ERP for Diagnosis and Prognosis of Traumatic Brain Injury

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OVERVIEW

The Centers for Disease Control and Prevention defines a traumatic brain injury (TBI) as *"a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury."*

The severity of a TBI may range from "mild" (i.e., a brief change in mental status or consciousness) to "severe" (i.e., an extended period of unconsciousness or memory loss after the injury). Mild TBIs (mTBI) are the most common[1], and the most challenging for clinicians to evaluate. Only a small minority of patients with mTBI present with intracranial CT scan abnormalities, and there is little evidence that traditional cognitive testing can provide a reliable and sensitive assessment of cognitive dysfunction after mTBI[2]. A recent systematic review of peer-reviewed published literature found that "*diagnostic accuracy for mTBI is currently insufficient for discriminating between the disease and co-occurring mental health conditions for both acute and historic mTBI.*"[3].

Event related potentials (ERPs) are an objective measure of cortical synaptic dysfunction that can result from mTBI, and are sensitive to cognitive deficits associated with even the milder injuries. Thus, ERP testing can improve patient management by providing clinicians with a more accurate assessment of patients' cognitive status after a traumatic event, especially in hard to evaluate mild cases.

EVENT RELATED POTENTIALS

ERPs are part of the EEG generated by sensory and cognitive processing of external stimuli, and reflect the summed synaptic activity produced when similarly oriented neurons fire in synchrony in response to the stimuli[4].

The stimuli of the ERP test are grouped into sequences of repeating sounds or visual cues. The type, timing, and sequence of stimuli (often called an "ERP paradigm") are organized to target specific cognitive processes such as selective attention, memory encoding, executive function, etc. While the brain subconsciously analyzes the incoming stimuli, EEG time-locked to each stimulus is recorded. At the end of the test, the time-locked EEG recordings are averaged according to stimulus type, and all brain activity not related to the specific stimulus group is "filtered out". What is left are the ERP waves that represent the physiological responses evoked by each stimulus type played during the test (Figure 1).

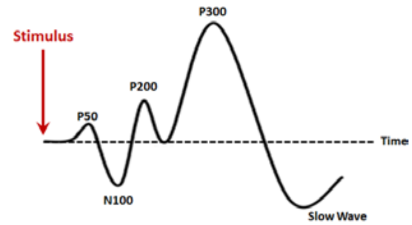

Figure 1: Example of an ERP wave

These ERP waves contain a sequence of positive and negative peaks, or "ERP Features", that have been extensively characterized in the scientific literature (for an overview see[5]). The early peaks are primarily "sensory" responses that depend largely on the physical parameters of the stimulus. Those sensory responses are followed by later "cognitive" peaks which reflect information processing, and can be used to detect and quantify cognitive deficits associated with mTBI[6].

ERP MEASURES FOR TBI

ERPs have been used to elucidate and characterize sensory and cognitive deficits that may follow brain injury since the early 1980s[7]. A large body of scientific literature on the usefulness of these biomarkers for diagnosis and prognosis of TBI has followed.

Recent reviews of published literature on electro-physiological methods for diagnosis of TBI have found that ERPs offer significant utility in TBI detection[8–11]. Indeed, **the American College of Occupational and Environmental Medicine (ACOEM) guidelines for TBI now recommend Cognitive Event-Related Potentials as a diagnostic measure for TBI**[12].

ERPs contribution to TBI diagnosis seems especially important to detect subtle deficits in information processing in patients that present with otherwise normal clinical findings[9–11,13].

There is good evidence for the use of ERPs as biomarkers to also support TBI prognosis. In a recent review Duncan et al. summarize the peer-reviewed published data as: "*The consensus would appear to be that the use of N100, MMN, P300, and perhaps P3a in various combinations, has great prognostic value for both awakening and cognitive recovery. The particular choice of components differs among investigators, but the use of ERPs in assessing coma would appear to be an essential, if not mandatory, aspect of medical practice.*"[9].

ERP testing provides flexibility in protocol design. ERP paradigms can be designed to produce measures that correlate with different sensory and cognitive domains (for an overview see[4]). Several ERP paradigms have been shown to detect deficits associated with TBI. An ERP test that is especially sensitive to those deficits is the Active Auditory Oddball Paradigm.

ACTIVE AUDITORY ODDBALL PARADIGM

In this ERP protocol, an infrequent (target) tone is played occasionally during a stimulus sequence of frequent (standard) stimuli. A third unexpected (distractor) tone can also be present. The test subject is instructed to respond when the infrequent target tone is heard[9].

The active oddball paradigm generates ERP features such as P3b, P3a and N200 that reflect aspects of information processing involved in stimulus discrimination, evaluation, and categorization[5], and are sensitive to cognitive deficits associated with TBI.

The P3b, or classic P300, is a positive-going component that is elicited by rare, attended (target) stimuli. It is of maximal amplitude at the centro-parietal electrodes and reflects an update in working memory (for review of the neuropsychological origins of the P3b, please see[14]). P3b amplitude is determined by the amount of attentional resources allocated when working memory is updated[15]. The peak latency reflects stimulus evaluation and classification speed[16,17].

P3b is a highly sensitive ERP measure for deficits in cortical synaptic function that follow TBI. In a study aimed at investigating neuropsychological and neurophysiological changes after sport concussion in children, adolescents and adults, Baillargeon et al. found that "*all concussed athletes had significantly lower amplitude for the P3b component compared to their non-injured teammates*"[18]. In another study to measure P3b components from patients with TBI, Doi and colleagues reported a significant decrease in the peak amplitude compared to healthy individuals[19].

P3b can show significant changes even in mild cases of the disease. A study that looked at ERP changes in college students after mild TBI reported a "*striking*" decrease in P3b amplitude. Moreover, the change in P3b amplitude was strongly related to the severity of post-concussion symptoms[20]. Similarly, a study that looked at the effects of a minor head injury on P3b found significant abnormalities in both peak amplitude and latency[21]. A study of neurophysiological anomalies in symptomatic and asymptomatic concussed athletes showed as significant reduction in P3b amplitude in both groups of subjects compared to controls[22], and another study that compared the performance of 10 well-functioning university students who had experienced a mild head injury an average of 6.4 years previously, and 12 controls on a series of standard psychometric tests and ERP measures also found a significant decrease in P3b amplitude in the mild head injury group[23].

The P3a is a positive-going peak that in an active two-deviant oddball paradigm is generated in response to the distractor stimulus and is of maximal amplitude at the centro-parietal electrodes[24]. The P3a is associated with engagement of attention and processing of novel information[14]. The peak amplitude is a measure of focal attention and has been shown to positively correlate with executive function[25]. Its latency reflects orientation to a non-target deviant stimulus[26].

Several studies have shown P3a changes after mTBI. A study in asymptomatic multiple concussed college football players reported significantly decreased P3a (and P3b) amplitude in study subjects that sustained their last concussion within a year of the ERP recording. The deficit was no longer present in athletes who sustained their concussions more than 2 years prior to testing[27]. Moore et al. have recently reported similar results in soccer players with a history of concussion[28]. In a study on moderate to severe TBI survivors, Solbakk et al. found that P3a amplitude was reduced compared to healthy controls when frontal or fronto-temporal brain regions were injured. In addition, TBI survivors also exhibited a trend towards prolonged peak latency[29]. Interestingly, in a study that correlated ERPs to malingered executive function Hoover et al. reported that malingerers were unable to produce a significant change in P3a response[30]. The study findings are consistent with the ACOEM guidelines for TBI that include ERPs as a recommended test under "Memory/Malingering Tests"[12], and suggest that ERP measures could help differentiate between malingerers and patients with genuine TBI.

Finally, the N200 is a component of negative polarity that in an active oddball paradigm is elicited by rare, attended (target) stimuli. The N200 precedes the P3b and is linked to the cognitive processes of stimulus identification and distinction[31]. The peak is maximal over fronto-central brain regions[24] and its latency has been shown to correlate with measures of executive function and attention[32].

N200 measures seem to be mostly affected in patients with a history of moderate or severe TBI. Sarno et al. have shown prolonged N200 latency in survivors of severe TBI[33]. In two similar studies, Duncan et al. reported smaller amplitude and prolonged latency for N200 in survivors of moderate and severe TBI[34,35]. In one of the studies significant correlations were also found between severity of head injury, as measured by length of unconsciousness, and N200 latency and amplitude[34].

ARE ERP NECESSARY FOR THE EVALUATION OF TBI?

When head trauma requires medical attention, clinicians will often request structural neuroimaging data provided by CT or MRI scans. However, these two neuroimaging techniques seem to underestimated brain injury and are poorly correlated with outcome (see for example[36–40]). The main reason for this seems to be that neither CT nor conventional MRI sequences detect diffuse axonal injuries, the most common form of TBI[41–46].

In their review on the potential usefulness of electrophysiological markers for cognitive deficits in TBI, Dockree and Robertson conclude that *"Cognitive testing and electrophysiological analysis provides sensitivity to impairments which are otherwise undetectable by general neuropsychological evaluation and standard MRI. It is noteworthy that studies which have restricted their analysis to mild TBI where cognitive sequelae are difficult to measure routinely have nevertheless identified ERP markers of more subtle deficits of visual processing speed[47] attention deployment[48–50] and error monitoring[51]. A World Health Organization investigation has reported that 70–90% of all treated for TBI were classified as mild severity[52]. Although it is important that electro-physiological markers are utilized across all severities of brain injury to understand the diversity of processing deficits, their use in conjunction with cognitive paradigms may be more sensitive to persistent cognitive dysfunction resulting from mild TBI where signs of damage may elude routine assessment."*[10].

In the latest revision of their guidelines for TBI, the American College of Occupational and Environmental Medicine now recommends cognitive ERPs for *"Post-TBI patients who either have symptoms of cognitive deficits and/or have sustained a TBI sufficient to cause same."*[12].

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