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## Review

## Electrophysiological assessments of cognition and sensory processing in TBI: Applications for diagnosis, prognosis and rehabilitation

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## ABSTRACT

Traumatic brain injuries are often associated with damage to sensory and cognitive processing pathways. Because evoked potentials (EPs) and event-related potentials (ERPs) are generated by neuronal activity, they are useful for assessing the integrity of neural processing capabilities in patients with traumatic brain injury (TBI). This review of somatosensory, auditory and visual ERPs in assessments of TBI patients is provided with the hope that it will be of interest to clinicians and researchers who conduct or interpret electrophysiological evaluations of this population. Because this article reviews ERP studies conducted in three different sensory modalities, involving patients with a wide range of TBI severity ratings and circumstances, it is difficult to provide a coherent summary of findings. However, some general trends emerge that give rise to the following observations and recommendations: 1) bilateral absence of somatosensory evoked potentials (SEPs) is often associated with poor clinical prognosis and outcome; 2) the presence of normal ERPs does not guarantee favorable outcome; 3) ERPs evoked by a variety of sensory stimuli should be used to evaluate TBI patients, especially those with severe injuries; 4) time since onset of injury should be taken into account when conducting ERP evaluations of TBI patients or interpreting results; 5) because sensory deficits (e.g., vision impairment or hearing loss) affect ERP results, tests of peripheral sensory integrity should be conducted in conjunction with ERP recordings; and 6) patients' state of consciousness, physical and cognitive abilities to respond and follow directions should be considered when conducting or interpreting ERP evaluations.

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## 1. Introduction

Event-related potentials (ERPs) are types of electroencephalographic (EEG) recordings used to evaluate patients who experienced traumatic brain injury (TBI). "Potential" refers to the electrical potential difference (or voltage) between two points, defined as the electrical force that would drive an electric current between those points. In the case of ERPs and EEG, the "two points" are electrodes attached to the patient's head that record voltages generated by neural activity from populations of neurons within a sensory pathway. These voltage changes result from movement of ions (e.g.,  $K^+$ ,  $Ca^{++}$ ,  $Na^+$ , and  $Cl^-$ ) and other charged particles within and between neurons in the brain. Evoked potentials (EPs), a subset of ERPs, are elicited by presenting stimuli (for example, light flashes, sounds,

electric shocks, images, words, odors or flavors) to the patient, then using a computer to average the EEG activity that is time-locked to the stimuli.

Traumatic brain injuries are often associated with damage to sensory organs and pathways. Because EPs are generated by neuronal activity, they are useful for assessing neural processing capabilities in TBI patients. Furthermore, EPs can provide information about the integrity of sensory pathways, including their efficiency for conducting input from the periphery to the central nervous system (CNS), the ability of CNS structures to process sensory input, and the ability of specific sensory systems to perceive and integrate stimuli. EPs and ERPs can also provide information about higher-order CNS processing, such as classification and categorization of multi-modality stimuli, and decoding/interpretation of language, images and other complex stimuli. For TBI patients, EPs can provide valuable information related to the severity of injury and its impact on neuronal pathways. ERPs can also provide information about patients' states of consciousness and cognitive functions. In fact, one of the driving interests of using ERPs in TBI research is the possibility of predicting outcomes of these patients.

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Because ERPs can be measured objectively in non-responsive patients, they may help with the prognosis of certain injuries. Thus, ERPs are non-invasive procedures that can contribute to the diagnosis, prognosis and rehabilitative assessments of TBI patients. This article reviews somatosensory, visual and auditory ERPs that have been used to assess TBI patients.

## 2. Mechanisms of injury in TBI

It is beyond the scope of this article to describe all of the mechanisms of injury that can occur in TBI. However, we will briefly discuss mechanisms of injury to sensory systems and pathways that can affect ERP recordings. For example, injuries that cause TBI can also result in damage to peripheral receptors (e.g., various parts of the eyes or ears) that impair their ability to receive and process sensory stimuli or to transmit information to the central nervous system (CNS). In some cases, ERPs can be used to assess the integrity of peripheral sensory systems and are especially useful when patients are unable to respond during standard behavioral tests. CNS damage in TBI can include diffuse axonal injury which results when shearing, stretching or angular forces pull on axons and small blood vessels (Mendez et al., 2005). This can result in axonal swelling, impaired neuronal transmission or disconnection (Hurley et al., 2004). Contusions occur when the brain impacts the skull interior, resulting in hemorrhage and bruising of the parenchyma (Taber et al., 2006). Edema—swelling of the brain caused by fluid accumulation—can occur in all types of TBI. The resultant increase in intracranial pressure can adversely affect many brain regions, including those distal from the site of initial injury.

Hinzman et al. (2010) demonstrated that brain injury can result in increased concentration of extracellular glutamate two or more days later which contributes to neuronal pathology and dysfunction. Increases in intracellular concentrations of calcium have also been implicated in TBI-related neuropathology. In an animal model, Sun et al. (2008) observed that calcium concentration was elevated within hippocampal neurons 1 and 7 days post-TBI, but returned to normal levels 30 days post-injury. In contrast, abnormalities in calcium ion homeostasis were found for as long as 30 days after TBI. Evaluation of the mechanisms underlying altered calcium homeostasis in TBI neurons indicated that long-term changes in calcium buffering or calcium sequestration/release mechanisms are responsible for these changes after TBI. Not only do these studies shed light on mechanisms of neuronal damage associated with TBI, they also help to explain the emergence or persistence of ERP abnormalities and functional disabilities that patients exhibit after initial injury.

## 3. Basic requirements for ERP recording

ERP recordings require some of the same equipment as EEG recordings:

- Recording electrodes (needle, cup, embedded in a stretch cap, etc.) in contact with the patient's scalp—at least one is needed, but more may be used (64, 128, 256 ...), depending on the purpose. These are sometimes called “non-inverting” electrodes. The other end of the electrode is attached to a “head box” or preamplifier.
- Reference electrode—sometimes called the “inverting” electrode. ERP voltages represent the potential difference between a recording electrode and a reference electrode. Each of these pairs represents one “channel.” Because each type of ERP (somatosensory, visual, and auditory) is generated by different neural structures, responses will be optimized by particular recording and reference electrode placements and pairings (montages). The morphology of ERP waveforms is determined by their neural generators and the orientation/location of those generators relative to scalp surface electrodes.

- Ground electrode placed somewhere on the patient's body—needed to complete the electrical circuit.
- Amplifier(s) and preamplifier(s)—one per channel. Voltages recorded from the scalp surface need to be amplified because they are small: in the micro-volt range.
- A stimulus generation/presentation system.
- A computer for EEG data collection. For ERPs, data collection must be synchronized with stimulus presentation. The computer can then “average” the time-locked EEG response to repeated stimuli, producing characteristic ERP waveforms for each sensory modality.
- Electronic filter(s)—help to delineate ERP waveforms and differentiate them from background noise/artifacts.

Before different types of ERPs and their roles in assessing TBI patients are discussed, it is important to consider the following factors that can have profound effects on electroencephalographic results:

- 1) Severity of TBI: mild, moderate or severe. Serious injuries are more likely to be associated with abnormal ERP results.
- 2) Patients' state of consciousness at the time of testing: alert, minimally conscious, asleep, comatose, persistent vegetative state, anesthetized, etc. Reduced or altered consciousness is more likely to affect long-latency ERPs (such as P300) than short-latency EPs.
- 3) Modality used for testing: somatosensory, visual, auditory, or others. Specific ERPs are more or less likely to be affected by different types or locations of neural damage, or causes of injury (falls, motor vehicle accidents, blasts, blunt force trauma, gunshots, etc.)
- 4) Age of patients and integrity of their sensory systems: intact and normal-functioning, impaired, damaged, etc. Also, impaired cognitive functioning of patients can affect longer-latency ERPs.
- 5) Types of stimuli and protocols used. Different forms, durations, intensities, configurations and presentations of stimuli can be used to assess various levels of the central or peripheral nervous systems and the effects of TBI on those systems.
- 6) Time of ERP recording relative to date of injury. Some studies record ERPs one or a few days post-injury, and again at future time points to correlate functional outcomes with electrophysiological results. Other studies record ERPs from subjects with histories of TBI that occurred one or more years earlier.
- 7) Medications taken by patients at the time of ERP recording. Some medications (such as potent analgesics, anxiolytics or sleep medications) can affect patients' behavioral performance and morphology of ERP waveforms.

## 4. Somatosensory EPs (SEPs)

It is possible to trace the conduction of a sensory impulse (initiated by touch, painful stimuli, or mild electrical stimulation of the skin) from a patient's leg or wrist, through the limb and spinal column, and to record its arrival in contralateral somatosensory cortex. To do this requires a series of recording electrodes placed on the body surface along the pathway. According to Chiappa et al. (1978): (1) waveforms are best recorded from electrode sites on the body surface closest to the presumed generator sources along the somatosensory pathways, and (2) studies of the potential-field distribution of each waveform of interest dictate the best techniques to be used. Chiappa (1997) recommends a minimum of 3 recording electrode locations for upper limb SEPs: one over Erb's point (2 cm above the midpoint of the patient's clavicle), one over cervical vertebra C2, and one over contralateral somatosensory cortex (Cc). If possible, one additional scalp electrode should be applied at Fz. To record upper limb SEPs, mild electrical pulses can be applied to skin over the patient's median, radial or ulnar nerves. See Fig. 1 for a characteristic SEP elicited by stimulating the median nerve.

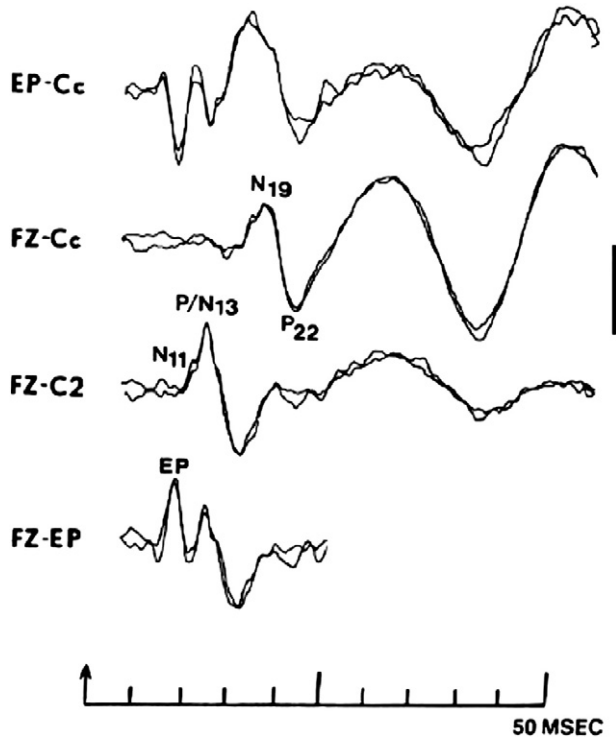


Fig. 1. Median nerve (upper limb) SEPs (vertical calibration mark is 2  $\mu$ V). From: Chiappa K.H., Ropper A.H., 1982. Evoked potentials in clinical medicine. N. Engl. J. Med. 306, 1140–1150.

Lower limb SEPs can be elicited by applying electrical stimulation to skin over the patient's tibial, peroneal, sural or saphenous nerves. Recording electrodes should be placed in the following locations:

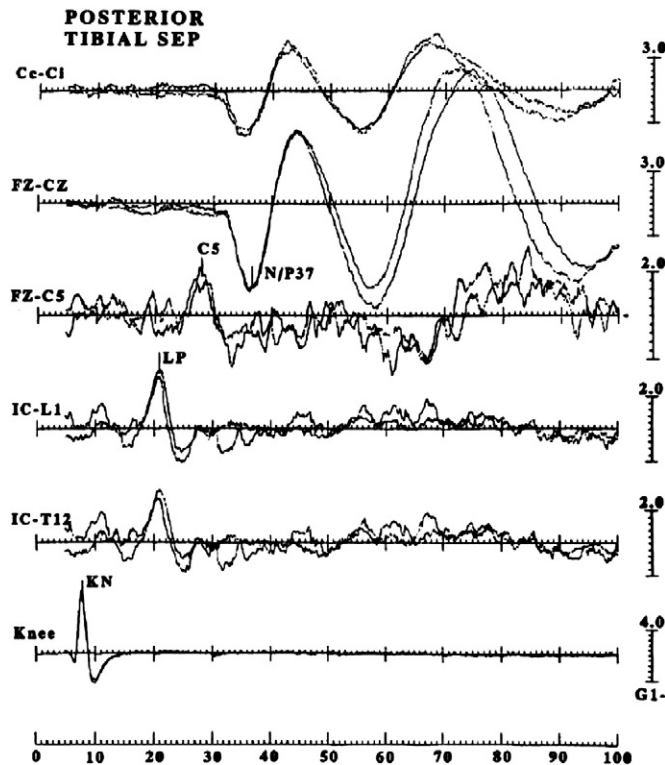


Fig. 2. Tibial nerve (lower limb) SEPs (horizontal axis is calibrated in ms; vertical axes are calibrated in  $\mu$ V). From: Chiappa K.H., 1997. Evoked potentials in clinical medicine. Philadelphia: Lippincott-Raven, page 302.

popliteal fossa crease (behind the patient's knee); over vertebrae L1, T12 and C5; on the iliac crest; and at scalp locations Cz, Fz, Cc, and Ci (ipsilateral somatosensory cortex). See Fig. 2 for a characteristic SEP elicited by stimulating the posterior tibial nerve.

SEPs provide assessments of neuronal conduction velocities and integrity of peripheral nerves, and central nervous system pathways that include the spinal cord and somatosensory cortex. Consequently, SEPs provide valuable information regarding the status and medical condition of many patients, including those who experienced TBI. SEPs can be recorded from anesthetized patients during surgery or from patients who have lost consciousness after injury. Somatosensory stimulation can also be used to elicit the P300 component, an indicator of cognitive functioning with generators in the frontal lobes, hippocampus, and other brain areas associated with attention, learning and memory. In fact, the P300 can be elicited in every sensory modality, provided that "novel" or "target" stimuli are presented in a way that facilitates generation of the component.

## 5. SEPs in assessments of TBI patients

SEPs are often recorded during assessments of TBI patients, especially those who experience serious injuries. Carter and Butt (2005) provided a listing of studies that used SEPs to evaluate patients who suffered severe brain injuries. In a systematic review, these authors compared the predictive powers of clinical examination (pupillary responses, motor responses and Glasgow Coma Scale, GCS), electroencephalography (EEG) and computed tomography (CT) to that of somatosensory evoked potentials (SEPs). For favorable outcome prediction, SEPs were superior in sensitivity, specificity and positive and negative predictive values, except for pupillary responses which had superior sensitivity and GCS which had higher specificity. SEPs had superior summary receiver operating characteristic curves, with the exception of motor responses, and superior ratio of odds ratios. For unfavorable outcome prediction, SEPs were superior to the other tests in sensitivity, specificity and positive and negative predictive values, except for motor and pupillary responses, GCS and CT scans which had superior sensitivity. Carter and Butt (2005) concluded that SEPs were the best single overall predictor of outcome among the methods they compared via literature review.

Robinson et al. (2003) reviewed studies that used median nerve SEPs to evaluate a total of 2701 comatose patients. Patients from multiple studies were divided into four groups: adults with hypoxic-ischemic encephalopathy ( $n = 1136$ ), adults with intracranial hemorrhage ( $n = 157$ ), adults and adolescents with traumatic brain injury ( $n = 838$ ), and children and adolescents with any etiologies ( $n = 570$ ). SEPs were categorized as normal, abnormal, or bilaterally absent, based on N19 or N20 components. Outcomes were categorized as persistent vegetative state or death vs. awakening. Of 838 TBI patients, 61% eventually awakened from coma. Looking at a subset of 232 TBI patients for whom SEPs were absent bilaterally, only 5% of the group awakened. Of 606 TBI patients who exhibited SEPs during initial evaluations, 82% of these patients awakened from coma. Robinson et al. (2003) concluded that SEPs predict the likelihood of non-awakening from coma with a high level of certainty.

In their study of 22 patients who suffered severe TBI, Lew et al. (2003) also reported that the bilateral absence of median nerve SEPs was predictive of poor outcome. Firsching and Frowein (1990) evaluated 112 comatose patients within 36 h of coma onset or hospital admission and observed that bilateral absence of SEPs, AEPs and VEPs was associated with a mortality rate of 98%. However, the presence of normal SEPs was associated with a 74% survival rate for patients in the study. Kane et al. (1996) recorded SEPs from 54 comatose TBI patients and reported that neural conduction times were correlated with Glasgow Outcome scores.

Rappaport et al. (1990) recorded intermediate (0–60 ms) and long latency (0–500 ms) SEPs from severe TBI patients in a long-term care

facility. Long latency (LL) SEP patterns correlated significantly with clinical disability as measured by the Disability Rating scale, while intermediate latency (IL) SEP patterns did not. The authors concluded that, “Evoked potential abnormality (EPA) scores based upon LL SEP patterns appear better able to reflect extent and severity of brain dysfunction and overall clinical condition than do IL SEP patterns for severe traumatic brain injury patients.”

Hughes et al. (2005) analyzed SEP data and the effects of amantadine on 123 patients with severe TBI who were comatose for one week or more. Because amantadine is sometimes used to reduce agitation in TBI patients, the authors wanted to determine if the medication facilitates recovery of consciousness for comatose patients. Hughes et al. concluded that amantadine had no effect on either emergence from coma or time to emerge from coma. However, the presence of SEPs was the best predictor of emergence from coma in the study ( $p=0.02$ ). Therefore, SEPs could be used as a physiological measure of efficacy for future rehabilitative interventions designed to facilitate recovery of consciousness.

Several studies have focused on patients with less severe injuries than those described above. For example, Wirsen et al. (1992) recorded SEPs from 18 frontal trauma patients and 17 age-matched control subjects. The findings were compared to the conventional EEG, frontal lesion volumes, severity of head injury, and outcome variables. The regional distribution of pathological EEG slowing corresponded well with the morphological lesions in most patients. There were no pathological findings in the SEPs, and all but one patient exhibited auditory P300 responses. Results from this and many other studies demonstrate that SEPs are more likely to be affected by severe TBI, and less likely to be affected by milder brain injuries.

Summary: Clearly, SEPs are valuable tools for assessment of sensory processing by patients who experience TBI. Not only can SEPs evaluate cortical processing of somatosensory stimuli, they can also provide vital information regarding the integrity and functionality of peripheral pathways and spinal tracts. Also, bilateral absence of SEPs is usually associated with poor prognosis and outcome for patients who suffer severe TBI.

## 6. Auditory event-related potentials (AERPs)

AERPs can be elicited in response to just about any sound a patient is able to hear, including clicks, tone pips, speech stimuli, music or environmental sounds. Different categories of AERPs can be used to assess auditory structures—from auditory nerve to auditory cortex—that are activated sequentially by sound stimulation (see Tables 1–3 for lists of putative neural generators for AERP components). The term “AERP” includes all of the possible electroencephalographic responses to sound, while the term auditory evoked potential (AEP) refers to responses that primarily reflect neural processing related to the physical characteristics of stimuli (such as sound intensity or frequency). Long-latency AEPs (with latencies between 90 and 250 ms) were the first to be discovered and described (Davis, 1939), probably because they have comparatively large amplitudes (see

**Table 1**  
Putative neural generators of auditory brainstem response (ABR) components.

Wave	Latency (ms)	Neural generator(s)
I	1.5–1.9	Auditory nerve
II	2.6–3.0	Auditory nerve, cochlear nucleus
III	3.7–4.1	Trapezoid body, superior olive
IV	4.8–5.4	Superior olive, lateral lemniscus
V	5.4–6.0	Lateral lemniscus, inferior colliculi
VI	7.0–7.6	Inferior colliculi, medial geniculate
VII	8–9	Medial geniculate, auditory cortex

**Table 2**  
Putative neural generators of auditory middle latency response (MLR) components.

Component	Latency (ms)	Neural generator(s)
Na	15–25	Medial geniculate, auditory cortex
Pa (P20)	25–35	Thalamo-cortical tracts, medial Heschl's gyrus
Nb	35–45	Thalamo-cortical tracts, lateral Supratemporal gyrus (STG)
Pb1 (a.k.a. P1 or P50)	40–65	Thalamo-cortical tracts, lateral Supratemporal gyrus (STG)
Pb2	60–85	Thalamo-cortical tracts, antero-lateral Heschl's gyrus

Fig. 3). The N100 and P200 components of long-latency AEPs are generated primarily by auditory cortex.

Middle latency responses (MLRs) were the next AERPs to be described (Geisler et al., 1958), and consist of components labeled Na, Pa, Nb and Pb (also known as P1 or P50). Auditory brainstem responses (ABRs), sometimes called BAERs, were not described until 1970 (by Jewett et al., 1970), probably because they have the smallest amplitudes and shortest latencies in this class of ERPs. Although they were described more recently in the AERP literature, ABRs have provided a great amount of clinical utility, especially in their utilization to assess the hearing of newborn babies and other populations unable to respond during conventional hearing tests. Because their generators include the auditory nerve and auditory brainstem, ABRs can be recorded from anesthetized patients during surgery or from other patients who have lost consciousness. ABR amplitudes tend to be greatest at scalp electrode Cz, which can be referenced to either earlobe or mastoid electrodes. For AERPs with latencies beyond the ABR, additional scalp electrodes can be added to enable topographic mapping of responses, source localization, and other post-hoc analyses.

In addition to the AERPs mentioned above, particular types and configurations of auditory stimuli can elicit P300 components (P300a or P300b), the mismatch negativity (MMN), the N400 component, contingent negative variation (CNV) and auditory steady state responses (ASSRs) among others. P300 is the AERP component used most often to evaluate cognitive functioning in TBI patients because its generators include neural structures that contribute to attentional states and abilities to differentiate among stimuli (see Table 3).

## 7. AERPs in assessments of TBI patients

### 7.1. Auditory brainstem response (ABR)

Hall et al. (1982) recorded click-evoked ABRs (using a rate of 21 clicks/s) from 20 patients with severe TBI and compared their responses with ABRs from 15 control subjects. All TBI patients were comatose at the time ABRs were recorded, within 76 h post-injury. Results showed abnormal ABRs in 80% of the patients. Abnormalities ranged from prolonged latency (waves I, III, V, and I–V interval) and reduced amplitude (wave V) of components to total absence of

**Table 3**  
Putative neural generators of auditory long-latency response (LLR) components.

Component	Latency (ms)	Neural generator(s)
N100 (N1)	75–140	Auditory Cortex; <i>plana temporale</i> and <i>polare</i>
P200 (P2)	150–230	Auditory Cortex; <i>plana temporale</i> and <i>polare</i>
Mismatch negativity (MMN)	150–250	Auditory Cortex, frontal cortex
P300 (P3)	250–350	Reticulothalamus, frontal cortex, medial septal area* (*connects to hypothalamus, hippocampus, amygdala)

discernable ABRs (see Fig. 3 and Table 1). Hall et al. (1982) reported the following relationships between ABR waveforms and functional outcome of the same patients one month later:

	Neurologic outcome one month post-injury			
	Good	Fair	Poor	Dead
Normal ABR	2	0	1	1
Mildly abnormal ABR	0	4	2	3
Moderately abnormal ABR	0	0	2	0
Markedly abnormal ABR	0	0	1	4

These results indicate a correlation between ABR morphology soon after injury and neurologic functions one month later, although exceptions obviously exist for this group of 20 patients. This is one of many studies that used ABRs to assess comatose patients. When we next describe other investigations of this kind, it will become clear that ABR results are not consistent across studies. Part of the explanation for this variability can be found in the description provided by Hall et al. (1982) of injuries suffered by their patients: The majority of patients were involved in motor vehicle accidents, but some were pedestrians, some were passengers, some were on motorcycles, and one was riding a bicycle. Other causes of head injury included gunshots, assaults, and falls. The gunshot victims sustained injuries to different regions of the brain: frontal, occipital, and parietal–occipital. All of the patients in this study suffered different types of injuries to a variety of brain areas. Here is what the patients had in common: they all sustained severe head injuries and they were all in comatose states at one time (although the depth of coma varied). Given this variability, it is not surprising that ABR results and functional outcome varied widely within the patient group. This variability among patients will also help to explain differences in ABR results reported in numerous studies of TBI patients that have been published during the last few decades.

Cant et al. (1986) recorded ABRs from 35 patients within 4 days of onset of post-traumatic coma. Although abnormal ABRs were associated with an unfavorable outcome in 6 of 7 patients, only 19 of 28 patients with normal ABRs had a favorable outcome. Cant and colleagues concluded that normal ABRs were therefore of little prognostic significance in this population. Shin et al. (1989), Rappaport et al. (1991a); Cusumano et al. (1992), Guérit et al. (1993), Keren et al. (1994), Soldner et al. (2001), Nölle et al. (2004), and Fischer et al. (2008) did not find ABRs to provide useful prognostic information in assessments of patients with severe TBI. However, Ganes and Lunder (1988), Kane et al. (1996), Liesiene et al.

(2008), and Munjal et al. (2010) reported that ABR results did correlate with functional outcomes of TBI patients.

A few studies used ABRs to assess the progress of TBI patients who received rehabilitative interventions. For example, Pape et al. (2009) reported the case study of a 26-year-old male patient who experienced severe TBI and remained in a vegetative state nine months post-injury. The authors recorded ABRs and median nerve SEPs from the patient before and after transcranial magnetic stimulation (TMS) was delivered to his right frontal scalp/cortex 5 days per week for 6 weeks. At baseline and after 30 TMS treatments, cortical SEPs could not be recorded from the patient in response to median nerve stimulation on either side. However, ABRs were present pre- and post-TMS. After 30 TMS sessions, the patient's ABRs improved in their morphology and exhibited reduced latencies for wave V and waves I–V interpeak values compared to baseline. Also, after 15 TMS treatments, the patient improved from being in a vegetative state to a minimally conscious state (MCS). This improvement in consciousness was sustained at least one year after the last TMS session. In this case, improvements in auditory processing appear to be correlated with improvements in consciousness that were facilitated by a neurological intervention. Therefore, ABRs might be useful physiological measures of progress for patients who experience severe TBI.

Summary: ABRs are useful for assessing auditory functions, especially in non-responsive patients. However, they might not be consistent indicators of functional outcomes.

## 7.2. Middle latency responses (MLRs) in assessments of TBI patients

Compared to ABRs and auditory long-latency responses (LLRs), relatively few investigators have used MLRs to assess TBI patients. Hall et al. (1983) recorded ABRs and MLRs from three patients who suffered severe TBI 1–4 days earlier. One of the patients exhibited normal MLRs, and the other two patients had abnormal MLR waveforms. These electrophysiological results correlated positively with neurological outcomes (including changes in Glasgow Coma Scores) several months post-injury.

In their study of 20 patients who experienced post-concussion symptoms after mild head injury, Gaetz and Weinberg (2000) reported that ABRs and MLRs recorded from patients and control subjects were not significantly different. A study by Munjal et al. (2010) helps to clarify the relationship between MLRs and severity of TBI. These authors collected data from 290 patients: 150 with mild TBI, 100 with moderate TBI, and 40 with severe TBI. Amplitudes of MLR components Na and Pa were positively correlated with severity of injury in this population (see Table 2 for generators of these components that were affected). In a study of 346 coma patients (96 with TBI), Fischer et al. (2004) reported that the presence of MLR was a predictor for awakening. Logi et al. (2003) observed that the Pa component was a predictor for regaining consciousness in their study of 131 comatose patients, 22 of whom had TBI.

Arciniegas et al. (2000) used an MLR protocol to assess sensory gating in 20 patients who sustained TBI one or more years earlier. Within this group, 5 patients had mild, 6 had moderate, and 9 had severe TBI. The protocol delivered pairs of brief auditory stimuli with a 0.5 sec inter-pair interval and a 10 sec inter-stimulus interval. Normal subjects generate a P50 component in response to the first stimulus in each pair, and a smaller or absent P50 to the second stimulus in the pair—an effect called auditory sensory gating. Many patients with schizophrenia do not exhibit normal sensory gating during this protocol; their P50 response to the second auditory stimulus is similar in amplitude to their P50 response to the first stimulus. Auditory sensory gating appears to depend on cholinergic systems, particularly those involving nicotinic receptors in the hippocampus. Results from the study by Arciniegas et al. (2000) indicated that TBI patients exhibited reduced sensory gating compared to control subjects. In

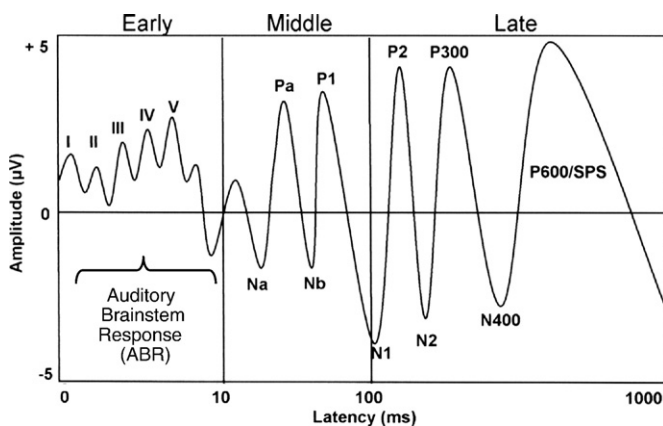


Fig. 3. Diagram of auditory ERPs recorded at electrode Cz (amplitudes are not drawn to scale).

From: Friesen, L.M., Tremblay, K.L., 2003. Electrophysiological Measures of Hearing, Speech, and Language. In S. Raymer (Ed.) *ASHA: Perspectives on Neurophysiology and Neurogenic Speech and Language Disorders*. 13(1), 3–10.

fact, each of the TBI sub-groups (mild, moderate, and severe) showed similar degrees of impaired auditory gating compared to controls.

Musiek et al. (2004) recorded MLRs and ABRs before and after an auditory rehabilitation program was administered to a patient who experienced mild TBI. The patient was a 41-year-old female who was thrown from a horse and struck the top of her head on the ground. After a brief loss of consciousness, she continued to experience post-concussive symptoms (headaches, dizziness, fatigue, attention and memory problems) more than one year post-injury. Although her pure-tone hearing thresholds were normal, the patient experienced difficulty comprehending complex auditory directives, and understanding speech if people spoke rapidly or if background noise was present. Abnormal results on tests of auditory processing indicated that the patient experienced central (as opposed to peripheral) deficits when processing complex auditory stimuli. ABRs and MLRs were recorded before and after the patient participated in an individualized auditory rehabilitation program, which included dichotic training, reading to herself, auditory memory tasks, speech discrimination and temporal sequence training. Post-training, the patient exhibited improvements in both auditory and cognitive processing. However, ABRs and MLRs recorded after training were not significantly different from ABRs and MLRs recorded at baseline. It is likely that these AERPs are not sensitive enough to detect subtle changes in neural and cognitive functions experienced by mild TBI patients. Future studies of this kind should employ auditory P300 protocols which might be able to reflect such changes in cognitive functions.

Summary: Because of their inconsistency and questionable relevance, MLRs are the least useful AERPs for assessment of TBI patients. A possible exception is the MLR protocol to assess sensory gating.

### 7.3. Long-latency responses (LLRs) in assessments of TBI patients

Many studies have presented auditory stimuli to TBI patients using the “oddball” protocol: “frequent” stimuli (such as 500 Hz tones) are presented a majority of the time (e.g., 80%), while “rare” or “target” stimuli (such as 1000 Hz tones) occur less often (20% of the time) and are interspersed among the frequent tones. In normal subjects, this protocol usually elicits a robust P300 component when either an active (response required) or passive (no response required) paradigm is used. Generators of the P300 include frontal cortex, reticulothalamus, and the medial septal area (which connects to the hypothalamus, hippocampus, and amygdala). Therefore, the P300 is sometimes called a “cognitive” component that can be used to assess patients’ state of attention and their ability to differentiate among stimuli.

Duncan et al. (2005) reviewed auditory ERP studies involving TBI patients and summarized their results. A common effect of TBI is reduced amplitude and/or increased latency of the P300 recorded from patients compared to control subjects. However, patients with mild TBI do not exhibit abnormal P300s in some studies (Potter et al., 2001; Sivák et al., 2008), but in other studies they do (Alberti et al., 2001; Segalowitz et al., 2001). Von Bierbrauer and Weissenborn (1998) recorded auditory P300s from 15 patients with mild TBI at four time points post-injury: 24 h, 1 week, 3 and 8 weeks. Because P300 latency was greater than controls in only 20% of patients, the authors concluded that, “in contrast to severe head injury, in general the P300 is not affected by minor head injury.”

Moderate and severe TBI are more likely than mild TBI to be associated with abnormal LLRs. In several different studies, Lew et al. (2004, 2007, 2009) reported reduced amplitude and increased latency P300 components from patients with severe TBI compared to controls. Similar results—increased latency and/or decreased amplitude P300s—were observed by Rugg et al. (1988), Harris and Hall (1990), Wirsén et al. (1992), Reinvang et al. (2000), Mazzini et al. (2001), Solbakk et al.

(2002), Elting et al. (2005), Duncan et al. (2005), Doi et al. (2007), and Reza et al. (2007) among others.

In addition to tones, other types of auditory stimuli can be used to elicit the P300 response component. For example, Folmer and Yingling (1997) recorded auditory P300s from normal subjects in response to their own first name. Perrin et al. (1999) demonstrated that normal subjects generate a P300 response to their own name even during stage II sleep. Lew et al. (2002) recorded P300s from 22 normal subjects in response to three different speech stimuli and observed the largest amplitude P300s for the subjects’ own name. Because clinicians and family members of TBI patients often try to elicit a response by calling the patient’s name, the electrophysiological protocol has been applied to this population. Mazzini et al. (2001) reported that patients who suffered severe TBI exhibited P300s in response to their name, but the latency of the component was later compared to P300s from control subjects. In response to tones, the same TBI patients had increased latency and decreased amplitude N100 components compared to controls. Perrin et al. (2006) recorded AERPs from 15 brain-damaged patients in response to their own first name. Five of these patients experienced TBI, 5 were in a vegetative state (VS), 6 were in a minimally conscious state (MCS) and 4 were affected by locked-in syndrome (LIS). A P300 component was observed in response to the patient’s name in all patients with locked-in syndrome, in all MCS patients, and in 3 of 5 patients in VS. P300 latency was significantly ( $P < 0.05$ ) delayed for MCS and VS patients compared with healthy volunteers. Perrin et al. (2006) concluded that partially preserved semantic processing could be observed in non-communicative brain-damaged patients, notably for the detection of salient stimuli, such as the subject’s own name. This function seems delayed in MCS and (if present) in VS patients. However, a P300 response does not necessarily reflect conscious perception and cannot be used to differentiate VS from MCS patients.

Schnakers et al. (2008) recorded AERPs in response to the subjects’ own name from 8 patients in a vegetative state (VS), 14 patients in a minimally conscious state (MCS), and 12 healthy volunteers. Like controls, MCS patients presented a larger P300 to their own name in both passive and active conditions. Also, P300s recorded from MCS patients in response to name stimuli had larger amplitudes in the active than in the passive condition, suggesting voluntary compliance to task instructions that was also exhibited by control subjects. These responses were even observed in patients with low behavioral responses (e.g., visual fixation and pursuit). In contrast, no P300s were observed for VS patients in response to their own name. Schnakers et al. (2008) concluded that active ERP paradigms may permit detection of voluntary brain function in patients with severe brain damage and disorders of consciousness, even when patients may present with limited signs of awareness. However, variability within each patient group must be taken into account when interpreting the results of this study. In the MCS group, 7 of 14 patients experienced TBI, 5 experienced anoxia, 1 experienced hemorrhage, and 1 had metabolic disorder listed as the etiology for brain injury. In the VS group, 3 of 8 patients experienced TBI, 3 experienced anoxia, 1 experienced stroke, and 1 had encephalitis listed as the etiology for brain injury. Time between onset of brain injury and time of ERP recording also varied substantially among patients: from 16 days to 23.7 years in the MCS group; and from 12 days to 7.6 years in the VS group. As discussed previously, this type of variability must be considered by anyone who attempts to apply the results or protocols to a different population of patients. For example, although all 14 of the MCS patients exhibited P300 components in the passive condition, only 5 of them generated P300s in the more demanding active condition. Of these 5 patients, 4 had TBI and 1 had anoxia as the cause of their brain injury.

Becker and Reinvang (2007) recorded long-latency AERPs from 8 patients (some of whom experienced TBI) before and after they

received speech-language therapy for aphasia. Three AERP protocols were used: passive syllable discrimination, passive tone discrimination, and active syllable discrimination/identification. After 3 or 4 months of speech-language therapy, patients exhibited significant improvements in aphasia and auditory comprehension scores. Also, ipsilesional N2 and P3 amplitudes increased significantly post-therapy. A significant shift in topographical distribution of the N2 component (from the contralesional to the ipsilesional hemisphere) was observed. The authors concluded that 1) AERP waveforms reflect individual differences in brain reorganization after TBI, and 2) AERPs are a potentially useful method for detecting individual activation patterns relevant to recovery in aphasia rehabilitation.

Summary: Auditory LLRs are clinically useful for assessment of higher-order neural functions and processing in TBI patients. Auditory P300 protocols can be used to assess cognitive functions in this population.

#### 7.4. Mismatch negativity (MMN) in assessments of TBI patients

The MMN is a response to a deviant stimulus within a sequence of otherwise regular stimuli and is generated when stimuli are presented in a many-to-one ratio (Näätänen and Escera, 2000). In a sequence of standard sounds, the deviant or oddball stimulus will elicit an MMN response if the duration of the interstimulus interval (ISI) is sufficiently brief. Shorter ISIs distinguish MMN protocols from P300 protocols; stimulus type and presentation are otherwise similar. The MMN, like the P300, can occur even if the subject is not consciously paying attention to the stimuli. The auditory MMN (which can occur in response to deviance in pitch, intensity, or duration) is a fronto-central negative potential with primary generators in auditory cortex and a typical latency of 150–250 ms after the onset of the deviant stimulus. Neural generators of the MMN might also include frontal cortex and thalamus (Näätänen et al., 2007). The amplitude and latency of the MMN are related to how different the deviant stimulus is from the standard. Large deviances elicit MMN at earlier latencies; for very large deviances, the MMN can overlap the auditory N100 component (Campbell et al., 2007).

Fischer et al. (2004) used the pupillary light reflex, MMN, MLR and auditory N100 components to assess 346 comatose patients, 96 of whom experienced TBI. One year later, the same patients were classified as “awake” or “not awake.” Results indicated that pupillary light reflex, N100, MLR, patient’s age, and etiology of TBI were the most discriminating factors for awakening. Statistical analysis showed that pupillary reflex was the strongest prognostic variable for awakening (estimated probability 79.7%). The estimated probability of awakening rose to 87% when N100 was present and to 89.9% when MLRs were present. When MMN was present, 88.6% of patients awakened. No patient in whom MMN was present became permanently vegetative.

In a study of 54 comatose TBI patients, Kane et al. (1996) reported that the presence of MMN predicted which patients returned to consciousness. Return of the MMN component also preceded changes in the Glasgow Coma Scale and was a good indicator of 90-day functional outcome for these patients. Wijnen et al. (2007) recorded MMNs from 10 patients in vegetative state and observed that MMN amplitude increased as patients returned to consciousness. In this study, MMN amplitude and latency measurements were good predictors of patients’ return to consciousness. In a study of 50 comatose patients (15 with TBI), Fischer et al. (2008) compared the prognostic value of MMN to auditory P300 elicited by the patient’s own name. MMN to deviants was found in 14/50 patients and a central-parietal P3 to the patient’s name was found in 21/50 patients. Four patients exhibited an MMN, but no P3 component. Eleven patients had a novelty P3, with a late parietal component for 5 of them, but no MMN. The presence of P3 was highly correlated with awakening. Compared to MMN, P3 showed as large a specificity for

awakening (0.85) and it showed a much higher sensitivity (0.71 vs. 0.42). All but one patient with a P3b component woke up. The authors concluded that the use of novelty P3 elicited by the patient’s name increases the prognostic value of MMN alone and improves the assessment of comatose patients by demonstrating the activation of higher-level cognitive functions. According to Fischer et al. (2008), this demonstrates that unconsciously-perceived stimuli are processed and activate brain areas similarly to consciously-perceived stimuli. Polo et al. (2002) used MMN to demonstrate the long-term effects of TBI. One year or more post-injury, a group of 11 TBI patients exhibited lower amplitude MMNs compared to 14 age-matched control subjects. These patients also had abnormal ERP responses to visual stimuli and slower reaction times compared to controls.

Summary: AERPs, like VERPs and somatosensory ERPs, can be used to evaluate the integrity of a sensory system from peripheral receptors to cortical processing of input. AERPs can also be utilized to assess states of consciousness and cognitive processing in TBI patients. Variability in patient and injury characteristics, AERP recording methods and parameters must be taken into account when interpreting or comparing results.

#### 8. Visual event-related potentials (VERPs)

Using scalp surface electrodes, neural activity can be recorded in response to a variety of visual stimuli, including flashes from a strobe light (which can be used even if the patient’s eyes are closed); different colors or patterns of light on a display screen; written letters, words, or sentences; drawings, photographs, symbols, scenes or facial expressions. In addition to display screens or monitors, these stimuli can also be presented via specialized goggles which allow control over input to each eye.

For pattern-shift visual evoked potentials (VEPs) used routinely for clinical evaluations, Chiappa (1997) recommends a minimum of two recording electrodes at Pz and Oz (according to the International 10–20 System) because VEPs usually have largest amplitudes in occipital or parietal regions of the patient’s scalp. Of course, additional scalp surface electrodes may be used to facilitate topographic mapping of VEP voltages or to identify neural generators via source localization analyses of components. Multiple scalp electrodes also provide additional options for post-hoc analyses of EPs using different

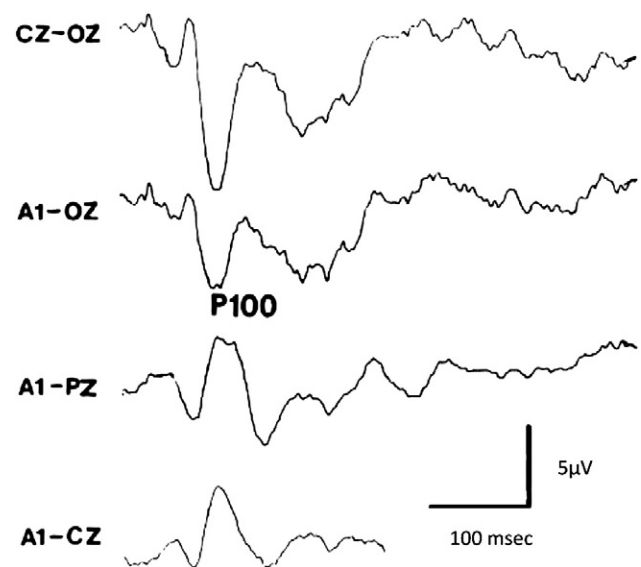


Fig. 4. Pattern shift VEPs from one eye of a normal subject (horizontal calibration mark is 100 ms; vertical calibration mark is 5  $\mu$ V). From: Chiappa K.H., 1997. Evoked potentials in clinical medicine. Philadelphia: Lippincott-Raven, page 40.

recording-reference electrode combinations/configurations. Fig. 4 shows a typical pattern-shift VEP elicited by one eye in response to a checkerboard pattern displayed on a computer monitor. The primary generator of the P100 component is visual cortex.

### 9. VERPs in assessments of TBI patients

Duncan et al. (2005) reviewed visual ERP studies involving TBI patients and summarized their results. One of the studies (Gaetz and Weinberg, 2000) recorded VERPs from 20 subjects with histories of TBI and persistent post-concussion symptoms (PCS). Gaetz and Weinberg (2000) used a reversing checkerboard pattern to elicit P100 components; a variety of words, numbers and shapes to elicit N2/P3 and contingent negative variation (CNV). The largest difference in the PCS vs. control groups was for visual P300 latency: 40% of PCS subjects were outside the normal range for visual shape, number or word stimuli. Visual CNV amplitudes were outside the normal range for 25% of the PCS subjects; P100 latencies were outside the normal range for 30% of the PCS subjects. The authors concluded that VERP latency may be a more reliable indicator than VERP amplitude for changes in brain function following TBI. Gaetz et al. (2000) conducted a different VERP study involving 271 hockey players who had histories of 0–3 or more concussions. Using stimuli similar to their previous study, the authors reported that a greater number of concussions were positively correlated with increased P300 latency. Subjects with 3 or more concussions also experienced more headaches, anxiety, memory and concentration problems than subjects with no history of concussion.

Several VERP studies of patients with mild TBI (mTBI) have been conducted. Chen et al. (2006) used flash stimuli to evaluate patients within 24 h of injury and again 3 months later. Results from the initial evaluation showed reduced amplitude N70–P100 components from patients compared to control subjects. However, this difference did not persist at follow-up 3 months later. Lachapelle et al. (2008) used a variety of stimuli to evaluate 17 patients with mild TBI: pattern reversal, simple motion, texture segregation, and a cognitive “oddball” protocol. Time between injury and VERP recording varied between 1 and 28 months among patients in the study. Participants with mTBI showed a statistically significant ( $p < 0.05$ ) amplitude reduction for cognitive ERPs and delayed latencies for texture segregation ( $p < 0.05$ ) and cognitive paradigms ( $p < 0.005$ ) compared to controls. Furthermore, participants with mTBI presenting texture segregation or cognitive ERP latency delays upon admission were at significantly ( $p < 0.01$ ) greater risk of negative vocational outcome than mTBI participants with normal electrophysiology.

Freed and Hellerstein (1997) used pattern-evoked VEPs to evaluate 50 patients with a history of mTBI, 18 of whom received optometric rehabilitation. During follow-up 12–18 months later, the treatment group exhibited fewer VEP abnormalities than the non-treatment group of patients. Granovsky et al. (1998) recorded VERPs from 13 mTBI patients in response to stressful, accident-related words (such as crashed car, head injury, and ambulance) and to neutral words (such as pigeon, field and joke). Overall, accident-related words produced a significantly larger P300 wave than neutral words in patients ( $P = 0.0001$ ), but not in controls ( $P = 0.5741$ ). Significant correlation was found between combined P300 amplitude difference (all stressful words vs. all neutral words) and the patient's Zung state anxiety score ( $r = 0.68$ ,  $P = 0.01$ ). This study provides a good example of utilization of ERPs in assessment of rehabilitative interventions.

Doi et al. (2007) recorded VERPs from 20 patients who suffered TBI an average of 25 months previously; mean GCS scores were 11.85 after resuscitation. P300 components were elicited using images of crying and smiling babies as visual stimuli. Results indicated that P300 amplitudes were significantly smaller in patients than in controls for the crying baby, but the amplitudes were similar between groups for the smiling baby. Control subjects showed smaller P300 amplitudes

for the smiling baby than for the crying baby, but patients showed no difference. In patients, the P300 latency for both smiling and crying babies was longer than in the controls. N200 latency in patients was significantly longer than in controls only for the crying baby. Patients' auditory ERPs showed smaller P300 amplitudes but similar P300 latencies compared with controls. The authors concluded that visual ERPs are potentially useful for evaluating cognitive dysfunction in patients after TBI.

VERPs have also been used to assess patients with moderate or severe head injuries. Lew et al. (2005) recorded VERPs from 13 such patients in response to images of angry or neutral faces. In this study, patients exhibited P300 components with smaller amplitudes and longer latencies than P300s from control subjects. In other studies of patients with histories of severe TBI, Lew et al. (2004, 2007, 2009) also reported smaller amplitude and longer latency P300 components from patients compared to controls. Patients in these studies also exhibited delayed reaction times compared to healthy control subjects. Duncan et al. (2005) evaluated TBI patients two or more years post-injury. In both the visual choice task and the continuous performance test, patients had significantly smaller P300 amplitudes compared to control subjects.

Muller et al. (2002) used a visual P300 protocol to assess 11 TBI patients 3–9 months post-injury. GCS scores for these patients ranged between 3 and 6 immediately post-trauma. The VERP protocol consisted of a digit discrimination test: when an odd digit was displayed on the screen, subjects were instructed to press a button with the middle finger of their right hand; when an even digit was displayed on the screen, subjects were instructed to press a button with the index finger of their right hand. At the time of initial testing, visual P300 latencies were significantly longer for TBI patients compared to control subjects. On subsequent VERP runs, continuous vibration was applied to the left extensor radialis (lower arm) muscle of subjects while they responded to digits displayed on the screen. While vibration had no effect on VERPs recorded from control subjects, P300 latency was reduced significantly for TBI patients who received vibratory stimulation during the visual discrimination task. Arm vibration also reduced target detection times in TBI patients, but not in control subjects. Muller et al. (2002) postulate that arm vibration improves thalamocortical processing which is deficient in the patient group. The authors suggest that muscle vibration may develop into a rehabilitative strategy for TBI patients to enhance cortical reorganization and plasticity. The visual P300 protocol would provide a useful physiological measure of efficacy for this therapeutic intervention.

Another application of VERPs in visual rehabilitation was reported by Padula et al. (1994) who evaluated 10 patients with histories of TBI and post-trauma vision syndrome (PTVS). Most of these patients exhibited visual abnormalities including tracking, convergence, exophoria, and retinoscopic variations. The authors state that many TBI patients have significant visual problems that cause binocular, accommodative and oculomotor dysfunction as well as reductions in acuity. These symptoms may be due to a disturbance of the ambient visual process, which in turn interferes with binocularity. This study implemented an intervention involving prisms and bi-nasal occluders which were used during a chessboard-pattern reversal VEP protocol displayed on a screen. The authors hypothesized that an increase in P100 amplitude should occur for the TBI group if the ambient visual process resumes its role in stabilizing the peripheral field and enhancing the foveation process. When TBI patients used base-in prisms and bi-nasal occluders, their P100 amplitude increased significantly compared to the non-compensated condition. These results indicate that binocular neurons in visual cortex of TBI patients had been damaged at some point. Padula et al. (1994) suggest that rehabilitative interventions might improve binocular functions for TBI patients, and VEPs could be used to assess the effectiveness of such treatments.

Like all of the ERPs described in this article, VERPs have been used to assess patients in comatose states. Guérit et al. (1993) assessed 184 comatose patients (132 of whom suffered TBI) using SEPs, VERPs and auditory brainstem responses (ABRs). Results indicated that some cortical and brain-stem responses were abnormal in head trauma patients. The abnormalities were clustered into four patterns: hemispheric damage without brainstem involvement (pattern 1), mesencephalic lesion (pattern 2), transtentorial herniation (pattern 3), and brain death (pattern 4). Patterns 3 and 4 were uniformly associated with death; patterns 1 and 2 were associated with a higher likelihood of awakening. However, Kane et al. (1996) recorded visual P300s from 54 comatose TBI patients and reported that the component's presence and characteristics were not correlated with Glasgow Outcome scores. In a study of 112 coma patients, Firsching and Frowein (1990) reported that normal VEPs were associated with a survival rate of 60%.

Summary: VERPs provide valuable information for assessment of visual pathways and processing in TBI patients. Patients' state of consciousness and cognitive functions can also be evaluated via ERP responses to a broad spectrum of visual stimuli. However, the collection of VERP studies described in this article illustrates the variability of electroencephalographic results that can occur due to differences in patient characteristics (including type and extent of injury), recording protocols and parameters. This high degree of variability compromises our ability to compare ERP results across studies and remains problematic in all sensory modalities.

## 10. Multi-modality event-related potentials

One example of a multi-modality ERP is the contingent negative variation (CNV). Walter et al. (1964) observed that a single click stimulus elicits a brief positive peak and a brief negative peak in patients' EEG pattern. Repetitive flashes of light can also elicit brief positive and negative peaks during electroencephalographic recordings. When a single click is followed by repetitive flashes which are terminated by a button press, there is a large gradual negative peak which ends sharply with the button press. This is the contingent negative variation, which appears after about 30 trials of paired stimuli, although this number can be reduced when the subject understands the task in advance. Paired stimuli such as light flashes, clicks, and tones have all been used to elicit the CNV which has a latency between 260 and 470 ms and putative generators within frontal cortex (Hultin et al., 1996; Zappoli, 2003). Walter et al. (1964) reported that CNV amplitude varies directly with subjective probability or expectancy of the imperative stimuli and Tecce (1972) suggested that the CNV is related to both subjects' attention and arousal level.

Gaetz and Weinberg (2000) used tones to elicit P300 and CNV components from 20 patients who experienced TBI and persistent post-concussion symptoms (PCS). Results indicated that more TBI patients than control subjects exhibited abnormal P300s and CNVs. However, a study of 10 patients with histories of mild TBI (Segalowitz et al., 2001) found no significant differences in patients' CNVs compared to control subjects.

Most the studies described in this article recorded ERPs in more than one sensory modality during assessments of TBI patients. A good example of the clinical utility of multi-modality ERPs is provided by Rappaport et al. (1991b) who evaluated seven severe TBI patients in a vegetative state using two conditions designed to elicit P300 responses: two auditory tones (unimodality condition), and a flash and auditory tone (bimodality condition). A third non-P300 condition using a single repetitive tone was also presented. Patients produced P300 responses under all three conditions, even though the severity of their clinical condition did not allow them to respond to even simple commands. No P300 latency differences were found, but P300 amplitude was significantly larger under the bimodality stimulus condition than either

the unimodality or non-P300 condition. P300 amplitude under the unimodality condition, in turn, was larger than the P300-like response in the non-P300 condition.

Firsching and Frowein (1990) recorded somatosensory, visual and auditory evoked potentials from 112 comatose patients within 36 h after the onset of coma or admission. Main causes of coma were head injury, and intracerebral and subarachnoid hemorrhage. The initial bilateral loss of any evoked potential was associated with a mortality of 98%. Normal somatosensory evoked potentials were associated with a survival rate of 74%, while normal visual and normal auditory evoked potentials had a survival rate of 60% and 66%, respectively.

Lew et al. (2003) used SEPs and speech-evoked AERPs to evaluate 22 patients with severe TBI. These authors concluded that, "although median nerve SEP continues to make reliable prediction of ominous outcome in severe traumatic brain injury, the addition of the speech-evoked ERPs may be helpful in predicting favorable outcomes. The strength of the latter test seems to complement the weakness of the former."

Duncan et al. (2005) found numerous differences in auditory processing in TBI patients compared to control subjects: longer reaction times (but normal accuracy), longer N200 and P300 latencies, and reduced N100 and N200 amplitudes. In contrast, on visual tasks, these authors reported that only reduced N200 VERP amplitude distinguished survivors and controls. Duncan et al. (2005) concluded that cognitive ERP components are more sensitive than sensory EP components to the effects of trauma. Specifically, in TBI survivors, the amplitudes of N200 and P300 are often reduced, and their latencies prolonged. In general, as compared with visual ERPs, auditory ERPs may be more susceptible to the effects of closed head injury, suggesting that the auditory processing system is more vulnerable to TBI than the visual system.

Several authors recommend using multi-modality ERPs to provide more global assessments of TBI patients than could be attained by recording ERPs in response to only one type of sensory stimuli (Guérit, 2005; Lew et al., 2003). Studies by Goodwin et al. (1991), Butinar and Gostisa (1996), Goldberg and Karazim (1998) and Balogh et al. (2001) concluded that ABR results combined with SEP results provided useful prognostic data. Because the type, extent and location of brain damage are so variable in TBI, it is advisable to use more than one modality of ERPs to evaluate the effects of injury on sensory processing and cognitive functions. As described in previous sections of this article, particular ERPs have more or less diagnostic and prognostic value for assessments of specific patients and types of injury. Also, because TBI can result in damage to more than one sensory system (Lew et al., 2010), it is important to evaluate as many modalities as possible in the time allowed. Results from multi-modality ERP recordings should be combined with other measures of patient evaluation to enhance the diagnostic and prognostic accuracy of assessment procedures for this population (Elting et al., 2008).

## 11. Correlations between sites of brain damage and ERP results

Physical or metabolic damage to the brain or peripheral receptors can result in impaired transmission of sensory information to the CNS and disrupt communication/processing within and between central pathways, contributing to abnormal ERPs in some cases. It is not difficult to imagine how neuronal damage and disruption results in ERP components that are delayed, reduced in amplitude, or absent. Because ERP components are generated by populations of neurons, waveform abnormalities can reflect damage to large numbers of cells or fibers within and between sensory pathways. However, because most ERP waveforms have multiple neural generators, it is often difficult to correlate specific ERP abnormalities with sites of lesion or extent of injury. Dr. Robert Knight and colleagues have been investigating these relationships for more than three decades. Knight et al. (1980) compared AERPs in patients with unilateral lesions of the

dorsolateral frontal cortex ( $n=10$ ) or temporal–parietal cortex ( $n=10$ ) to those of a group of age-matched normal subjects. For patients with frontal lesions, LLR amplitudes were larger in response to tones presented in the ear contralateral to the lesion than they were for tones presented ipsilaterally. Patients with unilateral temporal–parietal lesions exhibited N100 components that were markedly reduced in amplitude at all scalp sites. The P200 component, however, had similar amplitudes and latencies compared to normal subjects. These results underline the critical role played by the cortex of the posterior–superior temporal plane and the adjacent cortex of the parietal lobe in the production of the N100 component. A later study of patients with unilateral brain lesions by Knight et al. (1988) demonstrated that the superior temporal gyrus also plays a role in generating AERP components P50 and N100. Knight (1984) recorded auditory P300 components from subjects with unilateral prefrontal damage. These subjects generated P300 complexes to target stimuli that did not differ significantly from control subject responses. Prefrontal damage, however, resulted in a specific defect in the P300 response to an unexpected novel stimulus. Prefrontal patients showed neither N200 enhancement nor the fronto-central P300 response to the novel stimulus that was found in control subjects. These findings indicate that prefrontal regions are engaged during patients' response to unexpected novel stimuli. Abnormalities in prefrontal control of sensory–limbic integration may be responsible for the decreased P300 amplitude in response to novel stimuli found in these unilateral prefrontal lesioned patients. Knight (1984) suggested that major features of the human frontal lobe syndrome may be explained by a physiological inability to control attention and orientation systems after prefrontal damage. In a later study, Yamaguchi and Knight (1992) recorded somatosensory P300 components in response to target and novel stimuli delivered to the sole of the foot in 6 patients with unilateral temporal–parietal lesions. Age-matched controls generated a parietal maximal target P300 and a frontal–central maximal novelty P300 to foot stimulation. Unilateral temporal–parietal lesions abolished target and novelty P300 responses over all scalp sites for stimuli delivered contralateral to the lesion. The P300 was also reduced in response to ipsilateral stimuli at electrodes over the lesioned hemisphere, with partial P300 preservation observed at electrode sites over the non-lesioned hemisphere. These results parallel the findings for upper limb stimulation (Yamaguchi and Knight, 1991) and provide evidence that temporal–parietal cortex contributes to somatosensory P300 generation.

## 12. Discussion/recommendations

This article is not intended to be an exhaustive review of studies that have used ERPs to assess TBI patients. Instead, this overview is provided in the hope that it will be of interest to clinicians and researchers who conduct or interpret electrophysiological evaluations of this population. Because this article reviewed ERP studies that have been conducted in three different sensory modalities, involving patients with a wide range of TBI severity ratings and circumstances, it is difficult to provide a coherent summary of findings. However, some general trends emerge that give rise to the following observations and recommendations:

- Bilateral absence of EPs is often associated with poor clinical prognosis and outcome. However, the presence of normal ERPs does not guarantee favorable outcome.
- Shorter-latency ERPs (such as ABRs and short-latency SEPs) are often not affected by mild TBI. These ERPs are more likely to be abnormal in severe TBI, if at all. Therefore, severity of injury should be taken into account when deciding which ERPs to use during patient assessment.
- Longer-latency and cognitive ERPs should be used to evaluate all TBI patients, including those with mild TBI. Support for this recommendation comes from a study by Rappaport et al. (1991a) who recorded ABRs and auditory LLRs from 75 long-term TBI patients in a care facility. LLRs were found to be significantly correlated with clinical disability as measured by the Disability Rating Scale, while ABRs were not. Also, ABR patterns were consistently and significantly less abnormal and less sensitive to overall dysfunction than LLR patterns. Rappaport et al. (1991a) concluded that ABRs have relatively little utility for evaluating brain impairment in surviving TBI patients. In general, long latency ERPs are better able to reflect the extent and severity of brain dysfunction and overall clinical condition than are short latency EPs in long-term severe TBI patients. Therefore, long-latency ERPs should be obtained routinely in the evaluation of these patients.
- ERPs evoked by a variety of sensory stimuli should be used to evaluate TBI patients, especially those with severe injuries. This approach is recommended because multi-modality ERPs provide more global assessments of TBI patients than could be attained by recording ERPs in response to only one type of sensory stimuli.
- Appropriate ERP protocols should be combined with other assessment tools (such as behavioral tests, EEG and imaging) to provide more accurate diagnoses, prognoses and evaluations of sensory processing and cognitive functions of TBI patients (Elting et al., 2008).
- ERPs can and should be used to monitor patient progress in order to assess the efficacy of rehabilitative interventions. For example, Serruya and Kahana (2008) reviewed a variety of techniques and devices that have been developed to restore patients' cognitive abilities and functions. In their review of electrophysiological markers of cognitive deficits in TBI, Dockree and Robertson (in press) conclude that these markers "have primarily been utilized for understanding patients' impairments in the context of paradigmatic functions, but in the future they should also be investigated in the context of brain correlates of injury severity, cognitive training gains and novel rehabilitative approaches."
- Time since onset of injury should be taken into account when conducting ERP evaluations of TBI patients or interpreting results. Some studies include patients who sustained injuries days, weeks, months or years prior to the date of ERP recording.
- Because sensory deficits (e.g., vision impairment or hearing loss) affect ERP results, tests of peripheral sensory integrity should be conducted in conjunction with ERP recordings.
- Patients' state of consciousness, physical and cognitive abilities to respond and follow directions should be considered when conducting or interpreting ERP evaluations.
- Medications taken by patients at the time of ERP recording should be listed and taken into account when interpreting results. Some medications (such as potent analgesics, anxiolytics or sleep medications) can affect patients' behavioral performance and morphology of ERP waveforms.
- Variability within and between TBI patients makes interpretation of ERP results challenging. For example, some studies include patients with a wide range of TBI severity, states of consciousness or cognitive abilities. Clinicians, researchers and readers of such studies should be aware that group data (presented as ERP grand averages) often includes patients with heterogeneous characteristics that can have profound effects on ERP results.
- For the reasons given above, comparisons between ERP studies should be approached with caution. Variability in ERP recording protocols, equipment, stimulus type and presentation add to the challenge of comparing results across studies.

Studies described in this article represent the efforts of hundreds of clinicians and researchers to understand the relationships between ERPs and TBI. Results from these investigations help to increase the utility and efficacy of ERPs during diagnosis, prognosis and rehabilitation of brain injuries.

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