Authors:

Henry L. Lew, MD, PhD
Sureyya Dikmen, PhD
Jefferson Slimp, PhD
Nancy Temkin, PhD
Eun Ha Lee, MD, PhD
David Newell, MD
Lawrence R. Robinson, MD

Affiliations:

From the Physical Medicine and Rehabilitation Service, VA Palo Alto Health Care System, Stanford University School of Medicine, Palo Alto, California (HLL, EHL); and the Departments of Rehabilitation Medicine (SD, JS, NT, LRR) and Neurosurgery (DN), University of Washington/Harborview Medical Center, Seattle, Washington.

Disclosures:

Supported by the National Institutes of Health grant 5K12HD01097.

Presented, in part, at the Annual Meeting of the Association of Academic Physiatrists, Hilton Head, South Carolina, March 1–3, 2001.

Correspondence:

All correspondence and requests for reprints should be addressed to Henry L. Lew, MD, PhD, Comprehensive Rehabilitation Center, VAPAHCS, Physical Medicine and Rehabilitation Service, MS-B117, 3801 Miranda Avenue, Palo Alto, CA 94304.

0894-9115/03/8201-0053/0
American Journal of Physical Medicine & Rehabilitation

DOI: 10.1097/01.PHM.0000043771.90606.81

CME Article • 2003 Series • Number 1

Use of Somatosensory-Evoked Potentials and Cognitive Event-Related Potentials in Predicting Outcomes of Patients with Severe Traumatic Brain Injury

ABSTRACT

Lew HL, Dikmen S, Slimp J, Temkin N, Lee EH, Newell D, Robinson LR: Use of somatosensory-evoked potentials and cognitive event-related potentials in predicting outcomes of patients with severe traumatic brain injury. *Am J Phys Med Rehabil* 2003;82:53–61.

Objective: This study was performed to evaluate the usefulness of somatosensory-evoked potentials (SEPs) and cognitive event-related potentials (ERPs) in predicting functional outcomes of severe traumatic brain injury patients.

Design: Prospective study of 22 patients with severe traumatic brain injury. Demographic information, Glasgow Coma Scale, and electrophysiologic measurements were recorded. Functional outcomes, as quantified by the Glasgow Outcome Scale–Extended, were obtained.

Results: Bilateral absence of median nerve SEP was strongly predictive of the worst functional outcome. The specificity and positive predictive value of absent SEP for predicting death or persistent vegetative state at 6 mo after traumatic brain injury were as high as 100%. If the definition of unfavorable outcome was expanded to include Glasgow Outcome Scale–Extended 1–4, absence of ERP was equivalent to the absence of SEP in specificity and positive predictive value. On the other hand, normal ERPs showed higher sensitivity and negative predictive value for prognosticating the best outcomes compared with normal SEPs. If the definition of favorable outcome was expanded to include Glasgow Outcome Scale–Extended 5–8, ERP was still superior to SEP for prognosticating good outcome. Interestingly, the highest sensitivity and negative predictive value for favorable outcomes were associated with the presence of any discernible waveform.

Conclusions: Although median nerve SEP continues to make reliable prediction of ominous outcome in severe traumatic brain injury, the addition of the speech-evoked ERPs may be helpful in predicting favorable outcomes. The strength of the latter test seems to complement the weakness of the former.

Key Words: Traumatic Brain Injury, Event-Related Potentials, N100, P300, Somatosensory-Evoked Potential, Glasgow Coma Scale, Glasgow Outcome Scale–Extended, Functional Outcome

With advances in emergency and intensive care medicine, the number of survivors with severe traumatic brain injury (TBI) has a tendency to increase over time.[1] Specifically, comatose patients present a major challenge to physicians and patients' families regarding expectations of their awakening and functional outcome.

Presently, there are few reliable indicators to predict eventual functional recovery for patients with severe brain injury.[2] Various electrophysiologic techniques have been tested as objective predictors.[3–15] Review of current literature shows that somatosensory-evoked potentials (SEPs) may be predictive of ominous outcomes,[3–8] but they are not useful for prognosticating favorable outcomes.[4,6–8] On the other hand, cognitive event-related potentials (ERPs) may have theoretical implications in predicting good functional recovery.[9–15] However, the practicality of ERPs has been hampered by technical limitations,[14,15] and most previous studies have focused on a single evoked-potential paradigm for outcome prediction.[3,4,6,10–15] We propose to prospectively evaluate the predictability of both median nerve SEPs and speech-evoked ERPs recorded during the early course of hospitalization.

Generally, SEPs with peripheral nerve stimulation have the highest reliability in predicting poor prognosis.[4,6–8] SEPs can be readily recorded over the scalp in neurologically normal patients, even under general anesthesia. They reflect conduction through the peripheral nervous system, dorsal column of the spinal cord, lemniscal pathways in the brainstem, with eventual arrival at the cerebral somatosensory cortex. Bilateral absence of cortical responses is typically associated with death or persistent vegetative state.[4,6] However, the presence of a normal SEP does not correlate well with awakening or favorable functional outcome.[6,7]

The auditory ERP is a cognitive potential recorded over the scalp.[10,16] Traditionally, tone-evoked ERPs have been used to predict awakening in patients with severe brain injury.[10] However, because some normal people have very small tone-evoked P300 responses,[12,17] researchers have been experimenting with different auditory stimuli to generate more robust ERPs.[13–15] Our previous study comparing tone-evoked *vs.* speech-evoked ERPs showed significantly larger amplitudes in the latter condition.[14] Because of its innate involvement with cognitive processing, speech-evoked ERPs seemed promising in predicting good outcomes for patients with brain injury.

The purpose of this article is to define the usefulness of median nerve SEPs and speech-evoked ERPs in predicting functional outcomes of patients with severe TBI. For this purpose, we studied association between results of SEP and ERP testing with follow-up functional outcome data and sensitivity, specificity, and predictive values of each testing, either single or combined, for prognosticating functional outcome. The goal of this project is to provide preliminary data for more extensive studies, which may eventually assist family members and clinicians in making objective and reasonable decisions on planning critical management and provision of acute rehabilitative intervention.

SUBJECTS AND METHODS

Methods

Electrophysiologic data (median nerve SEP and speech-evoked ERP) were collected within 8 days after onset of TBI. Information on Glasgow Coma Scale (GCS) was also collected. Functional outcomes, as determined by Glasgow Outcome Scale–Extended (GOSE),[18,19] were obtained at 1, 3, and 6 mo after TBI.

Subjects

Inclusion Criteria. Subjects with acute and severe TBI (initial GCS score of 8 or less after resuscitation) were entered into the study. Age range of the subjects was between 17 and 70 yr. We set the age limits because previous literature showed that very young and very old patients with severe brain injury tend to have different outcomes when compared with the rest of the TBI population.[20] Both men and women were recruited in the study.

Exclusion Criteria. Subjects were excluded if they had a positive history of preexisting neurologic disorder, median neuropathy, hearing loss, de-

Objectives: On completion of this article, the reader should be able to (1) recognize the relative predictive abilities of somatosensory-evoked potentials and cognitive event-related potentials in patients with severe traumatic brain injury and to (2) identify the different scales used in evaluating functional outcome in patients with traumatic brain injury.

Level: Advanced.

Accreditation: The Association of Academic Physiatrists is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

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Disclosure: Disclosure statements have been obtained regarding the authors' relationships with financial supporters of this activity. There is no apparent conflict of interests related to the context of participation of the authors of this article.

mentia, psychiatric disorder, concurrent spinal cord injury, and current use of barbiturates or dopamine agonists or antagonists because of the potential influence of the above factors on the morphology of the electrophysiologic waveforms.[21,22] History regarding preexisting neurologic disorder, hearing loss, dementia, or psychiatric disorder was obtained from interviewing family members and reviewing medical records. Presence of concurrent spinal cord injury or barbiturate use was determined by reviewing the subject's current medical record. Subjects with median neuropathy (including carpal tunnel syndrome) were excluded by reviewing medical records, although the idealistic approach is to perform median nerve conduction study in both wrists. We confirmed the integrity of bilateral median nerve and peripheral conduction by identifying normal cervical SEP responses (C7 spine-Fz).

Institutional Review Board Status. The protocol was approved by the Medical Center's Human Subject Review Committee, and informed consent was obtained from each subject's family before the electrophysiologic testing.

Data Collection

Demographic Data. Demographic data were obtained from electronic medical records.

Clinical Information. The cause of brain injury, GCS scores (initial and at the time of electrophysiologic testing), current medications, medical and surgical history, and computer tomographic or magnetic resonance imaging findings were obtained from the medical charts.

Electrophysiologic Testing. SEPs with median nerve stimulation were performed within 8 days after onset of TBI. Stimulation was delivered to left and right wrists separately via bipolar electrode at 0.2 msec duration, with intensity of 1.5 times the motor twitch. SEPs were recorded at the scalp with a Nicolet Viking electrodiagnostic instrument (Nicolet Biomedical, Madison, WI) using sterile subdermal needle electrodes. The machine's rate of stimulation was 3.1 Hz for short latency recordings and 1.1 Hz for long latency recordings. The default filter bandpass was set at 5–3000 Hz for short-latency and 1–1000 Hz for long-latency recordings. In each patient, the following channels were recorded: C3'-Fz, C4'-Fz, C3'-C4', C3'/C4'-mastoid, Fz-mastoid, C7 spine-Fz, C7 spine-anterior neck, and upper arm referred to the shoulder. The default sweep time was 50 msec for short-latency and 200 msec for the long-latency recordings. Two sets of responses with an average of 500 sweeps were recorded. To ensure integrity of the nervous system up to the subcortical level, cervical responses (C7 spine-Fz) had to be present before we began evaluating the cortical responses. The amplitudes and latencies of cortical responses N1, P1, N3, and P3 were recorded for later analysis.

Speech-evoked ERP testing was also performed within 8 days after onset of TBI. The Cadwell Excel electrodiagnostic instrument (Cadwell Laboratories, Kennewick, WA), connected to a speech-generator box, was used for stimulus delivery and response recording. The frequent/common stimulus (80%) was a 1000-Hz tone, and the target/rare stimulus (20%) was the word "mommy," in a female voice. The common and rare stimuli were randomized so that there was no predictable sequence during testing. The auditory stimuli were presented through a binaural headphone at a level of 70 dB sound pressure level. The rate of presentation was one per 1.83 sec (0.55 Hz).

The passive ERP testing technique[10,15,16] was used. There were a total of 200 stimuli (160 common, 40 rare) for each test session. A total of four gold-cup surface electrodes were placed on each patient: active electrode at Cz, ground electrode over the forehead, and one reference electrode on each mastoid (linked reference). The patients' electroencephalographic responses to common and rare events were time-locked, sorted, averaged separately, and displayed on the screen. For better resolution, a 500-msec epoch was used. In cases in which the N100 or P300 could not be identified, or if the waveform extended beyond the oscilloscope, the 1000-msec epoch was then used. A bandpass filter of 12-dB/octave skirt was used, with low and high frequencies set at 0.16 Hz and 120 Hz, respectively. Amplitudes and latencies of the ERPs were determined by trough-to-peak method, using the built-in cursors of the Cadwell evoked-potential instrument.

Waveform Interpretation. The electrophysiologic testing involved both the median nerve SEP and speech-evoked ERP, which were performed within 24 hr of each other. In each case, the tester who performed the SEP (P. Mickelsen [see "ACKNOWLEDGMENTS"]) did not discuss the results with the person who performed the ERP testing (H. L. Lew). Two sets of waveforms were obtained during each recording, so as to ascertain reproducibility. The SEP and ERP waveforms were interpreted by authors L. R. Robinson and J. Slimp, respectively. The waveform interpreters were blinded to the clinical status of each patient. SEP results were categorized as follows: (A) normal (bilateral normal responses), (B) present but abnormal (The waveform could be either bilaterally present but abnormal, unilaterally normal, or unilaterally present but abnormal. Abnormal amplitude or latency was defined as >2 SD from the norm.), and (C) absent (bilateral absent responses). Results from ERP testing were categorized as: (A) normal (both N100 and P300 components were consistently present and reproduc-

ible), (B) present but abnormal (N100 consistently present but P300 absent or not reproducible), or (C) absent (N100 and P300 both absent).

Functional Outcome Measures. GOSE[18,19] was used as the functional outcome measure for this study. Traditionally, neurosurgeons have used Glasgow Outcome Scale (GOS)[23] as a quantifier of clinical outcome after severe brain injury. GOS briefly defines five categories: death, persistent vegetative state, severely disabled, moderately disabled, and good recovery. Although GOS is a very straightforward way to categorize outcome, its scoring system lacks the functional details faced by individual patients.[18] On the other hand, GOSE is an extended 8-point GOS, providing additional criteria to subdivide the upper three categories of GOS. The GOSE questionnaire includes items regarding social/leisure activities, work capacity, interaction with family/friends, independence in activities of daily living, and independence in shopping and travel. Its scoring system has eight categories: dead, vegetative state (VS), lower severe disability (lower SD), upper severe disability (upper SD), lower moderate disability (lower MD), upper moderate disability (upper MD), lower good recovery (lower GR), and upper good recovery (upper GR). Although not as thorough in functional description as the Disability Rating Scale,[24] GOSE provides relevant information pertinent to the needs of this study. The research nurse (P. Nelson [see "ACKNOWLEDGMENTS"]), physician (H. Lew), and research coordinator (J. Covey [see "ACKNOWLEDGMENTS"]), who did not review the electrophysiologic results, obtained the GOSE data via chart review and telephone interview of the patients' primary care provider. The outcome data were collected at 1, 3, and 6 mo after electrophysiologic testing.

Statistical Analysis

Results of SEP and ERP were compared with the GCS and GOSE scores. Kruskal-Wallis test was performed to determine statistical relationship between electrophysiologic results, GCS scores, and GOSE scores at 1, 3, and 6 mo after TBI. The level of significance was defined as $P < 0.05$. Functional outcomes were categorized as worst (GOSE 1 or 2), unfavorable (GOSE 1–4), favorable (GOSE 5–8), and best (GOSE 7 or 8). Sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

RESULTS

A total of 22 patients (8 women, 14 men) were tested. Their mean age was 35.6 ± 14.9 yr, and the average initial GCS score was 3.8 (range, 3–7). SEP and ERP tests were performed within 8 days after TBI (mean, 3.4 days after TBI), and 20 of 22 patients had a GCS score of 8 or less at the time of testing. Two subjects (patients h and i), who were tested at 5 and 8 days after TBI, respectively, showed a GCS score of 11 at the time of testing (their initial GCS scores were 7 and 3). They were still in the ICU for medical management, and their electrophysiologic results were both SEP (A) and ERP (B).

Table 1 shows the distribution of SEP and ERP results and their corresponding GCS scores. SEP responses were normal (A) in nine patients, present but abnormal (B) in eight patients, and absent (C) in five patients. ERP results showed normal response (A) in seven patients, present but abnormal (B) in five patients, and absent (C) in ten patients. It is apparent that the initial GCS scores were similar in all groups and had no significant correlation with either SEP or ERP results. On the other hand, GCS at the time of testing (test GCS) was correlated with SEP results but not with ERP results. Absent SEP (C) was associated with the lowest GCS at the time of testing ($P < 0.05$). However, test GCS had no statistical correlation with ERP results. Neither initial GCS nor test GCS was predictive of functional recovery.

Table 2 illustrates the functional outcomes (as determined by averaged GOSE scores) at 1, 3, and 6 mo after TBI. The upper half of the table shows that patients with SEP category C had significantly lower ($P < 0.005$) GOSE scores when compared with those with SEP category A or B. It should be noted that although SEP category C was correlated with poor prognosis, category A was not always associated with better prognosis than category B. In other words, there was no consistent incremental tendency in GOSE score from category C to B to A.

The results according to speech-evoked ERP showed a different pattern. This is demonstrated in the lower half of Table 2. At the 1-mo follow-up, patients with ERP category A had significantly better outcome than those with ERP category C ($P < 0.05$). At the 3 and 6 mo follow-ups, the difference was significant ($P < 0.005$). Interestingly, both ERP categories A and B were associated with better prognosis at 3 and 6 mo follow-ups when compared with category C. In contrast to SEP results, the pattern of functional improvement with time was more consistent with ERP results.

All 22 patients' SEP/ERP results and their corresponding follow-up GOSE data are illustrated in Table 3. Individual GOSE scores at 1, 3, and 6 mo after TBI are presented in a format to match with the corresponding electrophysiologic results. In the right lower corner, it is obvious that patients with absent SEP were either dead or remained in a persistent vegetative state at 1 mo after TBI and were all dead at 3 mo after TBI. Patients with normal or borderline SEP

TABLE 1
Electrophysiologic results and their corresponding Glasgow Coma Scale(GCS) scores

Electrophysiologic Testing Results	GCS (Mean ± SE) Initial	Test
SEP		
Bilateral normal responses (n = 9)	4.0 ± 0.5	6.7 ± 0.9
Present but abnormal (n = 8)	3.9 ± 0.4	6.1 ± 0.5
Bilaterally absent (n = 5)	3.2 ± 0.2	4.0[a] ± 0.5
ERP		
Normal (n = 7)	4.1 ± 0.6	5.9 ± 0.5
Present but abnormal (n = 5)	3.8 ± 0.8	7.8 ± 1.5
Absent (n = 10)	3.5 ± 0.3	4.9 ± 0.5

SEP, somatosensory evoked potentials; ERP, event-related potentials.
[a]Significantly smaller than the other two GCS scores immediately above it ($P < 0.05$).

(Table 3, patients a–g) had variable outcomes, with GOSE scores ranging from 3 to 5 at 3 mo and 2 to 7 at 6 mo.

On the other hand, patients with normal or borderline ERPs (middle and left vertical columns of Table 3) seemed to have more favorable outcomes, especially at 3 and 6 mo after TBI. The two exceptions in the category of bilateral normal responses were patients c and d, who suffered from brain abscess and pneumonia, respectively, at about 3 mo after TBI. The last column on the right depicts that patients with absent ERP showed little or no improvement at 3 and 6 mo follow-ups.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of various combinations of electrophysiologic testing were calculated and are summarized in Tables 4 and 5. Due to space limitations, and because previous research demonstrated that outcome data at 1 and 3 mo were too variable and thus premature to conjecture,[25] only follow-up data at 6 months were analyzed. GOSE scores at 6 mo were further subdivided as follows; (1) worst outcome (GOSE 1 or 2), (2) unfavorable outcome (GOSE 1–4), (3) best outcome (GOSE 7 or 8), and (4) favorable outcome (GOSE 5–8).

In predicting the worst outcome (death or persistent vegetative state), the most unfortunate scenario is a false-positive test (falsely labeling someone as having ominous outcome when, in fact, her or she may improve significantly over time), which may adversely influence the decision for continued medical and rehabilitation intervention. Ideally, we would like to keep the false-positive rate to a minimum. In this case, it is desirable to have the highest possible specificity and PPV. As one can see from the upper half of Table 4, SEP (C) showed the highest specificity (100%) and PPV (100%) for the worst outcome (GOSE 1 or 2). The sensitivity of SEP (C) for the worst outcome was less than ideal (83.3%), due to the fact that patient n, whose initial SEP was normal (A), had a deterioration of GOSE (from 3 to 2). In other words, he had a false-negative test. Review of the record showed that he developed hydrocephalus, and his overall medical condition worsened from 3 to 6 mo after TBI. Interestingly, his initial ERP was absent. Although ERP (C) had the highest sensitivity (100%) and NPV (100%), its specificity and PPV were considerably lower than SEP (C). Artificially combining ERP with SEP did not enhance the predictive values of SEP. Therefore, SEP (C) was the best predictor for the worst outcome (death or persistent vegetative state).

When unfavorable outcome is defined as GOSE scores of 1–4, which included the worst outcome (GOSE 1–2), plus lower and upper severe disability (GOSE 3–4), emphasis also should be placed on specificity and PPV, for the same reason elaborated

TABLE 2
Electrophysiologic results and their corresponding Glasgow Outcome Scale-Extended (GOSE) scores

Electrophysiologic Testing Results	Follow-Up GOSE (Mean ± SE) 1 mo	3 mo	6 mo
SEP			
Bilateral normal responses (n = 9)	2.8 ± 0.2	4.0 ± 0.3	3.7 ± 0.4
Present but abnormal (n = 8)	2.9 ± 0.2	3.9 ± 0.3	5.1 ± 0.6
Bilaterally absent (n = 5)	1.2[a] ± 0.2	1.0[a] ± 0.0	1.0[a] ± 0.0
ERP			
Normal (n = 7)	3.0[b] ± 0.2	4.4 ± 0.3	5.1 ± 0.0.6
Present but abnormal (n = 5)	2.8 ± 0.2	4.2 ± 0.4	4.8 ± 0.6
Absent (n = 10)	1.9[b] ± 0.3	2.0[a] ± 0.3	1.9[a] ± 0.3

SEP, somatosensory evoked potentials; ERP, event-related potentials.
[a]Significantly smaller than the other two GOSE scores immediately above it ($P < 0.005$).
[b]Significant difference between the two labeled GOSE scores (3.0 *vs.* 1.9; $P < 0.05$).

TABLE 3
Individual Glasgow Outcome Scale-Extended (GOSE) scores at 1, 3, and 6 mo follow-up and their corresponding electrophysiologic results

	Speech-Evoked ERP		
GOSE (At 1, 3, 6 Months)	Normal	Present but Abnormal	Absent
SEP			
Bilateral normal responses	a: 3—5—5	h: 3—5—5	m: 3—3—3
	b: 3—5—5	i: 3—5—4	n: 3—3—2
	c: 3—4—3		o: 2—3—3
	d: 2—3—3		
Present but abnormal	e: 4—5—7	j: 3—4—7	p: 3—3—3
	f: 3—5—7	k: 3—4—4	q: 2—3—3
	g: 3—4—6	l: 2—3—4	
Bilaterally absent			r: 1—1—1
			s: 1—1—1
			t: 1—1—1
			u: 1—1—1
			v: 2—1—1

ERP, event-related potentials; SEP, somatosensory-evoked potentials.

in the above paragraph. The results are depicted in the lower half of Table 4. Once again, SEP (C) had 100% specificity and PPV. Interestingly, specificity and PPV for ERP (C) were equivalent with SEP (C). Although sensitivity and NPV are not as critical (when compared with specificity and PPV) in predicting unfavorable outcome, it is intriguing to note that ERP (C) had higher sensitivity (66.7% *vs.* 33.3%) and NPV (58.3% *vs.* 41.2%) than SEP (C).

When the goal shifts to predicting the best outcome (GOSE 7 or 8), our perspective for statistical analysis changes as well. In this case, we want to identify as many potential candidates for rehabilitation as possible. Therefore, the most undesirable event is to miss a patient who may actually improve significantly over time (false-negative test). Our focus is to minimize false-negative rate and to maximize sensitivity and NPV.

As one can see from the upper half of Table 5, ERP (A) had a higher sensitivity (66.7% *vs.* 0%) and NPV (93.3% *vs.* 76.9%) than SEP (A). In other words, the presence of a normal ERP was more predictive of best outcome than a normal SEP. On further inspection, when we simply include the presence of an identifiable waveform from either SEP or ERP testing (A or B), the sensitivity and NPV reached 100% for both electrophysiologic testings. When favorable outcome was defined as GOSE scores of 5–8 (moderate disability to good recovery), the sensitivity (71.4% *vs.* 42.9%) and NPV (86.7% *vs.* 69.2%) for ERP (A) were still higher than SEP (A), as shown in the lower half of Table 5. Again, if a discernible waveform could be recorded from either ERP or SEP testing (A or B), the sensitivity and NPV reached 100%. The added value of ERP here is the higher specificity (86.7% in ERP [A] *vs.* 60% in SEP [A]) and higher PPV (71.4% in ERP [A] *vs.* 33.3% in SEP [A]).

Figure 1*a* shows a normal ERP response (A) recorded from patient f. This patient's SEP was abnormal but unilaterally present (B). As one can see from Table 3, this patient showed very favorable functional outcome, with GOSE scores of 3, 5, and 7 at 1, 3, and 6 mo, respectively. Due to space limitations and the readers' rel-

TABLE 4
Sensitivity, specificity, and predictive values for the worst outcomes and unfavorable outcomes at 6 mo after traumatic brain injury

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Worst Outcome (GOSE 1–2)				
SEP (C)	83.3	100.0	100.0	94.1
ERP (C)	100.0	75.0	60.0	100.0
SEP (C) and ERP (C)	83.3	100.0	100.0	94.1
SEP (B or C)	83.3	50.0	38.5	88.9
ERP (B or C)	100.0	43.8	40.0	100.0
SEP (B or C) and ERP (B or C)	83.3	68.8	50.0	91.7
Unfavorable Outcome (GOSE 1–4)				
SSEP (C)	33.3	100.0	100.0	41.2
ERP (C)	66.7	100.0	100.0	58.3
SSEP (C) and ERP (C)	66.7	100.0	100.0	58.3
SSEP (B or C)	60.0	42.9	69.2	33.2
ERP (B or C)	86.7	71.4	86.7	71.4
SSEP (B or C) and ERP (B or C)	86.7	28.6	72.2	50.0

GOSE, Glasgow Outcome Scale-Extended; PPV, positive predictive value; NPV, negative predictive value; SEP (B), somatosensory evoked potentials present but abnormal; SEP (C), bilaterally absent; ERP (B), event-related potentials present but abnormal; ERP (C), absent.

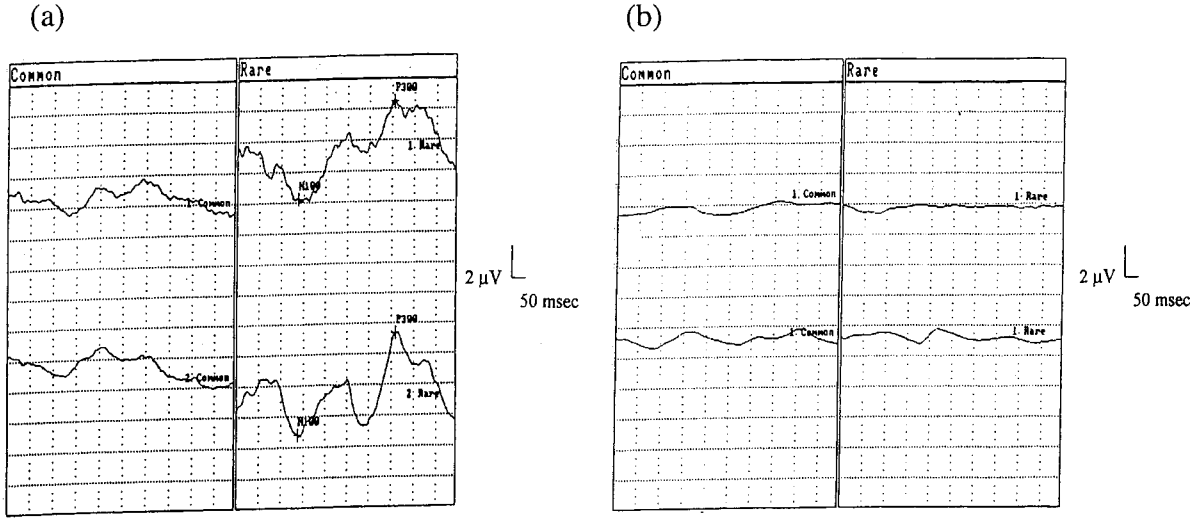

Figure 1: Two cases of speech-evoked event-related potentials of traumatic brain injury patients: (*a*) normal response (category A) and (*b*) an absent speech-evoked event-related potential (category C).

ative familiarity with SEP, the SEP waveforms were not shown. Figure 1*b* demonstrates an absent ERP waveform (C) obtained from patient t. Neither N100 nor P300 response was noticeable. His SEP was also absent bilaterally (C). Unfortunately, this patient died within 1 mo after his TBI.

DISCUSSION

In summary, our results can be divided into two parts. The first part deals with prediction of poor outcomes. Bilateral absence of cortically recorded median nerve SEP (category C) within 8 days of severe TBI was strongly predictive of the worst functional outcome ($P < 0.005$), which is death or persistent vegetative state. The specificity and PPV of SEP (C) for death or persistent vegetative state (GOSE 1–2) were as high as 100% at 6 mo after TBI. This is consistent with previous studies.[4,6–8,26] If the definition of the unfavorable outcome was expanded to include GOSE 1–4, ERP (C) was equivalent to SEP (C) in specificity and PPV.

The second portion of our analysis (predicting good outcomes) had rather mixed findings. Presence of a normal speech-evoked ERP waveform (category A) was more predictive of the best outcome (GOSE 7–8) than presence of a normal SEP (category A). Interestingly, the highest sensitivity and NPV (100%) were associated with the presence of any discernible waveform, whether it was ERP or SEP. When specificity and PPV were taken into consideration, ERP was a better predictor than SEP (Table 5). If the definition of favorable outcome was expanded to include GOSE 5–8, ERP was still superior to SEP for prognosticating good outcome.

During evaluation of individual waveforms, it has not escaped our attention that the latencies of the N100 and P300 components of the speech-evoked ERP in severe TBI patients seemed rather variable and

TABLE 5
Sensitivity, specificity, and predictive values for the best outcomes and favorable outcomes at 6 mo after traumatic brain injury

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Best outcome (GOSE 7–8)				
SEP (A)	0.0	52.6	0.0	76.9
ERP (A)	66.7	73.7	28.6	93.3
SEP (A) and ERP (A)	0.0	78.9	0.0	83.3
SEP (A or B)	100.0	26.3	17.6	100.0
ERP (A or B)	100.0	52.6	25.0	100.0
SEP (A or B) and ERP (A or B)	100.0	52.6	25.0	100.0
Favorable outcome (GOSE 5–8)				
SSEP (A)	42.9	60.0	33.3	69.2
ERP (A)	71.4	86.7	71.4	86.7
SSEP (A) and ERP (A)	28.6	86.7	50.0	72.2
SSEP (A or B)	100.0	33.3	41.2	100.0
ERP (A or B)	100.0	66.7	58.3	100.0
SSEP (A or B) and ERP (A or B)	100.0	66.7	58.3	100.0

GOSE, Glasgow Outcome Scale-Extended; PPV, positive predictive value; NPV, negative predictive value; SEP (A), somatosensory evoked potential bilateral normal responses; SEP (B), present but abnormal; ERP (A), normal event-related potentials; ERP (B), present but abnormal.

longer than normal individuals. For those who showed reproducible ERP results, latency/amplitude for N100 and P300 responses were 183.0 ± 20.8 msec/2.20 ± 0.81 μV and 499.6 ± 45.4 msec/3.83 ± 1.21 μV, respectively (mean ± standard error). This trend is consistent with the recently published data by Mazzini et al.[13] Kane et al.[9] also pointed out that latency and amplitude measurements of ERPs are unreliable indicators for outcome prediction, but the mere presence of ERP waveforms can predict a return of consciousness. For this reason, we chose not to elaborate on the absolute latency and amplitude measurements of individual ERP waveforms. Rather, we took a conglomerate approach, by dividing the waveforms into three separated categories (A, B, and C), as described above (see "METHODS").

The P300 component of the ERP has long been considered as an index of active cognitive processing.[14,27–29] Thus, its applications for outcome prediction in TBI have been investigated by various researchers.[9–15] The presence of an intact ERP waveform depends on both technical competence of the tester and the integrity of complex cortical/subcortical neural circuits.[30] Based on our experience and recent data published by other researchers,[13,14] we were not surprised to find that the P300 component (ERP category A) was associated with good clinical outcomes. However, we were slightly intrigued to find that the N100 component (category B) was also associated with favorable outcome. Traditionally, the N100 response was thought to be associated with passive perception of incoming sound.[28] However, there is also evidence to suggest its involvement with alertness and stimulus processing.[29] It is possible that both the N100 and P300 components are associated with active information processing.[13,14,27]

During the early hospitalization course, GCS alone has been useful but not consistently reliable as a predictor of clinical outcome in patients with TBI.[3,31,32] Our results are in general agreement with the above researchers. A more intriguing finding lies in the electrophysiologic studies. Although SEP continues to make reliable predictions of poor outcome, the addition of ERP testing may be useful in prognosticating favorable outcomes. The combination of SEP and ERP seems to be complementary in such a way that the strength of one test compensates for the weakness of the other.

In this specific study, we used the word "mommy" as the speech target. Clinically, while testing severe TBI patients in the intensive care unit, we were frequently asked by family members to record their voices and use the patient's first name or nickname as the speech target. From a theoretical standpoint, a person's own name supposedly carries more semantic content and, thus, would generate a more robust ERP response. By comparing three different speech targets (subject's own name, the word "mommy", and a meaningless speech sound), we have recently demonstrated that the subject's name was a viable target for eliciting cognitive ERP.[15] In future studies on patients with severe TBI, it may be better to use the patient's own name as vocalized by the closest family member.

Considering the small number of patients enrolled for this study, we were careful not to overgeneralize the results. Further studies with larger sample size are needed to understand the cognitive process of severe TBI patients during different stages of their recovery period, to differentiate cognitive *vs.* motor deficits, and to prognosticate their long-term functional outcome. It will be theoretically appealing to use ERPs with systematically chosen stimuli to understand residual cognitive processing and to determine whether the early electrophysiologic responses could be correlated with later cognitive deficits as the patients recover from TBI.

The clinical applications of ERPs can be extended to patients with moderate or even mild TBI. We plan to customize auditory and visual stimuli to correlate with neuropsychologic testing materials so as to gather electrophysiologic information regarding the brain's response to multimodality stimuli with various degrees of cognitive demand. Moreover, we are correlating our ERP results with functional magnetic resonance imaging findings. It is hoped that the ongoing series of projects on outcome predictions for TBI may eventually contribute to the decision-making process for family members and physicians regarding controversies in acute rehabilitative intervention *vs.* quality-of-life issues in the long term.

ACKNOWLEDGMENTS

We thank Pamela Nelson for assistance in recruiting the patients, Paula Mickelsen for assistance with SEP testing, Jennie Covey for obtaining the GOSE data, and Dr. John Whyte and Dr. Maurice Rappaport for advice and guidance.

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