Prognostic Determination in Anoxic-Ischemic and Traumatic Encephalopathies

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Abstract: Clinical assessment of the unresponsive patient is limited to examination of brainstem reflexes and simple motor responses to stimulation. It is thus difficult, especially if brainstem functions are intact, to give early, accurate prognostic information on comatose patients. Neurochemical tests and imaging have not been validated and have significant limitations. Electrophysiologic investigations provide a window into cerebral function and are tested, clinically useful, safe, available, and inexpensive. Persistent abnormalities of brainstem auditory evoked potentials and short-latency somatosensory evoked potentials reliably indicate the likelihood permanent vegetative state or death. Conversely, the presence of "cognitive" event-related brain potentials (e.g., P300 and mismatch negativity) reflects the functional integrity of higher-level information processing and, therefore, the likelihood of capacity for cognition. A combined clinical and electrophysiologic approach provides optimal prediction of outcome and level of disability.

Key Words: Anoxic-ischemic encephalopathy, Coma, Outcome, Prognosis, Trauma, Electrophysiological tests, Electroencephalography, Short-latency evoked potentials, Brainstem auditory evoked potentials, Short-latency somatosensory evoked potentials, Middle-latency auditory evoked potentials, Event-related brain potentials, P300, Mismatch negativity.

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Intensivists frequently request neurologic prognostic determination for comatose patients, most appropriately for conditions capable of causing neuronal death or severe, permanent brain dysfunction. Anoxic-ischemic encephalopathy (AIE) after cardiac arrest and traumatic brain injury (TBI) represent the most common etiologies. In current practice, prognostic decisions rest principally on clinical observations (Chiappa and Hill, 1998). However, these lack early specificity for an outcome no better than (permanent) vegetative state or death. The firm prediction of lack of recovery of the capacity for conscious awareness often results in withdrawal of high-level intensive care unit support. Other levels of survival, with preserved consciousness, are more difficult for management decisions. Conversely, the predictive values of tests for *favorable* outcomes should be considered in a prognostic battery.

In this discussion, unfavorable outcomes for AIE and TBI are discussed separately. Although the same clinical and other tests have been applied in both conditions, the results differ in their predictive values for different etiologies (Logi et al., 2003). This probably relates to marked differences in the pathophysiology and neuropathology in pure cases of these entities: anoxia-ischemia affects primarily gray matter structures in the brain, whereas trauma typically causes diffuse axonal injury. Finally, tests that use event-related potentials (ERPs) for predicting *favorable* outcomes are discussed together.

ANOXIC-ISCHEMIC ENCEPHALOPATHY

A number of clinical algorithms have been developed, beginning with that of Levy et al. (1985). Most, unfortunately, do not use vegetative state or death without recovery of consciousness as the ultimate end-points. They rely on the premise that severe brainstem dysfunction reflects even greater damage to rostral structures, which are usually more vulnerable to ischemic injury. Certainly coma lasting more than 3 days carries a greater than 90% risk of poor outcome (Levy et al., 1985). Independent existence did not occur with absence of pupillary light reflex at the time of initial evaluation; only 1 of 93 patients with decorticate or decerebrate responses at 24 hours recovered. Edgren et al. (1994) found absence of motor response at 3 days to be the best predictor of poor outcome. However, false prediction of poor recovery occurred in 5% to 10% in various clinical series, based on findings on admission and up to 3 days afterward (Bates 1991; Hamel et al., 1995; Longstreth et al., 1983).

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The Glasgow Coma Scale (GCS) is the most widely used formalized clinical assessment in intensive care units (Bates 1991). The GCS is based on the separate assessments of verbal, motor, and eye-opening responses of patients, which are then summed up for an overall measure. Mullie et al. (1988) applied the GCS at 2 days in 216 patients resuscitated from cardiac arrest. The sensitivity of the highest GCS score was 96% and the specificity was 86%, whereas the positive and negative predictive values were 97% and 77%, respectively. Thus, although the GCS is likely helpful, it is not sufficiently distinctive to support end-of-life decisions solely on its basis. Inherent problems with the GCS include the level of interrater reliability in scoring patients (Rowley and Fielding, 1991). Disagreements are exacerbated by pseudoscoring, i.e., giving an estimated score for an untestable response to avoid exclusions (Jorgenson and Holm, 1998). The GCS is insensitive in separating both adults and children with reversible coma from those without (Butinar and Gostisa, 1996; Goodwin et al., 1991).

In combination with clinical examination or used alone, neuroimaging scans (computed tomography, MRI), and serum and CSF chemical markers (neuron-specific enolase, S-100 glial protein, lactate dehydrogenase, glutamate oxaloacetate and the brain-specific isoenzyme for creatine kinase, CKBB) have also been studied as potential prognostic indicators in AIE (Arbelaezet al, 1999; Edgren et al., 1983; Wijdicks et al., 2001; Zandbergen et al., 2001). With the same type of shortcoming as clinical observations, all of these measurements produce values that overlap considerably between favorable and unfavorable outcomes, and are thus too insensitive to allow early intervention. Sample sizes have been too small and the study design flaws too serious for these to be definitive studies. Some of these testing modalities hold promise, either on their own or combined with other variables, including clinical and electrophysiologic, but more work is needed to assess these tests and recent observations of thyroid hormone correlations with outcome (Longstreth et al., 1996).

The above indicates that prediction of coma outcome is complex and difficult, demanding considerable experience, effort, and skill—qualities that are not generalizable. Electrophysiologic tests as prognostic tools have a number of advantages over clinical and biochemical tests, including correlation with clinical symptomatology, safety, ease of acquisition, and cost-effectiveness. They provide an objective, standardized, and noninvasive means of directly assessing brain activity.

EEG in Anoxic-Ischemic Encephalopathy

Hypothetically, EEG should be a suitable test for determining cortical function and prognosis (Young, 2000). The most sensitive neurons to anoxic-ischemic insult are the same large neocortical cells responsible for generating the scalp EEG signal. The EEG becomes isoelectric during circulatory arrest; this can persist for several hours after restoration of circulation (Jorgenson and Holm, 1998). Thus, one should wait for at least several hours before performing an EEG. Delayed neuronal death produces suppression that can occur 3 to 5 days later (Kinoro, 1982). Thus, it is often necessary to repeat EEGs over several days. Sedative drugs commonly confound the EEG: midazolam and propofol can suppress the EEG to a completely reversible burst-suppression pattern (Young, 2000). Suppression or burst-suppression may occur in severe, reversible septic encephalopathy (Young et al., 1992). Studies of EEG in comatose anoxic-ischemic encephalopathy lack numbers and precision: the threshold for suppression is often not defined, or the timing of the EEGs from the time of the arrest is unavailable (Young, 2000). There is certainly a correlation of poor outcome with the following patterns when "lumped" together: suppression, burst-suppression, alpha-theta pattern coma, and generalized periodic patterns (Young and Doig, in press). Some patterns, such as suppression of $<10\mu$V, a burst-suppression pattern with epileptiform activity within the bursts, are more specific for outcome no better than vegetative state, but series are small (Binnie and Prior, 1994; Prior, 1973; Young, 2000; Young et al., in press). Clearly, EEG has many obstacles (e.g., sedation and sepsis) and variability that require larger, more carefully performed studies with either serial or continuous EEG over several days before it can be established as a suitable prognostic tool for comatose survivors of cardiac arrest.

Not surprisingly, favorable EEGs with reactive, variable, and continuous wave forms are correlated with favorable outcomes (Young et al., in press).

Short-Latency Evoked Responses

Among neurophysiologic tests, measurement of short-latency evoked potentials is the most useful in the evaluation of specific sensory pathways traversing the central nervous system. An advantage of evoked potentials over clinical evaluations is that the former are not influenced by intensive care interventions, are relatively resistant to sedative and barbiturate drugs, and are very resistant to changes due to anything other than structural pathology (Chiappa 1997).

Somatosensory Evoked Responses

Somatosensory evoked potentials (SEP) are recorded in response to transient electrical stimulation of peripheral sensory nerves. Short-latency somatosensory evoked potentials (SSEP) refers to the primary response from the somatosensory cortex (S1). As illustrated in Fig. 1, the peripheral nerve most often stimulated is the median nerve at the wrist. The traditional recording sites are either C3′ or C4′ (2 cm behind the 10–20 system C3/C4 locations) with Fpz as the reference, along with the Erb's point (Chiappa 1997).

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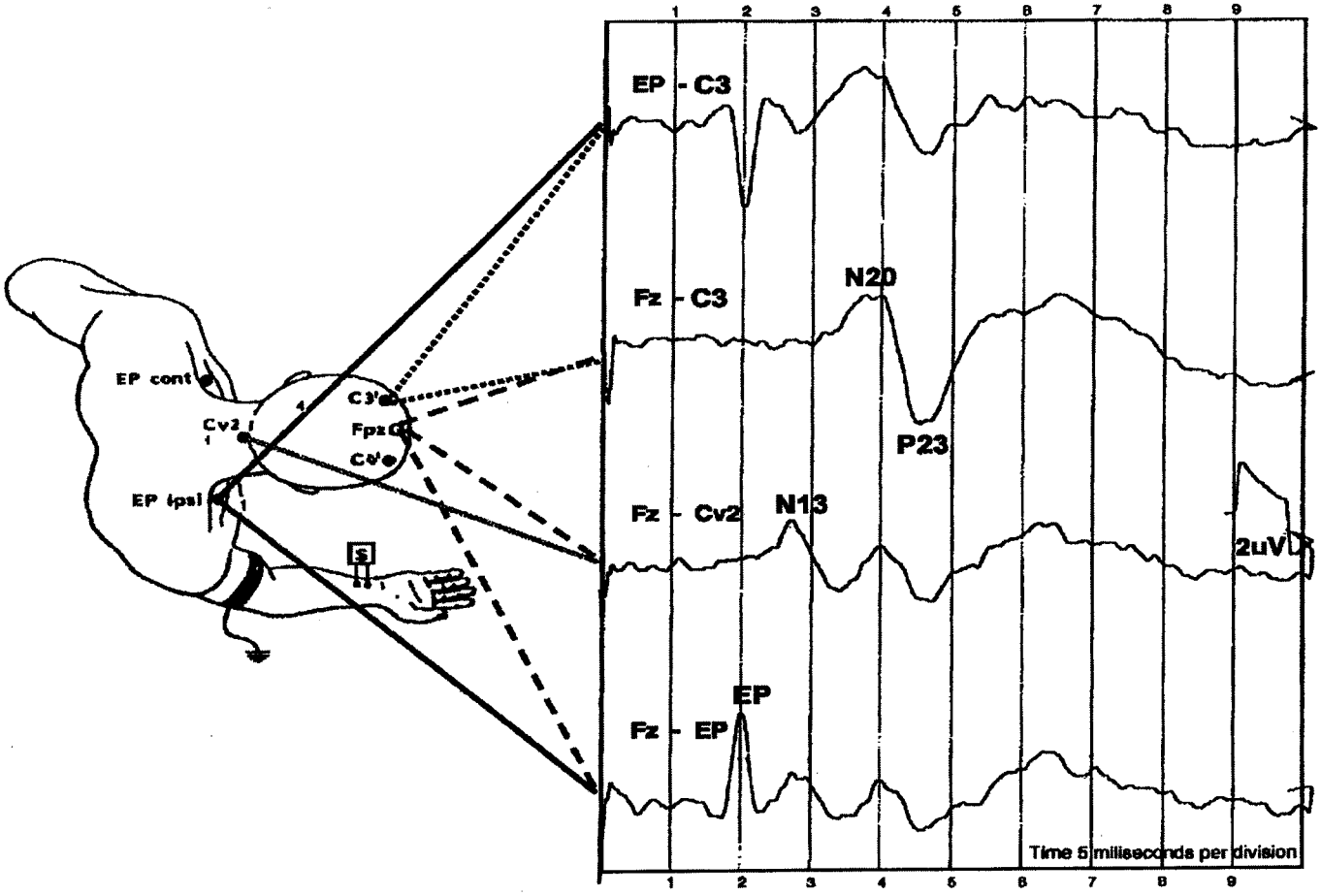


FIGURE 1. Normal SSEP waveforms in response to the stimulation on the median nerve at the right wrist. The technique used in recording SSEP is illustrated in the left side column. In the right side column, the top line displays the waveform recorded at the C3 and referred at the ipsilateral Erb's point (*EP*). The other three lines depict the waveforms recorded, respectively, at C3, Cv2 (neck), and EP that were referred to the frontal midline (*Fz*). Of note, N13 has also been labeled as P/N13 when recorded at the Fz-Cv2 channel. (Adapted from Rothstein et al. J Clin Neurophysiol 2000;17:489, with permission.)

Several studies demonstrated a correlation between SSEP and coma outcome. A significant correlation between the central conduction time of SSEP after median nerve stimulation and coma outcome has been repeatedly confirmed (Brunko and Zegers De Beyl, 1987; Walser et al., 1985). The absence of bilateral primary cortical responses (BLCR) of median SSEP was first reported by Goldie et al. (1981) as an accurate prognosticator of death or survival in a vegetative state. Subsequently, numerous studies have substantiated the role of the absent BLCR in predicting poor outcome of coma. It has been reported repeatedly that abolition of BLCR has 100% prognostic specificity for nonawakening in comatose patients secondary to AIE (Berek et al., 1995; Brunko and Zegers De Beyl, 1987; Logi et al., 2003; Madl et al., 2000; Rothstein et al., 1991; Sherman et al., 2000; Zandbergen et al., 1998). Table 1 summarizes the experience with SSEPs in postcardiac arrest coma.

TABLE 1. SSEPs in AIE: Absent N20 Response

Series	Day	Proportion With Sign	Proportion Recovering
Brunko and Zegers De Byl, 1987	<8 h	30/50	0/30
Rothstein, 2000	<2 h	19/40	0/19
Madl et al., 2000	<2 h	22/66	0/22
Chen et al., 2000	1–3	12/34	0/12
Total	< 3	83/190	0/83

There are isolated reports of exceptional patients with favorable outcomes with absent N20 responses. Pohlmann-Eden et al. (1997), Schwarz et al. (1999), and Wohlrab et al. (2001) identified comatose children with absent BLCR who

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achieved good recovery. These cases suggest that the absence of BLCR does not always indicate widespread, irreversible loss of neuronal function with structural lesions. It is generally accepted that, although recovery from states characterized by an absence of the BLCR is rare, there are dangers associated with reliance solely on the BLCR finding or without regard to the timing of SSEP recordings. Although early prediction with SSEP is possible, it is probably best to wait until day 3 before final decisions are made.

Although the persistent absence of BLCR in serial SEP recordings augurs for an outcome no better than vegetative state, the presence of the BLCR with normal amplitudes and latencies does not indicate favorable outcome, especially for anoxic ischemic coma. About half the patients with AIE in the latter category do not regain conscious awareness (Logi et al., 2003). Assurance of reliable recordings is essential. Testing should be repeated in at least two trials on each side. It is also recommended that recordings be taken from Erb's point (over the brachial plexus) and high cervical region to assure that potentials (e.g., N9 and N14) along the sensory pathway are present.

Brain Stem Auditory Evoked Potentials

Brainstem auditory evoked potentials (BAEPs) are neural responses occurring within 10 milliseconds of auditory click stimulus onset. BAEPs consist of six or seven positive and negative peaks (Sherg and Von Cramon, 1985) (Fig. 2). Wave I is a negative wave generated in the segment of the eighth nerve close to the cochlea. Wave III may be generated mainly by the ipsilateral cochlear nucleus, with the possible contribution of the superior olivary complex on the ipsilateral side. Wave V is thought to be generated in the upper pons or inferior colliculus. The generators of wave VI and VII are argued to be located, respectively, within the midbrain (or even in the diencephalon) and thalamocortical regions (Scherg and Von Cramon, 1985).

Because BAEP wave amplitudes show marked variation, their presence or absence is usually used to predict the outcome of comatose patients. Most comatose patients with no discernible BAEP waves, an absence of waves III to V, or an absence of waves IV and V[81] died or were left in an irreversible vegetative state (Balogh et al., 2001). It is evident that the prognostic determinant in coma arising from anoxia is mainly *cortical* function; this makes BAEP testing less sensitive for prognostic determination in this condition.

Transcranial Motor Evoked Responses

Motor evoked potentials, first recorded by Merton and Morton (1980), provide a noninvasive method of recording electromyographic responses (e.g., the muscle twitch recorded peripherally) evoked by transcranial electrical or magnetoelectric stimulation of the motor cortex through intact skull (Merton and Morton, 1980). Since then, they have been used in a wide range of neurologic disorders, including coma, for assessment of the functional status of descending motor pathways (Firsching et al., 1991; Kaneko 1995; Rohde and Zentner, 1991). However, the coma literature shows inconclusive results regarding their prognostic significance (Ying et al., 1992; Zentner and Rohde, 1992). Further investigations are therefore required to determine what contributory role motor evoked potentials will play.

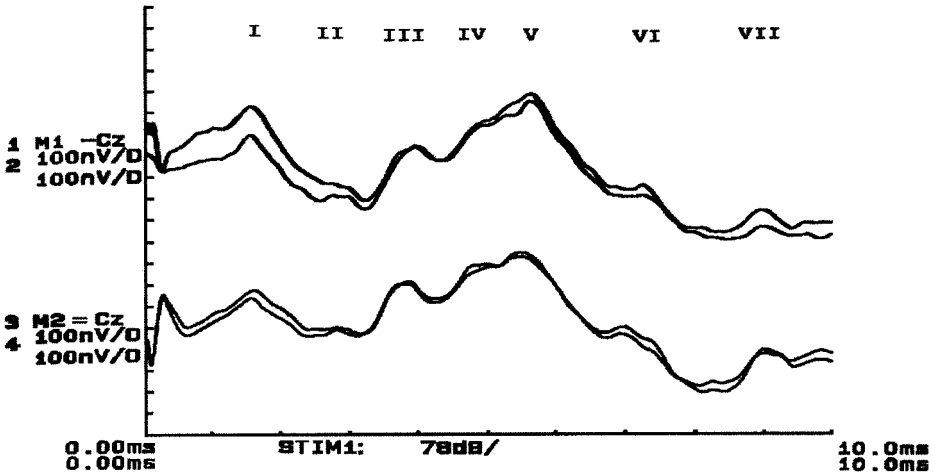


FIGURE 2. Normal BAEP waveforms elicited by monaurally presented click sounds with contralateral sound masking. The sound stimulation was set at 78 dB normal hearing level while the sound masking was at 60 dB normal hearing level. The stimulation frequency was set at 10 Hz. Waveforms were recorded at the mastoids (*M1, M2*) referred to the vertex (*Cz*). The upper two superimposed lines were the BAEP waveforms evoked by left ear stimulation and ipsilateral recording, whereas the bottom two lines represent right ear stimulation. (Adapted from Hu et al. Neurology 1997;48:1448, with permission.)

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Hypothermia

Since the advent of hypothermic therapy for patients with postcardiac arrest coma, clinical and electrophysiologic prognostic guidelines need to be revalidated (Bernard et al., 2002; The Hypothermia for Cardiac Arrest Study Group, 2002). A preliminary retrospective study suggests that clinical predictors are still valid, but these and electrophysiologic indicators need to be tested in a larger, prospective series (Young et al., 2004).

TRAUMATIC BRAIN INJURY

Using the GCS alone, 3 of 11 patients with epidural hematomas and GCS scores of 3 to 5 still had good outcomes (Ono et al., 2001). In the acute stage of coma, the GCS system is too insensitive to be of great utility in predicting death or good recovery in traumatic coma for the same reasons discussed earlier for AIE (Jennett et al., 1979). In addition, a number of confounders can invalidate rating: hearing can be affected selectively; motor response can be affected by spinal cord injury; verbal response is compromised by the presence of the endotracheal tube, mouth, or facial injuries; or the eyes may be swollen shut. The combination of the GCS with computed tomography findings considerably improved predictive values (Ono et al., 2001).

As with AIE, biochemical tests have been applied to victims of TBI without conclusive results, but further clinical research is needed (Al-Samsam et al., 2000; Ingebrigsten and Romner, 2002; Kochanek et al., 2000). Issues may be more complex with TBI, in which other organ injuries may confound results.

EEG in Traumatic Brain Injury

EEG has very limited prognostic usefulness for traumatic coma, possibly because the brunt of the damage is acute axonal injury, affecting the subcortical white matter and sparing (relatively) the EEG-generating neocortex (Young, 2000). Many metabolic conditions affect brain function in reversible fashion (Young, 2000). In our series of patients with acute structural brain lesions (mostly TBI), nearly 20% had nonconvulsive status epilepticus (Young and Doig, in press). If one accepts that such seizures, especially those of longer duration, contribute to mortality and morbidity, continuous EEG monitoring for at least 48 hours appears to be justified (Claassen et al., 2004; Young et al., 1996). Preliminary work from Vespa et al. (1999) indicates that continuous EEG monitoring in head injuries leads to enhanced outcomes, prevention of secondary insults and reduced intensive care unit length of stay.

Short-Latency Somatosensory Evoked Potentials

Studies on cerebrovascular and posttraumatic coma demonstrated a specificity of 87% to 99% for BLCR in predicting poor outcome (Lindsay et al., 1990; Logi et al., 2003; Pohlmann-Eden et al., 1997; Sleigh et al., 1999. Schwarz et al. (1999) described four adult comatose patients (three of whom had herniation syndromes, specifically stroke, head injury with subdural hematoma, and encephalitis, whereas the fourth had carbamazepine toxicity) who showed an absence of the BLCR yet experienced a good outcome.

Care should also be exercised when the traditional measure of SSEP is used in clinical practice. The standard SSEP is recorded from the scalp over parietal regions (at C3′ or C4′) with reference on Fz or Fpz, which mostly reflects the function of the thalamoparietal network. However, traditional SSEP recordings may not capture another somatosensory pathway connecting from the thalamus to the frontal cortex (Gutling et al., 1993). This observation is of particular importance for accurate prognosis. Patients in coma from TBI often have frontolimbic lesions, due to more severe damage to the thalamofrontal loop than the thalamoparietal loop (Gutling et al., 1993). Gutling et al. (1993) found a poor association between the absence of frontal (P20/22) and the loss of parietal (N20) components of SSEPs in 18 out of 40 surviving patients. Thus, traditional SSEP may not adequately represent the functional state of all somatosensory connections between the thalamus and the cerebral cortex, suggesting that combined use of frontal and parietal components of the SSEP has the potential to improve the accuracy in prognostication of coma outcome. Table 2 summarizes experience with SSEPs in TBI. The issue, as mentioned earlier, is more complex with TBI than with AIE, but overall the positive predictive value is not quite as high as with AIE.

Brainstem Auditory Evoked Potentials

Several studies have shown that after trauma, the absence of all BAEP waves beyond wave I is associated with an outcome no better than vegetative state (Seales et al., 1979; Tsubokawa et al., 1980). The measurement of interpeak latencies (I-III, III-V, I-V) and amplitude ratios (I/V) has been used as a criterion of abnormality for clinical interpretations. A significantly prolonged wave III-V interpeak latencies (central conduction time) in comatose patients from traumatic head injury (Lindsay et al., 1990; Facco et al., 1985), stroke (Haupt et al., 1995), and from other different origins (e.g., subarachnoid or hypertensive hemorrhage) is highly correlated with irreversible dysfunction. Although there is controversy about the prognostic value of the absence of BAEP waves for comatose trauma patients, most researchers agree that the persistent absence of wave V can be a reliable prognosticator for a poor outcome of coma unless wave I is also absent (Greenberg et al., 1981; Lindsay et al., 1981; Soustiel et al., 1983). Note that the absence of wave V without reliable presence of wave I cannot be used as a reliable prognosticator for unfavorable outcome given the possibility that the failure to elicit wave V may be the result

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TABLE 2. SSEPs and Trauma

Series	SSEP Timing	Follow-up (mo)	No. of Cases	Awake and Aware/Absent N20
Ahmed, 1988	1 d	6	20	0/3
Barelli et al., 1991	<1 d	6	21	1/3
Cant et al., 1986	1–4 d	> 52	35	1/7
Guerit et al., 1993	0–10 d	?	132	2/80
Gutling et al., 1994	2–3 d	3–6	50	1/10
Houlden et al., 1990	<7 d	> 6	51	0/13
Hutchinson et al., 1991	0–3 d	6	90	1/23
Judson et al., 1990	1–2 d	6	100	1/30
Moulton et al., 1994	0–5 d	3	65	2/19
Pohlman-Eden et al., 1997	1–10 d	3	15	0/15
Rumpl et al., 1988	2–6	1	34	1/5
Sleigh et al., 1999	2	12	105	1/11
Ying et al., 1992	1–50 d	20	11	0/0
Total			729	11/219 = 5% PPV = 0.95

PPV, positive predictive value of not awakening if there is bilateral absence of an N20 response.

of peripheral auditory damage. Wave VI and VII had not figured prominently in clinical practice until Balogh et al. (2001) reported that the absence of wave VI was highly specific for an unfavorable coma outcome.

Comatose patients, especially those with traumatic injuries and vascular infarcts, experience a dynamic rather than static process of neurologic deterioration. In particular, intracerebral hemorrhagic infarcts have great potential risks for late neurologic deterioration. Therefore, Garcia-Larrea et al. (1992) advocate continuous monitoring of BAEP. They observed that even one transient but significant change of BAEPs can be seen as a sign of a poor prognosis (Garcia-Larrea et al., 1992). Thus, the stability of BAEPs recorded repeatedly rather than the results of a single BAEP evaluation is the only finding that should be obtained during monitoring for coma emergence. Continuous BAEP measurement seems a reasonable test for predicting poor outcome. However, given the limited brain areas and functions able to be assessed by BAEP measures, the exclusive use of BAEP in predicting traumatic coma outcome may be unwise. Even in cases that involve major brainstem lesions, the BAEP (particularly waves I-IV) will fail to reflect serious neurologic impairment unless the lesions involve the rostrocaudal auditory tracts. Combining of BAEP with other measurements (e.g., evoked potentials, clinical evaluations, intracranial pressure measures, and computed tomography or MRI) appears reasonable. In particular, some studies focus mainly on a decision algorithm for the prediction of outcome in comatose patients based on the combined use of SSEP and BAEP (Facco et al. 1998; Goodwin et al., 1991; Lindsay et al., 1990).

EVENT-RELATED BRAIN POTENTIALS IN AIE AND TBI

Comatose, vegetative, and minimally responsive states represent prognostically difficult conditions for the reliable prediction of a *favorable* outcome. ERPs provide a method to objectively evaluate higher-level cognitive function (e.g., memory and language) in such patients. ERPs are long-latency responses (70–500 milliseconds after stimulus) generated by subcortical–cortical and cortical–cortical circuits. They rely on a more complex and extensive network of neural connections than do short-latency evoked potentials (Kane et al., 2000). As a consequence, ERPs provide a very promising tool to examine cerebral functional integrity.

P300

The P300 is a positive ERP component peaking about 300 milliseconds after the onset of a novel target or "oddball" stimulus that is presented randomly in a sequence of "standard" auditory stimuli (Fig. 3). Although the specific cognitive processes involved in the genesis of the P300 remain uncertain, it is generally agreed that it is associated with attention, expectancy, decision making, memory, and closure of a cognitive epoch. P300 has been widely reported to reflect changes of cognitive impairment in dementia and in confusional states (Goodin et al., 1983; Pfefferbaum et al., 1984; Polich et al., 1986; Pratap-Chand et al., 1988). The traditional paradigm to elicit the P300 has involved the active involvement of the participant who must attend to the rare stimulus and make a motor response to it (e.g., a button press). However, studies have shown that it can also be recorded in

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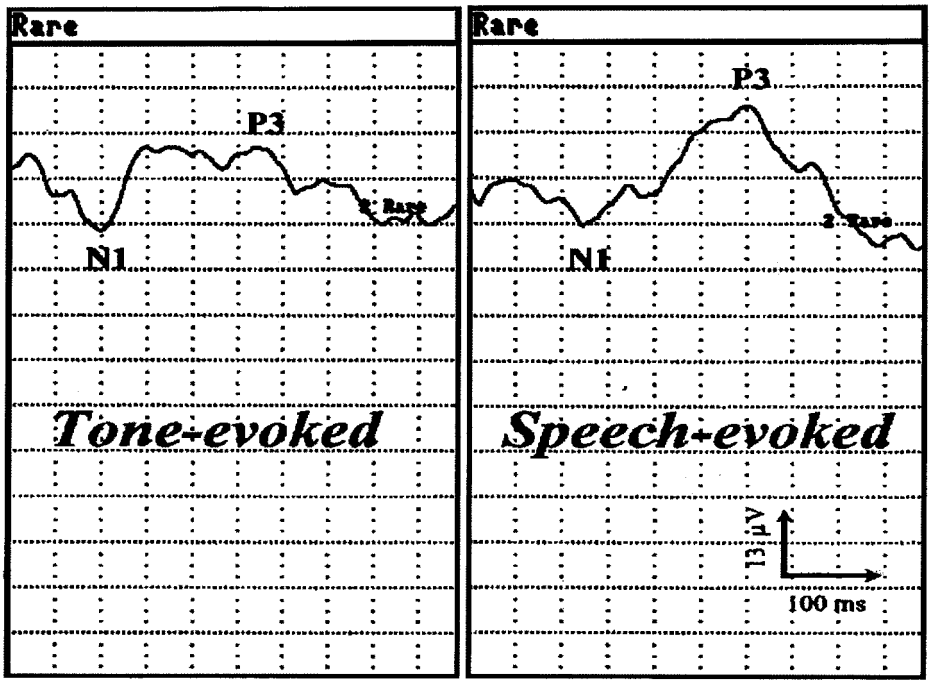


FIGURE 3. Normal P300 responses to rare tone (*left column*) and speech sound (*right column*) in a passive oddball paradigm. In the left column, P300 waveforms were evoked by a 500-Hz tone that was randomly presented with a probability of 20%. The frequent stimulus was a 1,000-Hz tone. Both tones were set at 70 dB sound pressure level. In the right column, the waveform was elicited by the word mommy intermixed with a 1,000-Hz frequent tone. The word "mommy" was spoken by a female speaker. The ratio of tonal and speech stimuli was 4:1. The stimuli were presented at a level of 70 dB. Waveforms were recorded at Cz and referred to linked mastoids. The amplitude of the P300 is sensitive to the stimulus type: the rare speech sound seemed to produce a larger P300 than the rare tone sound. (Adapted from Lew et al. *Am J Phys Med Rehabil* 1999;12:369, with permission.)

a state of passive attention, making it possible to investigate this component in comatose patients (Reuter and Linke, 1989).

Reuter and Linke (1989) first studied the passive tone "oddball" paradigm in comatose patients who had incurred closed-head injuries. In their study, four patients who exhibited discernible P300 activity emerged from coma and functioned independently 6 months after the injury. Later studies replicated and extended these findings in comatose patients of different etiologies (De Giorgio et al., 1993; Gott et al., 1991; Yingling et al., 1990;). The presence of a P300 is reliably associated with higher GCS scores for nontraumatic coma (Gott et al., 1991). SSEP and EEG are superior to the P300 in predicting nonawakening. In turn, the P300 and SEP are more effective than EEG in predicting awakening. In addition, the P300 was as specific (83.3%; five of six patients with a P300 awoke) as SEP (80%; 8 of 10 patients with moderate SEP abnormalities regained consciousness) in terms of predicting awakening but its sensitivity was lower (55.5% for P300 and 88.9% for SEP) (Gott et al., 1991). Sensitivity of the P300 for awakening is the percentage of later awakening patients that had a P300 response. Specificity of the P300 presence for awakening is the percentage of patients with the P300 presence who later awoke. Although larger numbers of patients need to be investigated for further confirmation, the presence of a P300 in the aforementioned studies indicates the existence of at least rudimentary processing of stimuli occurring in those patients that may be related to an element of functional integrity of the central nervous system.

However, the absence of P300 does not preclude a good prognosis. Some comatose patients who failed to show P300 activity later emerged from coma (Balogh et al., 2001). Also, the finding that not all fully alert, cooperative individuals (83%) exhibit a discernible P300 with the oddball paradigm (Seales et al., 1979) indicates that this approach is clearly inadequate to meet the needs of clinical evaluation of coma patients. To improve the likelihood of evoking the P300 in coma, some researchers have used a salient stimulus (the patient's name) or a conditioned stimulus (e.g., emotional content particular to the patient or speech sounds like "mummy" as rare stimuli versus tone as standard stimuli, as illustrated in Fig. 3) (Mazzini et al., 2001; Prevec et al., 1993; Rappaport et al., 1991). The use of such stimuli increased the percentage of patients who exhibited P300 activity during coma and subsequently emerged. This demonstrates the presence of certain complex cognitive functions in those patients

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during coma, a result of some clinical significance for assessment and possibly for prognosis.

P300 recordings to "salient" stimuli may extend the battery of neurophysiologic tests currently available for examining the functional integrity of the central nervous system and, possibly, the capacity for cognition in comatose patients. In addition, P300 latency was found to be abnormal after traumatic head injury both in the acute and subacute stages (Curry et al., 1986). The persistent occurrence of abnormal P300 latency does not predict cognitive impairment accurately (Olbrich et al., 1986).

Mismatch Negativity

One should not assume the capacity for vigilance or cognition in unresponsive patients. The P300 component is dependent on some level of vigilance in an individual. For this reason, clinical research has sought earlier ERP activity that does not demand patient awareness or vigilance yet is dependent on the functional integrity of higher level perceptual/processing systems. Mismatch negativity (MMN) is the earliest and most robust ERP component that reflects detection of a "deviant" stimulus in homogeneous series of repetitive "standard" sounds (Mecklinger et al., 1997). It is a negative-going component 100 to 250 milliseconds from the onset of a deviant stimulus. MMN was first elicited by a discriminable acoustic change in a sequence of "standard" stimuli. Subsequent studies have further shown that MMN is responsive to any infrequent perceptible physical change in an auditory stimulus. Because it can be reliably elicited without any requirement of voluntary attention on the part of the subject or patient, MMN was seen as a promising tool in attempts to determine perceptual capabilities of the comatose patient (Näätänen 2000).

Several studies have shown that MMN presence indicates a positive prognosis for emergence from coma, beginning with the original observation of Reuter and Linke (1989). Kane et al. (1996) reported a high specificity (100%) and sensitivity (89.7%) for the association of MMN and awakening from coma, with repeated testing over 48 hours. A single, one-time detection of MMN produced a high specificity (90.9%), albeit a low sensitivity (31.6%), in predicting awakening (Fischer et al., 1999). The different results for the sensitivity of MMN as a prognostic of awakening among the aforementioned studies may have been due to the cause of coma: posttraumatic comatose patients were selected in the studies of Kane and colleagues (1993, 1996), whereas comatose patients of various etiologies including head injury, temporary cardiac arrest, complications of neurosurgery, and encephalitis were chosen in the studies of Fischer et al. (1999). However, given limited available data, the prognostic value of MMN as a function of comatose etiologies remains to be determined. Another possible reason for the different results for MMN sensitivity may be differences in experimental design, related to the number and frequency of ERP recordings (e.g., a single recording session versus a series of closely spaced tests).

Only a few studies compared the MMN with BAEP, middle latency auditory evoked response (MLAEP), and auditory N100 (a negative ERP component peaking about 100 milliseconds after stimulus onset) in terms of predicting the outcome of comatose patients (Fisher et al., 1999; Morlet et al., 2000). Based on the studies of Fischer et al. (1999) and Morlet et al. (2000), BAEP is superior to the MMN, MLAEP, and the N100 in predicting unfavorable outcome. In turn, the combined results of both MMN and N100 presence are more effective than a normal BAEP in predicting the *return of consciousness*. In the study of Fischer et al. (1999), for instance, the presence of both MMN and N100 in association with a return of consciousness was more specific (90.9%; 30 of 33 patients with a MMN and N100 regained consciousness) than a normal BAEP (77.5%; 62 of 80 patients), a normal Pa component of MLAEP (83.3%; 15 of 18 patients), or the presence of N100 only (83.3%; 70 of 84 patients). The presence of both MMN and N100 is argued as a reliable predictor of awakening (Fisher et al.,1999; Morlet et al., 2000).

Mismatch negativity may be a better measure than the P300 in predicting coma emergence from head injury (Clark et al., 1992; Rugg et al., 1988). MMN's superiority is based primarily on its lower susceptibility to aging effects and the fact that it reflects functions that are earlier and more "hard-wired" in the neural sequence of auditory processing—functions that eventually initiate the P300 response. The P300 is generated by a network including limbic, multiple cortical and subcortical regions that is more complex than the MMN, which arises mainly from the temporal auditory cortex (Kropotov et al., 2000).

A common limitation of the MMN and the P300 is the vulnerability of both components to pharmacologic agents. Dopamine agonists, antagonists, and barbiturate drugs significantly influence the latency of P300, whereas the MMN amplitude in normal subjects becomes smaller or even absent as a function of the dosage of alcohol, sedative, and barbiturate drugs (Born et al., 1986, 1987). As a consequence, the ERP findings should be carefully interpreted in relation to clinical evaluations and ongoing therapeutics.

The N400 and Others

Connolly and colleagues (2000a,b) have further refined the electrophysiologic evaluation of cortical function, enabling evaluation of otherwise untestable patient populations. A neurotrauma patient, unable to respond behaviorally and presumed to be cognitively incapacitated, showed semantic comprehension of speech using the N400 (a negative ERP component peaking at ~400 milliseconds after stimulus onset) that involved a sentence comprehension protocol. This

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led to his successful rehabilitation and ultimate discharge from hospital (Connolly et al., 1999). In a second investigation, a group of left hemisphere stroke patients with varying degrees of language impairment were evaluated using an assessment measure (the Peabody Picture Vocabulary Test—Revised) administered traditionally and within an ERP protocol (D'Arcy et al., 2003). The ERP findings correlated (r = 0.86) with the results obtained with the traditional administration of the test, demonstrating, at an unprecedented level, the ability of cognitive ERP to measure cognitive abilities in a fashion virtually identical to traditional methods. This work also shows the ability to measure cognitive function in patients who are otherwise impossible or extremely difficult to assess. See Figure 4.

CONCLUSIONS

There is a need for reliable indicators for the early favorable and unfavorable prognoses of comatose patients. Clinical evaluation (e.g., GCS), chemical markers, intracranial pressure monitoring, and neuroimaging tests are not of adequate reliability for use in coma outcome prediction for either AIE or TBI. Continuous recording of evoked potentials (e.g., BAEP, SSEP, and MLAEP) and EEG together with clinical observations may provide reliable and objective early prognostic determination of unfavorable outcome of nontraumatic coma. For postanoxic coma in particular, the persistent abolition of BLCR and MLAEP combined with sustained abnormal EEG patterns (e.g., suppression, burst-suppression, and generalized periodic patterns) in the continuous 72 hours of monitoring after coma can be seen as a reliable index in terminating intensive care intervention. As for posttraumatic coma, EEG has limited value in predicting poor outcome. Along with structural neuroimaging data, continuous or serial monitoring of evoked potentials may provide reliable objective early prognostic determination of unfavorable outcome.

On the positive side, ERPs may help predict favorable coma outcome. The occurrence of the P300 and MMN components in continuous recording sessions reflects the functional integrity of higher level information processing and, possibly, the capacity for cognition. These two ERP components can be seen as potentially reliable predictors of not only emergence from coma but also the *quality* of life (i.e., awareness and cognition) on emergence. The prognostic value of ERP as a function of coma etiology remains to be determined.

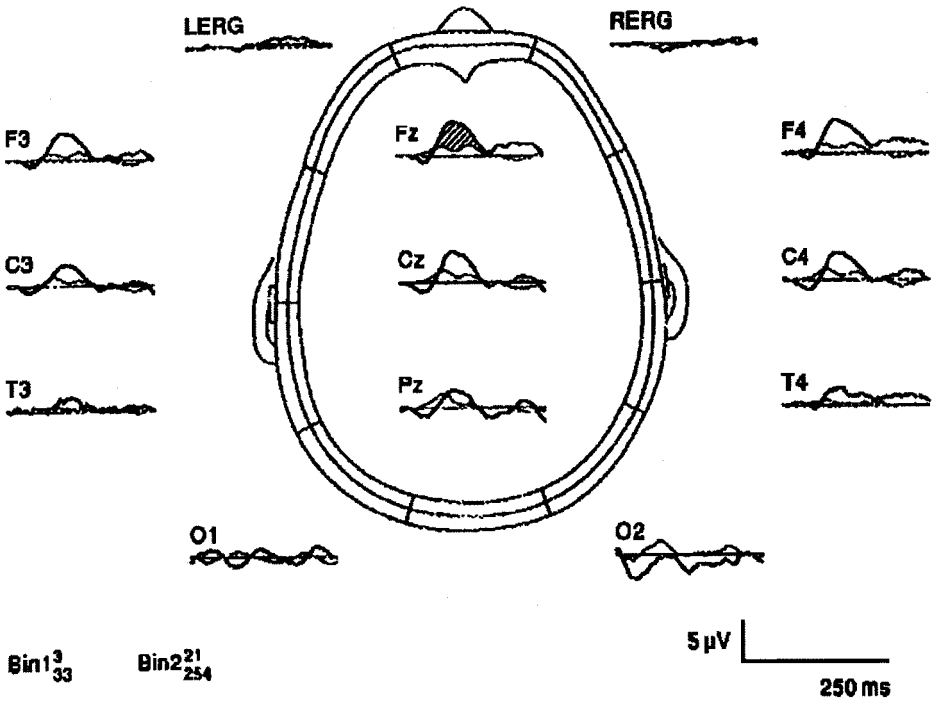


FIGURE 4. Normal MMN recorded in a passive oddball paradigm. Waveforms picked up at 11 scalp recording sites and referred at earlobes. The deviant auditory tone was set at 1600 Hz and presented randomly with a probability of 10% while the standard tone was at 800 Hz. Both stimuli were presented binaurally via earphones by stimulation intensity of 110 dB sound pressure level. The deviant tone evoked a negative, upward waveform (*bold line*) with respect to the waveform elicited by the standard tone (*thin line*). The MMN was shaded at the Fz electrode. (Adapted from Kane NM, Curry SH, Rowlands CA, et al. Event-related potentials: neurophysiological tools for predicting emergence and early outcome from traumatic coma. *Intensive Care Med* 1996;22:39–46.)

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Given the variety and complexity of EEG patterns, interrater and intrarater reliability is limited. Young et al. (1997) developed a simpler model that proved to have clearer EEG categories and higher interrater and intrarater reliability than other EEG classification systems published previously (e.g., Synek, 1988). Few studies have determined the interrater and intrarater reliability in measuring evoked potentials and ERP. Because of their direct and objective nature, measures of BAEP, SSEP, MLAEP, P300, and MMN are believed to be reliably reproducible across raters. Nonetheless, it is important to note that the skill of the electrophysiologist plays a critical role in reliable evoked potentials and ERP measurements in terms of interrater and intrarater reproducibility. When accurate electrode positions become difficult to define or access in, for example, patients after head injury or after neurosurgery, the technical "mishap" would decrease interrater reproducibility in assessing evoked potentials and ERP.

It should be feasible in the not-to-distant future to evaluate coma patients and offer not only a prognosis of the likelihood of their emergence from coma but also the functional capacities with which they will emerge. Therapeutic intervention with coma patients while they are still comatose may even be possible.

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