Exploring Electrophysiological Changes in Adolescents With and Without Concussion Across the First Month After Injury

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ABSTRACT

Exploring Electrophysiological Changes in Adolescents With and Without Concussion Across the First Month After Injury

Jeremy Pomerleau

Concussion recovery is primarily based on the full resolution of symptoms, but neurophysiological changes are present and may persist beyond clinical recovery. Our objectives were to 1) compare the evolution of electrophysiological and clinical outcomes between adolescents with and without concussion over the first month after injury and 2) determine the relationship between electrophysiological and clinical outcomes. Adolescents with concussion (n=53) were assessed within 10 days of and at 30-days post-injury, while adolescents without concussion (n=15) were tested at arbitrary dates but with a similar interval between sessions. Resting-state electroencephalography (EEG), Post-Concussion Symptom Inventory, Pediatric Quality of Life Inventory, and Revised Children's Depression and Anxiety Scale were completed at all study visits. Separate mixed-effects models evaluated the effect group, time, and their interaction on clinical and EEG (F3 delta power, F8 delta power, P4 delta power, T6 beta power, and O1 beta power) variables, with all models controlling for age and sex. Pearson's correlations examined the associations between EEG power and clinical symptoms, separately for each group and study visit. Results revealed that clinical measures improved over time (primarily driven by changes in the concussion group); however, no significant effects of group, time, or their interaction were observed for any EEG variable. Few significant correlations between EEG and clinical outcomes were observed. These results suggest that EEG outcomes do not change over the first month following concussion. Future studies should include larger sample sizes and different EEG features, which may be more sensitive to changes over time after concussion.

CONTRIBUTION OF AUTHORS

This thesis is the result of work conducted by Jeremy Pomerleau under the supervision of Elizabeth Teel, PhD in the Department of Health and Exercise Science at Concordia University.

The specific contributions are as follows:

- Jeremy Pomerleau: Conducted the literature review, recruited control group participants, collected and processed data for all control group participants, performed all analyses and visualizations presented for this project, and wrote the thesis in its entirety.

- Sofia Iuliano, MSc: Collected and processed data for the concussion group.

- Isabelle Gagnon PT, PhD & Stefanie Blain-Moraes PhD, P. Eng.: Provided access to patients and assisted with general administration and oversight for the larger project from which this data originates.

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LIST OF ABBREVIATIONS

AEC	Amplitude envelope correlation
dPLI	Directed phase lag index
EEG	Electroencephalography
PCSI	Post-concussion symptom inventory
PED	Pediatric emergency department
PPCS	Persistent post-concussion symptoms
wPLI	Weighted phase lag index
PCSI	Post-concussion symptom inventory
PedsQL	Pediatric quality of life
RCADS	Revised child anxiety and depression

INTRODUCTION

Pediatric concussions are a serious health concern, with pediatric emergency department visits for concussion increasing 2- to 4- fold over the last decade in Canada and the United States.[1] Typically, concussion symptoms will subside within 2 weeks of injury, however, around 30% of adolescents will experience persistent post-concussion symptoms (PPCS) lasting beyond 4 weeks.[2] PPCS results in lower quality of life and negatively impacts children's and adolescents' development since it can lead to (1) diminished academic performance, (2) increased school and social activity absences, and (3) negative mood and cognitive changes.[2]

Concussion is a brain injury caused by biomechanical forces that disrupts the normal functioning of the brain.[3] These forces cause microstructural damage that present as a variety of cognitive, somatic, behavioural, and physical signs and symptoms.[4,5] Pediatric concussion also burdens the family. Physical therapist and other healthcare providers cost upwards of US$200 per visit and can exceed US$15,000 per year after concussion,[6] creating a large financial burden on families. Parents who must drive or bring their younger children to various medical appointments often miss work, lose income, and can even be terminated from their positions due increased caregiving demands following their child's concussion.[6] These factors can also cause emotional distress, with parents feeling increased stress due to the financial challenges.[6]

Presently, concussion recovery is based on the full resolution of post-injury symptoms.[7,8] However, clinical recovery does not equate to physiological recovery after concussion.[9] Previous literature suggests that neurophysiological deficits and clinical symptoms recover with different timelines,[9] with physiological deficits persisting well beyond clinical recovery in children and adults with concussion. Repeat injury is more common following an unresolved concussion;[10,11] thus, current management approaches that rely only on clinical presentation may be problematic and predispose children to subsequent injury. Additionally, pre-mature return to activities prior to physiological recovery may result in (1) a repeat concussion occurring with less force, and (2) prolonged recovery following another impact.[12] Therefore, better tools are needed to identify full physiological recovery following concussion, which is vital to reducing the likelihood of repeat injury and prolonged recovery in adolescents.

EEG monitoring has found abnormalities in brain function in concussed adolescents up to 45 days post-injury,[13] with studies in adults showing physiological deficits persist for even longer after injury.[14] Furthermore, these EEG abnormalities were present after symptom resolution and clinical recovery was established.[13] In general, the resolution of electrophysiology deficits after concussion remains unclear as the timelines of return to normative values differ in the literature.

By comparing EEG features of healthy and acutely concussed adolescents over a month, our study aimed to determine the evolution of brain electrical activity across the subacute recovery period and its relationship to clinical presentation. We hypothesized that EEG features from healthy adolescents would differ from acutely concussed adolescents. Furthermore, we hypothesized that EEG features would be significantly correlated to clinical outcome scores in adolescents with and without concussion. In the future, this work can determine whether EEG is as an imaging tool capable of providing clinicians with objective biomarkers – defined as a medical

sign that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention[15] – to identify physiological recovery from concussion in adolescents.

LITERATURE REVIEW

Concussion Overview

A concussion is a traumatic brain injury (TBI) caused by a blow to the head, neck, or body that transmits an impulsive force and disrupts the normal functioning of the brain.[3] In Canada, it is estimated that the incidence of concussion is over 200,000 injuries annually.[16] In the last decade, rates of pediatric emergency department visits due to concussion and minor head injuries have increased 2- to 4- fold in Canada and the United States.[1] Additionally, up to 30% of individuals with concussion experience persistent post-concussion symptoms (symptoms lasting beyond the typical 4-week recovery period) and are, consequently, more likely to report having a diminished quality of life.[2,3,17,18] Thus, concussion is a major Canadian public health concern warranting further research.

Concussion Pathophysiology

Standard imaging tools such as MRI and X-ray cannot reliably detect concussion as concussion typically does not cause macrostructural injury such as fractures and brain bleeds.[19] However, modern advanced neuroimaging tools, such as diffusion tensor imaging, can detect microstructural injury resulting from the biomechanical forces that cause concussion.[20] Based on these findings, concussion is described as a neurometabolic cascade of events that broadly include ionic imbalances, axonal damage, autonomic nervous system (ANS) dysfunction, and cerebral blood flow alterations.[20,21]

Ionic Imbalance

Following the mechanical trauma of concussion, a shearing of axons occurs that result in a mechanoporation of the cellular membrane.[20,22] This disruption in cellular permeability causes an increase of extracellular potassium and intracellular sodium and calcium, thus creating a neuronal ionic imbalance.[20,23,24] Furthermore, unregulated amounts of glutamate are released which stimulates ligand-gated potassium channels, inducing a further efflux of potassium from the cell.[24,25] The resulting ionic imbalance overburdens adenosine-triphosphate (ATP) dependent cell membrane sodium-potassium pumps as they try to restore homeostasis, thus depleting available ATP.[20,25,26] As this metabolic energy crisis ensues, neuronal cell metabolism shifts from the oxidative system to the anaerobic glycolysis pathway, worsening ionic imbalances and causing lactate accumulation in the brain which further contributes to neuronal damage.[25,27]

Axonal Damage

Shearing forces in the brain may disrupt the integrity of the axons and lead to diffuse axonal injury.[25,28] Axonal stretching has the potential to disrupt normal neurotransmission in the brain due to reduced ability to transmit action potentials.[20,25] Furthermore, in more severe cases, complete axonal dissection and Wallerian degeneration of the distal segment can result in synapse isolation, thus halting neurotransmission completely.[20,25]

Autonomic Nervous System Dysfunction

ANS function is negatively impacted following concussion; however, the exact cause has only been speculated upon.[21,29–31] It is suggested that traumatic brain injury increases sympathetic

nervous system activity, causing an imbalance between the two branches of the ANS.[21] Heightened sympathetic drive is associated with increased anxiety, stress, and sleep disturbances, which are common concussion symptoms.[31] Furthermore, ANS dysfunction affects cardiovascular regulation by altering heart rate variability and baroreflex sensitivity, thus compromising cerebral vascular autoregulation and consequently impacting cerebral blood flow.[21,29,32]

Cerebral Blood Flow Alterations

The baroreflex is a feedback loop innervated by the ANS that senses changes in arterial mechanical stretch and carbon dioxide to maintain stable blood flow to the brain.[25,31] After concussion, this feedback loop may be negatively affected by ANS dysfunction, which may impair cerebral autoregulation and lead to reductions in cerebral blood flow.[25,31,33] These alterations in cerebral blood flow cause a mismatch between the supply and demand of glucose and oxygen, both worsening the energy crisis in the brain and potentially leading to symptoms, such as migraines, following a concussion.[25,34] Furthermore, cerebral blood flow alterations may linger even though clinical symptoms have subsided, indicating that physiological distress may still be present following an individual's apparent recovery.[25,34]

Brain-Derived Neurotrophic Factor Dysregulation

Brain-derived neurotrophic factor (BDNF) plays an important role in neuronal survival, growth, recovery, and plasticity.[35,36] Central levels of BDNF—found in the brain and cerebrospinal fluid—provide a more accurate measure of neuroplasticity and recovery following concussion; however, circulating BDNF—measured via venous blood draw—is more commonly used in clinical human studies due to its greater accessibility and ease of measurement.[37] Following severe TBI, central BDNF levels are increased, while circulating BDNF levels decreased, potentially due to redistribution across the blood-brain barrier.[38] However, the relationship between central levels of BDNF and circulating BDNF following concussion remains unclear as studies are limited. Following concussion, decreases in circulating BDNF have been observed; however, the mechanisms surrounding this dysregulation are not yet fully understood.[36] It is believed that lower levels of circulating BDNF is associated with worse traumatic brain injury prognosis due to its role in promoting synaptic plasticity and axonal restoration.[36]

Clinical Concussion Care

Although the transmitted biomechanical forces occurring as a result of concussion may cause neuropathological changes, concussion predominantly presents as clinical signs and symptoms of functional neurological disturbances rather than a structural injury that can be observed through standard imaging tools.[4] Such clinical signs and symptoms vary widely and may include somatic (headache, nausea, photophobia, etc.), cognitive (memory issues, mental fog, etc.), behavioural (depression, insomnia, irritability, etc.), and physical (balance issues, exercise intolerance, etc.) alterations[4,5]. However, signs and symptoms are heterogenous from person to person and may not present immediately after injury, rendering diagnosis difficult.[4,5] Children and adolescents aged 8-15 who experience a concussion are more likely to exhibit cognitive and somatic symptoms, and have a diminished academic performance than children with an orthopedic injury.[2,39] Furthermore, children and adolescents who experience persistant symptoms which last for a month or more following injury have an increased risk of experiencing lasting negative effects on both physical and psychosocial quality of life outcomes,[39] as well as an increased risk of missing out on social activity and having extended school absences.[2]

In addition to subjective symptoms, concussion results in a variety of objective deficits and disturbances. Post-concussion vestibular issues may arise, including benign paroxysmal positional vertigo (BPPV), vestibulo-ocular reflex (VOR) impairment, and postural balance dysfunction. [40] Oculomotor issues may also be present following concussion, including photosensitivity, accommodation and convergence insufficiency, impaired eye movements, and visual field disruptions.[40,41] Mechanical forces strong enough to produce a concussion exceed those necessary to produce a cervical spine injury.[42,43] Co-occurring neck injuries can cause concussion symptoms such as dizziness, headache, and balance dysfunction.[42,43]

Given the wide array of symptoms and objective deficits experienced by patients with concussion, in combination with the various clinical settings in which concussion is diagnosed and managed, a number of assessment tools have been created to better recognize injury and determine clinical recovery. Three categories of clinical concussion assessment tools exist: (1) screening tests (Standardized Assessment of Concussion [SAC], Balance Error Scoring System [BESS], and King-Devick [KD] Test), (2) confirmatory tests (Sport Concussion Assessment Tool [SCAT], ImmediatePost-Concussion Assessment Tool [ImPACT], and the Vestibular Occularmotor Screening [VOMS]), and (3) objective physiological examinations (imaging studies, and physiological markers).[44] Screening tests rely on symptoms and functional performance to assess an individual immediately after a suspected concussion, primarily used on the sideline in sport settings to remove athletes from the playing field.[45] Confirmatory tests assess a broader range of objective and subjective functional deficits experienced by an individual following concussion. Depending on the specific assessment and the required equipment, these tests may be used both on the sideline or in clinics to confirm a diagnosis of concussion.[44] Objective physiological examinations are tools that cannot be be intentionally manipulated by the patient or participant. These tools are primarily used in research settings and are not commonly used in clinical concussion care due to their cost, required expertise to administer and manage, and a lack of validation for clinical decision-making.[44]

Limitations in Clinical Management

Although numerous clinical tests have been developed to diagnose and manage concussion, they are limited by a number of factors. Screening and confirmatory tests, particularly more subjective tests used in sideline settings, are problematic because (1) concussion symptoms may not be apparent immediately after injury and may develop and evolve over time[4] and (2) athletes have a strong tendency to underreport symptoms because they want to return to the game.[46] Due to the natural evolution of concussion, it is highly unlikely to identify every concussed athlete at the time of presumed injury even when trained concussion recognition professionals are present,[47] as up to half of athletes that sustain a concussion do not experience an immediate onset of symptoms.[48] However, due to the absence of a physiological biomarker, screening and confirmatory tests remain at the forefront of concussion diagnosis and assessment.[45] This stands problematic as most current clinical tools do not have excellent validity and reliability,[49–52] and for those that do, their validity begins to decrease after a few days.[53]

Additionally, most current concussion assessment tools were developed for use on adults, with many not validated in or developmentally appropriate for children and adolescents. Three common tests have been modified for children, (1) the Standardized Assessment – Children

Version (SAC-C), (2) the Child Sport Concussion Assessment Tool (ChildSCAT), and (3) Child Immediate Post-Concussion Assessment and Cognitive Testing (cImPACT). Similar to the adult versions, the pediatric concussion assessments also suffer from issues with reliability and sensitivity to concussion. The SAC shows moderate test-retest reliabilty of 0.692 (95% CI=0.550-0.790) in adolescents aged 11 to 13 years old, however the reliabilty was (1) only tested on male football players, (2) not tested on children or adolescents of other age groups, and (3) not determined for the SAC-C test.[49] The SCAT5 and ChildSCAT5 shows a high validity in concussion diagnosis immediately after injury, however, the test loses its ability to accurate identify children with concussion around 5 days after injury.[53] Regarding the cImPACT test, initial evidence supports its use with children, however, only as an evaluation to measure post-concussion processing speed.[54]

Concussion Rehabilitation

Concussion is a highly heterogenous injury that manifests in a variety of symptoms and deficits; therefore, multiple rehabilitation strategies may be necessary to optimize recovery.[40] Depending on the etiology and symptoms, varying therapeutic interventions are implemented.[40] Repositioning maneuvers, gaze stability training, and balance exercises are used to treat post-concussion vestibular issues.[55–57] Post-concussion oculomotor rehabilitation involves vision exercises paired with tools such as eye patches, lenses, prisms, penlights, and mirrors to improve ocular muscle function.[40,41] Cervicogenic rehabilitation includes manual therapy consisting of joint mobilization and exercises targeting cervical motor and proprioceptive control.[42] While the treatment approaches described above are effective in individuals with specific post-injury clinical presentation, aerobic exercise is the most widely beneficial treatment for concussion.[10]

Recent evidence suggests the adoption of light to moderate intensity aerobic exercise is the most beneficial treatment for concussion recovery, expediting symptom resolution for most patients regardless of clinical presentation.[10,11,58,59] Current best practice recommendations advocate for relative rest (i.e. still completing activities of daily living) up to 2 days post-injury, whereafter light to moderate aerobic exercise performed at an intensity that does not elicit increased symptoms should be implemented to reduce post-injury symptoms and facilitate concussion recovery.[3,58,59] The adoption of sub-symptom threshold individualized aerobic exercise programs performed acutely after injury are safe for adolescents and adults over 13 years old when performed two or more days post injury.[60,61] Additionally, aerobic exercise interventions with appropriate timing, duration, intensity, and frequency can accelerate recovery, and these programs can thereby reduce the incidence of persistent post-concussion symptoms lasting beyond 30-days after injury.[59,61] Furthermore, it is suggested that aerobic exercise helps alleviate concussion symptoms regardless of whether they are cognitive, physical, somatic, or behavioural in nature;[61] thus, this treatment is broadly effective for all patients. It's important to note that sub-symptom threshold aerobic exercise programs are not synonymous with return-to-sport, which should only occur following full clinical recovery. Instead, aerobic exercise programs as concussion treatment must be completed outside of competitive sports settings to limit risk of reinjury.[61]

Differences Between Clinical and Physiological Recovery Following Concussion

Presently, as an objective concussion biomarker has yet to be validated for clinical care, concussion recovery is not defined by pathophysiologic processes but rather by the resolution of clinical symptoms and problems.[7] Graded exercise tests are a useful tool in determining clinical concussion recovery as they are useful to provoke physiological systems not stressed at rest. Patients are considered clinically recovered when, in addition to the resolution of symptoms and clinical problems at rest, they are able to exercise at high intensity without recurrence of symptoms.[7,60] However, clinical recovery does not necessarily mean that an individual is physiologically recovered, as residual alterations in brain function have been found after clinical recovery has been achieved.[9] While most studies find that adults with concussion recover within one to two weeks after injury, recent findings using advanced imaging technologies suggest that the duration of full physiological recovery after concussion extends well beyond this time frame.[13,62,63] This suggests that athletes may be deemed clinically recovered and cleared to play, while the brain has not returned to normal levels of cerebral and metabolic function.[63] Exact physiological recovery timelines remain unknown, as different studies have reported electrophysiological abnormalities lasting from 45 days,[13] to beyond 6 months,[64] and up to decades post-concussion.[65] Thus, the timeline for full physiological recovery following concussion, or if that phenomenon even exists, is unknown.

There is a major need to identify more objective, physiologically informed criteria to determine concussion recovery.This is particularly important for athletes, as current evidence suggests that the brain is more susceptible to repeat injury following an unresolved concussion.[10,11] It is suggested that if physiological recovery has not occurred that (1) a repeat concussion may occur with less force and (2) prolonged recovery may occur following another impact.[12] Current management approaches which use clinical recovery as the benchmark to clear individuals for return-to-sport may put adolescents at risk of repeat concussion and, ultimately, increased complications later in life.[9] Therefore, better diagnostic tools that detect full physiological recovery following concussion are vital to reduce the likelihood of repeat injury and prolonged recovery.

Functional Brain Monitoring

Electroencephalography

Electroencephalography (EEG) is a common non-invasive tool that measures electrical activity in the brain and is used extensively in clinical and research settings.[66] Typically, electrodes have a contact surface of 10mm in diameter and are held in place on the scalp by a headset.[67] An electrolytic paste or gel is applied to the contact point of the electrode and scalp to facilitate a current flow between the surrounding tissue and the electrode, generating an EEG signal.[67] EEG processes currents flowing in the extracellular spaces produced by ionic currents in the dendritic membranes of the pyramidal neurons in cortical layers IV-V.[67,68] The neuronal cell bodies in these cortical layers are arranged in a parallel manner with their dendrites extending superficially.[67,68] Electrical signals are generated by excitatory and inhibitory postsynaptic potentials.[67,68] Excitatory inputs are located more superficially than inhibitory inputs, which creates a dipole.[67] EEG electrodes do not record the electrical activity of a single neuron, but rather a summation of the synchronous activity of tens of thousands of neurons.[67,68]

EEG waveforms reflect the difference in voltage between an active electrode and a reference electrode.[68] In research, EEG recordings are usually performed from 32, 64, 128, or 256 channels.[68] EEG electrodes are typically placed in the standardized International 10-20 System, although other systems such as 10-10 and 10-5 have been developed.[67,68] This system uses anatomical reference points such as the nasion, inion, and left and right pre-auricular points and electrodes are placed at 10% or 20% of the total distances between those landmarks.[67,68] Electrode positioning is named with two symbols: (1) a letter corresponding to the brain region and (2) a number corresponding to a more precise position within that region.[67] The letter symbols are Fp (frontal-polar), F (frontal), C (central sulcus), P (parietal), O (occipital), and T (temporal).[67,68] Electrode positions along the midline are named with a "z" following the first letter.[67] Electrodes placed on the right side of the midline is denoted with even numbers, whereas the left side is odd-numbered.[67] Lastly, lower numbered electrodes are closer to the midline and higher numbered electrodes are farther from the midline.[67]

EEG activity is a reflection of synaptic activity at the cortical level.[69] Microscopic damage of neurons that lead to changes in synaptic neurotransmission has been detected using EEG in several clinical conditions such as post-anoxic encephalopathy, nervous system dysfunctions, acute strokes, and epilepsy.[69,70] EEG has also been shown to detect changes in sympathetic nervous system activity associated with heart rate variability in response to a video game stimulus.[71] Therefore, EEG has the potential to detect axonal damage, ANS dysfunction, and ionic imbalances that are associated with concussion.

Frequency Bands

In EEG research, there are five frequency bands: delta waves, theta waves, alpha waves, beta waves, and gamma waves.[68,72] Delta waves are very low-frequency waves ranging from 1-4Hz and typically have an amplitude of 20-200μV.[68,72] Delta waves are associated with deep sleep and pathological neural states such as loss of consciousness and coma, and it is suggested that delta wave activity serves as an inhibitory mechanism.[68] Theta waves are low-frequency waves ranging from 4-8Hz and have an amplitude of 8-10μV.[68,72] Theta wave activity is typically associated with specific sleep states, meditation, and drowsiness, but has also been associated to focused attention.[68] Alpha waves are medium-frequency waves ranging from 8-13Hz and typically have an amplitude of 20-200μV.[68,72] Alpha waves are associated with relaxed wakefulness, cognitive inactivity, and information processing.[68] Beta waves are high-frequency waves (13-25Hz) and have an amplitude of 5-10μV.[68,72] Beta waves are associated with task engagement, active concentration, excitement, anxiety, and vigilance, and it is suggested that beta activity serves as an excitatory mechanism.[68] Gamma waves are very high-frequency waves ranging from 25-200Hz and have an amplitude of 1-2μV.[68,72] Gamma wave activity is associated with arousal and peak performance.[68]

Signal Processing

EEG signals are subject to contamination from biological and non-biological sources, which must be removed prior to extracting EEG features.[68,73] Biological artifacts may include facial muscle activity, eye movement, eye blinking, and heartbeats, whereas potential non-biological artifacts include external electrical noise from nearby equipment, poor subject grounding, poor electrode contact, and cable movement.[68,73] For optimal EEG recording, the subject is placed in a soundproofed room that is electrically shielded, while the experimenter and

equipment is in another room.[68] However, this is not always feasible so there are other techniques that are commonly used for removing artifacts: (1) filtering EEG signals so that artifact activity not in the frequency range of interest is removed, (2) removing repetitive artifacts in the signal (e.g., eye blinks, heartbeats) through Independent Component Analyses, (3) removing entire EEG channels (e.g., bad channel rejection), and (4) manual artifact removal.[68]

Spectral Features

The purpose of spectral analysis is to assess the contribution each frequency band has on the measured EEG signal.[68] Spectral features include spectral power (a function of the amplitude of the EEG signal) and peak frequency (the frequency at which power spectrum peaked in each frequency band), which both reflect the oscillatory properties of the EEG signal.[68,74] Spectral analysis utilizes a Fast Fourier Transformation and characterize the signals into a sum of sinusoidal waves with varying frequencies and amplitudes, from which peak power (μV) and peak frequency (Hz) are calculated.[68,74]

Permutation Entropy

Permutation entropy evaluates the information content of the EEG signal, assessing the complexity or regularity of the signal at each individual electrode.[75] Furthermore, permutation entropy can measure signal complexity in the presence of observable signal noise.[76] Permutation entropy is measured as a range from 0 to 1, with lower values indicating the signal is predictable and regular, while a value closer to 1 would indicate the signal is chaotic and unpredictable.[77]

Functional Connectivity

Functional connectivity refers to the symmetrical statistical association or dependence of physiological signals in distinct regions of the brain.[78,79] Functional connectivity can be measured in several ways, but this project will focus on amplitude envelope correlation (AEC), weighted phase lag index (wPLI), and directed phase lag index (dPLI) methods. With AEC, specific frequency bands of interest are filtered, and a Hilbert transform is performed to create an amplitude envelope for the signal. Pearson's correlations are then computed between the amplitude envelopes of all electrode pairs to obtain connectivity measures between brain regions.[80] AEC values are measured between 0 and 1, with larger numbers representing stronger functional connectivity.[81] The wPLI estimates the extent of phase lead or lag relationship between a pair-wise combination of electrodes, without respect to the direction of the relationship.[81] wPLI values are measured between 0 and 1, with 1 representing stronger functional connectivity between regions.[81] Furthermore, it is suggested that using a wPLI approach could prevent the need to remove noisy channels or artifacts from EEG recordings.[82] The dPLI is computed to determine the direction of the phase lead or lag relationship between two electrodes.[83] The dPLI also ranges from 0 to 1, where a value above 0.5 indicates that electrode 1 is leading electrode 2, and a value below 0.5 indicates that electrode 1 lags behind electrode 2.[83]

Graph Theory

Graph theory is a modeling technique that maps the brain's structural and/or functional connections as a network of nodes (electrodes) connected by edges (structural or functional connections).[79] Graph theory describes networks through various measures such as node strength, clustering coefficient, path length and efficiency, betweenness centrality, modularity, and small-worldness.[79] Node strength quantifies how strongly a node is connected to other nodes in the

network.[79] A cluster refers to nodes that are directly connected to each other and the clustering coefficient measures the number of connections between a node and its neighbouring connections as a proportion of the maximum potential connections.[79] High clustering coefficients are associated with heightened local efficiency of information exchange.[79] Path length is the minimum number of edges between two nodes and efficiency is inversely related to path length; therefore, shorter path lengths increase the efficiency of information exchange between nodes.[79] Betweenness centrality measures how many of the shortest paths between two nodes in the network run through that node; therefore, a node with high centrality is important for efficient information exchange.[79] A module is a group of densely interconnected nodes and modularity measures the strength of the connection between different modules within a network.[79] Small-worldness is measured as a ratio of node clustering and path lengths, therefore high clustering of nodes and short path length indicates a high small-worldness[79]. High small-worldness indicates that nodes in a network are linked through relatively few steps, which signifies that the network has efficient information exchange[79].

EEG and Concussion

EEG can detect physiological abnormalities in the brain within days to months of injury;[84] however, EEG continues to detect diffuse slowing in individuals with persistent symptoms over a year after injury.[14] Decreases in alpha, beta, and gamma frequencies, and increases in delta and theta frequencies are observed following a concussion compared to uninjured individuals.[85] Furthermore, EEG data suggests that individuals with mild TBI are associated with increased slow wave activity during wakefulness.[86] An increase in delta frequency has been associated with brain injuries and learning and cognitive difficulties.[85] Delta waves have been associated as an inhibitory mechanism; therefore, increases in their frequency may explain their association with cognitive dysfunction.[68] An increase in theta wave frequency has been associated with increased anxiety levels and decreased mood, sleep quality, and concentration.[87] Decrease alpha is associated with reduced cortical excitability,[85] while decreased beta activity is associated with poor cognition and concentration difficulties.[85] Decreases in gamma frequency is related to increased delta activity, which has been associated to lower neuronal activity of regions that control behaviour.[85]

Permutation entropy has yet to be evaluated in the context of concussion; however, it shows promise in identifying changes in brain states in other pathological populations. EEG-derived permutation entropy features have been shown to (1) reliably capture the transition from a wakeful state to an anaesthetized state while being resistant to noise from eye-blinks[88] and (2) differentiated between epileptic seizures and a normal EEG with a sensitivity of 94.38% and specificity of 93.23%.[75]

EEG-derived functional connectivity and graph theory measures detect abnormalities including altered connectivity between regions of the brain and neuronal and axonal dysfunction.[13] Adolescent athletes with concussion showed no alterations in the efficiency of global resting-state networks; however, significant changes in local brain networks were observed.[89] In the same study, local increases in betweenness centrality following concussion corresponded to changes in the right dorsolateral pre-frontal cortex (DLPFC) and the right inferior frontal gyrus.[89] The right DLPFC plays a significant role in working memory, cognitive flexibility, abstract reasoning, and attention. The increase in betweenness centrality in this region suggests that it may be a key hub region following concussion, increasing connectivity to neighbouring areas.[89] It is suggested that

a loss in structural connectivity (i.e., changes to anatomical connections in the brain) following concussion is compensated for by an increase in functional connectivity in local circuits in the brain,[90] which decreases the efficiency and specificity of neural communication. It has also been suggested that increased connectivity might reflect an increased effort in recruiting the appropriate neural networks, and may reflect the natural response to injury and the recovery process.[89,91] Increased connectivity in brain networks related to attention may be associated with increased distractibility, headache, and cognitive fatigue, which are common post-concussion symptoms.[89]

Importantly, changes in brain electrical activity have been observed in concussed individuals that have passed a variety of functional tests.[92] This indicates that athletes may be cleared to return to sport because they have passed screening and/or confirmatory tests prior to complete physiological resolution, which may increase the risk of re-injury. This highlights the need for better physiological measures and objective tests to better inform concussion diagnosis and management than tests that rely on subjective symptom reporting, which EEG may provide. The ability of EEG to detect changes in electrophysiology in the brain after concussion even after symptom deficits have disappeared and beyond the point of observed clinical recovery[13,63] showcases its potential to provide an objective, physiological biomarker. Furthermore, a portable EEG may have the potential to aid in the identification and evaluation of brain dysfunction acutely and sub-acutely after concussion, making it a valuable neuroimaging tool in clinical concussion management and on sport sidelines.[63]

EEG and Concussion: Limitations

In a clinical context, EEG is mainly utilized as a diagnostic and prognostic tool for moderate to severe TBI.[84] While EEG detects abnormalities in brain electrical activity after concussion, it is not commonly used in clinical and athletic settings for patients with concussion, because (1) it has only been validated in a research setting currently, (2) it requires a trained expert to administer and interpret, which may not be available in certain out-patient clinical settings for concussion, and (3) EEG headsets may be too expensive to have available for athletic/sideline settings.[84,93] Therefore, it is primarily used in a research setting, and in terms of the population, research mainly focuses on adults with concussion and little research exists to support its use in children and adolescents with concussion.[84] Limited studies on children and adolescents with concussion may leave researchers with assumptions that neurophysiological changes post-concussion are the same across ages, which may be incorrect as developing brains may be affected differently than developed ones.

EEG and Concussion: Benefits

Despite the limitations defined above, there are several advantages to using EEG as a functional brain monitoring tool. EEG is a common non-invasive and portable neuroimaging tool that has the ability to capture the electrophysiology in the brain.[68] Compared to functional magnetic resonance imaging (fMRI), EEG has a superior temporal resolution when measuring neural activity and is comparably much less expensive, with fMRI costing upwards of USD$3,000,000 while prices for complex EEG headsets generally range from USD$50,000 - $100,000 and EEG systems containing fewer electrodes are even less expensive.[68] Furthermore, certain EEG headsets, such as the one proposed in the current study, use dry electrodes which accelerates the set-up, recording, and dismantling process, so that the entire procedure only takes 10 to 15 minutes.[68,94,95]

Thus, in the search for a biological marker of concussion, EEG remains a valuable and time efficient tool that has great potential for translation into clinical care settings.

METHODOLOGY

Study Design and Participants

This study used a prospective longitudinal cohort design. Participants with concussion were recruited through the Montreal Children's Hospital Pediatric Emergency Department. Adolescents in the injury group must have been diagnosed with a concussion by a licensed physician, be between 9-17 years old, speak either English or French, and be available for testing within 10 days of injury. Healthy adolescents were recruited from our local community and were included if they were aged 9 to 17 years old and speak either English or French. Exclusion criteria was the same across both groups. Participants in both the healthy group or concussion group were excluded if they had (1) any unresolved symptoms from a previously diagnosed concussion, (2) any diagnosed injuries or illnesses that may prevent completion of the study assessment, or (3) any diagnoses or medication use that affect EEG markers (e.g. antiepileptics, etc.). Written informed parent consent and child assent were obtained prior to data collection. This study was approved by the Concordia University Research Ethics Board (#30017577) and by the McGill University Health Centre Pediatrics Research Ethics Board (#2020-6435).

Data Collection Procedures

Data collection sessions for the healthy control group were performed at the Concussion Neurophysiology and Rehabilitation Research Lab at Concordia University's Loyola Campus or at a local high school, with necessary permission obtained from the class teacher and school principal. Data collection sessions for the concussion group were performed at the Montreal Children's Hospital. Data collection procedures were identical for both groups. Participants completed a demographic questionnaire (first visit only) and brief clinical assessment battery, which included symptom, quality of life, and self-reported anxiety/depression scales. Participants then completed a seated resting-state EEG using a dry, 19-channel EEG headset (DSI-24 from Wearable Sensing). Resting-state EEG measures were recorded in eyes-open and eyes-closed conditions while seated in a dark, quiet room. Each condition lasted for 5 minutes, and data was recorded at a frequency of 300Hz with the impedance set to 1 MΩ as per manufacturer recommendations. To determine if administration of the EEG elicits concussion-like symptoms, a brief symptom check-in questionnaire was completed at baseline (before the EEG assessment), following the EEG assessments, and at the end of the study visit. Sessions were paused (i.e., rest period provided) or terminated early if the participant reported a ≥6-point increase in symptoms from baseline evaluation that did not resolve with rest. Participants attended a second, identical visit between 21 to 27 days after the initial visit. Study participation concluded following completion of the second visit.

EEG Processing

The resting-state EEG signal collected during both the eyes-open and eye-closed conditions were filtered between frequencies of 0.5-50 Hz to remove low and high frequency noise recorded by the EEG headset. The signal was then re-referenced to the A1 & A2 (earlobe) electrodes. The continuous signal was split such that eyes open and eyes closed conditions are separated into individual files. Any channel determined to have excessive noise throughout the entire recording

was removed entirely as a bad channel. If there was any repetitive noise (i.e. eye movement, blinking, pulse, etc.) that appeared sporadically during the recording, an Independent Component Analysis was performed to remove artifacts without removing the entire channel. The data was then manually inspected, and any remaining artifact was removed manually. The EEGlab toolbox in MATLAB was used to process the EEG data.[96]

EEG Feature Extraction

The EEG signal was sliced into 10-second segments, so that each channel was comprised of continuous 10-second, non-overlapping windows. EEG features including (1) spectral features (spectral power and peak frequency), (2) entropy-based features (normalized permutation entropy), (3) functional connectivity (AEC, wPLI, and dPLI), and (4) graph theory (path length, global efficiency, clustering coefficient, small-worldness, modularity, and node strength) features were extracted from each 10-second window. Each feature was calculated at delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz) frequency bands and are described in detail in **Table 1**. EEG features were extracted using code from the Brain Connectivity Toolbox or custom MATLAB scripts.[96]

Table 1: EEG Features and Descriptions

General Feature and Description	Specific Feature	Specific Description
Spectral Features	Spectral Power	Measure of the signal power (microvolt^2/Hz)
	Peak Frequency	Frequency (Hz) where the peak power occured
Entropy Features	Permutation Entropy	Information content of the EEG signal
Functional Connectivity Features	Weighted Phase Lag Index	Measurement of the correlation between the phase angle of each pair of EEG electrodes
	Amplitude Envelope Correlation	Measurement of the correlation between an envelope generated on top of the EEG signal and all electrode pairs
	Directed Phase Lag Index	Measurement of the direction of the relationship between electrodes
Graph Theory Features	Path Length	The minimum number of connections for an electrode to be connected to another
	Global Efficiency	$\frac{1}{Path\ Length}$: Measurement of the efficiency of information exchange between electrodes.
	Clustering Coefficient	Measurement of the connections between an electrode and the electrodes surrounding that same electrode
	Small-Worldness	$\frac{Clustering\ Coefficient}{Path\ Length}$: Discovering areas of electrodes in which high clusters and shorter path lengths are present to determine areas where long distances are traveled efficiently
	Modularity	Measure of the strength of electrode division within the network
	Node Strength	Sum of all connections for each electrode

Clinical Outcome Measures

Demographics Form: The Demographics form (see **Supplementary Figure 1**) includes 8 questions regarding age, biological sex, gender, current grade, sport participation, concussion history, preferred language, and health condition. This assessment was performed at the first study visit only and was used to describe the sample and control for modifiers of concussion recovery as appropriate.

Pediatric Quality of Life Scale: The Pediatric Quality of Life Scale (PedsQL) (**Supplementary Table 1**) is a 23-question survey that evaluates a variety of health, behavioural, emotional, social, and school-related experiences. The patient scored each question based on their general experiences over the past month. Each question was scored from 0 (have not experienced it) to 4 (almost always experienced it). This was converted into a total score of 0 to 100, where higher scores represented better quality of life. The PedsQL was designed to measure quality of life in children and adolescents aged 2 to 18 years old.[97] It is both valid and reliable among children and adolescents with traumatic brain injuries[98] and has high internal consistency (α=0.74-0.93) and test-retest reliability (ICC=0.75-0.90).[98]

Revised Child Anxiety and Depression Scale: The Revised Child Anxiety and Depression Scale (RCADS) (**Supplementary Table 2**) is a 25-question survey that evaluates mood, anxiety, and depression in children and adolescents. Each question was rated from 0 (never experiencing) to 3 (always experiencing) based on the child's experiences over the past month. The RCADS was converted to a total score ranging from 0 (minimum anxiety and depression) and 75 (high anxiety and depression). The RCADS was shown to have a good internal consistency (α=0.70-0.96)[99] and a good test-retest reliability (ICC=0.77-0.85).[100]

Post-Concussion Symptoms Inventory: The Post-Concussion Symptoms Inventory (PCSI, **Supplementary Table 3**) is a self-reported symptom checklist with moderate to strong test-retest reliability (ICC=0.65-0.89), a good validity (r=0.8), and a strong internal consistency (α = 0.8–0.9).[101] The PCSI contains 20 non-specific symptoms (e.g., headache, dizziness, etc.) that are commonly reported after concussion; each item was rated from 0 (not present) to 6 (present and severe). The PCSI determined the presence and severity of concussion symptoms, with a range of 0 (no symptoms) to 120 (most frequent and severe symptoms).

Symptom Check-In: The Symptom Check-In form (**Supplementary Table 4**) scores 5 common post-concussion symptoms (headache, fatigue, concentration, irritability, and dizziness) on a scale of 0 (no symptom) to 6 (most severe symptom). The symptom check-in was completed 3 times: (1) at baseline (using PCSI scores), (2) after the EEG assessments, and (3) at the end of the study. Each symptom check-in was scored from between 0 (no symptoms) to 30 (most severe symptoms). The outcomes from this tool were not analyzed statistically; this assessment was only used for participant safety as part of our stopping criteria.

Statistical Analysis

All statistical analyses were performed in RStudio.[102] The independent variable for all analyses was group (acute concussion vs. healthy controls) and, for mixed models, time (visit 1 vs. visit 2). Descriptive statistics were performed for all demographic information and study

outcomes. Categorical variables were reported as frequencies with percentages, while continuous outcomes were presented as means and standard deviations. Differences in demographic outcomes were determined using Chi-Square (categorical) or Independent Samples T-tests (continuous). Due to limitations with data collection, change in post-concussion symptom outcomes were analyzed using Independent Samples T-tests. Generalized linear mixed-effects models evaluated the effect of group, time, and their interaction on the remaining clinical (PedsQL and RCADS questionnaires) and EEG features (Objective #1). Linear models adjusted for age and sex as appropriate. Fixed-effects included group, time, age, and sex, while random-effects (e.g., random intercepts) were added for participant. Pearson's correlations associated neurophysiological outcomes to clinical outcomes for adolescents with and without concussion (Objective #2). For this thesis, alpha was set to 0.01 to reduce the risk of type 1 error.

A subset of five EEG features were selected for analysis to improve our statistical power. Using previously collected, unpublished data from our laboratory, a binary classification machine learning model was built to accurately separate between adolescents with and without concussion. This model was built using EEG features described in this study (e.g., power, entropy, connectivity, and graph theory features at delta, theta, alpha, and beta frequency bands) for eyes open, resting-state data. Only the top five EEG features identified in the model (O1 beta power, T6 beta power, P4 delta power, F3 delta power, and F8 delta power) were analyzed in this thesis, while the remaining features will be utilized in future projects.

Sample Size

The proposed thesis is a sub-study of a larger project investigating the diagnosis and prognostic potential of EEG for clinical concussion care. Based on preliminary data (EEG prediction: AUC = 0.86; Physician prediction: AUC = 0.63), α=0.05, and 1-β=0.80, 28 participants/group are needed for the larger project. Data in adolescent participants with concussion has already been collected and 10% of data was lost due to contamination in the EEG signal (excessive movement/blinks) or loss to follow-up at the second study visit. Thus, 33 healthy controls were targeted for the current study

RESULTS

Participant Demographics

A total of sixty-eight participants were included in the study, comprising 53 individuals with concussion and 15 healthy controls. Demographic information for each group is summarized in **Table 2** below. Participants in the concussion group were assessed 6.00±2.30 (visit 1) and 28.90±2.02 (visit 2) days post-concussion, with the control group having a similar interval between sessions. The average age of participants was 13.1±2.7 years old, which was similar between groups (p=0.07). A greater proportion of healthy participants (n=9, 60.0%) identified as female compared to the concussion group (n=16, 30.2%); however, this difference was not statistically significant (p = 0.066). Only the primary language significantly differed between groups (p<0.001), with the healthy control group (n=14, 93.3%) being more anglophone than the concussion group (n=21, 39.6%). There were no significant group differences in pre-existing conditions, including concussion history (p=0.717), ADHD diagnosis (p=0.184), anxiety (p=1.00), depression (p=1.00), learning disability (p=0.569), or migraine history (p=1.00).

Table 2. Participant demographics presented overall and separately for each group. Variables are reported as means (standard deviations) or frequencies (percentages) as appropriate.

	Concussion (N=53)	**Healthy** (N=15)	**Overall** (N=68)	***P* Value**
Age (years)	12.8 (2.53)	14.5 (3.14)	13.1 (2.74)	0.0695
Sex				
Female	16 (30.2%)	9 (60.0%)	25 (36.8%)	0.0661
Male	37 (69.8%)	6 (40.0%)	43 (63.2%)	
Primary Language				
English	21 (39.6%)	14 (93.3%)	35 (51.5%)	<0.001
French	26 (49.1%)	1 (6.7%)	27 (39.7%)	
Other	6 (11.3%)	0 (0%)	6 (8.8%)	
Concussion History				
No	42 (79.2%)	13 (86.7%)	55 (80.9%)	0.717
Yes	11 (20.8%)	2 (13.3%)	13 (19.1%)	
Pre-Existing Conditions				
ADHD	8 (15.1%)	0 (0%)	8 (11.8%)	0.184
Anxiety	4 (7.5%)	1 (6.7%)	5 (7.4%)	1.00
Depression	0 (0%)	0 (0%)	0 (0%)	-
Learning Disability	4 (7.5%)	0 (0%)	4 (5.9%)	0.569
Migraine	1 (1.9%)	0 (0%)	1 (1.5%)	1.00
Psychiatric Conditions	0 (0%)	0 (0%)	0 (0%)	-
Any Pre-Existing Conditions	14 (26.4%)	0 (0%)	14 (20.6%)	0.0289
Days Since Injury				
Visit 1	6.00 (2.30)	NA		-
Visit 2	28.90 (2.02)	NA		-

Clinical Outcomes Improved Over Time for Concussion Patients

Concussion symptoms differed at the initial visit but were not evident at the second visit. At visit 1, concussed participants reported significantly higher PCSI scores (M= 29.15±18.35) compared to healthy controls (M=11.93±10.27, mean difference= 17.22; 95% CI=9.83, 24.60; $p < 0.001$). However, at visit 2, no significant group differences were observed ($p = 0.85$), indicating improved (i.e., lower) reported symptoms for the concussion group (**Figure 1**). PedsQL scores revealed a significant main effect of visit ($\beta=7.40$, $p < 0.001$), with both groups reporting improved quality of life at the second study visit (visit 1 mean: 77.09±13.55, visit 2 mean: 83.72±13.98). The concussion group had lower (i.e., worse) PedsQL scores overall than the healthy group, but these findings did not reach statistical significance ($p = 0.052$) (**Figure 2A**). A significant interaction effect was observed for RCADS total scores ($\beta = 6.28$, $p = 0.0014$). Both groups moved in opposing directions; the concussion group reported lower RCADS scores (i.e., reduced anxiety and depression symptoms over time) across study visits (visit 1 mean: 14.3±11.6; visit 2 mean: 9.79±9.97), while the healthy group reported higher RCADS scores/ increased anxiety and depression scores over time (visit 1 mean: 13.5±9.07, visit 2 mean: 15.3±11.7; **Figure 2B**).

Figure 1. Total symptom scores (from the PCSI) are presented separately by study visit.

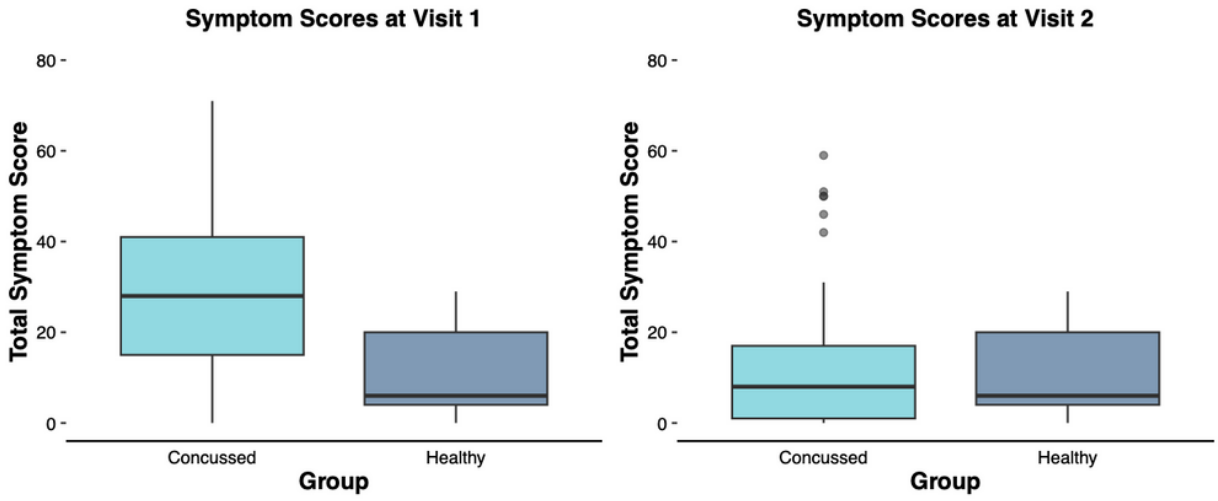
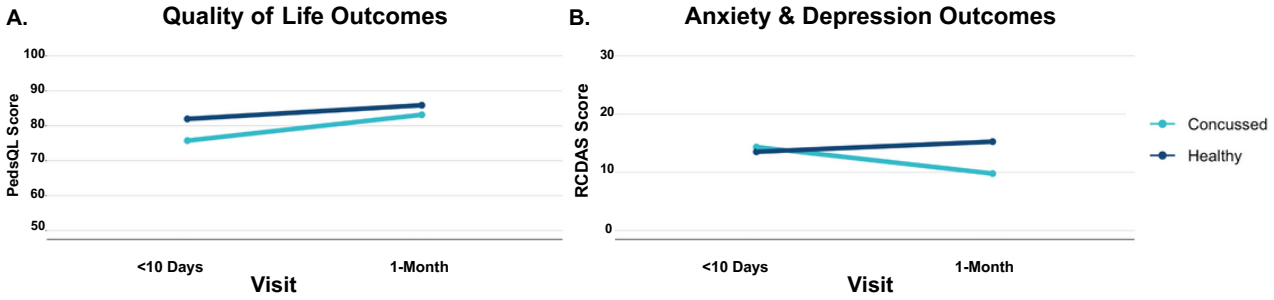


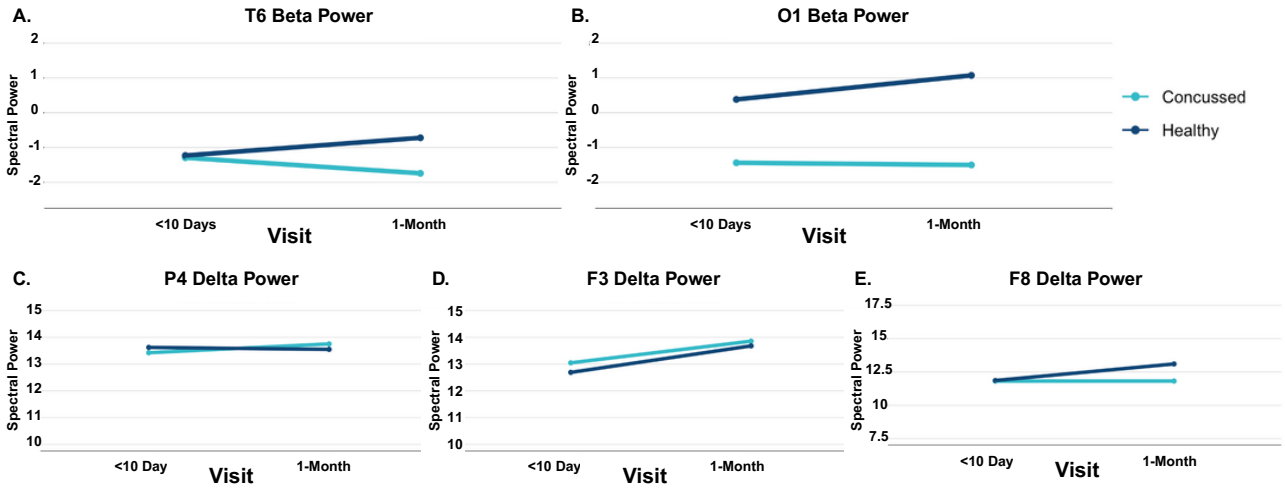
Figure 2. Average quality of life (A) and mood (B) scores, presented for each group and visit.



Neurophysiological Measures Do Not Change Over a 1-Month Period

No statistically significant effects were observed for EEG outcomes (**Figure 3**). Beta power at electrode O1 was higher in the healthy group across both visits and came closest to statistical significance ($p = 0.071$, **Figure 3B**). However, significant effects of age and sex were present in the mixed models. T6 beta power was significantly influenced by sex ($p = 0.007$), with females showing greater power irrespective of group or visit. Delta power at the F8, P4, and F3 electrodes was strongly predicted by age ($p < 0.001$), with older participants exhibiting lower delta power activity compared to younger participants.

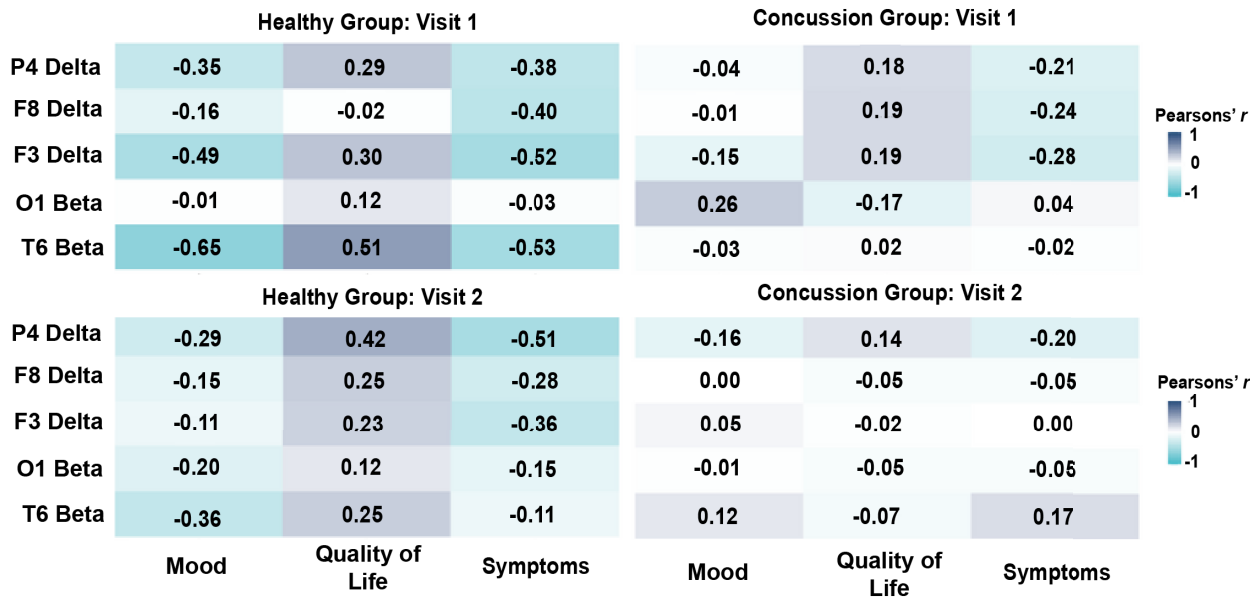
Figure 3. Average spectral power values for the five EEG features analyzed for this project, presented for each group and visit.



Clinical and Neurophysiological Outcomes Are Not Closely Correlated

Pearson correlation analyses are presented in **Figure 4**. A significant negative correlation was observed between T6 beta power and RCADS total score ($r = -0.65$, $p = 0.01$) at visit 1 for the healthy group only, indicating that higher beta power activity in the right temporal region was associated with fewer anxiety and depression symptoms. Higher F3 delta power was moderately correlated with lower PCSI scores in both healthy ($r = -0.52$, $p = 0.046$) and concussion ($r = -0.28$, $p = 0.044$) groups at visit one, and higher P4 delta power was moderately correlated with lower PCSI scores for the healthy group ($r = -0.38$, $p = 0.050$) at visit one only. While moderate correlations were observed, these findings did not reach significance due to our more conservative alpha-level of 0.01. No statistically significant correlations were found at visit 2.

Figure 4 (below). Correlations matrices between neurophysiological data (EEG) for each electrode and clinical data (RCADS [mood], PedsQL [quality of life], and PCSI [symptoms]). Correlations for the healthy group (left column) and concussion group (right column) are presented separately for visit 1 (top row) and visit 2 (bottom row).



DISCUSSION

Mixed-effects models showed significant changes in clinical outcomes over time; however, no such temporal changes were observed for the five EEG features analyzed in this study. Additionally, Pearson's correlations failed to capture significant association between EEG features and clinical outcomes, suggesting minimal relationships between these objective physiological outcomes and self-reported clinical data in adolescents with and without concussion.

Self-reported anxiety and depression scores, measured with the RCADS, revealed a significant interaction effect, with the concussion group showing improvements in RCADS scores (i.e. decreased total score) over time while RCADS scores for the healthy control group increased over time. This aligns with literature suggesting there is an increase in emotional symptoms following concussion.[5,47,103] Concussion can lead to disruption to routines and psychosocial stressors which may contribute to increased emotional symptoms and psychiatric challenges.[104,105] The reduction in anxiety and depression symptoms over time in the concussion group is consistent with prior research that self-reported mood outcomes in children and adolescents improve over the first month following injury.[2,105] However, it's important to note that while most children and adolescents recover without any long-term psychiatric issues following concussion, some children may develop clinical psychiatric problems (e.g., anxiety, depression) after concussion in very rare cases.[106] Conversely, healthy participants experienced a small increase in RCADS scores at the follow-up visit, which may be related to the timing of the visit (i.e., the second visit for most of the control group was completed near the end of the school year/before final exams). The timing of the follow-up could have captured potential stressors from the academic pressure present near the end of the school year, which can increase anxiety and depression symptoms.[107] While no minimal clinically important difference threshold has been established for the RCADS,[108] scores ≥65 are considered the threshold for clinical or borderline clinical levels of anxiety and depression. As our participants are well below this threshold, it's likely that clinically significant levels of anxiety and/or depression were not observed for either group.

As expected, the concussion group reported significantly more post-concussion symptoms, measured using the PCSI questionnaire, than the healthy control group at the initial visit. However, by the follow-up visit approximately one month later, there were no significant differences in post-concussion symptoms between groups. These findings align with the broader pediatric and adolescent concussion literature that suggest increased post-concussion symptoms acutely after injury,[2,109] followed by a gradual resolution of post-concussion symptom within one month.[1,110,111] Furthermore, the amount and severity of symptom reported by our participants also aligns with prior literature. Average symptom scores for individuals with concussion tended to range between 15-25 points higher than baseline (i.e., pre-injury) scores, while the symptoms scores for non-injured participants range from 10-15 points.[112]

We observed a main effect of time for quality-of-life outcomes, assessed using the PedsQL questionnaire, with both groups improving over time. These findings are consistent with the previous literature suggesting that pediatric and adolescent concussion can affect school participation, fatigue, and general well-being, thereby contributing to a worse perceived quality of life more acutely after injury.[17,18,113,114] The improvement seen in the healthy group could reflect the timing of the follow-up visit. Given the approach of the summer holidays, this may have

contributed to increased PedsQL scores, agreeing with the prior literature suggesting that quality of life improves during lower stress periods.[115] Changes of approximately 5 points are considered to be the minimal clinically important difference for the PedsQL.[115] In our study, the concussion group achieved an average increase of ~7.5 points, while the healthy group only improved ~3 points on average. This indicates that the improvements in quality of life represent a clinically meaningful differences for the concussion group only.

Beta power at the O1 electrode was moderately elevated in the healthy group compared to the concussion group. This effect failed to reach statistical significance but may be due to reduced statistical power (see limitations section for further discussion). This pattern is consistent with prior literature that there is decreased beta activity in individuals following concussion, potentially reflecting ongoing neural dysregulation, cortical slowing, or possible compensatory changes.[85,116] Furthermore, we found a significant negative correlation between T6 beta power and RCADS scores in the healthy group at visit 1, indicating higher temporal beta power may be associated with a reduction in self-reported anxiety and depression symptoms. Prior literature has associated higher beta temporal activity with lower anxiety and depressive symptoms in young adults and adults, and suggest increased temporal beta power may reflect enhanced emotional regulation and cognitive control.[117,118] However, literature in adolescent population contradicts our findings and found that higher temporal beta power was associated with higher social anxiety symptoms. One possible explanation is that the healthy participants in our sample were primarily older adolescents and may reflect temporal beta power patterns more often seen in younger adults as opposed to adolescents. Interestingly, no correlations between EEG features and clinical measures were found at visit 2 for either group. This may suggest that clinical symptoms and neuroelectric activity have distinct recovery trajectories, aligning with prior literature suggesting that neural dysfunction may persist beyond the resolution of post-concussion symptoms and clinical recovery has been achieved.[62,84]

T6 beta power was significantly higher in females, aligning with the prior studies suggesting that females have higher beta power than males.[120,121] No significant main effects of group or visit were found in F3, F8, and P4 delta power, but delta power was significantly reduced with increasing age. These findings align with the existing literature, reflecting typical brain maturation during childhood and adolescence from improved neural efficiency and reduced cortical excitability.[122,123] Importantly, the consistency of the literature and these findings suggest the importance of including age as a covariate in pediatric and adolescent EEG research, particularly when looking at delta power activity. Furthermore, we hypothesized that EEG differences between groups would be present and more pronounced at visit 1 and converge over time as recovery progressed. However, apart from F3 delta power, our data showed the opposite. More specifically, EEG data between concussed and healthy control groups were more similar at visit one but diverged more by visit 2. While not statistically significant, this unexpected and interesting result may suggest that neurophysiological changes may be delayed or evolve over time post-concussion, potentially becoming more apparent after the acute phase. This highlights the need for more long-term EEG monitoring post-concussion to observe neurophysiological patterns further along the recovery trajectory.

Strengths

This study combined objective neurophysiological data using EEG with subjective clinical assessments using questionnaires, offering a multimodal approach on observing concussion recovery. Relying solely on subjective reporting is limited as this information can be easily manipulated by the participant due to internal or external pressures and expectations.[46] This study employed a longitudinal design that tracked participants over two visits, which allowed us to examine the recovery trajectory of concussion over time rather than relying on a single timepoint. EEG-concussion studies have found alterations in brain activity following concussion; however, most of these studies evaluate EEG at a single timepoint, usually in the acute phase of recovery.[14,62] The evolution of EEG over time in a pediatric concussion population has only been studied once before to the best of our knowledge.[13] The timing of our study visits aligned with important clinical benchmarks, including an acute post-injury evaluation and a one-month follow up which aligns with typical symptom recovery timelines reported in the literature. Furthermore, the inclusion of both a concussion and healthy control group allowed us to compare differences between un-injured and injured brains. Finally, the use of a mixed-effects model allowed us to account for important covariates know to influence both concussion recovery and EEG outcomes, including age and sex, which have been shown to affect EEG measurements.[120–123]

Limitations

The main limitation in this study revolves around sample size and make-up. Firstly, there was a large difference in sample size between group (concussion: n=53, healthy: n=15), which can affect statistical power and increase the risk of Type II error. Secondly, while the original target recruitment age range was 10–17 years exclusively, challenges in recruitment resulting in the acceptance of children as young as 9 years old. Furthermore, the healthy control group skewed towards older adolescents due to our recruitment source (local high school). Additional limitations are related to EEG processing and analytical decisions. EEG data was averaged down to a single outcome per participant, which reduces the variability and makes it more challenging to find statistical differences. Due to our limited sample, our neurophysiological analysis was limited to a set of five EEG features that were selected based on a machine learning algorithm optimized for concussion diagnosis. Alternative features, such as functional connectivity and graph-theory metrics, may be more sensitive to capturing the effects of concussion over time and should be considered for future work. EEG data was limited to eyes-open seated conditions, while eyes-closed data may have revealed other differences in neurophysiological function. Finally, to reduce the risk of getting a type 1 error due to multiple comparisons and the limitations discussed above, we applied a stricter statistical significance threshold ($p = 0.01$) that may have led to potentially meaningful changes going undetected.

Clinical Implications

While clinical outcomes improved over time, neurophysiological measures did not demonstrate the same pattern of recovery. This suggests that while participants reported feeling better and appeared to reach the benchmark for clinical recovery, the underlying brain function did not change in similar or predictable ways. The adequacy of current return-to-sport and return-to-learn protocols, which rely on subjective reporting collected from questionnaires, have been questioned in the literature, but our results do not currently support of use of EEG to as an

objective, physiological marker of pediatric concussion recovery. However, it is possible that other EEG features not evaluated in this study may be better able to track concussion recovery over time. If brain alterations remain after symptom resolution, athletes may be cleared to return to sport before their brains have fully healed. This could increase the risk of re-injury or delayed recovery from more impacts,[20,63] therefore caution and informed decision making for return-to-sport should continue. Findings from this study support that concussion management should take a multimodal approach that incorporate subjective symptom reporting and objective measures to maximize safety for athletes returning from concussion. However, our study is unable to determine if EEG abnormalities ever return to pre-injury levels following concussion, therefore further research with longer-term follow-ups are required.

CONCLUSION

This study highlights that following a concussion, children and adolescents demonstrate elevated post-concussion symptoms, reduced quality of life, and increased anxiety and depression outcomes. These changes in clinical presentation were more severe shortly after injury and improved within a one-month timeframe. Notably, while subjective clinical measures significantly improved over time, neurophysiological measures (EEG) were not different between groups, did not change over time, and were rarely correlated to clinical outcomes. Our findings call into question the usefulness of EEG spectral power in observing concussion recovery in a pediatric concussion population. However, limitations surrounding statistical power, and the selection of evaluated EEG features evaluated in this project may have contributed to a lack of significant findings. Therefore, further research is needed to draw more conclusive findings on the usefulness of EEG for clinical concussion management in adolescents.

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SUPPLEMENTAL INFORMATION

Supplementary Figure 1: Demographics Form

Patient ID: _____

Date of Visit (MM/DD/YYYY): _____

Test Evaluator: _____

Demographic Information- Healthy Controls

1. Age: _____
2. Biological Sex (Circle Answer):
   a. Male
   b. Female
   c. Other/Prefer Not to Answer
3. Gender (Circle Answer):
   a. Male
   b. Female
   c. Gender Non-Conforming
   d. Other/Prefer Not to Answer
4. What grade are you currently in? _____
5. Do you currently play any organized sport(s)? a. Yes b. No
6. Have you ever experienced a concussion previously (e.g. been diagnosed with a concussion by a medical provider)? a. Yes. b. No

   6a. If yes, how many concussions have you been diagnosed with previously? _____

   6b. If yes, when was your most recent concussion (year and month)? _____

   6c. If yes, what was the longest symptom duration of all prior injuries (in weeks)? _____

7. What is your primary/preferred language? a. English b. French c. Other _____
8. Have you ever been f**ormally diagnosed** (by a healthcare professional) with any of the following health conditions (circle all that apply)?
   a. ADD/ADHD
   b. Depression
   c. Anxiety
   d. Learning Disability
   e. Migraines
   f. Seizure
   g. Psychiatric Condition
   h. Other: _____
   i. None of the above

Supplementary Table 1: Pediatric Quality of Life Scale

Over the past month:	Never	Almost Never	Sometimes	Often	Almost Always
1. It is hard for me to walk more than one block.	0	1	2	3	4
2. It is hard for me to run.	0	1	2	3	4
3. It is hard for me to do sport activities or exercise.	0	1	2	3	4
4. It is hard for me to lift something heavy.	0	1	2	3	4
5. It is hard for me to take a shower or bath by myself.	0	1	2	3	4
6. It is hard for me to do chores around the house.	0	1	2	3	4
7. I hurt or ache.	0	1	2	3	4
8. I have low energy.	0	1	2	3	4
9. I feel afraid or scared.	0	1	2	3	4
10. I feel sad or blue.	0	1	2	3	4
11. I feel angry.	0	1	2	3	4
12. I have trouble sleeping.	0	1	2	3	4
13. I worry about what will happen to me.	0	1	2	3	4
14. I have trouble getting along with other people my age.	0	1	2	3	4
15. Other people my age do not want to be my friend.	0	1	2	3	4
16. Other people my age tease me.	0	1	2	3	4
17. I cannot do things that other people my age can do.	0	1	2	3	4
18. It is hard to keep up with other people my age.	0	1	2	3	4
19. It is hard to pay attention in class.	0	1	2	3	4
20. I forget things.	0	1	2	3	4
21. I have trouble keeping up with my school work.	0	1	2	3	4
22. I miss school because of not feeling well.	0	1	2	3	4
23. I miss school to go to the doctor or hospital.	0	1	2	3	4

Supplementary Table 2: Revised Child Anxiety and Depression Scale

Over the past month:	Never	Sometimes	Often	Always
1. I feel sad or empty.	0	1	2	3
2. I worry when I think I have done poorly at something.	0	1	2	3
3. I would feel afraid of being on my own at home.	0	1	2	3
4. Nothing is much fun anymore.	0	1	2	3
5. I worry that something awful will happen to someone in my family.	0	1	2	3
6. I am afraid of being in crowded places (like the movies or busy playground).	0	1	2	3
7. I worry what other people think of me.	0	1	2	3
8. I have trouble sleeping.	0	1	2	3
9. I feel scared to sleep on my own.	0	1	2	3
10. I have problems with my appetite.	0	1	2	3
11. I suddenly become dizzy or faint for no reason.	0	1	2	3
12. I have to do some things over and over again (like hand washing, cleaning, or putting things in a certain order).	0	1	2	3
13. I have no energy for things.	0	1	2	3

14. I suddenly start to tremble or shake for no reason.	0	1	2	3
15. I cannot think clearly.	0	1	2	3
16. I feel worthless.	0	1	2	3
17. I have to think of special thoughts (like numbers or words) to stop bad things from happening.	0	1	2	3
18. I think about death.	0	1	2	3
19. I feel like I don't want to move.	0	1	2	3
20. I worry that I will suddenly get a scared feeling when there is nothing to be afraid of.	0	1	2	3
21. I am tired a lot.	0	1	2	3
22. I feel afraid that I will make a fool of myself in front of other people.	0	1	2	3
23. I have to do some things in just the right way to stop bad things from happening.	0	1	2	3
24. I feel restless.	0	1	2	3
25. I worry that something bad will happen to me.	0	1	2	3

Supplementary Table 3: Post-Concussion Symptoms Inventory Checklist

Headache	0	1	2	3	4	5	6
Nausea	0	1	2	3	4	5	6
Balance Problems	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Sensitivity to Light	0	1	2	3	4	5	6
Sensitivity to Noise	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervousness	0	1	2	3	4	5	6
Feeling More Emotional than Usual	0	1	2	3	4	5	6
Move Slower than Usual	0	1	2	3	4	5	6
Feeling Mentally “Foggy”	0	1	2	3	4	5	6
Difficulty Concentrating	0	1	2	3	4	5	6
Difficulty Remembering	0	1	2	3	4	5	6
Vision Problems	0	1	2	3	4	5	6
Confused	0	1	2	3	4	5	6
Move Clumsy	0	1	2	3	4	5	6
Answers Questions More Slowly Than Usual	0	1	2	3	4	5	6
In general, to what degree to you feel “differently” than normal for you?	No Difference				Major Difference		
	0	1	2	3	4		

Supplementary Table 4: Symptom Check-In Form

	Headache Mal de tête **(0-6)**	**Dizziness** Étourdissement **(0-6)**	**Fatigue** Fatigue **(0-6)**	**Concentration** Concentration **(0-6)**	**Irritability** Irritabilité **(0-6)**	**Total**
Baseline						
After EEG						
End of Session						