The Current Status of Electrophysiologic Procedures for the Assessment of Mild Traumatic Brain Injury

Design: This review examines studies that used spontaneous electroencephalography (EEG), evoked potentials (EP), event-related potentials (ERP), and magnetoencephalography (MEG) to detect brain dysfunction in mild traumatic brain injured (MTBI) subjects. **Conclusions:** The following conclusions are offered: (1) standard clinical EEG is not useful; however, newer analytical procedures may be proven valuable; (2) consistent with current theory of MTBI, cognitive ERPs seem to be more sensitive to injury than EPs; (3) development of an assessment battery that may include EEG, EPs, ERPs, and neuropsychologic testing is advocated. Key words: *electroencephalography, event-related potentials, evoked potentials, magnetoencephalography, mild traumatic brain injury*

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MILD TRAUMATIC brain injury (MTBI) was initially considered a temporary disturbance in consciousness resulting in no long-term cognitive sequelae.[1,2] This perspective continued to be advanced until the early 1990s, when Parkinson[3] hypothesized that concussion is completely reversible. Current research has offered a different perspective on these injuries: mild acceleration/deceleration forces may cause changes in brain structure[4–6] and function, with the potential outcome being persistent cognitive dysfunction.[7–9] In the latter half of the 1990s, many articles were published describing the acute and long-term effects of MTBI. These included advancements in experimental animal modeling, neuropsychologic testing, and structural and functional neuroimaging. However, although there was increasing clarity in a number of experimental areas, there continued to be considerable confusion in others. One

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example is the as yet unknown contributions of neural damage, vascular dysregulation, and psychologic trauma to the postconcussive state.[10]

The postconcussive state is often characterized by a variety of cognitive, physical, and emotional problems. These symptoms comprise the postconcussive syndrome (PCS) and are most common in the first months after injury. Unfortunately, the relationship between PCS symptoms and objective behavioral and physiologic measures is poor.[7] The most common objective neuropsychologic problems after MTBI seem to involve memory and attention.[11,12] Recent conceptualizations of the cognitive sequelae of MTBI have focused primarily on detriments to information processing speed and capacity, as well as detriments to working memory.[13–15]

With the vast increase in all areas of MTBI research, an increased understanding of the current status of the various imaging techniques will be beneficial for future research endeavors.

The purpose of this review is to provide such an overview for one area of assessment, electroencephalography (EEG), and the averaged EEG-evoked and event-related potentials (EP, ERP). These electroneurophysiologic procedures have been used to assess numerous medical disorders; however, their potential benefits for the assessment of MTBI have not been fully and properly explored. Structural imaging techniques are typically advocated to detect damage that occurs as the result of these injuries.[16] However, because a substantial amount of the damage caused by acceleration/deceleration forces may be diffuse in nature,[5,17,18] a standard structural imaging assessment procedure, such as computed tomography (CT), may be less sensitive compared with certain functional techniques.[9,19] Moreover, because the most common cognitive problems after MTBI are those involving information processing and working memory, functional techniques may be particularly valuable in detecting such impairment.

Similar problems have arisen for standard clinical EEG assessments, such as those provided in hospitals. This procedure is used primarily to detect focal slowing and epileptic activity and has not been demonstrated to be useful for the assessment of post-MTBI brain function.[20] This has caused some to globally label EEG as "generally useless" for MTBI assessment.[21] However, a number of electrophysiologic techniques have been used to describe the behavior of neural systems that operate as distributed functional networks.[22,23] Because most of the neural damage related to mild acceleration/deceleration forces is diffuse, these techniques, when applied in a precise and consistent manner, may be sensitive to changes in brain function that occur following MTBI. The purpose of this review is to examine the body of literature describing electrophysiologic assessment of MTBI within a well-defined population. A recent review of the literature will be an important contribution for researchers and clinicians alike, because it will help describe which EEG, EP, and ERP techniques are the most useful for assessing the acute and cumulative effects of MTBI in athletes and litigating and nonlitigating individuals.

DEFINITIONS

One of the problems faced by researchers is the lack of a universal definition for MTBI. Different definitions exist for mild head injury (MHI) and concussion. In fact, there are currently several definitions for concussion grading alone. The definition of MTBI used in this review will fall within the following broad yet commonly accepted criteria for MHI and concussion. The term MTBI used here includes the definition of MHI defined by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest

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Group of the American Congress of Rehabilitation Medicine[24] and the definition of Grade 3 concussion provided by the Report of the Quality Standards Subcommittee.[16] This definition includes very mild injuries, resulting in any alteration in mental state, to more severe injuries associated with loss of consciousness of less than 30 minutes and posttraumatic amnesia of less than 24 hours.

NEURAL BASIS AND TECHNICAL REQUIREMENTS OF ELECTROPHYSIOLOGIC PROCEDURES

Electrophysiologic techniques are among the most frequently used methods to provide information about the functioning of the human brain. These techniques are useful in that they are noninvasive, relatively inexpensive, and have a lengthy history dating back to the 1930s. Electroencephalography (EEG) records the electrical properties of neurons functioning within systems. Specifically, the EEG is a measure of extracellular current flow associated with the summed activity of several individual neurons. EEG activity is recorded by placing electrodes on the scalp. The electrodes are sensitive to changes in electrical activity that originates in the brain. These small signals are then sent to amplifiers through electrode leads. The amplified signals are then analyzed using a variety of methods and computer programs that are largely dependent on the type of brain response that is recorded.

Many different paradigms are used to record the electrical activity of the brain, including standard clinical EEG, quantitative or digital EEG (QEEG), evoked potentials (EP), and event-related potentials (ERP). EEG and QEEG are recordings of the electrical activity obtained in an ongoing or "spontaneous" manner. A standard clinical EEG can be "analog," meaning the electrical signals are transferred to pens that record the changes in electrical activity on paper, or quantitative, meaning the changes in electrical signals are digitized and transferred directly to a computer for display or subsequent analysis. Both the EEG and QEEG can be used for the visual detection of slow waves, epileptic activity, asynchronous waveforms, and analysis of the sleep EEG. The QEEG alone is used for frequency and coherence analysis, brain mapping, and more complex mathematical analyses.

EPs and ERP differ from the recording of spontaneous EEG in at least two ways: first, they are time-locked to the onset of a stimulus or stimuli, and second, these responses are averaged to enhance brain activity that is associated with the processing of the stimulus. Aside from these differences, the electrical activity recorded from the brain is identical. Differences also exist between EPs and ERPs regarding their clinical use and what aspects of brain function each technique measures. Traditionally, EPs have been used more often for clinical purposes, although this has started to change in recent years. Another difference is that ERPs presumably assess cognitive function, whereas EPs are taken to represent processing in the primary sensory pathways. EPs are generally considered to be an index of precortical or primary sensory cortical functioning. ERPs, on the other hand, tend to be associated with cognitive processing that is distributed through a number of cortical and subcortical generators.

EEG AND MTBI

Clinicians and researchers have used EEG to evaluate changes in the electrical activity of the brain following MTBI. Standard clinical EEG analyses are often provided in acute care facilities to detect the presence of focal slowing, often indicative of a pathologic condition, as well as to detect the presence of epileptiform activity related to brain injury.[25] Studies using standard EEG techniques have not

provided a clear depiction of functional change following MTBI. Early studies reported higher rates of EEG abnormality in subjects with postconcussion syndrome (PCS); however, these studies were often qualitative, had no modern radiologic information, lacked detailed analysis of paroxysmal activity (epileptic spike activity not associated with a major seizure), and included individuals outside the current definition of MTBI.[26–28] Other early studies did not demonstrate a higher incidence of abnormalities in the EEGs of MTBI patients than in the general population.[29] Similarly, in a sample of 54 primarily MTBI subjects who were symptomatic for PCS at the time of investigation, Jacome and Risko[30] observed no concurrent EEG abnormalities in 24-hour ambulatory monitoring alone. However, 9.2% of patients had either specific or nonspecific paroxysmal activity. In a more recent study, 12 patients with MTBI underwent a clinical examination within 24 hours after injury that included a standard clinical EEG assessment based on "current EEG criteria." No EEG abnormalities were recorded in these patients. Even in the patients with structural lesions, no focal changes or generalized slow activity have been found.[20] Therefore, LeBlanc's[21] negative characterization of standard clinical EEG for the assessment of MTBI, when compared with CT or MRI, may be somewhat warranted.

Although standard clinical EEG may be insensitive most changes in brain function after MTBI, there is a considerable body of experimental work suggesting that more complex EEG paradigms may one day be used to assess changes in brain function after injury. Thatcher and colleagues[31] have been foremost in describing the spontaneous changes that occur following MTBI and have used discriminant functions with high reliability to classify head-injured patients. Discriminant functions based on patterns of coherence, phase, and amplitude were most useful for the identification of individuals with MTBI vs control subjects. Three main findings were obtained: increased coherence and decreased phase between frontal and temporal areas, a reduction in power differences between anterior and posterior cortical regions in the alpha and beta frequency bands, and reduced alpha power in posterior regions. Subsequent work by this group has extended these results and correlated electrophysiologic abnormalities with MRI evidence of damage in subjects with varied injury severity.[32] In this study, delta frequency amplitude was significantly correlated with white matter T2 relaxation time compared with gray matter relaxation time mainly in the frontal poles (Fp1 and Fp2). Alpha and beta frequency amplitude was significantly correlated with gray matter T2 relaxation time in compared with white matter T2 relaxation time, primarily in the lateral frontal, prefrontal, and temporal cortices (F3/F4, C3/C4, and T3/T4). Therefore, damage to frontal white matter may be reflected in changes in frontal delta, whereas gray matter damage may be indexed by differences in frontal, prefrontal, and temporal high-frequency activity.[32]

Another study by this group investigated the relationship between changes in EEG coherence and MRI findings in individuals with mild to severe injury.[33] In this study, increased gray and white matter T2 relaxation times were negatively correlated with a decrease in EEG coherence in the 7-cm (short) interelectrode distances but was positively related to EEG coherence in the long interelectrode distances. Gray matter T2 was more highly correlated with a decrease in alpha coherence than white matter T2 in the anteroposterior direction. The results were interpreted as consistent with reduced integrity of the protein/lipid neural membranes and diminished efficiency of neural systems following MTBI.[33] In addition to this work, a recent

study has further demonstrated that EEG coherence can be used to distinguish controls from individuals with MTBI.[34] Taken together, these results suggested that patterns of spontaneous EEG might be used to classify individuals who sustained a MTBI versus those who had not. In addition, there seems to be a distinct relationship between changes in the spontaneous EEG and MRI findings in head-injured subjects.

Alterations in alpha band frequency seem to be among the most distinct changes that occur following MTBI. In one study, changes in the total power of the alpha band were not observed. The reason for this was a significant increase in alpha 1 power (lower half of the alpha band) with a decrease in the alpha 2 band power (upper half).[35] This finding is interesting in that a shift in the peak alpha frequency to lower values has been linked with increased pathologic conditions in various disorders.[36–38] Alpha/theta ratios index a postinjury reduction in theta with stable alpha levels and have been used to monitor short-term changes following MTBI. In one study, this ratio was maximal at the first postinjury recording time (time zero), with significant declines reported until 10 days after injury, followed by a return to near-baseline levels.[39] Alpha activity is also altered during the sleep cycle following MTBI. Parsons and colleagues[40] recorded sleep EEG in eight subjects at 72 hours, 6 weeks and 12 weeks after injury for the first and second REM and NREM cycles. Alpha1, as well as delta and theta activity, was significantly elevated 72 hours after injury. As postinjury time progressed, the power within these frequency bands decreased for cycles 1 and 2. Frontocentral theta cycle 1 was the only frequency band that decreased significantly within 6 weeks. Finally, there is preliminary evidence that the higher frequency bands (32 to 64 Hz) may also prove valuable in distinguishing MTBI patients from controls.[41]

To summarize, there seems to be merit in using EEG to index changes in brain function following MTBI. Nonstandard techniques, such as computerized frequency and coherence analysis, have been used to demonstrate changes in MTBI-related brain function. Furthermore, these changes correlate significantly with MRI evidence of gray and white matter damage. Activity in the lower half of the alpha band in waking and sleep EEG was reported most often.

The standard clinical techniques currently used in most acute care facilities were initially designed to detect seizure activity or abnormal activity associated with large focal lesions. As such, these techniques may be less useful for the detection of mild diffuse damage believed to occur with MTBI. Because standard techniques are often used in hospitals, their lack of sensitivity may mislead some to conclude that EEG is generally insensitive to damage. On the basis of the experimental work reviewed thus far, this does not seem to be the case. With continued progress, it is possible that newer paradigms will eventually be integrated into a standard battery for assessment, thus supplanting standard clinical techniques. This position is consistent with the American Academy of Neurology and American Clinical Neurophysiology Society Guidelines by Nuwer.[42] These guidelines stated that EEG studies on MTBI have resulted in "very interesting changes"; however, they were not recommended at that time as diagnostic procedures for PCS (p. 283). Using the identical rating procedures as these published guidelines, a more recent medical position paper has suggested a limited "positive recommendation" for the use of quantitative EEG in the assessment of PCS.[37]

EVOKED POTENTIALS

Evoked potentials differ from EEG in that they are averaged responses that are time

locked to the stimulus used to elicit the response. Because concussion has in the past been considered an injury that primarily affects the brainstem,[43] it is not surprising that numerous electrophysiologic studies use the brainstem auditory evoked potential (BAEP) to index postinjury changes in function. The BAEP is an index of primary auditory system function that occurs in the brainstem before primary auditory cortex. It is elicited using a series of clicks presented through headphones. The response consists of several "peaks," each being generated by one or more structures in the brainstem. Interpeak intervals are calculated and generally reflect central processing between brainstem structures such as eighth nerve and pons or pons and midbrain.

BAEP changes in absolute peak III latency have been reported after concussion[44]; however, subjects in this study also had increased peak I latencies. Thus, it is unclear whether the injury in this case was central (after eighth nerve) or peripheral (at or before eighth nerve). In a series of publications labeled the "Belfast Studies," BAEP changes were reported at day zero and 6 weeks after injury. No group differences were reported; however, BAEP interpeak intervals from the ear with the maximum delay were significantly increased between peaks I and V at day zero in 13 of 26 individuals. Of those with increased interpeak latencies, eight showed improvement at 6 weeks, whereas four subjects did not.[45,46] In a group of subjects with more severe injuries, 10 of 57 had BAEP interpeak intervals beyond the normal limit at an average of 39 days after injury.[47]

The large number of subjects in these studies with responses outside the normal range may be due to the use of a 2 standard deviation (SD) difference from the group mean as the normal limit. Increasing the limit of normality to 2.33 SD, Rowe and Carlson[48] observed a decrease in those considered to have abnormal BAEP responses from 3 of 8 to 1 of 8 for neck injured, and from 8 of 19 to 2 of 19 for concussed subjects. Nonetheless, even when the limit of normality used is 3 SD, BAEP abnormalities within 48 hours of the injury have been observed in up to 6 of 30 individuals.[49] It is noteworthy that there was no correlation with PCS in these individuals. In sum, the current available evidence seems to suggest that a relatively low proportion of individuals who experience concussion will show decrements in BAEP function after injury.

However, not all studies demonstrated BAEP changes after concussion. Werner and Vanderzant[50] reported no change in BAEP interpeak intervals with a 3 SD normal limit. In a large group of amateur boxers, no BAEP group differences were observed compared with other groups of athletes.[51] In groups of young and older subjects with persistent PCS, no significant group differences were observed when these subjects were compared with age-related normative databases.[9] In addition, only 1 of 10 subjects in the young group and none of the 10 subjects in the older group had interpeak interval values beyond a 2.5 SD normal limit. Thus, the percentage of BAEP responses beyond a 2.5 SD normal limit were similar to those observed in the control groups.[9] Other researchers have reported negative BAEP findings with MHI and whiplash.[52] Similarly, no significant differences were reported in peak I to V interpeak intervals after fluid percussion injuries in cats (experimental concussion).[53] Increasing the rate of stimulation does seem to result in an increased sensitivity of the BAEP to detect changes after injury. Podoshin et al[54] reported that no differences in BAEP function after injury were observed at a rate of 10 Hz. However, at 55 Hz, differences greater than 3 SD were observed. Soustiel et al[55] reported similar results, although BAEP changes did not predict outcome. The reason for this might be that axonal damage is

believed to be sensitive to the 10 Hz stimulation rate, whereas the higher rate of stimulation may be more sensitive to metabolic, ischemic, and vascular changes after injury.[54,56] In other words, the degree of axonal impairment that occurs at the level of brainstem may be minimal, whereas global changes to neurovascular system function may impair normal function of brainstem and other brain centers.

Auditory stimulation used to elicit BAEP responses can also be used to generate later peaks with thalamocortical origins. This response has been labeled the middle-latency auditory EP (MAEP). Proposed generators of early MAEP peaks (No, Po, and Na) are in subcortical structures,[57] whereas later peaks (Pa, Nb, and Pb) have been associated with sources near primary auditory cortex.[58,59] Most studies using MAEP to assess MTBI have yielded positive results. In one study, MAEP peaks No, Na, and Pa were abnormal in 15 of 40 patients, and early peaks No and Po were prolonged at the 3-month follow-up (although to a lesser extent than the first recordings) compared with a normal control group. Prolonged MAEP latencies correlated with outcome following MTBI.[55] Similarly, Drake et al[60] reported that Na and Pa amplitudes were lower, and Pa latencies were significantly longer in patients compared with controls. Finally, a recent study demonstrated that MAEP latencies for Na, Pa, and Nb were not beyond a 2.5 SD normal limit in PCS subjects regardless of age. No group differences were observed between young and older subjects and their age-related control groups.[9]

Studies investigating the effects of MTBI on primary visual system function using pattern visual EPs (PVEP) are fewer in number and have provided mixed results. Werner and Vanderzant[50] found no PVEP abnormalities beyond a 3 SD limit of normality. Papathanasopoulos et al[61] observed no differences compared with normal controls; however, they found a significant within-subject decrease over a period of 30 days. With a 2 SD normal limit, increased PVEP latencies were detected after concussion in 6 of 57 individuals with posttraumatic syndrome.[47] For subjects with persistent PCS, 3 of 10 young subjects and 3 of 10 older subjects had P100 latencies beyond a 2.5 SD normal limit. Significant group differences were also observed between each age group and age-related groups of normal subjects.[9] Significant improvements in PVEP latency and amplitude of concussed individuals have been reported after optometric rehabilitation.[62]

Other EPs used to assess brain dysfunction following MTBI include brainstem trigeminal nerve stimulation (BTEP), motor EPs (MEP), and somatosensory EPs (SEP). One article has been published on the dissociation between motor EPs (MEP) and somatosensory EPs (SEP) for the assessment of MTBI. In this study, 11.8% of 34 MTBI subjects had abnormal parietal and 35.3% had abnormal frontal SEPs (abnormal meaning a parameter beyond a 2.5 SD normal limit). An abnormal threshold for MEP stimulation was reported in 20.6% of subjects with abnormal MEP variability occurring in 26.5% of subjects. No significant statistical difference was found in SEP and MEP parameters between MTBI and control groups.[63] Finally, BTEPs were recorded in a group of 40 MTBI subjects with follow-up performed at 3 months. Significant prolongations in peak latency were observed in 15 of 40 subjects for two of the BTEP peaks (T3 and T5). The same peaks were delayed 3 months after injury compared with normal controls. However, this response was not useful in predicting outcome.[55]

To summarize, there is some support for the use of EPs to assess MTBI. Studies using BAEPs have offered mixed results. Several studies reported differences in primary auditory system function using this technique; however, when a 2.5 SD normal limit (or greater) was used,

the number of individuals with significant prolongations in peak latency, or interpeak interval, is reduced considerably. Nonetheless, several studies have reported increased BAEP response latencies in a small number of subjects following MTBI. Increasing the rate of stimulation was also effective in eliciting response latencies beyond a statistical normal limit, and this method was believed to index compromised function of neurovascular systems.

Fewer studies have been completed using MAEPs. Two of three studies suggested that MAEP responses showed significant peak amplitude attenuation and increased latencies after injury. This response was also related to outcome in one study. One study showed that no subjects with PCS had differences in MAEP response latency beyond a 2.5 SD normal limit. Therefore, there seems to be some value in using BAEP and MAEP to assess function in primary auditory pathways; however, identification of damage may be limited, because this may not be the area of maximal injury following MTBI.

Assessment of primary visual system function using PVEPs has also offered mixed results. Some studies showed no differences in response latency compared with normal controls. Other studies reported significant decreases in latency after a recovery period. One study reported increased P100 latencies in young and older subjects with persistent PCS compared with controls. BTEP responses were also effective in demonstrating differences after injury in one study, whereas MEP and SEP were not different compared with control subjects.

EVENT-RELATED POTENTIALS

ERPs differ from EPs in that they are associated with cognitive processes, such as attention, memory, and anticipation that occur after processing of information in primary sensory systems. In addition, ERPs often result from the activation of several subcortical and cortical areas of the brain functioning as a distributed system. Compared with behavioral tasks, where response strategy significantly affects performance, ERPs track ongoing information processing independent of response strategy.[64] One component of the cognitive ERP that deserves special attention with respect to MTBI is the N2/P3 response (P300). The generators of the N2/P3 response include rhinal cortex, hippocampus, superior temporal sulcus, ventrolateral prefrontal cortex, intraparietal sulcus, and anterobasal temporal lobe among others.[22] Therefore, it is probable that the N2/P3 is not generated in a single brain area but rather involves different areas as required by the processing task.[65] Given that MTBI is often associated with information processing difficulty, ERPs may be particularly well suited to detect such impairment.

Unfortunately, as with the EP studies, the research examining changes in N2/P3 responses following MTBI and in individuals with PCS is somewhat equivocal. Most of the studies performed thus far have used auditory stimuli. An animal analog to the N2/P3, labeled the late positive component, showed reduced amplitude in four of six animals after a fluid percussion injury. Recovery of the response occurred earlier in animals with minimal behavioral suppression, whereas animals with prolonged behavioral suppression demonstrated recovery between 2 and 10 days.[53] In humans, there is inconsistent evidence that auditory N2/P3 latency or amplitude changes after concussion or during postconcussion syndrome. In a mixed group of mild and moderately injured patients, those with resolved posttraumatic amnesia did not differ from controls but did have longer P3 latencies than confused patients with posttraumatic amnesia.[66] No differences in P3 latency or amplitude were observed between

amateur boxers with a high or low number of matches compared with soccer and track and field athletes. However, there was a significant correlation between the number of times an individual was "knocked out" and P3 latency, but not amplitude.[51] Several studies reported no change in auditory N2/P3 latency or amplitude following mild closed head injury.[15,50,67] One study was able to demonstrate auditory P3 latency changes in concussed patients compared with controls. On retesting, significant improvements were observed in P3 latency and amplitude and P2 latency.[68] In another study, auditory P3 latency and amplitude abnormalities were found in a group of mild to moderate head injured subjects an average of 3 years postinjury.[14] Another study reported a reduction in P2 amplitude in MTBI patients compared with frontal patients and controls under experimental conditions using a monaural presentation of infrequent auditory stimuli and during dichotic listening conditions in the unattended channel. N2/P3b to deviant tones were also different; and there was an attenuation of N2b and P3b amplitude in the MHI group compared with frontal and control groups.[69] Additional evidence for abnormal auditory P300 amplitude associated with MTBI is provided by a pair of studies involving university students with MTBI who do not have PCS[13,70] and by a study involving a large sample of MTBI subjects with PCS.[71] In a study comparing young and older groups of individuals with persistent PCS following MTBI to age-appropriate normative groups, 1 of 10 young subjects had auditory P3 latencies beyond a 2.5 SD normal limit compared with 2 of 10 in the older group. Statistically, both groups had latencies that differed from their respective normative databases.[9] Finally, Packard and Ham[72] reported an evaluation of cognitive evoked potentials in posttraumatic headache cases. From the total of 50 subjects with posttraumatic headache and memory and/or concentration difficulties, 8 had abnormal N100 and 27 had abnormal P3 latencies or amplitudes greater than a 2 SD normal limit.

Although fewer in number, studies using visual N2/P3 have demonstrated more pronounced differences between MTBI and control subjects. For instance, a study by Sangal and Sangal[73] reported no differences in auditory P3; however, significant differences were observed in visual P3 latency in six of eight patients with mild cognitive complaint. In groups of young and older individuals with persistent PCS following MTBI, 4 of 10 young subjects had visual P3 latencies beyond a 2.5 SD normal limit, as well as 4 of 10 in the older group. Statistically, both groups differed from their respective normative databases.[9] In addition, the cumulative effects of concussion have been demonstrated using a visual word N2/P3 paradigm. In this study, subjects who had experienced three or more concussions had significantly longer latencies than individuals who had never sustained a concussion. Because these individuals were young athletes of the same age and gender, the differences were attributed to MTBI as opposed to factors such as mental illness, alcohol or drug use, or chronic pain. Increased N2/P3 latencies were significantly correlated with self-reported PCS symptoms.[8] Finally, there is some evidence that individuals with MTBI have reduced visual P3 amplitude.[71]

The contingent negative variation (CNV) is another example of an ERP used to assess cognitive functioning. This is a slow negative potential, the early part of which is related to processing of the stimulus, and the later part of which is associated with anticipation of a second stimulus and the organization of a response. Like the N2/P3, the CNV is generated in multiple cortical and subcortical areas including orbitofrontal cortex, mesial prefrontal cortex, contralateral primary motor cortex, and supplementary motor cortex bilaterally, among others.[23,74]

Although there have been several studies on changes in CNV amplitude following moderate to severe closed head injury, there have been fewer studies on individuals that fall within the definition used in this review. Two recent studies[8,9] have examined the usefulness of this procedure for the assessment of persistent PCS following MTBI and the cumulative effects of concussion. In young subjects with persistent PCS, visual but not auditory CNV amplitude was significantly attenuated compared with noninjured controls from the same age group. In addition, 4 of 10 subjects had amplitude reductions beyond a 2.5 SD normal limit, whereas 2 of 10 subjects had auditory responses outside the normal range. However, in the older group of PCS subjects, significant decreases in maximum negative amplitude did not occur in PCS subjects compared with controls within the same age range. One of 10 subjects had visual CNV amplitude below a 2.5 SD normal limit, whereas none had auditory responses outside the normal range.[9] In another study, no differences in visual CNV amplitude were observed in subjects with three or more concussions compared with those who had never sustained a concussion.[8]

Finally, a study using a dichotic listening paradigm demonstrated significant differences in MTBI subjects compared with patients with frontal lobe damage and controls. Negative electrophysiologic activity results when auditory information is being processed in a dichotic listening (selective attention) paradigm, and this has been referred to as processing negativity. The negative difference (Nd) was calculated by subtracting the ERPs for standard stimuli when the subject was attending (one experimental condition) vs not attending (a different experimental condition). Under dichotic listening conditions, frontal patients had significantly longer P2 latencies than MTBI patients. Nde (early Nd component) for controls and frontal patients was more negatively displaced than the grand averages for the MTBI group. Moreover, the MTBI group had longer latencies than controls but similar latencies to the frontal patients. Controls had shorter Ndl (late component) latencies compared with both MTBI and frontal patients.[69]

To summarize, there seems to be mixed evidence involving the most frequently used ERP paradigm: auditory N2/P3 latency or amplitude changes following MTBI or PCS. The best evidence seems to derive from dichotic listening used to elicit the N2/P3 response. In addition to demonstrating differences in the auditory N2/P3, this technique offered different information regarding processing negativity, which also seemed to be sensitive to MTBI-related changes in brain function.

Studies using visual N2/P3 consistently offered differences both clinically and experimentally in PCS subjects and those with cumulative MTBI effects. CNV studies on the other hand are few in number for subjects within the current definition of MTBI. There is currently limited evidence for the effectiveness of this technique for the assessment of MTBI. Changes in CNV amplitude were not consistent between young and old age groups, suggesting that latency may be a more reliable indicator of changes in brain function. CNV amplitude is known to vary between subjects because of factors other than brain injury. However, it is possible that a variant of the CNV paradigm described could be useful for the assessment of MTBI in certain populations. An example of such a variant could be the comparison of postinjury CNV amplitudes to a preinjury baseline for the assessment of attention and the ability to anticipate MTBI in athletes.

MAGNETOENCEPHALOGRAPHY

MEG is a relatively new imaging technique that is closely related to the EEG. The

electrical activity recorded at the scalp with the EEG occurs as the results of ionic flow outside of neurons that is the consequence of intracellular current flow. Current flow within any conductor (such as a piece of wire or a neuron) also has a magnetic field that flows around that conductor. MEG is sensitive to magnetic fields that flow around electrical conductors. Examples of electrical conductors in the brain are sheets of cells aligned parallel to the brain's surface. MEG is measured using a superconductive quantum interference device (SQUID). Many individual SQUID sensors are housed in a "dewar," and the patient's head is fitted inside the dewar during recording. As such, the MEG differs from the EEG practically in that no electrode leads are attached to the patients, making recording easier and less time consuming. MEG has other advantages, including more accurate recording of tangential sources (activity that occurs in parallel to the skull), because magnetic fields are not altered by bone, skin, cerebrospinal fluid, or the dura mater.

MEG has been used experimentally to assess brain function following MTBI and in individuals with persistent PCS. In one study, 45% of patients with persistent PCS had abnormal spontaneous activity detectable with MEG compared with 20% for EEG and 20% for MRI. The combined use of MEG and MRI resulted in detection of abnormal activity in 65% of subjects with persistent PCS compared with 5% of normal subjects and 10% of asymptomatic MTBI subjects. The combined MEG/MRI technique was also able to track improvement in PCS subjects who underwent a repeat examination.[19] In another study, an EEG and MEG EP/ERP battery was used to examine the differences between the two techniques for assessing persistent PCS. Compared with EEG, the whole head MEG provided similar information regarding response latencies with a vast improvement as to the actual sources for various peaks. It was concluded that the MEG adds useful information about the distribution and strength of various components of EPs and ERPs. The EEG generally showed a similar distribution for different peaks of a response (eg, a vertex distribution for N2 and P3).[75]

As MEG is a relatively new technology, it exists in a small number of centers worldwide. The reasons for its limited use include cost and specialized requirements for housing these systems as a result of shielding of ambient magnetic "noise." Nonetheless, MEG is currently being used as a clinical diagnostic procedure for epilepsy and other disorders in medical centers in North America, Europe, and Asia. It currently serves as a useful experimental adjunct to the electrophysiologic procedures discussed in this review.

Table 1 lists each of the techniques covered in this review, along with the perceived clinical usefulness of the test and the studies supporting and opposing the use of each measure. **Table 1**

Electrophysiologic studies on posttraumatic stress disorder (PTSD) simulated malingering and the problem of distinguishing a mood disorder from a brain injury.

One of the most contentious issues in MTBI research today is the degree to which PCS symptoms are due to an injury process, either vascular or neural, mental illness present before the injury or as a result of the injury, stress related to the injury, or the cause of the injury or malingering.[76] Electrophysiologic assessment procedures may help to clarify this situation in a number of ways. First, techniques such as those described in this review, as well as others, may be sensitive to damage in neural systems and neurovascular systems.[54,56,77] Second, ERPs may be valuable for the assessment of PTSD.[78] Using a P3 word paradigm, Granovsky and colleagues found a significant effect for words related to automobile accidents. Patients produced significantly higher amplitudes for accident-related words than for

neutral words. A similar difference was not found with control subjects. Third, ERPs have also been used experimentally for the detection of malingering.[79] Here, ERPs may prove to be beneficial, because it is difficult to "fake" ERP responses.

Finally, one of the most important aspects of properly assessing subjects who have experienced PCS following MTBI is the degree to which symptoms are due to brain injury or other factors including chronic pain, anxiety, litigation stress, a mood disorder that predated the injury, or whether symptoms are in response to circumstances of the injury. Iverson and McCracken[80] have correctly pointed out that PCS symptoms that occur following MTBI also occur in conditions related to MTBI, such as chronic pain and major depression (MD). It has been suggested that MD is the best example of a psychiatric condition that complicates our understanding of recovery following MTBI.[81] Many of the symptoms of MD, and the problems associated with this condition, have considerable overlap with PCS symptoms. Therefore, it is currently difficult to determine whether a subject who has recently experienced a MTBI has a mild form of depression related to the injury, or whether the PCS symptoms are due to damage to the brain sustained at the time of injury.

Electrophysiologic procedures may in some cases be beneficial for determining whether PCS symptoms that occur following MTBI are related to depression versus trauma to the brain. For instance, latency of the P3 response has been reported to increase following MTBI in some subjects with persistent PCS and in subjects with cumulative effects of concussion (see earlier section). As such, this begs the following question: What is the available scientific evidence for increased P3 latency in subjects with major depression (MD)?

In a cursory review of studies on subjects with MD, without known or suspected dementia caused by neurovascular disease or AD, there are at least four studies* that report significant increases in P3 latency compared with a control group.[82–85] One study reported increased P3 latency in bipolar subjects only, and not those with MD.[86] Therefore, there seems to be limited support for the position that increased P3 latency occurs in subjects with MD. However, there is a substantial body of work suggesting that no change in P3 latency occurs in subjects with MD. Numerous studies exist reporting amplitude effects, but no latency effects for MD subjects versus controls.[87–94] A larger number of studies reported *no statistically significant increases in latency* for MD subjects versus a control group.[95–104] Furthermore, increased P3 latency was found to be unrelated to an experimentally manipulated neuroendocrine response[105] and was unrelated to mood scores.[106] The lack of a difference in P3 latency between MD subjects and controls has made MD subjects appropriate clinical controls for comparison with dementia patients.[98,107] Finally, the fact that MD seems to be unrelated to P3 latency suggests that P3 latency differences would also be unlikely to emerge among individuals with possible subthreshold depression, such as MTBI subjects.

In addition, abnormal P3 responses have been reported in subjects with posttraumatic headache and memory and/or concentration difficulties following mild head or neck injury. For these subjects, depression at the time of testing was not related to electrophysiologic abnormalities. Studies on athletes who have sustained MTBI are consistent with these results. Subjects who sustained three or more concussions had significantly longer visual P3 latencies and higher self-reported PCS symptoms related to cognitive deficits

Three of four of these articles appeared in regional journals. This result has not been sufficiently replicated in an internationally recognized psychiatric/scientific journal.

compared with those who had not sustained a concussion. No significant differences were reported for mood variables between these groups.[8] Therefore, when this large body of information is considered, there seems to be very little support for the position that increased P3 latency observed in subjects with PCS following MTBI is due to depression, even though there is considerable overlap between the symptoms profile for MD and PCS. Therefore, an electrophysiologic assessment battery used to assess factors such as PTSD, malingering, depression, and brain injury would be a beneficial addition to the host of currently used procedures.

Another potential confound that should be considered when assessing MTBI is the presence of a pre-existing learning disability (LD). Although fewer studies have been carried out in this area using EPs and ERPs, there is limited evidence for electrophysiologic differences in this population compared with normal control subjects. Increased P3 latencies have been reported in children with LD using lexical decisions tasks.[108,109] Other studies have not shown increased visual P3 latencies in LD subjects.[110,111] As such, the studies evaluating the assessment of LD with P3 latency are somewhat equivocal. When differences are reported between controls and subjects with LD, the effect size is small, and the means for LD subjects are within 1 SD of the control subjects.[109,110] Determining whether an individual had cognitive deficits caused by MTBI or LD could be assessed using a combination of electrophysiologic measures and neuropsychologic testing (see point four in conclusion).

METHODOLOGIC ISSUES AND FUTURE WORK

Many methodologic factors are known to complicate the picture of recovery following MTBI. Some criticisms are generally applicable to all MTBI research. One such criticism is that null results may in certain cases be due to factors such as *sample size*. Several studies in this review reporting null results included small numbers of subjects.[15,50,67] It is possible that the lack of an effect in these studies was due to low statistical power.

Other factors specific to clinical electrophysiology include using an adequate normal limit in conjunction with a normative database. Published guidelines are available for the use of evoked potentials in clinical settings.[112] These guidelines clearly state the requirements for using electrophysiologic procedures in clinical settings regarding variables such as appropriate normal limits and appropriate control subjects. Use of an adequate normal limit can decrease the number of false positives observed, even though the number of MTBI subjects with positive electrophysiologic findings will also be reduced. This was the case for many of the BAEP studies described in this review. When a slightly higher normal limit was used for BAEP interpeak intervals, the number of abnormal recordings was dramatically reduced.

In addition to appropriate control groups for use in clinical settings, the use of appropriate control groups will also be beneficial experimentally. Recently, Satz and colleagues[113] argued persuasively for the inclusion of other-injury controls (e.g., subjects with orthopedic injuries and those with chronic pain) in MTBI studies. Control groups consisting of subjects with similar mood scores should also be used to ensure that electrophysiologic differences observed in MTBI subjects are not due to factors such as depression. However, these groups must be selected cautiously. For instance, other-injury subjects used as controls must not have sustained their injury in a situation in which acceleration/deceleration forces were present. The kinematics of MTBI are such that acceleration/deceleration injuries to the brain can occur without

physical head trauma.[114] This has been demonstrated convincingly in nonimpact primate experiments.[1,18,115] In fact, this was one of the key observations noted by Denny-Brown and Russell[1]; that "acceleration concussion" is only produced when the head is allowed to move freely. When the head is stationary, an equally weighted pendulum striking the head will not cause concussion. As such, nonimpact trauma to the brain is possible whether it is perceived by the subject or not (in fact it could be argued that head-injured subjects are generally inaccurate regarding their postinjury levels of cognitive functioning). To rule out any possible confound caused by acceleration/deceleration injury, other-injury control subjects should be those with injuries resulting in similar amounts of time off work, for instance, but not those sustained in automobile accidents or a sporting events in which speed was a factor.

Future reviews of the MTBI literature should focus on the relative and combined contributions of electrophysiologic and neuropsychologic measures in the assessment of MTBI. Most MTBI research involves standard neuropsychologic assessment. In contrast, relatively little is known about the value of electrophysiologic procedures in the assessment of MTBI. This latter work is growing, and in the future, it will likely play an important role in the detection of subtle alterations to information processing associated with MTBI. In fact, it may be argued that procedures such as EEG, ERP, and MEG are better suited than standard neuropsychologic measures to detect subtle cognitive changes after MTBI. This review focuses on the current state of our knowledge regarding electrophysiology and MTBI. It is hoped that future reviews will directly compare electrophysiologic measures to other neuroimaging techniques such as positron emission tomography (PET), single positron emission tomography (SPECT), functional magnetic resonance imaging (fMRI), standard clinical MRI, and computed tomography (CT) in the assessment of MTBI. These techniques may prove clinically useful in the assessment of MTBI; however, far more work is needed before such usefulness is known.

CONCLUSIONS

1. Standard clinical EEG procedures, such as those used in hospitals, are not useful for the assessment of MTBI. These procedures were designed to detect gross morphologic changes such as large lesions and the presence of epileptiform activity. Techniques such as those described by Thatcher et al[31] that use more complex methods such as coherence, frequency, and phase analysis, combined as a discriminant function, may one day be used as standard clinical assessment procedures.
2. According to Gennarelli[17] and Povlishock,[5] MTBI often results in diffuse damage, and this damage occurs most often in the outer layers of the brain with mild forces, progressing inward as forces increase.[18] This position is consistent with the EP and ERP studiest discussed in this review. Damage to brainstem seems to be relatively minimal, because few studies show changes in BAEP interpeak interval following MTBI. Cognitive ERPs seem to be more sensitive to changes in brain function following MTBI. This position is consistent with related research suggesting that cognitive ERPs are the result of processing in distributed cortical and subcortical systems.[22,23] Moreover, the fact that attention and memory mechanisms, especially those responsible for information processing and working memory, seem to be among the most sensitive

to trauma substantiates Gennarelli's[116] claim that "the cerebral hemispheres rather than the brainstem are the recipient of mild forces" (p. 142).

1. Visual P3 latency seems to be the most sensitive electrophysiologic procedure covered in this review. All studies using this technique to assess MTBI have found differences in P3 latency compared with normal controls. In addition, the P3 word technique may be very useful for the simultaneous assessment of PTSD, malingering, and brain injury. This procedure seems to be sensitive to injury while resistant to false positives when a 2.5 SD normal limit is used.[9]
2. An electrophysiologic assessment battery may be the most effective method to detect differences in MTBI subjects who experience cognitive dysfunction. A combined battery may consist of EPs and ERPs,[9] EEG and EPs,[117] or a combination of electrophysiologic and neuropsychologic assessment procedures.[15] This is an important point, because no techniques, including neuropsychologic procedures, are currently sensitive enough to detect MTBI in all cases. With respect to the subtle nature of deficits associated with MTBI,[7] Binder et al[12] conducted a meta-analysis of the relationship between cognitive impairment and MTBI among patients with no PCS and found a small but significant overall effect size. This suggests that there is cognitive impairment, albeit quite subtle, associated with MTBI. Therefore, detection of these "minor cognitive impairments" is important, especially when one considers the cumulative effects of concussion.
3. Electrophysiologic testing may be of considerable use in the context of a multimodality assessment protocol. Electrophysiologic procedures have the advantages of being noninvasive, inexpensive, and easily administered. In addition, there is considerable flexibility regarding the number of paradigms that can be developed and used in conjunction with electrophysiologic procedures. In this context, they have considerable benefits compared with other functional imaging procedures such as PET SPECT, (which is not to say that these procedures are not useful, but may one day be complementary). fMRI may one day be used for the assessment of MTBI; however, this technique is relatively early in development and faces similar issues as the electrophysiologic procedures discussed in this review. Structural imaging procedures are beneficial for the detection of life-threatening aspects of trauma such as focal lesions and the development of intracerebral bleeding. However, there is considerable evidence suggesting that acceleration/deceleration forces cause diffuse neural trauma.[5,17,18] This type of injury may not be detectable using a standard clinical CT or MRI scan.[9,19]

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Table 1. Perceived usefulness of various electrophysiologic procedures in MTBI assessment

Measure	Perceived usefulness	Relevant studies	
		For use	Against use
Electroencephalography			
Standard	Poor	26–28	20, 21, 29, 30
Nonstandard	Promising	31–35, 39–41	
Evoked potentials			
BAEP	Mixed	43–49	50–55
MAEP	Promising	55, 60	9
PVEP	Mixed	9, 47	50, 61
BTEP	Promising	55	
MEP, SEP	Poor		63
Event-related potentials			
N2/P300			
Auditory amplitude	Moderate	13, 14, 53, 69–71	15, 50, 51, 67
Auditory latency	Moderate	9, 14, 51, 66, 68, 72	15, 50, 67, 73
Visual amplitude	Promising	71	
Visual latency	Good	8, 9, 73	
Processing negativity	Promising	69	
Contingent negative variation			
Auditory	Poor		8, 9, 13
Visual	Mixed	9	8
Magnetoencephalography	Promising	19, 75	

Note: Nonstandard EEG = frequency and coherence; BAEP = brainstem auditory–evoked potential; MAEP = middle-latency auditory–evoked potential; PVEP = pattern visual–evoked potential; BTEP = brainstem trigeminal nerve stimulation; MEP = motor-evoked potential; SEP = somatosensory-evoked potential.