Prognostic Value of Evoked Responses and Event-Related Brain Potentials in Coma

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ABSTRACT: The behaviourally unresponsive patient, unable to exhibit the presence of cognition, constitutes a conundrum for health care specialists. Prognostic uncertainty impedes accurate management decisions and the application of ethical principles. An early, reliable prognosis is highly desirable. In this review investigations studying comatose patients with coma of different etiologies were selected. It is concluded that objective prognostication is enhanced by the use of electrophysiological tests. Persistent abnormalities of brainstem auditory evoked potentials and short-latency somatosensory evoked potentials reliably indicate the likelihood of irreversible neurological deficit or death. Meanwhile, 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. An approach that combines clinical and electrophysiological values provides optimal prediction of outcome and level of disability.

RÉSUMÉ: Valeurpronostique des potentiels évoquées chez les patients comateux. Le patient qui ne répond pas aux stimuli et chez qui aucune fonction cognitive n'est évidente constitue une énigme pour les spécialistes. L'incertitude concernant le pronostic gêne la prise de décisions judicieuses quant au traitement et à l'application des principes éthiques. Il est donc souhaitable d'établir un pronostic précoce et fiable. Nous révisons des études de patients dont le coma était d'étiologies variées. Nous concluons que l'utilisation de tests électrophysiologiques favorise l'établissement d'un pronostic objectif. Des anomalies persistantes des potentiels évoqués auditifs du tronc cérébral et des potentiels évoqués somesthésiques de courte latence indiquent de façon fiable la probabilité de déficits neurologiques irréversibles ou de décès. La présence de potentiels évoqués cognitifs (P300 et négativité de discordance) reflète l'intégrité fonctionnelle du traitement de l'information au niveau mental supérieur et donc la probabilité de conservation de la fonction cognitive. Une approche qui combine des données cliniques et électrophysiologiques fournit une prédiction optimale de l'issue et du degré d'invalidité.

Can. J. Neurol. Sci. 2004; 31: 438-450

Coma is a state of unarousable unconsciousness due to dysfunction of the ascending reticular activating system (functionally and structurally represented in the rostral brainstem tegmentum, through the medial thalamus and projected to the cerebral hemispheres).[1] Advanced medical support and life-saving interventions allow some patients to have a good recovery.[2] The objective of rapid, accurate prediction of a comatose patient's outcome is motivated by two primary needs. The first is to be able to counsel the patient's family. The second is to provide the health care team with necessary information needed to rationalize life-sustaining therapies and limited resources on those patients most likely to gain benefit, and to minimize intensive treatment for patients who would remain in an irreversible vegetative state or die. The lack of reliable prognosticators may result in predictions that are either ambiguous or unduly optimistic or pessimistic.[3-6]

In current practice, prognostic decisions for comatose patients rest principally on clinical observations.[7,8] The fundamental weakness of clinical algorithms and grading systems is their less than 100% specificity for an outcome no better than (permanent) vegetative state or death. These categories, i.e., the lack of recovery of the capacity for conscious awareness, represent states that for most individuals and families would not warrant continued high level ICU support. Other levels of survival, with preserved consciousness, are more difficult for management decisions. Conversely, the predictive values of tests for excellent outcomes need to be considered in any prognostic battery.

A number of clinical algorithms have been developed, beginning with the seminal study of Levy et al.[9] These rely on the premise that severe brainstem dysfunction reflects even

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RECEIVED MARCH 10, 2004. ACCEPTED INFINALFORM JULY 19, 2004.

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greater damage to rostral structures, which are usually more vulnerable to ischemic injury. Certainly coma lasting more than three days carries a greater than 90% risk of poor outcome. Independent existence did not occur with absence of pupillary light reflex at the time of initial evaluation; only one of 93 patients with decorticate or decerebrate responses at 24 hours recovered. Edgren and colleagues[10] found absence of motor response at three days to be the best predictor of poor outcome. Poor outcome is usually defined as a severe disability, vegetative state or death. Unfortunately, the vegetative state or death were not the absolute end points. False prediction of poor recovery occurred in 16 of Longstreth's clinical series.[11]

Several clinical scoring systems have been developed and utilized in clinical patients. A recent review[8] suggests that clinical levels based on Hunt and Hess[12] and the World Federeation of Neurological Surgeons'Grading System[13,14] have strong association with the outcome of patients secondary to stroke. Unfortunately, when these scoring systems are applied to all comatose patients, they have very limited value in distinguishing patients with reversible encephalopathies from those who will die or remain in an irreversible vegetative state. Some cases of coma or "persistent vegetative state" are temporary. In a (permanent) vegetative state, the patient has irregular cyclic arousal although he/she is still not aware of self or the environment, as the patient is in a comatose state. An irreversible vegetative state commonly indicates the severity of the vegetative state, in which the patient hardly achieves good recovery. The Glasgow Coma Scale (GCS) is the most widely used formalized clinical assessment,[15-18] especially for scoring the extent of traumatic head injuries.[19] The scoring system using 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 and colleagues[20] correlated GCS at two days for outcome in 216 patients resuscitated from cardiac arrest. The sensitivity was 96%, the specificity 86%, while the positive and negative predictive values were 97% and 77%, respectively. Thus, although the GCS is likely helpful, it is not sufficiently definite to support end-of-life decisions solely on its basis. Using the GCS alone, three of 11 patients with epidural hematomas and GCS scores of 3-5 still had good outcomes.[21] The combination of the GCS with computed tomography (CT) scan findings considerably improved predictive values.[21] Inherent problems with the GCS include the level of inter-rater reliability in scoring patients: Kappa scores of 0.69-0.71 were found in a study involving neurosurgeons and registrars.[22] Furthermore, the consistency of rating is dependent upon experience: experienced nurses are more consistent in GCS rating scales than are junior nurses.[23] 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; eyes may be swollen shut, etc. Observer grading disagreements are exacerbated by pseudoscoring, i.e., giving an estimated score for an untestable response in order to avoid exclusions.[24,25] 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.[26] Although to a certain degree it is useful and well-validated in helping to determine the degree and duration of coma over pathological cause and anatomical site,[19] the application of clinical evaluations to prognostication in comatose patients is beset with limits. The scoring system using the GCS is insensitive in separating patients with reversible coma from those without,[8] and thereby increasing false pessimism – the error of predicting a bad outcome when a good outcome occurs.[27] Clinical evaluations cannot provide significant information at the critical time when meaningful interventions are feasible and potentially effective. For example, irreparable damage has been done when temporal lobe herniation reaches the stage of third cranial nerve compression and pupillary dilatation. The most important and unavoidable limit is that present intensive care measures (e.g., intubation, artificial respiration, pharmacological relaxation, and barbiturates) heavily mask neurological signs that are usually relied upon by clinical observations. In cases of traumatic coma, an accurate behavioural evaluation is often obscured by peripheral injuries, facial injuries, hypoxia, spontaneous fluctuations, and the subjective interpretation of the observer.[17]

In addition, the GCS has met with problems for use in children, especially those who are too young to understand commands. Butinar and Gostisa[28] argue that the GCS increases a false-negative rate of 25%, predicting survival, in children with a GCS score equal to 3. The Paediatric Coma Scale was developed to address this drawback. Simpson et al[29] studied the Paediatric Coma Scale in 66 children under 72 months of age and found a correlation with outcome. However, there were few children in coma in their study and, therefore, this scoring system needs further evaluation.

In combination with clinical examination or used alone, CT scans,[30,31] intracranial pressure monitoring,[32-34] serum and cerebrospinal fluid (CSF) chemical markers[35-39] and magnetic resonance imaging (MRI)[40-43] have also been studied as potential prognostic indicators. With the same type of shortcoming as clinical observations, all these measurements, except neuroimaging scans, produce values that overlap considerably between favorable and unfavorable outcomes and are thus, too insensitive to allow early intervention. Biochemical markers in the CSF and serum (neuron specific enolase, S-100 glial protein, lactate dehydrogenase, glutamate oxaloacetate and the brain specific isoenzyme for creatine kinase - CKBB) hold promise, but a meta-analysis by Zandbergen et al[39] showed that the confidence intervals (CIs) were too wide to allow for clinical application of these tests. The only one that showed a high prediction for poor outcome (with a pooled likelihood ratio of 33.2 and 95% CI of 4.8-230.2) was based on two retrospective studies in which the treating physicians were not blind to the results. Further studies with larger sample sizes are clearly needed. Although CTdoes not share the above shortcomings and provides an accurate assessment of both site and size of bleeding, of brain structural damage, and of the risk of vasospasm, it is not a reliable indicator of brain dysfunction.[8] Magnetic resonance imaging can detect lesions of brain structures close to the midline (e.g., basal ganglia and upper brainstem) which CT scans fail to capture. Studies on comatose patients have shown that extensive lesions detected by MRI (e.g., more than four insults observable with MRI[40]) are associated with an unfavorable outcome.[41,42] These data suggest that MRI in coma secondary to head injury can provide complementary information for prognosis. Although MRI scans show some preliminary promise, the published series

https://doi.org/10.1017/S0317167100003619 Published online by Cambridge University Press

have only a few cases each.[40-43] In our experience, the MRI, including diffusion-weighted and fluid attenuation inversion recovery sequences are not sufficiently sensitive for poor outcome, although they may ultimately be shown to have good specificity. In addition, the cost of MRI as well as the complicated transport of unstable patients has limited the further development of this MRI research. Parallel to the MRI research, proton magnetic resonance spectroscopy has recently been evaluated for prognostication in coma. This test can be performed on conventional MR equipment with advanced software and provides a more direct assessment of brain metabolism than a simple overview of brain structural damage.[44] It was found that abnormally high brain lactate values reliably indicate a poor prognosis in patients with ischemic damage.[45] Again, the need to transport the patient to the radiology suite and test availability limit its application.[7]

These problems make the accurate prediction of coma outcome complex and difficult, demanding considerable experience, effort and skill – qualities that are not generalizable. Electrophysiological tests as prognostic tools have attracted increasing attention of late due to their correlation with clinical symptomatology, safety, ease of acquisition, and cost effectiveness. They provide an objective, standardized, noninvasive means of directly assessing brain activity. Early research in trauma cases indicated that changes in the brain's electrical activity were correlated strongly with the force of impact[46] as well as the site and extent of brain damage.[47] Brain electrical activity provides a sensitive index of the pathophysiological response of the brain to acute traumatic damage and secondary cerebral insults and, therefore, may provide valuable information for patient outcome.[48] This review will focus mainly on neurophysiological investigations of prediction of patients' outcome from comas of different etiologies.

We surveyed electronic MEDLINE and PSYCINFO databases and collected studies in which early electrophysiological features of patients with coma of various etiologies were related to outcome. Keywords were: traumatic, head injury, nontraumatic, anoxic (cerebral), ischemia (cerebral), heart arrest, cardiac arrest, postoperative complications, stroke, shock, hypertensive hemorrhage, resuscitation, drowning, or lightning, combined with coma or GCS. Studies included patients with coma of different etiologies, and we distinguished between traumatic and nontraumatic coma. For nontraumatic comas, we focused on hypoxic-ischemic (postcardiac arrest) etiology, as other metabolic conditions have greater reversibility. The emphasis was on adult patients. Other criteria for study selection were: unequivocal description, classification, and timing of recording of electrophysiological features; presentation of outcome data such that the combined outcome of death or (permanent) vegetative state versus other outcome states could be determined, as these states are generally seen as unacceptable outcomes.

Electroencephalography (EEG)

From a hypothetical viewpoint, electroencephalography (EEG) should be a suitable test for cortical function and prognosis.[49] The neurons that are the most sensitive to anoxic-ischemic insult are those 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.[24] Thus, one should wait for at least several hours before performing the EEG. Delayed neuronal death may be responsible for deterioration in EEG voltage that can occur three to five days later.[50] Thus, timing and often the need to repeat EEGs are of great importance. Sedative drugs commonly confound the EEG. Midazolam and propofol are the most commonly used; these can suppress the EEG to a burst-suppression pattern that is completely reversible.[49] Suppression or burst-suppression may occur in severe, reversible septic encephalopathy.[51] Studies of EEG in comatose anoxic-ischemic encephalopathy lack numbers and precision: the threshold for suppression is often not defined, the timing of the EEGs from the time of the arrest is available.[49] 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.[52] Some patterns, such as suppression of <10μV, a burst-suppression pattern with epileptiform activity within the bursts, are more specific for outcome no better than vegetative state, but the series are small.[25,49,53-54] Clearly EEG has many obstacles (sedation, 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.

An EEG has very limited prognostic usefulness for other etiologies of coma. It has not been very helpful in traumatic head injury, possibly because the brunt of the damage is acute axonal injury, affecting the subcortical white matter and sparing (relatively) the EEG-generating neocortex.[49] Many metabolic conditions affect the brain mainly in a metabolic fashion that is mostly/largely potentially reversible.[49]

Of course, favorable EEGs, with reactive, variable and continuous wave forms, are correlated with favorable outcomes.[52] The EEG can also assist in management of seizures and depth of sedation; thus outcomes may be enhanced, secondary insults prevented and ICU length of stay shortened.[55]

Short-latency evoked potentials

Among neurophysiological tests, measurement of short-latency evoked potentials (EPs) is useful in the evaluation of specific sensory pathways traversing the central nervous system. An advantage of EPs over clinical evaluations is that the former are not influenced by intensive care interventions and are relatively resistant to sedative and barbiturate drugs.[56-61] Chiappa comments that EPs are very resistant to changes by anything other than structural pathology in the brain stem auditory tracts (for brainstem auditory evoked potentials (BAEP)) and/or somatosensory pathway (for SEP).[56] In this paper, two short-latency evoked potentials – BAEP and short latency somatosensory EPs (SSEP) – are reviewed, and the effectiveness of each in the evaluation of coma is discussed.

Motor evoked potentials are not reviewed in this paper in terms of their prognostic value in coma. Motor evoked potential testing provides a noninvasive method of recording electromyographic responses (e.g., the muscle twitch recorded

https://doi.org/10.1017/S0317167100003619 Published online by Cambridge University Press

peripherally) evoked by transcranial electrical or magneto-electric stimulation of the motor cortex through intact skull. Motor evoked potentials were first introduced by Merton and Morton in 1980.[62] Since then, they have been used in a wide range of neurological disorders for assessment of the functional status of descending motor pathways in awake patients.[63-66] Motor evoked potentials have also been studied in comatose patients to determine their prognostic value.[67-69] However, the coma literature shows inconclusive results regarding their prognostic significance.[70-74] Further investigations are therefore required.

BRAINSTEM AUDITORY EVOKED POTENTIALS (BAEP)

Brainstem auditory evoked potentials (BAEPs) are nervous system responses to transient click stimulation that occur within 10msec of stimulus onset. Brainstem auditory evoked potentials consist of six to seven positive and negative BAEPpeaks (Figure 1).[75] 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.[56] The generators of wave VI and VII are argued to be located, respectively, within the midbrain (or even in the diencephalon) and thalamocortical regions.[76-78]

Given that absolute amplitudes of each wave vary significantly across individuals, wave presence or absence is usually used to predict the outcome of comatose patients in some studies. For instance, all comatose patients with no discernible BAEP waves,[79] an absence of waves III to V,[80] or an absence of waves IV and V[81] died or were left in an irreversible vegetative state. Although there is controversy about the prognostic value of

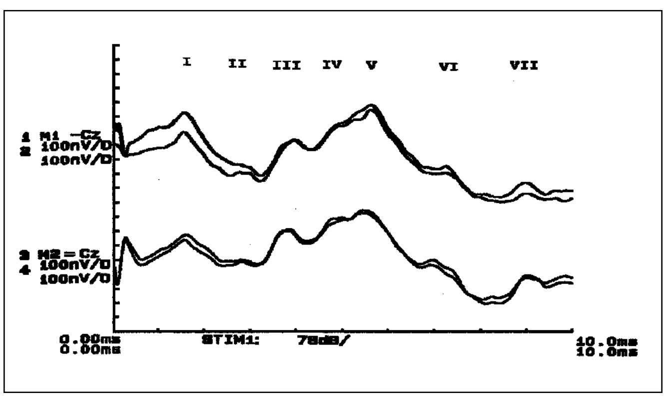

Figure 1: Normal BAEP waveforms elicited by monaurally presented click sounds with contralateral sound masking. The sound stimulation was set at 78 dB normal hearing level (NHL) while the sound masking was at 60 dB NHL. The stimulation frequency was set at 10 Hz. Waveforms were recorded at the mastoids (M1, M2) referred to the vortex (Cz). The upper two superimposed lines were the BAEP waveforms evoked by left ear stimulation and ipsilateral recording while the bottom two lines by right ear stimulation. (Adapted from Hu CJ, Chan KY, Lin TJ, et al. Traumatic brainstem deafness with normal brainstem auditory evoked potentials. Neurology 1997; 48:1448-1451.[75] Reprinted with permission from Lippincott, Williams & Wilkins.)

the absence of BAEP waves for comatose patients,[82-84] 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.[85-88] 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 of peripheral auditory damage which is normally indicated by the absence of wave I. Wave VI and VII had not figured prominently in clinical practice until wave VI was recently reported as a reliable prognostic measure for comatose patients; it was found that the absence of wave VI was highly specific for an unfavorable coma outcome.[78]

Equally, the measurement of interpeak latencies (IPL) (I-III, III-V, I-V) and amplitude ratios (I/V) has been used as a criterion of abnormality for clinical interpretations. It has been demonstrated that a significantly prolonged wave III-V IPL (central conduction time) in comatose patients from traumatic head injury,[88-89] stroke,[90] and from other different origins (e.g., subarachnoidal or hypertensive hemorrahage[8]) was highly correlated with irreversible dysfunction. Given the overdependence on a single, one-time measurement of the BAEP in most studies, Garcia-Larrea et al[91] argue that BAEP results may provide a false sense of optimism. Comatose patients, especially those with traumatic injuries and vascular infarcts, experience a dynamic rather than static process of neurological deterioration. In particular, intracerebral hemorrhagic infarcts have great potential risks for late neurological deterioration. In this regard, Garcia-Larrea et al[91] advocate continuous monitoring of BAEP. They observe that even one transient but significant change of BAEPs can be seen as a sign of a poor prognosis. 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 criterion, particularly 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 coma outcome may be ill-advised.[92] It is evident that the prognostic determinant in coma arising from some etiologies (e.g. anoxia) is mainly cortical function.[93] Even in cases that involve major brainstem lesions, the BAEP(particularly waves I-IV) will fail to reflect serious neurological impairment unless the lesions involve the rostrocaudal auditory tracts. In an attempt to obtain prognoses, the combining of BAEP with other measurements (e.g., EPs, clinical evaluations, intracranial pressure measures, and CT/MRI scan) has been recommended. In particular, many studies focus mainly on a decision algorithm for the prediction of outcome in comatose patients based on the combined use of SSEP and BAEP.[8,27,88]

To summarize, the prognostic value of BAEPis characterized by two features. Firstly, the absence of BAEPs can be seen as a reliable prognosticator for poor outcome when there is no evidence of peripheral auditory damage. On the other hand, the presence of normal BAEPs does not reliably indicate a good outcome. Secondly, although the anatomic specificity of BAEPs limits its general utility for prognosis in coma from different etiologies, the metabolic resistance of BAEPs makes it valuable in examining the integrity of relevant brainstem regions.

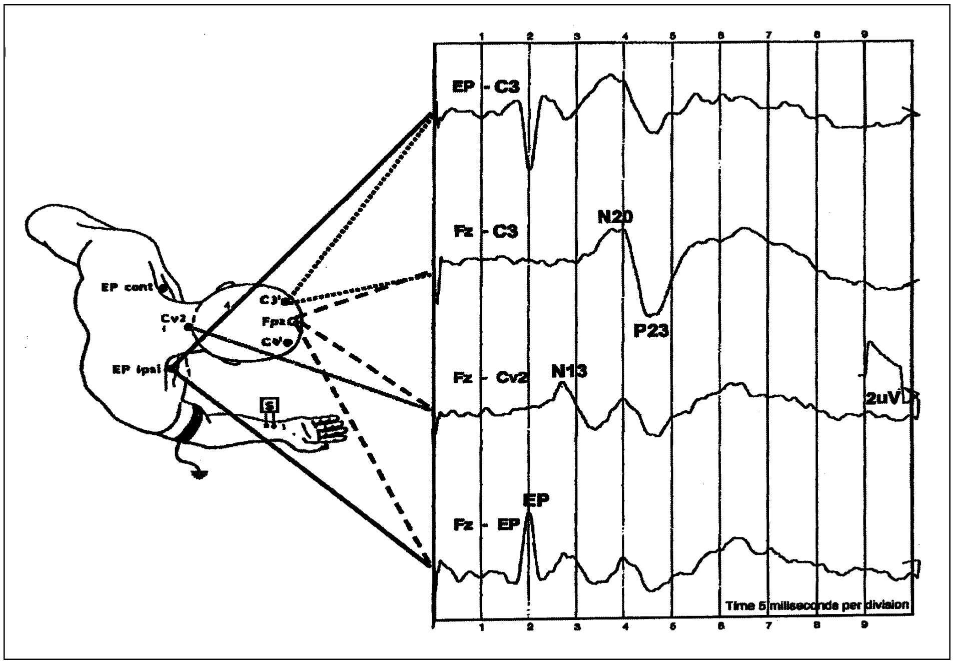

Figure 2: *Normal SSEP waveforms in response to the stimulation on the median nerve at the right wrist. The technique used in recording SSEP was illustrated in the left side column. In the right side column, the top line displayed the waveform recorded at the C3 and referred at the ipsilateral Erb's point (EP). The rest three lines depicts the waveforms recorded, respectively, at C3, Cv2 (neck), and EP that were referred to the frontal midline (Fz). (Adapted from Rothstein TL. The role of evoked potentials in anoxic-ischemic coma and severe brain trauma. J Clin Neurophysiol 2000; 17(5): 486-497.[18] Reprinted with permission from Lippincott, Williams & Wilkins.) Note that the N13 has also been labeled as P/N13 when recorded at the Fz-Cv2 channel.*

SHORT-LATENCY SOMATOSENSORY EVOKED POTENTIALS (SSEP)

Somatosensory evoked potentials are recorded in response to transient (usually electrical) stimulation of peripheral sensory nerves. Short latency SEPrefers to the primary response from the somatosensory cortex (S1). As illustrated in Figure 2, the peripheral nerve most often stimulated is the median nerve at the wrist. The traditional recording sites are either C3' or C4'(2cm behind the 10-20 system C3/C4 locations) with Fpz as the reference, along with the Erb's point.[18,56,94]

Several studies demonstrated correlations between SSEP and coma outcome. A significant correlation between the central conduction time of SSEP after median nerve stimulation and coma outcome has been widely reported.[73,95,96] The absence of bilateral primary cortical responses (BLCR) of median SSEP was first reported by Goldie et al[81] as an accurate prognosticator of death or survival in a vegetative state. Subsequently, the role of the absent BLCR in predicting poor outcome of coma has been substantiated by a considerable body of literature. It has been reported repeatedly that abolition of BLCR has 100% prognostic specificity for permanent vegetative state or death in patients with hypoxic-ischemic encephalopathy.[97-102] Studies on cerebrovascular and posttraumatic coma demonstrated a specificity of 87-99% for BLCR in predicting poor outcome.[88,102-104] In view of these findings, the absence of BLCR has been regarded as an excellent prognostic indicator of unfavorable outcome especially for hypoxic-ischemic encephalopathy coma.[7,102,105] Some argue that the persistent absence of BLCR in serial SEP recordings can be taken into account in the decision of terminating patients' medication or even intensive care treatment.[18] In contrast, the presence of the BLCR with normal amplitudes and latencies does not indicate favorable outcome especially for hypoxic-ischemic encephalopathy while it has been reported as an indicator for a good recovery in comatose patients secondary to traumatic or vascular brain injury.[102]

There are, however, isolated reports of some patients with bilateral absence of BLCR with favorable outcomes. Pohlmann-Schwarz et al[103] and Wohlrab et al,[106] respectively, found two and four paediatric comatose patients with BLCR absence who achieved good recovery. Schwarz et al[94] reported on four adult comatose patients (three of whom had herniation syndromes, specifically stroke, head injury with subdural hematoma, and encephalitis, while the fourth had carbamazepine toxicity) who showed an absence of the BLCR yet experienced a good outcome. These cases suggest that the absence of BLCR does not always indicate widespread, irreversible loss of neuronal function with structural lesions. This conclusion may be especially true for coma in children and coma secondary to nontraumatic insult (e.g., a lightning strike or near-drowning crisis). By this reasoning, it is possible that the BLCR loss in the three patients with herniation syndromes in the study by Schwarz et al[94] resulted from a clear but potentially reversible structural defect that affected the relevant anatomic pathway (e.g., brainstem compression). Subsequently, the absence of BLCR recorded 72 hours after coma onset has been recommended as a reliable variable for predicting poor outcome especially in anoxic-ischemic coma.[107] An alternative explanation for these conflicting findings is that BLCRs were masked by the combined effects of deep sedation and barbiturate therapy.[108-110] It is generally accepted that, although recovery from states characterized by an absence of the BLCR is rare, there are dangers associated with an over reliance on the BLCR finding alone, without regard to the timing of SSEP recordings. It is suggested that a combined approach, with continuous monitoring of brainstem function manifested by BAEP and cortical brain function by multimodal evoked potentials including middle latency auditory evoked potentials (MLAEPs),[102] extended beyond 24 hours, along with routine clinical evaluations, intracranial pressure recordings and neuroimaging scans, is advisable in order to optimize the predictive value of SSEP.

Meanwhile, care should also be exercised when the traditional measure of SSEP is used in clinical practice. The traditional, widely used SSEPis recorded from the scalp over the parietal regions (at C3' or C4') with reference on Fz or Fpz, which mostly reflects the function of the thalamoparietal network. However, it has been demonstrated that traditional SSEP recording may omit another somatosensory pathway connecting from the thalamus to the frontal cortex.[111] This observation is of particular importance to enhance accurate prognosis. Patients in coma secondary to traumatic injury often have frontolimbic lesions, which are more associated with the thalamofrontal loop than the thalamoparietal loop.[111] Gutling et al[111] first studied both frontal and parietal SSEPs and 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. It is argued that traditional SSEP value cannot represent the functional state of all somatosensory connections between the thalamus and the cerebral cortex. By this logic, the combined use of frontal and parietal components of the SSEP has the potential to improve the accuracy in prognostication of coma outcome. Additionally, this may also be an explanation for the survival of patients with the absence of BLCR.

In conclusion, consensus is growing that short latency EPs, including BAEP and SSEP, have limits but provide substantial information for accurate diagnosis and prognosis of irreversibility early in coma.[112] In particular, combined with clinical evaluations, neuroimaging scans, cerebral perfusion and intracranial pressure assessments, short latency EPs (SLEP) have significant merits in predicting poor prognostic outcome of coma patients. In contrast, normal SLEP responses do not predict equally well a good functional recovery from coma. Short latency EPs reflect the functional integrity of brainstem and thalamocortical connections. However, many patients suffer anoxia-ischemia that destroys much of the cerebral cortex yet spares some or all brainstem function, leading to “normal” BAEPs and SSEPs. Thus the presence/preservation of SLEPs may fail to predict the return of executive cognitive functions and an outcome better than the vegetative state, despite the return of simple wakening (eye opening) and arousability.[18] Clearly we need a reliable test of cerebral function that is more closely related to the potential for awareness and cognition.

MIDDLE LATENCYAUDITORY EVOKED POTENTIALS

Middle latency auditory evoked potentials refer to auditory system responses, to transient click or tone stimulation, which occur between 10 and 70 ms after stimulus onset. The principal sources of the Na-Pa complex of MLAEPs are believed to lie in the primary auditory cortex.[113] Only a few published studies investigated the prognostic value of MLAEPs in coma.[114,115] The absence of MLAEPs and SSEPs was reported to have a prognostic specificity of 100% for nonawakening in postanoxic coma.[116] It is argued that the abolition of MLAEPs and SSEPs can be used as criteria to stop intensive care interventions.[112] In addition, the combined results of MLAEPs and BAEP[116] also seem to provide valuable information for poor prognosis of coma. By contrast, sustained MLAEPs alone are not predictive of survival.[102,114,115] Also, MLAEPs are susceptible to central nervous system medications, biological variables, body temperature, and blood pressure.[116,117] This may be the reason that there are relatively few studies of MLAEPs in intensive care patients especially concerning outcome prediction.

EVENT-RELATED BRAIN POTENTIALS

Coma, vegetative and minimally responsive states represent prognostically difficult conditions, especially for the reliable prediction of a good outcome. Event-related brain potentials (ERPs) provide a method to objectively evaluate higher level cognitive function (e.g., memory and language) in such patients. Event-related brain potentials are long-latency responses (70-500ms post-stimulus) that are generated by subcortical-cortical and cortical-cortical circuits. They rely on a more complicated and extensive network of whole brain connections than do short latency EPs.[2] As a consequence, ERPs provide a very promising tool to examine cerebral functional integrity.

P300

Most contemporary clinical studies of ERPs focus on the auditory P300 component. The P300 is a positive ERP component peaking about 300ms after the onset of an improbable target or ‘oddball’ stimulus that is presented unexpectedly in a sequence of “standard” auditory stimuli (See Figure 3). While the specific cognitive processes involved in the genesis of the P300 remain diverse, it is generally agreed that it is associated with attention, expectancy, decision making, memory and closure of a cognitive epoch.[118] P300 has been widely reported to reflect changes of cognitive impairment in dementia and in confusional states.[119-122] 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, an increasing number of studies have demonstrated that it can also be recorded in a state of passive attention, making it possible to investigate this component in comatose patients.[123]

Reuter and Linke[123] 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 were found to function independently six months after the injury. Later studies replicated and extended the above findings in comatose patients

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of different etiologies.[124-127] A common finding is that the presence of a P300 has a significant correlation with favorable outcome of coma. For instance, five out of six nontraumatic comatose patients who showed a P300 awoke in one study.[126] Also, the presence of a P300 is reliably associated with higher GCS scores for nontraumatic coma.[125,126] Somatosensory EPs 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 more specific (83.3%; five of six patients with a P300 awoke) than SEP(80%; eight of ten 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).[125] The sensitivity of the P300 presence for awakening refers to the percentage of later awakening patients who had a P300 response. The specificity of the P300 presence for awakening refers to the percentage of patients who showed the P300 that 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 nontraumatic comatose patients who failed to show P300 activity, emerged later from coma.[78] Also, the finding that not all fully alert, cooperative individuals (83%) exhibit a discernible P300 with the oddball paradigm[79] indicates that this approach is clearly inadequate to meet the needs of clinical evaluation of coma patients. In order to improve the likelihood of evoking the P300 in coma, some researchers have used a salient stimulus (the patient's name)[128,129] or a conditioned stimulus (e.g., emotional content particular to the patient[130] or speech sounds like "mommy" as rare stimuli vs tone as standard stimuli as illustrated in Figure 3[131]). 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 during coma, a result of some clinical significance for assessment and possibly for prognosis.

P300 recordings to "salient" stimuli may extend the battery of neurophysiological tests currently available for examining the functional integrity of the CNS 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[124] and subacute stages.[132,133] The persistent

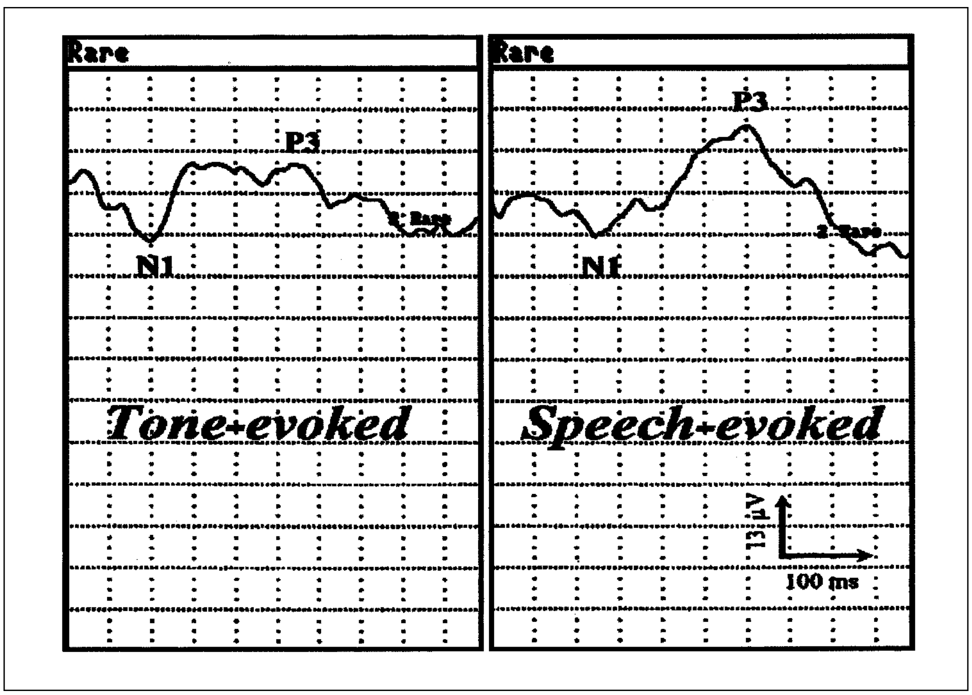

Figure 3: *Normal P300 responses to rare tone (left column) and speech sound (right column) in a passive oddball paradigm. In the left column, P300 waveforms were evoked by a 500-Hz tone that was randomly presented with a probability of 20%. The frequent stimulus was a 1000-Hz tone. Both tones were set at 70 dB sound pressure level (SPL). In the right column, the waveform was elicited by the word "mommy" intermixed with a 1000-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 level. Waveforms were recorded at Cz and referred to linked mastoids. As seen, 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 HL, Price R, Slimp J, Massagli T, Robinson L. Comparision of speech v tone-evoked P300 response: implications for predicting outcomes in brain injury. Am J Phys Med Rehab 1999; 78(4): 367-374.[131] Reprinted with permission from Lippincott, Williams & Wilkins.).*

occurrence of abnormal P300 latency does not predict cognitive impairment accurately. Olbrich et al[134] found that delayed P300 latency on the initial testing was correlated with clinical evaluation scores, but on the later retesting, the P300 latency remained delayed while the clinical scores had moved to the normal range and the patients had emerged from coma.

MISMATCH NEGATIVITY (MMN)

There can be no assumption of the capacity for vigilance in patients with impaired consciousness. 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 upon the functional integrity of higher level perceptual systems. The mismatch negativity (MMN) is the earliest and most robust ERPcomponent that reflects detection of a "deviant" stimulus in homogeneous series of repetitive "standard" sounds.[135] It is a negative-going component peaking at 100-250 ms from the onset of a deviant stimulus. The MMN was first elicited by a discriminable acoustic change in a sequence of "standard" stimuli.[136] Subsequent studies have further demonstrated that the MMN is responsive to any infrequent perceptible physical change in an auditory stimulus. To illustrate, the MMN can be reliably evoked by tonal changes in frequency, duration, or intensity.[137] An example of the MMN in response to a tonal frequency change is depicted in Figure 4. A variety of evidence suggests that the principal neural generators of MMN lie in and around primary auditory cortex as well as associated frontal regions.[138-140] Another feature of this response that is particularly relevant in the present context is that the MMN can be evoked in the absence of voluntarily directed attention, which has led to its being described as pre-attentive in nature. As it can be reliably elicited without any requirement of voluntary attention on the part of the subject or patient, the MMN has been seen as a promising tool in attempts to determine perceptual capabilities of the comatose patient.[141]

Reuter and Linke[123] first recorded the MMN in a patient who later emerged from coma. Subsequent studies have demonstrated that the occurrence of the MMN indicates a positive prognosis for emergence from coma. For instance, using a serial recording of MMN, Kane et al[142] found that four head injured patients who exhibited MMN all emerged from coma within 48 hours after detection of the MMN. Their follow-up study[143] reinforced this finding by demonstrating specificity (100%) and sensitivity (89.7%) of the presence of the MMN in predicting awakening from coma. With a single, one-time measure of MMN, a high specificity (90.9%), in spite of a low sensitivity (31.6%), for the presence of MMN was reported in predicting emergence from coma.[114] 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

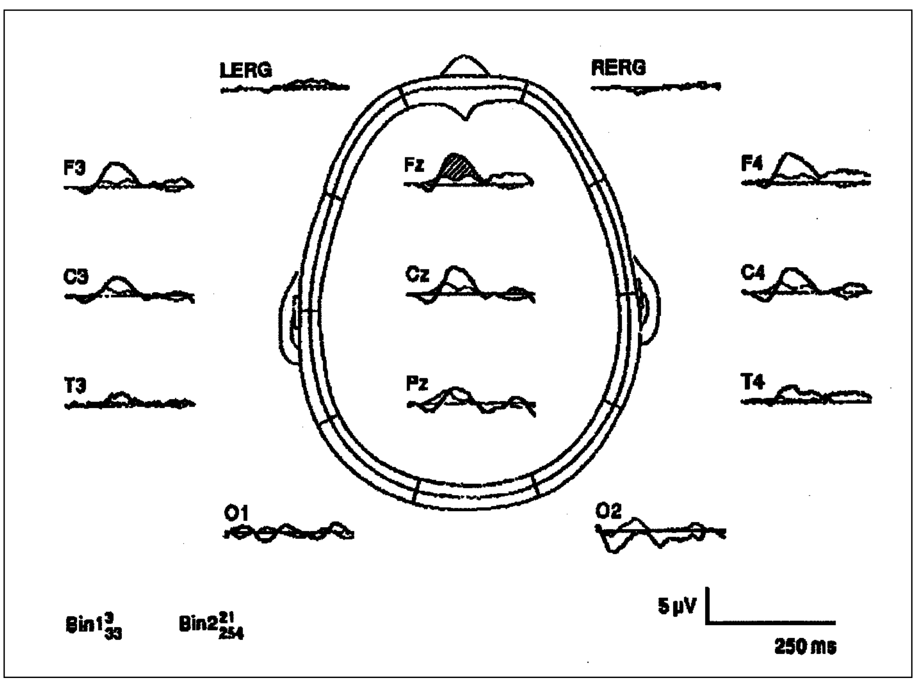

Figure 4: *Normal MMN recorded in a passive oddball paradigm. Waveforms picked up at 11 scalp recording sites and referred at earlobes. The deviant auditory tone was set at 1600 Hz and presented randomly with a probability of 10% while the standard tone was at 800 Hz. Both stimuli were presented binaurally 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.[143] Reprinted with permission from Springer Verlag©).*

patients were selected in Kane et al[142,143] studies while comatose patients of various etiologies including head injury, temporary cardiac arrest, complications of neurosurgery and encephalitis were chosen in Fischer et al[114] studies. 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 the MMN sensitivity may have been differences in experimental design centering on the number and frequency of ERP recordings (e.g., a single recording session versus a series of closely spaced tests). Morlet et al[115] conducted one case study with continuous recording of the MMN. This "dynamic" monitoring of the MMN was found to have greater prognostic significance with improvements in the sensitivity of MMN as a prognostic of coma emergence.

Only a few studies have compared the MMN with BAEP, MLAEP, and auditory N100 (a negative ERPcomponent peaking about 100 ms after stimulus onset) in terms of predicting the outcome of comatose patients.[92,114,115] Based on Fischer et al's[114] and Morlet et al's[115] study, 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 return to consciousness. In Fischer et al's[114] study, for instance, the presence of both MMN and N100 was more specific (90.9%; 30 of 33 patients with a MMN 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) in predicting return to consciousness. The presence of both MMN and N100 is argued as a reliable predictor of awakening.[92,114,115]

Although few clinical studies have evaluated the comparative worth of MMN and P300 in coma prognostication, there is a developing view that the MMN may be a better measure than the P300 in predicting coma emergence. This view of the 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. It is clear that the P300 is generated by a network including limbic, multiple cortical and subcortical regions[144-147] that is more complex than the MMN which arises mainly from the temporal auditory cortex.[138,148] In point of fact, two studies on head-injured patients have demonstrated that the occurrence and latency of the MMN was more sensitive than comparable P300 measures, to the effects of brain damage and the progress of recovery.[149,150]

However, there is evidence that both of these ERP components have drawbacks in predicting coma outcome. It has been suggested that the absence of either does not reliably indicate a poor outcome and cannot be used as a basis for withdrawing medical treatment. It has been suggested that the combined use of both ERP and short latency EP measures may facilitate the interpretation of each and, in turn, improve the power of electrophysiological measures in predicting coma outcome. It is proposed that this combination of measures can provide a general view of the functional integrity of a patient's brain from the primary sensory input to cognitive processing. In fact, the combination of these measures has been investigated to enhance the sensitivity of these ERP components in predicting poor outcome in coma.[114,115,125,149]

Another common limitation of the clinical utility of the MMN and the P300 is the vulnerability of both components to pharmacological agents. For example, dopamine agonists, antagonists and barbiturate drugs significantly influence the latency of P300.[151-153] The MMN amplitude in normal subjects becomes smaller or even absent as a function of the dosage of alcohol, sedative and barbiturate drugs as measured in serum.[115,117,154-156] This effect is sufficiently well-established that in the studies cited above, the MMN and the P300 were recorded in comatose patients only when the administration of sedative and barbiturate drugs was discontinued or remained at a very low dosage. As a consequence, the ERP findings should be carefully interpreted in relation to clinical evaluations and ongoing therapeutics.

The N400 and Others

Further refinement on the electrophysiological evaluation of cortical function has been provided by Connolly and colleagues,[157,158] enabling evaluation of otherwise untestable patient populations. A neurotrauma patient, unable to respond behaviourally and presumed to be cognitively incapacitated, was demonstrated to possess semantic comprehension of speech using the N400 (a negative ERP component peaking at ~400 ms post-stimulus onset) that involved a sentence comprehension protocol. This led to his successful rehabilitation and ultimate discharge from hospital.[159] 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.[160] 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 taken together also demonstrates the ability to measure cognitive function in patient populations who are otherwise impossible or extremely difficult to assess.

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 and intracranial pressure monitoring are not of adequate reliability for use in coma outcome prediction. Continuous recording of EPs (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., "lumped" EEG findings including suppression, burst-suppression, alpha-theta pattern coma 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. This cannot be generalized to all age groups, however; further studies on very young children are needed. For posttraumatic coma, EEG has limited value in predicting poor outcomes. Magnetic resonance imaging scans contribute to the prognostic evaluation of patients with structural brain lesions. When considered with clinical and imaging findings, continuous monitoring of EPs may provide reliable objective early prognostic determination of unfavorable outcome in trauma patients.

Conversely, ERP may help predict favorable outcome from unresponsive states. The presence of 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 ERPcomponents can be seen as potentially reliable predictors of not just emergence from coma but the quality of life, i.e., awareness and cognition, upon emergence. However, the full prognostic value of ERP in coma remains to be determined.

Given the variety and complexity of EEG patterns, inter- and intra-rater reliability is limited. A uniform classification system that is less ambiguous is suggested.[161] Few studies have determined the inter- and intra-rater reliability in measuring EP 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 EPand ERPmeasurements in terms of inter- and intra-rater reproducibility. When accurate electrode positions become uncertain, for example, in patients post-head injury or after neurosurgery, technical mishap would decrease inter-rater reproducibility in assessing EP and ERP.

This work combined with the other techniques discussed in this article makes it a realistic proposal that it will be feasible in the not-too-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. That being the case, therapeutic intervention with coma patients while they are still comatose may not be entirely unreasonable.

Acknowledgements

This research was supported by grants from the Canadian Institutes of Health Research (JFC & GBY) and a Killam Fellowship (JTW). The authors gratefully acknowledge the very helpful comments of three anonymous reviewers.

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