COGNISION® Testing for Diagnosis and Prognosis of Concussion

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OVERVIEW

The Centers for Disease Control and Prevention 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."[1]

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 (concussions) are the most common[2] and most challenging for clinicians to evaluate.

CONCUSSION DIAGNOSIS

Current "standard of care" guidelines for the diagnosis of concussion offer limited clinical options. For example, the Mayo Clinic describes their concussion diagnostic process like this:

"Your doctor will evaluate your signs and symptoms, review your medical history, and conduct a neurological examination. Signs and symptoms of a concussion may not appear until hours or days after the injury. Tests your doctor may perform or recommend include a neurological examination, cognitive testing, and imaging tests."[3]

When head trauma requires medical attention, clinicians may request structural neuroimaging provided by CT or MRI scans to rule out a potentially life-threatening cerebral hemorrhage.

However, these neuroimaging techniques underestimate mild traumatic injuries and correlate poorly with patient outcomes.[4–8] The main reason for this seems to be that neither CT nor conventional MRI sequences detect diffuse axonal injuries, the most common pathology of concussion[9–14], resulting in only a small minority of patients that present with intracranial CT scan abnormalities.[15] Additionally, the American Association of Neurological Surgeons (AANS) recommends against routine imaging studies in the diagnosis of concussion as they typically do not show significant pathology and can expose individuals to unnecessary radiation.[16]

Additionally, there is little evidence that a standard neurological examination or traditional cognitive testing can provide a reliable and sensitive assessment of brain injury after a mild concussion. The use of such limited 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 the University of Pittsburg Medical Center, 50% of concussions go undetected or unreported.[17]

This is especially true when there may be confounding or comorbid conditions with the patient:

"The diagnostic accuracy for mTBI is currently insufficient for discriminating between the disease and co-occurring mental health conditions for both acute and historic mTBI."[18]

Without an affirmative concussion diagnosis, patients are left with few options when follow-on treatment would otherwise be indicated.

ACOEM CONCUSSION DIAGNOSIS RECOMMENDATIONS

In 2017, the American College of Occupational and Environmental Medicine (ACOEM) published a 1,027-page consensus guideline that recommends (or does not recommend) specific diagnostic modalities for concussion, based on scientifically reported evidence, as clinically indicated for patients sustaining a concussion [19].

Additionally, ACOEM makes clear that *"A direct blow to the head is not required for TBI to occur because rapid acceleration or deceleration is a TBI mechanism."* Pg 19. The guidelines also present a definitive connection between cervical spine trauma and concussion, Pg 26, both of which commonly occur in motor vehicle accidents and sports injuries.

Among the testing modalities that were "recommended" in the consensus guidelines include:

- **Audiometry Tests**

  "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." Pg. 270

- **EEG Tests**

  "EEG is not invasive, has no adverse effects, is moderate cost, and has utility in the diagnosis and management of seizures related to TBI and is thus recommended for diagnosis of TBI." Pg. 123

- **Cognitive Event-Related Potentials**

  "Has evidence of diagnostic efficacy and is recommended for diagnosis of cognitive impacts of TBI." Pg. 238

- **Attention Tests**

  "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

- **Executive Function Tests**

  "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

- **Reaction Time Tests**

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

COGNISION® TESTING

The COGNISION® System includes the necessary hardware and software to order, perform, analyze, and report on a group of diagnostic procedures that can help a physician affirmatively detect abnormal brain activity caused by a concussion.

The COGNISION® System has already been validated to provide clinically relevant measures of brain function and how those processes change with disease.[20,21] This validation includes the practical implementation of the testing procedures in outpatient settings within various patient populations. A complete testing session can be performed in about 1 hour in a standard office environment with minimal patient discomfort.

During a COGNISION® testing session, three separate procedures are performed:

- Pure-tone Audiometry
- Resting-state EEG
- Event-Related Potentials (ERP)

Each of these tests (described in detail below) targets synaptic networks in the brain that are often damaged from a concussion.

At the end of the testing session, the data is available for analysis and interpretation by a physician and can be transferred to a patient report, which will show the audiogram, EEG frequency spectrum, and ERP waveforms, each with a table of clinical biomarkers.

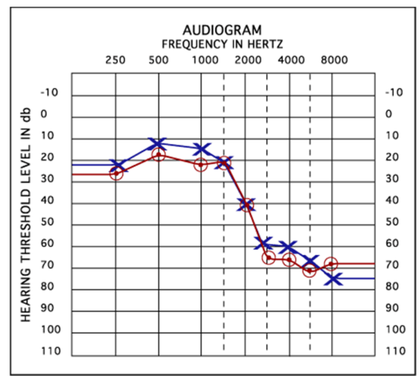
At this point, the physician can add specific biomarker and overall clinical findings that will automatically be included in the patient report.[22]

- **Audiometry**

Studies have shown that some form of hearing loss is common after a minor head injury.[23]

There are two primary causes of post-concussive hearing loss: mechanical damage or neurological damage.

For example, 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.



Example of an audiogram

On the other hand, if there is synaptic damage to parts of the brain that process hearing, 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.

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

- **Resting-state EEG**

Common head injuries not only result in macroscopic damage such as tissue injury, bone fractures, and bleeding but can also induce microscopic damage to cellular and synaptic structures in the brain. This 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.

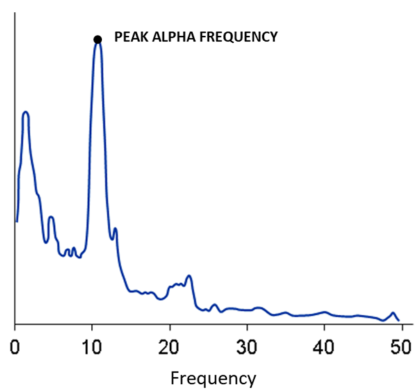
These pathologic consequences can manifest as diverse concussion symptoms that can not be detected by a CT scan. Alternatively, a brief resting-state EEG assessment can be an important tool to monitor and evaluate a wide range of brain networks and processes that may be impaired by concussion.

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

"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."[24]

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



Example of an EEG frequency spectrum

These qEEG measures 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."[25]

Conventional wisdom holds that most patients generally recover from a concussion within hours and would be symptom-free within about ten days post-injury. However, qEEG studies are showing that this conventional view may not always be the case.

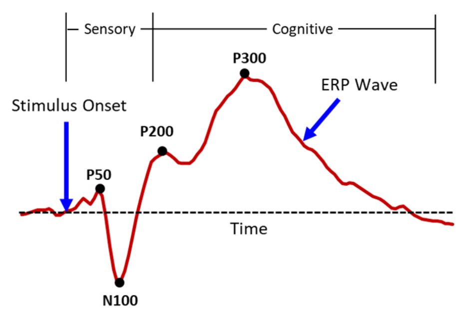
"There is growing evidence of an atypical evolution of mTBI whereby physical, neurocognitive, and emotional symptoms persist months or even years post-injury."[25]

- **Event-Related Potentials (ERP)**

ERP testing involves recording EEG signals while the patient listens to a sequence of auditory stimuli through the same earphones used during the pure-tone audiometry test. In fact, the audiometry test is a necessary procedure to ensure that the patient has sufficient hearing acuity to perform the ERP procedure. During the test, the patient is required to respond to certain auditory cues by pressing a button on the handset.

The type, timing, and sequence of stimuli (often called an "ERP paradigm") are designed to target specific cognitive processes such as selective attention, memory encoding, executive function, and other processes that can be impaired with a concussion.

While the brain subconsciously analyzes the incoming stimuli, EEG signals time-locked to each stimulus are recorded. At the end of the test, these 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.



Example of an ERP wave

ERPs are the part of the EEG generated by sensory and cognitive processing of external stimuli. They reflect the summed synaptic activity produced when similarly oriented neurons fire synchronously in response to each stimulus.[26]

The ERP contains a sequence of positive and negative peaks, such as P50, P300, etc., that have been extensively characterized in the scientific literature.[27]

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 and can be used to detect and quantify cognitive deficits associated with concussion.[28]

The accuracy and 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.[29]

ERP BIOMARKERS FOR CONCUSSION

ERPs have been used to elucidate and characterize sensory and cognitive deficits associated with brain injury and disease since the early 1980s[30]. A large body of scientific literature on the clinical utility of these biomarkers for diagnosis and prognosis of concussion has followed.

Recent reviews of published literature demonstrate that ERPs offer significant diagnostic utility to investigate sensory deficits, cognitive impairment, and motor dysfunction associated with concussion.[31–34] These diagnostic domains include several of the recommended testing modalities from the ACEOM guidance[19], including **attention**, **executive function**, and **reaction time**. Additional clinically relevant brain-based biomarkers can also be measured using ERPs, such as **speed of brain processing**[15,35,36] and **network activation asynchronies** associated with white matter damage.[37]

ERPs are especially important to detect subtle deficits in information processing in patients who present with otherwise normal clinical findings.[32–34,38]

There is also good evidence from the scientific literature for the use of ERP biomarkers to support brain injury prognosis as well:

"*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.*"[32]

ERP testing provides flexibility in protocol design that can produce measures that correlate with different sensory and cognitive domains.[26] Several ERP paradigms have been shown to be especially sensitive to detecting deficits associated with concussion. Of particular importance is the "Active Auditory Oddball ERP Paradigm" commonly used during a COGNISION® testing session.

COGNISION® uses an ERP paradigm that was specifically designed to probe brain function, which is commonly impaired with concussion.[32] 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.

This paradigm generates ERP features, including the P3b, P3a, and N200, that reflect aspects of information processing involved in stimulus discrimination, evaluation, and categorization[27] and are sensitive to cognitive deficits associated with concussion.

- **P3b (P300)**

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 (Pz) electrodes and reflects an update in working memory (for a review of the neuropsychological origins of the P3b, see[39]). P3b amplitude is determined by the amount of attentional resources allocated when working memory is updated.[40] The peak latency reflects stimulus evaluation and classification speed.[41,42]

P3b is a highly sensitive ERP measure for deficits in cortical synaptic function that follow a concussion. 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*".[43] Another study that measured P3b components from patients with concussion reported a significant decrease in the peak amplitude compared to healthy individuals.[44]

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.[45] Similarly, a study that looked at the effects of a minor head injury on P3b found significant abnormalities in both peak amplitude and latency.[46] A 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[47], 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.[48] 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."*[49]

- **P3a**

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.[50] The P3a is associated with engagement of attention and processing of novel information.[39] The peak amplitude is a measure of focal attention and has been shown to positively correlate with executive function.[51] Its latency reflects speed of orientation to a non-target deviant stimulus.[52]

Several studies have shown P3a changes after concussion. 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 two years prior to testing.[53] Investigators have recently reported similar results in soccer players with a history of concussion.[54] In a study on moderate to severe TBI survivors, the investigators found that P3a amplitude was reduced compared to healthy controls when frontal or frontotemporal brain regions were injured. In addition, TBI survivors also exhibited a trend towards prolonged peak latency.[55]

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[56]. The study findings are consistent with the ACOEM guidelines that include ERPs as a recommended test under "Memory/Malingering Tests"[57], and suggest that ERP measures could help differentiate between malingerers and patients with genuine concussion.

- **N200**

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.[58] The peak is maximal over fronto-central (Fz/Cz) brain regions[50], and its latency has been shown to correlate with measures of executive function and attention.[59]

N200 measures seem to be mostly affected in patients with a history of moderate or severe TBI. Investigators have shown prolonged N200 latency in survivors of severe TBI.[60,61,62] In one of the studies, significant correlations were also between severity of head injury, as measured by length of unconsciousness, N200 latency, and N200 amplitude.[61]

- **Reaction Time (RT)**

As discussed earlier, patients are instructed to press a button on the handset as fast as they can when they hear the target tone. The average latency of the button presses is a measure of how long it takes for the decision to press the button to initiate the motor response, commonly referred to as reaction time.

A recent 4-year ERP study of 364 student-athletes (33 with confirmed concussion) reported that when P300 amplitude and reaction time are combined, the concussed students can be distinguished from the controls with an accuracy of AUC=0.95.[63]

CONCLUSIONS

It is clear from the published clinical literature that 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. Another complicating factor is that patients with concussion can present with a wide range of sensory, cognitive, physical, and behavioral symptoms requiring an extensive diagnostic workup that can target the underlying mechanisms responsible for those symptoms.

The American College of Occupational and Environmental Medicine (ACOEM) has recognized these diagnostic shortcomings and has published a comprehensive clinical guidance to help enhance diagnosis and prognosis of patients with concussion and improve outcomes for those patients.

With the availability of practical, validated, and cost-effective instruments like COGNISION®, many patients can now receive a more thorough diagnostic workup from their physicians and can expect a more optimistic clinical outcome.

REFERENCES

1. Centers for Disease Control and Prevention. TBI: Get the Facts | Concussion | Traumatic Brain Injury | CDC Injury Center. U.S. Department of Health & Human Services. https://www.cdc.gov/traumaticbraininjury/get_the_facts.html. Published 2019. Accessed September 7, 2023.
2. National Center for Injury Prevention and Control. Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. *Centers Dis Control Prev Natl Cent Inj Prev Control*. 2003;(September):1-56. http://www.cdc.gov/traumaticbraininjury/pdf/mtbireport-a.pdf%5Cnpapers2://publication/uuid/C2643C39-C5DE-40A2-A290-A3D04BB6F7BC.
3. Mayo Clinic Concussion Diagnosis. https://www.mayoclinic.org/diseases-conditions/concussion/diagnosis-treatment/drc-20355600.
4. Arfanakis K, Haughton VM, Carew JD, Rogers BP, Dempsey RJ, Meyerand ME. Diffusion tensor MR

imaging in diffuse axonal injury. *AJNR Am J Neuroradiol*. 2002;23(5):794-802. http://www.ncbi.nlm.nih.gov/pubmed/12006280. Accessed August 9, 2018.

5. Gallagher CN, Hutchinson PJ, Pickard JD. Neuroimaging in trauma. *Curr Opin Neurol*. 2007;20(4):403-409. doi:10.1097/WCO.0b013e32821b987b
6. Hurley RA, McGowan JC, Arfanakis K, Taber KH. Traumatic axonal injury: novel insights into evolution and identification. *J Neuropsychiatry Clin Neurosci*. 2004;16(1):1-7. doi:10.1176/jnp.16.1.1
7. McAllister TW, Sparling MB, Flashman LA, Saykin AJ. Neuroimaging Findings in Mild Traumatic Brain Injury. *J Clin Exp Neuropsychol*. 2001;23(6):775-791. doi:10.1076/jcen.23.6.775.1026
8. Neil J, Miller J, Mukherjee P, Hüppi PS. Diffusion tensor imaging of normal and injured developing human brain - a technical review. *NMR Biomed*. 2002;15(7-8):543-552. doi:10.1002/nbm.784
9. Bazarian JJ, Zhong J, Blyth B, Zhu T, Kavcic V, Peterson D. Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. *J Neurotrauma*. 2007;24(9):1447-1459. doi:10.1089/neu.2007.0241
10. Capruso DX, Levin HS. Cognitive impairment following closed head injury. *Neurol Clin*. 1992;10(4):879-893. http://www.ncbi.nlm.nih.gov/pubmed/1435662. Accessed August 9, 2018.
11. Evans RW. The post-concussion syndrome and the sequelae of mild head injury. *Neurol Clin*. 1992;10(4):815-847. http://www.ncbi.nlm.nih.gov/pubmed/1435659. Accessed August 9, 2018.
12. Filley CM. Neurobehavioral Aspects of Cerebral White Matter Disorders. *Psychiatr Clin North Am*. 2005;28(3):685-700. doi:10.1016/j.psc.2005.05.008
13. Inglese M, Makani S, Johnson G, et al. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg*. 2005;103(2):298-303. doi:10.3171/jns.2005.103.2.0298
14. Levine B, Fujiwara E, O'Connor C, et al. In vivo characterization of traumatic brain injury neuropathology with structural and functional neuroimaging. *J Neurotrauma*. 2006;23(10):1396-1411. doi:10.1089/neu.2006.23.1396
15. Borg J, Holm L, Cassidy JD, et al. Diagnostic procedures in mild traumatic brain injury: results of the who collaborating centre task force on mild traumatic brain injury. *J Rehabil Med*. 2004;36(SUPPL. 43):61-75. doi:10.1080/16501960410023822
16. American Association of Neurological Surgeons. Concussion – Symptoms, Diagnosis and Safety Guidelines. https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Concussion. Published 2021. Accessed August 31, 2023.
17. UPMC Sports Medicine Concussion Program. Concussion Statistics and Facts | UPMC | Pittsburgh. UPMC. https://www.upmc.com/services/sports-medicine/services/concussion/about/facts-statistics. Published 2018. Accessed August 31, 2023.
18. Pape TL-B, High WM, St. Andre J, et al. Diagnostic Accuracy Studies in Mild Traumatic Brain Injury: A Systematic Review and Descriptive Analysis of Published Evidence. *PM&R*. 2013;5(10):856-881. doi:10.1016/j.pmrj.2013.06.007
19. ACOEM. Traumatic brain injury. *ACOEM Pract Guidel*. 2017;1-2(November 15):1-1027. doi:10.1055/s-2002-20587
20. Cecchi M, Moore DK, Sadowsky CH, et al. A clinical trial to validate event-related potential markers of Alzheimer's disease in outpatient settings. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2015;1(4):387-394. doi:10.1016/j.dadm.2015.08.004
21. Cecchi M, Adachi M, Basile A, et al. Validation of a suite of ERP and QEEG biomarkers in a pre-competitive , industry-led study in subjects with schizophrenia and healthy volunteers. *Schizophr Res*. 2023;254(April):178-189. doi:10.1016/j.schres.2023.02.018
22. COGNISION Patient Report - Concussion. 2023.
23. Bansal S. Assessment of Hearing Loss in Minor Head Injury: A Prospective Study. 2022.
24. Kerasidis H, Simmons J. Quantitative EEG Analysis in Clinical Practice: Concussion Injury. *Clin EEG Neurosci*. 2021;52(2):114 –118. doi:10.1177/1550059421989112
25. Slobounov, S; Sebastianelli, W; Hallett M. Residual brain dysfunction observed one year post-mild traumatic brain injury: combined EEG and balance study. *Clin Neurophysiol*. 2012;123(9):1755-1761. doi:10.1016/j.clinph.2011.12.022.Residual
26. Luck SJ. *An Introduction to the Event-Related Potential Technique*. (Gazzaniga M, ed.). Cambridge, Massachusetts: The MIT Press; 2005.
27. Key AP, Dove GO, Maguire MJ. Linking brainwaves to the brain: an ERP primer. *Dev Neuropsychol*. 2005;27(2):183-215. doi:10.1207/s15326942dn2702_1
28. Gosselin N, Erg CB, Chen JK, et al. Evaluating the cognitive consequences of mild traumatic brain injury and concussion by using electrophysiology. *Neurosurg Focus*. 2012;33(6). doi:10.3171/2012.10.FOCUS12253
29. Eckner JT, Kutcher JS, Broglio SP, Richardson JK. Effect of sport-related concussion on clinically measured simple reaction time. *Br J Sports Med*. 2014;48(2):112-118. doi:10.1136/bjsports-2012-091579
30. Knight RT, Hillyard SA, Woods DL, Neville HJ. The effects of frontal cortex lesions on event-related potentials during auditory selective attention. *Electroencephalogr Clin Neurophysiol*. 1981;52(6):571-582. http://www.ncbi.nlm.nih.gov/pubmed/6172256. Accessed June 15, 2018.
31. Rapp P, Keyser DO, Albano A, et al. Traumatic Brain Injury Detection Using Electrophysiological Methods. *Front Hum Neurosci*. 2015;9(February):1-32. doi:10.3389/fnhum.2015.00011
32. Duncan CC, Summers AC, Perla EJ, Coburn KL, Mirsky AF. Evaluation of traumatic brain injury: brain potentials in diagnosis, function, and prognosis. *Int J Psychophysiol*. 2011;82(1):24-40.
33. Dockree PM, Robertson IH. Electrophysiological markers of cognitive deficits in traumatic brain injury: a

review. *Int J Psychophysiol*. 2011;82(1):53-60. doi:10.1016/j.ijpsycho.2011.01.004

34. Broglio SP, Moore RD, Hillman CH. A history of sport-related concussion on event-related brain potential correlates of cognition. *Int J Psychophysiol*. 2011;82(1):16-23. doi:10.1016/j.ijpsycho.2011.02.010
35. Washnik NJ, Anjum J, Lundgren K, Phillips S. A Review of the Role of Auditory Evoked Potentials in Mild Traumatic Brain Injury Assessment. *Trends Hear*. 2019;23. doi:10.1177/2331216519840094
36. Brush CJ, Ehmann PJ, Olson RL, Bixby WR, Alderman BL. Do sport-related concussions result in long-term cognitive impairment? A review of event-related potential research. *Int J Psychophysiol*. 2018;132:124-134. doi:10.1016/J.IJPSYCHO.2017.10.006
37. Maruta J, Mallott JM, Sulioti G, Ghajar J, Palacios EM, Mukherjee P. Concussion Disrupts Normal Brain White Matter Microstructural Symmetry. *Front Neurol*. 2020;11(November):1-9. doi:10.3389/fneur.2020.548220
38. Levy-Reis I. Use of ERP markers in patients with whiplash and concussion with cognitive complains. In: *World Congress of Neurology*. Kyoto; 2017. doi:10.1016/j.jns.2017.08.2136
39. Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol*. 2007;118(10):2128-2148. doi:10.1016/j.clinph.2007.04.019
40. Donchin E, Coles MGH. Is the P300 component a manifestation of context updating? *Behav Brain Sci*. 1988;11(03):357. http://journals.cambridge.org/abstract_S0140525X00058027. Accessed April 27, 2015.
41. Duncan-Johnson CC, Donchin E. The P300 component of the event-related brain potential as an index of information processing. *Biol Psychol*. 1982;14(1):1-52. http://www.sciencedirect.com/science/article/pii/0301051182900163. Accessed November 11, 2013.
42. Kutas M, McCarthy G, Donchin E. Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. *Science*. 1977;197(4305):792-795. http://www.ncbi.nlm.nih.gov/pubmed/887923. Accessed April 27, 2015.
43. Baillargeon A, Lassonde M, Leclerc S, Ellemberg D. Neuropsychological and neurophysiological assessment of sport concussion in children, adolescents and adults. *Brain Inj*. 2012;26(3):211-220. http://www.ncbi.nlm.nih.gov/pubmed/22372409. Accessed March 20, 2012.
44. Doi R, Morita K, Shigemori M, Tokutomi T, Maeda H. Characteristics of cognitive function in patients after traumatic brain injury assessed by visual and auditory event-related potentials. *Am J Phys Med Rehabil*. 2007;86(8):641-649. doi:10.1097/PHM.0b013e318115aca9
45. Dupuis F, Johnston KM, Lavoie M, Lepore F, Lassonde M, Dupuis, François; Johnston, Karen M.; Lavoie, Marc; Lepore, Franco; Lassonde M. Concussions in athletes produce brain dysfunction as revealed by event-related potentials. *Clin Neurosci Neuropathol*. 2000;11(18):4087-4092. doi:10.1097/00001756-200012180-00035
46. Pratap-Chand R, Sinniah M, Salem FA. Cognitive evoked potential (P300): a metric for cerebral concussion. *Acta Neurol Scand*. 1988;78(3):185-189. http://www.ncbi.nlm.nih.gov/pubmed/3227804. Accessed December 16, 2015.
47. Gosselin N, Thériault M, Leclerc S, Montplaisir J, Lassonde M. Neurophysiological anomalies in symptomatic and asymptomatic concussed athletes. *Neurosurgery*. 2006;58(6):1151-1161. doi:10.1227/01.NEU.0000215953.44097.FA
48. Segalowitz SJ, Bernstein DM, Lawson S. P300 event-related potential decrements in well-functioning university students with mild head injury. *Brain Cogn*. 2001;45(3):342-356. http://dx.doi.org/10.1006/brcg.2000.1263. Accessed February 2, 2013.
49. Li H, Li N, Xing Y, et al. P300 as a Potential Indicator in the Evaluation of Neurocognitive Disorders After Traumatic Brain Injury. *Front Neurol*. 2021;12(September):1-9. doi:10.3389/fneur.2021.690792
50. McGeown WJ, Cecchi M, Fadem KC. Neuropsychological and Neuroanatomical Correlates of Event-Related Potentials in Patients with Alzheimer's Disease. In: *Alzheimer's Association International Conference*. London: Elsevier; 2017.
51. Fjell AM, Walhovd KB. P300 and neuropsychological tests as measures of aging: scalp topography and cognitive changes. *Brain Topogr*. 2001;14(1):25-40. http://www.ncbi.nlm.nih.gov/pubmed/11599530.
52. Vecchio F, Määttä S. The use of auditory event-related potentials in Alzheimer's disease diagnosis. *Int J Alzheimers Dis*. 2011;2011:1-7. doi:10.4061/2011/653173
53. Thériault M, De Beaumont L, Gosselin N, Filipinni M, Lassonde M. Electrophysiological abnormalities in well functioning multiple concussed athletes. *Brain Inj*. 2009;23(11):899-906. doi:10.1080/02699050903283189
54. Moore RD, Lepine J, Ellemberg D. The independent influence of concussive and sub-concussive impacts on soccer players' neurophysiological and neuropsychological function. *Int J Psychophysiol*. 2017;112:22-30. doi:10.1016/j.ijpsycho.2016.11.011
55. Solbakk A-K, Reinvang I, Andersson S. Assessment of P3a and P3b after moderate to severe brain injury. *Clin Electroencephalogr*. 2002;33(3):102-110. http://www.ncbi.nlm.nih.gov/pubmed/12192659. Accessed August 7, 2018.
56. Hoover S, Zottoli TM, Grose-Fifer J. ERP correlates of malingered executive dysfunction. *Int J Psychophysiol*. 2014;91(2):139-146. doi:10.1016/j.ijpsycho.2013.12.009
57. Traumatic brain injury. *Am Coll Occup Environ Med*. 2017;1-2(November 15). doi:10.1002/9781119756279.ch30
58. Patel SH, Azzam PN. Characterization of N200 and P300: selected studies of the Event-Related Potential. *Int J Med Sci*. 2005;2(4):147-154.

http://www.medsci.org/v02p0147.htm. Accessed April 15, 2014.

59. Bennys K, Portet F, Touchon J. Diagnostic Value of Event-Related Evoked Potentials N200 and P300 Subcomponents in Early Diagnosis of Alzheimer's Disease and Mild Cognitive Impairment. *J Clin Neurophysiol*. 2007;24(5):405-412.

60. Sarno S, Erasmus L-P, Frey M, Lippert G, Lipp B. Electrophysiological correlates of active and passive attentional states after severe traumatic brain injury. *Funct Neurol*. 2006;21(1):21-29. http://www.ncbi.nlm.nih.gov/pubmed/16734998. Accessed July 12, 2018.

61. Duncan CC, Kosmidis MH, Mirsky AF. Event-related potential assessment of information processing after closed head injury. *Psychophysiology*. 2003;40(1):45-59. http://www.ncbi.nlm.nih.gov/pubmed/12751803. Accessed July 12, 2018.

62. Duncan CC, Kosmidis MH, Mirsky AF. Closed head injury-related information processing deficits: An event-related potential analysis. *Int J Psychophysiol*. 2005;58(2-3):133-157. doi:10.1016/j.ijpsycho.2005.05.011

63. Clayton G, Davis N, Holliday A, et al. In-clinic event related potentials after sports concussion: A 4-year study. *J Pediatr Rehabil Med*. 2020;13(1):81-92. doi:10.3233/PRM-190620