another patient who had the same bilateral mean N20 and P25 amplitudes. This predictive value is further illustrated by the finding that patients with poor outcomes were more likely to exhibit bilateral mean N35 amplitudes that were abnormally small (i.e., 2.5 standard deviations below the healthy mean) than those with good outcomes. A similar, though weaker, relationship was also observed between the amplitude of the N20 and outcome. However, the predictive value of the N35 was greater than the N20 as demonstrated by the retention of only this component in the follow-up regression (see "Methods", "Outcome Prediction" sections).

Patient outcome in the current review was estimated on the basis of clinical reports made at the time of discharge from primary care, on average 1-month post-injury. As a result, the current predictive value of SSEPs relates to a patient's level of disability in the relatively short term, which may or may not be indicative of their long-term level of recovery. Nevertheless, our results suggest that N20 and N35 amplitudes may be used to accurately identify patients who will do well relatively quickly—i.e., achieve a good recovery within 1-month. This form of prognostication could, therefore, allow for treatment and rehabilitation efforts to be more rapidly and effectively targeted toward those patients who will not make a quick recovery.

All patients who died in primary care (i.e., GOS = 1) were excluded from our analyses as it was impossible to determine the extent to which withdrawal-of-treatment decisions were informed by the SSEPs at the time of assessment. These cases presented a potential "self-fulfilling prophecy" in which bilaterally absent SSEPs may have appeared to be predictive of death in this retrospective review simply because a decision to withdraw treatment was made on the basis of this result at the time. Therefore, the present study includes only those patients for whom a poor prognosis could not be confidently predicted from the SSEPs at the time of assessment. Indeed, none of the patients included in our analyses presented with bilaterally absent SSEPs—a known strong predictor of poor outcome. Our analyses, therefore, illustrate the predictive power of "present" (non-zero) SSEP components in isolation from the known predictive value of "absent" SSEPs.

The current data, therefore, suggest that a combination of approaches may allow for both positive and negative predictive power to be derived from the SSEP assessment following severe brain injury. For example, a first-level interpretation of the SSEPs would allow for predictions to be made on the basis of previously documented aspects of the short-latency cortical components, such as the absence of the N20 [3, 9, 10]. When outcome is ambiguous on the basis of these measures—e.g., N20s are present—the current data indicate that the absolute amplitude of the bilateral mean N35 component (and to a lesser extent, the N20) may inform the degree to which recovery beyond death can occur. Indeed, patients with abnormal bilateral mean N35 amplitudes were significantly less likely to make a good recovery than those patients with N35 amplitudes within the normal range (see Fig. 4). Combining these

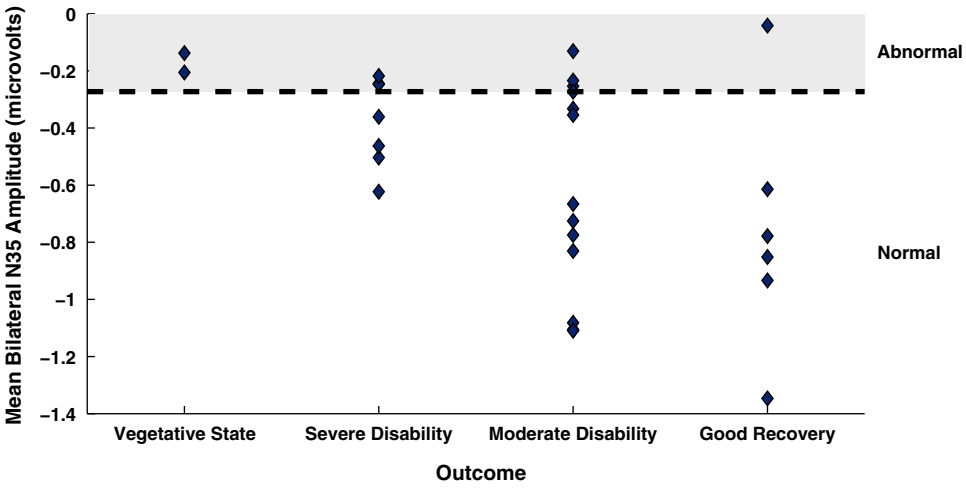

Fig. 4 The relationship between abnormal bilateral mean N35 amplitudes and outcome. Each *diamond* represents one patient. The *dotted line* demarcates normal and abnormal amplitudes (as derived from the healthy participants)

analytical approaches may thereby significantly improve overall prognostic accuracy in coma. Furthermore, as the value at which component amplitudes may be considered "abnormal" will vary slightly across stimulators and protocols, it is necessary for each clinical setting to acquire data from a healthy control group that spans the full age range.

The physiological mechanism underlying the predictive power of the N35 is unclear. The N35 component of the median-nerve SSEP appears to be generated near the central sulcus, somewhat more anteriorly to the first cortical SSEP component, the N20 [2]. Damage to the medial body of the thalamus has been associated with specific abnormalities in mid-latency median-nerve SSEP components—i.e., the N35 and P45 components [13]. Furthermore, the degree of chronic atrophy of nuclei in the medial thalamus has been shown to correlate with patients' levels of disability, as well as the likelihood of observing behavioral signs of awareness following brain injury [14]. Indeed, medial thalamus is thought to play a crucial role in the generation of consciousness, both through maintaining wakefulness, and its reciprocal connections to higher order cortical regions [15, 16]. The relative preservation of the amplitude of the median nerve N35 may, therefore, reflect the relative preservation of the structure of the medial thalamus, and thereby provide predictive information of the potential for future recovery. This interpretation is necessarily speculative, however, and requires further prospective study.

The exploratory quantitative analyses in this paper were performed on the average of the SSEPs from the two hemispheres. This was justified by the absence of statistically reliable relationships between outcome and the differences in amplitudes or latencies of the cortical components across hemispheres. While this is a non-conventional means of analyzing SSEP waveforms [1], it crucially reduces the dimensionality of the data and allows for a composite value to represent the relative preservation of each SSEP component bilaterally, allowing for quantitative analyses to be performed.

Despite the significant predictive power of the bilateral mean N20 and N35 amplitudes, the confidence intervals of these effects were wide. Indeed, on a single-patient basis, it was possible to predict scores on the GOS with 46 % accuracy. While this is significantly better than chance (chance = 25 %), it is far from ideal. It is clear, therefore, that predictions made on the basis of this form of SSEP assessment also suffer from unexplained variance. Nevertheless, it is reassuring to note that outcome predictions made from the amplitudes of the bilateral mean N20 and N35s were within one level of the GOS for 96 % of the patients (i.e., 27 of 28).

Our analyses were conducted across a group of patients from a range of aetiologies. Due to low patient numbers and low variance of outcome, it was not possible to determine the relative predictive power of our SSEP measures within etiological subgroups. While the current results are encouraging for prognostic accuracy in coma, further prospective study will elucidate the contributions of etiology to the predictive power of these SSEP measures.

Conclusions

The results of the current retrospective review indicate that the bilateral mean amplitudes of the N20 and N35 components of the median-nerve SSEP may be used to reliably predict short-term patient outcomes. For cases in which conventional SSEP measurements provide little predictive information—e.g., bilaterally present N20s—identification of the relative abnormality of the bilateral mean N20 and N35 may significantly increase prognostic accuracy. This may subsequently inform families and caregivers in their decision-making, and allow for rehabilitation efforts to be directed appropriately.

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Conflict of interest All authors declare that they have no conflicts of interest.

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