OFFICE-BASED NEUROPHYSIOLOGICAL ASSESSMENTS FOR DIAGNOSIS AND PROGNOSIS OF CONCUSSION

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Abstract

Patients suffering from concussion often receive insufficient and/or ineffective diagnostic workups. A limiting factor for a prompt and accurate diagnosis of the disease is the scarcity of practical and effective concussion diagnostics that can be used by private-practice physicians.
This gap in the diagnostic process can delay the implementation of crucial interventions. The absence of an affirmative concussion diagnosis leaves patients with few options when follow-on treatment would otherwise be indicated, potentially leading to worsening symptoms, prolonged recovery, and a higher likelihood of developing long-term complications.
Neurophysiological assessments such as electroencephalography (EEG) and event-related potentials (ERPs) offer an opportunity for an objective evaluation of brain deficits that may occur after a concussion. By detecting abnormalities in brain patterns that are often associated with concussive injuries, these tests can help a timely diagnosis and treatment of the disorder, thus reducing the likelihood of a chronification of post-concussive symptoms.
We review a battery of neurophysiological assessments that have been scientifically validated to detect the pathophysiological effects of concussion, and that can be performed in office settings by non-specialist technicians. These assessments are designed to help with diagnosis and prognosis of concussion, while also being accessible and practical to administer for private-practice physicians that can incorporate them into routine evaluations of their TBI patients.
The implementation of neurophysiological tools in primary care and outpatient settings has the potential to bridge the gap between symptom presentation and definitive diagnosis, thus mitigating the risk for long-term adverse outcomes.

Keywords: Concussion; TBI; Event-Related Potentials; ERP, EEG; Diagnosis; Prognosis; Office Settings

The Centers for Disease Control and Prevention (CDC) defines a concussion as:
"A type of traumatic brain injury—or TBI—caused by a bump, blow, or jolt to the head or by a hit to the body that causes the head and brain to move rapidly back and forth. This sudden movement can cause the brain to bounce around or twist in the skull, creating chemical changes in the brain and sometimes stretching and damaging brain cells"(Centers for Disease Control and Prevention, 2019).
The severity of a TBI may range from "mild" (i.e., a transient change in mental status or consciousness) to "severe" (i.e., an extended period of unconsciousness or memory loss after the injury). Mild TBIs, commonly referred to as "concussions", are the most common (National Center for Injury Prevention and Control, 2003) and challenging for clinicians to evaluate. Current guidelines for the diagnosis of concussion have recently been delineated by the American Congress of Rehabilitative Medicine Diagnostic Criteria for Mild Traumatic Brain Injury (Silverberg et al., 2023).
It's worth noticing that the primary clinical role of neuroimaging is to "*rule out head and brain injuries that might require neurosurgical or other medical intervention in an acute care setting.*"(Silverberg et al., 2023). Indeed, at present there are no radiological investigations that can diagnose a concussion (Arfanakis et al., 2002; Gallagher et al., 2007; Hurley et al., 2004; McAllister et al., 2001; Neil et al., 2002). A recent review article in the Cleveland Clinical Journal of Medicine titled "Concussion: Evaluation and Management" states:
"Current clinical brain imaging cannot diagnose a concussion. The purpose of neuroimaging is to assess for other etiologies or injuries, such as hemorrhage or contusion, that may cause similar symptoms but require different management." (Stillman et al., 2017).

There is also little evidence that a standard neurological examination or traditional cognitive testing can reliably detect the neuropathological effects of brain injury after a mild concussion (Gosselin, Bottari, et al., 2012).

Finally, there are currently no blood biomarkers to diagnose a concussion. While blood biomarkers are available that can determine the need to perform a CT scan, there are significant time restraints in performing these tests, as they are approved to be administered within 24 hours of the injury (Rauchman et al., 2023).

The use of inadequate protocols for concussion diagnosis can lead to a failure to recognize the

condition and/or provide poor diagnostic accuracy in a significant portion of patients. In fact, according to a 2023 University of Pittsburg Medical Center study, 50% of concussions go undetected or unreported(UPMC Sports Medicine Concussion Program, 2018).

While the majority of concussions improve within a month, 15-30% of patients develop persistent post-concussion symptoms (PPCS) previously known as post-concussion syndrome (Kureshi et al., 2024). PPCS is a nociplastic disorder with a time-dependent process that can potentially be interrupted. Indeed, multiple studies have now demonstrated that early, proactive care significantly improve concussion outcomes (Kureshi et al., 2024). Preventing PPCS is a major concern in concussion management. Thus, there needs to be an urgency in the diagnosis of concussion, so that tailored interventions can be applied promptly to prevent the neuroplastic changes that are responsible for pain chronification.

RECOMMENDATIONS FOR DIAGNOSTIC MODALITIES

In 2017, the American College of Occupational and Environmental Medicine (ACOEM) published a 1,027-page consensus guideline that recommends (or explicitly does not recommend) specific diagnostic modalities for concussion based on scientifically reported evidence (Hegmann et al., 2017).

In here, we review neurophysiological assessments which have been scientifically validated to detect the pathophysiological effects of concussion and can be performed in office settings.

Audiometry Testing

Studies have shown that some form of hearing loss is common after a minor head injury (Bansal, 2022). There are two primary causes of post-concussive hearing loss: mechanical damage and/or neurological damage (Alpsoy et al., 2021)

If an injury affects the delicate hearing structures, the ear may not effectively transmit sound to the brain. This is the most common cause of hearing loss after head injury and can often be detected by performing a pure-tone audiometry test and reviewing the resultant audiogram (Figure 1).

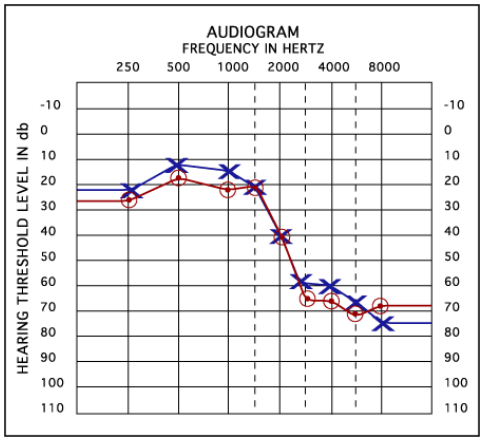

Figure 1. Example of an Audiogram

On the other hand, if there is synaptic damage to the auditory cortex the brain may no longer be able to properly process sounds. Therefore, even if the ear's anatomical structures function normally, a patient can still experience hearing problems. This presentation can often be identified by a patient complaining about hearing issues while having a normal audiogram.

The AECOM guideline recommendations for audiometry testing are as follows:

"To conclude, there is a high incidence of audiological deficits in head-injured subjects. Peripheral and central auditory areas are affected as revealed by the subjective as well as electrophysiologic auditory investigation."(Hegmann et al., 2017) Pg. 270.

An accurate audiogram result will also be essential in performing a valid ERP test (see ERP discussion below).

Electroencephalography (EEG) Testing

Common head injuries not only result in macroscopic damage such as tissue injury, bone fractures, and bleeding; mild injuries can also induce microscopic damage to cellular and synaptic structures in the brain. These cellular-level injuries can disrupt electrolyte homeostasis, trigger the release of excitatory neurotransmitters and other molecules with cytotoxic effects, and elevate the metabolic demand for neuronal repair and equilibrium restoration (Mckee & Daneshvar, 2015). The pathologic consequences can manifest as diverse concussion symptoms that cannot be detected by a CT or other imaging modalities.

A well-studied modality to monitor diffuse brain function is electroencephalography (EEG).

EEG is a recording of cortical function measured as voltage potentials on the surface of the scalp. This modality can be an important tool in examining and evaluating a wide range of brain networks and processes that may be impaired in a concussion.

A recent review paper on the application of EEG technology to concussion diagnosis in clinical practice states:

"Electroencephalography (EEG) is a well-suited technology for the evaluation of mTBI. This low-cost technology is rapid, portable, and easily deployed in multiple clinical settings. The development of computerized quantitative analysis (qEEG) has made this technology sensitive and specific to mTBI both in the acute and convalescent setting."(Kerasidis & Simmons, 2021).

Among the most useful qEEG analytical approaches, spectral analysis, is of particular interest in the study of concussion and post-concussive symptoms (Thornton, 2014). In this analysis, the raw EEG is transformed into frequency vs. power and plotted as a frequency spectrum (Figure 2).

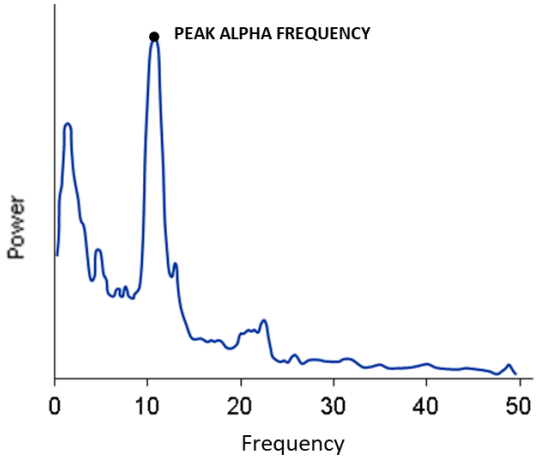

Figure 2. Example of an EEG frequency spectrum.

The power and frequency of the electrical energy generated by groups of cortical neurons varies with the level of synaptic/neuronal damage and with the integrity of the thalamocortical circuits in which they participate (i.e., injury to and/or dysfunction of those circuits results in a shift to slower frequencies and lower power recorded at scalp electrodes).

The same qEEG spectral analysis can also be a useful prognostic tool in predicting recovery from concussion:

"Alteration of the EEG alpha power dynamics in conjunction with balance data in the acute phase of injury with respect to baseline measures may predict the rate of recovery from a single concussive blow." (Slobounov, S; Sebastianelli, W; Hallett, 2012).

Cognitive Event-Related Potentials (ERP) Testing

ERPs are the part of the EEG generated by sensory and cognitive processing of external stimuli (for an overview of the ERP technique, see (Luck, 2014)). Most often, these external stimuli are auditory, in which cases a pure-tone audiometry test as described above is necessary to ensure that the patient has sufficient hearing acuity to perform the ERP procedure.

At the end of the ERP 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 neurophysiologic responses evoked by each stimulus type played during the test (Figure 3).

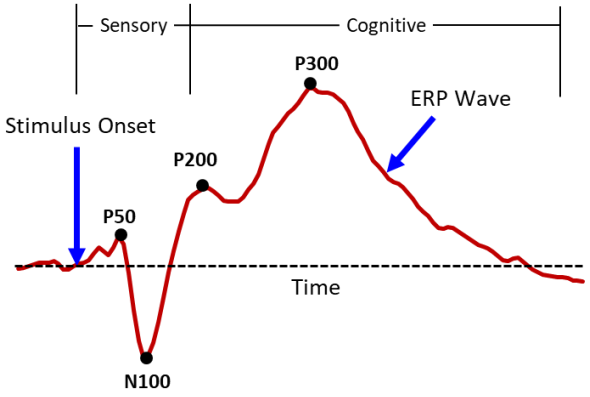

Figure 3. Example of an ERP waveform.

The ERP waveforms contain a series of positive and negative peaks (such as P50, N100, P200, and P300 as shown above) that have been extensively characterized in the scientific literature (Key et al., 2005).

The early peaks are primarily "sensory" responses that depend largely on the physical parameters of the stimulus. The sensory responses are followed by "cognitive" peaks, which reflect information processing (Gosselin et al., 2012).

ERPs have been used to elucidate and characterize sensory and cognitive deficits associated with brain injury and disease since the early 1980s (Knight et al., 1981). A large body of scientific

literature on the clinical utility of these biomarkers demonstrate that ERPs offer significant diagnostic utility to investigate sensory deficits, cognitive impairment, and motor dysfunction associated with concussion (Broglio et al., 2011; Dockree & Robertson, 2011; Duncan et al., 2011; Rapp et al., 2015). These diagnostic domains are referenced in several of the recommended testing modalities from the ACOEM guidance, including attention, executive function, and reaction time (Hegmann et al., 2017). Additional clinically relevant brain-based biomarkers can also be measured using ERPs, such as speed of brain processing (Borg et al., 2004; Brush et al., 2018; Washnik et al., 2019) and network activation asynchronies associated with white matter damage (Maruta et al., 2020).

ERPs are especially important to detect subtle deficits in information processing in patients who present with otherwise normal clinical findings (Broglio et al., 2011; Dockree & Robertson, 2011; Duncan et al., 2011; Levy-Reis, 2017). While most of the scientific literature reports on the diagnostic utility of ERPs for concussion, there is strong evidence to support post-injury prognosis as well (Duncan et al., 2011).

Of particular importance for the assessment of concussion is the "Active Auditory Oddball ERP Paradigm"(Duncan et al., 2011). In this paradigm, 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 by pressing a button on the handset as fast as they can when the infrequent target tone is heard, and reaction time is quantified.

The auditory oddball paradigm generates ERP waveforms with peaks, including the N200 and P300 or (P3a and P3b) that reflect aspects of information processing involved in stimulus discrimination, evaluation, and categorization (Key et al., 2005). The morphology of these peaks is sensitive to cognitive deficits associated with concussion. The reaction times of the button-press responses also provide sensitive measures of cognitive and motor networks within the brain and are sensitive to concussion-related injury to the cortex (Eckner et al., 2014).

Additional details on the "cognitive" peaks from the Active Auditory Oddball ERP Paradigm and their involvement in concussion are discussed in the table below (Table 1).

Table 1. Details of Important ERP Peaks.	
Peak	N200
Description	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 (Patel & Azzam, 2005) The peak is maximal over fronto-central (Fz/Cz) electrode locations (McGeown et al., 2017), and its latency has been shown to correlate with measures of executive function and attention (Bennys et al., 2007).
Involvement in Concussion	Abnormal N200 measures are most commonly reported in patients with a history of moderate or severe TBI. Investigators have shown prolonged N200 latency in survivors of severe TBI (Duncan et al., 2003, 2005; Sarno et al., 2006). In one of the studies, significant correlations were found between severity of head injury as measured by length of unconsciousness, N200 latency, and N200 amplitude (Duncan et al., 2003).
Peak	P3b (P300)
Description	The P3b (often referred to as the P300) is a positive-going component elicited by rare, attended (target) stimuli. It is of maximal amplitude at the parietal (Pz) electrode location, and it reflects an update in working memory (for a review of the neuropsychological origins of the P3b, see (Polich, 2007)). P3b amplitude is determined by the amount of attentional resources allocated when working memory is updated (Donchin & Coles, 1988). The peak latency reflects stimulus evaluation and classification speed (Duncan-Johnson & Donchin, 1982; Kutas et al., 1977).
Involvement in Concussion	The P3b is a highly sensitive ERP measure for deficits in cortical synaptic function that follow a concussion. A large scientific literature reports on post-concussion changes in P3b. In a study aimed at investigating neuropsychological and neurophysiological changes after sports-related concussion in children, adolescents, and adults, the investigators found that "*all concussed athletes had significantly lower amplitude for the P3b component compared to their non-injured teammates*" (Baillargeon et al., 2012). A separate study reported that P3b components from patients with concussion show a significant decrease in the peak amplitude compared to healthy individuals (Doi et al., 2007). The P3b can show significant changes even in mild cases. A study that looked at ERP changes in college students after mild concussion reported a "*striking*" decrease in P3b amplitude. Moreover, the change in P3b amplitude was strongly related to the severity of post-concussion symptoms (Dupuis et al., 2000). Similarly, a study that looked at the effects of a minor head injury on P3b found significant abnormalities in both peak amplitude and latency (Pratap-Chand et al., 1988). Another study of neurophysiological anomalies in symptomatic and asymptomatic concussed athletes showed a significant reduction in P3b amplitude in both groups of subjects compared to controls (Gosselin et al., 2006). An additional 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 (Segalowitz et al., 2001). The P3b can be used to evaluate the chronic effects of concussion. A 4-year ERP study of 364 student-athletes (33 with confirmed concussion) reported that when P3b (P300) amplitude and reaction time are combined, the concussed students can be distinguished from the controls with an accuracy of AUC=0.95 (Clayton et al., 2020).

	The P3b is correlated with neurocognitive deficits. Finally, a recent study reported that changes in the P3b (P300) after concussion were significantly correlated with various neurocognitive symptoms, including a reduction in intelligence quotients (IQ) scores, stating that *"The result showed that the intelligence quotients of patients were lower than those of healthy controls, which meant that patients with neurocognitive disorders after a TBI might suffer a mild intelligence impairment."*(Li et al., 2021).
Peak	P3a
Description	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 central-parietal (Cz/Pz) electrode locations (McGeown et al., 2017). The P3a is associated with engagement of attention and processing of novel information (Polich, 2007). The peak amplitude is a measure of focal attention and has been shown to positively correlate with executive function (Fjell & Walhovd, 2001). Its latency reflects speed of orientation to a non-target deviant stimulus (Vecchio & Määttä, 2011).
Involvement in Concussion	Numerous studies have reported abnormal P3a following concussion. A study in asymptomatic multiple-concussed college football players reported significantly decreased amplitude of P3a (and P3b) 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 two years prior to testing (Thériault et al., 2009). A study in soccer players with a history of concussion showed similar results (Moore et al., 2017). Interestingly, in a study that correlated ERPs to malingered executive function, the investigators reported that malingerers were unable to produce a significant change in P3a response (Hoover et al., 2014). The study findings are consistent with the ACOEM guidelines that include ERPs as a recommended test under "Memory/Malingering Tests"(Hegmann et al., 2017), and suggest that ERP measures could help differentiate between malingerers and patients with genuine concussion.

AECOM guideline recommendations for ERP testing:

As has been described previously, standard ERP testing evaluates attention, executive function, and reaction time, all of which are testing domains "recommended" in the ACOEM guidelines (Hegmann et al., 2017).

In fact, the guidelines assert that cognitive ERP testing *"Has evidence of diagnostic efficacy and is recommended for diagnosis of cognitive impacts of TBI."* Pg. 238

For tests of attention, the ACOEM guidelines state:

"Recent studies have shown that various aspects of attention are affected following TBI, especially after severe TBI. These deficits include the ability to attend to and encode information, information processing speed, maintain focus, shift attention, attention span,

supervisory attentional control, focused/selective attention, and sustain attention. May be used to target specific cognitive rehabilitation strategies. May help to determine the end of healing and extent of residual deficits, if any." Pg. 240

For tests of executive function, the AECOM guidelines state:

"Is not invasive, has no adverse events, is low cost, has some evidence of diagnostic efficacy, and is thus recommended for evaluation of TBI patients. Can identify and measure executive function difficulties, potentially allowing better tailoring of therapy(ies) to address any deficits." Pg. 255

For tests of reaction time, the AECOM guidelines suggest a supportive role for diagnosis of TBI:

"Is low cost, has evidence of diagnostic efficacy, and is recommended for diagnosis of TBI." Pg. 183

Timing and frequency of neurophysiological evaluations:

ACOEM guidelines for administration of ERP testing after TBI recommend:

"Baseline Evaluation. May be used to evaluate progress and/or residual cognitive deficits."

Indications for discontinuations include:

"Sufficient recovery, plateau, end of healing." Pg. 238

A neurophysiological assessment should be performed soon after a concussion to promptly detect and quantify abnormalities in brain function.

After an initial baseline evaluation, the frequency of follow-up testing is ultimately the decision of the treating clinician based on the patient's clinical course. While some patients may not require further studies, follow-up assessment may be appropriate at 90 or 180 days, or even 1, 2 or 3 years after the initial study based on clinical progression and clinician's judgment. Ultimately, each case should be evaluated independently, with follow-up testing conducted only if it is expected to provide valuable clinical and/or management information.

PRACTICAL TECHNOLOGY FOR PERFORMING IN-OFFICE NEUROPHYSIOLOGICAL ASSESSMENTS

A major factor limiting patients' access to effective concussion diagnostics and therapy is the scarcity of practical, ancillary or supportive concussion diagnostics that can be used by private

practice physicians. This requires technologies that are effective, affordable, and can be operated by non-specialist technicians in a standard office environment.

Over the past few years, a number of companies have introduced practical, FDA-cleared products which can detect neurophysiological deficits in brain injured patients. One clinically validated product is the COGNISION® System (from Neuronetrix Solutions, LLC) (Cecchi et al., 2015, 2023). This turnkey system includes all necessary hardware and software to order, perform, analyze, and report on a battery of neurodiagnostic procedures that can help physicians affirmatively detect abnormal brain activity caused by a concussion. With this single system, a physician can perform audiometry testing, EEG testing, and ERP testing during a single 1-hour session. Furthermore, these tests can be performed in a standard office environment with minimal patient discomfort, making these procedures practical to perform by private-practice physicians or their clinical technicians.

This battery of tests provides objective physiologic measures of various brain functions, including:

- auditory processing
- attention
- working memory
- executive function
- reaction time

These brain processes are sensitive measures of abnormal brain function that can provide objective evidence of injury.

At the end of the testing session, a patient report is produced that graphically displays an audiogram, EEG frequency spectrum, and ERP waveforms, along with a table of the important measures numerically quantified from each test. At this point, the physician can add their clinical interpretations of the reported biomarkers along with overall clinical findings that will be included in the patient report (COGNISION Patient Report - Concussion, 2023). Since the measures are objectively quantified, they can be very useful in tracking a patient's recovery over time (Duncan et al., 2011).

CONCLUSIONS

Many patients suffering from concussion receive insufficient and ineffective diagnostic workups. This is primarily due to the difficulty of directly evaluating complex brain processes, especially when the injury mostly involves cellular and synaptic structures within the brain.

The use of office-based neurophysiological assessments can assist in a more objective diagnosis of cognitive dysfunction in patients with concussion. This, in turn, can potentially lead to an earlier treatment of the disorder, thus reducing or resolving the cognitive dysfunction that occurs with acute concussion and significantly reducing the likelihood of PPCS.

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