Evaluating EEG as a prognostic tool to predict persistent symptoms in adolescents with concussion

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ABSTRACT

Evaluating EEG as a prognostic tool to predict persistent symptoms in adolescents with concussion

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Approximately 30% of children with concussion experience persistent post-concussion symptoms (PPCS), but no accurate prognostic tools are available. Electroencephalography (EEG) identifies alterations in electrical activity post-concussion, but its prognostic capability is unknown. Our objective was to determine if EEG outperforms current prognostic tools in predicting PPCS at 1-month post-concussion. Thirty-four adolescents (12.9 ± 2.2 years, 20 males) with concussion were recruited. The treating physician predicted the likelihood of PPCS (0-100) at diagnosis in the emergency room. Participants completed a resting-state EEG and a brief clinical assessment battery 6.4 ± 2.4 days post-injury and the Post-Concussion Symptom Inventory (PCSI) 28.9 ± 1.9 days post-injury. PPCS (yes/no) was defined as an increase of ≥7 points on the PCSI compared to pre-injury symptom ratings. Twelve (35.3%) participants experienced PPCS at 1-month post-injury. Independent t-tests found that F3 delta power ($p=0.04$), F4 delta power ($p=0.1$), and F4 theta power ($p=0.07$) differed in adolescents with and without PPCS, which were combined into a multivariable model. Using inferential approaches, the EEG model had an AUC=0.71 (sensitivity=75%, specificity=68.2%) compared to the 5P Score (AUC=0.66, sensitivity=75%, specificity=45.9%) and physician prediction (AUC=0.55, sensitivity=71.4%, specificity=38.9%) models. However, these differences were not statistically significant ($p=0.60$ and $p=0.32$ respectively). The optimal machine learning model (SVM radial kernel, C=0.2) found that only the EEG performed significantly better than random chance in the training (72.9% accuracy, $p<0.001$) and validation set (62%, $p<0.001$). EEG features have potential as a prognostic biomarker of PPCS. Future studies should include larger samples and different EEG systems and features.

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LIST OF ABBREVIATIONS

AEC	Amplitude envelope correlation
AUC	Area under the curve
dPLI	Directed phase lag index
EEG	Electroencephalography
PCSI	Post-concussion symptom inventory
PED	Pediatric emergency department
PPCS	Persistent post-concussion symptoms
ROC	Receiver operating curve
wPLI	Weighted phase lag index

INTRODUCTION

Pediatric concussions have become more prevalent and pose a significant burden on the healthcare system.[1] In Quebec between 2010 and 2014, pediatric concussion diagnosis increased by 2.4-fold for children aged 9 to 12 and by 2.6-fold for children aged 13 to 17.[2] Concussion accounts for approximately 1 in 70 pediatric emergency department visits in Canada annually.[3] Children and youth are at a greater risk for traumatic brain injury because their brains are developing, leading to a slower healing process.[4] Most children recover from concussion within 1 month of injury, but there is a possibility that symptoms persist beyond this point.[5] Approximately 30% of children with concussion experience persistent post-concussive symptoms (PPCS) that last beyond the first month of injury.[1,6–8] Persisting symptoms can include physical disturbances, cognitive impairments, and behaviour changes.[3,8]

PPCS is associated with negative outcomes, including decreased academic performance and quality of life.[1,6,8] The presence of prolonged symptoms in children can lead to the abstention from academic and recreational activities.[3,8] Children suffering from PPCS present with lower quality of life in terms of physical health, emotional well-being, social interactions, and academic life for up to 12 weeks post-injury.[8] Evidence also shows that children who sustain a concussion are at an increased risk of obtaining subsequent brain injuries, leading to more severe cognitive dysfunction and neuropsychiatric problems.[3] The pediatric concussion epidemic highlights the need for proper concussion assessment tools, early concussion recognition, and individualized treatment to avoid the negative outcomes associated with persistent post-concussive symptoms.

Effective post-concussion treatments are available to children and may prevent the occurrence of PPCS when started early after concussion diagnosis. However, a lack of accurate prognostic tools makes it difficult to identify which children with concussion are most in need of early intervention. Physician prediction and the Predicting and Preventing Post-concussive Problems in Pediatrics (5P) Clinical Risk Score are existing methods used to predict PPCS in children. Physician prediction is often used to inform parents and children about the expected duration of their concussion symptoms.[3,7] The variation between individuals' concussion experience and the subjectivity of a physician's opinion makes it difficult for physicians to accurately predict each children's concussion recovery and the likelihood of developing persistent symptoms over time.[3] The 5P Clinical Risk Score is a prognostic tool that analyzes nine outcomes to acutely predict individuals at high-risk of experiencing PPCS.[5] The 5P Clinical Risk Score has been validated in children in a pediatric emergency department setting but relies on self-reported measures and has only moderate predictive power (area under the curve (AUC)=0.68).[5,7] Additionally, not all individual components of the 5P Clinical Risk Score are associated with developing persistent post-concussive symptoms.[5] The subjectivity and lack of accuracy with physician's judgment and the 5P Clinical Risk Score to predict persistent post-concussive symptoms suggest the need for improved methods for concussion prognosis.

Concussion is a complex pathophysiological process affecting the brain that results in alterations in brain function.[9] Electroencephalography (EEG) is a feasible, cost-friendly, and widely available brain monitoring tool that can identify alterations in brain function post-concussion, giving healthcare providers objective measures to support clinical decision making.[4,9,10] EEG is able to detect abnormalities in brain electrical activity in individuals previously sustaining a concussion beyond the point of full recovery of concussion symptoms, cognitive function, and postural stability.[4,9,10] EEG has potential to uncover a prognostic biomarker of persistent post-concussion symptoms, but is unexplored in children. The purpose of this study is to determine if objective, physiological EEG biomarkers will outperform existing clinical measures (5P Clinical Risk Score and physician prediction) in predicting PPCS in adolescents with acute

concussion. We hypothesize EEG biomarkers will perform significantly better than physician's prediction and the 5P Clinical Risk Score in predicting PPCS in adolescents with acute concussion. We predict that EEG features will show higher sensitivity, specificity, and AUC values than both the physician prediction and the 5P Clinical Risk Score.

LITERATURE REVIEW

General Concussion Background

Definition

There is no universally agreed upon definition of concussion, with various expert groups proposing options throughout the years.[11] This lack of consensus around a unified definition makes it difficult to consistently diagnose concussion and initiate proper management across clinical settings. This project will use the 2022 Concussion in Sport Group consensus statement definition of concussion, which encompasses various criteria and is a commonly used definition in research and clinical settings.[12] Concussion is therefore defined as a traumatic brain injury caused by a direct blow to the head or body in which biomechanical forces are transmitted to the head resulting in neuropathological changes in the brain.[12] These changes result in functional disturbances which present as clinical symptoms rather than structural changes seen through standard imaging tools.[12]

Physiology of Concussions

The idea of concussion being solely a functional injury has been challenged as advanced neuroimaging technology shows microscopic structural damages in the brain as well as other neurophysiological disruptions. These changes can broadly be captured as ionic imbalance, axonal damage, autonomic nervous system (ANS) dysfunction, and reduction in cerebral blood flow.

Ionic Imbalance

When a concussion occurs, there is a disruption in the integrity of the cell membrane.[13] Due to this disruption, potassium ions begin to flow out of the cell and sodium ions begin to flow into the cell leading to an interference with the cell's homeostasis.[13–15] This ionic imbalance overworks the ion pumps of the cell membrane in an effort to restore homeostasis.[14,15] These pumps require energy such as adenosine 5'-triphosphate (ATP) to function, which is quickly depleted as the pumps are overused. This lack of ATP puts the cell in a state of energy crisis.[13,15] There is also a simultaneous accumulation of calcium in the cell leading to mitochondrial dysfunction.[13–15] Since the mitochondria is responsible for generating ATP to supply the cell with energy, the mismatch between energy supply and demand within the cell worsens. This puts the cell in a vulnerable position making it susceptible to re-injury.[13–15]

Axonal Damage

Axons are stretched during the injurious event due to the biomechanical (e.g., shear) forces transmitted to the brain, which may also affect the integrity of the axon.[13,14] This leads to a disruption of neurotransmission in the brain as the damaged axons fail to fully transmit action potentials in milder cases, while, in severe cases, axons become completely disconnected and neurotransmission is completely abandoned.[13] Myelinated axons have greater protection from shear forces transmitted to the brain than unmyelinated axons.[15] In younger brains, more unmyelinated axons may be present as the brain is still developing compared to adults.[15] This makes children and youth more vulnerable to axonal injury during concussion, which may lead to greater impairment in function.[15]

Autonomic Nervous System Dysfunction

Autonomic nervous system (ANS) dysfunction is common after concussion, although the mechanisms by which ANS dysfunction occurs are unclear.[16,17] Some authors suggest that the two branches (sympathetic nervous system and parasympathetic nervous system) of the ANS are vulnerable to injury through cervical spine whiplash or strains, leading to an imbalance between the two branches. Emotional distress has shown to be correlated to ANS dysfunction, as individuals with concussion reporting higher anxiety levels display higher ANS dysfunction.[17] The overstimulation of the sympathetic

nervous system may also contribute to higher anxiety levels.[17] The ANS is also responsible for regulating cerebral blood flow through (1) the baroreflex, a feedback look maintaining blood flow to the brain, and (2) its innervation of cerebral blood vessels.

Reduction in Cerebral Blood Flow

After a concussion occurs, the baroreflex, controlled by the ANS, is dysfunctional as there is a decrease in the brain's ability to respond to shifts in arterial carbon dioxide leading to a reduction of cerebral blood flow.[14,17] Smooth muscle responsiveness is decreased after trauma occurs to the brain resulting in impaired vasoreactivity of the blood vessels supplying the blood to the brain, ultimately altering normal cerebral blood flow.[14] Cerebral blood flow abnormalities may persist for weeks to months post-injury in individuals with concussion.[17]

Pediatric Concussions

Prevalence

Pediatric concussions have become more prevalent and pose a significant burden on the healthcare system. Concussions account for nearly 1 in 70 pediatric emergency department visits in Canada annually.[3] Between 2011 and 2017, brain injuries made up approximately 80% of all pediatric emergency department head injury visits from sport and recreation in Canada.[18] Specifically between 2016 and 2017, the National Ambulatory Care Reporting system reported 46,000 concussion diagnoses in children aged 5 to 19 in hospitals across Canada.[18] In Quebec between 2010 and 2014, pediatric concussion diagnosis by a physician increased by 2.4-fold for children aged 9 to 12 and by 2.6-fold for children aged 13 to 17.[2] Pediatric concussions are affecting Canadians, especially in the province of Quebec, in large numbers, but the prevalence may still be underestimated. Incidence of pediatric concussion is often measured through emergency department visits, although many children seek care in different settings (such as their pediatrician's office or in other clinical settings) or do not seek care at all.[19,20] Many pediatric concussions often go unreported due to lack of symptom reporting (e.g. not wanting to be pulled from a game), individuals believing their injury isn't serious enough to require medical attention, or lack of realization due to inadequate concussion education.[20]

Predisposing Factors

In addition to increased risk for sustaining a concussion due to on-going brain development,[15,21] children typically have larger heads relative to their bodies. This results in weaker neck musculature and makes children more vulnerable to injury.[22] There are specific intrinsic and extrinsic factors that further put certain children at higher risk of concussion. Intrinsic factors include (1) anatomical properties and (2) sex. Anatomical properties that increase concussion risk in children include greater skull thickness, more cerebrospinal fluid and limited cervical spine strength, range of motion and flexibility.[22] In terms of sex, girls tend to have higher concussion rates than boys,[22,23] similar to the adult population, and weaker neck musculature leading to less protection from concussion forces.[22] Extrinsic factors include previous head injuries; prior concussion puts children at greater risk of having a subsequent injury.[22]

Mechanisms of Injury

Children younger than 5 years old are more likely to receive a concussion from a fall related incident. Fall-related incidences include falling on the floor, falling down the stairs, and falling out of beds, chairs, or couches.[24] The proportion of concussions caused by falls begins to decrease after the age of 5, where mechanisms such as being struck by a person or object become more prevalent.[25] Children passed the age of 5 are three times more likely to sustain a concussion from sport, especially once the children reach 10 years old which is roughly the time when participation in organized sport begins.[25] Approximately 70% of all pediatric concussions are due to sport-related incidences, with football and

cycling being the team sport and individual sport most responsible for concussion respectively.[24,25] Other mechanisms of injury affecting mainly older children include motor vehicle collisions and assault.[24,25]

Current Clinical Diagnosis and Management for Pediatric Concussions

Pediatric Concussion Assessment

Concussion diagnosis currently relies heavily on the patient's willingness to report their symptoms, as many objective tools do not show macroscopic structural damage post-concussion.[26] Thus, clinical tools have been developed to aid in the diagnosis and management of concussion in children although no gold standard has been clearly identified due to the multifactorial nature of injury.[26] These clinical tools have been categorized as (1) screening tests, (2) confirmatory tests, and (3) objective examinations.[26] Screening tests are used to acutely identify concussion immediately after injury occurs when individuals may be in a pre-symptomatic or mild symptom stage and the occurrence of a concussion is unclear.[27] Confirmatory tests are used to diagnose the concussion while identifying specific functional deficits the individual is experiencing post-injury. Objective examinations, less commonly used in concussion assessment, are tools used to identify the presence of concussion and its deficits that are not subject to intentional participant manipulation. Broadly, these clinical assessment tools assess the domains of self-reported symptoms, cognition/mental status, balance, and vestibular/ocular functioning.

There are a wide variety of concussion assessment tools that exist due to the multifaceted nature of concussion. Concussion assessment tools include: (1) checklists designed to evaluate the presence of concussion symptoms as seen in **Table 1**, (2) the Standardized Assessment of Concussion (SAC) designed to evaluate the mental status of an athlete after head trauma, (3) the Balance Error Scoring system (BESS) designed to assess static balance, (4) the Sport Concussion Assessment Tool (SCAT5) designed to determine the presence of a concussion immediately after injury, (5) the King-Devick designed to evaluate saccadic eye movement, (6) the Vestibular Oculomotor Screening (VOMS) developed to determine the presence of oculomotor dysfunction after injury, (7) the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) developed to assess neurocognitive function, and many more.

These concussion assessment tools were originally designed for the adults, but three of them have been modified for children including: (1) the Standardized Assessment for Concussion – Child Version (SAC-C), (2) the Child Sport Concussion Assessment Tool (ChildSCAT), and (3) the Child Immediate Post-Concussion Assessment and Cognitive Testing (cImPACT). Validity and reliability testing of the present concussion assessment tools in children is limited. The SAC shows moderate test re-test reliability of 0.69 in youth 11 to 13 years old, although reliability was not tested on children of other ages and reliability of the SAC-C was not determined.[28] The BESS has an intra-rater reliability from 0.60 to 0.98 and an inter-rater reliability from 0.73 to 0.94 in developing children, although the BESS does not take into account that the balance abilities of the children may be affected by their growth spurts.[29] The SCAT5 and ChildSCAT5 has shown high validity immediately after concussion but this validity begins to decrease 3 to 5 days post-injury.[30] Although the King-Devick has shown high test re-test reliability of 0.90 in high school athletes, it has a high false positive rate with a specificity of 36% and it's accuracy begins to decrease 48 hours after injury.[31] The VOMS has shown to provoke symptoms in both non-concussed children (3-20%) and in concussed children (13-30%) aged 5-9 years old, making researchers question its appropriateness for use in children.[31] Preliminary evidence does support the use of the cImPACT in the assessment of speed and memory in children, although invalid performance may be as common as 35-55%.[32,33] Most adult concussion assessment tools have attempted validation in children, but the results vary between tests. Many of the reliability and validity studies in children look at specific age groups (e.g., 5-9, 11-13, or high school athletes), without broadly including children under the age of 18.

Pediatric Concussion Treatments

Concussion is a highly heterogeneous injury.[34] Each individual may present with different symptoms and deficits, making it difficult to identify a single rehabilitation strategy that will be effective for all concussion patients.[34] Specific interventions targeting each individual deficiency are necessary for optimal recovery, and typically include (1) aerobic exercise, (2) vestibular rehabilitation, (3) oculomotor rehabilitation, and/or (4) cervicogenic therapy.[34] Traditional concussion management advocated for physical and cognitive rest for an extended period of time as the ideal treatment for children but newer evidence shows that prolonged, unnecessary rest may be detrimental to recovery.[35–37] Light aerobic exercise is now suggested as soon as tolerated following an acute concussion with physical activity being an effective method to improve symptoms, cognitive function, and overall brain health in children.[35–37] Physical activity may improve recovery time in children with concussion through its contribution to neuroplasticity and improving cerebral blood flow, which is often diminished in children with concussion and persistent post-concussive symptoms.[38] Youth aged 5 to 17 years old prescribed aerobic exercise within 7 days of injury were more likely to recover within 1-month, and this treatment decreased the likelihood of developing persistent post-concussive symptoms by 48%.[36,39]

Common post-concussion vestibular impairments include benign paroxysmal positional vertigo, vestibular-ocular reflex impairment, visual motion sensitivity, and impaired postural control.[34] Targeted treatments include repositioning maneuvers designed to displace the inner ear crystals out of the semicircular canals,[40] gaze stability training,[41] exposing the patient to visually stimulating environments to allow their nervous system to adapt to the information around their body,[42] and static and dynamic balance training paired with sensory challenges.[43] Children with persistent dizziness and balance impairments benefit from individualized vestibular therapy as it demonstrates a reduction of symptoms and an improvement in vestibular-oculomotor performance.[44,45] Oculomotor disturbances post-concussion may include fixation, convergence, and accommodative insufficiency, sensitivity to light, visual field disruption, and impaired eye movements.[46] Oculomotor rehabilitation involves the use of eye patches, penlights, mirrors, lenses, and other tools with exercises to improve eye muscle strength and open up the visual field.[46] Visual therapy has shown to be over 90% effective in improving oculomotor performance in children, suggesting the presence of visual system plasticity which may ultimately facilitate progress in other domains of concussion rehabilitation.[47] Mechanisms of injury that cause concussions include whiplash, which directly affects the cervical spine.[48] It is common for cervical spine dysfunction to be related to other visual and vestibular deficiencies after concussion, making it can important part of the rehabilitation process.[48] Rehabilitation strategies for the cervical spine include a combination of manual therapy (e.g. mobilizations and massage) and therapeutic exercise to train cervical proprioception and motor control (e.g. endurance of deep cervical musculature).[48,49] Cervical spine therapy has shown to help pediatric patients return to sport sooner, and has been effective at reducing cervicogenic dizziness and headache.[49]

Unique Clinical Challenges for Pediatric Concussion Diagnosis and Management

There are many challenges when it comes to the assessment and management of pediatric concussion, as research has only recently begun investigating pediatric specific populations.[50] Even still, the existing pediatric concussion literature mainly focuses on high-school aged athletes, neglecting younger children and non-athlete populations.[50] This leaves clinicians using guidelines and recommendations based on adult and/or athletic populations,[50] and no differentiation between pre-adolescent, adolescent, and high-school aged children exists.[51] Many assessment tools and rehabilitation strategies have not been validated in the pediatric population but continue to be used in this population;[50,52] thus, they may not be effective or developmentally appropriate for younger cohorts.[50] Other challenges in the pediatric population include the difficulty to highlight the importance of treatment adherence and the underreporting of symptoms due to their desire to continuing play their sport even when injured.[50,52] It is

clear that more accurate and objective measures are needed for pediatric concussion assessment and management.

Persistent Post-Concussive Symptoms in Children

Definition and Prevalence

Most children with concussion fully recover within 1 month of injury.[53,54] However, approximately 30% of children with concussion and nearly half of all adolescents experience persistent post-concussive symptoms (PPCS) lasting beyond the first month of injury.[1,55–57] No true gold standard exists for classifying PPCS.[58] There is a lack of consistency in defining PPCS, which include the presence of various symptoms (number or type) and post-injury time points (e.g., 1-month, 3-months, etc.).[58] A common definition used in previous studies[5,7] is from the International Statistical Classification of Diseases and Related Health Problems which defines PPCS as three new or worsening concussion symptoms (relative to retrospective recall of pre-injury symptoms) at 1-month following injury.[59] However, it has been suggested that this definition of PPCS leads to the misclassification and overestimation of children developing PPCS,[58] as symptom ratings are subjective and many concussion-like symptoms are nonspecific.[60] To combat these issues, reliable change methods are emerging as the preferred method of classifying PPCS.[58] Brooks et al. classified PPCS as an increase of $\geq$7 points on the Post-Concussion Symptom Inventory (PCSI) post-injury score compared to retrospective recall of pre-injury symptoms 1-month following injury.[61] This cut-off score of 7 points is based on a reliable change method calculated using healthy children aged 13.9 $\pm$ 2.1[61] and Jacobson and Truax's clinical significance approach.[62] Our study administers the same symptom questions as Brooks et al. and will thus use their reliable change based definition of PPCS ($\geq$7 point change) to minimize the potential for overestimating PPCS in our sample.[61]

Predisposing Factors for PPCS in Children

Children with premorbid conditions such as learning disabilities, anxiety, depression, sleep problems, migraine disorders, or prior history of concussion are more likely to experience PPCS following concussion.[6] Children with a pre-existing anxiety disorder diagnosis prior to concussion are shown to require a longer amount of time for symptom resolution (median: 86 vs. 36 days) and take longer to return to school (median: 83 vs. 46 days) and physical activity (median: 90 vs. 47 days) compared to children without anxiety disorders.[53] Individuals with anxiety disorders experience heightened anxiety after injury, increasing post-concussion symptoms and ultimately extending recovery.[53] History of migraine disorders and prior history of concussion have also been shown to increase time to return to play by 10.7 days and 3.7 days respectively.[63]

Sex and age are also related to PPCS risk in children. Female children are predisposed to developing PPCS compared to male children,[1] a finding also replicated in the adult concussion literature.[64,65] Girls have longer recovery periods, requiring up to 12 weeks for full recovery.[66] There are several factors that may explain sex differences in both pediatric and adult populations. Societal norms may play a role in prolonged recovery in females, as females are more likely to admit vulnerability than males and are therefore more likely to report their symptoms.[1,66] Females are affected by anxiety and depression at a higher rate, which could exacerbate concussion symptoms as previously mentioned and lead to prolonged recovery.[53] Anatomical differences such as sex hormones and neck musculature may also play a role in explaining sex-based differences in PPCS prevalence.[1] Females show greater head-neck segment peak acceleration and displacement, with 43% less head-neck segment mass, 30% less neck girth, and 49% less isometric muscle strength than males.[67] With concussion being directly related to the amount of head acceleration, females therefore have less protection to combat the acceleration forces.[67] Older children may be more vulnerable to developing PPCS than younger children.[1] Older children are more

likely to sustain a concussion through more severe mechanisms of injury such as motor vehicle collisions, assaults, or collision sports, resulting in more post-injury deficits and leading to prolonged recovery.[25] Anxiety prevalence also increases in children aged 13 to 17 years old,[53] so older children are also more likely to have pre-existing mental health problems.

Negative Outcomes Associated with PPCS

Children experiencing PPCS not only have sustained post-injury symptoms, but can also experience continued decreases in cognitive function and negative behaviour changes.[68] Greater symptom burden is associated with negative physical and psychosocial quality of life at 1-month post-concussion.[69] Children with PPCS report lower quality of life for at least 12 weeks post-injury, related to poorer physical, emotional, social, and academic functioning.[8] Children with PPCS experience difficulties in school including diminished academic skills compared to pre-injury abilities, and these complaints may persist even after full clinical recovery.[8] A significant decline in grades has been associated with greater symptom severity.[70] PPCS also has a negative effect on social interaction, an important part of children's lives. Children with PPCS presenting with both cognitive decline and somatic (e.g. headaches, dizziness, nausea) symptoms are unable to participate in social activities leading to mood changes which may affect their developmental process.[71] Sustaining a concussion as a child has been associated with negative outcomes as an adult. Individuals exposed to concussion as a child were at an 18% to 52% increased risk of disability pension, psychiatric visits, inpatient hospitalisation, premature mortality, low educational attainment, and welfare recipiency compared to their uninjured siblings.[72,73] Thus, PPCS can not only have short-term repercussions on the child's developmental process but can have negative outcomes leading into adulthood.

Prognostic Tools for PPCS

There are currently two prognostic tools commonly used to predict recovery in children with concussion. Such prognostic tools are beneficial as they provide healthcare providers with information on which children are more at risk of prolonged recovery. Treatments can then be prioritized to the children most at risk to prevent PPCS and the associated negative outcomes. The common prognostic tools for PPCS are: (1) The Predicting and Preventing Post-concussive Problems in Pediatrics (5P) Clinical Risk Score and (2) physician prediction.

Predicting and Preventing Post-concussive Problems in Pediatrics Clinical Risk Score

The Predicting and Preventing Post-concussive Problems in Pediatrics (5P) Clinical Risk Score is comprised of nine patient characteristics and clinical outcomes to determine PPCS risk in children and youth with acute concussion.[3] These nine outcomes include (1) age, (2) sex, (3) concussion history and symptom duration, (4) migraine diagnosis, (5) BESS tandem stance, (6) headache, (7) sensitivity to noise, (8) fatigue, and (9) feeling slowed down.[3] Each of the nine clinical outcomes is assigned a score.[3] The total score is calculated by adding the components for all nine items together. This total score can be broken down to classify children as low ($\leq$ 3 points), medium (4-8 points), or high-risk ($\geq$ 9 points) of developing PPCS.[3] The 5P Clinical Risk Score has been validated for use in the emergency department to predict PPCS risk within 48 hours of concussion. However, it shows a moderate area under the curve (AUC) of 0.68 and is, at least in part, subjective in nature (e.g. relying on symptom reporting).[7] The 5P Clinical Risk Score has also been validated for clinical use to predict PPCS risk within 10 days of concussion showing an AUC of 0.75 but evidence shows each individual component of the 5P Clinical Risk Score is not independently associated with PPCS risk due to the multifaceted nature of concussion.[5]

Physician Prediction

Children with concussion often visit a physician for injury diagnosis. Physicians obtain a medical history, complete a physical examination, and combine this information with clinical assessments (described above) and their professional experience to diagnose the child with a concussion.[74] Physicians are also responsible for providing the children and their parents with the necessary concussion education to facilitate recovery.[74–76] The majority (90%) of Canadian health care providers are able to properly diagnose pediatric concussions.[76] A small percentage (18%) of Canadian health care providers refer their patients to concussion specialists.[76] In addition to diagnosis, physicians can use their expertise and experience to predict PPCS, as healthcare providers often provide children and their parents with a predicted recovery timeline for the concussion.[7] However, physician prediction of PPCS has shown a weak AUC of 0.55, indicating poor ability in predicting PPCS risk.[7]

Both the 5P Clinical Risk Score and Physician Prediction have been used to predict PPCS risk in children. The subjective nature of these two methods and their overall poor-to-moderate sensitivity indicates the need for an alternative prognostic tool to more accurately and objectively predict PPCS in children. This information will aid in identifying the children most likely to develop PPCS, which can help clinicians prioritize resources and treatment services to patients who are most in need of early intervention.

Electroencephalography

General Background

Electroencephalography (EEG) is a non-invasive tool that measures brain function and is commonly used in both clinical and research settings.[77] Electrodes placed on the surface of the scalp record the electrical activity of the brain, generating an EEG signal.[78,79] Given the size of EEG electrodes and their placement on the scalp, EEG cannot capture the individual electrical activity of a single neuron; instead, EEG captures the collective electrical activity emitted by hundreds of thousands of neurons.[78] EEG oscillations demonstrate the summation of excitatory and inhibitory post-synaptic potentials in these large groups of neurons captured during recording.[78,79] EEG waveforms display the difference in voltage between an active electrode and a pre-determined reference electrode.[78] EEG biomarkers help health care providers with the diagnosis and classification of a wide variety of neurological disorders, including epilepsy, Alzheimer's and Parkinson's disease.[80] However, this tool is underutilized in pediatric concussion.

EEG and Post-Concussion Physiology

Microscopic damage of neurons has been captured and related to brain behaviour through EEG patterns.[81] Changes in synaptic neurotransmission have been detected using EEG in various conditions such as post anoxic encephalopathy, metabolic encephalopathies, nervous system dysfunctions, and acute strokes.[81] EEG can detect the speed of ANS response to an emotional stimulus[82] and detect an increase in sympathetic nervous system activity during video game play (associated with an increase in heart rate).[83] Electrical activity of the brain captured by EEG has also shown to provide information about cerebral blood flow, specifically in the slower wave frequency bands.[84] Cerebral blood flow has been studied using EEG in the adult population in individuals with cerebrovascular disorders, brain tumours, coma, and metabolic disorders.[84] Thus, there is potential for EEG to detect axonal damage and ionic imbalance post-concussion.[85]

Outcome Measures and Analysis

Removing Noise/Signal Processing

EEG recordings are subject to inevitable contamination. Biological and non-biological artifacts may contaminate the EEG signals, which must be detected and removed prior to extracting features (e.g., outcomes) from the EEG signal. Potential biological artifacts include: (1) facial muscle activities, (2) voluntary or involuntary eye movement, and (3) vascular activity.[78] Non-biological artifacts that may contaminate the EEG signal include: (1) external electrical noise (e.g. power lines, electric lights, or computers), (2) poor subject grounding, (3) poor electrode contact to the scalp, and (4) cable movement.[78] Ideally when EEG is recorded, the evaluator is in a room with the equipment and the subject is in a separate room which is electrically shielded and soundproof to minimize potential artifacts.[78] However, as this is often not feasible, there are other techniques for removing artifacts which include: 1) filtering, in which artifact activity outside the frequency range of interest is removed,[78] 2) Independent Component Analysis to remove repetitive noise in the signal, particularly ocular artifacts (i.e. eye blinks),[78] 3) bad channel rejection, in which an entire EEG channel is removed, and 4) manual artifact rejection in which snippets of noisy sections of the signal across all channels are removed.[78]

Frequency Bands

EEG frequency bands include: (1) delta waves, (2) theta waves, (3) alpha waves, (4) beta waves, and (5) gamma waves.[78] Delta waves range from 1-4 Hz, characterized as very low-frequency activity.[78] Delta waves have been associated with deep sleep in healthy humans and neural states such as loss of consciousness or coma.[78] The amplitude of the delta waves is between 20 and 200 μV.[78] Theta waves range from 4-8 Hz, characterized as low-frequency activity.[78] Theta waves have been associated with certain sleep states, mediation, and drowsiness.[78] The amplitude of the theta waves is between 8 and 10 μV.[78] Alpha waves range between 8-13 Hz, characterized as medium-frequency activity.[78] Alpha waves have been associated with states of relaxed wakefulness in healthy adults and information processing.[78] The amplitude of alpha waves is between 20 and 200 μV.[78] Beta waves range between 13-25 Hz, characterized as high-frequency activity.[78] Beta waves have been associated with concentration and task management, and feelings such as anxiety and excitement.[78] The amplitude of beta waves is between 5 and 10 μV.[78] Gamma waves range between 25-200 Hz, characterized by very high-frequency activity.[78] Gamma waves are associated with arousal and perception.[78] The amplitude of the gamma waves is between 1 and 2 μV.[78] Our study will not incorporate the gamma wave frequency band because (1) muscle activity (~20-300Hz) overlaps entirely with the gamma band, increasing the potential for contamination in this frequency range,[86] and (2) lower frequency bands are typically associated with concussion while the gamma frequency band is associated with psychiatric illnesses such as schizophrenia or Alzheimer's disease.[87,88]

Spectral Features

Spectral features characterize the oscillatory properties of the EEG signal.[78] Spectral features include: (1) spectral power and (2) peak frequency. Spectral power is a measure of the power of the EEG signal. Peak frequency is frequency (in Hz) the where the most power (i.e., highest point on the power spectrum) can be found in the EEG signal.[78]

Permutation Entropy

Permutation entropy processes the information of the EEG signal, identifying the regularity or complexity of each individual signal.[89] The smaller the permutation entropy, the more regular the signal, while a permutation entropy closer to 1 suggests a noisy and random signal.[90]

Functional Connectivity

Functional connectivity demonstrates the statistical dependence of physiological signals from distinct brain regions by correlating data across recording sites.[91] Functional connectivity between electrodes can be estimated using several approaches, but this project will focus on: (1) weighted phase lag index (wPLI), (2) amplitude envelope correlation, and (3) directed phase lag index (dPLI). Weighted phase lag index measures the consistency of one electrode phase leading or lagging compared to another electrode.[92] Once the phase difference is calculated between each electrode, it is weighted by the magnitude of the imaginary component of the cross-spectrum.[92] Weighted phase lag index values range between 0 and 1, with 1 indicating a perfect functional relationship.[92] To determine the direction of the phase lead/lag relationships between electrode pairs, the directed phase lag index can be computed.[93] The dPLI also ranges between 0 and 1, where dPLI values between 0.5 - 1 indicates that electrode 1 leads electrode 2, 0 - 0.5 indicates that electrode 2 leads electrode 1, and dPLI = 0.5 indicates no consistent phase lead/lag relationship. Amplitude envelope correlation measures how the envelope of one signal (e.g., electrode) is correlated to the envelope of a second signal.[94] Envelopes are obtained through Hilbert transformations, with Pearson correlations determining the statistical dependence between the envelope signals of electrode pairs.[94] Similar to wPLI, AEC values range between 0 and 1, with 1 indicating a perfect functional relationship.[92]

Graph Theory

Graph theory synthesizes the brain's structural or functional connections on the network-level using nodes (voxels or electrodes) linked by edges (functional or structural connections).[91] Graph theory is described by a number of different measures including: (1) path length, (2) global efficiency, (3) clustering coefficient, (4) small-worldness, (5) modularity, (6) node strength, and (7) betweenness centrality. Path length is the minimum number of edges that connect one node to another.[91] Global efficiency is inversely related to the path length, measuring the efficiency of information exchange between nodes.[91] Shorter path length between nodes increases the global efficiency of information transfer from one node to another.[91] Clustering coefficient quantifies the connections between a node and its neighbouring connections, which is referred to as a cluster.[91] High clustering coefficient is associated with high efficiency of information transfer.[91] Small-worldness is the ratio of clustering coefficient to path length; high clustering and smaller path lengths indicate more small-worldness and effective short- and long-distance neural communication.[91] Modularity measures the strength of the connection between different modules within complex brain networks.[91] The node strength measures the number of connections that connect a single node to all other nodes in the network.[91] Betweenness centrality measures the influence of an electrode on the flow of information in the network.[95]

EEG Findings in Patients with Concussion

Alterations in brain function persist beyond clinical recovery of concussion, making EEG a relevant tool to detect abnormalities in patients with concussion at various timepoints post-injury.[9] EEG shows a 96.2% sensitivity and a 90.5% specificity in separating patients with concussion with healthy controls.[96] EEG also shows a high validity and high test-retest reliability (between 0.78 and 0.92) in when applied to individuals with concussion.[97] When a concussion occurs, EEG activity shows an initial increase in electrical brain activity followed by a general decrease in cortical activity.[98] Changes in frequency bands immediately after injury include a (1) decrease in alpha and beta frequency, (2) an increase in theta and delta activity, and (3) and increase in theta to alpha frequency ratio.[4,99–102] The increase in delta frequency activity may be associated with learning problems and cognitive dysfunction. Increased theta oscillations are typically found in individuals with higher anxiety levels, decreased mood, decreased sleep quality, and decreased concentration, ultimately negatively affecting reaction time.[103] The

decrease in alpha and beta frequency may be associated with reduced cortical excitability, difficulty concentrating, and cognitive dysfunction.[4]

It remains unknown exactly how long EEG abnormalities persist after concussion, as various studies look at different timepoints. Generalized slowing of the brain, decreased alpha frequency band and increased delta frequency are present immediately after injury[100] and may persist for 6 months to a year post-injury.[104] The majority (90%) of EEG changes resolve within a year of concussion.[104] Persistent EEG slowing, higher power in the delta frequency band, and lower power in the alpha frequency band have been found in adults with persisting concussion symptoms.[105] EEG slowing in adults with persisting symptoms is predominantly in the left temporal regions of the brain.[105] Other EEG abnormalities from concussion include changes in connectivity between brain regions and neuronal dysfunction.[9] Male adolescent athletes (n=9) with sports-related concussion show increased connectivity in the right prefrontal cortex, suggesting compensation occurring in the brain after injury.[106] The same population showed a decreased connectivity in the parieto-occipital regions, which has been hypothesized to be associated with a higher number of symptoms.[106] EEG has shown a decrease in signal transmission between the frontal and frontal-temporal regions of the brain in concussed individuals,[96] as well as a decrease in alpha and beta power differences between the anterior and posterior cortical regions.[96] EEG abnormalities to frontal regions have been hypothesized to be related to microscopic axonal damage while changes in posterior cortical regions have been hypothesized to relate to posterior cervicogenic injury.[96] EEG analysis shows that individuals with concussion demonstrate persistent changes in brain function despite being asymptomatic.[4,9]

Limitations in EEG Research in Patients with Concussion

Although EEG research has identified many significant alterations in brain function after concussion, there are many common limitations to note. One major limitation is that use of EEG for concussion has only been validated in a research setting run by trained experts in a controlled environment.[107,108] EEG is often used in a clinical setting for moderate to severe traumatic brain injury, but the use of EEG in a clinical or athletic setting for patients with concussion has not been studied.[108] In terms of the population, there is little research done on the brain electrical activity in children and adolescents with concussion.[107,108] Limited research on young populations leaves researchers assuming the changes in electrical activity of a young brain are the same as an adult brain, which may be incorrect as concussions affect pediatric and adult populations differently. EEG features extracted and analysed differ between studies making it difficult to identify which features may provide a biomarker of concussion.[108–110] The most common EEG feature analysed are the spectral features, specifically spectral power.[108,109] Neglecting other EEG features or not extensively studying certain EEG features may result in missing out on a potential biomarker for concussion. When reporting EEG procedures and analyses, insufficient details are often provided making it difficult to reproduce the study methods. With various ways of completing EEG analyses, the best method has yet to be determined.[108,110] Other limitations include limited evidence connecting EEG findings with the neurophysiology of concussion and functional status in patients, studies merging EEG findings of all traumatic brain injuries from mild to severe, and inconsistency in the time points when EEG is recorded post-concussion (e.g. varying from a few days post-injury up to 7 years post-injury).[107] Our study will fill certain gaps in the EEG literature by (1) focusing on the brain's electrical activity in the pediatric population post-concussion and (2) by extracting a variety of EEG features to determine the best prognostic biomarker of PPCS.

Benefits of EEG

EEG has the ability to capture the neurophysiology of the brain in a non-invasive manner, and can detect changes in brain function that are not visible on other brain imaging tools such as computed

tomographic scan and magnetic resonance imaging.[78] EEG has excellent temporal resolution, meaning it has the ability to measure the timing (within milliseconds) of the neuronal activity of the brain, and it is a relatively cost friendly brain imaging tool.[78] Simple EEG systems with fewer electrodes may cost around $99 - $1,000 USD.[78] Although more complex EEG systems may cost anywhere $50,000 - $100,000 USD, it remains less expensive than a magnetic resonance imaging machine which can cost up to $3,000,000 USD.[78] EEG is a feasible tool and can be portable. Select wearable systems take around 10-15 minutes to set-up, record the signal, and disassemble making it a valuable tool for research and showing potential for clinical use.[78,80] These benefits of EEG make it a valuable assessment tool and show its potential to uncover a prognostic biomarker of concussion.

METHODS

Study Design and Participants

This study was a prospective longitudinal cohort design. Participants were recruited through the Montreal Children's Hospital Pediatric Emergency Department (PED). Adolescents aged 10 to 17 that were diagnosed with a concussion by a physician in the PED and speak English or French were included in the study. Participants were excluded if they had (1) lingering symptoms from a previous unresolved concussion, (2) any impairments that would prevent the completion of study assessments (e.g. lower extremity injury affecting balance), (3) diagnosed medical disorders or medication use that may affect EEG biomarkers, or (4) if they were experiencing more severe forms of brain injury such as moderate-to-severe traumatic brain injury, brain bleeds, or skull fractures. Parent consent and child assent were obtained prior to data collection. This study was approved by the McGill University Health Centre Pediatrics Research Ethics Board (#2020-6435) and the Concordia University Research Ethics Board (#30017577).

Data Collection Procedure

Upon initial presentation to the PED, the diagnosis of concussion was confirmed, and the treating physician provided a prediction of the child's likelihood of experiencing PPCS at 1-month post-injury. Participants returned to the hospital within 10 days of injury to complete a (1) demographic questionnaire, (2) clinical assessments (including the BESS and the Post-Concussion Symptom Inventory (PCSI) symptom checklist) to determine the 5P Clinical Risk Score, and a (3) resting-state EEG. A brief symptom check-in (headache, dizziness, fatigue, trouble concentrating, and irritability on a 0-6 scale) were tracked at baseline (beginning of data collection session), post-EEG assessment, and the end of the study visit. If the total symptom number and severity of symptoms endorsed increased by 6 or more points, participants were also given a brief rest period (up to 5 minutes). If symptoms did not improve after 5 minutes, the session was terminated. **Figure 2** depicts the methods and the study assessment forms can be found in the **Appendix**.

Children with concussion returned to the hospital 1-month post-injury and were re-assessed on the PCSI to determine if PPCS is present. Children were also re-administered the resting-state EEG and clinical assessment battery as part of a larger study, but those findings are not reported throughout this document. Only the resting-state EEG from the ≤10day hospital visit and symptom checklist from the 1-month hospital visit (to determine whether the study definition of PPCS is met) were analyzed in this thesis.

Electroencephalography (EEG) Procedures

A resting-state EEG using a dry, 19-channel EEG headset (DSI-24, Wearable Sensing, **Figure 1**) was completed to record the neuroelectric activity of participants.[111] Resting-state EEG was recorded during eyes-opened and eyes-closed seated conditions, with each condition lasting for 5 minutes. Data was recorded at 300 Hz and impedance was set to 1 MΩ as per manufacturer recommendations. The Pz electrode was set as the reference during recording.

EEG Processing: The resting-state EEG signal was filtered between 0.5-50 Hz to remove low and high-frequency noise and then re-referenced to A1 & A2 electrodes. Eyes-opened and eyes-closed EEG signal were epoched (i.e., split) into separate files. Bad channels (if present) were removed if excessive noise was identified within that channel throughout the entire recording. An Independent Component Analysis was completed to remove repetitive noise (e.g. eye movement, blinking, pulse) that periodically appeared throughout the signal without segmenting the data. Data were visually inspected, and any

remaining artifacts were removed by manual rejection. EEG processing was completed using the EEGlab toolbox in MATLAB.[112]

EEG Feature Extraction: The clean EEG signal was epoched into 10-second windows and windows were moved using 10-second (i.e. non-overlapping) step sizes. EEG features were extracted from each 10-second window, including: 1) spectral features: spectral power and peak frequency, 2) entropy-based features: normalized permutation entropy, 3) functional connectivity features: weighted phase lag index (undirected), amplitude envelope correlation (undirected), and directed phase lag index (directed), and 4) graph theory features: path length, global efficiency, clustering coefficient, small-worldness, modularity, and node strength (see **Table 2** for descriptions). Each feature was calculated at delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz) frequency bands. Features were extracted using code from the Brain Connectivity Toolbox or custom MATLAB scripts.[112]

Clinical Outcome Measures

Presence of Persistent Post-Concussive Symptoms

The Post-Concussion Symptom Inventory (PCSI) is a self-reported symptom checklist with moderate-to-high inter-rater reliability and validity. The PCSI includes 20 concussion symptoms (see **Figure 2**) in cognitive, emotional, sleep, and physical domains. Each symptom is rated on a scale from 0 (not present) to 6 (severe), with a maximum score of 120. The PCSI was used to determine PPCS status, which was defined as an increase of $\geq$7 points on the PCSI post-injury score compared to retrospective recall of pre-injury symptoms at one-month following injury.[61] The definition was based on reliable change and suggests a clinically meaningful difference.[61]

The Predicting and Preventing Post-concussive Problems in Pediatrics (5P) Clinical Risk Score

The 5P Clinical Risk Score is a tool to predict PPCS in children and youth with acute concussion.[7] The nine outcomes used to calculate the score include demographic (age, sex, concussion history, migraine diagnosis), Balance Error Scoring System (tandem stance), and PCSI symptom checklist (headache, sensitivity to noise, fatigue, and feeling slowed down) outcomes.[5] **Table 3** describes the clinical assessments and scoring system for the 5P Clinical Risk Score. This study analyzed the total score (0-12), which higher scores suggesting an increased risk for PPCS.

Physician Prediction

The physician responsible for diagnosing the child with a concussion rated the likelihood the child would go on to experience PPCS. Physicians were asked: "Please rate the likelihood this patient will still be experiencing symptoms at 4-weeks post-injury from 0 (completely confident the patient will be asymptomatic) to 100 (completely confident the patient will remain symptomatic)." The rating was based solely on the physician's judgement of the patient's clinical presentation, with no prompts or information provided to assist the physician's prediction.

Statistical Analysis

This is a novel study that explored many potential EEG outcomes of interest, as no previous studies have ever identified EEG features that are related to PPCS. Due to our modest sample size, we made an a priori decision to reduce the number of EEG features of interest to improve our statistical power. Preliminary (unpublished) data from within our laboratory identified 19 key EEG features (see **Table 4**) that can accurately separate children with concussion from healthy controls. Only these 19 key EEG features were analyzed, while remaining features will be explored in future projects. As some research suggests that machine learning models performing superiorly to inferential statistics approaches,[113] and

given the novelty of our research question, all models were re-analyzed using a machine learning approach to compare performance for PPCS classification.

Descriptive Statistics

Descriptive statistics were performed on all demographic information and study outcomes. Categorical variables were reported as frequencies with percentages. Continuous variables were reported as means with standard deviations.

Logistic Regression Models

Inferential statistics were performed in RStudio.[114] Separate independent t-tests determined whether the 19 key EEG features differed between adolescents with PPCS and without PPCS. Any EEG feature which independently had a $p<0.10$[115] were combined into a multivariable model. Separate logistic regression models analyzed the ability of EEG feature (multivariable model), physician prediction, and the 5P Clinical Risk Score outcomes to predict the presence of PPCS (yes or no) at 1-month post-concussion. Receiver Operating Curves calculated the sensitivity, specificity, and AUC values for each logistic regression model, while DeLong's Test compared model performance (i.e. AUC values) between the EEG, physician prediction, and 5P models.

Machine Learning Binary Classification Algorithms

All inferential statistics models were re-analyzed using a machine learning approach in scikit-learn.[116] The predictors for each machine learning model matched the inferential statistics approach exactly (i.e., multivariable EEG model with identical features included, physician prediction, and 5P Clinical Risk Score). The machine learning framework was implemented using a binary classification of PPCS or no PPCS. As the numeric values obtained for each EEG feature in this analysis are variable, a standard scaler normalization was performed to ensure equal weighting. The observation space (i.e., the total number of 10-second epochs in the study dataset) was n=799 (Eyes-closed: no PPCS = 516, PPCS = 283). Each dataset (e.g., multivariable EEG, 5P Clinical Risk Score, and physician prediction) was randomly split into train/test (80% of full dataset) and validation (20% of full dataset) sets.

Model Selection

The model selection step was performed on the train/test dataset. As no previous studies have sought to classify PPCS using machine learning approaches, multiple binary classification algorithms were evaluated to identify the optimal approach to separate patients with and without PPCS. The models included Logistic Regression, Support Vector Machine (SVM), Decision Trees, and Linear-Discriminant Analysis (LDA). Various hyperparameters were evaluated to tune each model. The C parameter (c=0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 5.0, 10) was swept for the logistic regression and SVM models. Additionally, kernel type (linear or radial) was evaluated for the SVM models, while criterion (gini or entropy) was assessed for the decision tree models. Multiple EEG epochs (e.g., multiple 10-sec slices) arise from each participant, and these values are highly correlated and not independent. Thus, leave-one-subject-out (LOSO) cross-validation approach was used. The overall model accuracy was reported as the average accuracy obtained for each LOSO repetition. The machine learning model and associated hyperparameter(s) with the highest accuracy was labeled the optimal model for PPCS classification and selected for the remaining analyses.

Model Performance

The best model (determined via the model selection steps above) was re-run using the validation set to obtain final model performance. Permutation testing and bootstrapping were performed on the best model to obtain statistical significance (i.e., a p-value) and a 95% confidence interval, respectively. Model accuracy was calculated on 1,000 repetitions of the permutated dataset, whereby the labels (PPCS or no PPCS) where randomly shuffled on each of the 1,000 repetitions. Model performance was considered statistically significant if the accuracy of the true model (e.g., accurate labels of PPCS and no PCCS) was greater than the permutated model (e.g., random labels of PPCS and no PPCS) at a level of $p<0.05$. Bootstrapped datasets were created by sampling from the original dataset with replacement, such that a row of data from the original dataset could be included in the bootstrapped dataset 0, 1, or 2+ occasions. Model accuracy was calculated on 1,000 bootstrapped datasets to create a distribution of model accuracy. The 2.5 and 97.5 percentiles of the bootstrapped distribution created the lower and upper bounds of the 95% confidence intervals.

RESULTS

Participant Demographics

Forty-four participants enrolled in the study. Seven participants dropped out prior to the <10-day visit, and three participants did not attend the 1-month visit; thus, a total of 34 participants were included in the analysis. We were unable to obtain physician prediction for nine (26.5%) participants in the PED; these participants excluded from the physician prediction model only. Participants were assessed approximately 6.4 ± 2.4 and 28.9 ± 1.9 days post-concussion. Twelve (35.3%) out of 34 participants met our study definition of PPCS. Participants that developed PPCS were on average 13.4 ± 1.7 years old, with the majority (n=7, 58.3%) being male. There were no statistically significant differences in participant demographics between adolescents with and without PPCS, with **Table 5** displaying the full demographic characteristics for study participants. As seen in **Figure 3A**, participants who developed PPCS had an average 5P Clinical Risk Score of 6.83 ± 1.8 (range: 4-9) similar to participants who did not develop PPCS (mean: 5.77 ± 1.9, range: 2-9, p=0.12). Similarly, physician prediction scores did not differ between patients who did (mean: 14.3 ± 17.9, range: 0 -50) and did not (mean: 16.8 ± 18.9, range: 0-65) go on to experience PPCS (p=0.76, **Figure 3B**).

EEG is Tolerable for Children with Acute Concussion

The data collection sessions (e.g., EEG recording and clinical questionnaires) did not meaningfully increase post-concussion symptoms. No sessions were terminated early, and no participants required a brief rest period following the EEG recording. Scores on the brief symptom check-in form were similar from baseline (e.g., start of the data collection visit) to after the EEG recording (mean difference= 0.11 ± 2.38pts [decrease from baseline]) and from baseline to the end of the session (mean difference= 0.15 ± 2.34pts [decrease from baseline]).

EEG Features Better Predicted PPCS than Clinical Assessments in Adolescents with Concussion

Three of the nineteen EEG features assessed were statistically different (p≤0.1) in adolescents with and without PPCS: F3 delta power (p=0.04), F4 delta power (p=0.10), and F4 theta power (p=0.07). These three features were found to be statistically different in the eyes-closed conditions only and no differences between PPCS and no PPCS patients were observed in the eyes-open condition; therefore, all subsequent analyses (inferential and machine learning) were completed with eyes-closed data only. As seen in **Table 6,** the significant EEG features of interest included two delta power features and one theta power feature. For all three features, spectral power values were decreased in adolescents with PPCS compared to children without persistent symptom at 4-weeks following concussion (**Figure 4**). The three significant EEG features were combined into a multivariable model that had moderate ability to predict PPCS (AUC=0.71, sensitivity=75%, specificity=68.2%), while the 5P Clinical Risk Score model had low ability to predict PPCS (AUC=0.66, sensitivity=75%, specificity=45.9%) and the physician prediction model performed poorest (AUC=0.55, sensitivity=71.4%, and specificity=38.9%, **Figure 5**). However, DeLong's Test revealed that both the 5P Clinical Risk Score model (p=0.60) and the physician prediction model different (p=0.32) were not statistically different than the EEG model.

The best performing machine learning model was a SVM with a radial kernel and regularization parameter of C=0.2; this model and hyperparameters were used for all machine learning models (e.g., EEG, physician prediction, and 5P Clinical Risk Score models). In the training set, the EEG model performed with an accuracy of 72.9% (95% CI= 70.8, 73.1, p<0.001), classifying PPCS at an accuracy higher than random chance (67.6%). In the validation set, the EEG model performed with a lower accuracy of 62% (95% CI= 61.4, 62.2, p<0.001), but continued to outperform random chance (60.8%). In contrast, the 5P Clinical Risk Score model had an accuracy of 65.4% in the training set, which was not statistically

different (p=0.99) than random chance (65.4%). These results held in the validation set (62.5% model accuracy, 62.5% random chance, p=0.99). Similar findings were observed for physician prediction, which did not outperform chance in either the training (model accuracy= 68.4%; 68.4% random chance, p=0.99) or validation set (model accuracy= 66.7%, 66.7% random chance, p=0.99).

DISCUSSION

The multivariable EEG model incorporating spectral power features outperformed both the 5P Clinical Risk Score and physician prediction models, but these results only achieved statistical significance in the machine learning analysis. Our study is the first to examine to potential of resting-state EEG as a prognostic tool for pediatric concussion. The multivariable EEG model was the best performing model in our study and only one to achieve moderate predictive capacity, showing an AUC > 0.7 which the minimum value needed for clinical translation.[117] Despite these positive findings, we hypothesized that EEG would significantly outperform the two clinical prognostic tools, which occurred only in the machine learning analysis. This suggests that it may be difficult to predict self-reported outcomes (i.e., PPCS which is solely based on subjective symptom scores) using objective measures of brain function. Previous literature demonstrates that changes in electrical brain activity persists from a few months to a few years following concussion, often despite individuals being completely asymptomatic and clinically recovered from injury.[109,110,118,119] Thus, changes in electrical brain activity after concussion may persist beyond and be independent of symptom reporting, but future, longitudinal studies with a healthy control group are needed to better tease out these relationships.

The modest predictive ability of acute EEG features was driven by acute frontal power in the delta and theta frequency bands from the eyes closed condition. Microscopic axonal injury occurs after concussion due to shearing forces to the brain,[13,14] which may be greater in pediatric concussion as developing brains have more unmyelinated axons.[15] Delta waves have been shown to indicate neuronal healing and restoration of the brain.[120,121] Adolescents recovering within 1-month of injury (i.e., no PPCS group) showed higher delta power within 10 days of their concussion, which may suggest that neuronal healing is either more advanced or beginning earlier after injury in these patients. Increased delta activity is also correlated to a reduction in cerebral blood flow during sleep.[122,123] Concussion is associated with a reduction in cerebral blood flow that may persist for weeks to months post-injury,[14,17] and is primarily present in the frontal region of the brain.[124,125] This prior literature is consistent with studies in adult cohorts reporting increased delta power after concussion,[102] which may be tied to this expected decreased in cerebral blood flow post-injury. However, our findings contradict this notion, as adolescents with PPCS show decreased delta activity which we would expect to be reflective of increased cerebral blood flow. Spectral power decreases with age across the lifespan,[126,127] which may explain the discrepancies between adult and pediatric concussion. Future studies should compare EEG and cerebral blood flow activity in tandem to better explain this relationship in children with concussion. Theta waves, specifically in the frontal brain regions, have been related to cognition,[103,128] which is negatively affected by concussion.[129] Adolescents with PPCS in our study showed decreased theta power, potentially indicating persistent deficits in cognitive performance due to the concussion. Furthermore, longer recovery times from sports-related concussions have been associated with reduced volume in the frontal lobes.[130] Together, these findings highlight the importance of examining frontal brain regions for concussion prognosis.

Our findings for the predictive ability of the 5P Clinical Risk Score and physician prediction models are consistent with previous literature. Zemek et al. found the 5P Clinical Risk Score (AUC=0.68) and physician prediction (AUC=0.55) showed a poor ability to predict pediatric PPCS at 1-month post-injury in the PED within 48hrs of injury.[7] Similarly, Howell et al. found that the 5P Clinical Risk Score had a moderate predictive ability (AUC=0.75) in a clinical setting up to 10 days post-injury, but did not include physician prediction in their study.[5] These studies align with our findings (5P Clinical Risk Score AUC= 0.66, physician prediction AUC= 0.55), increasing confidence that our results are capturing the true predictive ability of each prognostic tool including the EEG model. The 5P Clinical Risk Score considers patient characteristics that may lead to a child developing PPCS. Our sample differs somewhat in these predisposing factors from the prior literature, which may explain why the slightly lower 5P

Clinical Risk Score accuracy in our study. Our participants were aged 10-17 years. Both prior studies assessed children 5-17 years;[5,7] thus, our patients our generally older and this adolescent age group is consistently shown to have a higher risk of prolonged recovery.[1] Conversely, female children are more likely to develop PPCS,[22] but the majority of our sample that developed PPCS was male. Only three adolescents that developed PPCS had a previous history of concussion lasting longer than a week, but adolescents with a history of concussion have been shown to have prolonged recovery.[67] None of the participants developing PPCS had a history of migraine disorder, which was an important factor identified in the original 5P study.[63] Previous literature shows that not all 9 predictors of the 5P Clinical Risk Score are significantly associated with PPCS,[5] which further explains its predictive ability in our study.

PPCS was largely underestimated by the physicians in our study, with the highest value provided representing a 65% likelihood (on a 0 to 100 scale) that a patient would go on to experience PPCS in 1-month. Physicians may have the knowledge to recognize and diagnose concussions,[76] but physicians have consistently shown poor predictive ability in concussion prognosis.[7] Physician prediction, in this thesis and in similar studies, reflects the physician's opinion on how likely an adolescent with concussion is to experience PPCS and is based solely on the clinical knowledge and subjective opinion of the physician. This suggests there may be a knowledge gap provided to physicians and medical students in Canada with regards to concussion prognosis, indicating there is a need for improvement in the curriculum.[131,132]As previously mentioned, there are certain predisposing factors that can influence the development of PPCS in children, including: pre-existing mental health disorders,[53,133] migraine disorders,[6,63] concussion history,[63,134] age,[1,25] and sex.[1,66] The poor performance of physician prediction in our study and the literature more broadly suggests that clinicians are either unaware of these factors or do not consider them when providing prognostic information following concussion. Physicians may benefit from enhanced education on factors increasing the risk of prolonged recovery following concussion,[135] which may help them provide better patient education and may improve referral to specialty care for patients.

There is no universally agreed upon definition of PPCS, with current PPCS classification relying solely on symptom reporting.[58] The lack of universal definition limits the ability to develop prognostic tools, as different research teams work to create models to predict different phenomenon. Furthermore, PPCS is a complex, multi-factorial condition that is influenced by a variety of personal and injury specific factors, including neurophysiological changes post-concussion,[109] patient demographics,[25,63,66] psychosocial factors,[53] and access to treatment.[37] Despite the complex and interrelated factors influencing PPCS, it is defined solely on self-reported symptom presentation, which is highly subjective and variable between patients. Until a concrete definition of PPCS is developed and multiple factors are taken into consideration, it is unlikely the current prognostic tools will perform strongly in predicting PPCS. As PPCS is indicative of prolonged recovery from concussion, more holistic definitions of PPCS should be a priority to ensure better prognostic information and earlier treatment enrollment is provided to patients most at risk of poor outcome following concussion.

Strengths

To our knowledge, this is the first study to evaluate EEG as a prognostic tool for persistent symptoms after concussion. Both machine learning and inferential statistics approaches were performed and provided us with similar results. Furthermore, our findings regarding the prognostic capabilities of the 5P Score and physician prediction were similar to previous literature. Together, this increases confidence in our findings regarding the performance of all models, including the multivariable EEG model. The DSI-19 headset uses dry electrodes to capture electrical brain activity. This headset was chosen due to its feasibility and greater potential for clinical translation, as it requires minimal time to set up and is fully portable. While wet electrodes are considered the gold standard when recording brain activity to limit impedance (i.e. caused by hair and other factors),[136] dry electrodes perform comparably to wet

electrodes which further supports their potential as a clinical tool.[136] We used a more stringent definition of PPCS using reliable change (≥7pt change from baseline) compared to other studies, which often define PPCS using a change of ≥3pts relative to baseline. This increases the likelihood that patients labeled as having PPCS in our study were experiencing more meaningful and clinically significant changes from pre-injury levels.

Limitations

The main limitations of the study are the small sample size, with 34 participants completing the full study. This small sample size was exacerbated by loss-to-follow up, with three participants failing to attend the second visit needed to determine PPCS status and therefore being excluded from the analyses. However, significant findings were achieved for the machine learning analyses, suggesting statistical power was at least partially sufficient. Select participants enrolled in the study after their emergency department visit. For these patients, we were unable to collect the physician prediction outcome and they were excluded from the physician prediction model, which may affect accuracy. Due to our small sample size, our models were incapable of evaluating all EEG features generated. EEG is underutilized in pediatric concussion and no prior studies have suggested EEG features relevant for PPCS in adolescents. Thus, we evaluated a subset of 19 EEG features based off of existing preliminary data in our laboratory. It is possible our models failed to evaluate EEG features that may be more significant for predicting PPCS, which is at least partially supported by our findings. For example, the maps in **Figure 4** visualize delta and theta power across the entire scalp for patients with and without PPCS. These topographic maps show clear differences in the central and parietal regions of the brain between children with and without PPCS. However, these electrodes were not included in the 19 key EEG features we specified a priori and therefore weren't analyzed in our study. Thus, there may be other EEG features or electrode positions for pediatric concussion prognosis that we captured but were unable to analyze currently due to the sample size. While the DSI-19 offers distinct advantages in terms of clinical translation, its sparser electrode array may limit our ability to capture information from different brain regions. Previous studies have shown high density systems outperform lower density systems (e.g., better capture electrophysiological differences) in other clinical populations.[137] This finding might also hold true for PPCS in adolescents, but it is important to note that all brain regions were captured with the DSI-19.

Clinical Implications

PPCS has a negative impact of quality of life and academic performance in children.[8,68–70] Effective post-concussion treatments are available[34] and early enrolment can decrease recovery time,[36,39] ultimately decreasing the likelihood of PPCS and its negative associated outcomes from developing. Incorporating EEG into clinical concussion care can provide health care professionals with valuable information on physiological recovery in adolescents with concussion, allowing for prioritization of treatment services. With its moderate predictive ability and absence of symptom exacerbation in our study, EEG has demonstrated potential for PPCS prognosis in adolescents with concussion. The DSI-24 Wearable Sensing headset is fully portable, low-cost (relative to other neuroimaging tools) and time-efficient, taking less than 20 minutes to fit the cap and collect the required data. Thus, similar portable EEG headsets may be a feasible tool in a variety of relevant clinical settings for pediatric concussion, including sideline settings, schools, and sports medicine clinics.

CONCLUSION

EEG features, particularly spectral power in the delta and theta frequency bands, show potential as a prognostic biomarker of PPCS in adolescents with concussion. EEG features displayed moderate predictive abilities and outperformed current clinical tools used to predict PPCS; however, these results only achieved statistical significance when using machine learning methods. Future studies should continue to explore the potential for EEG in pediatric concussion prognosis, including larger samples and different EEG systems and features. Furthermore, futures studies should consider the inclusion of a healthy control group, which would allow for better understanding of changes in brain physiology that occur after concussion in adolescents with and without PPCS.

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TABLES

Table 1. Common post-concussion symptoms and their respective domains.[138,139]

Physical	Cognitive	Emotional	Sleep
Headache	Feeling "In a fog"	Feeling more emotional	Trouble falling asleep
Nausea	Feeling slowed down	Irritability	Fatigue or low energy
Vomiting	Difficulty concentrating	Sadness	Drowsiness
Balance Problems	Difficulty remembering	Nervousness	
Dizziness			
Blurred vision			
Sensitivity to light			
Sensitivity to noise			

Table 2. The complete list of EEG features that were extracted in this study and their descriptions.

Feature Type	Specific Feature	Specific Description
Spectral Features	Spectral Power	Measure of the signal power (microvolt^2/Hz)
	Peak Frequency	Frequency (Hz) where the peak power can be found
Entropy-Based Features	Normalized Permutation Entropy	Information processing of the EEG signal
Functional Connectivity Features	Weighted Phase Lag Index	Measurement of the phase angle of an electrode
	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	The sum of all connections associated to an electrode
	Betweenness centrality	The influence a node has on the flow of information.

Table 3. The variables included in the 5P Clinical Risk Score with their descriptions and scores.

Assessment	5P Outcome	5P Score
Demographics	Age Group	5-7 years: 0 points 8-12 years: 1 point 13-18 years: 2 points
	Sex	Male: 0 points Female: 2 points
	Prior Concussions (y/n); Symptom Duration (days)	No or Yes (< 7 days): 0 points Yes (≥ 7 day): 1 point
	History of migraine	Yes: 1 point
Balance Error Scoring System	mBESS Score	0-3 errors: 0 points 4-10 errors 1 point
Post-Concussion Symptom Inventory	Answers questions slowly	Yes: 1 point
	Headache	Yes: 1 point
	Sensitivity to Noise	Yes: 1 point
	Fatigue	Yes: 2 points

Table 4. The 19 key EEG features that can accurately differentiate between healthy controls and children with concussion. Only these specific features were analyzed in this study to determine their potential for PPCS prognosis.

Spectral Features	Functional Connectivity Features	Graph Theory Features
F3 delta power	T3 theta AEC	Theta AEC betweenness centrality
F7 delta power	Pz theta dPLI	Theta dPLI node strength
F4 delta power	T6 beta dPLI	
P4 delta power		
F8 delta power		
F4 theta power		
F7 alpha power		
F4 alpha power		
P4 alpha power		
T6 beta power		
Pz beta power		
O1 beta power		
O2 beta power		

Table 5. Participant demographics presented overall and separately for PPCS (Yes/No) groups. Continuous variables are reported as means (standard deviations), while categorical outcomes are presented as frequencies (percentages).

	No PPCS (N=22)	Yes PPCS (N=12)	Overall (N=34)	P Value
Age (years)	12.7 (2.36)	13.4 (1.68)	12.9 (2.15)	0.301
Sex				
Female	9 (40.9%)	5 (41.7%)	14 (41.2%)	1
Male	13 (59.1%)	7 (58.3%)	20 (58.8%)	
Concussion Hx				
No	18 (81.8%)	8 (66.7%)	26 (76.5%)	0.41
Yes	4 (18.2%)	4 (33.3%)	8 (23.5%)	
Mechanism of Injury				
Fall	5 (22.7%)	1 (8.3%)	6 (17.6%)	
Other	4 (18.2%)	1 (8.3%)	5 (14.7%)	0.419
Sport	13 (59.1%)	10 (83.3%)	23 (67.6%)	
Primary Language				
English	8 (36.4%)	6 (50.0%)	14 (41.2%)	
French	13 (59.1%)	5 (41.7%)	18 (52.9%)	0.53
Other	1 (4.5%)	1 (8.3%)	2 (5.9%)	
ADHD Diagnosis				
No	20 (90.9%)	8 (66.7%)	28 (82.4%)	0.154
Yes	2 (9.1%)	4 (33.3%)	6 (17.6%)	
Learning Disability Diagnosis				
No	19 (86.4%)	12 (100%)	31 (91.2%)	0.537
Yes	3 (13.6%)	0 (0%)	3 (8.8%)	
Anxiety Diagnosis				
No	21 (95.5%)	10 (83.3%)	31 (91.2%)	0.279
Yes	1 (4.5%)	2 (16.7%)	3 (8.8%)	

Table 6. The three EEG features that differed in adolescents with and without PPCS in the eyes closed condition. The delta and theta spectral power was significantly lower in adolescents with PPCS.

EEG Feature	**PPCS (n=12)**	**No PPCS (n=22)**	P value
F3 delta power	12.4 $\mu V^2/Hz$	14.3 $\mu V^2/Hz$	0.04
F4 delta power	11.7 $\mu V^2/Hz$	13.5 $\mu V^2/Hz$	0.10
F4 theta power	6.9 $\mu V^2/Hz$	8.8 $\mu V^2/Hz$	0.07

FIGURES

Figure 1. The DSI-24 19-channel EEG headset (A) used in the study and a map (B) of the 19 electrodes.

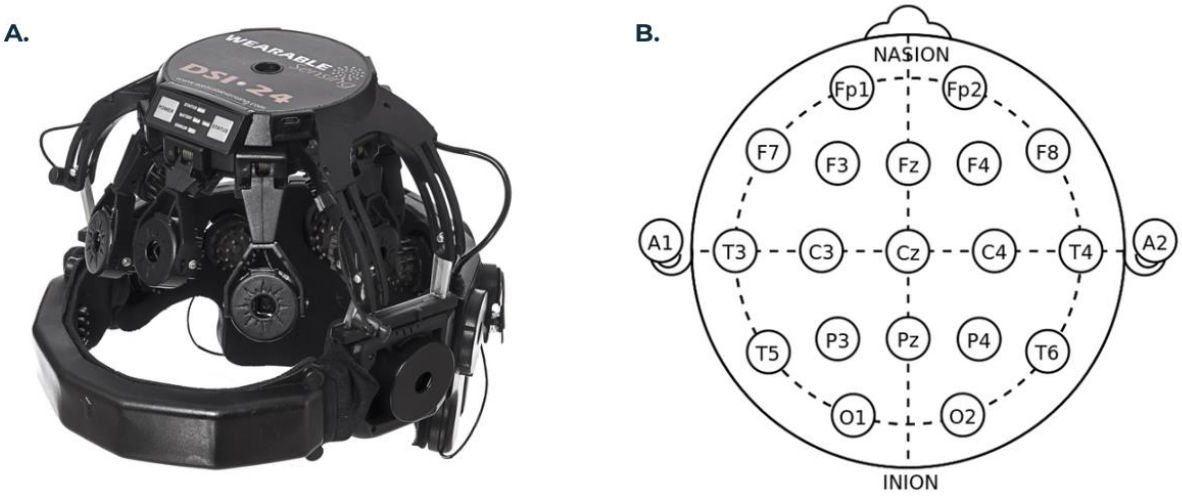


Figure 2. The complete timeline of all study assessment points (A) and a detailed schematic of the first (≤10 days post-concussion) visit (B).

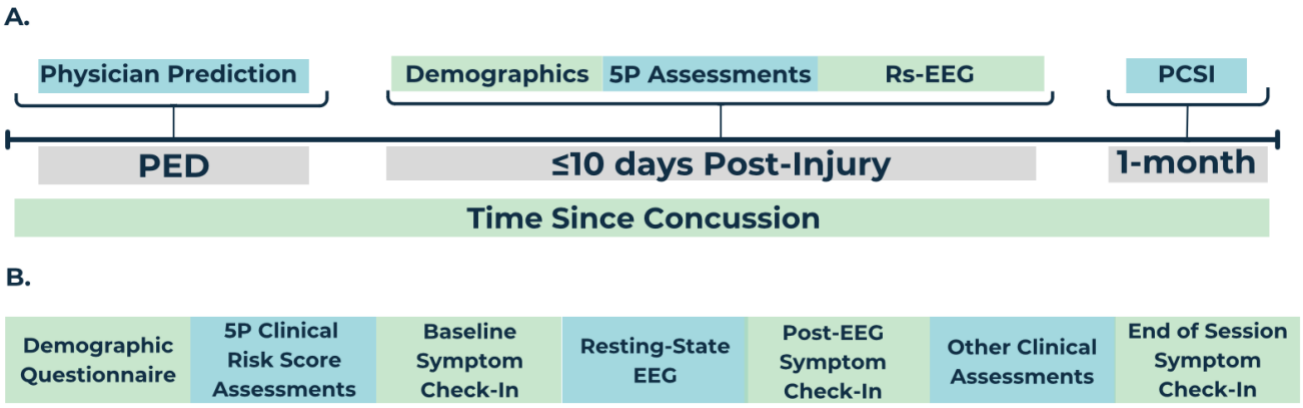


Figure 3. The total 5P Clinical Risk Scores (A) and physician prediction scores (B) presented separately for PPCS (Yes/No) groups.

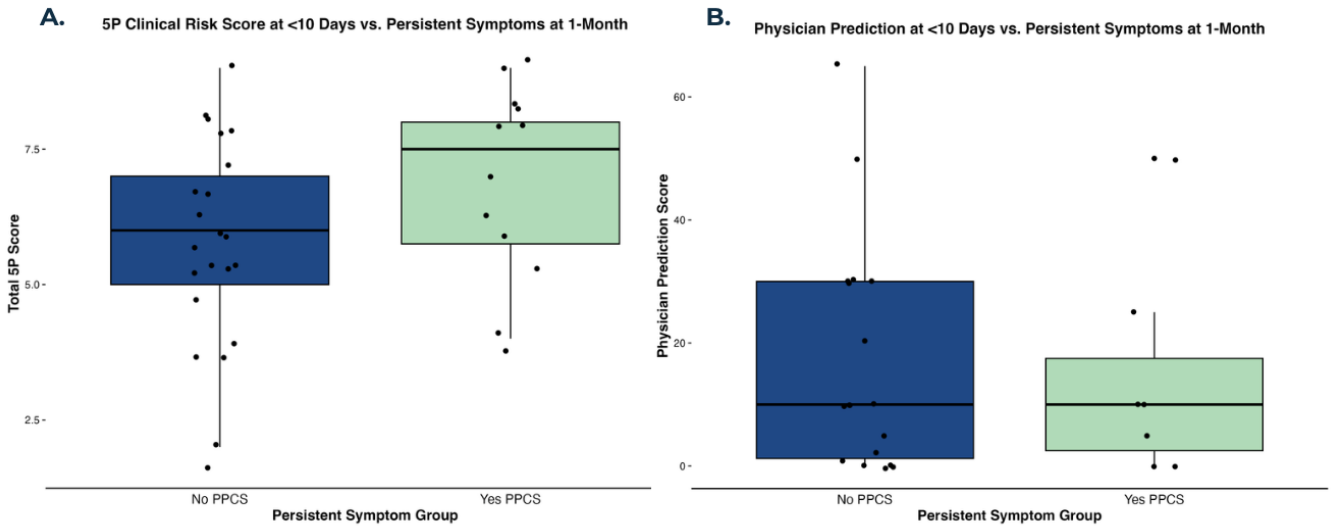


Figure 4. Delta power (top row) and theta power (bottom row) represented as topographic maps. The PPCS group is on the left (Panels A & C), while the no PPCS group is on the right (Panels B & D). * denotes electrodes where a significant group difference was observed.

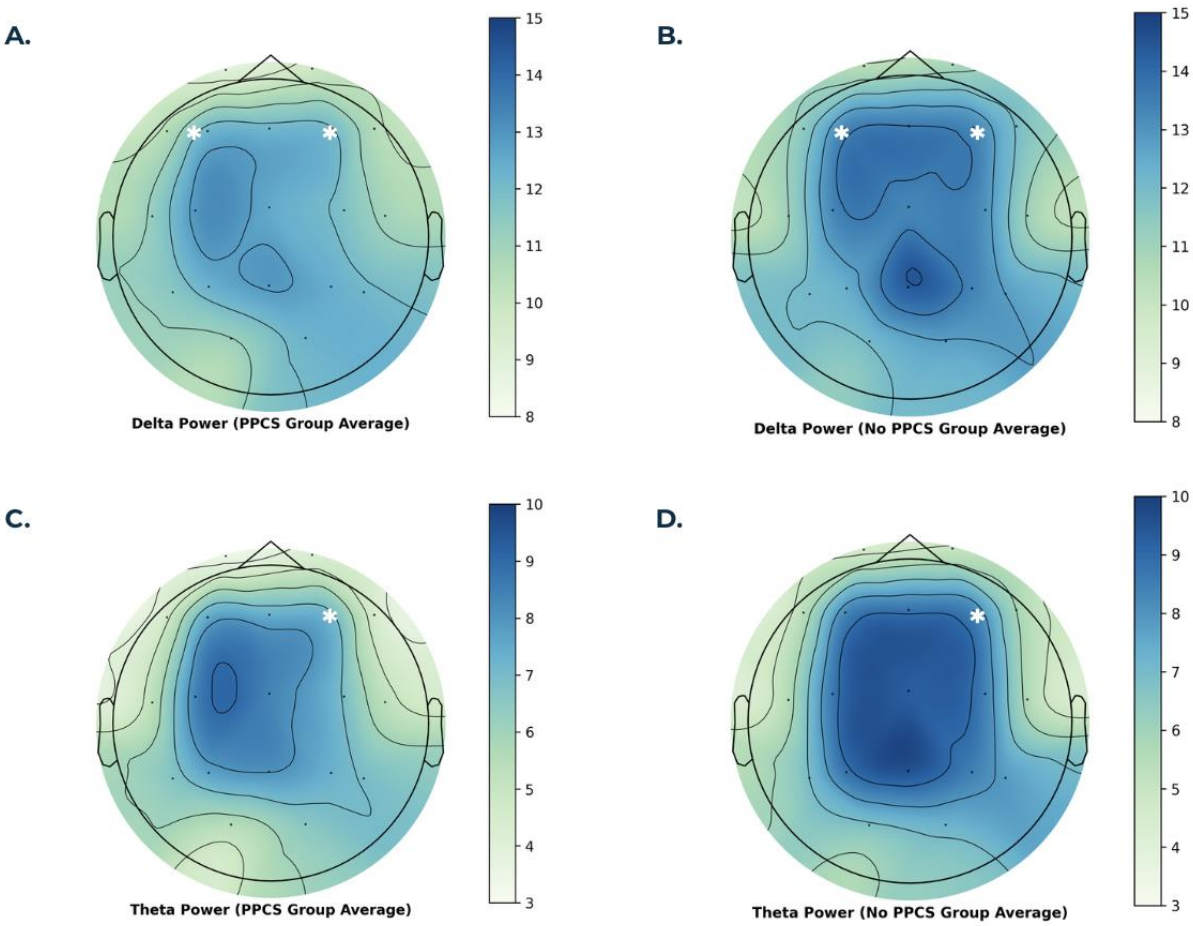
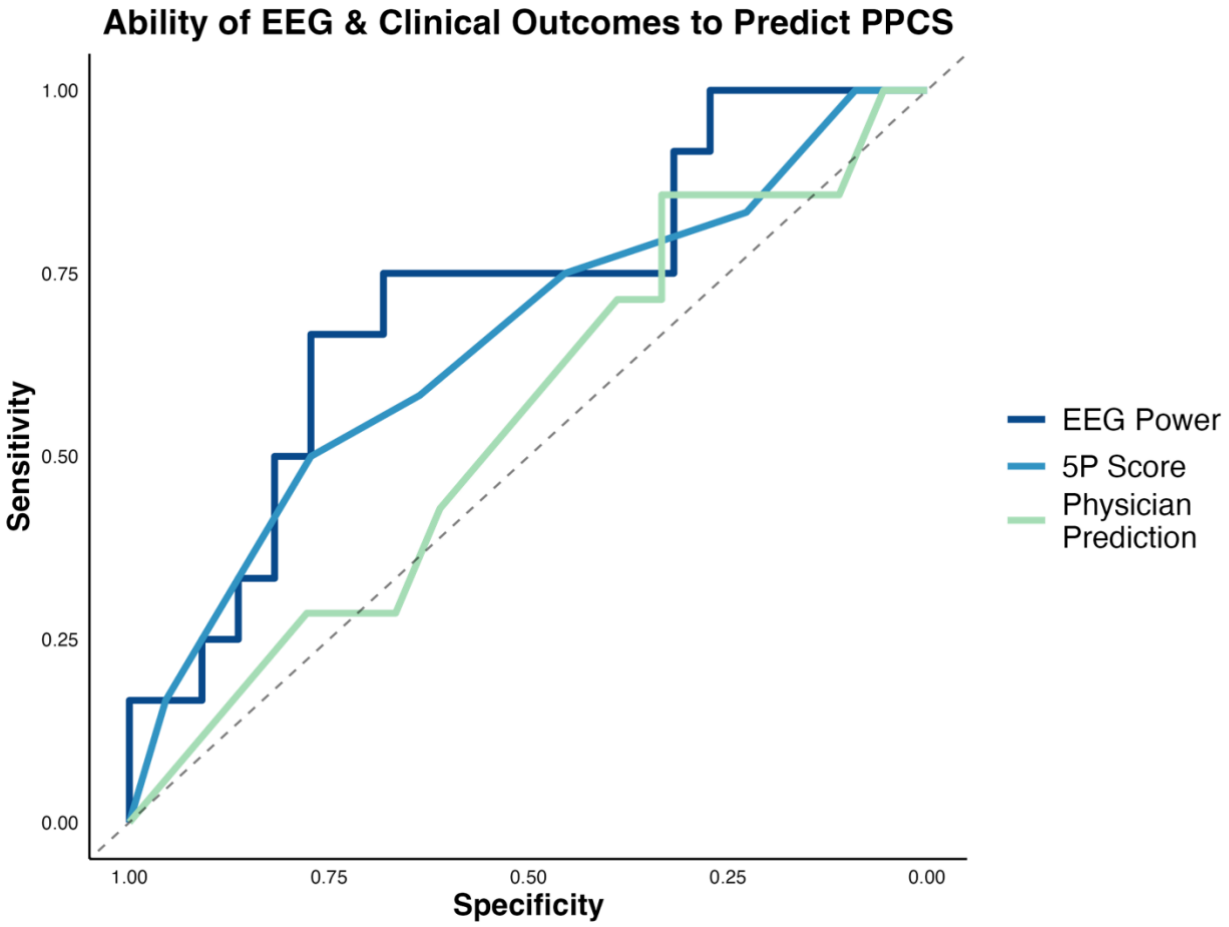


Figure 5. The receiver operating curves of the multivariable EEG, 5P Clinical Risk Score, and physician prediction models.



APPENDIX: STUDY ASSESSMENTS

Patient ID: _____
Date of Visit (MM/DD/YYYY): _____
Test Evaluator: _____

Demographic Information- Children with Concussion

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. How did your concussion occur?
   a. Sport/recreational activity
   b. Motor vehicle accident
   c. Slip/fall
   d. Other (please describe): _____

6. What was the date of your concussion? _____

7. As of today, have you returned to school following your concussion?
   a. Yes, school **with no** accommodations
   b. Yes, school **with** accommodations (i.e., part time, no quizzes/tests, extra time for assignments, etc.)
   c. No, not back in school

8. Do you currently play any organized sport(s)? a. Yes b. No

9. As of today, have you returned to sport following the concussion?
   a. Yes, back at my sport full time
   b. Yes, back at my sport but cannot participate fully (i.e., no competitions, no contact, etc.)
   c. No, not back at my sport
   d. Not applicable/do not play organized sport

10. Besides the current injury, have you ever experienced a concussion previously (e.g., concussion diagnosed by a medical provider)? a. Yes. b. No

    10a. If yes, how many concussions have you been diagnosed with previously? _____

    10b. If yes, when was your most recent concussion (year and month)? _____

    10c. If yes, what was the longest symptom duration of all prior injuries (in weeks)? _____

11. What is your primary/preferred language? a. English b. French c. Other _____

12. Have you ever been f**ormally diagnosed** (by a healthcare provider) with any of the following (circle all that apply)?
    a. ADD/ADHD
    b. Depression
    c. Anxiety
    d. Learning Disability
    e. Migraines
    f. Seizures
    g. Psychiatric Condition
    h. Other (please describe): _____
    i. None of the above

Patient ID: _____

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

Please circle the study visit: **Visit 1** **Visit 2**

Test Evaluator: _____

5P Clinical Risk Score Collection Form

1. Right after your injury, did you answer questions more slowly than usual (i.e., did it take you longer to process questions, formulate an answer, and respond to the question)?

Yes _____ No _____

2. BESS Tandem Stance
Non-dominant foot in back, feet together touching heel-to-toe

What foot is the dominant foot? Left _____ Right _____

Total Number of Errors (Out of 10): _____

BESS Errors
Moving hands off of the iliac crests
Opening the eyes
Step, stumble, fall
Abduction/flexion of the hip >30°
Lifting the forefoot/heel off the testing surface
Remaining out of the test position for >5sec

If a participant commits multiple errors simultaneously (i.e., opens eyes, lifts hands off hips, and takes a step), they are only credited with committing **one** error

*** If a participant cannot maintain the proper test position for 5 consecutive seconds, a score of 10 is automatically given for that condition.***

Notes (please explain missing data, issues during data collection, etc.):

Patient ID: _____

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

Please circle the study visit: **Visit 1** **Visit 2**

Test Evaluator: _____

Post-Concussion Symptom Inventory														
	Pre-Injury Rating							***Post-Injury Rating***						
Headache	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Nausea	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Balance Problems	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Sensitivity to Light	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Sensitivity to Noise	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Nervousness	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Feeling More Emotional than Usual	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Move Slower than Usual	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Feeling Mentally “Foggy”	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Difficulty Concentrating	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Difficulty Remembering	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Vision Problems	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Confused	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Move Clumsy	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Answers Questions More Slowly Than Usual	0	1	2	3	4	5	6	0	1	2	3	4	5	6
In general, to what degree to you feel “differently” then before your injury?	No Difference 0 1 2 3 4 Major Difference													

Patient ID: _____

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

Please circle the study visit: **Visit 1** **Visit 2**

Test Evaluator: _____

Symptom Check-In

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

If a patient reports **≥3-point change** in symptoms (total score) **from baseline,** they should be given a **brief rest period (up to 5 minutes)** before continuing.

If a patient reports **≥6-point change** in symptoms (total score) **from baseline,** they should be given a **brief rest period (up to 5 minutes).** Check in and **re-evaluate symptoms** following rest. If the total score remains **≥6-points or higher than baseline,** the session should be **ended.**

Notes: *Include details about rest period (when they were given and for how long) and any feedback from patients regarding their symptoms.*