Oculomotor and Vestibulo-Ocular Function Post-Concussion in Children and Adolescents

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ABSTRACT

Objective: The objectives of this study were (1) to document oculomotor (OM) and vestibulo-ocular (VO) function in children who sustained a concussion and were symptomatic at the time of assessment, and to compare them to that of children with prior concussion who were clinically recovered (asymptomatic) and of uninjured children, and (2) to document the extent to which OM and VO function relate to post-concussion symptom severity in children with symptomatic and asymptomatic concussion. *Study Design:* A prospective cross-sectional study that included 108 symptomatic/clinically recovered pediatric patients with concussion and 79 healthy youth, between 9 and 18 years of age. *Setting:* Participants with concussion were recruited from a speciality concussion clinic at the Montreal Children's Hospital, McGill University Health Center. *Methods:* OM (smooth pursuit, saccades, anti-saccades and vergence) and VO (average vestibulo-ocular reflex gain) function were acquired with a commercial VR eye-tracking system (Saccade Analytics, InSight software). Post-concussion symptoms were scored with the Post-Concussion Symptom Inventory (PCSI) and were obtained from the patient's concussion clinic electronic medical records, as were number of previous concussions and premorbid conditions. A series of one-way ANOVA tests and Pearson r correlations were used to address the two objectives. *Results:* There was a significant main effect at the $p<.05$ level for vergence during smooth pursuit [$F(2,176) = 10.90$, $p<.05$], mean latency during saccades [$F(2, 171) = 5.99$, $p=.003$] and mean response delay during anti-saccades [$F(2,177=9.07$, p.<05]. For VO, there was a significant main effect for average vestibular ocular reflex gain in the horizontal leftward [$F(2,168) = 7$, $p=.001$] and rightward directions [$W(2,163) = 13.08$, $p <.05$] and vertical upward [$F(2,147) = 7.60$, $p=.001$] and downward directions [$W(2,144) = 13.70$, $p <.05$]. Significant group differences in OM and VO function highlighted that children with symptomatic

concussion showed poorer performance when compared to clinically recovered and healthy children. The Pearson correlation test indicated a significant strong positive correlation between mean saccade error and total PCSI scores for the younger (8-12-year-olds) clinically recovered children. Additionally, children with greater symptom scores on the PCSI tended to preform worse on the OM/VO eye tracking tasks than children who reported lower symptom scores. *Conclusion:* Our results lead us to conclude that children with symptomatic concussion do indeed present with clinical oculomotor and vestibulo-ocular function impairments and tend to report more severe post- concussion symptoms when compared to healthy and recovered children. The significant group differences between the symptomatic children, recovered and healthy children suggests that VR eye tracking may be an effective tool for identifying OM and VO deficits in the acute phase of concussion. Although more investigation is needed, VR eye tracking of OM and VO function has the potential to provide clinicians with a measurement tool that is both objective and developmentally appropriate for use with children.

ABRÉGÉ

Objectifs : Les objectifs de cette étude étaient de 1) documenter la fonction oculomotrice (OM) et vestibulo-oculaire (VO) d'enfants ayant subi une commotion cérébrale, symptomatiques au moment de l'évaluation, et de la comparer à celle d'enfants asymptomatiques suite à leur commotion cérébrale et à celle d'enfants non blessés, et 2) documenter dans quelle mesure les fonctions OM ou VO varient en fonction de la sévérité des symptômes post-commotionnels chez les enfants symptomatiques et asymptomatiques suite à leur commotion cérébrale. *Devis* : une étude transversale prospective comprenant 108 patients pédiatriques symptomatiques ou asymptomatiques suite à une commotion cérébrale et 79 jeunes en bonne santé, âgés de 9 à 18 ans. *Milieu*: Les participants souffrant d'une commotion cérébrale furent recrutés au sein d'une clinique spécialisée dans le suivi des commotions cérébrales à l'Hôpital de Montréal pour enfants, Centre universitaire de santé McGill. *Méthodes*: La fonction OM (poursuite lente, saccades, anti-saccades et vergence) et VO (gain du réflexe vestibulo-oculaire) fut mesurée à l'aide d'un système d'oculométrie commercial (Saccade Analytics, appareil InSight). La sévérité des symptômes post-commotionnels fut déterminée à l'aide du *Post-Concussion Symptom Inventory* (PCSI) dont les scores furent relevés à partir du dossier médical électronique de l'enfant, tout comme le nombre de commotions cérébrales et de conditions prémorbides antérieures. Une série de tests ANOVA univariés et de corrélations de Pearson r ont été utilisées pour répondre aux deux objectifs. *Résultats*: Un effet principal significatif au niveau $p < 0,05$ fut identifié pour la vergence pendant la poursuite lente [$F(2\ 176) = 10,90$, $p < 0,05$], la latence moyenne pendant les saccades [$F(2, 171) = 5,99$, $p = .003$] et le temps de réponse moyen pendant les anti-saccades [$F(2\ 177 = 9,07$, p. <05]. Pour la VO, il y avait un effet principal significatif pour le gain réflexe vestibulo-oculaire moyen horizontal vers la gauche [$F(2\ 168) = 7$, $p = .001$] et vers la droite [$W(2163) = 13,08$, $p < 0,05$] de

même qu'en vertical vers le haut [F (2147) = 7,60, p = 0,001] et vers le bas [W (2144) = 13,70, p < .05]. Les différences significatives dans les fonctions OM et VO entre les groupes confirment que les enfants souffrant d'une commotion cérébrale symptomatique montrent de moins bonnes performances par rapport aux enfants asymptomatiques ou en bonne santé. Le test de corrélation de Pearson a indiqué une forte corrélation positive significative entre le niveau moyen d'erreur pendant les saccades et le total au PCSI chez les plus jeunes enfants asymptomatiques (8 à 12 ans). De plus, les enfants présentant le plus de symptômes réussissaient moins bien les tâches OM / VO que les enfants ayant des scores de symptômes inférieurs. *Conclusion*: Nos résultats nous amènent à conclure que les enfants ayant subi une commotion cérébrale et qui sont encore symptomatiques présentent des troubles cliniques de la fonction oculomotrice et vestibulo-oculaire, et ont tendance à signaler des symptômes post-commotion cérébrale plus sévères que les enfants sains ou asymptomatiques suite à leur blessure. Les différences significatives entre les enfants symptomatiques et les ceux en bonne santé ou asymptomatiques suggèrent que le l'oculométrie par réalité virtuelle peut être un outil utile dans la phase aiguë de la commotion cérébrale. Bien que plus de recherche soit nécessaire, une évaluation de la fonction OM et VO aurait le potentiel de fournir aux cliniciens un outil de mesure à la fois objectif et approprié au développement pour une utilisation avec des enfants.

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PREFACE

Contributions of Authors:

There were many steps involved in the successful completion of this thesis. Initially, a proposal was written by Dakota Treleaven and was approved by supervisor Dr. Isabelle Gagnon and committee members, Dr. Mimi Galiana and Dr. Anouk Lamontagne. The research proposal was then submitted and approved by the Integrated Program in Neuroscience at McGill University. Data collection took place throughout this process to which the author, Dakota Treleaven participated. Next, the data was extracted from the already assembled Concussion Clinic Database. In addition, since this study required access to details in the participants medical history, this information was retrieved from the patient's electronic medical record at the Montreal Children's Hospital. The next step involved data analysis, which was overseen by supervisor Dr. Isabelle Gagnon and Saccade Analytics CEO Isabel Galiana. The thesis was written by Dakota Treleaven under the close supervision of Dr. Isabelle Gagnon and feedback from the supervisory committee.

Thesis Format:

The global aim of this thesis was to explore the relationship between oculomotor and vestibulo-ocular function in children with and without a history of concussion. Following the regulations of Graduate and Post-doctoral Studies (GPS), a manuscript-based style has been adopted for this thesis, with the intention of submission to a scientific journal for publication. It is required by the GPS to include a literature review and a conclusion that are separate from the manuscript. Thus, the possibility for redundancy of material is inevitable.

Chapter 1 is the literature review, which is divided into five sections. *Section 1* is dedicated to background information regarding the incidence of concussion in children, symptomatology, premorbid and comorbid disorders that may put a child at increased risk of a subsequent head injury, exacerbated symptoms or prolonged recovery, the pathophysiology of concussion and research addressing the diagnosis and management of concussion in children. *Section 2* introduces the visual system and covers the basic visual pathway and the relationship between visual function and concussion. This section also introduces the oculomotor system and focuses on anatomical pathways of the system and the eye movements involved (smooth pursuit, vergence, saccades, anti-saccades). *Section 3* describes the vestibulo-ocular system, its neuroanatomical structures and the interaction between the visual and vestibular systems. *Section 4* reviews common assessment tools for the oculomotor and vestibular systems, highlights some of the more complex diagnostic tools and addresses common properties of eye tracking devices and their application in concussion research.

Chapter 2 highlights the rationale and objectives of the study.

Chapter 3 consists of the manuscript with a standard format: introduction, methodology, results, discussion and conclusion.

Chapter 4 is the final and concluding chapter of this thesis. It includes a global summary and the overall conclusions of the thesis.

Appendices includes a sample report from the eye tracking assessment (InSight Software), the Post- Concussion Symptom Inventory versions 5-12 years of age and 13-18 years of age and a summary table of the important variables addressed in this study.

The References chapter includes a complete list of references outside of those referred to in the manuscript.

CHAPTER 1

REVIEW OF THE LITERATURE

Section 1: Concussion/Mild Traumatic Brain Injury

1.1.1 Definition and Incidence

The most commonly used definition of concussion in clinical practice and research is provided by the 2016 Berlin Consensus Statement on Concussion in Sport which states that a concussion is " a traumatic brain injury induced by biomechanical forces."[1] It also states that there are "several common features that may be utilised in clinically defining the nature of a concussive head injury"[1] The following criteria are applied: "1) may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an 'impulsive' force transmitted to the head. 2) Typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, symptoms and signs may evolve over several minutes or hours. 3) May result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury, and as such, no abnormality is seen on standard structural neuroimaging studies. 4) Results in a range of clinical signs and symptoms that may or may not involve a loss of consciousness"[1].

The World Health Organization (WHO) task force on mild traumatic brain injury (mTBI) defines it as an "acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include (1) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, posttraumatic amnesia for less than 24 h, and/or other transient neurological abnormalities such

as focal signs, seizure, and intracranial lesion not requiring surgery and; (2) Glasgow Coma Scale score of 13–15 30 minutes post-injury or later upon presentation for healthcare; (3); the manifestations of mTBI must not be related to other systematic injuries, the use of drugs, alcohol or medications, or a craniocerebral injury." [2]. The terms concussion and mTBI have often been used interchangeably but researchers are now suggesting they be treated as a continuum with concussion representing the least severe end of the spectrum [3]. For the purpose of this thesis, the two terms (concussion and mTBI) will be used equivalently.

Data from the Center of Disease Control suggests that up to 3.8 million concussions occur annually and that approximately 65 % of reported concussions occur in the pediatric and adolescent population [4]. Children have a unique vulnerability to concussion because of mechanical and neurobiological factors that underlie brain maturation [5]. Reports suggest that children have more severe and prolonged symptoms and are at an increased risk of repeat injury [6].

1.1.2 Symptomatology

There has been growing recognition that concussions can have adverse affects on children and adolescents across varying aspects of their lives. This includes their home life, academic performance, social relationships, and sport participation. Symptoms of concussion are generally divided into 4 main categories: Physical, cognitive, emotional, and sleep-related [8]. It is normal to experience a variety of these symptoms during the first 72 hours post injury and for some of these symptoms to linger up to 3 months after injury [9]. The resolution of the clinical and cognitive symptoms typically follows a sequential course. However, it is important to note that in some cases, symptoms may be prolonged [1]. If symptoms persist past the 3 month mark,

a diagnosis of persistent post concussion symptoms and prolonged recovery becomes increasingly more likely [10]. In an attempt to describe the natural progression of symptom change by age group (5-7, 8-12 and 13-18 years of age) and sex (n=2716), Ledoux [11]found that in younger children, symptom change primarily occurs in the first week after injury. Whereas in children over the age of 8, symptom change is prominent in the first two weeks and flattens between 3-4 weeks. In a pediatric study in Alberta, Canada (n=670) 58.5 % of children diagnosed with concussion remained symptomatic in the initial 30 days following concussion, 11% at 90 days and 2.3% at one-year post injury[12]. Persist symptoms limit participation in academic and recreational activities which can have a negative impact on patients' quality of life. In one study of 1667 children, researchers found that 510 participants experienced persist symptoms (complaints of a minimum of 3 symptoms on the Post-Concussion Symptom Inventory) 1 month after injury, and those children reported significantly lower scores on the Pediatric Quality of Life Inventory Version 4.0.[13] Further, the difference in scores remained consistent at two- and three-month follow-ups.[13]

Physical Symptoms. Headache is the most reported symptom after a concussion, with the prevalence ranging between 30 and 50 percent on the day of injury [14]. An mTBI can affect various anatomical sites in the brain and may be associated with neck pain [15]. Dizziness is another commonly experienced symptom following mTBI that may be caused by central or peripheral dysfunction in the vestibular system [16] Vision changes, such as blurred and or double vision can also occur, which can lead to difficulty sustaining near vision for prolonged time periods [17]. One research study determined that presentation of somatic symptoms within 28 days post injury was categorized as the strongest contributor to delayed recovery in children and adolescents [18].

Cognitive Symptoms. The most common cognitive symptoms post-concussion include difficulty paying attention or multi-tasking, memory deficits and disorientation [19]. Rieger [20] compared cognitive performance in children who had sustained a concussion to those with an orthopaedic injury. Results concluded that the participants with concussion performed significantly worse on visual memory tests and that memory impairment following concussion appear to involve working memory [21]. After sustaining an mTBI the patient may report feeling 'foggy' or 'sluggish' and have trouble concentrating and following directions or conversations [9].

Emotional Symptoms. The most common emotional symptoms experienced following an mTBI include increased irritability, nervousness, anxiety and sadness/ depressed mood [9]. One longitudinal cohort study of 179 children with concussion (ages 8-18) found that children with delayed recovery (>3 months) reported greater scores on measures of postinjury anxiety and preinjury somaticizing tendencies than those who saw symptom resolution within 1 month post injury [22]. Although emotional symptoms in children post concussion is not well researched, studies do show that concussed athletes show alterations in functional connectivity in regions associated with emotional processing [23, 24]. Specifically, researchers found an inverse correlation between depressed mood and connectivity of the left angular gyrus to supplementary motor areas [23].

Sleep-related Symptoms. Although few studies address sleep in children and adolescents after concussion, Pillar [25] found that excessive sleep was the most common complaint (40 % of participants) and that trouble falling asleep had the most severe consequences on children aged 12-17 years old. Complaints of sleep quality and quantity are also frequent after concussion [9]. In one pediatric study, Wiseman-Hakes [26] found that children

and youth have transient alterations in daytime sleepiness related to concussion symptoms, and that younger children (ages 6-11 years old) are more susceptible to disturbances in sleep than older children (ages 12-18 years old). The disruption to sleep that frequently occurs subsequent to mTBI may impede recovery in the short term and could lead to a protracted course of recovery in the long term.

1.1.3 Predictors of Prolonged Symptoms/ Recovery

Current evidence shows that severe and acute symptoms, delayed removal from play, history of mental illness, headaches and/or migraines are predictors for prolonged and difficult recovery. In a literature review of 561 studies, Zemek [27]concluded that the risk for persistent concussion symptoms is increased in older children when there is a loss of consciousness, headache, nausea or vomiting and dizziness at the time of injury. Additionally, Zemek [27] found that patients with premorbid conditions such as previous head injury, learning difficulties and/or behavioural problems may also be at increased risk of lingering symptoms. One study that addressed the comorbidity of headaches, depression and concussion in 212 participants indicated that most participants (65%) reported new or worse headaches during baseline assessment and that, there was an increase in comorbidity from 11 percent at baseline to 25% at 1-year post injury for depression. A high-risk ratio was also found in cases where both headache and depression increased significantly between baseline and 1-year post- injury [28].

Gender is one factor that contributes to concussion incidence and recovery. It has been suggested that females are at a higher risk of mTBI due to higher rates of glucose metabolism, weaker musculoskeletal head support and changes in estrogen and progesterone throughout their monthly cycle [29]. Although females experience greater decline from baseline, report more

post-concussion symptoms and are cognitively impaired at a rate nearly 2 times that of males [30], men are more likely to have difficulty with externalizing behaviours and emotional regulation when compared to females [31]. According to Ledoux [11], adolescent females show the longest recovery times in children between the ages of 5 and 18 years of age with over half of the female adolescents failing to recover by 12 weeks post-injury.

Participation in sports and recreational programs also puts children and adolescents at an increased risk of brain injury. Specifically, 30 % of head injuries reported in children and youth between the ages of 5 and 19 are sports related [32]. However, Grool [33] found that children and adolescents (n= 2413, mean age =12 years old) who returned to light aerobic exercise in the first 7 days post injury are at lower risk of persistent post concussive symptoms., suggesting that gradual resumption of physical activity; that does not aggravate symptoms or increase the risk of re-injury should begin as soon as possible following an acute concussion [34].

The age at which a concussion occurs also impacts the number and type of symptoms reported, with middle aged children (5-13) reporting having more overall symptoms than young children (under 5) or adolescents [35]. Young children report symptoms such as feeling sick, vomiting and headaches whereas children over the age of 5 are more likely to report symptoms related to memory, anxiety and dizziness [35].

1.1.4 Comorbid Conditions

Neck injury during mTBI has been linked to persistent post concussive symptoms. Hynes and Dickey [36] found a strong correlation between whiplash neck injuries and the symptoms experienced post concussion in a sample of male college level hockey players. Their results showed that whiplash- associated disorders and concussion occurred together in all 183 participants regardless of how the injury was sustained. Further, the number of symptoms was not strongly associated with the severity of the injury and the whiplash related and concussion symptoms did not resolve at the same rate. Recent studies also show that females who sustain an mTBI between the ages of 5 and 49 years old have a significantly higher rate of comorbid neck injuries than males [15].

1.1.5 Pathophysiology

Most of the research into the biomechanics of mTBI has focused on animal models in which trained technicians intentionally induce a brain injury event using experimental techniques. Mechanically induced brain injury initiates ionic, metabolic, inflammatory, mitochondrial and neurovascular changes in the CNS, creating a mismatch between energy supply and demand [37]. This evokes an energy crisis following mTBI as the body attempts to restore ionic homeostasis. This energy crisis is believed to be related to the increased vulnerability of sustaining a secondary impact during the recovery period [38].

With a growing awareness of the possible long-term consequences of mTBI, it has sparked a search for objective biomarkers of concussion. Although the exact mechanism of brain injury following mTBI is not well understood, research shows a complex cascade of ionic, metabolic and pathophysiological events that lead to the disruption of brain function [39]. The

acceleration and deceleration forces that occur during a concussion initiate a sequence of neurochemical and metabolic events that can alter homeostasis. The sudden stretch and shearing forces cause a temporary perturbation in the plasma membrane. This initiates a flux of ions including excessive glutamate release, an efflux of potassium, influx of sodium and calcium and an alteration in the function of voltage gated ion channels [40].

Changes in Cerebral Blood Flow (CBF). Following an mTBI, patients may experience changes in cerebral blood flow. Regional blood flow is decreased in frontal and temporal lobes in regions that are involved in autonomic regulation and the processing of emotions [41]. A prospective experimental study of female college athletes who sustained a sport related mTBI indicated that participants with a history of concussion had significantly lower minute ventilation and abnormal CBF regulation during a treadmill exercise [42] reports that children who experience delayed symptom recovery (greater than 40 days) have higher global CBF when compared to participants who recovered within 2 weeks and uninjured controls. Following that study, Brooks [44] used MRI technology to measure cerebral blood flow in patients between the ages of 8 and 19 up to 90 days post injury. Results indicated no significant differences between the mTBI group and controls for global CBF, but youth with prior concussions had regions of hypoperfusion in the left and right lingual gyrus, right inferior frontal gyrus and the left fusiform gyrus. This suggests that mTBI may have a different impact on CBF in adults compared to children and adolescents.

Axonal Injury. Due to the highly structured organization and anatomical make up, axons are especially vulnerable to tissue damage post-mTBI. Axonal dysfunction and changes in neurotransmission are often to blame for the slowed reaction time and cognitive difficulties experienced after a concussive injury. Specifically, the rapid head deceleration induces axonal

shearing because excessive force is transferred onto the affected neurons [38]. It is the impact velocity rather than force that predicts axonal injury, with greater impact velocity associated with greater neuronal shearing and prolonged tissue recovery [38].

MTBI also induces impairments in cerebral energy metabolism which can hinder tissue repair. Prins [45] used an animal model focused on juvenile rats from 3 conditions; single mTBI, repeat injury and sham control. The introduction of a second injury within 24 hours of the initial impact resulted in increased axonal damage and memory impairments when compared to rats who had only received one impact. The key biochemical issue lies in the incomplete resolution of the initial energetic crisis triggered by the first impact.

White matter injuries occur when bundles of myelinated axons become damaged [46]. White matter makes up about sixty percent of the brains volume and acts as a rely station to allow communication between different brain areas. A study of college football players used Magnetic Resonance Imagining (MRI) to explore changes in white matter post mTBI. The scans showed that in comparison to controls, the mTBI participants had a reduction in water diffusion throughout the white matter at time periods of 24 hours, 6 days, and 6 months post injury. When compared to symptom reports, a positive correlation was found between the severity of symptoms reported post mTBI and the extent of white matter damage [46]. In a prospective longitudinal study, Van Beek [47] examined mathematical abilities and white matter in a group of 20 children (ages 7-14) post mTBI. White matter and cognitive abnormalities seen at 1-month post injury had resolved by follow up at 6 months, but children continued to show working memory deficits compared to controls. At the 6 months follow up, control participants showed normal maturation of the corpus callosum, where as mTBI children had marked deficits in

maturation. Taken together the research suggests different patterns of recovery in white matter tissue between children and young adults.

Changes in the Blood Brain Barrier. The blood brain barrier (BBB) is an important part of the neurovascular system. Its primary role is to create a restrictive barrier between the CNS and the rest of the body, but it is also responsible for the reuptake of molecules and acting as a regulator for cerebral blood flow [48]. BBB disruption and the neuroinflammation that accompanies it is a marked characteristic of severe TBI and is less prevalent in cases of mild injury [48]. Although research has shown that BBB leakage can occur after experimental concussion. Johnson [49] used a swine model of head acceleration based on human concussions to explore BBB integrity after concussion. At 6-72 hours post injury, researchers found multifocal disruption of the BBB in experimental pigs when compared to sham controls. Interestingly, leakage of proteins was more likely to be found along the gray-white matter boundary suggesting that interfaces between regions of tissue with varying material properties are at greater risk of leaked proteins post mTBI. In one study of 67 college football players, researchers took blood samples and found that those with the most concussive injuries had elevated levels of s100B antibodies (a glial-specific protein secreted by cells in the central nervous system that is used as a marker of BBB disruption). Further, they found that post-season; elevated s100B levels were correlated with impulse control and balance problems [50].

Functional Connectivity. Functional brain connectivity refers to temporally correlated activity in spatially distinct brain areas [51]. It is responsible for binding different regions together and integrating dimensions of cognition such as emotion, memory and motor planning. A balance in the increase and decrease of connectivity at different time points throughout the brain is vital for optimal brain function [52]. Neurophysiological changes have been found in the

early weeks after mTBI using fMRI, suggesting that mTBI may alter functional connectivity between different brain regions. Using MEG, Zouridakis [53] compared patterns of functional connectivity in a group of 10 right-handed mTBI patients and matched controls. For local connections, both groups showed similar densely connected networks. Although, mTBI participants had mostly peripheral connections and had significantly less density in centroparietal regions when compared to controls. In long range connections, mTBI participants had significantly less connections and asymmetric connections between the two hemispheres in occipital and frontal areas. This suggests that long range connections are more susceptible to the accelerated impact and may constitute a reliable biomarker for mTBI.

1.1.6 Diagnosis & Management

Effective diagnosis and management of concussion requires several evaluations at different time points post- injury. Patients do not always seek immediate medical care, so medical professionals must be prepared to provide effective care for any point in recovery. According to Mathews [19], concussions should be evaluated at three important time points: immediately after a suspected head injury, within the first 24 hours, and in the weeks following the diagnosis. The immediate assessment is focused on ruling out severe spinal cord or brain injury and immediate removal from activity to avoid a second impact. In the first 24 hours post injury, management is focused on evaluating signs and symptoms, reviewing medical history and conducting a neurological examination which includes aspects such as vision, hearing, strength, sensation, balance, coordination and reflexes. Cognitive assessments that evaluate memory, concentration and the ability to recall information are also important in diagnosing concussion

[19]. In cases where there is a suspected bleed, structural damage or noticeable motor and/or neurological deficits, a doctor may request imaging such as an MRI or CT scan [49].

Self Report Assessments. In early research, most concussion assessments used a Likert scale to document the number and severity of concussion related symptoms. These assessments predominantly focus on neurological state, self-report, and subjective recall of the traumatic event and post-injury symptoms [54]. These types of assessments have high susceptibility to response bias [55] lack objective markers and rely on baseline scores to determine if there has been a change in a patient's physical, emotion or neurological state [56]. One example of these types of assessments is the Post-Concussion Symptom Inventory (PCSI) [57]. Most of the factors that jeopardize the validity of concussion assessments can be limited by standardizing the testing environment, having appropriately trained personnel, providing clear and concise instructions and examining baseline scores for any inconsistency that may suggest a lack of understanding or intentional poor performance [56].

Multi-dimensional Assessments. In recent years, there has been a change to a more multi-dimensional approach which is done in a clinical setting and involves a battery of tests to assess a combination of physical, psychological and neurological abilities [9]. Assessments such as the Sport Concussion Assessment Tool 5 (SCAT5) and the Standardized Assessment of Concussion (SAC) include both symptom scores and objective clinical aspects. The SCAT 5 includes an immediate on field assessment of observable signs, memory tasks, completion of the Glasgow Coma Scale and a cervical spine assessment. A secondary off field assessment is conducted in a distraction free environment with the individual in a resting state. It involves a detailed background check, symptom Likert scale, a cognitive and a neurological screening [58]. To try and limit the chance of error, clinicians often rely on change scores and confidence

intervals. For example, one study showed that if a SAC score declined by five or more points between baseline and injury, the clinician can have a 99% confidence that the change is related to something other than normal test-retest variability [56].

Computerized Assessments. Popular computerized concussion assessments include the Immediate Post Concussion Assessment and Cognitive Testing (ImPACT), Concussion Sentinel and the Headminder Concussion Resolution Index (CRI). ImPACT assesses concussions by providing pre and post head injury evaluations and includes a series of timed questions that compute 4 composite scores including verbal memory, visual memory, visual-motor processing speed and reaction time. [59]. The Concussion Sentinel uses seven tests to develop 5 five output scores including verbal memory, visual memory, visual motor speed, reaction time and impulse control [60]. The CRI uses 6 tests to produce 5 index scores including processing speed, simple reaction time, complex reaction time and reaction time errors [60]. Broglio [61] explored the test-retest reliability of these three assessment programs and found low to moderate reliability coefficients in a sample (n=188) of healthy university students.

In recent years, the addition of vision-based testing to symptom report, cognitive and balance testing has enhanced the effectiveness of concussion assessment. For example, in a cohort of 243 youth athletes, Galetta [62] examined the effectiveness of the King-Devick test, the SAC and a timed gait test of balance. Of the three, the vision-based King-Devick test showed the greatest capacity for distinguishing concussed children from healthy children. This suggests that the visual system may play a greater role in concussion diagnosis and management then previously alleged.

Section 2: Vision and Oculomotor Function

1.2.1 Basic Visual Pathway

The visual pathway includes the retina, optic nerve, optic chiasm, optic tract, lateral geniculate nucleus, optic radiations and the striate cortex [63, 64]. t starts with the projection of ganglion cell axons from the retina to the optic nerve which then project to the opposite hemisphere of the brain. The eyes are located at the front of the head so the visual fields of the two retinas overlap at the center of each visual hemifield. Each retina projects axons to both hemispheres. Those located in the nasal retina send their projects to the contralateral hemisphere, while those of the temporal retina send axons to the ipsilateral hemisphere [63]. The striate cortex (V1) is located almost entirely on the medial surface of the occipital lobe, has a thickness of approximately 2 mm and is organized into horizontal and vertical columns [65]. The visual cortex is the area of the brain where objects are analyzed both in and out of their visual context. Different cells respond to different aspects of an object such as its edges, curvature, direction of movement and colour. The visual cortex is the first location in which signals from the two eyes converge and begin analyzing disparity in objects presented within the visual field.

The expansiveness of the visual system required to produce eye movements makes it an attractive area for research on concussion. Disruption in the visual system is common following a concussion, with approximately 70% of children and adolescents experiencing at least 1 visual abnormality post mTBI [66]. Visual symptoms attributed to poor oculomotor control include diplopia, eyestrain, impaired visual scanning and blurred vision [67].

1.2.2 Neuroanatomy

The oculomotor system is part of the central nervous system. Its primary function is to maintain visual stability and control eye movements to keep an image on the center of the fovea [68]. The ocular muscles are subdivided into two categories: involuntary intrinsic muscles and voluntary extrinsic muscles. The intrinsic muscles include the ciliary muscle, the iris sphincter and the iris dilator, which are located within the eye and control the movement of internal ocular structures [69]. The 6 extraocular muscles are the medial rectus, lateral rectus, superior rectus, inferior rectus, superior oblique and inferior oblique, which control the movement of the eye globe [68]. All eye movements are defined by the rotation around one or more axes. These axes divide the globe into quadrants that intersect at the center of rotation [68]. Movements that involve only one eye are referred to as ductions and involve rotations in both the vertical and horizonal planes. Movements that involve both eyes are referred to as vergences or versions, dependent on the direction of movement [65].

Oculomotor function begins at the level of the brainstem and involves three different cranial nerves. The abducens nerve (cranial nerve 6) exits the midbrain at the junction of the pons and medulla and controls the lateral rectus of the ipsilateral eye. The abducens enters the subarachnoid space and runs upward to the dura mater, through the cavernous sinus and enters through the superior orbital fissure where it innervates the lateral rectus of the eye [63]. The trochlear nerve (cranial nerve 4) controls the superior oblique of the contralateral eye. The trochlear nerve exists the dorsal region of the brainstem and passes between the superior and posterior cerebral arteries before piercing the dura. Although it has the smallest number of axons of all the cranial nerves, it also expands over the greatest intracranial length [63]. The oculomotor nerve (cranial nerve 3) exists the brainstem at the base of the midbrain, passes

through the cavernous sinus and proceeds through the supraorbital fissure to reach the orbit of the eye and has both somatic and autonomic fibers that are important for different eye movements[63].

The extraocular muscles are densely innervated resulting in precise fine motor control and high velocity during ocular movements [68]. The individual action of each muscles depends on the shape of the orbit, the insertion point, and the initial position of the eye [69]. The medial and lateral rectus are innervated by three cranial nerves and work together to control horizontal eye movements. The actions of these two muscles are antagonistic, meaning one must contract while the other remains relaxed. The remaining four muscles work together to control vertical eye movements and rotation around the mid-orbital axis [63]. The superior rectus produces eye elevation whereas the superior oblique produces eye depression and is also responsible for medial rotation and abduction. The inferior rectus produces eye depression whereas the inferior oblique produces eye elevation, lateral rotation and abduction [70].

1.2.3 Eye Movements

Smooth Pursuit. Smooth pursuit of a predictable target is based on input from the retina and is coordinated by the cerebellum [71] which requires attention, expectancy and working memory to maintain gaze fixation [72]. Smooth pursuit is routinely tested by clinicians by asking a subject to track a moving object within the visual field. Such movements are under voluntary control. Smooth pursuit movements show characteristics; the delay is shorter and maximal velocity is higher than in simple eye tracking. In a laboratory setting, pursuits can be broken down into several different functions: (1) initiation of the eye movement, (2) pursuit maintenance and (3)

using the knowledge of predicable movement of the target [73]. Initiation of the pursuit involves measures of pursuit latency (the time period prior to pursuit initiation. Typically, 90 -150 ms) and pursuit eye velocity that occur in the first 100 ms when feedback is not yet available [74]. Pursuit maintenance uses a measure of retinal slip (motion of the visual image on the surface of the retina) to control eye velocity and close the feedback loop [73]. The system performance at this stage is quantified by pursuit gain (ratio of eye to target velocity). Lastly, the knowledge of predictable movement of the target requires the differentiation of the eye position signal be compared to the stimulus.

Smooth Pursuit and mTBI. Abnormalities in smooth pursuit can be easily missed during standard clinical examination because the dysfunction (reduced tracking accuracy) is so subtle that it is difficult to detect by the human eye [71]. A recent study that included 36 adolescent athletes (18 concussion patients and 18 age matched controls) by Murray [75] used an eye tracking device to increase precision in measuring eye movements. They found statistically significant between-group differences in smooth pursuit velocity (measure of the speed of the pursuit) but not in smooth pursuit amplitude (denoted using gain: the ratio of the actual pursuit size compared to the desired size). More precisely, the eyes moved in the horizontal direction at the same average distance in the two groups but adolescents in the mTBI group had much slower movements and thus more difficulty tracking the target accurately.

Saccades. According to Murray [75] smooth pursuit and saccades are both required for successful object tracking. A saccade is a quick, simultaneous movement of both eyes between two or more phases of fixation [76]**.** For saccade generation, the visuospatial information produced by the stimulus is relayed from the occipital lobe and then processed in the posterior parietal cortex. Saccades are then generated and executed in different areas of the parietal and frontal lobe

including the frontal eye field, dorsolateral cortex and supplementary motor areas [77]. Visual saccades are under voluntary control and occur in both the horizontal and vertical planes to bring stationary visual targets onto the center of the fovea where acuity is at its highest [78]. The neural representation of the motor command for saccadic responses takes place at the level of the brainstem [79]. The ocular motor neurons encode characteristics of a saccade in terms of temporal discharge to evaluate the size of the saccade and how proportional it is to the number of discharge spikes [80]. Saccades last between 15 and 100 ms, can reach velocity levels that exceed 700 degrees per second, vary in size, and typically occur with a latency of 200- 250 ms [68].

During a saccade there is a high frequency burst of phasic activity in the agonist ocular muscle and its corresponding ocular motoneurons that occurs approximately eight milliseconds before the eye starts to move [63]. This burst is responsible for generating the force necessary to move the eye quickly from one point to another. At the end of the saccade the agonist muscle and its ocular motoneurons assume a new, higher level of tonic innervation to hold the eye in its new position [80].

Saccades and mTBI. Saccadic eye movements are the most frequently studied oculomotor measure in mTBI research [81]. Patients with mTBI demonstrate increased saccadic latencies, higher directional errors, poorer spatial accuracy, and longer intervals between saccades when compared to healthy controls. [82, 83]. Patients who recently experienced a concussion (within 90 days of presentation to the clinic) generate fewer self-activated saccades with research showing a negative correlation between the total number of saccades and the severity of symptoms [84]. A negative correlation is also said to exist between the number of saccades and performance on neurological tests that examine executive function. In a systematic review, researchers determined that the most commonly reported findings across the literature are greater amplitudes, smaller peak

accelerations, slower velocities, and less accurate target prediction during saccade tasks in participants with mTBI when compared to healthy controls [85]

Anti-Saccades. An anti-saccade is a voluntary eye movement made in the direction opposite to the side where a stimulus is presented [63]. The anti-saccade task involves two mental processes: the inhibition of triggering a reflexive saccade toward the stimulus and the inversion of the visual target vector (the amplitude of the stimulus from one hemifield to the other [86]. Anti-saccades are a form of predictive visual tracking and require both attention and working memory [3]. The prefrontal cortex is believed to be an important substrate for coordinating and executing these types of functions. Anti-saccades carry a high cognitive load, which makes errors and latencies produced during the task a possible indicator of abnormal activity in the frontal lobe [86].

Anti- Saccades and mTBI. Adults with mTBI show increased latencies, higher directional errors and poorer spatial accuracy during anti-saccades [87]. Although studies that address anti-saccadic eye movements in children with concussion are sparse, one study by Phillipou [76] found that children with mTBI (n=26) showed increased latency and a greater number of errors than age matched controls (n=29) during a battery of saccadic eye movement tasks. Research by Heitger [88] suggests that anti-saccade latency tends to return to normal 1week post injury, but accuracy differences are found up to a few months post-mTBI suggesting a greater impact of mTBI on the ability to invert the visual vector than the ability to inhibit the reflexive saccade system.

Vergence. Vergence refers to the movement of the eyes when tracking objects at varying degrees of depth in the binocular visual field (convergence for closer targets (+), divergence for distant targets (-)) [69]. Vergence in the binocular system can be caused by amblyopia, or more relevant here, by any asymmetry in bilateral neural responses to selected stimuli. Continuous small, highly accurate adjustments in vergence are necessary to maintain binocular alignment in

order to avoid diplopia or partially overlapping images [89]. Vergence movements change over the course of development, and this is especially prominent in a measure known as the near point of convergence (NPC). NPC is a measure of the amplitude of convergence, or the closest point in space where an individual can hold fusion and see a target [89]. The mean NPC decreases significantly between the ages of 2 and 17 years old. Thus, children can fuse images at a closer proximity in early years then later stages of development [90].

Vergence and mTBI. Vergence appears to be an important component of the oculomotor system with approximately 40-60% of patients presenting accommodative or vergence issues following mTBI [91]. Szymanowicz [92]explored the wide range of static and dynamic aspects of vergence in mTBI patients. Their results indicate that participants with concussion show decreased peak velocity and longer latencies when performing both convergence and divergence tasks. Although research has yet to explore vergence in children with concussion exclusively, one study with participants between the ages of 9 and 35 found that when assessing static parameters concussed individuals show reduced near point convergence and when the task involves dynamic parameters the response of those with mTBI are slowed, variable, and delayed [93].

Section 3: Vestibulo-Ocular Function

1.3.1 The Vestibular System

The main function of the vestibular system is to detect the position and movement of the head in space for the purpose of coordinating balance, movement, and spatial orientation [94]. It is composed of various structures including the bony and membranous labyrinth and specialized sensory hair cells located in the inner ear. There are three semicircular canals (SCC) located in the inner ear responsible for facilitating the extraocular muscles on one side, while inhibiting muscles on the opposite side and providing sensory neural input related to angular acceleration in order to coordinate head and eye movements through the vestibular ocular reflex (VOR) [95]. Primarily the VOR provides stable vision during head movements and helps to perceive spatial information from the surrounding environment [69]. There are two remaining reflexes; the vestibulo-collic (VC) and vestibulo-spinal reflexes (VS). The VCR shapes head movements and supresses reflex response to active, intended head motions and the VS works to stabilize the head and generate compensatory movements of the body [96]

1.3.2 Neuroanatomy

Central processing of vestibular information primarily takes place in the brainstem through afferent fibers of the 8^{th} cranial nerve [96]. The signals enter the brainstem at a point near the medulla and pons known as the vestibular nuclear complex [97]. This complex is comprised of four major nuclei located at the floor of the fourth ventricle. The vestibular nuclei of the brainstem exchanges signals regarding body movement and position and sends signals down a variety of projection pathways [98]. Signals are sent bilaterally to the cerebellum [99]

which acts as a processor and modulator of vestibular information. Signals sent to the reticular formation communicate postural changes and signals sent to the spinal cord provide quick reflex reactions to regain balance after the change in posture [96]. Important projections are also made to the thalamus which allows for motor control and conscious awareness of body position in space [97].

1.3.3 VO Function

Vestibular Ocular Reflex. The VOR is a reflexive eye movement that occurs to stabilize images on the retina during head movements [100]. It responds to a head movement with an eye movement of equal velocity in the opposite direction in order to preserve the image on the center of the visual field. The velocity of head movement is detected by the vestibular organ and provides information about both angular and linear acceleration [73]. Testing the peripheral functions of the VOR can be done in multiple ways including irrigation of the vestibular organ by cold and warm water, quick rotations of the head while a subject maintains fixation or whole-body rotations with sudden stops to induce nystagmus [73].

VOR and mTBI. Peripheral vestibular disorders are caused by injury to the vestibular nerve and labyrinth. The most observed deficits include blurred vision, balance issues and vertigo [94]. Central vestibular disorders are much more common with mild traumatic head injury and occur when there is damage to the cerebellum or white matter [101]. Although there is minimal research covering VO function in children and adolescents, vestibular symptoms following mTBI are commonly reported, with dizziness being one of the primary predictors of prolonged recovery [94]. When the gain error between head and eye velocity is too great it can

result in symptoms of dizziness, unsteadiness, and oscillopsia [102]. In paediatric patients vestibulo-ocular dysfunctions are most apparent in visually stimulating environments including school and sports settings. Ellis [103] found the most common complaints from children include difficulty working on a computer for long periods, skipping words or loosing a spot while reading, anxiety and nausea with motion or when starring down the hallways. Postural and visual symptoms related to the vestibulo- ocular system include dizziness, difficulty focusing or tracking moving objects, and trouble perceiving depth. These symptoms often result in impaired balance and or gait [104].

1.3.4 Visual-Vestibular Interaction

Although the visual and vestibular systems are inherently separate, they must work together to integrate information required to use visual input to manage motion in a three-dimensional space. When the head and eyes move together to track a single object the VOR must be suppressed to keep focused on the target. Disruption in this suppression can lead to motion hypersensitivity [105]. Some research suggests that vestibular projections to prefrontal areas (dorsolateral prefrontal and frontal eye field) play a role in smooth pursuit, saccades, convergence and accommodation [98]. Interaction between the oculomotor and vestibular systems are also important for encoding object and self motion [106]. Wright [107] investigated the role of visual-vestibular processing deficits following concussion in adults and found that postural and visual-vestibular tasks most closely linked to spatial and self motion perception had the greatest discriminatory outcomes. These findings suggest that parieto-occipital centers and pathways may also be involved in concussion.

Section 4: Assessment Tools for OM and VO Function

1.4.1 Standardized Assessments

The King Devick (KD) is a quick and easy to administer test based on measurement of the speed of rapid number naming to identify correlates of suboptimal brain functioning including impairment of eye movements, attention and language [62]. It was originally developed as a reading fluency and comprehension assessment and results are found to correlate strongly with validated attention, processing speed, and visual scanning tests [108, 109]. When compared to pre-season baseline testing, an increase in the time taken to complete the test is indicative of a concussion with sensitivity and specificity values near 90 percent [110]. The KD has high efficacy as a sideline assessment tool but shows low test-retest reliability because of its susceptibility to learning effects [111].

The Vestibular Ocular Motor Screen (VOMS) measures 5 different eye movements: smooth pursuit, saccades, near point convergence, VOR and visual motion sensitivity. It is a clinical tool used to assess vestibular and ocular motor impairment through self-reported symptom provocation on 7 test items. It is performed by an examiner who records the patient's symptom provocation for each assessment on a 10-point Likert scale. In a study of 64 mTBI participants with a mean age of 14 years old, 60 % of patients reported symptom provocation on at least 1 VOMS item. When compared to healthy age- matched controls (n=78), symptom provocation during the VOR and visual motion sensitivity items is most predictive of a history of concussion. [112]. The assessment focuses on symptom reports and includes a measure of NPC that is measured three times. An NPC distance of greater than 5 cm along with a VOMS item symptom score of 2 or more is predictive of abnormal vestibulo-ocular function [112].

Although the VOMS is readily accessible to clinicians and does not require baseline data, it is designed to provoke vestibular symptoms, which make it susceptible to false positive results [56]. The VOMS takes only 5-10 minutes to administer and can be done on the sideline, but is sensitive to instruction and interpretation bias by the examiner which can weakening it's reliability [112].

The Dynamic Visual Acuity test (DVA) is specifically designed to assess vestibular loss. The test is performed in a sitting position as the participant reads each line on the Snellen chart. The examiner flexes the participants head by 20 degrees in order to isolate the horizontal canal and then rotates the head back and forth in the horizontal plane at a frequency of 2 Hz. The smallest line read with less than three errors is recorded while the head is moving. The sensitivity and specificity of the test varies greatly depending on the examiner's experience and the specific methodology used for the test. Variations include self versus active head movements, position of head and frequency of head movements [98]. The expected result in a healthy participant is a drop of zero to two lines on the chart and the cut-off for abnormal scores is a drop of three or more lines. Regardless of performance, any provocation of symptoms during the test suggests injury-induced alteration.

The Head Impulse Test (HIT) is a widely used clinical assessment technique used to assess the angular vestibulo-ocular reflex. It assesses horizontal semicircular canal and superior vestibular nerve function in response to small amplitude, high acceleration rotational head impulses [56]. During the test, the patient fixates on a target while the examiner generates a rapid head impulse and monitors the patient's eyes for corrective or compensatory saccades[113]. The clinical HIT is not scored and aVOR function is evaluated as normal or abnormal by the presentation of a compensatory saccade [114]. Use of high-speed video in a laboratory setting has

provided measurement of aVOR gain and eye movement latencies to validate the HIT. The video head impulse test (vHIT) is primarily focused on gain values, which can vary depending on several factors such as how tightly the headband in placed around the patient's head or the examiners interpretation. Korsager [115] calculated the interclass correlation between gain values for 4 examiners and found that 30-40 % of the variances for both healthy and mTBI patients are caused by interpretation discrepancies between examiners.

1.4.2 Eye Tracking Systems

One method of objective assessment of OM and VO function that has sparked a growing interest in concussion research is the use of portable eye tracking systems. The most readily used are video based eye-trackers, where two cameras record the two eyes at rest or during various tasks. Until recently, head movements have been restricted so that eye orientation simply determined the gaze direction. Modern eye tracking involves an array of infrared or near infrared light sources [116] and have been extended to head-free protocols where head movement is tracked with linear and angular accelerometers, while both eyes are recorded with video. This allows controlled study of ocular reflexes and eye-head coordination in more natural tasks. Data is often analyzed using automated software algorithms and compared against a normative sample associated with the chosen test.

The most common eye movement patterns recorded include smooth pursuit, saccades, fixation, anti-saccades and vestibular or optokinetic reflexes. Various metrics are extracted including direction, gain, velocity, amplitude, accuracy, and response time. Eye movement recordings offer the benefit of recording multiple parameters simultaneously at high rates.

Abnormalities in visual tracking have been reported in mTBI patients, using video-oculography [117].

Bin Zahid [118]explored the use of automated eye tracking as a biomarker for concussion post- injury in a sample of mTBI children. Results indicate group differences between the concussed and healthy controls on 12 out of the 15 metrics. In the concussed sample (n= 56), 70-90 % of participants experienced symptoms during horizontal and/or vertical saccades. They also compared their results to a previous cohort of adults with and without concussion and found that some metrics (ratio of horizontal and vertical variance during VOR) were only significant in pediatric cases. This suggests that VOR changes might be more prevalent in the pediatric population than in adult populations, and highlights VOR dysfunction as an important aspect to consider when comparing OM and VO function in different age groups.

Abnormal eye movement patterns during gaze tracking have been found to accompany abnormal MRI results in mTBI patients. Participants performed fixation, anti-saccades and smooth pursuit while undergoing fMRI. Results indicate that mTBI subjects display longer latencies, worse position errors and fewer self paced saccades compared to normal volunteers. Additionally, concussed patients show recruitment of additional brain regions and larger activation sites than controls, as evidenced by fMRI [49]. This increased activity suggests that a compensatory process may exist to improve functional performance when there are small deficits in the network. Further, there may be a relationship between ocular motor deficits and the affected anatomical sites in the brain that could be best understood by recording eye movement patterns.

1.4.3 Virtual Reality Assessments

Virtual Reality (VR) devices are readily available to the public and are equipped for use in both professional and leisure activities. In a clinical setting, VR systems are most often used for medical simulation, in the treatment of phobias and addictions [119] and have been used effectively to detect lingering balance deficits in clinical concussion care [120]. Using a prospective design, Nolin [121] compared the use of immersive VR to a standard computerized neuropsychological test in 25 sports-concussed and 25 non sport-concussed adolescents. VR showed greater sensitivity to the effects of sports concussion compared to the traditional test, which showed no between group differences. Sports concussions were also associated with greater deficits in attention and inhibition on both the VR and computer assessment when compared to adolescents with non sport-related concussion. Most research explores head mounted VR devices in situations that require mobility, which can be problematic for participants with motor and/or cognitive impairments because of the risk of falls and/ or subsequent injuries.

Although VR systems may have a potential utility in understanding visual and vestibular deficits following concussion, previous literature contains small sample sizes, focuses on lingering deficits, and does not address feelings of cyber sickness; a common vestibular concern after concussion [119, 122]. Further, the hardware and software required to run VR systems are often costly, large and bulky and are highly technically advanced [120].

1.3.4 VR combined with Eye Tracking

Head-mounted virtual reality (HMVR) combined with eye tracking cameras have been advocated as a user-friendly, cost-effective, portable and non-invasive method to record eye-head trajectories [123]. These systems need to be comprehensible for therapists and patients and require strict calibration processes for accuracy. Findings of clinical efficacy of VR for vision and vestibular assessment are inconsistent and can vary greatly with and without performance feedback. The feasibility and clinical significance of VR combined with eye tracking is impacted by two main factors 1) number of repetitions of the task 2) guidance from an external supervisor [124]. One study in a sample of young adults (n=18) concluded that the addition of feedback during a VR saccade task increased specificity from 65 % to 80% [124]. VR is highly immersive, so it is vital that intervention be kept at a minimum. One way in which this can be accomplished is by providing a live video of the patient's eyes so that the clinician can offer subtle feedback without large disruptions throughout the task.

Additionally, eye movement tests often require baseline data or highly complex equipment. Current eye tracking systems have limitations that can greatly impact their sensitivity. First, recalibration is required every time the head mounted device is adjusted or moved, and user acceptance of re-calibration procedures are low [119]. Secondly, specificity depends greatly on the combination of 2 factors 1) fixation detection 2) spatial proximity, which is not always available because it is heavily dependent on the fit of the headset [119]. Thirdly, when combining eye tracking with VR, synchronization of the recorded data and software needs to be highly precise. This is not always the case and can be affected by WIFI connection and delayed communication between the two systems [125]

In summary, children and adolescents have a unique susceptibility to severe and prolonged symptoms and are at an increased risk of repeat injuries [3, 6]. Symptoms of concussion are variable in nature and include a combination of physical, cognitive, emotional and sleep related changes that impact neurological, psychological and social developmental processes [126]. Concussion assessments are plentiful in nature and commonly address self report of symptoms, measures of balance and gait, neurological function, assessment of motor skills and recording of eye movements [3]. The expansiveness and complexity of the visual system makes it an attractive area for research on concussion. Oculomotor and vestibulo-ocular assessment with eye tracking has proven to be one technique that can provide quick, objective, and reliable feedback that pertains to the physiological aspects of the eye [127] Thus, by combining VR and eye tracking technology into one tool it will increases tracking accuracy, improve usability, and hopefully simplify the diagnosis and management of concussion in children.

CHAPTER 2

Rationale and Objectives for Manuscript

Mild traumatic brain injury has become a growing concern in the pediatric population and can result in a combination of subjective symptoms and objective deficits which may include visual complaints and/or visual dysfunction. Approximately 70% of children and adolescents aged 11-17 years old report at least 1 visual symptom following a concussion [66]. Although this suggests that vision-related symptoms may be an important aspect of post-concussion assessments, the physiological mechanisms that underlie these symptoms are not well understood. Psychophysics has focused primarily on documenting convergence and saccades [128] leaving other important aspects of OM (anti-saccades) and VO function (VOR, visual slip, etc.) virtually unresearched.

Although children and adolescents are highly susceptible to concussion, the pediatric population is poorly represented in research on OM and VO deficits. Due to the high visual work load of school and extra-curricular activities, adolescents and children are especially limited by symptoms and impairments related to the visual system [129]. Current clinical assessments and self-report questionnaires have a high susceptibility to response bias and may not detect subtle abnormalities after concussion. Existing computerized and technology-based assessments of OM and VO are expensive, highly complex and not easily accessible to clinicians caring for children with concussions. Traditional eye tracking methods are large and bulky, involve complex hardware systems (infrared lights, sensors etc.) and are restricted to highly controlled environments, limiting their practical utility [130]. This is especially pertinent in pediatric clinical research because of the need for developmentally appropriate outcome measures and adaptations

required in research procedures and settings to accommodate children's physical, cognitive and emotional development [131].

Although both self-report symptom scales and technological advances such as eye tracking demonstrate usability in concussion assessment, literature has yet to address similarities or differences in outcomes related to OM and VO function. The next step should be to identify unique eye movement patterns/ abnormalities that occur following a concussion and relate them to symptom etiology. According to a systematic review of 561 studies by Zemek, Farion [132], there was minimal and at times contradictive evidence to associate clinically available predictors with the development of post-concussion symptoms in children. Without a tool that is both accurate and affordable; clinicians have been left to rely on imprecise measurement tools. In recent years, recording and studying movement patterns of the eyes has become more accessible and has been suggested as one method to help fill existing gaps in the literature.

Two specific but related **research questions** were addressed in this study:

(1) To what extent do children with symptomatic mTBI differ from recovered or uninjured children for oculomotor (smooth pursuit, saccade, anti-saccades, vergence) and vestibulo-ocular (VOR) function?

(2) To what extent does OM and VO function relate to post-concussion symptoms severity in children with mTBI?

The study therefore addressed the following **objective**s and hypotheses:

(1) To document OM and VO function in children who sustained an mTBI and were symptomatic at the time of assessment, and to compare them to that of clinically recovered children with prior mTBI as well as uninjured (healthy) children matched for age and sex;

We hypothesized that

H1a: Children who were symptomatic after an mTBI would present with significantly different OM and VO function when compared to children who were clinically recovered or uninjured.

H1b: Children who were symptomatic after an mTBI would present with similar OM and VO function when compared to children who were clinically recovered or uninjured.

(2) To relate OM and VO function to the severity of post-mTBI symptoms

We hypothesized that

H2: OM and VO function in children with symptomatic mTBI would be inversely related to the severity of their overall post-mTBI symptoms

CHAPTER 3

THE MANUSCRIPT

Oculomotor and Vestibulo-Ocular Function Post- Concussion in Children and Adolescents

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3.1 Introduction

Concussion or mild traumatic brain injury (mTBI) has become a growing concern in the pediatric population. It can result in a combination of subjective symptoms and objective deficits which may include visual complaints and/or visual dysfunction. Approximately 70% of children and adolescents aged 11-17 years old report at least 1 visual symptom (blurred or double vision, sensitivity to light, visual motion sensitivity, decreased peripheral vision, ocular pain and/or abnormal eye movements) following a concussion [1]. The visual system is particularly vulnerable to the effects of brain injury because of its expansive anatomy and connective pathways throughout the brain [2].

Emerging research has detailed the effect of concussion on visual outcomes in children, with poorer performance observed post-injury [1]. Although visual symptoms are often reported, the physiological properties of the visual and vestibular system that underlie these symptoms and the natural progression of symptom change and recovery is poorly defined in children following concussion [3]. Objective assessment tools are expensive and are not portable which makes them difficult to access for studies on concussed children. In some respects, clinical research involving children and adolescents can be more challenging than research involving adults. These challenges include the need for developmentally appropriate outcome measures, the added complexity of parental involvement and family decision making, and adaptations required in research procedures and settings to accommodate children's physical, cognitive and emotional development [4].

In recent years, recording and studying movement patterns of the eyes has been suggested as one method to overcome barriers associated with concussion diagnosis. These barriers include self report bias, (over or under reporting of symptoms) , the need for a quick, reliable and portable

sideline tool with objective biomarkers [5], and an assessment that can be easily adjusted for developmental appropriateness [6].

Eye tracking refers to recording and studying eye movements in response to a stationary or moving objects/targets in either a naturalistic or laboratory setting [7]. For each eye, there are 6 muscles that work together to control eye position and movement in 3D. The motor neurons that control these muscles coordinate their activities to produce eye elevation and depression, lateral and medial rotation, as well as eye adduction and abduction [8]. Together these movements contribute to optimal functioning of the eyes during visual tracking of moving objects and image stabilization during body locomotion [9]. Following a concussion, everyday tasks that require eye movements may become heavily impaired. For example, the ability to scan the visual environment for threats or move the eyes inward and outward to focus on objects of varying depths [10].

There are two functional classes of eye movements that are involved in visual function. Oculomotor (OM) function refers to the control of eye movements, such as the ability to locate and fixate on objects in one's visual field. Vestibulo-ocular (VO) function refers to one's ability to make compensatory movements of the eyes in relation to those of the head to stabilize vision when fixating on stationary and/ or moving objects [11]. OM and VO function require complex circuits in both cortical and subcortical structures that may be affected by concussion.

Eye tracking devices reliably detect and objectively record the movements of the eyes during simple or complex visual tasks [12] and are highly versatile, allowing tasks to be easily adapted for different age groups [13]. Thus, eye tracking during OM and VO assessments may prove to be an objective and sensitive marker of visual function following a concussion.

The purpose of this study was therefore to compare oculomotor and vestibulo-ocular function in symptomatic, clinically recovered, and healthy children (aged 8-18 years old) using a novel eye tracking device and relate those functions to the severity of post-concussion symptom.

3.2 Methodology

Study Design:

A prospective cross-sectional design was used to document OM/VO function using a computerized eye-tracking assessment and post-concussion symptoms in three groups of children and adolescents: those with symptomatic concussion, those with asymptomatic (clinically recovered) concussion, and healthy uninjured controls. The study was conducted in a speciality Concussion Clinic in a tertiary care pediatric trauma center. Computerized eye tracking assessment of OM and VO function was performed prospectively, and data was collected as part of the Concussion Clinic clinical activities, as were other clinical outcomes and important event dates (date of injury, date of assessments, date of discharge when applicable). Data for this project was extracted from the Concussion Clinic Database at the Montreal University Health Center (Montreal, Canada).

Participants:

The study was approved by the Research Ethics Board committee (REB) of the MUHC. Data from all children and adolescents having presented to the MCH Concussion Clinic between June 1st, 2018 and March 31st, 2019 between the ages of 8 and 18 years old having sustained a concussion in the last three months were considered for the study. Individuals who sustained a previous concussion within the last 12 months, had a prolonged period (>90 days) between their

injury date and OM/VO assessment, and/or reported any known existing visual disorders or learning disabilities were excluded from the study. Concussed participants who meet the inclusion criteria and for whom computerized OM/VO function assessment were available were separated into two groups; 1) symptomatic or 2) recovered at the time of OM and VO testing (as determined by professionals of the Concussion Clinic). The symptomatic group consisted of children and adolescents with post-concussion symptoms at the time of assessment, whereas the recovered sample were the participants whose symptoms had subsided and who had been cleared to return to all activities. Although participants were not matched by age and sex 1:1, anonymized OM and VO data from a sample of participants of similar age and sex were selected from an existing normative database of healthy uninjured athletes aged 11 to 15 years old, tested in the winter of 2019 and provided by collaborators at Saccade Analytics. After applying the inclusion and exclusion criteria, a total of 187 children between the ages of 8 and 18 years old were selected to participate in the study.

Outcome Measures:

Oculomotor and Vestibulo-Ocular Function

Oculomotor (smooth pursuit, saccades, anti-saccades and vergence) and vestibulo-ocular (vestibular ocular reflex or VOR) function were acquired with a commercial eye tracking system (Saccade Analytics, InSight$^{TM)1}$. The device includes head mounted virtual reality googles made by FOVE[2]. The goggles provide ocular and head tracking to gain information. Head angular and

[1] Saccade Analytics, InSight^{TM} device, Montreal, Quebec, https://saccadeanalytics.com/product/

[2] FOVE (FOVE Inc., San Mateo, California, https://www.getfove.com/

linear acceleration were recorded with accelerometers at 100 Hz for all head channels (3D rotation and 3D linear acceleration). Eye data channels are interpolated from 60 Hz to 100 Hz to synchronize with head. The original hardware sampling intervals are ~17ms in eye data collection mapped to 10 ms at 100Hz. FOVE reports a precision of +/- 1 degrees for eye and +/- 2 degrees for gaze (eye+head). Before each test, a screen displays a description of the test and instructions for both tester (on laptop screen) and subject (inside goggles). Before commencing, the administrator explains the test and answers any questions asked by the patient.

The Insight system provided by Saccade Analytics uses software programs for two stages of data collection and interpretation. (1) Insight-R is the package that automates the data collection stage. During tests, an 'eye link' video display on the laptop screen allows the operator to monitor videos of the two eyes. Once the protocol sequence is executed, data is then passed to (2) NeuroFlex via the Cloud, a software that automates production of test-specific metrics from the data matrices. The Cloud site is compliant with privacy laws, with data from the participants identified by a randomly assigned eight-digit ID number. The cloud features an analytic platform that makes the results easier to understand, manage, and share. NeuroFlex first applies a sequence of analysis blocks shared by all tests: i) data denoising; removes only the random component of any signal without distorting the desired ocular signals and saccade trajectories. This is not a classical filter based on bandwidth rejection which would distort (smooth/attenuate) nystagmus corners. ii) Detection of blinks to mark 'bad' data; detected with a threshold which time interval is excluded from the analysis step and iii) classification of records into slow and fast phases for saccades. The classifier is proprietary to Saccade Analytics' and is based on AI detection methods. In all cases, if the desired information is slow phased, then all fast intervals are excluded from the calculations and vice versa. All this is totally automated and not affected by the participant or

tester. All submitted tests for a given subject are analyzed and metrics are returned to the user within 1 min, after a testing period of ~ 5 min. Refer to Appendix 1 for a sample report.

A summary of tests performed and metrics, along with their definitions can be found in Table 3.2.1.

Symptom Assessment: Post-Concussion Symptoms (PCSI)

Global concussion symptoms (including vision and vestibular related symptoms such as sensitivity to light, double vision, dizziness, balance problems and moving in a clumsy matter) were obtained from the Post-Concussion Symptom Inventory (PCSI) filled out by a clinician at each visit. The PCSI is a symptom inventory, developed and validated for use in children and adolescents to assess the number and severity of concussion-related symptoms [14]. Participants were asked to rate a list of symptoms reflecting their recall of their pre-injury level of symptoms and of their symptoms at the time of testing [14]. In one study aimed at addressing the retrospective recall of pre-injury ratings, a sample of children aged 5-17 (n= 3,069) completed the pre- injury PCSI. Results indicated little dispersion and high stability in recall of pre-injury levels in the 3 month's post injury suggesting that children aged 5-17 recall their pre-injury levels of post-concussion symptoms with high accuracy.

There are 3 versions of the Post-Concussion Symptom Inventory (PCSI) adapted for use with children and adolescents. For younger children aged 5-12 years old, a version of the PCSI including 18 items is adapted to increase readability and concreteness [14] . Children aged 7 and younger only complete the first 5 items whereas children aged 8-12 complete the full 18 items. In the 5-12 years old version the patient is asked to answer all the items to the best of their ability and to circle a number from 0-2 (0=No, 1= A little, 2= A lot) that best describes the severity of their

symptoms both before the injury, and yesterday/ today (Appendix 2). For adolescents aged 13 to 18 years, a version of the PCSI containing 21 symptom items is used. The patient is asked to answer all the questions to the best of their ability and rate their symptoms on a scale of 0-6 (0= not a problem, 3= moderate problem, 6= severe problem) both pre-injury and yesterday/today (Appendix 2). The assessment focuses on cognitive, emotional, physical and sleep-related symptoms. For this project only the 8-12 and 13-18 age bracket versions was used since our sample was limited to children 8 years of age and over. The PCSI shows strong internal consistency for total scores, moderate to high test-retest reliability particularly in children 12 and up, and low to moderate concordance between self and parent reports [14].

Data Analysis:

The exposure for this study was categorical with the following three groups; symptomatic, clinically recovered and healthy. All the outcomes were treated as continuous variables. To address objective 1, a series of one-way ANOVA tests was used for between group comparisons. For any metric that did not meet the equality of variance assessment, a Welch AVONA was used in place of the standard 1-way ANOVA. Post-hoc pairwise comparisons were used to compare the estimated marginal means between the three groups (Bonferroni/ Game's Howell). The Bonferroni correction for multiple comparisons was also applied to control the joint error rate for the entire series of comparisons.

One covariate that can impact this type of research is developmental age. Age plays a critical factor in performance on cognitive assessments, symptom reporting, concussion morbidity and oculomotor function. Although research has shown that younger children demonstrate longer saccade latencies, lower gain during smooth pursuit [16] and make more

directional and acquisition errors during anti-saccades than older children [17], age was not found to be a relevant covariate in this study. Early analysis with ANCOVA showed no association between developmental age and OM or VO performance on any of the eye tracking metrics. The age spread was not significantly large in this sample. Participants ranged in age from 8 and 18, with the mean age between 14 and 15 years of age for all 3 groups.

To address objective 2, symptom scores for the PCSI were related to OM and VO function with Pearson r correlations. For the scope of this project, the global PCSI score was used as a measure of concussion symptom severity. The outcomes are also presented as a continuous variable. Cohen's standard was used to evaluate the correlation coefficient and determine the strength of the relationship between the severity of symptoms and performance on the oculomotor and vestibulo-ocular tasks. A value of d below 0.20 was considered small, 0.50 medium, and 0.80 large [18]. The total concussion sample was split into two age groups (8-12 and 13-18) and analyzed separately due to the difference in inventory scales used on the PCSI (0-2; 0-6). All statistical analyses were carried out in SPSS version 26 and the level of significance was set to $p<.05$.

3.3 Results

187 participants were included in the study (72 with symptomatic mTBI; 36 with recovered mTBI; 79 healthy controls). Table 3.2.2 summarizes the demographic information for all three groups. Significant group differences were found for age of participants [$F(2,186) = 4.963$, $p=0.0080$]. Bonferroni post hoc assessments indicated that the mean age of healthy children was significantly lower than the mean age of *mTBI Recovered* children. There was also

a difference in sex between groups. For healthy children, 63 % of the sample population were male participants compared to only 34 % for the mTBI symptomatic sample. There was a significant difference in the mean number of days between injury and assessment for the two mTBI groups [F (2,108) = 11.528, p<.05] with *mTBI Recovered* children showing much longer time frames. There was a significant difference in the number of previous concussions between groups at the p<.05 level [f (2,186) = 7.775, p=0.001]. Post hoc comparisons indicated significant mean differences in the number of previous concussions between healthy children and both *mTBI Recovered* and *mTBI Symptomatic* children. In both concussion samples, over half of the participants had experienced at least one previous mTBI. Although no significant mean difference was found for PCSI delta scores between the symptomatic and recovered concussion groups for children 12 and under, there was a significant mean difference for PCSI delta scores between the two groups for children 13- 18 years old [F (2,89) = 7.778, p<.05]. For the scope of this project, the researchers did not compare the two age groups due to the difference in PCSI scales. Symptomatic children reported more severe symptom scores than recovered children. The mechanism of injury was available for 80 out of the 110 participants and sports related incidents were the reported cause of mTBI in 56 % of participating children.

Oculomotor and Vestibulo- Ocular Assessments

Descriptive statistics on oculomotor and vestibulo-ocular tests are presented in Table 3.2.3, while detailed differences between groups are presented in table 3.2.4 for those measures which reached statistical significance in the main analysis.

Smooth Pursuit

Mean Pursuit Error. Only one metric was analyzed for smooth pursuit. *Recovered mTBI* children tended to present with more errors in degree than both healthy and *symptomatic mTBI* children but this difference was not statistically significant [W (2,170) = 2.97, p =0.06].

Vergence

Vergence during Smooth Pursuit. There was a significant group effect for vergence during smooth pursuit [F (2,176) =10.90, p<.05]. Post hoc comparisons using the Bonferroni test indicated that the mean degree score for the healthy controls was significantly lower than both the *recovered* and *symptomatic mTBI* conditions. However, there were no statistically significant differences in vergence between the two mTBI groups.

Saccades

Mean Saccade Latency. There was a significant group effect for the mean latency during saccades [F (2, 171) = 5.99, p=.003]. Bonferroni post hoc comparisons showed significantly shorter latency periods in milliseconds for healthy children compared to children with *symptomatic mTBI*. Children with *recovered mTBI* did not significantly differ from the healthy or *symptomatic* children. The mean saccade values for the three groups are presented in Figure 3.3.2

Mean Saccade Error. Both *mTBI symptomatic* and *mTBI recovered* children tended to make more errors in degrees during saccades when compared to healthy controls, but the difference did not reach significance at the p<.05 level [W (2,170) = 1.13, p=0.33].

Anti-Saccades

Directional Accuracy. Both *mTBI symptomatic* and *mTBI recovered* children tended to have poorer directional accuracy (lower percentage) when compared to healthy controls but the difference did not reach significance at the p<.05 level [F (2,181) = 1.24, p=0.29].

Mean Response Time. There was a significant group effect for mean response delay during anti-saccades at the p<.05 level [F (2,177=9.07, p.<05]. Bonferroni post-hoc comparisons indicated significantly longer mean response delay in milliseconds for *mTBI symptomatic* children when compared the healthy and *mTBI recovered* children. However, the mean score did not significantly differ for mTBI recovered children when compared to healthy children. The mean response time values for the three groups are presented in Figure 3.3.3.

Mean Acquisition Error. *mTBI symptomatic* and *mTBI recovered* children tended to make more acquisition errors in degrees during the anti-saccade task than the healthy controls but these results did not reach significance at the p<.05 level [F (2,184) = 1.74, p=0.18].

AVOR

Horizontal AVOR Gain. There was a significant group effect for horizontal VOR gain in both the leftward [F (2,168) = 7, p=.001] and rightward directions [W (2,163) = 13.08, p <.05]. Bonferroni post-hoc tests showed that healthy children had significantly lower mean percentages than *mTBI recovered,* and *mTBI symptomatic* children in the left VOR task. Games-Howell post-hoc tests further indicated that healthy children also had significantly lower mean percentages than *mTBI recovered* and *mTBI symptomatic* children in the right AVOR task. However, there were no statistically significant difference in mean scores between the two mTBI

samples for either direction. The mean horizontal AVOR values for the three groups are presented in figure 3.3.4

Vertical AVOR Gain. There was a significant effect of mTBI on vertical vergence in both the upward [F (2,147) = 7.60, p=.001] and downward directions [W (2,144) = 13.70, p <.05]. Bonferroni post-hoc comparisons indicated that healthy children had significantly lower mean gain percentages than *mTBI symptomatic* children. No significant differences were observed between healthy and *mTBI recovered* children. Games-Howell post-hoc tests also indicated that healthy children had significantly lower mean percentages than *mTBI recovered* and *mTBI symptomatic* children in the downward AVOR task. However, there was no significant mean difference in scores for the two mTBI subgroups in either vertical directions.

Post-Concussion Symptoms and OM/VO Function

Post-concussion symptoms reported on the PCSI were related to OM/VO performance, but most results did not reach significant levels. For the 12 years of age and under category, the Pearson correlation test revealed a significant strong positive correlation between mean saccade error and total PCSI scores for the *mTBI recovered* children (r= 0.89, p< .05). There were no other significant findings for *mTBI recovered or symptomatic* children in either age category. A summary table of Pearson r correlations and p values for all SA assessments and total PCSI scores can be found in table 3.2.5.

3.4 Discussion

To address hypothesis 1, the primary objective of this study was to document OM and VO function in children who sustained an mTBI and were symptomatic at the time of assessment and to compare them to that of children with prior mTBI (clinically recovered) and uninjured children. Results indicated significant group differences in OM function for vergence during smooth pursuit, mean latency during saccades and mean response delay during anti-saccades. For VO function, significant group differences were found for AVOR gain in both the horizontal and vertical planes. Although no significant findings were documented for the remaining OM metrics (mean pursuit error, mean saccade error and directional accuracy and anti-saccade acquisition error), children with symptomatic mTBI tended to show poorer performance when compared to clinically recovered and healthy children.

To address hypothesis 2, a secondary objective of this study was to document the extent to which OM and VO function related to post-concussion severity in children with mTBI (both symptomatic and clinically discharged). The relationship between mean saccade error and symptom scores in children 8-12 years old was the only significant relationship, with greater errors correlating with more severe symptoms. Although there were no significant relationships for the remaining OM/VO metrics, children who reported an increased number of and/or more severe symptoms on the PCSI tended to perform worse on the OM/VO eye tracking task than children who reported lower symptom scores.

Oculomotor Function

Smooth Pursuit. The smooth pursuit task demonstrates how well a participant can follow a slowly moving visual target. Successful pursuit is constrained by the individual's ability to obtain and process information about the target's trajectory and velocity. Previous research indicates that mTBI can affect the accuracy of the pursuit response. Indeed, DiCesare [19], compared smooth pursuit performance in high school students who had experienced an mTBI (n=17) to controls matched for age and sex (n=17). Results indicated that mTBI adolescents show a longer phase lag and make significantly more directional errors than controls. These results are further supported by a more recent study by Murray [20] who found significant differences in smooth pursuit velocity between mTBI and healthy participants. Interestingly, Murray [20] also found that smooth pursuit amplitudes were virtually identical in both groups.

Contrasting previous research, children in our sample with symptomatic mTBI did not significantly differ from clinically recovered or healthy children; the mean error was similar for all groups. This may have occurred because our assessment of smooth pursuit was based purely on the degree of error and did not include a measure of speed.

Vergence. The average absolute of vergence (angle between the two eyes) during smooth pursuit can be increased following mTBI due to the imposed imbalance in the gaze orientation system. In this sample, mTBI participants demonstrated greater convergence when executing smooth pursuits than both healthy controls (athletes) and mTBI recovered children. This suggests that they presumed the target appeared at a closer distance than it was presented at (all targets were presented at 1 meter from the participant). The InSight metric used to define vergence is influenced by the vergence during the pursuit itself, but also by the intruding saccades that occur during the pursuit. Every time there is a saccade, there is a fast divergence while the eyes move

to the new target followed by a longer phase of convergence during the acquisition of the new target. The more intruding saccades presented during the task, the greater the vergence angles. This explains why the mTBI children showed greater convergence than the controls.

Another factor that could influence these findings is changes in depth perception post mTBI. This explanation is supported by Mihalik [21] who explored gaze depth perception in a sample of high school and college athletes (n=224). Results clearly indicated that student-athletes with a history of concussion responded more slowly and with less accurate predictions during a primary gaze depth perception task than student-athletes with no history of concussion. This suggests that mTBI may impact the motor / ocular cortices and associated pathways that are required to determine the exact distance of an object or target. Although not all of our participants were athletes; 80/110 concussion participants sustained their injury during sports play and the entire healthy population was made up of competitive soccer players. Thus, it is possible that athletic ability may have contributed to/ impacted our findings.

Saccades. The goal of this assessment is to evaluate the saccadic system when the head remains in a fixed position. Oculomotor research in children is quite challenging due to a limited number of studies on saccades in children, and the fact that saccadic parameters tend to show variation with age throughout maturation. Previous research in adult populations show that patients who experienced an mTBI demonstrate increased saccadic latencies and longer intervals between saccades when compared to healthy controls [22, 23]. In our sample, results indicated a significant delay in saccadic responses for symptomatic vs. healthy children; extending research on adult populations to a paediatric sample for the first time.

Present results, however, did not point to any significant differences in the average degree error for saccades in mTBI children when compared to healthy children, which contrasts findings

in adult populations in which patients with mTBI show greater directional and end point errors when compared to healthy controls [22, 24] . Previous research (n=1893) found that the most significant differences between two groups (mTBI vs. healthy controls) were related to reaction time during a saccade task. Consistent with our findings, reaction times for participants with a history of mTBI were much more variable, showing larger standard deviations than healthy age and sex matched controls [25].

Anti-Saccades. The anti-saccade task adds a cognitive stage and visual map rotations before executing the saccade, and can be used to evaluate the function of the visual cortex. Although both mTBI symptomatic and recovered children had poorer directional accuracy and acquisition error when compared to healthy children, these parameters did not reach significance levels.

There was a significant effect of mTBI on the response time during anti-saccades with the greatest response times seen in symptomatic children, followed by recovered children, and then healthy children. Heitger [26] indicated that anti-saccade latency tends to return to normal at 1-week post-mTBI, whereas anti- saccade errors tend to remain relatively stable up to a few months post-injury. For this project, the average number of days between injury and assessment was 25 days, providing a contrast to those found in previous studies of adult participants [24, 27]. One possible explanation for this difference could be the age of participants. Latency during saccade and anti-saccades tends to decrease significantly with age as neural circuits responsible for making saccades quick and accurate develop. For example, in a sample of healthy children (n=40) saccade and anti-saccade latency decreased between 25- 60 ms across the 8-19 age range of the participants [28].

Interestingly, mean response time during anti-saccade was the only oculomotor parameter in which significant mean differences were found between symptomatic ($x = 518.91, \pm 101.98$) and recovered ($x = 465.66 \pm 94.45$) mTBI children. But again, this could be related to the extent of time between injury and assessment. Specifically, the average number of days between injury and assessment was far greater for recovered (approximately 60 days) than for symptomatic children (approximately 20 days). This is the first time that research has shown a significant effect of mTBI on anti-saccades, contributing to a growing body of literature that has focused exclusively on adults up until now.

Vestibulo-Ocular Function

AVOR Gain. Previous studies show wide variations in the prevalence of VO dysfunction, ranging from 30 -80 % in mTBI adolescents [1, 29]. When the VOR is disrupted there is a mismatch in gain between head and eye movements that are necessary for stabilizing an image on the fovea. Consistent with previous research in adult populations, children in this study who had experienced mTBI (both symptomatic and recovered) showed differences in VO function when compared to healthy children. Specifically, children with mTBI showed lower gain values during the VOR task, suggesting that their eye movements did not adequately adjust to match their head movements.

mTBI Symptoms and OM/VO Function

There was a significant relationship between saccade error and post-concussion symptoms in children between the ages of 8 and 12. Correlations between symptom scores and OM function were contrasting for recovered and symptomatic children in both smooth pursuits and saccades with recovered children showed very small positive correlations whereas symptomatic children tended to show small negative correlations.

For anti-saccades, children with symptomatic and recovered mTBI showed positive correlations for directional accuracy, and negative correlations for mean response time and acquisition error, suggesting that anti-saccades may serve as an effective biomarker of concussion in children. In line with previous studies, this suggests that children who reported greater symptoms tended to make more errors and have longer latencies between the presentation of the flashed target and the onset of eye movement in the opposite direction of the stimulus [22].

Like previous work by Ellis [29] who assessed VO dysfunction and post concussion symptoms in a sample of pediatric athletes (n=101) our results suggest that children with VO dysfunction tend to report greater post- concussion symptom scores.

Strengths and Limitations

One noticeable strength of this study was the size of the sample population and the fact that it included a control group as well as an ‘mTBI recovered’ sample for comparisons. Although these results are promising, this study is not without its limitations. Unequal sample groups and the fact that all concussion subjects were recruited from a single clinic, increased the risk of false positive/negative findings, and opened the results to concerns of generalizability.

Additionally, for symptom comparisons, participants had to be evaluated separately based on the different Likert scales and types of questions in the different age appropriate versions of the PCSI. The equality of variances assumption for ANOVA was not met for many parameters, which limited the use of more powerful statistical analyses. This study also raises issues of content validity because the authors were trying to explore the relationship between visual symptoms and OM/VO function but used the delta score for the entire PCSI. This may explain why some of the correlations were highly variable and inconsistent with previous literature.

3.5 Conclusion

Oculomotor and vestibulo-ocular function were assessed in children ranging in age from 8-18 years old who were symptomatic at the time of testing or recovered (clinically discharged) and compared to that of healthy children. Both symptomatic and recovered children presented with clinical oculomotor and vestibulo-ocular dysfunction in the three months post injury. Children with mTBI showed greater vergence scores, slower saccade and anti-saccades and less VOR activity. Although OM and VO performance were not directly related to post-concussion symptoms; children who reported more symptoms, also tended to show poorer performance in the eye tracking task. Therefore, this study supports the inclusion of a combination of both OM/ VO assessments and post-concussion symptom evaluations for the diagnosis and management of mTBI in the pediatric population.

To the knowledge of its authors, this is the first study to address multiple ocular motor and vestibulo-ocular parameters simultaneously as well as compare OM and VO eye tracking results to post-concussion symptom scores. Future studies should aim to replicate results in a

larger and more cohesive sample size. This is very much the key component in future attempts to increase the statistical power of similar findings. One possible avenue for future investigators could be to include assessments of optokinetic nystagmus (OKN), considering that in a sample of high school students Kelly [30] found that out of all eye tracking metrics, OKN assessments showed the greatest difference between healthy and concussed children, and that decreases in OKN were associated more with prolonged expression of concussion symptoms than measures of smooth pursuit or saccades. Further studies should also investigate why recovered and symptomatic children did not differ significantly in OM and VO performance, because it raises a possible concern that current clinic assessments are not sensitive enough to pick up subtle deficits. In such, children may be prematurely discharged which puts them at a higher risk of sustaining a second impact or experiencing long term OM/VO dysfunction which could have detrimental effects on their future.

References

1. Master, C.L., et al., *Vision Diagnoses Are Common After Concussion in Adolescents.* Clin Pediatr (Phila), 2016. **55**(3): p. 260-7.
2. Ventura, R.E., et al., *Diagnostic tests for concussion: is vision part of the puzzle?* J Neuroophthalmol, 2015. **35**(1): p. 73-81.
3. Leddy, J.J., et al., *Rehabilitation of Concussion and Post-concussion Syndrome.* Sports health, 2012. **4**(2): p. 147-54.
4. National Academy of Sciences, *The Necessity and Challenges of Clinical Research Involving Children*, in *Ethical Conduct of Clinical Research Involving Children* 2004, National Academies Press Washington, DC.
5. Samadani, U., *A new tool for monitoring brain functionL eye tracking goes beyond assessing attention to measuring central nervous system physiology.* Neural Regression Research, 2015. **10**(8): p. 1231-1233.
6. Bin Zahid, A., et al., *Eye Tracking as a Biomarker for Concussion in Children.* Clin J Sport Med, 2018.
7. McDevitt, J., et al., *Vestibular and Oculomotor Assessments May Increase Accuracy of Subacute Concussion Assessment.* Int J Sports Med, 2016. **37**(9): p. 738-47.
8. Leigh, R.J. and D.S. Zee, *The Neurology of Eye Movements*. 2015.
9. Lappi, O., *Eye movements in the wild: Oculomotor control, gaze behaviours & frames of reference.* Neurosci Biobehav Rev, 2016. **69**: p. 49-68.
10. Ventura, R.E., Balcer, L.J. Galetta, S.L., & Rucker, J.C., *Ocular motor assessment in concussion: Current status and future directions.* Journal of the Neurological Sciences, 2016. **361**: p. 79-86.
11. Taghdiri, B. Varriano, and M.C. Tartaglia, *Assessment of Oculomotor Function in Patients With Postconcussion Syndrome: A Systematic Review.* Journal of Head Trauma Rehabilitation, 2017. **32**(5): p. E55-E67.
12. Samadani, U., et al., *Eye tracking detects disconjugate eye movements associated with structural traumatic brain injury and concussion.* J Neurotrauma, 2015. **32**(8): p. 548-56.
13. Wass, S., *The Use of Eye Tracking with Infants and Children*, in *Practical Research in Children*, J.H. Prior, J., Editor. 2016, Taylor & Francis: London. p. 24-44.
14. Sady, M.D., C.G. Vaughan, and G.A. Gioia, *Psychometric characteristics of the postconcussion symptom inventory in children and adolescents.* Arch Clin Neuropsychol, 2014. **29**(4): p. 348-63.
15. Teel, E.F., Zemek, R.L., Tang, K., Gioia, G., Vaughan, C., Sady, M. & Gagnon, I.J., *The stability of retrospective pre-injury symptom ratings following pediatric concussion.* Frontiers in Neurology, 2019. **10**(672): p. 1-10.
16. Doettl, S.M. and D.L. McCaslin, *Oculomotor Assessment in Children.* Semin Hear, 2018. **39**(3): p. 275-287.
17. Treleaven, D., Teel, E., Beaulieu, C., Friedman, D., Grill, L., Hong, L., Mackenzie, S., & Gagnon, I. , *The effect of sex, age, concussion history, and symptom severity on anti-saccades in children and youth with mTBI.* , in *IBIA World Congress 2019*. 2019, International Brain Injury Association Toronto, ON.
18. Cohen, J., *Chapter 4: Differences between Correlation Coefficients*, in *Statistical Power Analysis for the Behavioural Sciences (Revised Edition)*. 1988, Academic Press Inc: New York, NY. p. 109-143.

19. DiCesare, C., Kiefer, A.W., Nalepka, P., & Myer, G.D., *Quantification and analysis of saccadic and smooth pursuit eye movements and fixations to detect oculomotor deficits.* Behavior Research Methods, 2017. **49**: p. 258-266.
20. Murray, N.G., Szekely, B., Islas, A., Munkasy, B., Gore, R., Berryhill, M., & Reed-Jones, R. J., *Smooth Pursuit and Saccades after Sport-Related Concussion.* Journal of neurotrauma, 2020. **37**(2): p. 340-346.
21. Mihalik, J.P., Wasserman, E.B. & Gffeller, M. , *Depth perception differences in athletes reporting a concussion history.* Exercise and Sport Science, 2016. **10**.
22. Cifu, D.X., et al., *Differential eye movements in mild traumatic brain injury versus normal controls.* J Head Trauma Rehabil, 2015. **30**(1): p. 21-8.
23. Heitger, M.H., et al., *Eye movement and visuomotor arm movement deficits following mild closed head injury.* Brain, 2004. **127**(Pt 3): p. 575-90.
24. Heitger, M.H., et al., *Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability.* Brain, 2009. **132**(Pt 10): p. 2850-70.
25. Lange, B., Hunfalvay, M., Murrary, N., Roberts, C.M. & Bolter,T. , *Reliability of computerized eye-tracking reaction time tests in non-athletes, athletes, and individuals with traumatic brain injury.* Optometry and Visual Performance, 2018. **6**(3).
26. Heitger, M.H., Anderson, T. J., Jones, R. D., Dalrymple-Alford, J. C., Frampton, C. M., & Ardagh, M. W., *Eye movement and visuomotor arm movement deficits following mild closed head injury.* Brain : a journal of neurology, 2004. **127**(Pt 3): p. 575-90.
27. Ventura, R.E., et al., *Ocular motor assessment in concussion: Current status and future directions.* J Neurol Sci, 2016. **361**: p. 79-86.
28. Salman, M.S., Sharpe, J.A., Eizenman, M., Lillakas, L., Westall, C., To, T., Dennis, M. & Steinbach, M., *Saccades in children.* Vision Research, 2006. **46**.
29. Ellis, M.J., Cordungely, D., Vis, S., Reimer, K., Leiter, J. & Russell, K., *Vestibulo-ocular dysfunction in pediatric sports-related concussion.* Journal of NeuroSurgery Pediatrics, 2015. **16**.
30. Kelly, K.M., Kiderman, A., Akhavan, S., Quigley, M.R., Snell, E.D., Happ, E., Synowiec, A.S., Miller, E.R., Bauer, M.A., Oakes, L.P., Eydelman, Y., Gallagher, C.W., Dinehart, T., Schroeder, J.H., & Ashmore, R. C., *Oculomotor, Vestibular, and Reaction Time Effects of Sports-Related Concussion: Video-Oculography in Assessing Sports-Related Concussion.* The Journal of head trauma rehabilitation, 2019. **34**(3): p. 176-188.

Tables

Table 3.2.1. Summary of Insight eye tracking measures

Eye Movement Pattern	Test Name & Definition	Test Metrics	Test Metric Definition	Saccade Analytic Assessment specifics
Oculomotor function				
Smooth pursuit	**Visual target pursuit in 2D**			
	Head-free pursuit demonstrates how well a subject can follow a slowly moving visual target with his/her gaze (= [eye+head] vector).	1. Mean pursuit error	measure of smooth pursuit accuracy in degrees. The difference between the position of gaze and target position.	The target moves at over the screen and the subject tries to follow it closely. Allows head-free pursuit of a foveal target moving smoothly in 2D space (horizontal, vertical) perceptually at ~ 1m from the subject's face, and within 30 degrees maximal eccentricity.
		2. Mean vergence	Measure of the angle sub intended by the fovea. Represents convergence or divergence	
Saccades	**Saccades to 2D stationary targets**			
	Visually triggered saccades are evaluated using random 2D flashed targets dispersed in the four quadrants, which are helpful in identifying the location of spatial located visual deficits	1. Mean saccade latency	Measure of saccade reaction time. Time between the presentation of the target and the saccadic eye movement in milliseconds.	The participant is asked to fixate on each flashed target while holding the head still. The eye tracking system records the saccade reaction time (time between the presentation of the flashed target and fixation) and saccade accuracy
		2. Mean saccade error	Measure of saccade accuracy in degrees to represent the difference between the position of the fovea and the position of the fixation target	
Antisaccades	**Anti-saccades to horizontal stationary objects**			
	Assesses the participant's ability to suppress the reflexive saccadic system and adds a cognitive stage that requires visual map rotations before a saccade is executed. Detects saccades in the opposite direction as correct and those in the same direction as incorrect.	1. Mean directional accuracy	Percentage of accuracy in mirroring the target's position at the same distance on the opposite side of the horizontal meridian	A flashed target is displayed on a dark screen at either 10, 20, or 30 degrees to the left or right of the midline on the horizontal plane. The participant is instructed not to look at the flashed target. Instead the participant is asked to orient onto the target's mirror image at approximately the same distance on the opposite side of the meridian. Since target velocities are zero, the gaze velocity near each target is a measure of retinal slip and the performance of the VOR over the range of targets.
		2. Reaction Time	Measure of the time in milliseconds between the presentation of the target and the onset of eye movement.	
		3. Mean acquisition error	Measure of anti-saccade accuracy in degrees to represent the virtual position error when the target is equal and opposite to the flash	
Vestibulo-ocular				
AVOR gain	**Visual target stabilization between saccades**			
	assesses the vestibulo-ocular reflex by using active, self-generated head movements to demonstrate how well the eyes compensate for head movements in 2 sequential tests in the horizontal or vertical planes	1. Average conjugate gain	Average VOR gain (eye velocity/ head velocity) in the left, right, up and down directions at the preselected head velocity of 25 degs/s.	Flashed targets (vision) are used to elicit head movements (vestibular & neck elements) in the desired range/speed (visual element). The metric calculated finds the level of gaze stabilization between fast saccades and gaze velocity during the fixations. Number of Repetitions:

Table 3.2.2. Participant characteristics

Variable		Healthy (N=79)	mTBI Recovered (N=36)	mTBI Symptomatic (N=72)	P value for overall difference
Age		14	15	14.8	p=0.001
Sex					p=0.001
	Male	50	18	25	
	Female	29	19	47	
Time since injury (days)		N/A	43	22	p<.05
Previous concussion					p=0.001
	0	79	28	37	
	1	0	5	22	
	2 or more	0	3	13	
PCSI delta score		N/A	-0.32	15.60	p<.05
PCSI feels different					
	yes	N/A	31	7	
	no	N/A	5	65	

Table 3.2.3. Oculomotor and vestibulo-ocular descriptive statistics for all children

Eye Tracking Assessment	Measurement	Healthy	Controls	mTBI	Recovered	mTBI	Symptomatic	F or W and Sig
		n	mean, SD	n	mean,SD	n	mean, SD	
Oculomotor								
Smooth Pursuit								
	Error (◦)	72	3.2 ± .90	33	3.68 ± 1.22	68	3.42 ± 1.25	W=2.97, p=0.06
Saccades								
	Latency (ms)	76	213.58 ±26.00	32	222.72 ±21.83	66	230.44 ±34.73	F=6.00, p=0.003
	Error (◦)	74	3.88 ±1.14	34	4.37 ±1.86	65	4.06 ±1.17	W=4.01, p=0.33
Anti-Saccades								
	Directional Accuracy (%)	78	60.16 ± 19.86	35	57.62 ±19.95	71	54.69 ±23.00	F=1.24, p=0.291
	Mean Response Time (ms)	75	452.61 ±91.60	36	465.66 ±94.45	69	518.91 ±101.98	F=9.07, p<.05
	Error (◦)	79	7.99 ±2.21	36	7.38 ±1.74	72	8.22 ±2.37	F=1.74, p=0.178
Vergence								
	during smooth pursuit(◦)	74	-1.00 ±1.50	37	0.40 ±2.19	68	0.30 ±2.10	F= 10.90, p<.05
Vestibulo-ocular								
Horizontal VOR Gain								
	Left(%)	76	65.39 ±13.24	33	73.29 ±11.55	62	74.32 ±14.85	F=7.00, p=0.001
	Right(%)	75	66.41 ±16.23	30	79.3 ±9.15	61	73.75 ±13.60	W=2.36, p<.05
Vertical VOR Gain								
	Upward (%)	63	75.88 ±21.22	35	80.72 ±21.38	52	90.46 ±17.79	F=7.57, p=0.001
	Downward (%)	65	71.36 ±21.01	28	84.74 ±11.38	54	88.9 ±16.35	W=4.01, p=0.33

Table 3.2.4. Between group differences for statistically significant metrics

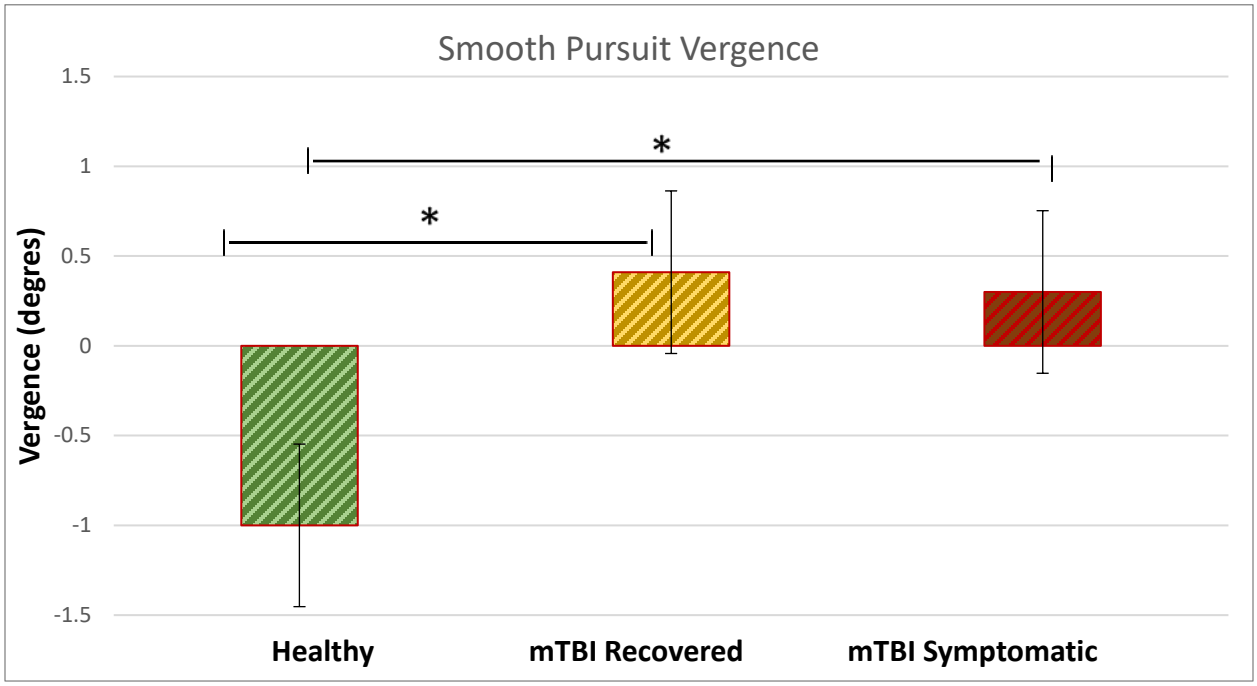
Eye Tracking Measure	Group	Group 2	Mean Difference	Sig (p value)
Oculomotor				
Saccade Latency				
	Healthy	mTBI Recovered	-9.136	0.411
		mTBI Symptomatic	-16.863	0.002*
	mTBI Recovered	Healthy	9.136	0.411
		mTBI Symptomatic	-7.726	0.654
	mTBI Symptomatic	mTBI Recovered	7.726	0.654
		Healthy	16.863	0.002*
Anti-Saccade Response Time				
	Healthy	mTBI Recovered	13.048	1.00
		mTBI Symptomatic	-66.295	0.00*
	mTBI Recovered	Healthy	13.048	1.00
		mTBI Symptomatic	-53.247	0.023*
	mTBI Symptomatic	mTBI Recovered	53.247	0.023*
		Healthy	66.295	0.00*
Vergence during Smooth Pursuit				
	Healthy	mTBI Recovered	-1.409	0.001*
		mTBI Symptomatic	-1.300	0.00*
	mTBI Recovered	Healthy	1.409	0.001*
		mTBI Symptomatic	.1093	1.00
	mTBI Symptomatic	mTBI Recovered	-0.1093	1.00
		Healthy	1.300	0.00*
Vestibulo-Ocular				
Horizontal VOR Gain Left				
	Healthy	mTBI Recovered	-7.901	0.036*
		mTBI Symptomatic	-8.93	0.002*
	mTBI Recovered	Healthy	7.901	0.036*
		mTBI Symptomatic	-1.028	1.00
	mTBI Symptomatic	mTBI Recovered	1.028	1.00
		Healthy	8.93	0.002*
Horizontal VOR Gain Right				
	Healthy	mTBI Recovered	-12.884	0.00*
		mTBI Symptomatic	-7.342	0.013*
	mTBI Recovered	Healthy	12.884	0.00*
		mTBI Symptomatic	5.542	0.062
	mTBI Symptomatic	mTBI Recovered	-5.542	0.062
		Healthy	7.342	0.013*
Vertical VOR Gain Upward				
	Healthy	mTBI Recovered	-4.834	0.77
		mTBI Symptomatic	-14.575	0.001*
	mTBI Recovered	Healthy	4.834	0.77
		mTBI Symptomatic	-9.74	0.085
	mTBI Symptomatic	mTBI Recovered	9.74	0.085
		Healthy	14.575	0.001*

Table 3.2.5. Pearson correlation coefficients between oculomotor and vestibulo-ocular function and PCSI scores

Age	Eye Tracking Assessment	Measurement	mTBI	Recovered	mTBI	Symptomatic
			Correlation	Significance	Correlation	Significance
5-12 years old						
	Oculomotor					
	Smooth Pursuit					
		Error (◦)	-0.692	0.308	-0.143	0.693
	Saccades					
		Latency (ms)	0.289	0.637	-0.642	0.062
		Error (◦)	0.886	0.046*	0.019	0.959
	Anti-Saccades					
		Directional Accuracy (%)	0.766	0.131	0.095	0.78
		Mean Response Time (ms)	-0.435	0.464	-0.043	0.899
		Error (◦)	-0.485	0.407	0.065	0.849
	Vergence During Pursuit					
		Error (◦)	-0.745	0.148	0.046	0.906
	Vestibulo-ocular					
	Horizontal VOR Gain					
		Left(%)	-0.139	0.824	0.136	0.708
		Right(%)	0.2	0.8	-0.334	0.345
	Vertical VOR Gain					
		Upward (%)	-0.051	0.94	-0.121	0.76
		Downward (%)	0.485	0.68	0.32	0.37
13- 18 years old						
	Oculomotor					
	Smooth Pursuit					
		Error (◦)	0.349	0.111	0.104	0.457
	Saccades					
		Latency (ms)	0.057	0.806	-0.108	0.44
		Error (◦)	0.262	0.239	-0.109	0.452
	Anti-Saccades					
		Directional Accuracy (%)	-0.16	0.465	0.047	0.736
		Mean Response Time (ms)	0.335	0.109	0.006	0.965
		Error (◦)	0.31	0.141	-0.108	0.433
	Vergence During pursuit					
		Error (◦)	-0.26	0.903	0.035*	0.805
	Vestibulo-ocular					
	Horizontal VOR Gain					
		Left(%)	-0.167	0.446	0.139	0.346
		Right(%)	-0.084	0.723	0.078	0.604
	Vertical VOR Gain					
		Upward (%)	-0.348	0.096	-0.032	0.843
		Downward (%)	-0.428	0.059	0.164	0.307

Figures

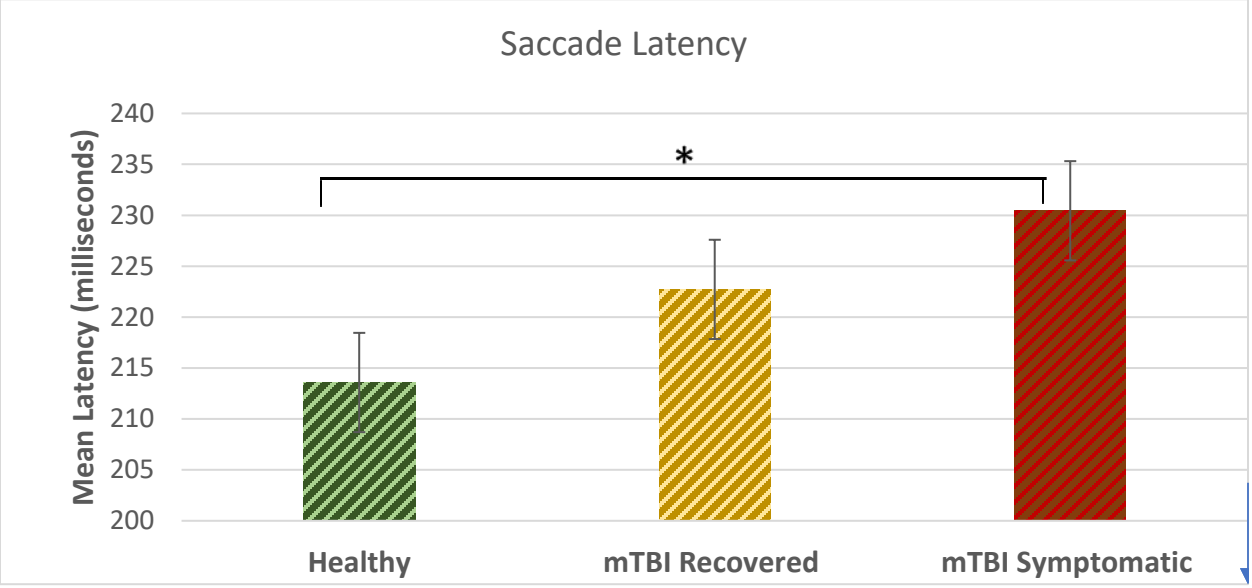
Figure 3.3.1. Mean vergence in degrees during smooth pursuit



Mean pursuit vergence (degrees) for healthy, mTBI symptomatic and mTBI recovered children.

* A significant difference in mean pursuit vergence [F (2,176) =10.90, p<.05]. Error bars presented represent the standard error for within group comparisons. Please refer to table 3.2.1 for further clarification regarding vergence results.

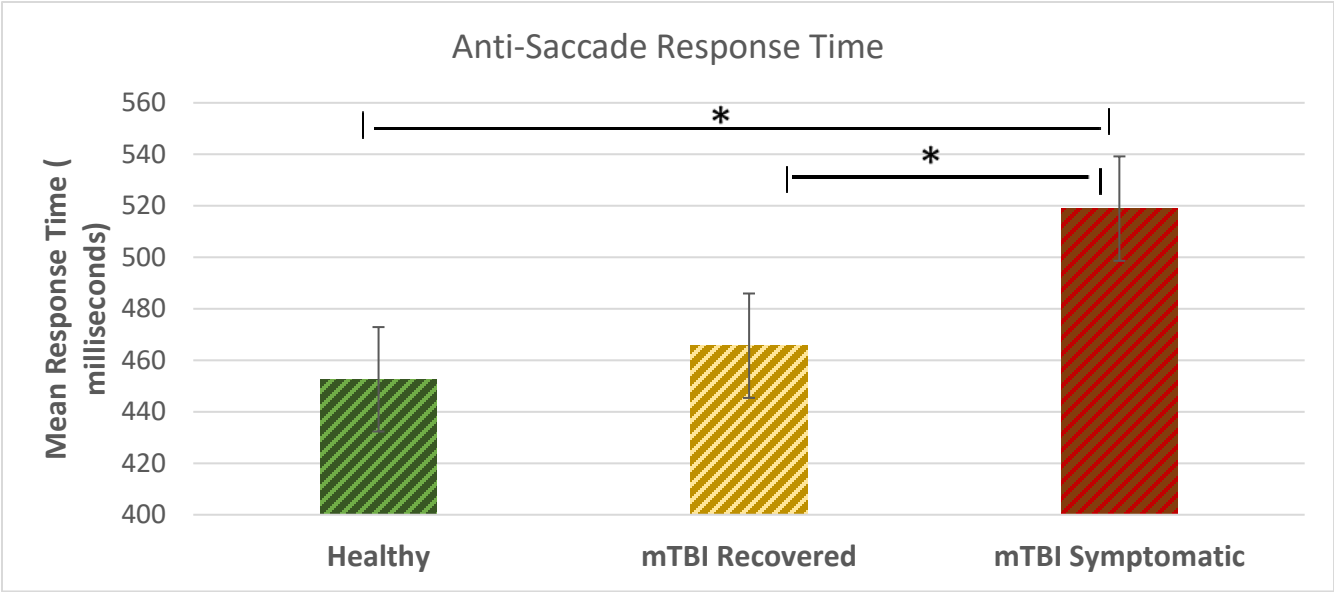
Figure 3.3.2. Mean latency in milliseconds during the saccade task



Mean saccade latencies between stimulus presentation and eye movement for healthy, mTBI symptomatic and mTBI recovered children.

*A significant difference ($p<.05$) in mean saccade latency [$F(2,177=9.07$, p.<05. Error bars presented represent the standard error for within group comparisons.

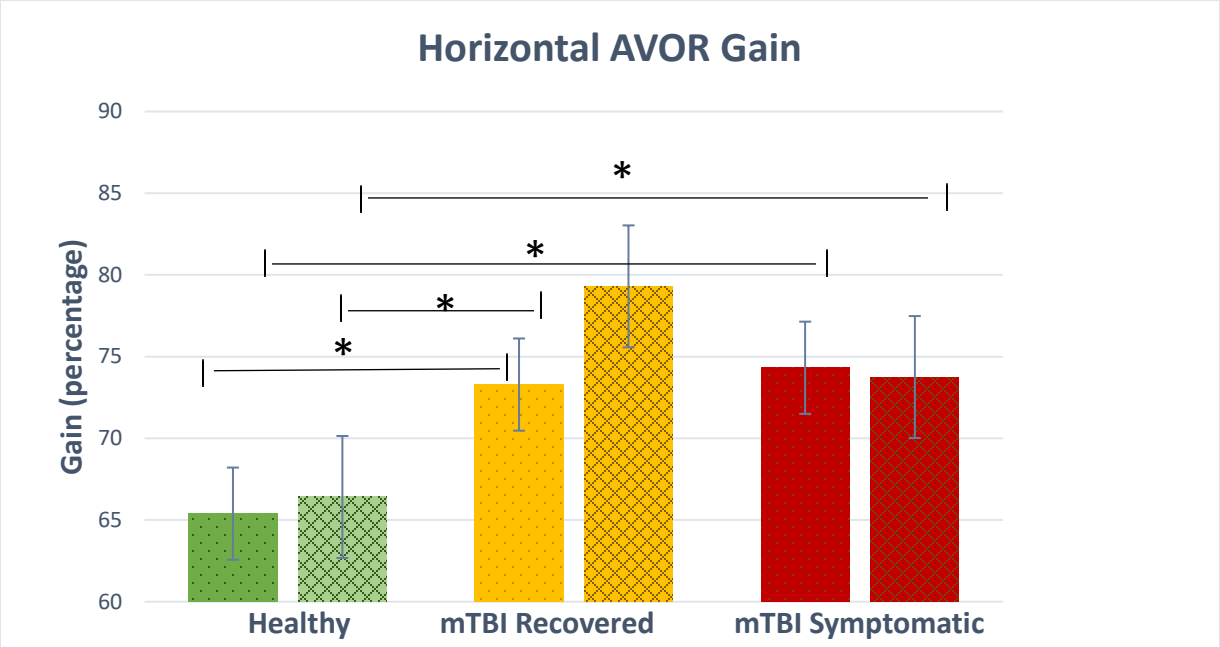
Figure 3.3.3. Mean response delay in milliseconds during the anti-saccade task



Mean response time (milliseconds) for healthy, mTBI symptomatic and mTBI recovered children.

*A significant difference ($p<.05$) in mean response time during anti-saccades [$F(2, 171) = 5.99$, $p=.003$]. Error bars presented represent the standard error for within group comparisons,

Figure 3.3.4. Mean AVOR gain percentage during horizontal VOR task



Mean horizontal AVOR gain (percentage) for healthy, mTBI symptomatic and mTBI recovered children.

* A significant difference ($p<.05$) in mean horizontal VOR gain at 25 degs/sec in the leftward direction [$F(2,168) = 7$, $p=.001$]; + a significant difference ($p<.05$) in the rightward direction [$W(2,163) = 13.08$, $p <.05$]. Error bars presented represent standard error for within group comparisons.

References

1. Master, C.L., et al., *Vision Diagnoses Are Common After Concussion in Adolescents.* Clin Pediatr (Phila), 2016. **55**(3): p. 260-7.
2. Ventura, R.E., et al., *Diagnostic tests for concussion: is vision part of the puzzle?* J Neuroophthalmol, 2015. **35**(1): p. 73-81.
3. Leddy, J.J., et al., *Rehabilitation of Concussion and Post-concussion Syndrome.* Sports health, 2012. **4**(2): p. 147-54.
4. National Academy of Sciences, *The Necessity and Challenges of Clinical Research Involving Children*, in *Ethical Conduct of Clinical Research Involving Children* 2004, National Academies Press Washington, DC.
5. Samadani, U., *A new tool for monitoring brain functionL eye tracking goes beyond assessing attention to measuring central nervous system physiology.* Neural Regression Research, 2015. **10**(8): p. 1231-1233.
6. Bin Zahid, A., et al., *Eye Tracking as a Biomarker for Concussion in Children.* Clin J Sport Med, 2018.
7. McDevitt, J., et al., *Vestibular and Oculomotor Assessments May Increase Accuracy of Subacute Concussion Assessment.* Int J Sports Med, 2016. **37**(9): p. 738-47.
8. Leigh, R.J. and D.S. Zee, *The Neurology of Eye Movements*. 2015.
9. Lappi, O., *Eye movements in the wild: Oculomotor control, gaze behaviours & frames of reference.* Neurosci Biobehav Rev, 2016. **69**: p. 49-68.
10. Ventura, R.E., Balcer, L.J. Galetta, S.L., & Rucker, J.C., *Ocular motor assessment in concussion: Current status and future directions.* Journal of the Neurological Sciences, 2016. **361**: p. 79-86.
11. Taghdiri, B. Varriano, and M.C. Tartaglia, *Assessment of Oculomotor Function in Patients With Postconcussion Syndrome: A Systematic Review.* Journal of Head Trauma Rehabilitation, 2017. **32**(5): p. E55-E67.
12. Samadani, U., et al., *Eye tracking detects disconjugate eye movements associated with structural traumatic brain injury and concussion.* J Neurotrauma, 2015. **32**(8): p. 548-56.
13. Wass, S., *The Use of Eye Tracking with Infants and Children*, in *Practical Research in Children*, J.H. Prior, J., Editor. 2016, Taylor & Francis: London. p. 24-44.
14. Sady, M.D., C.G. Vaughan, and G.A. Gioia, *Psychometric characteristics of the postconcussion symptom inventory in children and adolescents.* Arch Clin Neuropsychol, 2014. **29**(4): p. 348-63.
15. Teel, E.F., Zemek, R.L., Tang, K., Gioia, G., Vaughan, C., Sady, M. & Gagnon, I.J., *The stability of retrospective pre-injury symptom ratings following pediatric concussion.* Frontiers in Neurology, 2019. **10**(672): p. 1-10.
16. Doettl, S.M. and D.L. McCaslin, *Oculomotor Assessment in Children.* Semin Hear, 2018. **39**(3): p. 275-287.
17. Treleaven, D., Teel, E., Beaulieu, C., Friedman, D., Grill, L., Hong, L., Mackenzie, S., & Gagnon, I. , *The effect of sex, age, concussion history, and symptom severity on anti-saccades in children and youth with mTBI.* , in *IBIA World Congress 2019*. 2019, International Brain Injury Association Toronto, ON.
18. Cohen, J., *Chapter 4: Differences between Correlation Coefficients*, in *Statistical Power Analysis for the Behavioural Sciences (Revised Edition)*. 1988, Academic Press Inc: New York, NY. p. 109-143.

19. DiCesare, C., Kiefer, A.W., Nalepka, P., & Myer, G.D., *Quantification and analysis of saccadic and smooth pursuit eye movements and fixations to detect oculomotor deficits.* Behavior Research Methods, 2017. **49**: p. 258-266.
20. Murray, N.G., et al., *Smooth Pursuit and Saccades after Sport-Related Concussion.* J Neurotrauma, 2020. **37**(2): p. 340-346.
21. Mihalik, J.P., Wasserman, E.B. & Gffeller, M. , *Depth perception differences in athletes reporting a concussion history.* Exercise and Sport Science, 2016. **10**.
22. Cifu, D.X., et al., *Differential eye movements in mild traumatic brain injury versus normal controls.* J Head Trauma Rehabil, 2015. **30**(1): p. 21-8.
23. Heitger, M.H., et al., *Eye movement and visuomotor arm movement deficits following mild closed head injury.* Brain, 2004. **127**(Pt 3): p. 575-90.
24. Heitger, M.H., et al., *Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability.* Brain, 2009. **132**(Pt 10): p. 2850-70.
25. Lange, B., Hunfalvay, M., Murrary, N., Roberts, C.M. & Bolter,T. , *Reliability of computerized eye-tracking reaction time tests in non-athletes, athletes, and individuals with traumatic brain injury.* Optometry and Visual Performance, 2018. **6**(3).
26. Ventura, R.E., et al., *Ocular motor assessment in concussion: Current status and future directions.* J Neurol Sci, 2016. **361**: p. 79-86.
27. Salman, M.S., Sharpe, J.A., Eizenman, M., Lillakas, L., Westall, C., To, T., Dennis, M. & Steinbach, M., *Saccades in children.* Vision Research, 2006. **46**.
28. Ellis, M.J., Cordungely, D., Vis, S., Reimer, K., Leiter, J. & Russell, K., *Vestibulo-ocular dysfunction in pediatric sports-related concussion.* Journal of NeuroSurgery Pediatrics, 2015. **16**.
29. Kelly, K.M., et al., *Oculomotor, Vestibular, and Reaction Time Effects of Sports-Related Concussion: Video-Oculography in Assessing Sports-Related Concussion.* The Journal of head trauma rehabilitation, 2019. **34**(3): p. 176-188.
30. Galetta, S.L., Morganroth, J., Moehringer, N., Mueller, B., Hasanaj, L., Webb, N., Civitano, S.L., & Balcer,L., *Adding vision to concussion testing: a perspective study of sideline testing in youth and collegiate athletes.* Journal of Neuro-Opthamology, 2015.
31. Maruta, J., et al., *Association of Visual Tracking Metrics With Post-concussion Symptomatology.* Front Neurol, 2018. **9**: p. 611.

CHAPTER 4

SUMMARY AND CONCLUSION

It is widely accepted that visual symptoms are common after concussion in children and adolescents [62, 66, 133]. What is less researched, are the underlying physiological properties of these complaints. Thus, the focus of this study was on oculomotor and vestibulo- ocular processes that are subject to the negative effects of mild traumatic brain injuries. The primary objective of this study was to document OM and VO function in children who sustained an mTBI and were symptomatic at the time of assessment and compare these results to clinically recovered and healthy children. A secondary objective was to explore the relationship between OM and VO function and the severity of total post-mTBI symptoms.

Our results lead us to conclude that children with symptomatic mTBI do indeed present with clinical oculomotor and vestibulo-ocular function impairments and tend to report more severe post- concussion symptoms when compared to healthy and recovered (clinically discharged) children. More specifically, children with symptomatic mTBI show significant mean group differences for vergence during smooth pursuit, mean latency during saccades and mean response time during anti-saccades when compared to healthy controls. Interestingly, saccade-mean response time also showed significant differences between clinically recovered and symptomatic children.

Although these results are promising, out of all the metrics explored it was only vergence and response time that demonstrated significant findings. This could be due to several factors including but not limited to; unequal sample groups, lack of specificity in the eye tracking assessments or simply that vergence and reaction time are the only aspects of eye movements

that are impacted by concussion. From our findings it appears that children with symptomatic mTBI can perform eye movements with comparable accuracy to healthy and recovered children, it just takes them longer to accomplish the task.

One question that remains unanswered is why recovered and symptomatic children did not significantly differ in OM and VO performance. An obvious possible explanation could be that currently relied on clinic assessments are not sensitive to subtle OM/VO dysfunction. Another possible explanation has been presented by Maruta, Spielman [134] who found that visual tracking performance is most reliable when the assessment is completed within two weeks of the date of injury. Following the elapsed time, visual and vestibular function have been shown to improve rapidly. This time interval was not the case for our recovered sample, as our average number of days between injury and testing was 43 days for this group. On the contrary, it is also possible that a lack of significant difference between recovered and symptomatic children may simply occur because the intervention methods relied on in the clinical setting do not adequately address visual and vestibular changes after concussion.

Although there was only one significant finding; mean saccade error in children aged 8-12 years old, our results lead us to conclude that children who report a greater number of and/or severity of symptoms on the PCSI tend to preform worse on OM/VO tasks. Our results are comparable to previous studies such as Zahid et al., (2018), who explored the relationship between 12 different eye tracking metrics and mTBI symptoms in a sample of children who had sustained an mTBI (n=56). Although these results suggest that eye tracking metrics relate well with post-concussion symptoms in the pediatric sample, our findings suggest the PCSI may not adequately address symptoms that are necessary to appropriately compare symptom scores to OM and VO function.

To the knowledge of its authors, this is one of the first studies to address multiple ocular motor and vestibulo-ocular parameters simultaneously as well as compare OM and VO eye tracking results to post-concussion symptom scores. In this study, VR eye tracking has proven to be an effective tool for recording oculomotor and vestibulo-ocular function post-concussion. Future research similar in nature would benefit from the use of a larger sample of clinical participants who were matched 1-1 for age and sex. Future studies should also include participants from different clinics in order to prevent sample bias.

Children and youth are highly susceptible to concussion but have unique needs when it comes to clinical care. Thus, results from research can not be reliably compared to adult samples of both injured and healthy participants. The findings of this study, and specifically in the control group, can be used by clinicians to formulate a database of 'normal ranges' for clinical comparison. The results from this project contribute to the growing body of literature on visual function after concussion and has demonstrated the value of incorporating quantitative measures of OM and VO function into pediatric post-concussion care.

Appendices

Appendix 1
Sample Report from Saccade Analytics

Report Summary

Patient ID	Date of Birth	Sex	Test Date / Time
54152481	December 2001	Female	March 07, 2019 (10:37:40 AM)

Visual Target Pursuit in 2D

Metric	Direction	Value	Normal Range	Conclusion
Mean Pursuit Error		2.0	x < 3.5deg	in the normal range
Mean Vergence		0.4 ± 1.3		
Head Contribution to Pursuit	Overall	75.3	x > 30.0%	in the normal range
Head Contribution to Pursuit	Horizontal	83.3	x > 30.0%	in the normal range
Head Contribution to Pursuit	Vertical	69.1	x > 30.0%	in the normal range

Active Visual VOR (Horizontal)

Metric	Direction	Value	Normal Range	Conclusion
Mean Vergence		-0.3 ± 1.6		
Hor. AVOR Gain at 25deg/s	Left	82.5	60.0 % < x < 110.0 %	in the normal range
Hor. AVOR Gain at 25deg/s	Right	76.6	60.0 % < x < 110.0 %	in the normal range

Hor. AVOR Gain at 50deg/s	Left	86.2	60.0 % < x < 110.0 %	in the normal range
Hor. AVOR Gain at 50deg/s	Right	77.6	60.0 % < x < 110.0 %	in the normal range
Hor. AVOR Gain at 75deg/s	Left	73.0	50.0 % < x < 110.0 %	in the normal range
Hor. AVOR Gain at 75deg/s	Right	66.0	50.0 % < x < 110.0 %	in the normal range

Active Visual VOR (Vertical)

Metric	Direction	Value	Normal Range	Conclusion
Mean Vergence		0.6 ± 1.1		
Ver. AVOR Gain at 25 deg/s	Up	90.2	60.0 % < x < 110.0 %	in the normal range
Ver. AVOR Gain at 25 deg/s	Down	93.5	60.0 % < x < 110.0 %	in the normal range
Ver. AVOR Gain at 50 deg/s	Up	84.1	50.0 % < x < 110.0 %	in the normal range
Ver. AVOR Gain at 50 deg/s	Down	87.6	50.0 % < x < 110.0 %	in the normal range
Ver. AVOR Gain at 75 deg/s	Down	75.5	40.0 % < x < 110.0 %	in the normal range

Saccades to 2D Stationary Targets

Metric	Direction	Value	Normal Range	Conclusion
Mean Vergence		-0.4 ± 1.1		

Mean Saccade Latency (Reaction Time)		248.7	x < 260.0ms	in the normal range
Mean Saccade Acquisition Error		2.4	x < 3.0deg	in the normal range

Antisaccades

Metric	Direction	Value	Normal Range	Conclusion
Directional Accuracy		91.7	x > 60.0%	in the normal range
Mean Latency (Reaction Time)		413.1	x < 500.0ms	in the normal range
Acquisition Error		7.3	x < 5.0deg	not in the normal range

Appendix 2: Post Concussion Symptom Inventory (5-12)

Post-Concussion Symptom Inventory for Children (PCSI-C)

Version 5 to 12

Name:_____ Today's date:_____ Birthdate:_____ Age_____ Grade:_____

Instructions: We would like to know if you have had any of these symptoms before your injury. Next, we would like to know if these symptoms have changed after your injury.

I am going to ask you to tell me about your symptom at two points in time - Before the Injury and Yesterday / Today. Interviewer: Please circle only one answer.

	0 = No 1 = A little 2 = A lot	Before the Injury /Pre-Injury				Current Symptoms/ Yesterday and Today		
1	Have you had headaches? Has your head hurt?	0	1	2		0	1	2
2	Have you felt sick to your stomach or nauseous?	0	1	2		0	1	2
3	Have you felt dizzy? (like things around you were spinning or moving)	0	1	2		0	1	2
4	Have you felt grumpy or irritable? (like you were in a bad mood)	0	1	2		0	1	2
5	Has it been hard for you to pay attention to what you are doing? (like homework or chores, listening to someone, or playing a game)	0	1	2		0	1	2
	Continue if age 8 or older							
6	Have you felt more drowsy or sleepy than usual?	0	1	2		0	1	2
7	Have bright lights bothered you more than usual? (like when you were in the sunlight, when you looked at lights, or watched TV)	0	1	2		0	1	2
8	Have loud noises bothered you more than usual? (like when people were talking, when you heard sounds, watched TV, or listened to loud music)	0	1	2		0	1	2
9	Have you had any balance problems or have you felt like you might fall when you walk, run or stand?	0	1	2		0	1	2
10	Have you felt sad?	0	1	2		0	1	2
11	Have you felt nervous or worried?	0	1	2		0	1	2
12	Have you felt like you are moving more slowly?	0	1	2		0	1	2
13	Have you felt like you are thinking more slowly?	0	1	2		0	1	2
14	Has it been hard to think clearly?	0	1	2		0	1	2
15	Have you felt more tired than usual?	0	1	2		0	1	2
16	Has it been hard for you to remember things? (like things you heard or saw, or places you have gone)	0	1	2		0	1	2
17	Have things looked blurry?	0	1	2		0	1	2
18	**Do you feel "different" than usual?**					0	1	2

Appendix 3: Post Concussion Symptom Inventory (12-18)

Post-Concussion Symptom Inventory (PCSI)
Self-Report Assessment Form
Pre and Post-Injury Report
Ages 13-18

Patient Name:_____ **Today's date:**_____
Birthdate:_____ **Age:**_____

Instructions: We would like to know if you have had any of these symptoms before your injury. Next, we would like to know if these symptoms have changed after your injury. Please rate the symptom at two points in time- Before the Injury/Pre-Injury and Currently.

Please answer all the items the best that you can. Do not skip any items. Circle the number to tell us how much of a problem this symptom has been for you.

0 = Not a problem 3 = Moderate problem 6 = Severe problem

		Before the Injury/ Pre-Injury								Current Symptoms/ Yesterday and Today						
1	Headache	0	1	2	3	4	5	6		0	1	2	3	4	5	6
2	Nausea	0	1	2	3	4	5	6		0	1	2	3	4	5	6
3	Balance problems	0	1	2	3	4	5	6		0	1	2	3	4	5	6
4	Dizziness	0	1	2	3	4	5	6		0	1	2	3	4	5	6
5	Fatigue	0	1	2	3	4	5	6		0	1	2	3	4	5	6
6	Drowsiness	0	1	2	3	4	5	6		0	1	2	3	4	5	6
7	Sensitivity to light	0	1	2	3	4	5	6		0	1	2	3	4	5	6
8	Sensitivity to noise	0	1	2	3	4	5	6		0	1	2	3	4	5	6
9	Irritability	0	1	2	3	4	5	6		0	1	2	3	4	5	6
10	Sadness	0	1	2	3	4	5	6		0	1	2	3	4	5	6
11	Nervousness	0	1	2	3	4	5	6		0	1	2	3	4	5	6
12	Feeling more emotional	0	1	2	3	4	5	6		0	1	2	3	4	5	6
13	Feeling slowed down	0	1	2	3	4	5	6		0	1	2	3	4	5	6
14	Feeling mentally "foggy"	0	1	2	3	4	5	6		0	1	2	3	4	5	6
15	Difficulty concentrating	0	1	2	3	4	5	6		0	1	2	3	4	5	6
16	Difficulty remembering	0	1	2	3	4	5	6		0	1	2	3	4	5	6
17	Visual problems (double vision, blurring)	0	1	2	3	4	5	6		0	1	2	3	4	5	6
18	Get confused with directions or tasks	0	1	2	3	4	5	6		0	1	2	3	4	5	6
19	Move in a clumsy manner	0	1	2	3	4	5	6		0	1	2	3	4	5	6
20	Answer questions more slowly than usual	0	1	2	3	4	5	6		0	1	2	3	4	5	6
21	In general, to what degree do you feel "differently" than before the injury (not feeling like yourself)?	**No Difference 0 1 2 3 4 Major Difference** *Circle your rating with "0" indicating "Normal" (No Difference) and "4" indicating "Very Different" (Major Difference)*														

Appendix 4: Summary Table of Variables

Variable	Definition	Type	Scale
Group	Concussion Group: Children and adolescents having presented to the MCH Concussion Clinic between April 1, 2018 and March 31, 2019, having sustained a concussion in the previous 3 months. Participants will be further separated into two groups: 1. **Symptomatic:** children and adolescents with active post-concussion symptoms at the time of assessment 2. **Recovered:** participants whose symptoms have subsided and are cleared to return to all activities. Healthy Group: age- and sex-matched uninjured participants with no known history of concussion or other visual disorders (strabismus, diplopia, vertigo etc.) or learning disabilities will be selected from an existing normative database of healthy children.	Exposure	Categorical
Oculomotor 1. smooth pursuit 2. Saccades 3. Anti-Saccade 4. Vergence	Oculomotor: Visual function that controls eye movements, such as the ability to locate and fixate on objects in one's visual field (gaze shifting). **1. Smooth Pursuit:** voluntary slow tracking movements of the eyes designed to keep a moving stimulus on the fovea Metrics: • Mean pursuit error (degrees): The difference between the position of gaze and target position. The angle subtended by the fovea. **2. Saccades:** a rapid, ballistic movement of both eyes that abruptly changes the point of fixation Metrics: • Saccade latency (milliseconds): time elapsed between the presentation of the visual stimulus and the onset of eye movement. • Mean saccade error (degrees): The difference between the position of the fovea and the position of the fixation target **3. Anti- Saccades:** voluntary eye movement made in the direction opposite to the side at which a stimulus is present. Metrics: • Directional accuracy (percentage): the average accuracy of anti-saccade direction based on the target position in both the leftward and rightward direction. • Mean reaction time (milliseconds): the time elapsed between the presentation of the visual stimulus and the onset of eye movement • Acquisition error (degrees): the difference between the anti-target estimation and the anti-targets actual end position **4. Vergence:** the movement of the eyes when tracking objects at varying degrees of depth in the binocular visual field Metrics: • Mean vergence (degrees) during pursuit: mean vergence during smooth pursuit task. Vergence modulation is not required for this task so its presence suggests an asymmetry	Outcome	Continuous

Vestibular Ocular 1. Vestibular Ocular Reflex (VOR)	Vestibulo- Ocular: Visual function that refers to one's ability to make compensatory movements of the eyes in the opposite direction of the head in order to stabilize vision (gaze stabilization) **1. Vestibular Ocular Reflex**: Involuntary reflexive movement of the eyes in response to displacement of the head in order to prevent visual images from slipping on the surface of the retina Metrics: • Average VOR gain (percentage): the average conjugate VOR gain (eye velocity/ head velocity) in left, right, up and down directions • Retinal Slip (degrees): gaze velocity - target velocity	Outcome	Continuous
Symptom Report **1. PCSI post-injury score**	Both global and visual- based symptoms will be recorded with the Post-Concussion Symptom Inventory (PCSI). The PCSI is a symptom inventory, developed and validated for use in children and adolescents to assess the number and severity of concussion-related symptoms. Metrics: 1. PCSI post- injury score: the total symptom score at the time of OM and VO assessment	Outcome	Continuous
Age	The age of the participant at the time of testing.	Covariant	Continuous

References

1. McCrory, P., et al., *Consensus Statement on Concussion in Sport - The 5th international conference on concussion in sport held in Berlin, October 2016.* British Journal of Sports Medicine, 2017(51): p. 838-847.
2. Kristman, V.L., Borg, J., Godbolt, A.K., Salmi, R., Cancelliere, C., Carroll, L.J., Holm, L., Nygren-de Boussard, C., Hartvigsen, J., Donovan, J., & Cassidy, D., *Methodological issues and research recommendations for prognosis after milt traumatic brain injury: Results of the international collaboration on mild traumatic brain injury prognosis* Archives of Physical Medicine and Rehabilitation, 2014. **95**(3): p. 265-277.
3. Clayton, G.H., et al., *Concussion in Children and Adolescents.* Current Physical Medicine and Rehabilitation Reports, 2013. **1**(2): p. 88-96.
4. National Center for Injury Prevention and Control, *Report to Congress: The Management of Traumatic Brain Injury in Children*, J.K. Haarbauer- Krupa, Ann, G., Kurowski, B., & Breiding, M.J., Editor. 2018, Centers for Disease Control and Prevention: https://www.cdc.gov/traumaticbraininjury/pdf/reportstocongress/managementoftbiinchildren/TBI-ReporttoCongress-508.pdf.
5. Institute of Medicine & National Research Council, *Neuroscience, biomechanics, and risks of concussion in the developing brain* in *Sports-related concussions in youth: Improving the science, changing the culture.*, R. Graham, Rivara, F.P., Ford, M.A., & Spicer, C.M., Editor. 2014, The National Academic Press: Washington, DC. p. 55-80.
6. Shrey, D.W., Griesbach, G.S., & Giza, C.C., *The pathophysiology of concussions in youth.* Physical Medicine and Rehabilitation Clinics of North America, 2011. **22**(4): p. 577-602.
7. Barlow, K.M., Crawford, S., Stevenson, A., Sandhu, S.S., Belanger, F., & Dewey, D., *Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury* Pediatrics, 2010. **126**(2): p. 374- 381.
8. Gosselin, N., Lassonde, M., & Petit, D., *Sleep following sport-related concussions.* Sleep Medicine, 2009. **5**: p. 875-882.
9. Blume, H.K., Lucas, S., & Bell, K.R., *Subacute concussion- related symptoms in youth.* Physical Medicine and Rehabilitation Clinics of North America, 2011. **22**(4): p. 665-681.
10. Ponsford, J., et al., *Predictors of postconcussive symptoms 3 months after mild traumatic brain injury.* Neuropsychology, 2012. **26**(3): p. 304-313.
11. Ledoux, A.A., Tang, K., Yeates, K. O., Pusic, M. V., Boutis, K., Craig, W. R., Gravel, J., Freedman, S. B., Gagnon, I., Gioia, G. A., Osmond, M. H., Zemek, R. L., *Natural Progression of Symptom Change and Recovery From Concussion in a Pediatric Population.* JAMA pediatrics, 2019. **173**(1): p. e183820.
12. Barlow, K.M., et al., *Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury.* Pediatrics, 2010. **126**(2): p. 374-81.
13. Novak, Z., et al., *Association of Persistent Postconcussion Symptoms With Pediatric Quality of Life.* JAMA pediatrics, 2016. **170**(12): p. e162900.
14. Babcock, L., Byczkowski, T., Wade, S.L., Ho, M., Mookerjee, S., * Bazarian, J.J., *Predicting postconcussion syndrome after mild traumatic brain injury in children and adolescents w ho present to the emergency department.* Pediatrics, 2013. **2**.
15. Sutton, M., et al., *Neck Injury Comorbidity in Concussion-Related Emergency Department Visits: A Population-Based Study of Sex Differences Across the Life Span.* J Womens Health (Larchmt), 2019. **28**(4): p. 473-482.
16. Fife, T.D. and C. Giza, *Posttraumatic Vertigo and Dizziness.* Semin Neurol, 2013. **33**(3): p. 238-243.

17. Sen, N., *An insight into the vision impairment following traumatic brain injury.* Neurochemistry international, 2017. **111**: p. 103-107.
18. Howell., O.B., Beasley., Mannix & Meehan *Inital somatic symptoms are associated with prolonged symptom duration following concussion in adolescents.* Acute Pedatrics, 2016. **105**(9).
19. Mathews, A., Iboaya, A., Smith, J,A., & Bell, K.R., *Acute Management of Concussion and Diagnostic Criteria* in *Concussion: Assessment, Management and Rehabilitation*, B.C.C. Eapen, D.X. , Editor. 2020, Elsevier Inc: LA, California. p. 1-12.
20. Rieger, B.P.L., L.J., Callahan, J.M., Spenceley, A.T., Gathje,R. & Miller, L.A., *A prospective study of symptoms and neurocognitive outcomes in youth with concussion vs orthopaedic injuries.* Brain Injury, 2013. **27**(2).
21. Junn, C., et al., *Symptoms of Concussion and Comorbid Disorders.* Curr Pain Headache Rep, 2015. **19**(9): p. 46.
22. Grubenhoff, J.A., Currie, D., Comstock, D.R., Juarez- Colunga, E., Bajaj, L., & Kirkwood, M.W., *Psychological factors associated with delayed symptom resolution in children with concussion.* The Journal of Pediatrics, 2016. **174**: p. 27-32.
23. McCuddy, W.T., Espana, L.Y., NElson, L.D., Birn, R.M., Mayer, A.R., & Meier, T.B., *Association of acute depressive symptoms and functional connectivity of emotional processing regions following sport- related concussion.* Neuroimage Clin, 2018. **19**: p. 434-442.
24. Iyer, K., Barlow, K.M., Brooks, B., Ofoghi, Z., Zalesky, A., & Cocchi, L., *Relating brain conenctivity with persistent symptoms in pediatric concussion.* Annals of Clinical and Translational Neurology, 2019. **6**(5): p. 954-961.
25. Pillar, G., Averbooch, E., Katz, N., Kaufman, Y., & Shahard, E. , *Prevalence and risk of sleep disturbances in adolescents after minor head injury* Pediatric Neurology 2003. **29**(2): p. 131-135.
26. Wiseman-Hakes, C., Gosselin, N., Sharma, B., Langer, L., & Gagnon, I. *A Longitudinal Investigation of Sleep and Daytime Wakefulness in Children and Youth With Concussion*. ASN Neuro, 2019. DOI: 10.1177/1759091418822405.
27. Zemek, R.L., Farion, K. J., Sampson, M., & McGahern, C., *Prognosticators of persistent symptoms following pediatric concussion: a systematic review.* JAMA pediatrics, 2013. **167**(3): p. 259-65.
28. Lucas, S., et al., *A prospective study of prevalence and characterization of headache following mild traumatic brain injury.* Cephalalgia, 2014. **34**(2): p. 93-102.
29. Webb, F.M., & Salinas, C.M., *Sport neurology for children*, in *Handbook of Pediatric Neuropsychology*. 2011, Springer Publishing Company. p. 1095-1109.
30. Broshek, D.K., Kaushik, T., Freeman, J.R., Erlanger, D., Webbe. F., & Barth, J.T., *Sex differences in outcome following sports-related concusison.* Journal of Neurosurgery, 2005. **102**.
31. Covassin, T., Schatz, P., & Swanik, K.M, *Sex differences in neuropsychological function and post0concussion symptoms of concussed collegiate athletes.* Neurosurgery, 2007. **61**: p. 345-350.
32. Howell, D.R., Wilson, J.C., Kirkwood, M.W., & Grubenhoff, J.A., *Quality of life and symptom burden 1 month after concusion in children and adolescents* Clinical Pediatrics, 2019. **58**(1): p. 42-49.
33. Grool, A.M., Aglipay, M., Momoli, F., Meehan, W. P., Freedman, S. B., Yeates, K. O., Gravel, J., Gagnon, I., Boutis, K., Meeuwisse, W., Barrowman, N., Ledoux, A. A., Osmond, M. H., Zemek, R., *Association Between Early Participation in Physical Activity Following Acute Concussion and Persistent Postconcussive Symptoms in Children and Adolescents.* JAMA, 2016. **316**(23): p. 2504-2514.
34. Silverberg, N.D. and G.L. Iverson, *Is Rest After Concussion "The Best Medicine?": Recommendations for Activity Resumption Following Concussion in Athletes, Civilians, and Military Service Members.* The Journal of Head Trauma Rehabilitation, 2013. **28**(4): p. 250-259.

35. McKinlay, A., V. Ligteringen, and M. Than, *A comparison of concussive symptoms reported by parents for preschool versus school-aged children.* J Head Trauma Rehabil, 2014. **29**(3): p. 233-8.
36. Hynes, L.M. and J.P. Dickey, *Is there a relationship between whiplash-associated disorders and concussion in hockey? A preliminary study.* Brain Inj, 2006. **20**(2): p. 179-88.
37. Giza, C.C.H., D.A., *The Neurometabolic Cascade of Concussion.* Journal of Athletic Training, 2001. **36**(3): p. 228-235.
38. Romeau- Meja, R., Clza, C.G., & Goldman, J.T., *Concussion pathophysiology and injury biomechanics.* Current Review in Musculoskeletal Medicine, 2019. **12**.
39. Signoretti, A., Lazzarino, G., Tavazzi, B. & Vagnozzi,R., *The pathophysiology of concussion* the Journal of Injury, FFunction, and Rehabilitation, 2011. **3**(10).
40. Signoretti, S., et al., *The pathophysiology of concussion.* PM & R : the journal of injury, function, and rehabilitation, 2011. **3**(10 Suppl 2): p. 359-68.
41. Churchill, N.W., . Hutchison, M.G.,, Grahamd, S.J., & Schweizera, T.A., *Symptom correlates of cerebral blood flow following acute concussion.* NeuroImage Clinical, 2017. **16**.
42. Clausen, M., et al., *Cerebral Blood Flow During Treadmill Exercise Is a Marker of Physiological Postconcussion Syndrome in Female Athletes.* The Journal of head trauma rehabilitation, 2016. **31**(3): p. 215-24.
43. Barlow, K.M., Marcil, L.D., Carlson, H.L., MacMaster, F.P., Brooks, B.L., & Lebel, M.R., *Cerebral perfusion changes in post-concussion syndrome: a prospective controlled cohort study.* Journal of Neurotrauma, 2017. **34**.
44. Brooks, B.L., Low, T. A., Plourde, V., Virani, S., Jadavji, Z., MacMaster, F. P., Barlow, K.M., Lebel, M.R., & Yeates, K.O., , *Cerebral blood flow in children and adolescents several years after concussion.* Brain Injury, 2019. **33**(2): p. 233-241.
45. Prins, M.L., Hales, A., Giza, C.C., & Hovda, D.A., *Repeat taumatic brain injury in the juvenile rat is associated with increased axonal injury and cognitive impairments.* Developmental Science, 2019. **32**.
46. Lancaster, M.A., et al., *Acute white matter changes following sport-related concussion: A serial diffusion tensor and diffusion kurtosis tensor imaging study.* Hum Brain Mapp, 2016. **37**(11): p. 3821-3834.
47. Van Beek, L., Vanderauwera, J., Ghesquière, P., Lagae, L., & De Smedt, B., *Longitudinal changes in mathematical abilities and white matter following paediatric mild traumatic brain injury.* Brain injury, 2015. **29**(13-14): p. 1701-10.
48. Price, L., Wilson, C., & Grant, G., *Blood- Brain Barrier Pathophysiology following Traumatic Brain Injury*, in *Translational Research in Traumatic Brain Injury*, S.A. Simon, Editor. 2016, CRC Press Taylor & Francis Group: London, New York.
49. Johnson, B., Zhang, K., Hallett, M., & Slobounov, S., *Functional neuroimaging of acute oculomotor deficits in concussed athletes.* Brain Imaging Behav, 2015. **9**(3): p. 564-73.
50. Sahyouni, R., Gutierrez, P., Gold, E., Robertson, R.T., & Cummings, B.J., *Effects of concussion on the blood-brain barrier in humans and rodents.* Journal of Concussion, 2017. **1**: p. 2-26.
51. Zouridakis, G., et al., *Functional Connectivity Changes in Mild Traumatic Brain Injury Assessed Using Magnetoencephalography.* Journal of Mechanics in Medicine and Biology, 2012. **12**(02).
52. Dimitriadis, S.I., et al., *Functional connectivity changes detected with magnetoencephalography after mild traumatic brain injury.* Neuroimage Clin, 2015. **9**: p. 519-31.
53. Zouridakis, G., Patidar, U., Situ, N., Rezaie, R., Castillo, E. M., Papanicolaou, A. C., & Levin, H. S., *Functional connectivity changes in mild traumatic brain injury assessed using magnetoencephalography.* Journal of Mechanics in Medicine and Biology, 2012. **12**(2).

54. Darby, A., Victoroff, J., & Giza, C.C., *Pediatric concussion: understanding, assessment, and management, with special attention to sports- related brain injury.* Concussion and Traumatic Encephalopathy, 2019.
55. Weiss, B., *Immediate " On- the- Field" Assessment of Concussion*, in *Pediatric and Adolescent Concussion: Diagnosis, Management, and Outcomes*, J. Niskala, & Walter, K.D., Editor. 2012, Springer: Milwaukee, WI, USA.
56. Broglio, S.P., et al., *Test-Retest Reliability and Interpretation of Common Concussion Assessment Tools: Findings from the NCAA-DoD CARE Consortium.* Sports Medicine, 2018. **48**(5): p. 1255-1268.
57. Sady, M.D., C.G. Vaughan, and G.A. Gioia, *Psychometric characteristics of the postconcussion symptom inventory in children and adolescents.* Arch Clin Neuropsychol, 2014. **29**(4): p. 348-63.
58. Davis, G.A., *SCAT5: Sport Concussion Assessment Tool- 5th Edition.* British Journal of Sports Medicine, 2017: p. 1-8.
59. Schatz, P., *Long-term test-retest reliability of baseline cognitive assessments using ImPACT.* Am J Sports Med, 2010. **38**(1): p. 47-53.
60. Resch, J.E., McCrea, M.A., & Cullum, C.M., *Computerized neurocognitive testing in the management of sport-related concussion: An update.* Neuropsychology Review, 2013. **23**: p. 335-349.
61. Broglio, S.P., Ferrara, M.S., Macciocchi, S.N., Baumgartner, T.A., & Elliot, R. , *Test-retest reliability of computerized concussion assessment programs.* Journal of Athletic Training, 2007. **42**(4): p. 509-514.
62. Galetta, S.L., Morganroth, J., Moehringer, N., Mueller, B., Hasanaj, L., Webb, N., Civitano, S.L., & Balcer,L., *Adding vision to concussion testing: a perspective study of sideline testing in youth and collegiate athletes.* Journal of Neuro-Opthamology, 2015.
63. Hejtmancik, J.F., et al., *Vision*, in *Conn's Translational Neuroscience*. 2017. p. 399-438.
64. Galetta, K.M., et al., *Screening Utility of the King-Devick Test in Mild Cognitive Impairment and Alzheimer Disease Dementia.* Alzheimer disease and associated disorders, 2017. **31**(2): p. 152-158.
65. Remington, L.A., *Chapter 1: Visual System* in *Clinical Anatomy and Physiology of the Visual System*. 2012, Elsevier: St. Louis, Mo.
66. Master, C.L., et al., *Vision Diagnoses Are Common After Concussion in Adolescents.* Clin Pediatr (Phila), 2016. **55**(3): p. 260-7.
67. Ventura, R.E., L.J. Balcer, and S.L. Galetta, *The Concussion Toolbox: The Role of Vision in the Assessment of Concussion.* Semin Neurol, 2015. **35**(5): p. 599-606.
68. Büttner-Ennever, J.A., *The extraocular motor nuclei: organization and functional neuroanatomy*, in *Neuroanatomy of the Oculomotor System*. 2006. p. 95-125.
69. Snowden, R., Thompson, P., & Troscianko, T., *Basic Vision: An introduction to visual perception* Vision and action 2012, Oxford, United Kingdom: Oxford University Press.
70. Joyce, C., Le, P.H. & Peterson, D.C., *Neuroanatomy, Cranial Nerve 3 (Oculomotor)*. 2019, Treasure Island, Florida: StatPearls Publishing.
71. Lappi, O., *Eye movements in the wild: Oculomotor control, gaze behaviours & frames of reference.* Neurosci Biobehav Rev, 2016. **69**: p. 49-68.
72. Liu, G., Volpe, N.J., Galetta, S.L, *Neuto-Opthalmology: Diagnosis and Management*. Vol. 2. 2010, Philadephia: Saunders.
73. Lencer, R., Sprenger, A., & Trillenberg, P., *Smooth Eye Movements in Humans: Smooth Pursuit, Optokinetic Nystagmus and Vestibular Ocular Reflex*, in *Eye Movement Research: An Introduction to its Scientific Foundations and Applications*, C.E. Klein, U., Editor. 2019, Springer: Bonn, Nordrhein- Westfalen, Germany.

74. Erkelens, C.J., *Coordination of smooth pursuit and sacacdes.* Vision Research 2006. **46**(1): p. 163-170.
75. Murray, N.G., Szekely, B., Islas, A., Munkasy, B., Gore, R., Berryhill, M., & Reed-Jones, R. J., *Smooth Pursuit and Saccades after Sport-Related Concussion.* Journal of neurotrauma, 2020. **37**(2): p. 340-346.
76. Phillipou, A., Douglas, J., Krieser, D., Ayton, L., & Abel, L., *changes in saccadic eye movement and memory function after mild closed head injury in children.* Developmental Medicine & Child Neurology, 2013. **56**(4): p. 337-346.
77. Bender, J., Tark, K-J., Reuter, B., Kathmann, N., Curtis, C.E., *Differential roles of the frontal and parietal cortices in the control of saccades.* Brain and Cognition, 2013. **83**(1): p. 1-9.
78. Salman, M.S., Sharpe, J.A., Eizenman, M., Lillakas, L., Westall, C., To, T., Dennis, M. & Steinbach, M., *Saccades in children.* Vision Research, 2006. **46**.
79. Sparks, D., *The brainstem control of saccadic eye movements.* Nat Rev Neurosci, 2002. **3**: p. 952-964.
80. Leigh, R.J. and D.S. Zee, *The Neurology of Eye Movements*. 2015.
81. Armstrong, R.A., *Visual problems associated with traumatic brain injury.* Clin Exp Optom, 2018. **101**(6): p. 716-726.
82. Cifu, D.X., et al., *Differential eye movements in mild traumatic brain injury versus normal controls.* J Head Trauma Rehabil, 2015. **30**(1): p. 21-8.
83. Heitger, M.H., et al., *Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability.* Brain, 2009. **132**(Pt 10): p. 2850-70.
84. Taghdiri, F., et al., *Decreased Number of Self-Paced Saccades in Post-Concussion Syndrome Associated with Higher Symptom Burden and Reduced White Matter Integrity.* Journal of neurotrauma, 2018. **35**(5): p. 719-729.
85. Hunt, A.W., et al., *Oculomotor-Based Vision Assessment in Mild Traumatic Brain Injury: A Systematic Review.* J Head Trauma Rehabil, 2016. **31**(4): p. 252-61.
86. Domagalik, A., et al., *Neural networks related to pro-saccades and anti-saccades revealed by independent component analysis.* NeuroImage, 2012. **62**(3): p. 1325-33.
87. Ventura, R.E., Balcer, L.J. Galetta, S.L., & Rucker, J.C., *Ocular motor assessment in concussion: Current status and future directions.* Journal of the Neurological Sciences, 2016. **361**: p. 79-86.
88. Heitger, M.H., Anderson, T. J., Jones, R. D., Dalrymple-Alford, J. C., Frampton, C. M., & Ardagh, M. W., *Eye movement and visuomotor arm movement deficits following mild closed head injury.* Brain : a journal of neurology, 2004. **127**(Pt 3): p. 575-90.
89. Brune, A.J., & Eggenberger, E.R., *Disorders of vergence eye movements.* Neurological Opthalmology and Otology, 2018. **20**: p. 2-8.
90. Chen, A.H., D.J. O'Leary, and E.R. Howell, *Near visual function in young children. Part I: near point of convergence. Part II: amplitude of accommodation. Part III: near heterophoria.* Ophthalmic and Physiological Optics, 2000. **20**(3): p. 185-198.
91. Ciuffreda, K.J., et al., *Occurrence of oculomotor dysfunctions in acquired brain injury: a retrospective analysis.* Optometry, 2007. **78**(4): p. 155-61.
92. Szymanowicz, D., Ciuffreda, K. J., Thiagarajan, P., Ludlam, D. P., Green, W., & Kapoor, N., *Vergence in mild traumatic brain injury: a pilot study.* Journal of rehabilitation research and development, 2012. **49**(7): p. 1083-100.
93. Scheiman, M., Talasan, H., Mitchell, G.L., & Alvarez, T.L., *Objective assessment of vergence after treatment of concussion related CI: a pilot study* Optom Vis Sci, 2017. **1**: p. 74-88.
94. Masters, C.L., ... *Vision and vestibular system dysfunction predicts prolonged concussion recovery in children.* Clin J Sport Med, 2018. **28**: p. 139-145.

95. Uchino, Y. and K. Kushiro, *Differences between otolith- and semicircular canal-activated neural circuitry in the vestibular system.* Neurosci Res, 2011. **71**(4): p. 315-27.
96. Purves, D., Augustine, G.J., Fitzpatrick, D., Katz, L.C., LaMantia, A., O'McNamara, J., & Williams, S.M. , *Chapter 13: The Vestibular System*, in *Neuroscience, 3rd Edition*. 2004, Sinauer Associates Inc: Sunderland, MA.
97. Mucha, A., et al., *A Brief Vestibular/Ocular Motor Screening (VOMS) assessment to evaluate concussions: preliminary findings.* The American journal of sports medicine, 2014. **42**(10): p. 2479-86.
98. Wallace, B. and J. Lifshitz, *Traumatic brain injury and vestibulo-ocular function: current challenges and future prospects.* Eye Brain, 2016. **8**: p. 153-164.
99. Dieterich, M. and T. Brandt, *The bilateral central vestibular system: its pathways, functions, and disorders.* Ann N Y Acad Sci, 2015. **1343**: p. 10-26.
100. Purves, D., Augustine, G.J., Fitzpatrick, D., Hall, W.C., LaMantia, A., McNamara, J., & Williams, M., *Unit 2: Sensation and Sensory Processing*, in *Neuroscience, 3rd edition* D. Fitzpatrick, Editor. 2004

Sinauer Associates Inc: Sunderland, MA. p. 189-337.
101. Van Beek, L., et al., *Longitudinal changes in mathematical abilities and white matter following paediatric mild traumatic brain injury.* Brain Inj, 2015. **29**(13-14): p. 1701-10.
102. Hoffer, M.E., Gottshall, K.R., Moore, R., Balough, B.J. & Wester, D., *Characterizing and treating dizziness after mild head trauma.* Otology & Neurology, 2004. **25**.
103. Ellis, M.J., Cordungely, D., Vis, S., Reimer, K., Leiter, J. & Russell, K., *Vestibulo-ocular dysfunction in pediatric sports-related concussion.* Journal of NeuroSurgery Pediatrics, 2015. **16**.
104. Broglio, S.P., et al., *Current and emerging rehabilitation for concussion: a review of the evidence.* Clin Sports Med, 2015. **34**(2): p. 213-31.
105. Wright, W.G., R.T. Tierney, and J. McDevitt, *Visual-vestibular processing deficits in mild traumatic brain injury.* J Vestib Res, 2017. **27**(1): p. 27-37.
106. Trenner, M.U., et al., *Human cortical areas involved in sustaining perceptual stability during smooth pursuit eye movements.* Hum Brain Mapp, 2008. **29**(3): p. 300-11.
107. Wright, W.G., Tierney, R. T., & McDevitt, J., *Visual-vestibular processing deficits in mild traumatic brain injury.* Journal of vestibular research : equilibrium & orientation, 2017. **27**(1): p. 27-37.
108. Galetta, et al., *Screening Utility of the King-Devick Test in Mild Cognitive Impairment and Alzheimer Disease Dementia.* Alzheimer Disease & Associated Disorders, 2017. **31**(2): p. 152-158.
109. Galetta, K.M., et al., *Screening Utility of the King-Devick Test in Mild Cognitive Impairment and Alzheimer Disease Dementia.* Alzheimer Disease & Associated Disorders, 2017. **31**(2): p. 152-158.
110. Broglio, S.P., et al., *Current and Emerging Rehabilitation for Concussion: A Review of the Evidence.* Clinics in Sports Medicine, 2015. **34**(2): p. 213-231.
111. Worts, P.R. and S.O. Burkhart, *Test Performance and Test-Retest Reliability of the Vestibular/Ocular Motor Screening and King-Devick Test in Adolescent Athletes During a Competitive Sport Season: Response.* Am J Sports Med, 2019. **47**(2): p. NP16-NP18.
112. Mucha, A., et al., *A Brief Vestibular/Ocular Motor Screening (VOMS) assessment to evaluate concussions: preliminary findings.* Am J Sports Med, 2014. **42**(10): p. 2479-86.
113. MacDougall, H.G., Weber, K.P., McGarvie, L.A., Halmagyi, M., & Curthoys, I.S. , *The video head impulse test: Diagnostic accuracy in peripheral vestibulopathy.* Neurology, 2009. **73**(14): p. 1134-1141.
114. Halmagyi, G.M., et al., *The Video Head Impulse Test.* Front Neurol, 2017. **8**: p. 258.

115. Korsager, L.E., Schmidt, J.V., Faber, C., & Wanscher, J.H. , *Reliability and comparison of gain values with occurrence of saccades in the EyeSeeCam video head impulse test (vHIT).* European Archives of Oto-Rhino-Laryngology : and Head & Neck, 2016. **273**(12): p. 4273-4279.
116. Holmqvist, K., Nystrom, M., Andersson, R., Dewhurst, R., Jarodszka, H., & Van de Weijer, J., *Eye traacking: a comprehensive guide to methods and measures*. 2011, Oxford: Oxford University Press.
117. Ciuffreda, K.J., et al., *Vision therapy for oculomotor dysfunctions in acquired brain injury: a retrospective analysis.* Optometry, 2008. **79**(1): p. 18-22.
118. Bin Zahid, A., Hubbard, M.E., Lockyer, J., Podolak, O., Dammavalam, V.M., Grady, M., Nance, M., Scheiman, M., Samadani, U., & Master, C.L., *Eye Tracking as a Biomarker for Concussion in Children.* Clinical Journal of Sport Medicine, 2018. **Ahead of Print**.
119. Lutz, O., Burmeister, C., Ferreira dos Santos. L., Morkisch, N., Dohle, C., & Kruger, J., *Application of head-mounted devices with eye tracking in virtual reality therapy.* Current Directions in Biomedical Engineering 2017. **3**(1): p. 53-56.
120. Teel, E.F., et al., *Differential sensitivity between a virtual reality (VR) balance module and clinically used concussion balance modalities.* Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine, 2016. **26**(2): p. 162-166.
121. Nolin, P., Stipanicic, A., Henry, M., Joyal, C. C., & Allain, P., *Virtual reality as a screening tool for sports concussion in adolescents.* Brain injury, 2012. **26**(13-14): p. 1564-73.
122. Krohn, S., Tromp, J., Quinque, E.M., Belger, J., Klotzsche, F., Gaebler, M., Thone- Otto, A., & Finke, C., *Multidimensional assessment of virtual reality applications in clinical neuropsychology: The " VR- Check" protocol*, in *International Conference on Virtual Rehabilitation*. 2019, IEEE: Tel Aviv, Israel.
123. Zanier, E.R., et al., *Virtual Reality for Traumatic Brain Injury.* Front Neurol, 2018. **9**: p. 345.
124. Park, J.H., Jeon, H.J., Lim, E.C., Koo, J.W., Lee, H.J., Kim, H.J., Lee, J.S., Song, C.G., & Hong, S.K., *Feasibility of eye tracking assissted vestibular rehabilitation strategy using immersive virtual reality.* Clinical and Experimental Otorhinoaryngology, 2019. **12**(4): p. 376-384.
125. Clay, V., Koenig, S., & Konig, P., *Eye Tracking In Virtual Reality* Journal of Eye Movement Research, 2019. **12**(1): p. 1-18.
126. Trefan, L., et al., *Epidemiology of children with head injury: a national overview.* Arch Dis Child, 2016. **101**(6): p. 527-532.
127. Bin Zahid, A., et al., *Eye Tracking as a Biomarker for Concussion in Children.* Clin J Sport Med, 2018.
128. Cornelissen, F.W., Peters, E.M., & Palmer, J. , *The Eyelink toolbox: eye tracking with MATLAB and the psychophysics toolbox.* Behavior Research Methods, Instruments & Computers, 2002. **34**: p. 613-617.
129. Samadani, U., et al., *Eye tracking detects disconjugate eye movements associated with structural traumatic brain injury and concussion.* J Neurotrauma, 2015. **32**(8): p. 548-56.
130. Wang, K., & Ji, Q., *Real time eye gaze tracking with 3D deformable eye-face model.*, in *The International Conference on Computer Vision*. 2017.
131. National Academy of Sciences, *The Necessity and Challenges of Clinical Research Involving Children*, in *Ethical Conduct of Clinical Research Involving Children* 2004, National Academies Press Washington, DC.
132. Zemek, R.L., et al., *Prognosticators of Persistent Symptoms Following Pediatric Concussion: A Systematic Review.* JAMA Pediatrics, 2013. **167**(3): p. 259-265.
133. Ventura, R.E., et al., *Diagnostic tests for concussion: is vision part of the puzzle?* J Neuroophthalmol, 2015. **35**(1): p. 73-81.

134. Maruta, J., et al., *Association of Visual Tracking Metrics With Post-concussion Symptomatology.* Front Neurol, 2018. **9**: p. 611.