2021

Neurophysiological and Behavioral Correlates of Post-Concussion Syndrome: A scoping review and validation of methods

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Honors College of Arts & Sciences Undergraduate Thesis

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Acknowledgments

The research presented in this thesis was conducted under the advisory of Dr. Sambit Mohapatra. Therefore, I would like to thank him for his guidance throughout this process. I would also like to thank members of the Department of Rehabilitation and Movement Science, including Hannah Bernier, Birgitta Carlson, Sarah Knakal, Jordan Mousley, and Lucas Van-Horn for their assistance with this project. Additionally, I would like to thank Gary Atwood for his advisory in conducting database searches and Juhee Lee for her assistance in learning how to use EEG. Lastly, I would like to thank my thesis committee members Dr. Lisa Schnell, Dr. Sayamwong Hammack, and Dr. Sambit Mohapatra for taking time to review and provide feedback on my thesis.

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ABSTRACT

INTRODUCTION: Mild traumatic brain injury (mTBI) is caused by an impact or jolt to the head which results in a physiological disruption to the brain. While typically symptoms such as headache, nausea, dizziness, and fatigue subside within the first 2 weeks, a subset of patients fail to recover within this time span and develop prolonged neurophysiological and behavioral symptoms characteristic of post-concussion syndrome (PCS). While there are numerous studies assessing the behavioral and neurophysiological correlates of PCS, there remains a need for these papers to be gathered and reviewed. Therefore, the objective of this paper was to conduct a scoping review of the literature reporting on the neurophysiological and behavioral correlates of patients in the subacute and chronic phase following mTBI. **METHODS:** MEDLINE/Ovid, Web of Science, CINAHL, Cochrane, and PsycINFO were searched in November 2020 for studies that investigated the neurophysiological and behavioral correlates in the subacute and chronic phase following mTBI. Inclusion and exclusion criteria were determined, and all studies were selected following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines (**Figure 1**). In total 336 citations were identified, of which 24 studies were eligible for inclusion in the primary analysis. **RESULTS:** All significant outcomes pertaining to neurophysiological and behavioral correlates were charted and can be found in **Table 1**. **DISCUSSION:** This scoping review suggests a need for a multimodal assessment of mTBI that includes both neurophysiological and behavioral measures. Additionally, more research is needed to further elucidate the progression as well as the neurological underpinnings of PCS.

1. Introduction

Mild traumatic brain injury (mTBI), otherwise known as concussion, is the most common form of traumatic brain injury[1]. An estimated 42 million people sustain an mTBI every year worldwide[2]. mTBI is caused by traumatic biomechanical forces to the head which lead to a complex pathophysiological process affecting the brain[3]. The US Department of Defense characterizes mTBI as experiencing one or more of the following symptoms: confused or disoriented state which lasts less than 24 hours; or loss of consciousness for up to 30 minutes; or memory loss lasting less than 24 hours[4]. The majority of mTBIs resolve within a 2-week period[5]. However, a subset of patients has symptoms that persist beyond this period[5]. This abnormal persistence of symptoms is known as Post-concussion Syndrome (PCS)[6].

Individuals with PCS may have symptoms such as headache, sleep dysregulation, reduced cognitive function, depression, and posttraumatic stress disorder (PTSD) that last for months to years post-injury resulting in a decreased quality of life[5-8]. Additionally, the presence of these uncomfortable symptoms can lead to underemployment and a loss in productivity[8]. Furthermore, repetitive head trauma may be linked to fatal progressive neurodegenerative diseases such as Chronic Traumatic Encephalopathy (CTE) and Alzheimer's Disease (AD)[9,10]. Therefore, it is important to have the ability to diagnose and manage symptoms in a prompt and precise manner[8]. With this, there is a growing body of evidence investigating the prolonged behavioral and neurophysiological abnormalities that result from mTBI[9,11]. These studies have utilized a variety of measurements that assess cognitive, psychological, physical, and neurophysiological processes[9].

Cognitive and psychological measures include a battery of neuropsychological assessments and self-report questionnaires that assess sequelae associated with PCS[12]. Cognitive

domains that are commonly assessed include: executive function, memory, and attention[10]. Self-report questionnaires are also utilized to assess general health, symptoms, and other emotional and psychological states such as anxiety and depression[13]. These neuropsychological assessments and self-report questionnaires are commonly utilized in clinical determinations[5]. However, many studies that have relied solely on neuropsychological measurements have been inconclusive in their results[9]. Additionally, self-report questionnaires are subjective and cannot be completely relied on[9]. Therefore, additional neurophysiological measurements are often used in conjunction with these assessments and have shown evidence of abnormal functioning when neuropsychological assessments have failed to do so[12].

Postural stability, balance, and gait have also been correlated with PCS symptomatology. These correlates are commonly studied in conjunction with neurophysiological measurements[11,14-16] that have the potential to investigate abnormal neuronal functions[11]. There are clinical assessments to test balance, however these have been proven to be unreliable[17]. Furthermore, studies that assess postural stability often utilize objective posturographic measurements (e.g., force plate) and various postural tasks such as standing, sitting, eyes closed and eyes open[11,15,17]. Additionally, balance problems in mTBI patients have been associated with the disruption of functions in the brain responsible for postural stability[11]. Another motor impairment that has been studied as a correlate of PCS is gait[16]. Studies often utilize a dual-task paradigm for gait analysis, where the participant must walk and perform a cognitive task[16]. With this, researchers can investigate whether PCS patients show any differences in gait when performing a cognitive task[16].

Neurophysiological measures combined with behavioral measures have provided an objective way to assess functional neuronal abnormalities in patients with PCS[12]. While standard imaging techniques such as CT-scan or magnetic resonance imaging (MRI) have failed to show

gross structural damage to the brain following concussion, functional neuroimaging techniques have been able to detect the "silent" pathophysiological or molecular mTBI induced changes that occur in the brain[13,18]. Neurophysiological measures frequently utilized in PCS research include: electroencephalogram (EEG), transcranial magnetic stimulation (TMS), and other functional neuroimaging techniques[12,13,16,18,19]. In particular, EEG and event-related potentials (ERP) have emerged as useful tools for detecting cognitive deficits[19]. EEG is also commonly utilized along with posturographic measurements to assess for any abnormalities in cortical functioning that correlate to postural tasks[11]. Additionally, there is a growing body of literature utilizing TMS which is able to investigate abnormalities in motor cortex function[16]. Ultimately, these measures provide more in-depth information of functional anomalies in the brain which can be utilized to create a more refined and effective diagnostic technique[19].

Although there is an extensive body of research investigating the deficits correlated with PCS, there is currently no standardized protocol for assessing the long-term effects following mTBI[5,7,20]. Additionally, researchers have yet to demonstrate a full understanding of the potential structural and functional changes induced by mTBI and how they correlate to physical, cognitive, and psychological effects[5]. While there are numerous studies assessing the behavioral and neurophysiological correlates of PCS, with my knowledge, there remains a need for these papers to be gathered and reviewed. Therefore, the objective of this paper was to conduct a scoping review of the literature reporting on various neurophysiological and behavioral measures of patients in the subacute and chronic phase (i.e., > 2 weeks days post-injury) following mTBI. This review is merited as it highlights effective diagnostic techniques for post-concussion syndrome which may be used to further develop diagnostic and treatment protocols. Furthermore, it summarizes the current understanding of some of the long-term sequelae of mTBI and their correlation with

potential functional changes in the brain as well as highlights gaps in the knowledge where further research is needed.

2. Methods

2.1 Database Search

The literature search was conducted by identifying behavioral and neurophysiological measures commonly utilized to assess patients after a traumatic brain injury (TBI). The following electronic databases were searched: MEDLINE/Ovid, Web of Science, Cochrane, CINAHL and PsycINFO. The literature search was conducted in November 2020. Additionally, all studies included were from 1994 onward because it is the earliest point at which PCS was defined in the Diagnostics and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[21]. The keywords that were utilized in this literature search were as follows: (i) Diagnosis ("post concussion syndrome" OR "post-concussion syndrome" OR "post concussive symptoms" OR mTBI OR "mild traumatic brain injury" OR "mild brain injury" OR TBI OR "brain concussion" OR "Traumatic brain injury"); and (ii) Behavioral measures ("standing balance" OR posture OR "postural control" OR "standing posture" OR walking OR "postural stability" OR gait OR cognition OR "Neuropsychological tests"); and (iii) Neurophysiological measures (EEG OR Electroencephalogram OR TMS OR "Transcranial Magnetic Stimulation" OR tDCS OR "transcranial direct current stimulation" OR "noninvasive brain stimulation").

2.2 Data extraction and selection

Established exclusion criteria were used for this analysis. The exclusion criteria were as follows: (i) treatment or intervention studies; (ii) moderate or severe TBI, post traumatic stress disorder (PTSD) or psychological symptoms as a primary diagnosis; (iii) age of participants under the age of 19; (iv) animal studies and studies including cells, tissue, or histology; (v) studies

including patients currently enrolled in pharmacological or non-pharmacological therapy or treatment; and (vi) studies including deep brain stimulation. Only electronically available English full-text articles were included. Additionally, studies included had to be conducted in the subacute and chronic phase (i.e., >2 weeks post-injury) characteristic of PCS. The total number of studies from the initial literature search was 336. The titles and abstracts were then screened. After this initial screening duplicates were removed. The remaining full-text articles were assessed for inclusion eligibility in the final analysis. Out of the 336 articles screened, 24 met our eligibility criteria and were included in this review. A flow chart following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines[22] shows the study selection process (**Figure 1**).

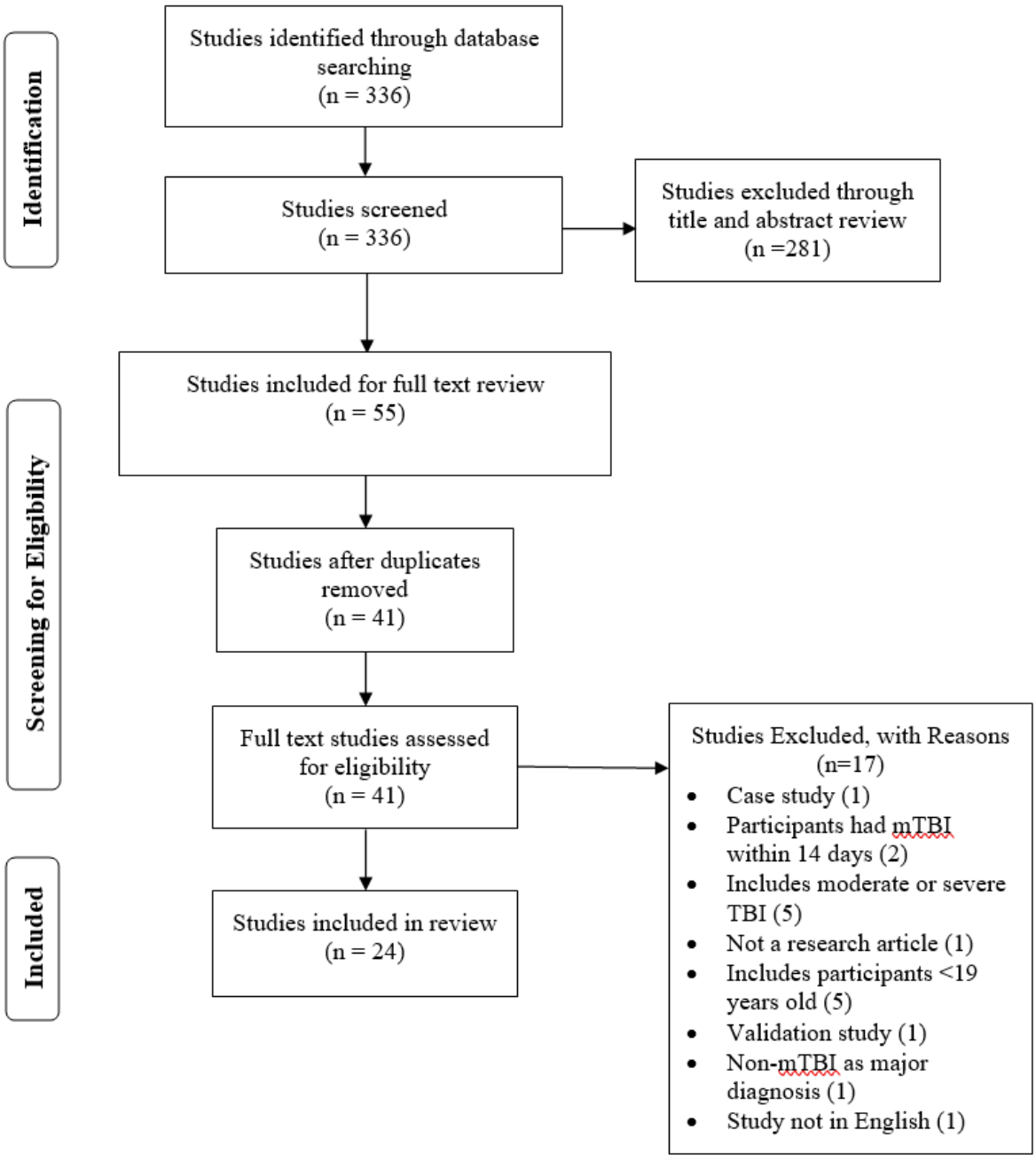


Figure 1. Prisma Flow Diagram outlining the data search and selection process

2.3 Quality Assessment & Data Collection

All final papers were reviewed in a journal club style by seven reviewers under the supervision of a faculty research advisor in the Department of Rehabilitation and Movement Science at the University of Vermont. As the principal investigator, I assigned myself and all other

reviewers a paper to discuss during each journal club meeting. Additionally, I was responsible for reading all full-text articles that were reviewed and fielding any questions that other reviewers had during these meetings. This process was done to ensure that all papers fit the inclusion and exclusion criteria.

In addition to assessing the eligibility of these papers, all relevant data and outcomes were discussed. After each paper was discussed, all relevant data was charted. Data that was charted, as seen in **Table 1**, included the following: General Information: first author and year of publication, Methods: study design, number of participants, age of participants, time since last injury, number of injuries, and diagnostic tool(s) and Results: Significant outcomes relating to neurophysiological and behavioral correlates of PCS

3. Results

3.1 Behavioral Measures

All results pertaining to behavioral measures were identified in each study and charted in **Table 1**. 20 studies were identified as utilizing self-report or neuropsychological measures[9,12-16,22-35]. Additionally, four studies assessed postural stability[11,15,27,36], one study assessed gait[16], and two studies assessed coordination[9,27].

In fifteen studies it was reported that the mTBI group performed the same as controls on neuropsychological tests[9,12-16,22-24,26,30,32-35]. In addition, nine studies found that concussed patients and controls performed the same on self-report questionnaires[15,22,24,27,29,31,33-35]. However, seven studies found significant differences between previously concussed individuals and controls on neuropsychological tests reflecting deficits in executive functioning, attention, information processing, and memory in the mTBI cohort[9,14,22,25,28,30,32]. Additionally, seven studies found that the mTBI cohort reported increased symptoms compared to controls on self-report questionnaires[12-14,22,25,29,31]. Two studies reported sleep dysregulation[14,22], five studies reported

increased depressive symptomatology[12-14,29,31,], and three studies reported increased symptoms (e.g. headache, dizziness, difficulty concentrating, irritability, sadness) in the mTBI cohort[12-14].

Postural stability, coordination, and gait were other behavioral measures that were reported on within this scoping review. Four different studies investigated persistent deficits in postural stability among an mTBI cohort[11,15,27,36]. Two studies found that those with a previous concussion had an increased center of pressure (COP) compared to controls[11,15], and one study found that the mTBI cohort had decreased COP oscillation randomness[27]. In contrast, one study found no significant difference in COP among the mTBI cohort in comparison to controls[36]. Additionally, in two studies participants completed a rapid alternating movement (RAM) task to assess coordination[9,27]. Whereas the mTBI cohort had significantly decreased velocity in one study[9], there were no significant differences between the mTBI and control groups in a different study[27]. Lastly, a single study that investigated gait, saw that walking speed was not affected by performing a cognitive task beyond the acute phase[16].

3.2 Neurophysiological Measures

Information pertaining to neurophysiological measures was also extracted from each study and charted in **Table 1**. The neurophysiological measures which were utilized in these studies included: EEG, magnetoencephalography (MEG), TMS, and proton magnetic resonance spectroscopy (H-MRS). 13 studies utilized EEG[9,11,12,15,22-24,26,32,33,35-37], two studies utilized Quantitative EEG (QEEG)[14,25], and one study included EEG wavelet information quality (EEG-IQ)[34]. Additionally, one study utilized MEG[13], five studies utilized TMS[9,16,18,27,28], and one study utilized H-MRS[18].

EEG detected prolonged aberrant ERPs following an mTBI[9,12,22,23,32,33,35,37]. Seven papers found that the mTBI cohort exhibited abnormalities in the P300 component[9,12,22,23,32,33,35]. These

abnormalities included reduced amplitude and latency delays[9,12,22,23,32,33,35]. While three papers focused on the P300 component as a whole[22,32,33], four papers broke down this component further into P3a and P3b components[9,12,23,35]. All seven papers found that previously concussed individuals had attenuated amplitude in the P300 component compared to controls[9,12,22,23,32,33,35]. Additionally, the mTBI cohort showed significant latency delays in the P3b component in two studies[9,12], and the P3a component in one study[9]. Other ERPs that showed abnormalities included: N1, N2, N2b, P1, and Mismatch Negativity (MMN)[12,23,32,37]. Broglio et al. (2009) detected an attenuated N2 amplitude in individuals with a history of concussion[23]. In contrast, a study conducted by Moore et al. (2014b) reported that the N2 amplitude was increased in the mTBI cohort[37]. Furthermore, a study conducted by Ruiter et al. (2014) found that N1, MMN, and N2b amplitudes were all significantly reduced in the mTBI cohort[12]. Lastly, one study found that those with a history of concussion had an attenuated P1 amplitude[37].

Furthermore, five studies found discrepancies in alpha, beta, delta, and theta frequency bands between the mTBI cohort and controls[11,13-15,25]. One study reported decreased amplitude in alpha, alpha2, beta, beta2, delta and theta in individuals with mTBI compared to controls[11]. Additionally, a study conducted by Slobounov et al. (2012) showed suppression in alpha power in those with a previous mTBI[15]. Furthermore, two studies utilized QEEG to investigate prolonged neuroelectric indices[14,25]. Utilizing QEEG, it was found that those with increased mTBI symptomatology had decreased power in alpha, delta, and theta bands[25]. An additional study that used QEEG reported increased relative delta activity and a reduction in relative alpha power during waking state in previously concussed individuals[14]. Furthermore, a study utilizing MEG found increased low-frequency amplitudes as well as significant long-range increases in resting state functional connectivity in delta, theta, and alpha bands in the mTBI cohort[13]. Three additional

studies utilized different EEG techniques to assess functional neuroelectric deficits[24,26,36]. One study utilized EEG to analyze the Shannon Entropy of the Peak Frequency Shifting (SEPFS) and found a decrease of SEPFS in occipital, parietal, and temporal regions in mTBI patients[24]. Cudmore et al. (2000) investigated EEG coherence and showed that frontal-parietal coherence increased during a more difficult task in those with a history of concussion[26]. Finally, EEG was used to analyze Movement-Related Cortical Potentials (MRCP) and a prolonged reduction in MRCP amplitude in individuals with a previous mTBI[36].

TMS was also utilized as a diagnostic tool in multiple studies to investigate deviant cortical activity[9,16,18,27,28]. Four studies that utilized TMS found prolonged abnormalities in the mTBI cohort[9,18,27,28]. Three studies showed a prolonged cortical silent period (CSP) in individuals with a previous mTBI[9,27,28]. One study showed that the mTBI cohort has an enhanced long-interval intracortical inhibition (LICI) ratio[28], whereas another study showed that the mTBI cohort had a decreased LICI ratio[27]. In a study conducted by Beaumont et al. (2012), paired associative stimulus (PAS) was utilized to induce long-term depression (LTD) and long-term potentiation (LTP)-like effects and found suppressed PAS-induced LTP and LTD-like synaptic plasticity among the mTBI cohort[28]. Another study utilized both TMS and H-MRS and found that there was a significant correlation between the LICI ratio and Gamma aminobutyric acid (GABA) in previously concussed individuals[18]. This study also found that there was a slight metabolic imbalance between Glutamate and GABA in the mTBI cohort through utilizing H-MRS[18]. However, there were two studies that found no differences between the mBTI cohort and controls in intracortical inhibition through utilizing TMS[16,18].

Table 1. Summary of search results: Studies investigating neurophysiological and behavioral correlates of PCS

First Author, year	Study Design	n	Age mean (SD)	Last Injury mean (SD)	# of injuries	Diagnostic Tool	Results
Bernstein, 2002	Case-control study	mTBI: 13, controls: 10	mTBI: 20.85(1.81), controls: 20.02(1.49)	8 years	≥1	CFQ, Memory Questionnaire, PCS checklist, WAIS-R, EEG/ERP, auditory oddball, visual oddball, CNV, PVEP	mTBI: No significant differences on self-report questionnaires, performed same on all tasks except Digit Symbol Substitution task and difficult dual task, decreased P300 amplitudes on easy and difficult auditory discrimination task
Broglio, 2009	Cross-sectional study	mTBI: 46, controls: 44	mTBI: 20(1.20), controls: 19.4(1.3)	3.4(3.3) years	1.7(1.1)	EEG/ERP, visual oddball, ImPACT test	mTBI: No significant difference on ImPACT test, significantly attenuated N2 and P3b amplitudes
Cao, 2011	Cross-sectional study	mTBI: 30, controls: 30	male subjects: 21.3; female subjects: 20.8	30 +/- 3days	1	EEG, Subjective Symptom Rating Scale, Symbol Digit Substitution Test, Trails "B" test, HVLT	mTBI: No significant difference on neuropsychological tests, Significant decrease of SEPFS in occipital, parietal, and temporal regions
Corradini, 2014	Case-control study	mTBI (mild impairment): 8, mTBI (moderate-severe impairment): 9, controls: 9	40(16.3)	5.6(5.2) years	≥1	QEEG, s-LORETA, Halstead-Reitan Battery, Conditioned Spatial Association Test	mTBI (moderate-severe impairment): Shorter microstates, decreased power in alpha band, and lower power in theta and delta bands in caudal regions
Cudmore, 2000	Case-control study	mTBI:19 (unconsciousness < 20min), 19 (unconsciousness ≥ 30min), controls: 19	mTBI (unconsciousness < 20min): 20, mTBI (unconsciousness > 30min): 22, controls: 20	mTBI (unconsciousness < 20min): 7.3 years, mTBI (unconsciousness ≥ 30min): 6.8 years	≥1	EEG coherence, auditory oddball	mTBI (unconsciousness < 20min; unconsciousness ≥ 30min): No significant difference on auditory oddball task, frontal-parietal coherence in the left hemisphere increased from single to dual task

Dunkley, 2015	Case-control study	mTBI: 20, controls: 21	mTBI: 31.4(6.87), controls: 27(5)	32.2(17.98) days	1	MEG, MRI, WAIS, AUDIT, Conners Attention-Deficit Hyperactivity Disorder Test, GAD-7, PHQ9, SCAT2	mTBI: Significantly greater scores on attentional problems, anxiety, depression, and number and severity of symptoms which correlated to altered resting state neurophysiological network connectivity across frequency bands
De Beaumont, 2009	Case-control study	mTBI: 19, controls: 21	mTBI: 60.79(5.16), controls: 58.89(9.07)	34.74(9.21) years	1-5	MMSE, RCFT, Flanker, EEG/ERP, auditory oddball, TMS, RAM	mTBI: P3 and CSP as well as neuropsychological and motor measures were abnormal over 30 years post mTBI
De Beaumont, 2011	Case-control study	mTBI: 21, controls: 15	22.3(3.45)	19.03(13.77) months	2.65(1.45)	PCSS, Forceplate/COP, TMS, RAM	mTBI: Lower COP oscillation randomness in the anteroposterior direction, normal performance on RAM, increased M1 intracortical inhibition which was related to number of previous concussions
De Beaumont, 2012	Case-control study	mTBI: 13, controls: 19	23.4(3.11)	13.74(6.26) months	2.87(1.41)	TMS/PAS, SRTT, PCSS	mTBI: Increased intracortical inhibition in M1, suppressed PAS-induced LTP/LTD-like synaptic plasticity which was related to reduced implicit motor learning on SRTT
Gosselin, 2009	Case-control study	mTBI: 10, controls: 11	mTBI: 24.3(6.1), controls: 22.6(2.4)	1-11 months	4.6(2.1)	QEEG, CogSport computer battery, Battery of neuropsychological tests and self-report questionnaires	mTBI: More mTBI symptoms, worse sleep quality, more symptoms of depression, increased relative delta activity and a reduction in relative alpha power during waking QEEG
Hessen, 2007	Prospective longitudinal study	mTBI: 119	45.2(14.6)	23 years	≥1	WAIS, Wechsler Memory Scale–Revised, Halstead-Reitan Neuropsychological test Battery	mTBI: Both pediatric and adult groups scored in normal range on neuropsychological test battery, poorer outcomes seen in pediatric groups with PTA > 30 minutes and pathological EEG within the first 24 hours after head injury
Hessen, 2008	Prospective longitudinal study	mTBI: 41	32.1(3.4)	23 years	≥1	MMPI-2	mTBI: Predictors for poor outcome on MMPI-2 23 years after pediatric mTBI were skull fracture, PTA > 30 minutes, and pathological EEG within the first 24 hours after mTBI with increased scores for Hypochondrias, Depression, Hysteria, and Psychopathic deviate

Hessen, 2009	Prospective longitudinal study	mTBI: 97	41.5(10.8)	23 years	≥1	MMPI-2	mTBI: PTA > 30 minutes or PTA > 30 minutes with pathological EEG within the first 24 hours after head injury significantly predicted abnormal elevation of MMPI-2 subscales Hypochondrias, Depression, and Hysteria
Moore, 2014	Cross-sectional study	mTBI: 18, controls: 18	mTBI: 21.6(2.6), controls: 21.5(2.8)	6.7(3.9) years	≥1	EEG/pattern-reversal visual task	mTBI: Decreased amplitude in P1
Moore, 2014	Cross-sectional study	mTBI: 19, controls: 21	21.3(2.4)	7.1(4) years	≥1	EEG/3-stimulus oddball task/numeric switch task/modified flanker task, K-BIT	mTBI: Decreased P3b amplitude during target detection in oddball task and heterogeneous condition of switch task, increased N2 amplitude during heterogeneous condition of switch task, decreased response accuracy during flanker task
Ozen, 2013	Case-control study	mTBI: 17, controls:17	mTBI: 20.88(1.4), controls: 19.71(1.21)	> 6 months	≥1	EEG/N-back, Digit Span Forward and Backward tasks, Trail Making A and B tests, Digit-Symbol Substitution task, BDI, STAI, ARCES, MFS	mTBI: No differences on neuropsychological task performance or self-report measures, and decreased P300 amplitude for match trials of N-back task
Ruiter, 2019	Case-control study	mTBI: 19, controls:18	mTBI: 57.6, controls: 53.7	28.1 years	4.05	EEG, MMN, Auditory oddball, ImPACT, BDI II, PCSS	mTBI: No significant difference on ImPACT scores, increase in mTBI symptomatology, higher levels of depression, reduced N2b, P3a, P3b, N1, MMN amplitudes, and delayed response latency for P3b
Slobounov, 2005	Prospective cohort study	mTBI: 8	20.95	3, 10 and 30 days	1	EEG/MRCP, Forceplate	mTBI: No significant difference in COP after 10 days, showed reduction in MRCP amplitude after 30 days
Slobounov, 2009	Prospective cohort study	mTBI: 21	18-25	7, 14 and 21 days	2	Subjective symptom rating scale, symbol digit substitution test, Trails "B" test, EEG-IQ	mTBI: No clinical symptoms or difference in neuropsychological scores after 7 days, decreased EEG-IQ values in all ROIs but predominantly in occipital, parietal and temporal ROIs and especially pronounced after 2nd mTBI within 3 weeks

Slobounov, 2012	Prospective cohort study	mTBI: 49	18-25	7 days, 15 days, 30 days, 6 months, 12 months	1	Subjective Symptom Rating scale, Symbol Digit Substitution test, trails ‘‘B’’ test, EEG, force plate	mTBI: Percent Alpha suppression from standing to sitting postural conditions and COP area decreased over time, subjects who showed more than 20% of alphapower suppression in acute phase of injury did not return to pre-injury status up to 12 months post-injury
Thériault, 2009	Case-control study	recent mTBI: 10, late mTBI: 10, controls:10	recent mTBI: 22.6(1.5), late mTBI: 22.9(3.3), controls: 22.1(1.4)	recent: 9.1(2.0) months, late: 33.2(15.4)	recent: 2.9(1.1), late: 2.5(0.7)	EEG, auditory oddball, neuropsychological tests and self-report questionnaires	recent mTBI: Significantly decreased P3a and P3b amplitudes to controls Recent and late mTBI: No differences on neuropsychological task performance or self-report measures
Thompson, 2005	Case-control study	mTBI: 12, controls:12	20.95	89.4 days	≥1	EEG, Forceplate/COP	mTBI: Significantly larger area of COP during eyes closed static standing, decreased amplitude across spectrum (delta, theta, alpha, alpha2, beta, and beta2) especially during standing postures
Tremblay, 2015	Case-control study	mTBI: 16, controls:14	mTBI: 22(1.09), controls: 22.03(1.08)	3.05 years and 2.06 months	1.88(0.89)	H-MRS, TMS, MRI, MACACC	mTBI: Slight metabolic imbalance between GABA and glutamate concentrations in M1
Yasen, 2017	Prospective cohort study	mTBI: 20, controls: 20	mTBI: 21.2(4.4), controls: 21.4(4.6)	72 h, 1wk, 2 wk, 1 month, 2 months	≤ 2	TMS, Gait analysis, ANT	mTBI: Cognitive and motor impairments were not significant past 72h, intracortical inhibition was not significantly different and had no correlation to recovery

Abbreviations: ARCES=Attention-Related Cognitive Errors Scale; AUDIT=Alcohol Use Disorders Identification Test; ANT=Attentional Network test; BDI=Beck's Depression Inventory; CFQ=Cognitive Failures Questionnaire; CNV=Contingent Negative Variation; COP=center of pressure; CSP=Cortical silent period; EEG=Electroencephalogram EEG-IQ=Electroencephalogram wavelet information quality; ERP=Event related potential; GABA=Gamma aminobutyric acid; GAD-7=Generalized Anxiety Disorder 7 test; H-MRS=Proton Magnetic Spectroscopy; HVLT=Hopkins Verbal Learning Test Revised Stroop Tests; ImPACT=Immediate Post-Concussion Assessment and Cognitive Testing; K-BIT=Kaufman Brief Intelligence Test; LTD=long-term depression; LTP=long term potentiation; M1=primary motor cortex; MACACC=Mapping Anatomical Correlations Across Cerebral Cortex; MEG=Magnetoencephalography; MFS=Memory Failures Scale; MMN=Mismatch Negativity; MMPI-2=Minnesota Multiphasic Personality Inventory; MMSE=Mini-Mental Status Examination; MRCP=Movement-related cortical potentials; MRI=magnetic resonance imaging; mTBI=mild Traumatic Brain Injury; PAS=Paired Associative Stimulation PHQ9=Personalized Health Questionnaire 9-scale item for depression; PCS=Post Concussion Symptoms; PCSS= Postconcussion symptom scale; PVEP=Pattern Visual Evoked Potential; QEEG=Quantitative Electroencephalogram; RAM=Rapid Alternating Movements; RCFT=Rey-Osterrieth Complex Figure Test; ROI= region of interest; SCAT2=Sport Concussion Assessment 2; SEPFS=Shannon Entropy of the peak frequency shifting; s-LORETA=standardized low-resolution electromagnetic tomography; SRTT=serial reaction time task; STAI=State-Trait Anxiety Inventory; TMS=transcranial magnetic stimulation; WAIS=Wechsler Abbreviated Scale of Intelligence; WAIS-R=Wechsler Abbreviated Scale of Intelligence Revised

4. Discussion

Currently, self-report questionnaires, neuropsychological tests, and postural stability assessments are utilized in clinical practice to diagnose and monitor mTBIs[38]. However, many studies indicate that solely utilizing behavioral measures may be insufficient for detecting subacute and chronic deficits characteristic of PCS[12,22,34]. Based on the results from this scoping review, it is indicated that a multimodal approach utilizing both behavioral and neurophysiological diagnostic tools would be a more effective approach to diagnosing and monitoring mTBI. This approach would provide a more comprehensive diagnosis and may lead to a more accurate prognosis and improved recovery and treatment protocols. Furthermore, there is still not a complete understanding of the neurological underpinnings related to the cognitive and behavioral impairments associated with PCS[5]. Consequently, more research is needed to further investigate residual structural and functional impairments imposed on the brain.

Behavioral correlates of post-concussion syndrome

Through this scoping review it was found that behavioral assessments were used to investigate presence and severity of symptoms, cognitive deficits (e.g., memory, information processing, attention, and executive function) and motor impairments[9,11-16,22-36]. However, most patients with a history of concussion reported that they were asymptomatic[15,22,24,27,29,31,33-35] and exhibited similar cognitive abilities to that of controls in the subacute and chronic stages post-injury[9,12-16,22-24,26,27,29-35]. Conversely, studies that reported symptoms characteristic of PCS amongst the mTBI population found impairments such as: sleep dysregulation, attentional problems, depressive symptomatology, anxiety, and abnormal scores on personality trait questionnaires[12-14,22,25,29,31]. Furthermore, the cognitive domains that were reported as impaired in

the mTBI cohort included: memory, executive function, attention, information processing, and resource allocation[9,14,22,25,28,30,32].

Additionally, postural stability assessments exhibited evidence of balance impairments in concussed patients[11,15,27]. This finding may be attributed to deficits in sensory interaction between visual, vestibular, and somatosensory systems[11]. In addition, it was noted that mTBI patients may enact a compensatory mechanism in which they contract their ankle muscles to gain control over postural sway and achieve similar levels of postural stability as controls[27]. Furthermore, decreased postural stability was commonly reported as a transient issue which resolved in the acute period after a concussion so that there were no chronic differences between controls and previously concussed individuals[11,15,27]. In addition to balance deficits, patients with mTBI also reported impairment in coordination[9]. However, another study found that previously concussed individuals did not exhibit coordination deficits[27]. Although this was attributed to performance motivation and a speed-accuracy tradeoff among a younger mTBI cohort[27]. Therefore, the coordination impairments seen in the older cohort may be a result of aging with a history of mTBI[27].

Neurophysiological correlates of post-concussion syndrome

Neurophysiological measures of PCS are traditionally studied by identifying abnormal neuroelectric indices by various noninvasive tools such as EEG and TMS[9,11,12,15,16,18,22-24,26-28,32,33,35-37]. Notably, EEG was able to identify symptoms of PCS including aberrant ERP's as well as abnormal frequency bands[9,11,12,15,22-24,26,32,33,35-37]. ERPs reflect changes in ongoing neuroelectric activity that occur either in response to, or in preparation for, a stimulus or response[23]. EEG can be utilized to detect patterns in voltage change while a cognitive task is performed[23]. Moreover, ERP's have been identified and correlated to cognitive functions[23]. For instance, the P3 component

is a well-studied ERP that consists of two components: P3a and P3b[23]. The P3a component is specifically linked to focal attention and has a fronto-parietal distribution that peaks at ~300 ms, whereas the P3b component has a centro-parietal distribution that peaks at ~450ms and is linked to the allocation of attentional resources[12]. Abnormalities in the P3a and P3b components were identified in the mTBI cohort in this review[9,12,22,23,32,33,35]. Consequently, these findings were associated with deficits in cognitive domains in the concussed individuals compared to controls[9,12,22,23,32,33,35]. These cognitive deficits included reduced ability to shift and allocate attentional resources, and slower cognitive processing speeds[9,12,22,23,32,33,35]. In addition, other ERPs that were found to be abnormal in those with a previous history of concussion include: N1, MMN, N2, and P1[12,23,32,37]. These ERPs reflected further cognitive deficits in auditory processing, pre-attentive processing, response inhibition, and visual processing[12,23,32,37]. Furthermore, EEG was able to detect differences in ERP's even though the concussed patients performed similarly to controls on cognitive tasks[9,12,22,23,33,35]. This further supports the need for multimodal evaluations as these cognitive deficits are typically missed using standard neuropsychological assessments.

In addition to ERP, EEG detected differences in waveforms has also been observed in individuals with concussion[11,13-15,25]. In this scoping review, deficits were detected in delta (0.5-4 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (13-30 Hz) frequency bands[11,13-15,25,39]. These frequency bands are representative of brain waves which are detected by EEG[39]. Brain waves are elicited at different frequencies (i.e., the number of times a wave repeats itself within a second) during different states (e.g., sleeping, awake)[39]. Delta is elicited during deep sleep, whereas theta reflects the state between wakefulness and sleep and relates to the subconscious mind[39]. Additionally, alpha is the major rhythm seen in normal relaxed adults, and beta is associated with alertness and mental activity[39]. Corresponding with this, abnormalities in these waveforms were

generally associated with cognitive deficits such as: insufficient brain resource allocation, inability to focus attention, decreased efficiency and proficiency of memory, and an abnormal balance of excitatory and inhibitory drives[11,13-15,25]. Furthermore, abnormal frequency bands may be associated with greater feelings of fatigue in PCS[14]. Overall, EEG was able to detect deficits in cognitive domains including executive functioning, information processing, attention, memory, response inhibition, and resource allocation.

Besides EEG, TMS has also been shown as an effective tool for identifying neuroelectric sequela of PCS[9,18,27,28]. TMS is commonly used to elicit motor evoked potentials (MEP) from which abnormal neuronal activity can be detected[9,18,27,28]. By analyzing MEPs it was found that the mTBI cohort exhibited differences relative to their non-concussed counterparts[9,18,27,28]. These abnormalities indicate increased levels of intracortical inhibition[9,18,27,28]. Specifically, it has been hypothesized that this is related to persistent elevations in GABA-B receptor activity which is responsible for increasing intracortical inhibition in the primary motor cortex[9,18,27,28]. This suggests an imbalance between excitatory and inhibitory mechanisms in M1[9,18,27,28].

Limitations

There are some important limitations to consider in this scoping review. First, the results of this scoping review do not include any pediatric participants. Additionally, studies prior to 1994 were excluded. Thus, any study that may have defined PCS differently is not included in this study. In addition, all treatment studies, which may have a diagnostic component were not reviewed in this scoping review. Along with this, our search strategy did not include a complete list of neurophysiology and behavioral techniques. This additionally limited the findings, as there may be other effective diagnostic tools which report significant correlates of PCS.

5. Conclusions

Ultimately, this scoping review highlighted the need for both neurophysiological and behavioral measures in clinical assessments to provide a more comprehensive diagnosis and prognosis of PCS. Additionally, this will lead to the development of improved treatment protocols and help to reduce the number of people suffering from PCS[27]. Also, this more comprehensive approach will help mitigate the potential for re-injury which is shown to lead to worsened effects[34]. Furthermore, this scoping review revealed the need for more longitudinal studies[9,14,22,23,27,37]. These will help enhance the understanding of how PCS progresses and provide further knowledge of the underlying neuropathology[37]. Overall, it is important to further our understanding of this injury as it will enhance diagnosis, prevent worsened effects, and provide better treatments for the several that continue to suffer from the effects of PCS.

Validation of Methods

Equipment:
EEG system (ANT Neuro, The Netherlands), Chronos response pad and E-prime software (Psychology Software Tools, PA, USA)

Consumables:
Electroconductive EEG gel, syringe, measuring tape

Cognitive Tasks:

I. Flanker task

Objective: To identify the direction of the central arrow. Assesses participants ability to filter irrelevant flanking stimuli (i.e., inhibitory control) and overcome proponent response tendencies to execute an accurate response[37].

3 Conditions: Incongruent, Congruent, and Neutral

- Incongruent: Flanking arrows pointing in the opposite direction as central arrow (e.g., > > < > >)
- Congruent: Flanking arrows pointing in the same direction as central arrow (e.g., >>>>>)
- Neutral: Different shapes flanking central arrow (e.g., x x > x x)

II. N-back task

Objective: To identify the correct target. Assesses working memory.[33]

Conditions: 1-back, 2-back, 3-back

- 1-back: A target is identified when the letter on the screen matches the one shown immediately before it
- 2-back: A target is identified when the letter on the screen matches the letter shown two trials previously
- 3-back: A target is identified when the letter on the screen matches the letter shown three trials previously

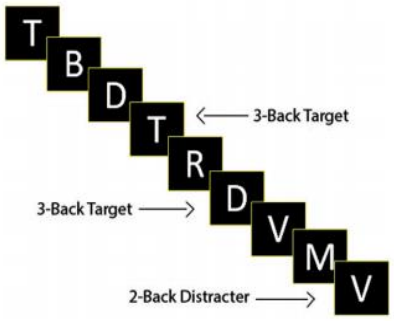


Figure 2. Schematic representation of the 3-back load condition of the *n*-back task.

Experimental Setup:

I. Before Participant arrives:

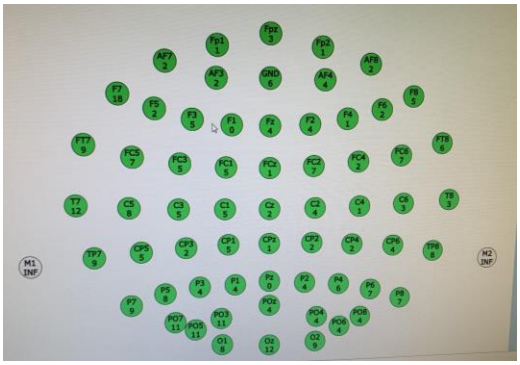
1. The experimenter ensures the data acquisition computers and EEGo amplifier are on and running
2. E-prime and EEGo Software are opened

   E-prime folder → Tasks → Flanker/N-back → blue 'es' file

   EEGo Software → select 'Acquire' → select 'New subject' → type in participants last and first name
3. The syringes are then filled up with Electro-Gel

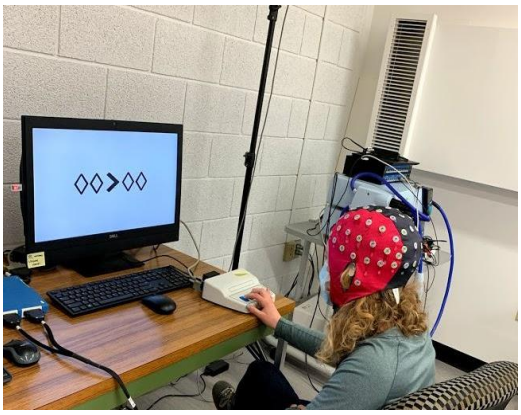
II. Preparation of the participant

1. The participants head size is measured to select the best EEG cap size
2. Then the EEG cap is placed on the participant and positioned well so that the midline electrodes are over the nasion-inion line
3. Following this, the cables of the EEG cap are plugged into their corresponding port in the EEGo amplifier
4. Next the correct subject must be selected on EEGo software.
5. Once this is done select 'Next' and then select 'Impedance'
6. Now begin filling electrodes with gel starting with GND and CPz electrodes
7. Wait until the GND and CPz have a good impedance (< 20) which is shown by the corresponding electrodes turning green on the computer
8. Continue to add gel to all electrodes in any order until all are filled (excluding M1 and M2)
9. Once all electrodes have a good impedance select 'Stop impedance'



III. EEG data acquisition

1. Once all electrodes have good impedance select 'Record'
2. Then select the blue 'es' file for Flanker task to run task and type in participants number
3. Before beginning, explain the flanker task and how to respond using the Chronos response pad
4. Next have participant complete flanker task (~10 min)
5. Once the participant finishes the flanker task, select blue 'es' file for N-back task and type in participants number
6. Then explain N-back task and how to respond on the keyboard
7. Following this, have the participant complete the N-back task (~50 min)
8. Once they are finished, select 'Stop Record'
9. After this, double check all data is saved
10. Finally, remove the EEG cap from participant and thoroughly clean it



****We were unable to complete this EEG study because of the restrictions set in place due to COVID-19*

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