Ocular impairment in pediatric mild Traumatic Brain Injury

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CONTENTS

ABSTRACT

[Français]

Les Traumatismes Crâniens Légers (TCL) et les commotions cérébrales sont des blessures complexes auxquelles les enfants et les adolescents sont particulièrement à risque. Il n'existe pas actuellement d'outil objectif pour le diagnostic et le monitorage de ces blessures, qui sont difficiles à gérer en raison de la grande hétérogénéité clinique qui les caractérise. Un nombre grandissant d'études indique que les TCL peuvent engendrer une dysfonction au niveau des mouvements oculaires chez les adultes, et que ces troubles visuels pourraient servir de marqueurs efficaces pour la détection. La question n'a jamais été posée chez les enfants. Ce projet tente d'apporter une réponse préliminaire, d'abord en évaluant l'intégrité des Mouvements de Poursuite Visuelle (MPV) et de fixation chez des enfants et adolescents atteints d'un TCL, puis en comparant leur performance à celle de sujets contrôles n'ayant pas subi de blessure à la tête. Les résultats obtenus sont mixtes. Aucune dysfonction au niveau des mouvements de fixation n'a été décelée; toutes les mesures utilisées pour évaluer les capacités de fixation étaient comparables par groupe. En revanche, des troubles sélectifs ont été détectés au niveau des MPV. Les patients atteints de TCL éprouvaient en moyenne plus de difficulté à synchroniser le mouvement de leurs yeux avec le mouvement d'une cible. La précision et la vélocité du mouvement ne semblaient pas toutefois affectées. Les résultats ne permettent pas de trancher sur la nature exacte du trouble observé, ce dernier pouvant être causé à la fois par une dysfonction au niveau des circuits visuo-moteurs propre, et par une dysfonction au niveau de structures de plus haut niveau modulant les MPV. Ces résultats préliminaires indiquent que l'évaluation des MPV pourrait contribuer au diagnostic et au monitorage de TCL pédiatriques, et renforcent le besoin d'investigations additionnelles dans ce domaine.

[English]

Mild Traumatic Brain Injuries (mTBI) and concussions are complex injuries with high incidence rates in children and adolescents. There currently exists no 'gold standard' for the diagnosis of concussions, and detection and monitoring are made challenging by highly variable clinical presentations. There is growing evidence that mTBI is associated with oculomotor impairment in adults, and that this type of deficit may serve as a marker for the injury. The literature indicates the question has never been addressed in pediatric mTBI. The research presented here sought to address this knowledge gap by first evaluating smooth pursuit and fixational eye movement integrity in a cohort of children and adolescents suffering from mTBI, and then comparing their performances to control participants not having sustained a head injury. The research yielded mixed findings. On the one hand, we found that fixational eye movements are not impaired in pediatric mTBI; measures of fixational eye movement integrity were comparable across groups. On the other hand, selective deficits in smooth pursuit eye movements were found. Synchronization of eye movement with target motion was significantly poorer for mTBI patients. Their abilities to trace target trajectory accurately and to match target velocity, however, were not found to be impaired. It remains unclear whether the observed deficits were caused by disrupted function of the smooth pursuit system proper, by damage to areas that modulate smooth pursuit through top-down influence, or by a combination of both. These preliminary results suggest that select smooth pursuit paradigms could play a role for diagnosing pediatric mTBI, and reinforce the need for further studies in this novel area of research.

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LIST OF ABBREVIATIONS

ACRM: American Congress for Rehabilitation Medicine

ANOVA: Analysis of Variance

CT: Computed Tomography

DLPFC: Dorsolateral Prefrontal Cortex

DTI: Diffusion Tensor Imaging

EAA: Excitatory Amino Acid

ED: Emergency Department

FEF: Frontal Eye Field

fMRI: functional Magnetic Resonance Imaging

ICCS: International Conference on Concussion in Sports

IQ: Intelligence Quotient

IQR: Interquartile Range

MCH: Montreal Children's Hospital

MEM: working Memory

MRI: Magnetic Resonance Imaging

MST: Medial Superior Temporal

MT: Medial Temporal

mTBI: mild Traumatic Brain Injury

PCS: Post-Concussion Symptoms

PCSS-R: Revised Post-Concussion Symptom Scale

SEF: Supplemental Eye Field

SI: Saccadic Intrusion

SMA: Supplemental Motor Area

SP: Ocular Smooth Pursuit

TBI: Traumatic Brain Injury

TPI: Time Post-Injury at testing

WHO: World Health Organization

WM: White Matter

1. INTRODUCTION

1.1 Rationale

Traumatic Brain Injury (TBI) is a public health concern of major national and international significance. Concussions and mild TBI (mTBI) make up 70-90% of brain injuries (CDC, 2003). The World Health Organization (WHO) estimates yearly population-based rates of mTBI to be 600/100 000 in Europe and North American countries (Cassidy et al., 2004), which translates to roughly 200 000 cases per year in Canada. Not only are there worries about the high prevalence of mTBI, there is also mounting concern about cumulative brain damage resulting from repeated concussive episodes (Guskiewicz et al., 2003). Many concussions, especially in youth sports, go undiagnosed, partly because there is considerable variability in clinical presentation (Eckner & Kutcher, 2010). Moreover, standard imaging tools such as anatomical Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are of limited use for detection of concussions because neural injury from mTBI is largely beneath their detection threshold (American Congress of Rehabilitation Medicine, 1993). More recently developed imaging techniques such as Diffusion Tensor Imaging (DTI) and functional MRI (fMRI) hold promise, but they are costly and of limited accessibility for routine testing and monitoring. Neuropsychological testing is commonly used as a diagnostic and monitoring tool for mTBI, but there are conflicting reports concerning its validity (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Iverson, 2005). The need for a clinically viable tool for effective mTBI management is urgent. The consensus statement of the 3rd

International Conference on Concussions in Sports (ICCS; McCrory et al., 2009) has in fact highlighted the need for clinical assessment of mTBI that does not require a baseline evaluation.

1.2 Objectives

To address this need, this project aims to evaluate the integrity of eye movements in children and teenagers following a concussion. There is evidence that oculomotor function is sensitive to mTBI neuropathology, and that quantitative assessment of eye movement function may therefore be an efficient tool for diagnosis and management of mTBI. Specifically, Post-Concussion Symptoms (PCS) have been linked to reduced performance on a number of visual tasks, including the tracking of a continuously moving target, also known as ocular Smooth Pursuit (SP; Heitger et al., 2009; Maruta, Lee, Jacobs, & Ghajar, 2010). This is consistent with neuroanatomical evidence indicating that key components of the oculomotor system are positioned in brain regions known to be susceptible to mTBI-induced damage. Research on oculomotor movements following mTBI remains limited, however. To our knowledge, there have been no studies to date investigating oculomotor sequelae of mTBI in children and teenagers, two particularly at-risk populations (Langlois, Rutland-Brown, & Thomas, 2006). Nor have there been investigations into the effects of mTBI on eye movements that occur during fixation, which account for as much as 80% of all eye movements. Thus, the overarching objective of this project is to address these two knowledge gaps.

2. BACKGROUND

2.1 MTBI: characterization of an injury

2.1.1 *Definition*

The term ‘mild Traumatic Brain Injury’ was first introduced in the early 1990s by the American Congress of Rehabilitation Medicine (ACRM) in an attempt to sensitize health practitioners, as well as society at large, to the potential perils of less severe head traumas (American Congress of Rehabilitation Medicine, 1993; Barth, Ruff, & Espe-Pfeifer, 2006). A decade later, the WHO Collaborative Center Task Force on Mild Traumatic Brain Injury offered its definition of mTBI:

> MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004).

Continuing reflection since the WHO definition underscores the need for a revised standardized definition of mTBI (Ruff, 2011). For instance, a number of terms currently refer to roughly the same injury construct: minor closed-head injury, mild closed-head injury, mTBI and concussion (Yeates & Taylor, 2005). The latter two are the most prevalent, particularly in the sports concussion literature (Carroll et al., 2004). Some use 'mTBI' and 'concussion' interchangeably (McCrea, 2008), while others consider that 'mTBI' inaccurately conveys the injury's etiology, and therefore condemn the term's usage (McCrory, 2001). Others, still, have found that the term 'concussion' leads to systematic under-estimation of injury severity (DeMatteo et al., 2010; McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). The consensus statement of the 2008 ICCS in Zurich agreed that the two "terms refer to different injury constructs and should not be used interchangeably" (McCrory et al., 2009). The definition now emphasizes the transient nature of the disruption in neurological function and the potential alteration in consciousness, while also mentioning concomitant cognitive symptoms. In addition, the ICCS definition designates concussions as head injuries spanning a narrow portion of the less severe side of the TBI severity spectrum – notably, by declaring that abnormal results on standard neuroimaging procedures preclude a diagnosis of concussion. The view that concussions are a subtype of mTBI lying on the far end of the TBI spectrum has been adopted by others as well (Gioia, Isquith, Schneider, & Vaughan, 2009), including, most recently, by the American Medical Society for Sports Medicine (Harmon et al., 2013). In this manuscript, the term 'mTBI' is used to refer to concussions and more severe mTBIs alike.

The discrepancies with respect to the definition of mTBI may stem from a misunderstanding of its pathophysiology (Giza & Difiori, 2011). It stands to reason that identification of a marker for mTBI – one that is independent of the patient's cognitive input and that can be reliably measured – would provide much needed guidance to clinicians and help refine mTBI terminology. Following next section's brief discussion on the epidemiology of mTBI, section **2.1.3** will provide an overview of what is currently known about mTBI pathophysiology.

2.1.2 *Epidemiology*

According to the WHO Collaborating Centre Task Force on MTBI, it is estimated that yearly population-based rates exceed 600/100 000 (Cassidy et al., 2004). This approximation seems to hold for Canadian provinces as well; an investigation into mTBI incidence in Ontario based on records from both Emergency Department (ED) and family physician revealed population-based rates as high as 653/100 000 (Ryu, Feinstein, Colantonio, Streiner, & Dawson, 2009).

Children and adolescents are two populations at high risk for mTBI with higher rates of brain injury-related hospital admissions and ED visits relative to adults (Faul, Xu, Wald, & Coronado, 2010; Jennett, 1996). Close to 90% of TBIs in children and young adults can be classified as mild (J. F. Kraus, Rock, & Hemyari, 1990; McKinlay et al., 2008; Thurman D, 1999). The incidence of mTBI is highest for children under the age of 5 and adolescents aged 15-19 (Faul et al., 2010; Langlois, Rutland-Brown, & Thomas, 2005; Luerssen, Klauber, & Marshall, 1988), although injury etiologies differ between these two groups.

Whereas most mTBIs in children under the age of 14 are attributed to falls, motor vehicle accidents are the primary cause of mTBI in adults and older adolescents (McKinlay et al., 2008; Satz, Zaucha, McCleary, & Light, 1997).

2.1.3. *Pathophysiology*

The pathophysiology of mTBI is characterized by a complex cascade of neurometabolic events (Giza & Hovda, 2001). MTBI results from external mechanical energy being transferred to the head (Zhang, Yang, & King, 2004). Although there is agreement that the rotational and acceleration forces of mTBI-inducing impacts do not cause axonal shearing or tearing (Povlishock, Becker, Cheng, & Vaughan, 1983), post-injury investigations reveal that mTBI is characterized by diffuse axonal injury (Kirov et al., 2013). DTI studies have revealed that fractional anisotropy values are abnormally high in mTBI patients (Wilde et al., 2008), due to decreased radial diffusivity (Mayer et al., 2010). Axonal sodium channels are thought to be particularly vulnerable to the mechanical forces induced by mTBI (Shcherbatko, Ono, Mandel, & Brehm, 1999). The mechanical strain of mTBI-inducing impacts perturbs sodium channel activity, causing deregulated sodium influx into the cell (Wolf, Stys, Lusardi, Meaney, & Smith, 2001) and a sharp rise in intra-axonal calcium levels (Fineman, Hovda, Smith, Yoshino, & Becker, 1993). Cells depolarize in response to increased calcium levels, and excitatory amino acids (EAA) – most prominently glutamate – are indiscriminately released into axonal synaptic clefs (Katayama, Becker, Tamura, & Hovda, 1990). EAA saturation of post-synaptic receptors ensues, resulting in massive potassium efflux (Katayama et al., 1990). Ionic pump

activity is significantly increased to counter ionic imbalances (Barkhoudarian, Hovda, & Giza, 2011) and to make up for the loss of glial cells' regulatory role, which is also disrupted following impact (D'Ambrosio, Maris, Grady, Winn, & Janigro, 1999). Increased energy demands cause a shift from anaerobic to glycolytic, lactate-producing (Kawamata, Katayama, Hovda, Yoshino, & Becker, 1995), glucose metabolism; cortical and hippocampal glycolysis rates, in particular, increase dramatically (Yoshino, Hovda, Kawamata, Katayama, & Becker, 1991). The hypermetabolic state is followed by a depression in glucose consumption (**Appendix I, Figure 2.1**), which begins as soon as six hours following impact and that lasts for up to five days in rodent models (Yoshino et al., 1991).

Although the metabolic repercussions of mTBI are widespread, there is important regional variability in the damage induced by mTBI. The vulnerability of white matter (WM) and WM tracts, in particular, has been extensively reported on (Cecil et al., 1998; M. F. Kraus, Susmaras, et al., 2007; Mayer et al., 2010; Messé et al., 2011). Investigations into grey matter integrity following mTBI have, in contrast, failed to identify structural or metabolical abnormalities (Messé et al., 2011). Evidence for abnormal metabolism following mTBI is most robust for the corpus callosum (Johnson, Gay, et al., 2012; Kirov et al., 2013; Wilde et al., 2008; Yeo et al., 2011), whose proximity to the cerebral falx makes it highly susceptible to damage from rotational forces (Nishimoto & Murakami, 1998). Metabolic abnormalities have also been reported in the inferior (Niogi et al., 2008), superior (Smits et al., 2011), and medial longitudinal (Hsu, Chen, Lu, & Liang, 2001) fasciculi, although evidence for the latter is more limited. Abnormal

metabolic profiles tied to mTBI have also been found in cortical regions, with evidence suggesting impaired function of the frontal cortex in both the acute (Henry, Tremblay, Boulanger, Ellemberg, & Lassonde, 2010) and sub-acute (Henry et al., 2011) periods post-injury. Sub-cortically, the thalami and striatum have been identified as structures highly susceptible to mTBI. Metabolic abnormalities have been reported in the thalamus in the days (Yoshino et al., 1991), months (Grossman et al., 2012), and even years (Yang et al., 2012), following mTBI in patients with persistent PCS (Kirov et al., 2007), as well as in those whose symptoms have resolved (Johnson, Zhang, Gay, Neuberger, et al., 2012). Evidence for striatal dysfunction is more limited, but has also been reported in the acute post-impact period (Fineman et al., 1993; Hamberger, Viano, Säljö, & Bolouri, 2009), and has been associated with persisting PCS, particularly in mTBI patients suffering from depression (Chen, Johnston, Petrides, & Ptito, 2008).

2.1.4. *Clinical presentation*

The acute signs and symptoms of mTBI are diverse. In the immediate post-injury period, patients typically show signs of confusion, memory impairment, and balance deficits (Kelly & Rosenberg, 1997; McCrory et al., 2013). In the hours to days following injury, patients frequently develop a number of PCS (McCrory et al., 2013). PCS are highly non-specific and heterogeneous (Rosenbaum & Lipton, 2012), but can reliably be classified into three distinct sub-types (Ayr, Yeates, Taylor, & Browne, 2009): somatic (e.g. headache and

dizziness), cognitive (e.g. forgetfulness) and emotional (e.g. depression and irritability).

The long-term outcomes of mTBI are poorly understood. Two widely cited meta-analytic studies (Binder, Rohling, & Larrabee, 1997; Frencham, Fox, & Maybery, 2005) concluded that mTBI is not associated with enduring neuropsychological deficits in adults. These studies, however, have been criticized from a methodological standpoint (Pertab, James, & Bigler, 2009), and there have since been accounts both supporting (Ponsford et al., 2012), and contradicting (Tay, Ang, Lau, Meyyappan, & Collinson, 2010) their findings. The latter studies are supported by animal models, which show reduced performance on cognitive tasks and impaired long-term learning abilities following mTBI (Zohar et al., 2003). Therefore, conflicting evidence and the questionable methodologies of some studies make it difficult to conclude on the neuropsychological outcomes of adult mTBI. Moreover, there are accounts indicating that children may necessitate more time for recovery following mTBI than adults (Field, Collins, Lovell, & Maroon, 2003). The potential differences in the evolution of injury in adults and youths further limit the generalizability of results. Clearly, further investigations into the long-term neuropsychological outcomes of mTBI are necessary.

Long-term somatic outcomes of mTBI have been associated with a number of physiological abnormalities, including cardiovascular-autonomic dysregulation and higher rates of early mortality (Hilz et al., 2011), abnormal cerebral metabolic rates lasting one to five years post-injury (Gross, Kling, Henry, Herndon, & Lavretsky, 1996), persisting balance deficits lasting beyond one year

post-injury (Slobounov, Sebastianelli, & Hallett, 2012; Vanderploeg, Curtiss, Luis, & Salazar, 2007), visual impairments (Greenwald, Kapoor, & Singh, 2012; Vanderploeg et al., 2007) and headache pain (Faux & Sheedy, 2008). Although clinical symptoms may clear within two weeks following injury, evidence has been found for lingering visual-motor disintegration up to one month after injury, even in asymptomatic patients (Slobounov, Slobounov, Sebastianelli, Cao, & Newell, 2007). Similar findings have been reported in children with respect to balance deficits (Gagnon, Swaine, Friedman, & Forget, 2004), alterations in cerebral blood flow (Maugans, Farley, Altaye, Leach, & Cecil, 2012), and headache pain (Blume et al., 2012). The physiological repercussions of mTBI that extend beyond the acute and sub-acute injury phases and, particularly, the impact they have on child development, have gained increased attention in recent years, but, overall, there remains a dearth of studies investigating these issues (Keightley, Chen, & Ptito, 2012).

2.1.5. *Diagnosis*

Diagnosis of mTBI is notoriously difficult. One reason for this is the lack of a unified definition. A second reason is that the pathology and clinical presentation of mTBI are highly heterogeneous (Rosenbaum & Lipton, 2012). Pre-morbid factors, such as age, gender, and psychosocial situation (Lannsjö, Backheden, Johansson, Af Geijerstam, & Borg, 2012; McCrory, Davis, & Makdissi, 2012; Ponsford et al., 2012), as well as injury biomechanics (e.g. different acceleration forces associated to sports concussion versus motor vehicle accident) likely influence head impact outcomes (Rosenbaum & Lipton, 2012).

Diagnosis and clinical management of youth mTBI is made especially challenging by age-related differences, which significantly increase the variability of the clinical presentation (Thiessen & Woolridge, 2006). Moreover, neurological function, behavior, and mental status can be more difficult to evaluate in children than in adults (Thiessen & Woolridge, 2006).

Third, traditional tools and techniques used for diagnosis of head injury such as CT, MRI and routine Electro-Encephalogram (EEG) and neurological examinations, are largely insensitive to mTBI pathology (American Congress of Rehabilitation Medicine, 1993). CT scans are often relied upon to establish injury severity, but patients presenting to the ED with Glasgow Coma Scales of 15 and 13 show intracranial CT abnormalities in only five and thirty percent of cases, respectively, and only 1% of cases require neurosurgical intervention (Borg et al., 2004). There have been reports suggesting that mTBIs for which CT scan results are positive – indicating an intracranial injury – are associated more strongly with symptoms that persist beyond the year mark than mTBIs with negative CT scan results (Sadowski-Cron et al., 2006), but more recent results go against these findings (Lannsjö et al., 2012). 3-Tesla MRI is more sensitive to parenchymal lesions than CT (Lee et al., 2008), but for the most part, MRI is also of limited use for detection of concussions (Ptito, Chen, & Johnston, 2007) because neural injury from mTBI is largely beneath the detection threshold of such scans (American Congress of Rehabilitation Medicine, 1993).

Fourth, all too often, a systematic approach to diagnosis and management of mTBI patients is not employed in EDs. A large proportion of mTBI research has focused on elite athletes (Chen et al., 2004; De Beaumont, Tremblay, Poirier,

Lassonde, & Théoret, 2012; Henry et al., 2011; Schnebel, Gwin, Anderson, & Gatlin, 2007; Vagnozzi et al., 2010; Zafonte, 2011) and soldiers (Hoge et al., 2008; Theeler & Erickson, 2009; Theeler, Flynn, & Erickson, 2010). These two populations are at inherent risk for mTBI, and are increasingly being followed by healthcare personnel who have education and expertise in the management of mTBI. The general public, in contrast, relies primarily on ED providers to recognize and treat symptoms of mTBI (Bazarian, McClung, Cheng, Flesher, & Schneider, 2005). There is evidence that mTBI cases are easily missed by ED staff in the presence of comorbidities (Stuart, Mandleco, Wilshaw, Beckstrand, & Heaston, 2012), and that patient education and post-discharge follow-up care is often lacking (Bazarian et al., 2005; Sharpe, Kool, Shepherd, Dalziel, & Ameratunga, 2012).

Fortunately, a number of novel diagnosis techniques for mTBI are being investigated that have the potential of making important contributions to management of this injury. New imaging methods – fMRI, DTI, and Resting-state fMRI (R-fMRI) in particular – are at the forefront of innovation in this field. FMRI has enabled mapping of the cognitive repercussions of mTBI (Shumskaya, Andriessen, Norris, & Vos, 2012), and DTI has been instrumental in identifying the extent of WM damage following injury (Mayer et al., 2010). Recent R-fMRI investigations into resting-state activity levels show that baseline functional connectivity is reduced following mTBI (Johnson, Zhang, Gay, Horovitz, et al., 2012) and support R-fMRI's potential role as a tool for mTBI diagnosis (Hunter, Wilde, Tong, & Holshouser, 2012). These technologies, however, are costly and

of limited accessibility for routine testing and monitoring (Sistrom & McKay, 2005).

Two other diagnosis methods that have been garnering attention are blood tests and eye-tracking. Blood tests are being developed for ED usage in the acute post-impact time period to quantify protein whose concentrations are known to fluctuate following neuronal insult [see (Zetterberg, Smith, & Blennow, 2013), for a review]. Blood tests are an appealing alternative to cranial CT scans for detection of intracranial injury; an effective blood test would reduce unnecessary irradiation exposure for patients, while also reducing hospital operating costs (Bouvier et al., 2012). Although this approach to managing pediatric mTBI shows promise, evidence is currently too conflicting and too limited for clinical usage (Geyer, Ulrich, Gräfe, Stach, & Till, 2009). Eye-tracking also avoids some of the aforementioned limitation. A detailed discussion on the promise it holds follows.

2.2. Oculomotor impairment and mTBI

The earlier discussion on mTBI pathophysiology highlighted a number of brain areas that are susceptible to mTBI: among these were the frontal lobes, portions of the corpus callosum, and the thalamus. These brain regions are made up of a number of structures that play key roles in oculomotor movement (Leigh & Zee, 2006). In light of the neuroanatomical overlap between eye-movement circuitry and mTBI pathophysiology, one is justified in expecting that visual deficits might follow mTBI. Accordingly, various paradigms have been used to assess distinct oculomotor dysfunctions following mTBI, some with promising results. Most of these paradigms use targets displayed on a computer screen to

drive specific eye movements while a camera – usually infrared – records eye position data for off-line analysis. Typically, eye-tracking experiments rely on prosaccade (direct gaze towards target), anti-saccade (direct gaze away from target), or SP (maintain gaze on moving target) tasks.

2.2.1 *Prosaccades*

MTBI patients show deficits on certain prosaccade tasks (Heitger et al., 2009; M. F. Kraus, Little, et al., 2007). Many earlier investigations into mTBI prosaccade generation focused on *reflexive saccades*. In a typical reflexive saccade task, an initial fixation cross is presented at the center of the screen, followed by flashing of a target in the periphery. Participants are required to make a reflexive saccade to the peripheral target as rapidly as they can. Performance on this task seems unimpaired in mTBI suggesting that saccade circuitry is not affected by this injury (Heitger et al., 2004; Heitger et al., 2009), although there is evidence showing that mTBI patients have longer response latencies as well as reduced accuracy on variations of this task that include a cognitive component (Drew et al., 2007; M. F. Kraus, Little, et al., 2007). S*elf-paced saccade* generation, which instructs participants to look back and forth between two targets, is an experimental paradigm used for probing *intentional* prosaccade mechanisms. Heitger and colleagues (2009) found that post-concussion symptomatology was associated with production of fewer self-paced saccades, longer intersaccadic latencies, and lower saccade peak-velocities (Heitger et al., 2009).

Single neuron recordings (Bruce & Goldberg, 1985) and lesion studies in non-human primates (Schiller & Chou, 1998) have demonstrated the crucial role of the Frontal Eye Fields (FEF) in reflexive saccade preparation and generation. The FEFs occupy a region located on the lateral frontal lobe, approximately one to two centimeters rostral to the hand, arm or face areas of the primary motor cortex (Yamamoto et al., 2004), in the vicinity of the central and precentral sulci (Paus, 1996). The FEFs are implicated in a wide range of ocular movements, and are highly interconnected with other parts of the saccadic system (**Appendix I, Figure 2.2a**). Important projections to and from the superior colliculi (SC) carry a wide range of movement, memory, and visual information (Sommer & Wurtz, 2004) that are crucial for the modulation of saccadic eye movements (Berman, Joiner, Cavanaugh, & Wurtz, 2009). The SC also serve as a necessary relay station for FEF-brainstem connections that ensure saccade execution (Hanes & Wurtz, 2001). The SC in turn mediates information to the FEFs via the mediodorsal thalamus (Sommer & Wurtz, 2004). Connections between the FEFs and the Posterior Parietal Cortex (PCC; specifically, the superior portion of the angular gyrus) and the Dorsolateral Prefrontal Cortex (DLPFC) have key roles in saccade generation; both these areas have been found necessary for the triggering of reflexive saccades (Coubard & Kapoula, 2006; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991).

Recent EEG investigations into movement related cortical potentials demonstrate crucial involvement of the FEFs, Supplemental Eye Fields (SEF) and intra-parietal sulcus in the generation of intentional prosaccades (Berchicci, Stella, Pitzalis, Spinelli, & Di Russo, 2012). It is unlikely, however, that the lower

saccade velocities reported for mTBI patients can be accounted for by these regions alone, since cortical areas are usually not involved in regulating saccadic eye-movement metrics (Coubard & Kapoula, 2006; Funahashi, Bruce, & Goldman-Rakic, 1993). Self-paced saccade generation requires subcortical signaling; activity in both the central thalamus and basal ganglia has been observed during self-paced saccades, indicating that this kind of eye movement may be reliant on the basal-thalamocortical loop (Petit et al., 1993; Tanaka, 2006). Reports of impaired intentional saccade generation in mTBI, then, are consistent with the abnormal patterns of subcortical metabolic activity found following mTBI that were mentioned in section **2.1.3**.

2.2.2 *Anti-saccades*

Anti-saccade paradigms are also sensitive to mTBI pathology. In this type of task, following initial fixation and flashing of a target in the periphery, participants are required to inhibit the reflexive saccade to the peripheral target, and instead generate a saccade to the opposite, mirror location, of the screen. Thus, the anti-saccade task requires both suppression of the automatic saccade response as well as inversion of the stimulus vector for generation of an anti-saccade (Munoz & Everling, 2004). Evidence for impaired performance of mTBI patients on this task is divided. While some have reported that suppression of reflexive saccades is normal following mTBI (Crevits, Hanse, Tummers, & Van Maele, 2000), others have found that the ability to inhibit is impaired on a variation of the anti-saccade task that introduces a gap (i.e. a blank screen) between initial fixation and peripheral target presentation (M. F. Kraus, Little, et

al., 2007; Reingold & Stampe, 2002). Heitger et al. (2009) found that the saccade generation phase of the anti-saccade response is also impaired; final absolute gaze position errors were significantly higher in chronic PCS patients than for controls in their study (Heitger et al., 2009).

Appropriate response on the anti-saccade task is also heavily reliant on activity in those regions identified as being sensitive to mTBI. Specifically, anti-saccade paradigms have been associated with heightened activity in the right DLPFC, the anterior cingulate cortex, the pre-SEFs (Ford, Goltz, Brown, & Everling, 2005), the putamen (which makes up part of the striatum) and the thalamus (O'Driscoll et al., 1995). Successful inhibition of reflexive saccades is reliant on DLPFC activity; lesions to the DLPFC, but not to adjacent FEFs or Supplementary Motor Area (SMA), are associated with an increase in misdirected saccades on this task (Pierrot-Deseilligny et al., 1991). The SC (Reingold & Stampe, 2002), ventrolateral frontal cortex (Hodgson et al., 2007), and to a lesser extent, the substantia nigra (Hikosaka, Takikawa, & Kawagoe, 2000) have all been implicated in the saccadic suppression component of the anti-saccade task (Munoz & Everling, 2004).

2.2.3 *Ocular smooth pursuit*

Evidence regarding insult to the SP system following mTBI is less split. Heitger et al. (2004) found that oculomotor SP was selectively impaired following mTBI, as manifested by a significantly larger lag on a random SP task (Heitger et al., 2004). More recently, the same group reported significant differences in SP lag time between mTBI patients with chronic PCS and patients not having

developed PCS (Heitger et al., 2009). In addition, tracking velocity was significantly slower in a sine SP task for the PCS group, and mean absolute error was larger in both random and sine SP tasks (Heitger et al., 2009). MTBI patients have also been shown to be impaired on *predictive* SP tasks – which require that participants track a target as it traces a highly predictable path. Phase error (the phase difference between the target and the eye at a given time *t* as the participant tracks the target), low-velocity gains, and gaze positional error are reportedly higher for mTBI patients relative to control participants (Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010).

SP task execution recruits circuits that are distinct from those involved in saccade paradigms (Leigh & Zee, 2006). Of those regions identified as being highly vulnerable to mTBI, the FEF, SEF, DLPFC and the thalamus (Tanaka, 2005) have the most prominent roles in SP (**Appendix I, Figure 2.2b**). Of these structures, involvement of the FEF is most robust. Neurophysiological recordings in monkeys have revealed the existence of directionally selective *pursuit neurons*, distinct from those involved in saccade generation, in the arcuate fundus and posterior bank of the FEFs (Gottlieb, MacAvoy, & Bruce, 1994). Stimulation at these sites during visual fixation induces SP, while stimulation during SP increases the movement's velocity (Tanaka & Lisberger, 2002), which suggests that these neurons have an important part to play in SP initiation and SP dynamic gain control (Nuding et al., 2009). In humans, the inferior lateral FEF also appears to be heavily solicited during SP (Petit, Clark, Ingeholm, & Haxby, 1997). The SEF and DLPFC play a less direct, higher-order modulatory role, by regulating the cognitive dimensions (e.g. storage of target trajectory and movement

prediction) of SP (K. Fukushima, Fukushima, Warabi, & Barnes, 2013b). There are several more posterior cortical areas that are important for SP, but evidence for their vulnerability to mTBI is more limited. Still, the Middle temporal (MT) and Medial Superior temporal (MST) visual areas, which provide visual-motion information to the SP system (Newsome, Wurtz, & Komatsu, 1988) by encoding target velocity and target direction (Dursteler & Wurtz, 1988; Maunsell & Van Essen, 1983) are worthy of mention because of their prominent role in SP and because abnormal metabolic activity has been reported in the temporal lobes following mTBI (Abdel-Dayem et al., 1998). Sub-cortically, single-neuron thalamic recordings have revealed the presence of neurons in the ventromedial thalamus that show directional modulation to SP movement (Tanaka, 2005), and a number of studies have found direct projections from specific thalamic nuclei to the caudal FEF (Lynch & Tian, 2006).

2.2.4 *Outstanding questions*

To our knowledge, eye movements that occur during *fixation* have yet to be investigated in mTBI. Fixational eye movement integrity following mTBI is worth assessing for two reasons. First, it is surprising that fixation has not been studied in mTBI, considering that 80% of waking time is spent fixating (Martinez-Conde, 2006) – one would think that if damage to the oculomotor system were suspected, fixational movements would be the first to be investigated. There is considerable overlap between brain networks that regulate fixation and saccade generation (Hafed & Krauzlis, 2012) and, therefore, the hypothesized susceptibility of the saccadic system to mTBI carries over to the fixational system.

Indeed, the FEFs and SEFs – two areas situated in the at-risk frontal cortex – and the thalami, also sensitive to mTBI, have been shown to play a key role in fixation (Petit et al., 1995; Rafal, McGrath, Machado, & Hindle, 2004).

There is particularly high overlap between brain structures that generate saccades and those that generate high velocity fixational eye movements called microsaccades (Hafed & Krauzlis, 2012; Martinez-Conde, Otero-Millan, & MacKnik, 2013; Otero-Millan, Macknik, Serra, Leigh, & Martinez-Conde, 2011; Van Horn & Cullen, 2012). Microsaccades are one of three types of miniature and involuntary eye movements that occur during fixation, the two others being high-frequency tremor and slow drift (Leigh & Zee, 2006). Microsaccades have garnered most attention because they are the fastest of the three and as a result are more readily detectable (Leigh & Zee, 2006). They are necessary to prevent both foveal and peripheral visual fading during fixation (Martinez-Conde, Macknik, Troncoso, & Dyar, 2006; McCamy et al., 2012) and are triggered in response to low retinal slip (Engbert & Kliegl, 2003). The electro-neurophysiological cascades that drive microsaccade and saccade generation are nearly identical. The main difference between the two lies in how their respective signals are initiated. Both saccadic and microsaccadic pulses originate in brainstem burst neurons, which in their default state are under tonic inhibition (Goldberg, 2000). For a saccade to occur, the tonic inhibition must be lifted in its entirety (Goldberg, 2000). For microsaccades, only partial release of the inhibition is required (Inagaki, Hirata, & Usui, 2011).

A second reason for studying eye-movement integrity with fixation tasks, then, is that these can provide clues about the integrity of the saccadic generation

circuitry, while also circumventing some of the pitfalls of standard prosaccade paradigms. Because saccade and microsaccade generation share the same subcortical neuronal substrates, some key characteristics of saccades are also found for microsaccades. Specifically, there exists a linear relationship between a saccade's peak velocity and its amplitude called the saccadic *main sequence* (Bahill, Clark, & Stark, 1975). By assessing the strength of the relationship between saccade peak velocity and amplitude, an index for the integrity of the saccade generation system is provided; the main sequence has been used as an indicator of ocular pathology and neurological disorder (Garbutt, Harwood, & Harris, 2001). The stereotyped relationship of these parameters is the same for small saccades as it is for microsaccades (Inagaki et al., 2011). Therefore, analysis of the Microsaccadic Main Sequence (MMS) yields direct information about the integrity of the microsaccade generation circuitry, as well as indirect information concerning the integrity of the saccade system. The advantage of using fixational tasks to assess saccade circuitry integrity over standard prosaccade paradigms is twofold. First, fixational tasks are much less prone to demand characteristics; participants are rarely aware of what is being evaluated during the fixation tasks, and microsaccade generation is largely involuntary. This is significant because a number of diagnosis methods for mTBI have been criticized for the potential influence of demand characteristics on results (Iverson, 2005). Second, fixation tasks require generation of movements that are of much smaller amplitudes than those required for prosaccades tasks, and may therefore be less taxing for patient populations suffering from fatigue and visual disturbances.

Selection of an appropriate eye-tracking paradigm for probing oculomotor function in mTBI requires careful consideration of oculomotor system neuroanatomy and of the literature on ocular deficits following mTBI. In addition to highlighting the brain regions that are differentially involved in various eye-tracking paradigms, the above paragraphs also point to a number of knowledge gaps in our understanding of visual impairment following mTBI. Two are worth highlighting. First, to our knowledge, all reported studies have been conducted on adult participants; none have evaluated visual impairment in children and adolescents, a particularly at-risk population for mTBI (Karlin, 2011; Sabini & Reddy, 2010). Second, as was explicitly stated, it is currently unknown how fixational eye movements are affected following mTBI. This project's objective was to address these outstanding questions by performing eye-tracking on a cohort of mTBI patients, using two tasks designed to probe discrete brain networks for mTBI-induced damage.

3. AIMS AND HYPOTHESES

The aims of this project were as follows:

1) To evaluate oculomotor function in children and adolescents suffering from mTBI. Specifically, we sought to evaluate gaze holding abilities (i.e. eye movements occurring during fixation and SP) following pediatric mTBI. It was hypothesized that the mTBI group would show impaired performance on both types of eye movements relative to control participants not having sustained a head injury. The predictions were that the test group would show reduced gaze acuity in both tasks, increased microsaccade rate in the fixation task, and reduced eye-target synchronization and gain in the SP task. In addition, we sought to characterize the microsaccadic main sequence to verify integrity of the saccade generation circuitry.
2) To use measures of oculomotor performance for retrospective prediction of participant group membership, to test eye-tracking's potential contributions to mTBI diagnosis. We hoped to use oculomotor measures identified in aim 1) as being sensitive to mTBI for inclusion in the model. We predicted that the model would be successful in distinguishing mTBI cases from healthy participants.
3) To document and compare symptoms in children suffering from mTBI and minor orthopedic injury. We expected that PCSS-R scores would be significantly higher in the mTBI group. We also sought to correlate severity of symptoms with mTBI-induced ocular impairment. We

expected mTBI patients with high somatic symptom load (determined through PCSS-R questionnaire scores) to perform worst on measures of oculomotor performance identified in aim 1) as being sensitive to mTBI.

4. METHODS

4.1 Design

The project was carried out as a case-control study consisting of one test group made up of mTBI patients and two control groups: one group of healthy children and adolescents, and one group of patients having recently sustained a minor orthopedic injury not involving the head or neck.

4.2 Participants

MTBI group patients were recruited from the Montreal Children's Hospital's (MCH) concussion clinic. The clinic coordinator and two clinic physiotherapists informed eligible families about the study, pre-screened participants, and linked interested parties to the researcher. Eligible participants had to have sustained an mTBI within the past six months. Participants qualified for inclusion if *one* of the two following conditions was additionally met: i) testing could be scheduled within the first two weeks following injury (a period corresponding to the acute phase of the injury); or ii) the participant was symptomatic, where symptomatic was defined as not yet being cleared for return to normal activities by clinic staff.

The *orthopedic injury control group* was recruited from the MCH ED. The use of non-injured comparison groups has been criticized as a methodological shortcoming of many studies in the mTBI literature (Yeates & Taylor, 2005) and we sought to circumvent this pitfall. With the help of a recruiter working exclusively at the MCH ED, we approached patients having sustained a minor orthopedic injury (e.g. sprained wrist), not requiring hospitalization, not involving

injury to the neck or the head. These patients were selected as controls to account for the considerable – if temporary – life changes that accompany a traumatic injury (e.g. psychological stress of injury, ED visit, clinical appointments and time away from school and sports), as well as to account for pre-morbid differences in injury susceptibility (Yeates & Taylor, 2005). Potential participants for this group were not eligible if an mTBI had been sustained within the past year.

It was imperative that we be able to dissociate generalized injury effects on ocular function from those specifically tied to mTBI. Thus inclusion of a *healthy control* group was necessary. Participants in the healthy control group were recruited either from injury group participant siblings, or through family friends and colleagues. As was the case for the orthopedic injury control group, potential healthy control participants were excluded if they reported an mTBI within the past year.

Additional inclusion and exclusion criteria that applied to all participants were as follows. All participants had to be between 7 and 18 years of age. We chose seven as the minimum age for inclusion in the study following considerations about testing feasibility in young children; the testing required that participants be able to sit still for relatively long periods of time, and it was agreed that this could prove challenging for children under the age of seven. Exclusion criteria for all participants included any history of moderate or severe head trauma, any behavioral or psychiatric disorders, use of psychoactive medications,

visual impairment[1], or any chronic medical conditions. These exclusion criteria were screened for with a general health questionnaire.

4.3 Ethical considerations

The Research Ethics Board of the Montreal Neurological Institute approved the study, and use of MCH office space for conducting testing was allowed by the MCH Director of Professional Services. The present study was added to a larger, already existing, longitudinal study being run through the MCH Trauma Unit, as an additional means of evaluating outcomes after concussion. An amendment to the larger study for inclusion of the eye-tracking procedures was approved. Informed written consent was obtained from all participants. Participants were informed that they could withdraw from the study at any point. They were compensated $25 for their time, and parking fees were reimbursed.

4.4 Visual acuity testing

The testing session began with evaluation of visual acuity. Visual acuity testing was carried out to identify any significant and unreported visual impairment, as well as to ensure that gaze accuracy was sufficient for carrying out oculomotor tasks (Contreras, Ghajar, Bahar, & Suh, 2011). Visual acuity testing for both eyes was performed using the SLOAN letters for 10 feet (Ferris, Kassoff, Bresnick, & Bailey, 1982). Participants were instructed to stand with both heels placed on a piece of tape placed 10 feet away from the wall-mounted SLOAN

[1] Recruitment and testing of the mTBI group was carried out prior to recruitment and testing of the two control groups in an attempt to subsequently match control groups in age and sex. During recruitment of the mTBI group, a history of only *gross* visual impairment (e.g. strabismus) was used as an exclusion criterion; use of glasses or contact lenses was permitted to maximize recruitment. In the end, none of the mTBI participants had a history of using corrective visual aids. Although the eye tracking apparatus we used is designed to accommodate corrective visual aids, these can introduce additional noise in the recordings. As such, 20/20 uncorrected vision was added as an additional inclusion criterion for recruitment of the two control groups.

chart. Participants were asked to cover their left eye with their left hand, and read out letters on the chart's different lines, starting at row 20/50 (all letters must be read out correctly to move to higher level of difficulty) and ending with the 20/20 row (for the 20/30 and 20/20 rows, two errors per line are permissible). The same procedure was then carried out for the right eye. See **Appendix I, Figure 4.1** for a picture of the SLOAN chart.

4.5 Post-concussion symptomatology assessment

The Revised Post-Concussion Symptom Scale (PCSS-R; see **Appendix I, Figure 4.2**) questionnaire was administered to both injury groups to assess PCS severity. For the orthopedic injury group, headings on the PCSS-R were modified to hide its association to mTBI and present it as a symptom assessment questionnaire applicable to all injuries. The PCSS-R asks subjects to rate the severity of 22 symptoms commonly experienced following head injury (e.g. headaches, dizziness, light sensitivity) and has proven sensitive to PCS of varying severities (Chen, Johnston, Collie, McCrory, & Ptito, 2007). Each symptom is rated on a scale of 0 (no symptom) to 6 (severe). Total PCSS-R scores range from 0 to a maximum of 132. Moreover, PCSS-R scores for each subclass of symptoms, namely somatic, cognitive, and emotional, were also calculated. Maximum scores for these categories are respectively 84, 24 and 24.

4.6 Oculomotor testing

4.6.1 *Experimental setup*

Eye-movements were recorded using the EyeLink® 1000 (SR Research Ltd.; Kanata, ON) infrared video-oculography device. The camera was desktop

mounted and equipped with a 25*mm* lens, as is appropriate for binocular recording (SR Research Ltd., 2008). To ensure that lighting conditions remained constant across all experimental sessions, testing was carried out in a windowless room at the Research Institute of the MCH. Subjects were seated in front of a computer screen (Dell® E190S 19-inch Black Flat Panel LCD Monitor @ 60*Hz* refresh rate) with eyes 57*cm* away from the screen, their head stabilized by a chin and forehead rest, with their eyes set to fall on the upper half of the screen, as recommended by the eye tracker manufacturer (SR Research Ltd., 2008). Eye positions were sampled binocularly at 1000*Hz* and recorded for off-line analysis.

Recordings were performed while subjects carried out two randomly sequenced visual tasks, each one eliciting a distinct type of oculomotor movement. The computerized stimulus presentation was designed using SR Research's Python™-based Experiment Builder software. Prior to each task, participants were instructed to stay as still as possible, while camera calibration was performed. Calibration was performed using a nine-point grid with a black circular target appearing at each of the nine grid positions in random order. Calibration target size was matched to task-specific target size. Binocular drift check was performed manually between all trials. If fixation error exceeded 2° in either eye, the experiment was paused, and calibration and validation were repeated. A 50% grey uniform background was used for all displays (i.e. camera adjustment, calibration, trials and drift correct), to make viewing conditions most comfortable for a patient population that is prone to photosensitivity (Greenwald et al., 2012).

4.6.2 *Smooth pursuit task*

Participants were instructed to follow a black disk subtending 0.246° as it moved clockwise in a circular pattern. The target movement had a frequency of 0.4 cycles per second and an amplitude subtending 12°, which made for a target velocity of 15.08°/s. One practice trial and five test trials were administered consecutively, each trial lasting 15000*ms*. Key measures for the SP task were absolute *gaze error*, velocity *gain*, and *phase error* (see section **3.6.2** for more detail on these measures).

Event detection was done by the Eyelink on-line parser, which uses motion (°), velocity (°/s) and acceleration ($°/s^2$) thresholds to identify saccades and blinks. The EyeLink 1000 offers a number of pre-set parser configurations. We selected the Cognitive configuration, which uses the following settings:

saccade_motion_threshold = 0.15

saccade_velocity_threshold = 30

saccade_acceleration_threshold = 8000

The EyeLink 1000 also offers a psychophysical configuration that uses lower detection thresholds. The psychophysical configuration is more sensitive to small saccades, and is recommended by the manufacturer for parsing of SP data (SR Research Ltd., 2008). We decided against using the psychophysical configuration for two reasons. First, the saccadic component of SP eye movement was not of interest for addressing the research questions put forth. Selection of outcome measures was based on findings in the adult mTBI literature when possible. Although two studies have reported larger number of saccades generated by mTBI patients relative to healthy controls during SP (Heitger, Macaskill,

Jones, & Anderson, 2005; Suh, Kolster, Sarkar, McCandliss, & Ghajar, 2006), a third study found that these differences might be accounted for by differences in IQ (Intelligence Quotient; Heitger et al., 2009). A neuropsychological assessment was not performed on our cohort of participants. This precluded the possibility of adjusting for IQ differences, and therefore, we opted to ignore saccade generation during SP as a measure of SP performance. Second, had SP saccade generation rates been of interest, there is evidence that it is large anticipatory saccades – readily detectable by the cognitive parser settings – that are associated with poor performance in circular SP (Maruta, Heaton, Kryskow, Maule, & Ghajar, 2013). Therefore, the cognitive configuration, which is less prone to noise, was favored.

4.6.3 *Fixation Task*

Participants were asked to fixate a centered black disk (subtending 0.11°) for 5000*ms* per trial. Blinks were not permitted during the 5000*ms* fixation periods for two reasons. First, to prevent loss of valuable data due to blinking (Engbert & Mergenthaler, 2006). Second, because blinks have been shown to modulate microsaccade rates (Katnani, van Opstal, & Gandhi, 2012). Automatic online-blink detection was used to monitor blinks (defined as any time period for which pupil diameter in either eyes is inferior to 8 arbitrary units). When a blink was detected, the trial was immediately ended, and a screen was presented (3000*ms*) to notify participants that a blink had occurred and that the trial would be reinitiated. Trials were also re-initiated if the gaze wandered outside an invisible square box (10*x*10°) drawn around the fixation target. The box was relatively large considering typical microsaccade amplitudes, but these

dimensions were deemed necessary to capture Saccadic Intrusions (SI) should they occur. An SI is an involuntary eye movement that can occur during fixation, whereby the eye produces a horizontal saccade away from the fixation target, pauses, then returns (Abadi, 2003). Typically, SI amplitudes are three to four times that of standard microsaccades, but can sometimes reach up to 5.0° (Abadi, 2003). Although we did not expect SIs to be pathophysiologically induced by mTBI, SIs have been associated with neurological conditions affecting areas that are also vulnerable to mTBI (Otero-Millan, Serra, et al., 2011; Zhang et al., 2004). Any eye movement occurring beyond the box boundaries would be due to either a lack of attention or to artifact (e.g. slight movement of the head, even though normally controlled for by chin and forehead rest, can cause an artifact that is manifested through appearance of large, high velocity, saccade). Successful fixations were followed by presentation of a photograph (4500*ms*), to allow participants to blink and make inspection saccades between trials (Engbert & Mergenthaler, 2006). Photographs were of natural scenes (found using "landscape" and "mountain" as key words in Google® image search) and were void of human-made or animate objects. Video-based recordings of small eye movements are especially susceptible to artifacts born of unwanted pupil size fluctuations (Wyatt, 2010). To minimize luminosity difference between the fixation and "rest" screens, photographs were contrast adjusted and reduced to grayscale using the MATLAB® (MathWorks; Natick, MA) Image Processing Toolbox™. Although background structure[2] has been found to influence saccade latency (White, Stritzke, & Gegenfurtner, 2008), microsaccade rates do not seem

[2] A background can be uniform, and homogenous, or structured and heterogeneous.

to be affected by the background's degree of homogeneity (Sinn & Engbert, 2011). It seemed unlikely, then, that differences in photograph texture could carry-over to the recording sequence and influence microsaccade generation. For this reason, the degree of heterogeneity of the photographs was not systematically assessed and controlled for. Following display of the photograph, and preceding initiation of the next trial, a binocular drift check was performed manually, using the same screen as the recording screen (50% gray background and centered black 4*x*4 pixel target subtending 0.11°). If fixation error exceeded 2° in either eye, calibration and validation were repeated. Performing a manual drift check also had the advantage of avoiding potential confounds induced by the display change from photograph to recording screen. Display changes are known to modulate microsaccade rate for up to 400*ms* (Engbert & Kliegl, 2003). The drift check procedure requires first that the participant make a prosaccade to the center of the screen and initiate a fixation, that the experimenter visually confirm on the monitoring screen that the participant's gaze is centered, and finally that the experimenter initiate the drift check and recording sequence with a click of the mouse. Although these steps can occur rapidly (especially if the patient's gaze is close to being centered prior to the display change), elapsed time between display change and trial initiation are not likely to occur under 400*ms*, since saccades on behalf of both the participant and the experimenter, as well as a reaction from the experimenter, are required before trial initiation. Thus, it is unlikely that display changes impacted recorded microsaccade rates. Key measures were number of *microsaccade rate* (*Hz*), microsaccadic main sequence *slope* (unit-less), and *gaze error* (*arcmin*).

4.7 Data Analysis

4.7.1 *Smooth pursuit data*

Preprocessing

Eyelink Data Files were opened in SR Research's Data Viewer analysis software for pre-processing, and practice trials were discarded. Raw SP -*x* and -*y* position and velocity samples were exported from Data Viewer for analysis in MATLAB. Pre-processing of the eye signal during SP requires removal of blinks and saccades, and linear interpolation of resulting gaps (Ebisawa, Minamitani, Mori, & Takase, 1988). Identification of data segments to be interpolated was done in five steps. First, all rows for which samples were missing due to blinks were readily identifiable in the exported Data Viewer data (denoted by a "." value) and indices for these rows were computed through logical indexing. Second, the Data Viewer "Saccade Report" generates two column vectors for each eye indicating start and end times of all saccades detected during the SP recordings. These column vectors were imported into MATLAB and used to identify indices of all SP data rows corresponding to saccades. Third, there are a few hundred milliseconds at the end of each trial during which the target disappears while the camera continues to record eye position. These portions of each trial were readily identifiable for removal by finding all trial samples for which no velocity data were available (denoted by "." value). Fourth, since visual motion processing for the initiation of SP occurs in the first 100*ms* of the SP movement (Lisberger & Westbrook, 1985), these data points were removed for every trial, because eye movement during the initiation phase is characteristically

different from that observed once pursuit has been initiated and is modulated by corrective feedback (Tychsen & Lisberger, 1986). Finally, the number of samples labeled as blinks or saccades was counted. Because these samples would be used for interpolation, they could be considered as 'missing' data points. In light of this, if the proportion of samples coded for interpolation exceeded 40% the number of 'missing' data was considered large (Noor, Abdullah, Yahaya, & Ramli, 2007) and the entire trial was discarded.

Following completion of the above five steps, interpolation was carried out over SP -*x* and -*y* position and velocity data for each eye using the built-in MATLAB 1-D interpolation function:

$$\mathbf{y_i = interp1(x, y, x_i, 'spline').}$$

Indices for blinks and saccades were combined, and used as x_i values for *cubic spline* interpolation (Engel, Anderson, & Soechting, 2000) of y_i values, where y_i is the position (or velocity in the case of interpolation of velocity values) of the eye at time x_i. The relationship between x_i and y_i is determined first by evaluating then by mirroring the function $y = f(x)$, where y is the actual eye position (or velocity) recorded at time point x. In other words, x represents times at which an eye position y was recorded and at which the eye is neither in a saccade nor a blink. Following visual inspection of the recorded eye traces and interpolated data, it was decided that the EyeLink parser output data was satisfactory and that no

further pre-processing (e.g. smoothing [3]) was necessary. All subsequent calculations were made on interpolated data.

Absolute gaze error

Absolute gaze error was defined as the distance in minutes of arc between a sample (i.e. recorded eye position) and the closest point to that sample situated on the target trajectory. Absolute gaze error was obtained by first calculating the distance between each data point (using -*x* and -*y* eye sample coordinates) and the target trajectory center, then by subtracting the target trajectory radius from this value.

Smooth pursuit gain

SP gain is defined as the ratio between eye velocity and target velocity. Values of 1 indicate a perfect match between eye and target velocities, while values under 1 indicate that the eye is moving too slowly. Similarly, values exceeding 1 indicate that the eye is moving at a velocity that is higher than the target's.

Smooth pursuit phase shift

SP phase shift is a measure of the synchronization between the eye and targets movements in time. Because the target is moving at a constant velocity and its trajectory is a circle, decomposing both the eye and target movements into their respective -*x* and -*y* components yields two sine-type wave type signals of nearly constant frequencies and amplitudes. Plotting the horizontal or vertical component of both the eye and target trajectories against time produces two sine

[3] Some opt to further pre-process smooth pursuit recordings by smoothing eye position data with a second-order low-pass Butterworth filter to remove unwanted noise (Berryhill, Chiu, & Hughes, 2006; Spering, Schütz, Braun, & Gegenfurtner, 2011).

waves. The eye and target signals share a common component, namely trajectory, and as such the horizontal and vertical components of the two signals will be very similar in appearance, but the eye signal may be delayed in time or even ahead of the target position signal. In other words, although horizontal and vertical sine waves generated by the target and eye movements may share very similar amplitudes and frequencies, they still may be displaced relative to one another with regards to time. This displacement is the phase shift (**Appendix I, Figure 4.3**).

Cross-correlation analysis was carried out to identify phase shifts between eye and target movements. This method has been validated for calculation of SP phase shift in mTBI (Suh et al., 2006) and in other neurological conditions (Clementz, Grove, Iacono, & Sweeney, 1992; Katz & Rimmer, 1989). We used the built-in MATLAB cross-correlation function to conduct our cross-correlation analysis:

$$\texttt{[c,lags] = xcorr(}s_{eye}\texttt{,}s_{target}\texttt{)}.$$

The cross correlation function holds the vertical or horizontal component of the target signal s_{target} static and shifts the corresponding component of the eye signal, s_{eye}, along the -*x* axis (representing time), calculating the correlation *c* between the two signals at every position of -*x*, where correlation is understood as the sum of the point-wise products of each signal's value at every position of -*x* (Woolfson & Woolfson, 2007). The *xcorr* function provides the number of samples, or *lags*, by which s_{eye} was shifted for every value of *c*. The value of the cross-correlation function *c* peaks when s_{target} and s_{eye} are best aligned, meaning best synchronized. Thus, the phase shift is simply the value of *lags* at the maximum value of *c*. The phase shift can be either negative, indicating that the eye movement is lagging in

time with regards to the target movement, or positive, indicating that the eye movement is leading the target movement in time. If the phase shift is zero, then the signals must be interpreted as being perfectly synchronized. Thus, high values of phase shift, either positive or negative, are indicative of poor synchronization between eye and target movements. Therefore, we used *phase error*, the absolute value of phase shifts, as a measure of performance on the SP task. This value was calculated separately for the horizontal and vertical components of SP.

4.7.2 Fixation data

Preprocessing

Fixation data were also pre-processed using the DataViewer software. Aborted trials and practice trials were identified and removed. Raw -*x* and -*y* pupil coordinates and target coordinates were exported and opened in MATLAB for analysis. Trial recording typically begins a few hundred milliseconds prior to target appearance, and ends a few hundred milliseconds post target disappearance. During these brief periods, no target is present to guide eye positioning, and therefore these small portions of the recordings were removed by identifying samples for which no target position was available.

Microsaccade detection

Microsaccades were detected using a widely-used algorithm developed by Ralf Engbert (Engbert & Mergenthaler, 2006). The algorithm's design makes two fundamental assumptions about microsaccades. First, the algorithm detects microsaccades using a velocity threshold. Based on raw -*x* and -*y* sample positions, a velocity vector is calculated at all eye positions for each eye. The

algorithm calculates the standard deviation of these velocity vectors and the value of this standard deviation is used as a threshold for distinguishing slow drift movements from high-speed microsaccades. In other words, consecutive samples for which the velocity surpasses the standard deviation of computed velocities are labeled as monocular microsaccades. A minimum duration (i.e. number of samples) of 3 milliseconds and minimum velocity of 5$^{o}/_{s}$ are used to reduce noise (Engbert & Kliegl, 2003), but beyond these two fixed values, detection of microsaccades rests solely on calculation of relative values that are intrinsic to the workings of each participant's oculomotor system. Thus, the algorithm is reliable across participants and experimental conditions (Engbert & Kliegl, 2003).

Second, the Engbert and Mergenthaler algorithm treats microsaccades as conjugate phenomena (Engbert & Kliegl, 2003; Engbert & Mergenthaler, 2006), which is consistent with the microsaccade literature (Leigh & Zee, 2006; Martinez-Conde et al., 2013; Van Horn & Cullen, 2012). The algorithm labels a microsaccade as such only if two monocular micosaccades occur within overlapping time periods. The minimum required overlap is one data sample, or 1 millisecond.

The algorithm output is a *k*-row by *14*-column matrix, where each row provides information for two conjugate microsaccades. Specifically, each row lists values for the peak-velocity, average velocity, amplitudes, and start and end times of pairs of overlapping monocular microsaccades. The pairs of values obtained in each row can be averaged to obtain a precise estimate of the characteristics of one binocular microsaccade. For all participants, *k* binocular microsaccades were detected individually for each trial, and key microsaccade

measures were averaged across all trials. Thus, calculation of average microsaccade rate was done by dividing the number of output rows for one trial by the trial duration, repeating the procedure for every trial, and averaging across all trials.

Microsaccadic Main sequence

For each participant, microsaccade data for all trials were combined and used for characterization of the MMS (i.e. the relationship between peak velocity and amplitude). To find the peak velocity and amplitude of conjugate microsaccades, we averaged the peak velocities and amplitudes of overlapping microsaccades provided in the microsaccade detection algorithm output and converted these to a base ten logarithmic scale (Engbert & Kliegl, 2003). To find the slope of the best fitting line between log values of peak velocity and amplitude, the MATLAB polynomial curve fitting function was used:

```
coefficients = polyfit(x,y,n).
```

This function finds the coefficients (line slope and -*y* axis intercept) of the polynomial of degree *n* that best fits data *x* and *y*. Since the predicted relationship between amplitude and peak velocity was linear, we specified $n = 1$ in all cases.

Fixation stability

Fixation stability was defined as the participant's ability to maintain the eye as close as possible to the target across trials. Because one eye is always more accurate than the other (Porac & Coren, 1976), we calculated the mean difference between absolute eye position and the fixation target across all trials for each eye, and selected only the most precise eye for assessing gaze stability.

4.7.3 *Statistical analyses*

All statistical operations were carried out with SPSS® v.21 (SPSS Inc., Chicago, IL). Descriptive tables and distribution plots were generated for all measures across all three groups using the SPSS "Explore" function prior to carrying out statistical comparison tests. Analysis of Variance (ANOVA) was conducted to compare groups on all measures of oculomotor performance. Post-hoc analyses for the ANOVAs were carried-out through pairwise comparisons between groups using *Hochberg's GT2* when group variances were homogenous, and *Games-Howell* when groups had unequal variances (Field, 2007). *Eta squared* (η^2) was used as an index of effect size for the ANOVAs. Because mTBI has clinically heterogeneous presentations, we expected more important variance in the (larger) mTBI group compared to other groups. Therefore, *Levene's Test for Homogeneity of variances* was used to evaluate differences in variance. When Levene's Test was significant, we used the *F*-statistic generated by *Welch's Robust Test of Equality of Means*, which is less sensitive to differences in variance, to evaluate significance of the ANOVAs.

To reduce the number of comparisons between groups and reduce the risk of inflated *Type I* errors, we identified outcome measures that were highly correlated and for which there were theoretical grounds for suspecting that the correlation was intrinsic to the measurement method. In such instances, there is no need to include both measures in subsequent analyses because there is a high likelihood that the two highly correlated outcome measures are simply two expressions of the same outcome variable (Tabachnick, 2001). We suspected that

this might be the case for pairs of -*x* and -*y* outcome measures, since both were derived from eye position at time *t*. Eliminating one outcome measures, or, in our case, averaging -*x* and -*y* values, provides a more appropriate measurement for comparison. With these considerations in mind, we generated a correlation matrix for all -*x* and -*y* outcome measures. Pearson's Correlation coefficient *r* was used to assess levels of linear dependence between different measures. In cases where the correlation between pairs was high ($r \geq 0.8$), -*x* and -*y* values were combined for between-group comparisons on that measure. Pearson's Correlation coefficient was also used to evaluate both linear dependency between measures of oculomotor performance and PCSS-R scores and effect sizes on comparisons of injury characteristics between the mTBI and orthopedic injury groups.

Differences in injury characteristics between the two injury groups were evaluated with *t-tests for independent samples* and *Fisher's Exact Test*, respectively for continuous and categorical measures. *Multinomial logistic regression* was performed in SPSS for predictions of group membership, selecting model-fit, classification rates, and likelihood-ratio tests as output options. An alpha significance level of $\alpha = 0.05$ was used for all statistical tests.

5. RESULTS

5.1 Participant demographics

Testing was carried out on a total of 19 mTBI patients (10 males, mean age = 13.8, σ = 2.5, range = 8-18), 12 healthy participants (8 males, mean age = 13.9, σ = 2.6, range = 10-18), and 6 orthopedic injury patients (5 males, mean age = 12, σ = 2, range = 7-15). Participant demographic data for each group, including age, gender, schooling years, and history of mTBI, are presented in **Table 5.1**.

Table 5.1 Participant demographics

Variable	MTBI n = 19	Orthopedic injury n =6	Healthy n = 12
Age (*yr*)	13.8 ± 2.5	12 ± 2	13.9 ± 2.6
Age range (*yr*)	8-18	7-15	10-18
Males/Females	10/9	5/1	8/4
Schooling (*yr*)	8 ± 2	7 ± 3	9 ± 3
Previous mTBI, No. (%)	8 (42)	0 (0)	2 (17)

± Standard deviation.

Recruitment proved challenging and ultimately our groups were not matched in size. Despite this limitation, demographic data for age and education were not substantially different between groups, though the orthopedic control group was slightly younger than the two others. More important differences were observed with regards to gender. While the head injury group was balanced in this regard (approximately 1:1 ratio), the control groups were not (male to female ratios of 2:1 and 5:1 for the healthy and orthopedic injury control groups, respectively). Therefore, assessments of gender effects on measures of oculomotor performance were carried out for both tasks. MTBI group participants

were also more likely to have sustained a previous mTBI than participants in both control groups.

Comparison of the two injury groups revealed significant differences in PCS load and Time Post-Injury at testing (TPI), but no differences in injury etiology. Surprisingly, although overall scores on the PCSS-R were higher for the mTBI group (M = 26, σ = 22) relative to the orthopedic control group (M = 9, σ = 8), these differences were not significant (p = .08, r = .36). The mTBI group did, however, report significantly more somatic symptoms (M = 16, σ = 14) than did the orthopedic group (M = 6, σ = 5, p = 0.01, r = .52), and in particular, visual complaints (e.g. blurriness), were significantly higher in the mTBI group (M = 1, σ = 2) than they were in the orthopedic group (M = 0, σ = .2, p = .014, r = .49). In contrast, mean scores for self-reported cognitive (p = .113) and emotional (p = .307) PCS were not significantly different between groups. Means for these were lower than those observed for somatic PCS. MTBI group means for cognitive and emotional PCS were respectively of 6 (σ = 6) and 2 (σ = 4), while those for the orthopedic control group were of 3 (σ = 6) and 1 (σ = 1).

TPI was significantly longer for the mTBI group (M = 28 *days*, σ = 25) than for the orthopedic injury group (M = 13 *days*, σ = 5, p = .017, r = .48). TPI was shorter and less varied in the orthopedic injury group because testing sessions for orthopedic injury participants were usually scheduled on the same day as follow-up visits with their doctor. These were typically scheduled within one to four weeks post injury. In contrast, patients in the mTBI group were tested whenever possible, and TPIs for this group ranged from 3 to 87 days. Injury etiologies across the two injury groups were not significantly different (p = .446),

with all but one injury in either group resulting from sports-related physical activity – in both cases, due to a fall. Injury etiology, PCSS-R scores, injury severity, TPI, and history of head injury are summarized for the two injury groups in **Table 5.2**.

Table 5.2 Injury group characteristics

Variable	MTBI n = 19	Orthopedic injury n =6	*P*-value[a,b]
Injury etiology, No. (*%*)			
Sports	18 (95)	5 (83)	0.18[†]
Fall	1 (5)	1 (17)	
PCSS-R scores[c]			
Somatic	16 (14)	6 (5)	**0.01**
Cognitive	6 (6)	2 (4)	0.11
Behavioral	3 (6)	1 (1)	0.31
Total	26 (22)	9 (8)	0.08
Visual complaints			
Patients reporting, No. (*%*)	10 (53)	1 (17)	0.43[†]
PCSS-R score[d]	1 (2)	0 (0.2)	**0.01**
Time post-injury (*days*)	28 (25)	13 (5)	**0.02**

[a] Bolded p-values indicate statistical significance at the .05 level.
[b] P-values calculated for Fisher's Exact Test are marked with [†].
[c] Maximum scores for somatic, cognitive, and emotional components of the PCSS-R are respectively 84, 24 and 24, while maximum total score is 132.
[d] Maximum score for PCSS-R visual symptoms is 6.

Importantly, data for both tasks were not collected for all mTBI group participants. The testing session was terminated if a patient reported being unable to continue. Between tasks – and in some cases, between trials – the experimenter checked with the participant to ensure that he or she felt comfortable carrying on. Details of task completion are presented below alongside results from the individual tasks.

5.2 Visual acuity testing

SLOAN letter chart testing revealed uncorrected 20/20 visual acuity in the dominant eye for all but two participants belonging to the mTBI group, who reported moderate and severe visual disturbance on the "Visual problems" item of the PCSS-R questionnaire (scores of 3 and 6, respectively). Neither patient had a history of wearing glasses or contact lenses, and in both cases, the onset of visual complaints coincided with the concussive episode. Thus in both these cases, poor performance on the SLOAN letter chart testing could be attributed to the mTBI. As a result, both patients were retained for the study and allowed to perform the tests with uncorrected vision.

5.3 Oculomotor performance

5.3.1 *Smooth pursuit eye movement*

SP data were collected from all healthy ($n_{healthy}$ = 12) and orthopedic injury (n_{ortho} = 6) participants. Data for one male mTBI group participant were not collected because the testing session for this participant was terminated due to self-reported symptom exacerbation (n_{mTBI} = 18). As described above, three markers were used to evaluate performance on the SP task: accuracy of eye trajectory, tracking speed, and eye-target synchronicity. A total of five outcome measures were used to compare groups on this task: -*x* and -*y gain*, absolute *gaze error*, and -*x* and -*y phase errors*. Pearson's *r* correlation coefficients revealed highly correlated pairs of -*x* and -*y* values for gain (r_{gain} = 0.927). All other measures, including phase errors -*x* and -*y* (r_{phase}= .227), were not highly

correlated. Therefore gain values averaged over *-x* and *-y* were used to evaluate SP tracking speed, while *-x* and *-y* phase error values were retained as indicators of eye-target synchronicity, and *gaze error* was retained as a measure of eye accuracy. The correlation matrix for this analysis is shown in **Appendix I, Table 5.1.** Examples of good and poor performance on the task are illustrated in **Appendix I**, **Figures 5.1a and 5.1b**, respectively.

Prior to comparing performances on the SP task between our test group and our controls groups, we evaluated whether males and females differed significantly on the four outcome measures, irrespective of group. Results from this preliminary analysis are summarized in **Appendix I**, **Table 5.2**. There were no significant differences between genders on measures of *phase error* and *gaze error*, although a trend for gain ($p = 0.07$) was noted.

Next, we looked at how the four measures were distributed among the test and control groups. For all four SP measures, standard deviations and ranges were largest for the mTBI group, as illustrated by **Appendix I**, **Figure 5.2** box plots. Levene's test for homogeneity of variances was used to compare within-group variance across groups on all four measures of SP performance. The test was not significant for measures of *phase error -y* ($F = .56$, $p = .58$) and *gain* ($F = 2.45$, $p = 0.09$) but was highly significant for measures of *phase error -x* ($F = 13.33$, $p < .00$) and *gaze error* ($F = 5.63$, $p = 0.01$). For *phase error -x*, variance in the mTBI group was significantly higher than variance in either control groups (**Appendix I, Figure 5.2.a***)*. For *gaze error,* differences in variance were more nuanced. While variances for the orthopedic and mTBI groups were clearly the smallest and largest, respectively, variance for the healthy control group fell between the two.

To establish whether the overall *F* for Levene's test pointed to significant differences between the two control groups and the mTBI group, or, alternatively, between the orthopedic injury group and the healthy and mTBI groups, two additional pair-wise comparisons of variance were calculated. Comparison of the orthopedic injury group and healthy control group *gaze error* variances was non-significant ($F = 2.81$, $p = .113$). In contrast, comparison of healthy control and mTBI group *gaze error* variances was significant ($F = 4.74$, $p = .038$). Therefore, for both *phase error -x* and *gaze error*, variance was significantly higher in the mTBI group relative to both control groups.

The box plots also revealed the presence of mild outliers. Two of the thirty-six dataset values (one from the mTBI group and one from the healthy control group) were outliers for *phase error -y*. A single value was found in each of *phase error -x* and *gain* measures, respectively for the healthy control and mTBI groups. The differences between the outliers and the others were relatively small as they fell beyond 1.5 times the Interquartile Range (IQR), but less than 3 times the IQR. Because values were not large, it was unlikely that they were due to measurement errors or improper data manipulation. Therefore, outliers were retained and the original dataset was used for comparisons of group means.

Results from one-way ANOVAs comparing means across groups on measures of SP are shown in **Table 5.3** along with group means and standard deviations. ANOVAs were statistically significant for *phase error -x*, $F(2, 21.58) = 4.77$, $p = 0.02$, $\eta^2 = .21$, *phase error -y*, $F(2, 33) = 3.20$, $p = 0.05$, $\eta^2 = .16$ and *gaze error*, $F(2, 21.2) = 5.12$, $p = .01$, $\eta^2 = .24$. The overall *F* was not statistically significant for measures of *gain*, $F(2, 33) = .437$, $p = .65$, $\eta^2 = .03$.

Table 5.3 Smooth pursuit performance by group

	MTBI	Orthopedic	Healthy	ANOVA	
Measure	**n = 19**	**n = 6**	**n = 12**	**F-statistic**[a]	**p-value**[b]
Phase error -x	9.98 ± 11.81	1.1 ± 1.25	1.62 ± 2.21	4.81†	**0.02**
Phase error -y	33.41 ± 17.50	25.51 ± 11.07	18.07 ± 16.48	3.2	**0.05**
Gaze error	74.04 ± 32.88	53.89 ± 9.23	43.33 ± 18.75	5.12†	**0.01**
Gain	0.81 ± 0.27	0.73 ± 0.07	0.76 ± 0.10	0.44	0.65

[a] *F*-statistics computed with Welch's Robust Test of equality of means are marked with †.
[b] Bolded p-values show significance at the 0.05 level.

Post-hoc comparisons revealed significantly different group means between *both* control groups and the test group for horizontal *phase error* only. The mTBI group mean for *phase error -x* (M = 9.98 *ms*, σ = 11.8) was significantly higher than healthy control (M = 1.6 *ms*, σ = 2.21, p = 0.02) and injury control (M = 1.1 *ms*, σ = 1.25, p = 0.02) group means. Mean *phase error -y* was also highest for the mTBI group (M = 33.41 *ms*, σ = 25.51). This difference, however, was only statistically significant between the mTBI and the healthy control (M = 18.07 *ms*, σ = 16.48, p = 0.05) groups. Pairwise comparison between mTBI patients and injury controls (M = 25.51, σ = 11.07, p = 0.67) was not significant. Similar results were found for *gaze error*, with the highest mean in the mTBI group (M = 74.04 *arcmin*, σ = 32.88). Pairwise comparisons for *gaze error* were significant between the mTBI group and the healthy controls (M = 43.33 *arcmin*, σ = 18.75, p = 0.01) but only trended towards significance between mTBI patients and injury controls (M = 53.89 *arcmin*, σ = 9.23, p = .07).

5.3.2 *Fixational eye movements*

Fixation data were collected for all healthy ($n_{healthy}$ = 12) and orthopedic injury (n_{ortho} = 6) participants. We were unable to collect fixation data for three mTBI patients (n_{mTBI} = 16). Two of them opted out after completing the SP task, reporting increased fatigue. The third was unable to fixate with eyes fully open causing artifacts and making signal acquisition unreliable. Consequently, fixation data for this participant were discarded. **Appendix I, Figure 5.3** provides an example of a typical eye-trace detected during a single 5000*ms* fixation trial, with drift and microsaccadic components clearly identified.

As was done for the SP measures, we evaluated whether males and females differed significantly on three fixation measures, irrespective of group. Results from this preliminary analysis are summarized in **Appendix I**, **Table 5.3**. There were no significant differences between genders on all three measures.

Variance in the mTBI group was comparable to variance in the two control groups for the three fixation task measures – Levene's test for homogeneity of variances was non-significant in all three cases ($p >> .5$). Normality box plots revealed the presence of a mild outlier in the mTBI group for measures of *microsaccade rate* and *gaze error* (**Appendix I, Figure 5.4**). A closer look revealed that both values were generated by the same participant, and – as our hypotheses would have it – indicative of impairment.

Results from one-way ANOVAs comparing means across groups for the fixation task measures are shown in **Table 5.4**. There were no differences between the control groups and the mTBI group on all three fixation task measures. *Slope*

values for the mTBI group (M = .89, σ = .05) were comparable to those of the healthy control (M = .87, σ = .06) and injury control (M = .85, σ = .04) groups; the overall F for slope was statistically non-significant, with $F(2,31) = 1.23$, $p = .31$, $\eta^2 = .07$. Similar results were found for *microsaccade rate*, $F(2,31) = .03$, $p = .98$, $\eta^2 < .01$, and *gaze error*, $F(2,31) = .13$, $p = .88$, $\eta^2 = .01$, with highly similar means across groups. Mean microsaccade rate was $M = 1.13Hz$ (σ = .55) for the mTBI group, $M = 1.16Hz$ (σ = .59) for the healthy control group, and $M = 1.18Hz$ (σ = .55) for the injury control group. Mean *gaze error* was of M = 31.13 *arcmin* (σ = 8.54) for the mTBI group, M = 30.66 *arcmin* (σ = 10.83) for the healthy controls, and M = 31.78 *arcmin* (σ = 6.98).

Table 5.4 Fixation task performance per group

	MTBI	Orthopedic	Healthy	ANOVA	
Measure	**n=16**	**n=6**	**n=12**	**F-statistic**	**p-value**[a]
f_{msac}	1.22 ± 0.66	1.18 ± 0.55	1.16 ± 0.59	0.03	0.98
Gaze error[b]	32.9 ± 13.04	31.78 ± 6.92	30.66 ± 10.83	0.13	0.88
MSS	0.89 ± 0.05	0.85 ± 0.04	0.87 ± 0.06	1.23	0.31

Abbreviations: f_{msac} = microsaccade rate (*Hz*); MMS: microsaccadic main sequence slope (unit-less).
[a] Bolded p-values show significance at the 0.05 level.
[b] Gaze error values are given in *minutes of arc.*
± Standard deviation.

5.3.3. *Predictions of group membership*

A multinomial logistic regression analysis was performed to see if membership to each of the three groups could be predicted from performance on oculomotor testing. The outcome variable *group membership* was coded **1** = *healthy control*, **2** = *injury control*, and **3** = *mTBI*. Three predictor variables were

used for the analysis, namely SP *phase errors -x* and *-y* and *gaze error*, because overall *F*s for one-way ANOVA were significant for these measures. None of the fixation data measures were used as predictor variables because of the lack of observed differences between groups. As a result, participants for this analysis were identical to those used in our analyses of SP data; a total of 36 cases were included.

A test of the full model compared to a constant-only model was statistically significant, χ^2 (6) = 22.09, $p < .01$, indicating that the predictors as a set could be reliably used to discriminate among groups. The fit of the model to the data was good, with χ^2 (64) = 50.75, and $p = .89$, by the Deviance criterion (Tabachnick, 2001). Moreover, the strength of the association was strong, as indicated by *Nagelkerke*'s $R^2 = .59$.

Classification rates for the full model are summarized in **Table 5.5**. The overall classification rate was unremarkable, with the model accurately classifying 64% of cases. Success rates for the mTBI and healthy control groups were of 78% (8/12) and 67% (14/18) respectively. Rates were much lower for the control injury group, with only 1/6 cases (17%) appropriately classified.

Likelihood Ratio Tests, which calculate each predictor's individual contribution to the model, were significant for *phase error -x* ($p = .014$), but not for *gaze error* ($p=.063$) or *phase error -y* ($p = .524$), indicating that the model was degraded by removal of *phase error -x*, but not by removal of *phase error -y* or *gaze error*, though in the latter case a trend toward significance was observed. In other words, group membership could be predicted most reliably by *phase error -x* (**Appendix I, Table 5.4**).

Table 5.5 Logistic regression classification table

Observed	Predicted			
	Healthy	Orthopedic	mTBI	Percent Correct
Healthy	8	0	4	66.7%
Orthopedic	3	1	2	16.7%
mTBI	3	1	14	77.8%
Overall Percentage	38.9%	5.6%	55.6%	63.9%

5.3.4. *Correlations of visual impairment with symptom load and time post-injury*

To rule out the possibility that the important heterogeneity observed for mTBI group SP task performances could be attributed at least in part to quantified demographic differences within the group, we carried out two correlations analyses. In the first, Pearson's correlation coefficients were calculated between scores on the somatic components of PCSS-R and each of the two measures of oculomotor performance for which variance in the mTBI group was found to be significantly higher than that of the control groups namely, *phase error -x* and *gaze error* (see section **5.3.1**). In the second, correlations between the same two measures of oculomotor performance and elapsed time post-injury at testing were calculated. None of the correlations were significant. Detailed results from both analyses are presented in **Appendix I, Table 5.5**.

6. DISCUSSION

The above results show a link between pediatric mTBI and impairment of ocular movements. The nature of this impairment is specific: performance on a SP task was significantly inferior for mTBI patients relative to two control groups not having sustained a head injury. In contrast, measures of fixational eye movement integrity were no different across groups. In this section, we elaborate on the results from both tasks and identify study limitations. The section closes with recommendations for future research.

6.1 Oculomotor function following pediatric mTBI

6.1.1 *Smooth pursuit deficits*

Eye-target synchronization

Our main finding is that pediatric mTBI is associated with selective deficits in predictive SP. Synchronization of eye movement with target motion – as evaluated by phase error – was found to be significantly poorer for mTBI patients relative to both control groups. In contrast, the ability to trace target trajectory accurately (i.e. gaze precision) and to match target velocity (i.e. gain) were not impaired. Moreover, synchronization deficits were limited only to horizontal synchronization of the eye with target movement. The strong effect size we detected for this finding ($\eta^2 > .2$) is impressive considering the relatively small size of our sample, and suggests that horizontal phase error has the potential to serve as a marker for pediatric mTBI.

Crucially, horizontal synchronization was much *better* for all three groups than was vertical synchronization – vertical phase error was as much as one order

of magnitude greater than horizontal phase error for some participants. Horizontal synchronization was accurate and comparable across control participants; healthy and injury control group means for horizontal phase error were below 2 milliseconds. In stark contrast, mean horizontal phase error for mTBI patients (M_{mTBI} = 9.98*ms*) was over five times higher than means of either control group. Importantly, this number was still noticeably smaller than the lowest group mean for vertical phase error, which, predictably, belonged to the healthy control group ($M_{healthy}$ = 18.05*ms*). This finding is in line with evidence that horizontal eye movements are easier to execute than their vertical counterparts (Kettner, Leung, & Peterson, 1996). The higher degree of difficulty associated with vertical eye movements may explain the large inter-individual variability that was observed for vertical synchronization performance across all groups, and suggests that vertical phase error may be a less reliable measure for assessing the impact of mTBI SP movement integrity than horizontal phase error.

Accuracy

SP accuracy was poorer for the mTBI group (*gaze error* of *M* = 74.04 *arcmin*) relative to both the healthy (*M* = 43.33 *arcmin*) and injury (*M* = 58.89 *arcmin*) control groups, although the differences between the mTBI and injury control group were not statistically significant. One important observation was the presence of large variance across performances within the mTBI group. Measurements for the best performances in this group were comparable to those in the healthy control group, while measurements for the worst performances were markedly different from anything seen in either control group. Visual inspection of eye traces illustrated this well (**Appendix I, Figure 5.1**). Eye traces

similar to the one shown for the healthy control participant were observed in the mTBI group, but, conversely, the high degree of imprecision observed in several mTBI participant eye traces was never seen in healthy controls. These results provide further evidence that mTBI group performances are heterogeneous, and indicate that SP accuracy is likely impaired following pediatric mTBI, but only in a sub-population of patients.

Velocity

We had hypothesized that the mTBI group would show reduced tracking velocity relative to controls. Our findings showed that measures of gain were in fact comparable across groups. Mean values for all groups were below those reported in studies using similar target velocities (Meyer, Lasker, & Robinson, 1985). These studies, however, were conducted on adults, and therefore the discrepancy may be explained by oculomotor differences that are known to exist between adult and pediatric populations (Katsanis, Iacono, & Harris, 1998). The mTBI group's mean was slightly *higher* than the mean of either control groups, which, at first glance, would be indicative of better performance by the mTBI group. This unexpected finding, however, could be attributed to the significantly higher variability of gain values found in the mTBI group relative to other groups, as was also found for *gaze error*. Both the smallest ($gain_{min} = 0.53$) and the highest ($gain_{max} = 1.15$) gain values belonged to participants in the mTBI group. Crucially, two mTBI patients had gain values that exceeded 1. In other words, these patients routinely generated a tracking movement that exceeded target velocity. In contrast, no participants from either control group had gain values exceeding 1. The broader range of gain values in the mTBI group and their

abnormally high value in a sub-population of our mTBI participants replicate findings from previous work with mTBI patients (Maruta, Suh, et al., 2010), and reinforce the possibility that pediatric mTBI is associated with an impaired ability to *compute* and *evaluate* target velocity during SP, rather than to a deficit in the ability to generate high velocity SP movements.

6.1.2 *Integrity of fixational eye movements*

The fixation data produced null results across the board, disconfirming our hypothesis that fixation is impaired in pediatric mTBI. Results for all three fixation task outcome measures are discussed.

Microsaccadic Main sequence slope

We found that MMS were comparable across groups – all group means exceeded .8 out of a theoretical maximum of 1, indicating a strong relationship between peak velocities and amplitude. Thus, our results suggest that pediatric mTBI does not alter the microsaccadic peak velocity-amplitude relationship, and that microsaccade generation circuitry is not affected by mTBI.

Our findings for MMS also suggest that the integrity of the saccade generation circuitry is unaffected by pediatric mTBI. This measure was included in our analyses because it allowed going a step beyond microsaccades and making generalizations concerning the integrity of the saccade generation system. We had little to rely on to guide our hypotheses concerning the effect of pediatric mTBI on MMS. On the one hand, most studies investigating reflexive saccade generation following mTBI have found no deficit for this patient group relative to healthy controls (Heitger et al., 2004; Heitger et al., 2006; Heitger et al., 2009;

Heitger et al., 2005). On the other hand, to our knowledge, no such data exist for pediatric mTBI. Furthermore, it is known that children and adolescents are more vulnerable to the effects of head injury than are adults (Cernak et al., 2010) and that oculomotor function is different in adults and pediatric populations (Katsanis et al., 1998). Our results, then, lend support to findings from the adult mTBI literature.

A recent paper by Di Stasi et al. (In Press) reinforces the idea that fixation tasks can be used as effective tools for evaluating function of neurological systems other than the fixation network proper. The authors describe fixation tasks and concomitant microsaccade detection as 'neuroergonomic' tools showing promise for assessing attentional fatigue following long periods of visual search (Di Stasi et al., In Press). They report MMS and saccadic main sequence slope values that are nearly identical. The rationale and findings from Di Stasi and colleagues' (In Press) study provides further support to our conclusions regarding integrity of the saccadic system following pediatric mTBI because they validate the methodological framework through which our conclusions were attained. Evidently, microsaccades were employed to probe the function of fundamentally different neurological functions in the current project and in Di Stasi et al's study. In both cases though, MMS measurements were carried out because they offered glimpses into neurological functions that are more challenging to assess reliably with conventional eye-tracking paradigms, which have reduced ecological validity and are often less comfortable for participants.

Microsaccade rates

We had hypothesized that microsaccade rates would be significantly higher in the mTBI group relative to the two control groups because higher rates are associated with retinal fatigue (Engbert & Kliegl, 2003) and possible dysfunction of the oculomotor system. Group means, however, were nearly identical across groups, and contrary to what was observed for the SP data, variance of microsaccade rates was comparable across groups. Importantly though, variance across groups was high, with standard deviation values in each group roughly equivalent to half the group mean. This finding has been reported in the adult microsaccade literature as well (Engbert & Mergenthaler, 2006). These results lead us to conclude that mTBI may have little consequence on microsaccade rates. The possibility, however, cannot entirely be rule out – pre-injury baseline measures would also be necessary for a more unequivocal answer to the question.

Fixation acuity

Fixational gaze error was not only comparable across groups, but variability on this measure was greatest for the healthy control group, and not for the mTBI group. Moreover, variance within groups was much lower than it was for microsaccade rates. It is hence unlikely that a significant impact of mTBI on fixation acuity is being masked by high inter-individual variability. We therefore conclude that pediatric mTBI is not associated with defects in fixation acuity.

6.1.3 *Neuroanatomical correlates of observed ocular deficits*

The mTBI group's impaired ability to synchronize eye movement with target motion is suggestive of cortical dysfunction. *Prediction* is an essential component of the circular SP paradigm we used. SP is primarily a reactive phenomenon in which the brain constantly computes visual motion information and generates eye-velocity commands (K. Fukushima et al., 2008). The SP system relies on prediction to overcome delays tied to processing of motion characteristics and to maintain accurate eye-movement (Barnes, 2008; K. Fukushima et al., 2008; K. Fukushima, Fukushima, Warabi, & Barnes, 2013a; K. Fukushima, Yamanobe, Shinmei, & Fukushima, 2002). At least two types of predictions need to occur for effective tracking to be maintained (Maruta et al., 2013). First, anticipation of target movement in space must be made to keep the eye as close as possible to the target trajectory (Maruta et al., 2013). Second, anticipation of target movement in time must be made to keep the eye as close as possible to the target itself as it moves along its trajectory (Maruta et al., 2013). The observed impairment on measures of phase error suggests that temporal predictions, not spatial predictions, were impaired in our mTBI group.

The observed deficits in predicting target motion are most strongly suggestive of disrupted function of the SEF. Although degradation of predictive SP performance occurs following lesions and chemical inactivation of FEF pursuit neurons (Krauzlis, 2004), the FEF's key role in SP gain control and the observed lack of significant differences between groups on this measure suggests that FEF function is at least somewhat conserved (Schoppik, Nagel, & Lisberger,

2008). The SEF have a stronger part to play in the memory and planning of SP than does the FEF and are not implicated in SP gain (J. Fukushima et al., 2011; K. Fukushima et al., 2013b). The SEF lies in the dorsomedial frontal cortex, in a region corresponding to the anterior portion of the SMA (Yamamoto et al., 2004). Single-neuron recordings show that predictable target motion elicits greater activation in SEF neurons than does unpredictable target motion (Heinen & Liu, 1997). Moreover, activity in SEF neurons has been found to vary along with duration of target presentation, suggesting that these cells encode information tied specifically to predictive timing of SP (Heinen & Liu, 1997). SEF role in predicting target motion is compatible with SMA's established role in timing of motor events, and its involvement in the generation of predictable motor or saccadic sequences (Makoshi, Kroliczak, & Van Donkelaar, 2011). There are a few studies showing SMA vulnerability to mTBI (Jantzen, Anderson, Steinberg, & Kelso, 2004), but evidence is much less robust than for the other areas discussed hitherto. Interestingly, one study in which a lesion to the anterior SMA caused impaired SP timing impairments did not find SP gain to be impaired (Heide, Kurzidim, & Kömpf, 1996), closely mirroring our results, and providing additional support for the possibility of selective impairment of the SEF in pediatric mTBI.

The observed deficits in predictive timing also point to impaired function of the DLPFC. The temporal and spatial predictions discussed in the above paragraph rely on storage of visual motion information in Working Memory (MEM). The DLPFC's prominent role in MEM (Smith & Jonides, 1999) and its heavy connections to the FEF as well as to the MT and MST areas of the temporal

lobes (Zaksas & Pasternak, 2006), where visual-motion processing for SP primarily takes place (Newsome et al., 1988), make it a likely candidate for the seat of this memory storage (Schmid, Rees, Frith, & Barnes, 2001). FMRI investigations into the DLPFC's role in SP support this line of thinking; this structure has been found to be heavily recruited in paradigms requiring prediction of target motion (Ding, Powell, & Jiang, 2009; Pierrot-Deseilligny et al., 2003).

Overall, then, our findings provide support for the vulnerability of the frontal cortex to mTBI. This conclusion is in line with the bulk of the mTBI literature discussed in section **2.2**. The observed impairment may reflect damage to MEM networks, to SP cortical areas, or to both. The key question, put more generally, is as follows: are the deficits we identified reflective of damage to SP circuits, damage to areas that modulate SP through a top-down influence, or to a combination of both? Impaired DLPFC function following mTBI has been reported in numerous studies and therefore can legitimately be suspected here. Evidence for impaired function of the SP system is more limited; Heitger and colleagues (2004) found that lag on a random SP task – a task much less reliant on MEM than circular SP – was higher in a cohort of mTBI patients relative to controls (Heitger et al., 2004), suggesting that function of the FEF pursuit area is also impaired following mTBI. Therefore, it is probable that damage to both SP circuitry and areas that modulate SP – or connections to these areas – are occurring. Our results, however, leave all possibilities open.

6.2 Diagnostic value of eye-tracking for pediatric mTBI

The clinical relevance of our findings is best embodied by results from our logistic regression analysis. The results provide evidence that eye-tracking may be useful as a tool for diagnosis of pediatric mTBI. Using a statistical classification model that relied solely on SP outcome measures, we were able to retrospectively predict the likelihood of mTBI. Our study design makes it impossible to address questions concerning the predictive value of the SP eye-tracking paradigm we employed. Our results do, however, allow for a preliminary discussion of the test's sensitivity and specificity.

6.2.1 *Sensitivity*

Classification rates obtained through the logistic regression show that the SP eye-tracking paradigm we employed is sensitive to pediatric mTBI, where *sensitivity* is understood as the capacity of a diagnostic test to positively identify patients having the condition being tested for (Fletcher & Fletcher, 2005). The full version of the logistic regression model, in which SP vertical and horizontal phase errors and gaze error were entered as predictors, was significantly better at predicting overall group membership than the constant only model. Although overall rates were not impressive (64% correct), classification was not homogenous across groups. Classification of mTBI into the head injury group (true positive) was 78% accurate. Classification rates observed for the mTBI and the healthy control (67%) groups contrasted starkly with the low classification rates observed for the injury control group (17%). Even though the model misclassified 4 of the 12 healthy controls into the mTBI group, misclassification

of mTBI group participants into the healthy control group and the observed split in the classification of the injury control group participants (3 classified as healthy and 2 classified as mTBI) shows that the model was not simply over classifying all participants into the head injury group, and suggests a degree of robustness.

Establishing the proportion of mTBI patients who develop eye movement deficits will key to determining eye-tracking's sensitivity to pediatric mTBI. The most straightforward, but also least probable answer is that all mTBI patients develop some form of oculomotor impairment. Our results indicate that this is not the case; again, the best performances in the mTBI group were often on par with the best in the two control groups. Thus, eye-tracking cannot be used as a stand-alone marker of mTBI; it should be used in conjunction with other monitoring tools to make appropriate clinical judgments about the presence and severity of the injury. A second, only slightly more probable possibility is that only a specific sub-group of mTBI patients, clearly identifiable by a set of clinical manifestations, develop eye movement impairment. For instance, it could be that all patients with persistent PCS experience eye movement deficits – that may or may not be apparent to them. The results of this study cannot address this question. The third and most probable possibility is that only a sub-group of mTBI patients develop oculomotor deficits following an mTBI, with few shared characteristics beyond eye movement dysfunction. If this is the case, then eye movement assessment might provide important guidance to clinical decision making, but should be used in conjunction with other approaches to diagnosis. Our results support this third possibility most strongly.

6.2.2 *Specificity*

Diagnostic *specificity* is understood as the proportion of non-disease cases appropriately identified as negative by the diagnostic procedure (Fletcher & Fletcher, 2005). The classification of non-mTBI cases (which combine cases from the healthy control group as well as well as from the orthopedic injury group) into the non-mTBI category was correct for 12 of 18 cases. It must be emphasized that only rates of true negatives (non-mTBI classified as such) and false positives (non-mTBI classified as mTBI) are relevant to the specificity of a diagnostic test. The SP eye-tracking paradigm was employed for detection of mTBI, and mTBI only. Therefore, misclassifications of orthopedic injury cases into the healthy control group (which occurred for 50% of orthopedic injury cases), are not problematic for when considering SP eye-tracking's potential specificity for mTBI diagnosis.

An important determinant of the diagnostic specificity of SP eye-tracking paradigms will be the effect general injury factors have on oculomotor performance, since false positives will presumably be high if performance is found to be significantly impacted by non-specific injury factors. The regression predictor contributions table (**Appendix I, Table 5.4**) shows that only *phase -x* was a reliable predictor of group membership. This was also the only measure of oculomotor performance whose mean was found to be significantly different between the mTBI group and both control groups in the ANOVAs. Between group comparisons revealed that performance of the two control groups was comparable for synchronization of the eye with the horizontal component of target

movement, indicating that there was no general effect of injury on *phase error -x*. Because *phase error -x* was the only reliable predictor of group membership, it was foreseeable that membership predictions for the orthopedic injury group would be inaccurate. In other words, the success rate of the regression model for classification of orthopedic injury group participants was low precisely because *phase error -x* measures were not affected by general injury factors.

The lack of significant differences between the healthy control group and the orthopedic control on all ANOVA post-hoc tests group seemingly extends our observation about *phase error -x* and general injury factors to the other measures of SP performance. A closer look at differences between SP outcome measure group means (**Tables 5.4**), however, provides grounds for a less straightforward interpretation. For all three measures of SP error (i.e. *gaze error* and *phase errors -x* and *-y*), means were highest for the mTBI group. For *phase error -x*, both control groups performed comparably – mean horizontal phase error was even slightly lower for the orthopedic group, and far surpassed overall performance of the mTBI group. This finding again suggests that the general effect of injury on SP performance – if there is one – is negligible for horizontal synchronization.

The relationship between means for *phase error -y* and *gaze error*, however, were different from the one just described in two regards. First, for both these outcome measures, means were noticeably lower for the healthy control group relative to the orthopedic control group. Second, for both measures the lowest means (i.e. healthy control group) and the highest (mTBI group) were within a multiplicative range of less than twofold, which contrasts starkly with the differences observed for horizontal phase error described above. The numbers

suggest that if vertical synchronization ability and tracking accuracy are affected by mTBI, this effect is subtler than it is for horizontal synchronization. Moreover, the noticeably poorer (if non-significantly different) performance of the injury control group relative to the healthy control group on these two measures indicate that general injury factors may affect SP tracking. In the case of *phase error -y* and *gaze error*, post hoc comparisons were significant ($p < .05$) between healthy controls and mTBI patients. Means for the injury control group were lodged between, and not significantly different from either other group. Thus, it is possible that general injury factors were exerting a subtle influence on SP by increasing vertical synchronization and gaze acuity errors in the orthopedic injury group.

SP *gain* measures and data from the fixation task were largely comparable across all groups, suggesting no effect of general injury on fixational eye movements and SP velocity. The lack of differences between means on these measures, however, does not speak to the possibility that general injury factors could have been influencing the SP vertical synchronization and SP gaze error. Therefore, the association between general effects of injury and oculomotor performance may be selective. Although this conclusion remains tentative, our considerations do highlight the potential potency of SP horizontal synchronization measures as probes for ocular function in pediatric mTBI, because of all our measures, *phase error -x* made the most significant contributions to the model's predictions, while also seemingly being the least affected by general injury factors.

6.3 Reliability of self-reported PCS

Three of our findings pertaining to self-report of PCS are worth discussing. First, our results are in agreement with a large body of literature showing the prevalence of somatic symptoms following mTBI. Of the three classes of symptoms evaluated by the PCSS-R (i.e. somatic, cognitive, emotional), somatic symptoms were the most often reported for our mTBI sample. The same has repeatedly been found both in adult (Villemure, Nolin, & Le Sage, 2011) and pediatric mTBI (Ayr et al., 2009). Broader implications of this finding are briefly touched upon in subsection 6.8.

Second, our findings speak to the specificity of somatic PCS. PCS have repeatedly been documented following mTBI (see section 2.1.4), but some argue that PCS are best predicted by factors unrelated to head injury, such as underlying behavioral disorders and IQ (Meares et al., 2008). Results from this project suggest that somatic PCS are specific to mTBI; the mTBI group reported significantly more PCS symptoms than did the orthopedic injury control group, despite, on average, having been tested at longer times post-injury. Moreover, these differences could not be attributed to behavioral disorders because these were screened for in all participants. The possibility that IQ differences were present between injury groups cannot be rejected, however, because no neuropsychological assessment was carried out in this study. In contrast, results from this project suggest that that emotional and cognitive PCS are not specific to mTBI – self reported symptom load for the latter two classes of PCS symptoms were not significantly different between the injury control group and the mTBI

group. Thus, our results on the specificity of PCS are split and add to the debate; more research will be needed to determine the specificity and clinical utility of self-reported PCS, especially for those symptoms that are cognitive or emotional in nature.

Third, the lack of a correlation between self-reported symptom load and oculomotor performance in the mTBI group was surprising. Although our results showed that horizontal phase error was, overall, poorer for the mTBI group relative to both control groups, there was important variation between mTBI patients in their ability to synchronize to horizontal target movement. A natural assumption, therefore, was to expect that horizontal phase error would increase with symptom load – especially somatic symptom load. The null result has several possible explanations. One obvious possibility is that patients may not have been accurately reporting their symptoms and that a more objective measure of symptom load would have correlated positively with measures of horizontal phase error. Another equally probable scenario that has been reported in the literature (Slobounov et al., 2007) is that PCS report was accurate, but that brain dysfunction – as indicated by high horizontal phase error – was occurring in the absence of somatic PCS. This latter possibility re-emphasizes the urgent need for an objective tool for monitoring mTBI. Importantly, the lack of a correlation between horizontal phase error and PCSS-R scores does not go against our finding that somatic PCS are specific to mTBI.

6.4 Study limitations

6.4.1 *Sample*

The most important limitation to this study's results is the small size of our groups, which may consequently not be representative of the populations they were intended to sample. At least two additional features of our sample further restrict the generalizability of our findings.

Heterogeneity of mTBI cases

A distinguishing feature of our sample is the heterogeneity of the mTBI group. As was described above, both the load and the type of self-reported symptoms varied considerably between mTBI patients. This is in keeping with the medical literature (Rosenbaum & Lipton, 2012). Two features of our study design, however, introduced additional variability within the mTBI group. First, there was a wide-range of times post-injury at which patients were tested, ranging from 3 to 87 days. The mTBI group combined cases for which treatment was sought in the acute and semi-acute injury periods, as well as cases in which treatment was sought for persisting symptomatology. It is important to emphasize that all patients were only tested once. Patients tested at later times post-injury were still being treated for their symptom load – sometimes these patients reported higher symptom load than did those tested at shorter times post-injury. Therefore, those tested at the longest times post-injury were experiencing abnormally lengthy recovery (surpassing the standard two weeks). These longer recovery times could be indicative of an injury of higher severity, or of patients on their way to developing chronic PCS. Statistically speaking, the pool of mTBI participants tested at earlier times post-injury had a higher likelihood of "normal" recovery, since we would expect only 11% to develop persisting PCS beyond the 3-month mark (Barlow et al., 2010).

An important limiting factor for interpretation of our results was that our mTBI group combined patients likely to follow a normal path to recovery, and others already showing prolonged recovery times. At a minimum, good outcomes should be separable from poor outcomes (Messé et al., 2011). Perfect classification of outcomes requires designs that take repeated measures within-subjects, or that are retrospective. Our attempts at sub-classification of mTBI group participants were unsuccessful. Contrary to our expectations, we found no association between injury severity and oculomotor performance; correlations between each of *phase error -x*, *phase error -y* and *gaze error* and PCSS-R scores – an index of injury severity – were not significant. Although the validity of the PCSS-R scale has been demonstrated (Chen et al., 2007), it still lacks the reliability that an objective measure of injury severity for mTBI would provide. Thus, assuming that oculomotor deficits were indeed present, it remains unclear whether the lack of a correlation between measures of oculomotor performance and PCSS-R scores is indicative of a lack of association between oculomotor deficits and PCS, or alternatively, of an unreliability of PCSS-R scores for pediatric populations. If the latter holds, oculomotor dysfunction may have been associated with PCS in our sample, but the relationship may not have been readily detectable using the PCSS-R.

A second feature of our design that could have introduced additional variability was the large age range of mTBI participants, spanning across salient neurodevelopmental stages. It is possible that performance on oculomotor tasks could at least partly be explained by differences in oculomotor system maturation. A discussion of the genetic and environmental factors influencing maturation of

the oculomotor networks falls beyond the scope of this project. The heterogeneity brought on by the combination of non-injury related factors, as well as intrinsic and extrinsic injury factors, translated into larger variances on nearly all measures of oculomotor performance for the mTBI group relative to the control groups. In other words, the performance of certain mTBI group participants was sometimes on par with that of control group participants, while others from the mTBI group showed clear deficits.

In sum, interpretation of our results is made difficult by the heterogeneous clinical presentations and the uncertainties concerning injury severity. There are, however, important benefits to having worked with such a heterogeneous patient group. One of the main objectives of this project was to test a novel eye-tracking paradigm, and to validate its implementation within a clinical population. In this sense, the heterogeneity of the sample, despite preventing generalizability of study results, does allow for broader conclusions regarding applicability of this diagnosis method to patients on the entire scale of mTBI severity and who are at different stages of recovery.

Gender differences

Gender differences were not controlled for in this project. Our initial study design was to match mTBI patients with control participants of the same age and gender. Unfortunately, a slow recruitment process made this unfeasible. Although our hypotheses made no predictions about gender differences, unequal male-to-female group ratios demanded that some assessment of gender effects on oculomotor performance be made. A statistically sound method for doing so would probe both main effects *and* interaction effects of gender with measures of

oculomotor performance. The former was carried out and no statistically significant differences were found between genders on all measures of oculomotor performance. The small sample size of our control groups, however, made testing for interactions between group and gender impractical; results from statistical procedures enabling such analyses would have been unreliable due to the small size of our sample. Both control groups had a larger proportion of males than females; the injury control group was made up of 5 males and 1 female (5:1 ratio), while the healthy control group was made up of 8 males and 4 females (2:1 ratio). In contrast, the proportion of males to females in the mTBI group was of 1:1 in the SP task and of 9:7 in the fixation task. Control group gender ratios remained the same across tasks. Therefore, in both tasks, the control groups had a higher proportion of males than females relative to the mTBI group. Therefore, the reported differences in performance on oculomotor tasks between the mTBI group and the two control groups could be attributable to gender differences that were not uncovered here, rather than to effects of mTBI. Further research into this question is needed.

6.4.2 *Methodological considerations*

The study has a number of methodological limitations. The most important of these concern selection of tasks and outcomes measures. In terms of task selection, this project did not *directly* investigate the integrity of the saccade generation system. To validate results obtained from our analysis of the MMS and to warrant generalizations about the integrity of the saccade generation system, reflexive saccades should be investigated in pediatric mTBI and calculations for

their saccadic main sequences should be compared to those obtained for the MMS. Moreover, for the tasks that were included in the study, there are outcome measures that were not assessed but that should be evaluated in subsequent projects. Specifically, the presence of saccadic square-wave intrusions in fixation and some characteristics of SP initiation have both been associated with neurological abnormalities (Leigh & Zee, 2006), and their investigation in mTBI could yield important insights.

Interpretation of our results is also limited by the statistical procedures that were employed. Multivariate analyses of variance should be favored to separate univariate ANOVAs when comparing groups on several outcome measures because they reduce the number of statistical tests to be carried out and avoid *Type I* error rate inflation, while also providing information on the inter-correlation between outcome measures (Tabachnick, 2001). They also yield insights into how groups differ when compared on multiple measurements at the same time (Warner, 2013). Unfortunately, the small size of our sample precluded this kind of analysis.

6.5 Future directions

Results from this project raise new questions and re-emphasize several pre-existing ones. The most pressing questions that remain to be answered concern the integrity of the oculomotor system following pediatric mTBI. This project offers preliminary evidence that SP eye movements are impaired in pediatric mTBI. It remains unclear whether these deficits might be caused by dysfunction of the SP machinery, or by damage to higher level structures that

modulate SP. Differences in performance between predictable SP and random SP – which is less reliant on contributions from higher-order cortical areas – should be evaluated in future studies. If our results are replicated, the diagnostic of value of SP eye-tracking paradigms for pediatric mTBI will have to be established. Video-oculography is gaining clinical applications in the field of neurology – a recent study showed that this technology could be effectively used in the ED to quickly differentiate between a stroke and an impairment of vestibular function (Newman-Toker et al., 2013). Therefore, clinical usage of eye-tracking may be feasible from a cost-utility perspective. Further investigations, however, will be necessary to determine both the specificity and the sensitivity of this diagnostic test for adult and pediatric mTBI.

Findings from this project may also be used to inform experimental design. In terms of eye-tracking paradigm selection, tasks should allow for measurement of the vertical counterpart of any horizontal outcome measure being evaluated. In terms of participant selection, a control injury group should be used to control for the possibility of non-specific effects of injury on eye-tracking performance. Moreover, within the mTBI group, it is crucial that good outcomes be dissociable from poor outcomes – a repeated measures design is recommended when feasible.

The high prevalence of somatic PCS observed in this project and reported in the literature warrants investigations into the integrity of neurological systems whose dysfunction is associated with somatic manifestations that resemble those seen in PCS. Assessment of oculomotor deficits following pediatric mTBI adheres to this logic. So too do closely related investigations into the integrity of the

vestibular system. There is considerable overlap in the cortical circuitry of both these systems. Vestibular caloric stimulation increases blood flow to a network of cortical and subcortical structures that are key to the generation of eye movements: the prefrontal cortex, the FEFs, and the parietal cortex, cortically, and the putamen, thalamus and midbrain, subcortically (Dieterich, Bense, Stephan, Yousry, & Brandt, 2003). Moreover, vestibular complaints – such as nausea and vertigo – are highly prevalent following mTBI (Gottshall, 2011). Thus, investigations into the integrity of the vestibular system following pediatric mTBI may provide unique insights into this complex condition and are recommended. Eye-tracking and vestibular system integrity assessment may prove to be complementary measures of neurological dysfunction following mTBI, and together may provide valuable clues for mTBI diagnosis. Incidentally, the high prevalence of vestibular symptoms following mTBI, and the overlap of the vestibular and oculomotor systems, provide further credence for the possibility of impaired oculomotor function following mTBI.

Eye-tracking may be a valuable tool for gaining insight into factors that affect recovery from injury. Our study design was not intended to address this question, and therefore no conclusions can be made on this particular topic. More severe ocular impairment may predict poor outcomes such as chronic PCS. To address this question, a much larger sample size would be necessary, since only 11% of children and adolescents typically experience symptoms that persist beyond the three month mark (Barlow et al., 2010). In our sample size of nineteen, following these numbers, one or two would have been expected to develop the condition. Thus the possibility for both SP and fixational assessment

to serve as a tool for monitoring mTBI cannot be discarded in spite of the null results obtained on the fixation task in this project and should be investigated in subsequent studies , since gaining a better understanding of mTBI prognosis is an item deemed urgent on the mTBI research agenda (Carroll et al., 2004).

Our discussion of the potential clinical contributions of eye-tracking has emphasized its role in diagnosis. Importantly, eye-tracking could also be used to inform treatment for mTBI. Therapeutic strategies for recovery from mTBI are limited, with patients often complaining of the lack of proactive measures taken. Treatment guidelines emphasize rest – both physical and cognitive (McCrory et al., 2009) – frequent evaluation, and patient education (Petraglia, Maroon, & Bailes, 2012). Advances in the development of proactive treatments options, such as pharmacological intervention (Petraglia et al., 2012) and Cognitive Behavioral Therapy, require objective measures of patient improvement. Further research will have to determine if eye-tracking can serve as a tool for gauging mTBI treatment efficacy and if eye movement measures can be integrated in clinical research protocols as reliable indicators of patient outcomes.

7. CONCLUSION

This project sought to explore a basic question: might ocular impairment serve as a marker for pediatric mTBI? As an initial response, our study offers five contributions to the question. First, despite the acknowledged limitations, the data seem to offer evidence that pediatric mTBI is associated with selective deficits in gaze holding oculomotor function. The results show that SP, but not fixation, may be impaired in pediatric mTBI. The SP impairment we report is specific, and limited to synchronization of the eye with the target motion, which may be caused by difficulties in predicting target motion with respect to time. Second, the results offer *indirect* evidence that the integrity of the saccade generation system is not affected by pediatric mTBI. Third, clinically, our findings suggest that there may be merits to using eye-tracking to detect oculomotor impairment in pediatric populations. We show how a statistical model built on measures of oculomotor performance can predict the likelihood of existing mTBI pathophysiology. Fourth, though preliminary, the findings raise important methodological questions, and may thus inform the design of future investigations into pediatric mTBI.

Finally, the project offers contributions beyond the findings from the experiments. The underlying research for the study reviews literature on the overlap of structures that are both involved in oculomotor function and particularly susceptible to mTBI pathophysiology. We found no such review in the existing literature. Moreover, this project tested a novel framework for indirectly testing the integrity of the saccadic generation system through a fixation task. Microsaccades have been used to probe neurological conditions, but never

has the microsaccadic main sequence been used as a clinical indicator of oculomotor integrity. This study provides theoretical grounds for doing so.

Our results are preliminary and of restricted generalizability. The project was based on limited evidence from the adult mTBI literature. Accordingly, the investigations we performed were novel; they had, to our knowledge, never before been carried out in pediatric mTBI. If this project's findings can be replicated in larger studies, and if further explorations into the questions raised by this project are carried out, they will help advance the case for inclusion of eye-tracking in what will inevitably have to be a multi-faceted approach to improving detection and treatment of pediatric mTBI.

APPENDIX I: TABLES AND FIGURES

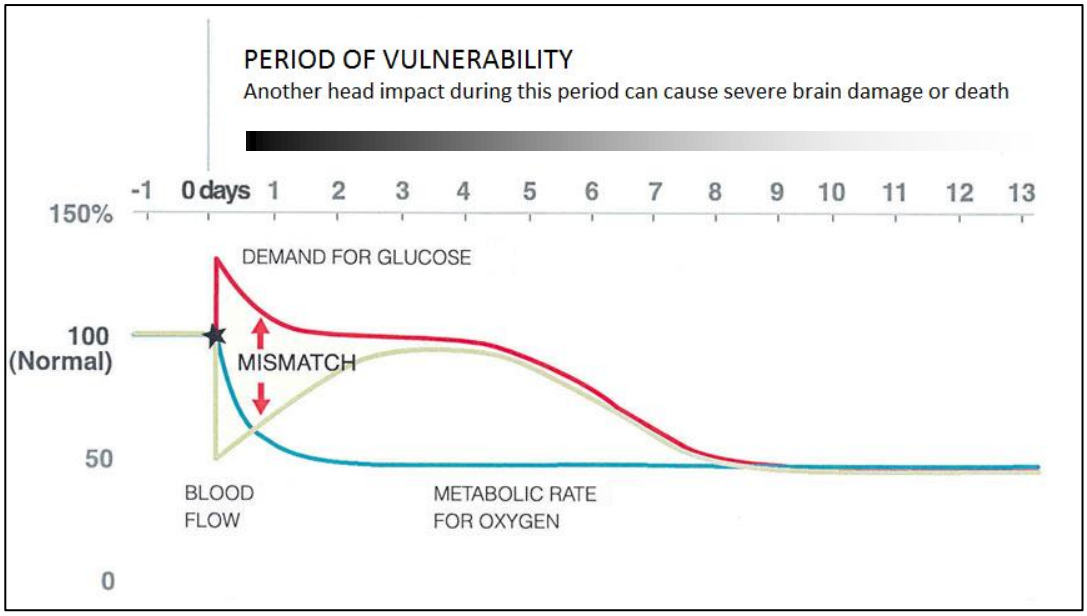

Figure 2.1 Vulnerability following mTBI. The neurometabolic cascade of mTBI induces an energy crisis that culminates in cerebral hypometabolism. During this period of depressed neurometabolic activity, the brain is highly vulnerable to subsequent head impacts. Adapted from McKinley (2000) with permission.

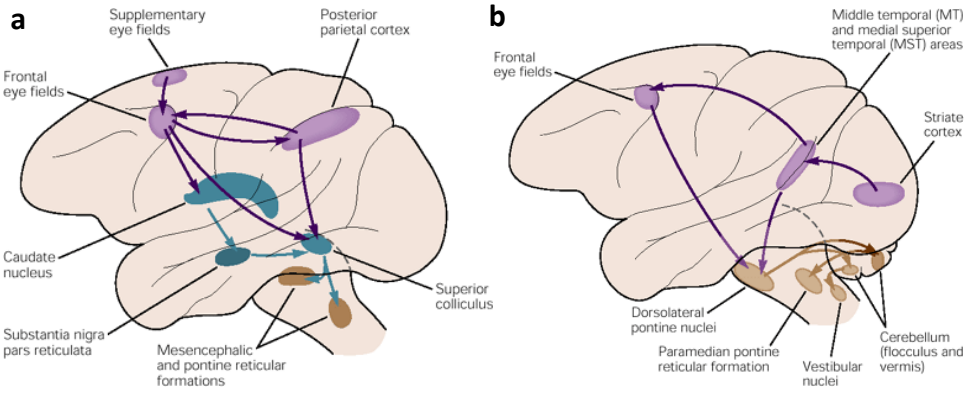

Figure 2.2 Oculomotor circuits. (a) Saccadic system in the monkey. (b) Ocular smooth pursuit system in the monkey. Replicated with permission from figures 39-11 and 39-12 in Goldberg (2000).

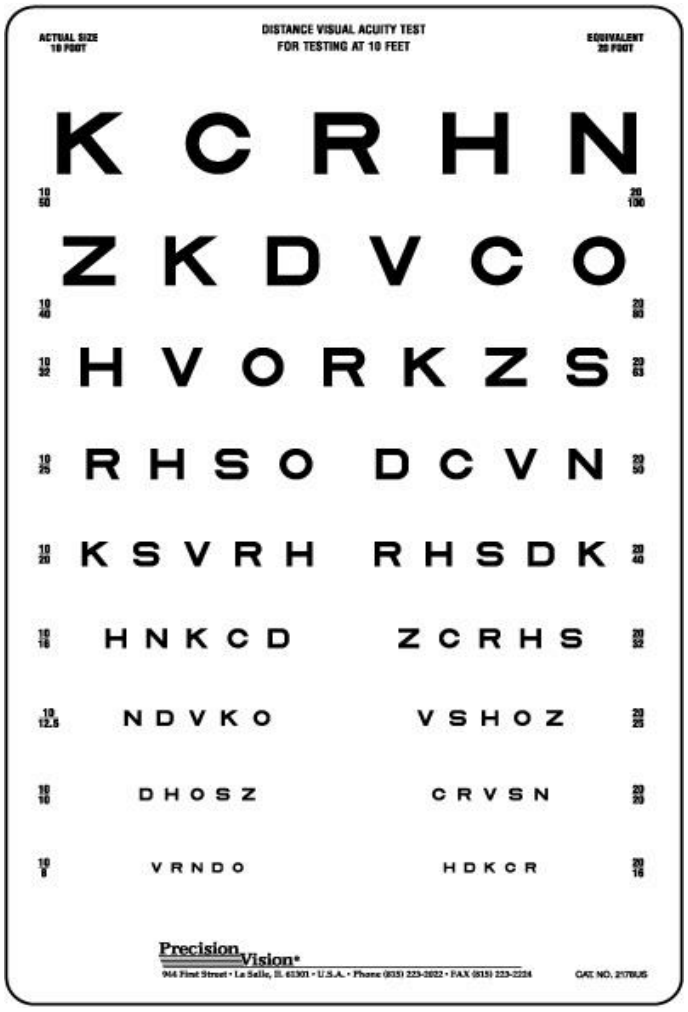

Figure 4.1 SLOAN chart for testing of visual acuity at 10 feet

Postconcussion Scale – Revised

SYMPTOM	Rating						
	None		Moderate			Severe	
Headache	0	1	2	3	4	5	6
Nausea	0	1	2	3	4	5	6
Vomiting	0	1	2	3	4	5	6
Balance Problems	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Trouble falling asleep	0	1	2	3	4	5	6
Sleeping more than usual	0	1	2	3	4	5	6
Sleeping less than usual	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervousness	0	1	2	3	4	5	6
Feeling more emotional	0	1	2	3	4	5	6
Numbness or tingling	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling mentally "foggy"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
TOTAL SCORE							

Figure 4.2 Post-concussion symptom scale

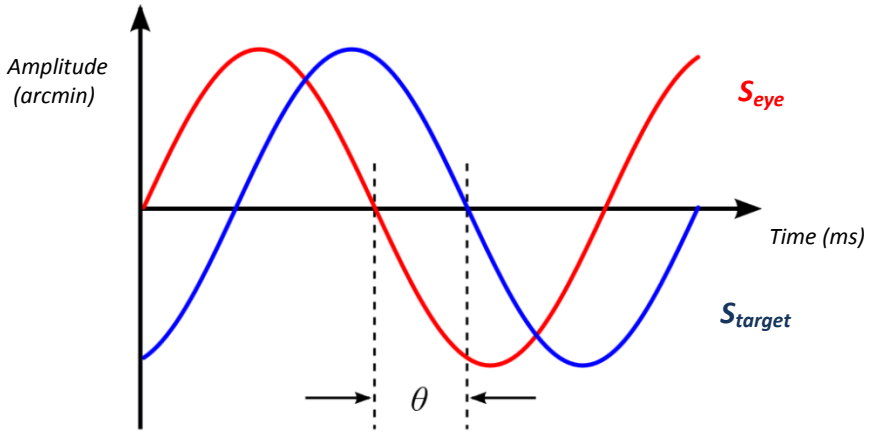

Figure 4.3 Sine smooth pursuit phase error. In this theoretical example, the eye signal S_{eye} (corresponding to either the *-x* or the *-y* component of the eye movement) is lagging the target signal S_{target} (corresponding to the equivalent component of the target movement) by a duration of θ milliseconds, where θ represents the *phase shift* between the two signals. In this case, θ would take on a negative value because the eye is lagging the target. The *phase error* is obtained by taking the absolute value of θ. Adapted from Wikimedia Commons figure by Peppergrower (Own work) [CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0) or GFDL (http://www.gnu.org/copyleft/fdl.html)].

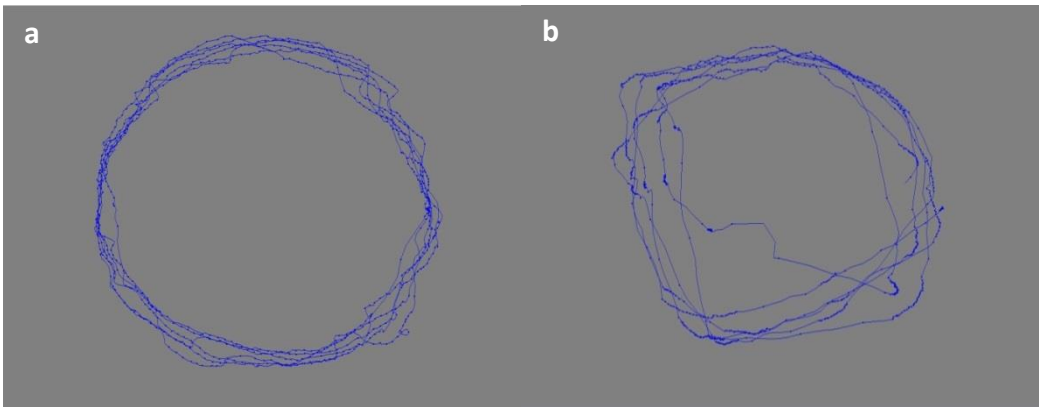

Figure 5.1 Smooth pursuit eye traces. Eye-traces for a healthy control (a) and an mTBI patient (b) with a PCSS-R score of 40, at 39 days post-injury. Traces are shown for a single 1500 millisecond SP trial. The mTBI patient shows marked impairment on execution of the task relative to the control. Note that the mTBI trial was selected to highlight the possible extent of the impairment. Traces for mTBI participants who performed best resembled those of healthy participants. The same was not true with regards to worst performances; in no cases were such impairments as those observed in (b) observed for healthy participants.

Measure	Phase error -x	Phase error -y	Gaze error	Gain -x	Gain -y
Phase error -x	1	0.23	0.28	-0.14	0.04
Phase error -y		1	0.4	-0.14	-0.12
Gaze error			1	0.03	-0.01
Gain -x				1	0.93*
Gain -y					1

Table 5.1 Correlation matrix for smooth pursuit measures. Pearson's correlation coefficient *r* was used to evaluate the degree of linear dependence between all SP outcome measures to minimize the number of comparisons performed between groups. There was a strong association between horizontal and vertical gain values. Therefore these two measures were averaged to provide a single measure of gain.

* $r \geq .08$.

	Male	Female	T-Test	
Measure	n =22	N = 14	t-statistic	p-value
Phase error -x	4.62 ± 11.81	7.43 ± 2.21	0.76	0.46
Phase error -y	24.07 ± 17.5	31.55 ± 16.48	1.27	0.21
Gaze error	54.83 ± 32.88	69.26 ± 18.75	1.47	0.15
Gain	0.83 ± 0.27	0.71 ± 0.10	-1.86	0.07

Table 5.2 Gender differences in smooth pursuit performance. Gender differences in performance on the SP task were compared using t-tests for independent samples. Performance was somewhat better for males on all measures of performance, but differences were not statistically significant at the 0.05 level.

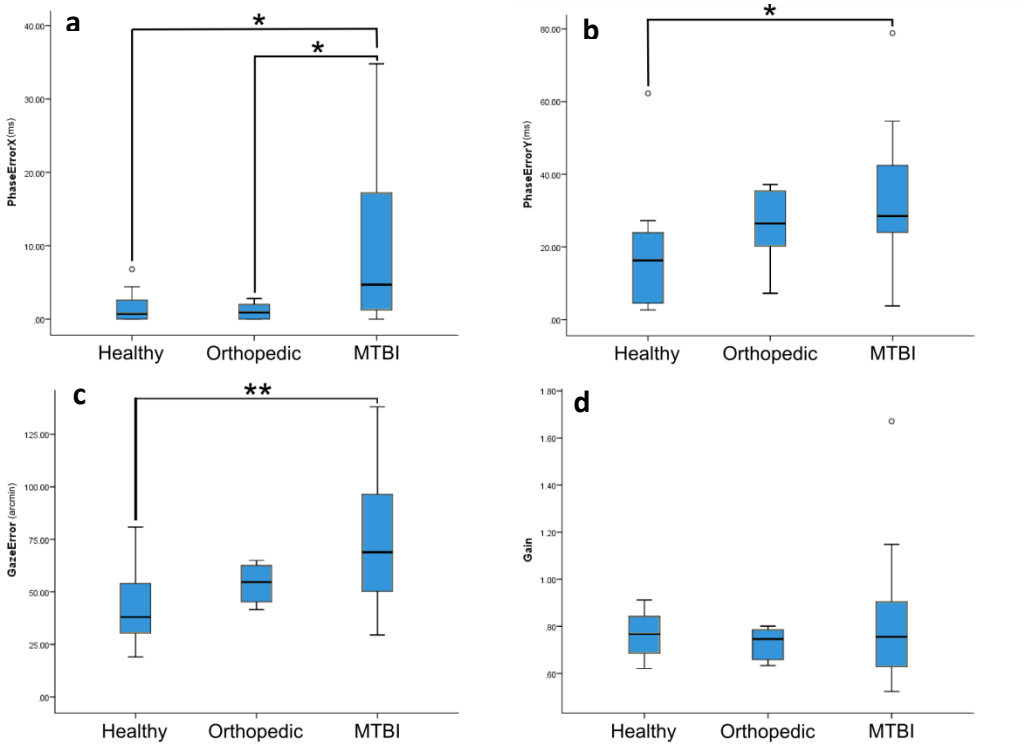

Figure 5.2 Smooth pursuit box plots. Box plots were generated to visualize group distribution for each measure of performance on the SP task, namely *phase errors -x* (a) and *-y* (b), *gaze error* (c) and *gain* (d). IQRs – indicated by blue boxes – were visibly larger for the mTBI group relative to the two control groups for measures of *phase error -x*, *gaze error*, and *gain*. Moreover, the mTBI group had a larger range of values than did the other groups on all measures, as indicated by whiskers (data points falling outside the IQR but still within 1.5 times IQR) and/or circles (mild outliers). These observations are indicative of high participant heterogeneity in the mTBI group. Also included in this figure are results from post-hoc comparisons of means for *phase error -x* and *-y* and *gaze error*. The presence of two statistically different homogenous subsets was only found in post-hoc comparisons for *phase error -x*, which revealed higher error in the mTBI group relative to both control groups. * Statistical significance at the 0.05 level. ** Statistical significance at the 0.01 level. ° Mild outlier.

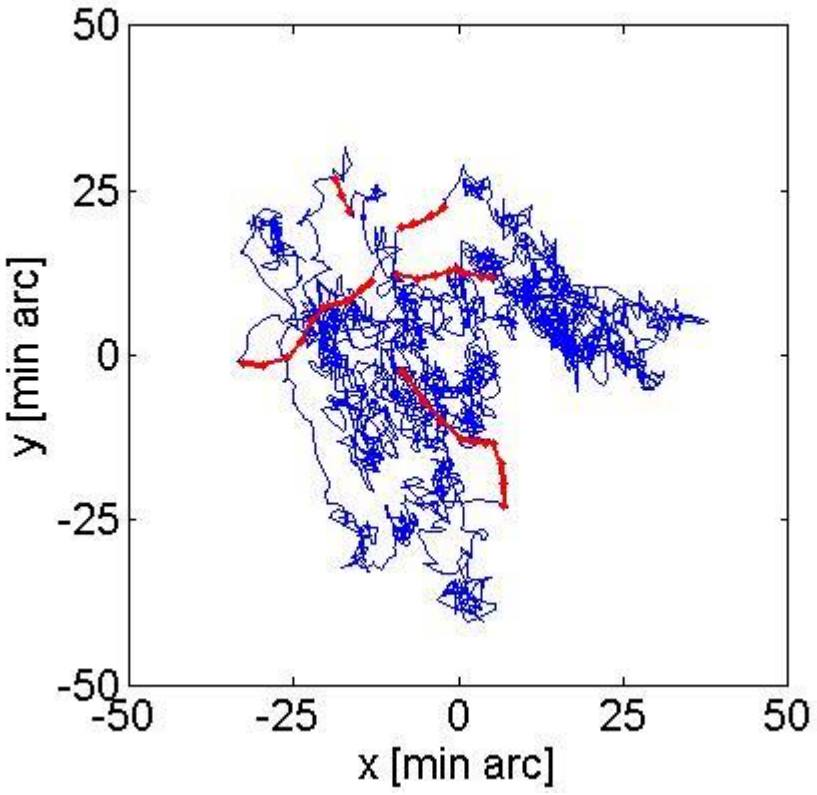

Figure 5.3 Microsaccade detection. Binocular eye-trace sampled at 1000*Hz* for a single 5000 millisecond fixation trial in a healthy control participant. The blue trace represents the slow-drift component of the fixational eye movement. High-velocity microsaccades appear in red (f =0.98Hz). The fixation target is not shown but is located at coordinates (0,0), where 1 minute of arc (*arcmin*) is equivalent 1/60 visual degrees. Figure generated using Engbert and Mergenthaler (2006) microsaccade generation algorithm.

	Male	Female	T-test	
Measure	n = 22	n = 14	t-statistic	p-value
MMS	0.87 ± 0.05	0.87 ± 0.07	0.11	0.99
f_{msac}	1.11 ± .57	1.34 ± 0.80	0.97	0.34
Gaze error	31.0 ± 8.76	33.6 ± 14.93	0.64	0.53

Table 5.3 Gender differences in fixation performance. Gender differences in performance on the fixation task were compared using t-tests for independent samples. Performances were comparable across genders, with no statistically significant differences at the 0.05 level. MMS = Microsaccadic Main sequence Slope; f_{msac} = Microsaccade rate.

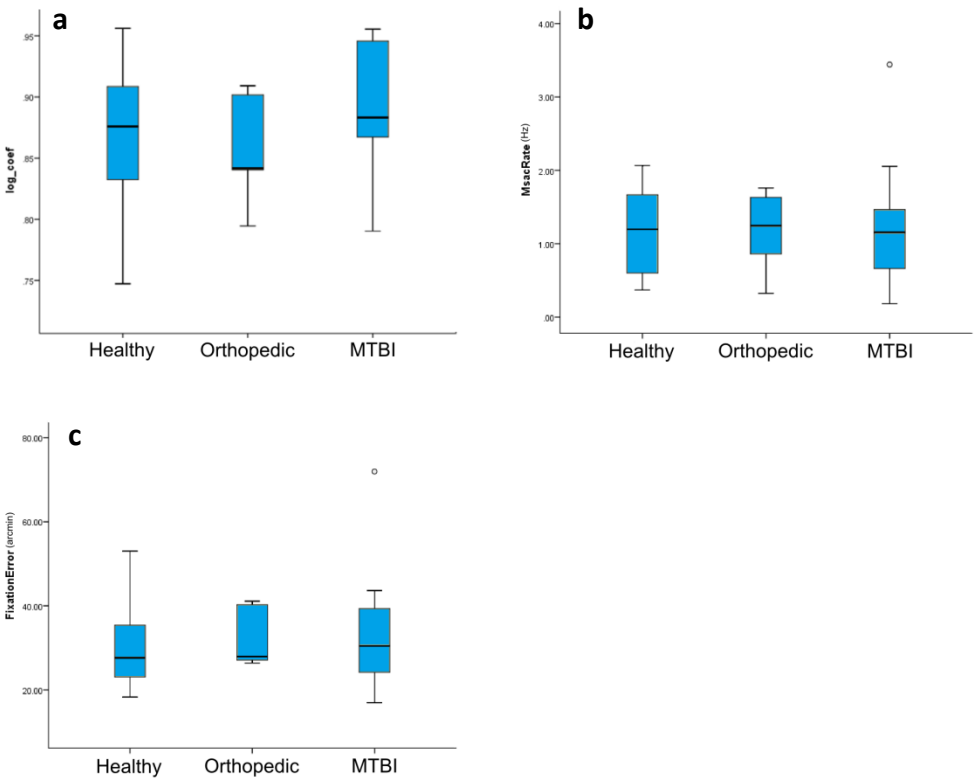

Figure 5.4 Fixation box plots. Box plots were generated to visualize group distribution for each measure of performance on the fixation task. Differences in group variance were not as pronounced as for the SP data. IQRs were not visibly larger for the mTBI group relative to the two control groups, but the mTBI group did have larger range of values for *microsaccade rate* (b). The largest variation for *microsaccade main sequence slope* (a) and *fixation error* (c) were found in the healthy control group, and not in the mTBI group, which is what we would have expected. Post-hoc comparisons of means were not performed for these measures because ANOVAs for each of these measures were non-significant. These preliminary results suggest no impact of mTBI on fixation task performance. ° Shows presence of a mild outlier.

Effect	Log-likelihood tests statistics	
	Chi-Square	p-value
Intercept	10.62	0.01**
Phase error -x	8.57	0.01**
Phase error -y	1.29	0.52
Gaze error	5.53	0.06

Table 5.4 Logistic regression predictor contributions table. Log-likelihood test statistics for multivariate regression indicate whether or not the regression model predicting group membership is significantly degraded by removal of individual predictors (i.e. oculomotor outcome measures). The model was degraded by removal of *phase -x* (p = .01), but not by removal of *phase error -y* (p = .52) or *gaze error* (p = .06), although a trend toward significance is evident for the latter. These results suggest that of all oculomotor measures assessed in the study, only *phase error -x* is a reliable predictor of group membership. *Statistical significance at the 0.05 level. ** Statistical significance at the 0.01 level.

Measure	PCSS-R somatic		Time Post Injury	
	Pearson's r	p-value	Pearson's r	p-value
Phase error -x	-.187	.456	-.145	.565
Gaze error	-.092	.717	-.026	.919

Table 5.5 Association of PCSS-R and TPI with measures of oculomotor performance. Variance for *phase error -x* and *gaze error* were significantly higher for the mTBI group relative to both control groups. Therefore, we investigated the possibility that high variances in the mTBI group might be explained at least in part by differences in reported symptom load and elapsed time since injury at testing. None of the associations between measures of oculomotor performance and these potential sources of additional variance were significant at the 0.05 level.

APPENDIX II: REFERENCES

Abadi, R. V., Clement, R. A., & Gowen, E. (2003). Levels of fixation. In L. Harris & M. Jenkins (Eds.), *Levels of perception* (pp. 213–229). New York: Springer.

Abdel-Dayem, H. M., Abu-Judeh, H., Kumar, M., Atay, S., Naddaf, S., El-Zeftawy, H., & Luo, J. Q. (1998). SPECT brain perfusion abnormalities in mild or moderate traumatic brain injury. *Clinical Nuclear Medicine, 23*(5), 309-317.

American Congress of Rehabilitation Medicine. (1993). Definition of mild traumatic brain injury. *Journal of Head Trauma Rehabiliation, 8*(3), 86-87.

Ayr, L. K., Yeates, K. O., Taylor, H. G., & Browne, M. (2009). Dimensions of postconcussive symptoms in children with mild traumatic brain injuries. *Journal of the International Neuropsychological Society, 15*(1), 19-30.

Bahill, A. T., Clark, M. R., & Stark, L. (1975). The main sequence, a tool for studying human eye movements. *Mathematical Biosciences, 24*(3-4), 191-204.

Barkhoudarian, G., Hovda, D. A., & Giza, C. C. (2011). The Molecular Pathophysiology of Concussive Brain Injury. *Clinics in Sports Medicine, 30*(1), 33-48.

Barlow, K. M., Crawford, S., Stevenson, A., Sandhu, S. S., Belanger, F., & Dewey, D. (2010). Epidemiology of Postconcussion Syndrome in Pediatric Mild Traumatic Brain Injury. *Pediatrics, 126*(2), 374-381.

Barnes, G. R. (2008). Cognitive processes involved in smooth pursuit eye movements. *Brain and Cognition, 68*(3), 309-326.

Barth, J., Ruff, R. M., & Espe-Pfeifer, P. (2006). Mild Traumatic Brain Injury: Definitions. In G. Young, K. Nicholson & A. Kane (Eds.), *Psychological Knowledge in Court* (pp. 271-278): Springer US.

Bazarian, J. J., McClung, J., Cheng, Y. T., Flesher, W., & Schneider, S. M. (2005). Emergency department management of mild traumatic brain injury in the USA. *Emergency Medicine Journal, 22*(7), 473-477.

Belanger, H., Curtiss, G., Demery, J., Lebowitz, B., & Vanderploeg, R. (2005). Factors moderating neuropsychological outcomes following mild traumatic brain injury: A meta-analysis. *Journal of the International Neuropsychological Society, 11*(03), 215-227.

Berchicci, M., Stella, A., Pitzalis, S., Spinelli, D., & Di Russo, F. (2012). Spatio-temporal mapping of motor preparation for self-paced saccades. *Biological Psychology, 90*(1), 10-17.

Berman, R. A., Joiner, W. M., Cavanaugh, J., & Wurtz, R. H. (2009). Modulation of Presaccadic Activity in the Frontal Eye Field by the Superior Colliculus. *Journal of Neurophysiology, 101*(6), 2934-2942.

Berryhill, M. E., Chiu, T., & Hughes, H. C. (2006). Smooth Pursuit of Nonvisual Motion. *Journal of Neurophysiology, 96*(1), 461-465.

Binder, L. M., Rohling, M. L., & Larrabee, G. J. (1997). A review of mild head trauma. Part I: Meta-analytic review of neuropsychological studies. *Journal of Clinical and Experimental Neuropsychology, 19*(3), 421-431.

Blume, H. K., Vavilala, M. S., Jaffe, K. M., Koepsell, T. D., Wang, J., Temkin, N., . . . Rivara, F. P. (2012). Headache after pediatric traumatic brain injury: A cohort study. *Pediatrics, 129*(1), e31-e39.

Borg, J., Holm, L., Cassidy, J. D., Peloso, P. M., Carroll, L. J., von Holst, H., & Ericson, K. (2004). Diagnostic procedures in mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *Journal of Rehabilitation Medicine*(43 Suppl), 61-75.

Bouvier, D., Fournier, M., Dauphin, J. B., Amat, F., Ughetto, S., Labbé, A., & Sapin, V. (2012). Serum S100B determination in the management of pediatric mild traumatic brain injury. *Clinical Chemistry, 58*(7), 1116-1122.

Bruce, C. J., & Goldberg, M. E. (1985). Primate frontal eye fields. I. Single neurons discharging before saccades. *Journal of Neurophysiology, 53*(3), 603-635.

Carroll, L. J., Cassidy, J. D., Holm, L., Kraus, J., & Coronado, V. G. (2004). Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *Journal of Rehabilitation Medicine*(43 Suppl), 113-125.

Cassidy, D., Carroll, L., Peloso, P., Borg, R., Holst, H. v., Holm, L., . . . Coronado, V. (2004). Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO collaborating centre task force on mild traumatic brain injury. *Journal of Rehabilitation Medicine, 36*(Supplement 43), 28-60.

CDC. (2003). *Report to Congress on mild traumatic brain injury in the United States: steps to prevent a serious public health problem*. Atlanta, GA: Centers for Disease Control and Prevention.

Cecil, K. M., Hills, E. C., Sandel, M. E., Smith, D. H., McIntosh, T. K., Mannon, L. J., . . . Lenkinski, R. E. (1998). Proton magnetic resonance spectroscopy for detection of axonal injury in the splenium of the corpus callosum of brain-injured patients. *Journal of Neurosurgery, 88*(5), 795-801.

Cernak, I., Chang, T., Ahmed, F. A., Cruz, M. I., Vink, R., Stoica, B., & Faden, A. I. (2010). Pathophysiological response to experimental diffuse brain trauma differs as a function of developmental age. *Developmental Neuroscience, 32*(5-6), 442-453.

Chen, J. K., Johnston, K. M., Collie, A., McCrory, P., & Ptito, A. (2007). A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. *Journal of Neurology, Neurosurgery and Psychiatry, 78*(11), 1231-1238.

Chen, J. K., Johnston, K. M., Frey, S., Petrides, M., Worsley, K., & Ptito, A. (2004). Functional abnormalities in symptomatic concussed athletes: an fMRI study. *NeuroImage, 22*(1), 68-82.

Chen, J. K., Johnston, K. M., Petrides, M., & Ptito, A. (2008). Neural substrates of symptoms of depression following concussion in male athletes with persisting postconcussion symptoms. *Archives of General Psychiatry, 65*(1), 81-89.

Clementz, B. A., Grove, W. M., Iacono, W. G., & Sweeney, J. A. (1992). Smooth-Pursuit Eye Movement Dysfunction and Liability for Schizophrenia: Implications for Genetic Modeling. *Journal of Abnormal Psychology, 101*(1), 117-129.

Contreras, R., Ghajar, J., Bahar, S., & Suh, M. (2011). Effect of cognitive load on eye-target synchronization during smooth pursuit eye movement. *Brain Research, 1398*, 55-63.

Coubard, O. A., & Kapoula, Z. (2006). Dorsolateral Prefrontal Cortex Prevents Short-latency Saccade and Vergence: a TMS Study. *Cerebral Cortex, 16*(3), 425-436.

Crevits, L., Hanse, M. C., Tummers, P., & Van Maele, G. (2000). Antisaccades and remembered saccades in mild traumatic brain injury. *Journal of Neurology, 247*(3), 179-182.

D'Ambrosio, R., Maris, D. O., Grady, M. S., Winn, H. R., & Janigro, D. (1999). Impaired K+ Homeostasis and Altered Electrophysiological Properties of Post-Traumatic Hippocampal Glia. *The Journal of Neuroscience, 19*(18), 8152-8162.

De Beaumont, L., Tremblay, S., Poirier, J., Lassonde, M., & Théoret, H. (2012). Altered bidirectional plasticity and reduced implicit motor learning in concussed athletes. *Cerebral Cortex, 22*(1), 112-121.

DeMatteo, C., Hanna, S., Mahoney, W., Hollenberg, R., Scott, L., Law, M., . . . Xu, L. (2010). "My Child Doesn't Have a Brain Injury, He Only Has a Concussion". *Pediatrics, 125*(2), 327-334.

Di Stasi, L. L., McCamy, M. B., Catena, A., Macknik, S. L., Cañas, J. J., & Martinez-Conde, S. (In Press). Microsaccade and drift dynamics reflect mental fatigue. *European Journal of Neuroscience*.

Dieterich, M., Bense, S., Stephan, T., Yousry, T., & Brandt, T. (2003). fMRI signal increases and decreases in cortical areas during small-field optokinetic stimulation and central fixation. *Experimental Brain Research, 148*(1), 117-127.

Ding, J., Powell, D., & Jiang, Y. (2009). Dissociable frontal controls during visible and memory-guided eye-tracking of moving targets. *Human Brain Mapping, 30*(11), 3541-3552.

Drew, A. S., Langan, J., Halterman, C., Osternig, L. R., Chou, L. S., & van Donkelaar, P. (2007). Attentional disengagement dysfunction following mTBI assessed with the gap saccade task. *Neuroscience Letters, 417*(1), 61-65.

Dursteler, M. R., & Wurtz, R. H. (1988). Pursuit and optokinetic deficits following chemical lesions of cortical areas MT and MST. *Journal of Neurophysiology, 60*(3), 940-965.

Ebisawa, Y., Minamitani, H., Mori, Y., & Takase, M. (1988). New methods for removing saccades in analysis of smooth pursuit eye movement. *Biological Cybernetics, 60*(2), 111-119.

Eckner, J. T., & Kutcher, J. S. (2010). Concussion Symptom Scales and Sideline Assessment Tools: A Critical Literature Update. *Current Sports Medicine Reports, 9*(1).

Engbert, R., & Kliegl, R. (2003). Microsaccades uncover the orientation of covert attention. *Vision Research, 43*(9), 1035-1045.

Engbert, R., & Mergenthaler, K. (2006). Microsaccades are triggered by low retinal image slip. *Proceedings of the National Academy of Sciences, 103*(18), 7192-7197.

Engel, K. C., Anderson, J. H., & Soechting, J. F. (2000). Similarity in the Response of Smooth Pursuit and Manual Tracking to a Change in the Direction of Target Motion. *Journal of Neurophysiology, 84*(3), 1149-1156.

Faul, M., Xu, L., Wald, M. M., & Coronado, V. G. (2010). *Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

Faux, S., & Sheedy, J. (2008). A prospective controlled study in the prevalence of posttraumatic headache following mild traumatic brain injury. *Pain Medicine, 9*(8), 1001-1011.

Ferris, F. L., Kassoff, A., Bresnick, G. H., & Bailey, L. (1982). New visual acuity charts for clinical research. *American Journal of Ophthalmology, 94*(1), 91-96.

Field, A. (2007). *Discovering statistics using SPSS* (3rd ed.). London: SAGE Publications.

Fineman, I., Hovda, D. A., Smith, M., Yoshino, A., & Becker, D. P. (1993). Concussive brain injury is associated with a prolonged accumulation of calcium: a45Ca autoradiographic study. *Brain Research, 624*(1–2), 94-102.

Fletcher, R., & Fletcher, S. (2005). Diagnosis *Clinical Epidemiology: The Essentials* (5 ed., pp. 35-58). Baltimore, MD: Lippincott Williams & Wilkins.

Ford, K. A., Goltz, H. C., Brown, M. R. G., & Everling, S. (2005). Neural processes associated with antisaccade task performance investigated with event-related fMRI. *Journal of Neurophysiology, 94*(1), 429-440.

Frencham, K. A. R., Fox, A. M., & Maybery, M. T. (2005). Neuropsychological studies of mild traumatic brain injury: A meta-analytic review of research since 1995. *Journal of Clinical and Experimental Neuropsychology, 27*(3), 334-351.

Fukushima, J., Akao, T., Shichinohe, N., Kurkin, S., Kaneko, C., & Fukushima, K. (2011). Neuronal Activity in the Caudal Frontal Eye Fields of Monkeys during Memory-Based Smooth Pursuit Eye Movements: Comparison with the Supplementary Eye Fields. *Cerebral Cortex, 21*(8), 1910-1924.

Fukushima, K., Akao, T., Shichinohe, N., Nitta, T., Kurkin, S., & Fukushima, J. (2008). Predictive signals in the pursuit area of the monkey frontal eye fields. In K. Christopher & R. J. Leigh (Eds.), *Progress in Brain Research* (Vol. 171, pp. 433-440). New York: Elsevier.

Fukushima, K., Fukushima, J., Warabi, T., & Barnes, G. R. (2013a). Cognitive processes involved in smooth pursuit eye movements: Behavioral evidence, neural substrate and clinical correlation. *Frontiers in Systems Neuroscience*(March).

Fukushima, K., Fukushima, J., Warabi, T., & Barnes, G. R. (2013b). Cognitive processes involved in smooth pursuit eye movements: Behavioral evidence, neural substrate and clinical correlation. *Frontiers in Systems Neuroscience, 7*(4), 1-28.

Fukushima, K., Yamanobe, T., Shinmei, Y., & Fukushima, J. (2002). Predictive responses of periarcuate pursuit neurons to visual target motion. *Experimental Brain Research, 145*(1), 104-120.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1993). Dorsolateral prefrontal lesions and oculomotor delayed-response performance: Evidence for mnemonic 'scotomas'. *Journal of Neuroscience, 13*(4), 1479-1497.

Gagnon, I., Swaine, B., Friedman, D., & Forget, R. (2004). Children show decreased dynamic balance after mild traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 85*(3), 444-452.

Garbutt, S., Harwood, M., & Harris, C. (2001). Comparison of the main sequence of reflexive saccades and the quick phases of optokinetic nystagmus. *British Journal of Ophthalmology, 85*(12), 1477-1483.

Geyer, C., Ulrich, A., Gräfe, G., Stach, B., & Till, H. (2009). Diagnostic value of S100B and neuron-specific enolase in mild pediatric traumatic brain injury: Clinical article. *Journal of Neurosurgery: Pediatrics, 4*(4), 339-344.

Gioia, G. A., Isquith, P. K., Schneider, J. C., & Vaughan, C. G. (2009). New approaches to assessment and monitoring of concussion in children. *Topics in Language Disorders, 29*(3), 266-281.

Giza, C. C., & Difiori, J. P. (2011). Pathophysiology of sports-related concussion: An update on basic science and translational research. *Sports Health, 3*(1), 46-51.

Giza, C. C., & Hovda, D. A. (2001). The Neurometabolic Cascade of Concussion. *Journal of Athletic Training, 36*(3), 228-235.

Goldberg, M. E. (2000). The Control of Gaze. In E. Kandel, J. Schwarz, T. Jessell, S. Siegelbaum & A. Hudspeth (Eds.), *Principles of Neural Science* (4 ed., pp. 782-800). New York: McGraw-Hill.

Gottshall, K. (2011). Vestibular rehabilitation after mild traumatic brain injury with vestibular pathology. *NeuroRehabilitation, 29*(2), 167-171.

Greenwald, B., Kapoor, N., & Singh, A. (2012). Visual impairments in the first year after traumatic brain injury. *Brain Injury, 26*(11), 1338-1359.

Gross, H., Kling, A., Henry, G., Herndon, C., & Lavretsky, H. (1996). Local cerebral glucose metabolism in patients with long-term behavioral and cognitive deficits following mild traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences, 8*(3), 324-334.

Grossman, E. J., Ge, Y., Jensen, J. H., Babb, J. S., Miles, L., Reaume, J., . . . Inglese, M. (2012). Thalamus and cognitive impairment in mild traumatic brain

injury: a diffusional kurtosis imaging study. *Journal of Neurotrauma, 29*(13), 2318-2327.

Guskiewicz, K. M., McCrea, M., Marshall, S. W., Cantu, R. C., Randolph, C., Barr, W., . . . Kelly, J. P. (2003). Cumulative Effects Associated With Recurrent Concussion in Collegiate Football Players. *JAMA: The Journal of the American Medical Association, 290*(19), 2549-2555.

Hafed, Z. M., & Krauzlis, R. J. (2012). Similarity of superior colliculus involvement in microsaccade and saccade generation. *Journal of Neurophysiology, 107*(7), 1904-1916.

Hamberger, A., Viano, D. C., Säljö, A., & Bolouri, H. (2009). Concussion in professional football: Morphology of brain injuries in the NFL concussion model - Part 16. *Neurosurgery, 64*(6), 1174-1182.

Hanes, D. P., & Wurtz, R. H. (2001). Interaction of the Frontal Eye Field and Superior Colliculus for Saccade Generation. *Journal of Neurophysiology, 85*(2), 804-815.

Harmon, K. G., Drezner, J. A., Gammons, M., Guskiewicz, K. M., Halstead, M., Herring, S. A., . . . Roberts, W. O. (2013). American Medical Society for Sports Medicine position statement: concussion in sport. *British Journal of Sports Medicine, 47*(1), 15-26.

Heide, W., Kurzidim, K., & Kömpf, D. (1996). Deficits of smooth pursuit eye movements after frontal and parietal lesions. *Brain, 119*(6), 1951-1969.

Heinen, S. J., & Liu, M. (1997). Single-neuron activity in the dorsomedial frontal cortex during smooth-pursuit eye movements to predictable target motion. *Visual Neuroscience, 14*(5), 853-865.

Heitger, M., Anderson, T., Jones, R., Dalrymple-Alford, J., Frampton, C., & Ardagh, M. (2004). Eye movement and visuomotor arm movement deficits following mild closed head injury. *Brain, 127*(3), 575-590.

Heitger, M., Jones, R., Dalrymple-Alford, J., Frampton, C., Ardagh, M., & Anderson, T. (2006). Motor deficits and recovery during the first year following mild closed head injury. *Brain Injury, 20*(8), 807-824.

Heitger, M., Jones, R., Macleod, A., Snell, D., Frampton, C., & Anderson, T. (2009). Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability. *Brain, 132*(10), 2850-2870.

Heitger, M., Macaskill, M., Jones, R., & Anderson, T. (2005). The impact of mild closed head injury on involuntary saccadic adaptation: Evidence for the preservation of implicit motor learning. *Brain Injury, 19*(2), 109-117.

Henry, L., Tremblay, S., Boulanger, Y., Ellemberg, D., & Lassonde, M. (2010). Neurometabolic changes in the acute phase after sports concussions correlate with symptom severity. *Journal of Neurotrauma, 27*(1), 65-76.

Henry, L., Tremblay, S., Leclerc, S., Khiat, A., Boulanger, Y., Ellemberg, D., & Lassonde, M. (2011). Metabolic changes in concussed American football players during the acute and chronic post-injury phases. *BMC Neurology, 11*.

Hikosaka, O., Takikawa, Y., & Kawagoe, R. (2000). Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiological Reviews, 80*(3), 953-978.

Hilz, M. J., Defina, P. A., Anders, S., Koehn, J., Lang, C. J., Pauli, E., . . . Marthol, H. (2011). Frequency analysis unveils cardiac autonomic dysfunction after mild traumatic brain injury. *Journal of Neurotrauma, 28*(9), 1727-1738.

Hodgson, T., Chamberlain, M., Parris, B., James, M., Gutowski, N., Husain, M., & Kennard, C. (2007). The role of the ventrolateral frontal cortex in inhibitory oculomotor control. *Brain, 130*(6), 1525-1537.

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., & Castro, C. A. (2008). Mild traumatic brain injury in U.S. soldiers returning from Iraq. *New England Journal of Medicine, 358*(5), 453-463.

Hsu, H.-C., Chen, H.-J., Lu, K., & Liang, C.-L. (2001). Reversible bilateral internuclear ophthalmoplegia following head injury. *Acta Ophthalmologica Scandinavica, 79*(1), 57-59.

Hunter, J. V., Wilde, E. A., Tong, K. A., & Holshouser, B. A. (2012). Emerging imaging tools for use with traumatic brain injury research. *Journal of Neurotrauma, 29*(4), 654-671.

Inagaki, K., Hirata, Y., & Usui, S. (2011). A model-based theory on the signal transformation for microsaccade generation. *Neural Networks, 24*(9), 990-997.

Iverson, G. L. (2005). Outcome from mild traumatic brain injury. *Current Opinions in Psychiatry, 18*(3), 301-317.

Jantzen, K. J., Anderson, B., Steinberg, F. L., & Kelso, J. A. S. (2004). A prospective functional MR imaging study of mild traumatic brain injury in college football players. *American Journal of Neuroradiology, 25*(5), 738-745.

Jennett, B. (1996). Epidemiology of head injury. *Journal of Neurology Neurosurgery and Psychiatry, 60*(4), 362-369.

Johnson, B., Gay, M., Zhang, K., Neuberger, T., Horovitz, S. G., Hallett, M., . . . Slobounov, S. (2012). The use of magnetic resonance spectroscopy in the subacute evaluation of athletes recovering from single and multiple mild traumatic brain injury. *Journal of Neurotrauma, 29*(13), 2297-2304.

Johnson, B., Zhang, K., Gay, M., Horovitz, S., Hallett, M., Sebastianelli, W., & Slobounov, S. (2012). Alteration of brain default network in subacute phase of injury in concussed individuals: Resting-state fMRI study. *NeuroImage, 59*(1), 511-518.

Johnson, B., Zhang, K., Gay, M., Neuberger, T., Horovitz, S., Hallett, M., . . . Slobounov, S. (2012). Metabolic alterations in corpus callosum may compromise brain functional connectivity in MTBI patients: An 1H-MRS study. *Neuroscience Letters, 509*(1), 5-8.

Karlin, A. M. (2011). Concussion in the Pediatric and Adolescent Population: “Different Population, Different Concerns”. *PM&R, 3*(10, Supplement 2), S369-S379.

Katayama, Y., Becker, D. P., Tamura, T., & Hovda, D. A. (1990). Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *Journal of Neurosurgery, 73*(6), 889-900.

Katnani, H. A., van Opstal, A. J., & Gandhi, N. J. (2012). Blink Perturbation Effects on Saccades Evoked by Microstimulation of the Superior Colliculus. *PLoS ONE, 7*(12).

Katsanis, J., Iacono, W. G., & Harris, M. (1998). Development of oculomotor functioning in preadolescence, adolescence, and adulthood. *Psychophysiology, 35*(1), 64-72.

Katz, B., & Rimmer, S. (1989). Ophthalmologic manifestations of Alzheimer's disease. *Survey of Ophthalmology, 34*(1), 31-43.

Kawamata, T., Katayama, Y., Hovda, D. A., Yoshino, A., & Becker, D. P. (1995). Lactate accumulation following concussive brain injury: the role of ionic fluxes induced by excitatory amino acids. *Brain Research, 674*(2), 196-204.

Keightley, M. L., Chen, J. K., & Ptito, A. (2012). Examining the neural impact of pediatric concussion: A scoping review of multimodal and integrative approaches using functional and structural MRI techniques. *Current Opinion in Pediatrics, 24*(6), 709-716.

Kelly, J. P., & Rosenberg, J. H. (1997). Diagnosis and management of concussion in sports. *Neurology, 48*(3), 575-580.

Kettner, R., Leung, H.-C., & Peterson, B. (1996). Predictive smooth pursuit of complex two-dimensional trajectories in monkey: component interactions. *Experimental Brain Research, 108*(2), 221-235.

Kirov, I., Fleysher, L., Babb, J. S., Silver, J. M., Grossman, R. I., & Gonen, O. (2007). Characterizing 'mild' in traumatic brain injury with proton MR spectroscopy in the thalamus: Initial findings. *Brain Injury, 21*(11), 1147-1154.

Kirov, I., Tal, A., Babb, J. S., Lui, Y. W., Grossman, R. I., & Gonen, O. (2013). Diffuse axonal injury in mild traumatic brain injury: A 3D multivoxel proton MR spectroscopy study. *Journal of Neurology, 260*(1), 242-252.

Kraus, J. F., Rock, A., & Hemyari, P. (1990). Brain injuries among infants, children, adolescents, and young adults. *American Journal of Diseases of Children, 144*(6), 684-691.

Kraus, M. F., Little, D. M., Donnell, A. J., Reilly, J. L., Simonian, N., & Sweeney, J. A. (2007). Oculomotor Function in Chronic Traumatic Brain Injury. *Cognitive and Behavioral Neurology, 20*(3), 170-178.

Kraus, M. F., Susmaras, T., Caughlin, B. P., Walker, C. J., Sweeney, J. A., & Little, D. M. (2007). White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain, 130*(10), 2508-2519.

Krauzlis, R. J. (2004). Recasting the Smooth Pursuit Eye Movement System. *Journal of Neurophysiology, 91*(2), 591-603.

Langlois, J., Rutland-Brown, W., & Thomas, K. (2006). *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Atlanta, Ga: Centers for Disease Control and Prevention.

Langlois, J., Rutland-Brown, W., & Thomas, K. E. (2005). The incidence of traumatic brain injury among children in the United States: Differences by race. *Journal of Head Trauma Rehabilitation, 20*(3), 229-238.

Lannsjö, M., Backheden, M., Johansson, U., Af Geijerstam, J. L., & Borg, J. (2012). Does head CT scan pathology predict outcome after mild traumatic brain injury. *European Journal of Neurology*.

Lee, H., Wintermark, M., Gean, A. D., Ghajar, J., Manley, G. T., & Mukherjee, P. (2008). Focal lesions in acute mild traumatic brain injury and neurocognitive outcome: CT versus 3T MRI. *Journal of Neurotrauma, 25*(9), 1049-1056.

Leigh, R. J., & Zee, D. S. (2006). *The Neurology of Eye Movements*. New York: Oxford University Press.

Lisberger, S. G., & Westbrook, L. E. (1985). Properties of visual inputs that initiate horizontal smooth pursuit eye movements in monkeys. *Journal of Neuroscience, 5*(6), 1662-1673.

Luerssen, T. G., Klauber, M. R., & Marshall, L. F. (1988). Outcome from head injury related to patient's age. A longitudinal prospective study of adult and pediatric head injury. *Journal of Neurosurgery, 68*(3), 409-416.

Lynch, J. C., & Tian, J. R. (2006). Cortico-cortical networks and cortico-subcortical loops for the higher control of eye movements. In J. A. Büttner-Ennever (Ed.), *Progress in Brain Research* (Vol. 151, pp. 461-501). New York: Elsevier.

Makoshi, Z., Kroliczak, G., & Van Donkelaar, P. (2011). Human supplementary motor area contribution to predictive motor planning. *Journal of Motor Behavior, 43*(4), 303-309.

Martinez-Conde, S. (2006). Fixational eye movements in normal and pathological vision. In S. Martinez-Conde, S. Macknik, L. Martinez, J. Alonso & P. Tse (Eds.), *Progress in Brain Research* (Vol. 154, Part A, pp. 151-176). New York: Elsevier.

Martinez-Conde, S., Macknik, S. L., Troncoso, X. G., & Dyar, T. A. (2006). Microsaccades counteract visual fading during fixation. *Neuron, 49*(2), 297-305.

Martinez-Conde, S., Otero-Millan, J., & MacKnik, S. (2013). The impact of microsaccades on vision: Towards a unified theory of saccadic function. *Nature Reviews Neuroscience, 14*(2), 83-96.

Maruta, J., Heaton, K., Kryskow, E., Maule, A., & Ghajar, J. (2013). Dynamic visuomotor synchronization: Quantification of predictive timing. *Behavior Research Methods, 45*(1), 289-300.

Maruta, J., Lee, S. W., Jacobs, E. F., & Ghajar, J. (2010). A unified science of concussion. *Annals of the New York Academy of Sciences, 1208*(1), 58-66.

Maruta, J., Suh, M., Niogi, S. N., Mukherjee, P., & Ghajar, J. (2010). Visual tracking synchronization as a metric for concussion screening. *Journal of Head Trauma Rehabilitation, 25*(4), 293-305.

Maugans, T. A., Farley, C., Altaye, M., Leach, J., & Cecil, K. M. (2012). Pediatric sports-related concussion produces cerebral blood flow alterations. *Pediatrics, 129*(1), 28-37.

Maunsell, J. H., & Van Essen, D. C. (1983). Functional properties of neurons in middle temporal visual area of the macaque monkey. I. Selectivity for stimulus direction, speed, and orientation. *Journal of Neurophysiology, 49*(5), 1127-1147.

Mayer, A. R., Ling, J., Mannell, M. V., Gasparovic, C., Phillips, J. P., Doezema, D., . . . Yeo, R. A. (2010). A prospective diffusion tensor imaging study in mild traumatic brain injury. *Neurology, 74*(8), 643-650.

McCamy, M. B., Otero-Millan, J., Macknik, S. L., Yang, Y., Troncoso, X. G., Baer, S. M., . . . Martinez-Conde, S. (2012). Microsaccadic Efficacy and Contribution to Foveal and Peripheral Vision. *The Journal of Neuroscience, 32*(27), 9194-9204.

McCrea, M. (2008). Introduction *Mild Traumatic Brain Injury and Postconcussion Syndrome* (pp. ix-xii). New York: Oxford University Press.

McCrea, M., Hammeke, T., Olsen, G., Leo, P., & Guskiewicz, K. (2004). Unreported Concussion in High School Football Players: Implications for Prevention. *Clinical Journal of Sport Medicine, 14*(1), 13-17.

McCrory, P. (2001). What's in a name? *British Journal of Sports Medicine, 35*(5), 285-286.

McCrory, P., Davis, G., & Makdissi, M. (2012). Second impact syndrome or cerebral swelling after sporting head injury. *Current Sports Medicine Reports, 11*(1), 21-23.

McCrory, P., Meeuwisse, W., Echemendia, R., Iverson, G., Dvořák, J., & Kutcher, J. (2013). What is the lowest threshold to make a diagnosis of concussion? *British Journal of Sports Medicine, 47*(5), 268-271.

McCrory, P., Meeuwisse, W., Johnston, K. M., Dvorak, J., Aubry, M., Molloy, M., & Cantu, R. (2009). Consensus Statement on Concussion in Sport: the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *British Journal of Sports Medicine, 43*(SUPPL. 1), i76-i84.

McKinlay, A., Grace, R. C., Horwood, L. J., Fergusson, D. M., Ridder, E. M., & MacFarlane, M. R. (2008). Prevalence of traumatic brain injury among children, adolescents and young adults: Prospective evidence from a birth cohort. *Brain Injury, 22*(2), 175-181.

McKinley, J. (2000, May 11). A Perplexing Foe Takes an Awful Toll, *New York Times*.

Meares, S., Shores, E. A., Taylor, A. J., Batchelor, J., Bryant, R. A., Baguley, I. J., . . . Marosszeky, J. E. (2008). Mild traumatic brain injury does not predict acute postconcussion syndrome. *Journal of Neurology, Neurosurgery and Psychiatry, 79*(3), 300-306.

Messé, A., Caplain, S., Paradot, G., Garrigue, D., Mineo, J. F., Soto Ares, G., . . . Lehéricy, S. (2011). Diffusion tensor imaging and white matter lesions at the subacute stage in mild traumatic brain injury with persistent neurobehavioral impairment. *Human Brain Mapping, 32*(6), 999-1011.

Meyer, C. H., Lasker, A. G., & Robinson, D. A. (1985). The upper limit of human smooth pursuit velocity. *Vision Research, 25*(4), 561-563.

Munoz, D. P., & Everling, S. (2004). Look away: the anti-saccade task and the voluntary control of eye movement. *Nature Reviews Neuroscience, 5*(3), 218-228.

Newman-Toker, D. E., Tehrani, A. S. S., Mantokoudis, G., Pula, J. H., Guede, C. I., Kerber, K. A., . . . Kattah, J. C. (2013). Quantitative Video-Oculography to Help Diagnose Stroke in Acute Vertigo and Dizziness: Toward an ECG for the Eyes. *Stroke*.

Newsome, W. T., Wurtz, R. H., & Komatsu, H. (1988). Relation of cortical areas MT and MST to pursuit eye movements. II. Differentiation of retinal from extraretinal inputs. *Journal of Neurophysiology, 60*(2), 604-620.

Niogi, S. N., Mukherjee, P., Ghajar, J., Johnson, C., Kolster, R. A., Sarkar, R., . . . McCandliss, B. D. (2008). Extent of Microstructural White Matter Injury in Postconcussive Syndrome Correlates with Impaired Cognitive Reaction Time: A 3T Diffusion Tensor Imaging Study of Mild Traumatic Brain Injury. *American Journal of Neuroradiology, 29*(5), 967-973.

Nishimoto, T., & Murakami, S. (1998). Relation between diffuse axonal injury and internal head structures on blunt impact. *Journal of Biomechanical Engineering, 120*(1), 140-147.

Noor, N., Abdullah, M., Yahaya, A., & Ramli, N. (2007). *Comparison of linear interpolation method and mean method to replace the missing values in environmental data set*. Paper presented at the International Conference On Sustainable Materials, Penang, Malaysia.

Nuding, U., Kalla, R., Muggleton, N. G., Büttner, U., Walsh, V., & Glasauer, S. (2009). TMS Evidence for Smooth Pursuit Gain Control by the Frontal Eye Fields. *Cerebral Cortex, 19*(5), 1144-1150.

O'Driscoll, G. A., Alpert, N. M., Matthysse, S. W., Levy, D. L., Rauch, S. L., & Holzman, P. S. (1995). Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography. *Proceedings of the National Academy of Sciences, 92*(3), 925-929.

Otero-Millan, J., Macknik, S. L., Serra, A., Leigh, R. J., & Martinez-Conde, S. (2011). Triggering mechanisms in microsaccade and saccade generation: a novel proposal. *Annals of the New York Academy of Sciences, 1233*(1), 107-116.

Otero-Millan, J., Serra, A., Leigh, R. J., Troncoso, X. G., Macknik, S. L., & Martinez-Conde, S. (2011). Distinctive Features of Saccadic Intrusions and Microsaccades in Progressive Supranuclear Palsy. *The Journal of Neuroscience, 31*(12), 4379-4387.

Paus, T. (1996). Location and function of the human frontal eye-field: A selective review. *Neuropsychologia, 34*(6), 475-483.

Pertab, J. L., James, K. M., & Bigler, E. D. (2009). Limitations of mild traumatic brain injury meta-analyses. *Brain Injury, 23*(6), 498-508.

Petit, L., Clark, V. P., Ingeholm, J., & Haxby, J. V. (1997). Dissociation of saccade-related and pursuit-related activation in human frontal eye fields as revealed by fmRI. *Journal of Neurophysiology, 77*(6), 3386-3390.

Petit, L., Orssaud, C., Tzourio, N., Salamon, G., Mazoyer, B., & Berthoz, A. (1993). PET study of voluntary saccadic eye movements in humans: basal ganglia-thalamocortical system and cingulate cortex involvement. *Journal of Neurophysiology, 69*(4), 1009-1017.

Petit, L., Tzourio, N., Orssaud, C., Pietrzyk, U., Berthoz, A., & Mazoyer, B. (1995). Functional neuroanatomy of the human visual fixation system. *European Journal of Neuroscience, 7*(1), 169-174.

Petraglia, A. L., Maroon, J. C., & Bailes, J. E. (2012). From the field of play to the field of combat: A review of the pharmacological management of concussion. *Neurosurgery, 70*(6), 1520-1533.

Pierrot-Deseilligny, C., Müri, R. M., Ploner, C. J., Gaymard, B., Demeret, S., & Rivaud-Pechoux, S. (2003). Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. *Brain, 126*(6), 1460-1473.

Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., & Agid, Y. (1991). Cortical Control of Reflexive Visually-guided saccades. *Brain, 114*(3), 1473-1485.

Ponsford, J., Cameron, P., Fitzgerald, M., Grant, M., Mikocka-Walus, A., & Schönberger, M. (2012). Predictors of postconcussive symptoms 3 months after mild traumatic brain injury. *Neuropsychology, 26*(3), 304-313.

Porac, C., & Coren, S. (1976). The dominant eye. *Psychological Bulletin, 83*(5), 880-897.

Povlishock, J. T., Becker, D. P., Cheng, C. L., & Vaughan, G. W. (1983). Axonal change in minor head injury. *Journal of Neuropathology and Experimental Neurology, 42*(3), 225-242.

Ptito, A., Chen, J.-K., & Johnston, K. M. (2007). Contributions of functional Magnetic Resonance Imaging (fMRI) to sport concussion evaluation. *NeuroRehabilitation, 22*(3), 217-227.

Rafal, R., McGrath, M., Machado, L., & Hindle, J. (2004). Effects of lesions of the human posterior thalamus on ocular fixation during voluntary and visually triggered saccades. *Journal of Neurology, Neurosurgy and Psychiatry, 75*(11), 1602-1606.

Reingold, E. M., & Stampe, D. M. (2002). Saccadic inhibition in voluntary and reflexive saccades. *Journal of Cognitive Neuroscience, 14*(3), 371-388.

Rosenbaum, S. B., & Lipton, M. L. (2012). Embracing chaos: The scope and importance of clinical and pathological heterogeneity in mTBI. *Brain Imaging and Behavior, 6*(2), 255-282.

Ruff, R. M. (2011). Mild traumatic brain injury and neural recovery: Rethinking the debate. *NeuroRehabilitation, 28*(3), 167-180.

Ryu, W. H., Feinstein, A., Colantonio, A., Streiner, D. L., & Dawson, D. R. (2009). Early identification and incidence of mild TBI in Ontario. *Canadian Journal of Neurological Sciences, 36*(4), 429-435.

Sabini, R. C., & Reddy, C. C. (2010). Concussion management and treatment considerations in the adolescent population. *Physician and Sportsmedicine, 38*(1), 139-146.

Sadowski-Cron, C., Schneider, J., Senn, P., Radanov, B. P., Ballinari, P., & Zimmermann, H. (2006). Patients with mild traumatic brain injury: Immediate and long-term outcome compared to intra-cranial injuries on CT scan. *Brain Injury, 20*(11), 1131-1137.

Satz, P., Zaucha, K., McCleary, C., & Light, R. (1997). Mild head injury in children and adolescents: A review of studies (1970–1995). *Psychological Bulletin, 122*(2), 107-131.

Schiller, P. H., & Chou, I. H. (1998). The effects of frontal eye field and dorsomedial frontal cortex lesions on visually guided eye movements. *Nature Neuroscience, 1*(3), 248-253.

Schmid, A., Rees, G., Frith, C., & Barnes, G. (2001). An fMRI study of anticipation and learning of smooth pursuit eye movements in humans. *Neuroreport, 12*(7), 1409-1414.

Schnebel, B., Gwin, J. T., Anderson, S., & Gatlin, R. (2007). In vivo study of head impacts in football: A comparison of National Collegiate Athletic Association Division I versus high school impacts. *Neurosurgery, 60*(3), 490-495.

Schoppik, D., Nagel, K. I., & Lisberger, S. G. (2008). Cortical Mechanisms of Smooth Eye Movements Revealed by Dynamic Covariations of Neural and Behavioral Responses. *Neuron, 58*(2), 248-260.

Sharpe, S., Kool, B., Shepherd, M., Dalziel, S., & Ameratunga, S. (2012). Mild traumatic brain injury: Improving quality of care in the paediatric emergency department setting. *Journal of Paediatrics and Child Health, 48*(2), 170-176.

Shcherbatko, A., Ono, F., Mandel, G., & Brehm, P. (1999). Voltage-dependent sodium channel function is regulated through membrane mechanics. *Biophysical Journal, 77*(4), 1945-1959.

Shumskaya, E., Andriessen, T. M. J. C., Norris, D. G., & Vos, P. E. (2012). Abnormal whole-brain functional networks in homogeneous acute mild traumatic brain injury. *Neurology, 79*(2), 175-182.

Sinn, P., & Engbert, R. (2011). Saccadic facilitation by modulation of microsaccades in natural backgrounds. *Attention, Perception, & Psychophysics, 73*(4), 1029-1033.

Sistrom, C. L., & McKay, N. L. (2005). Costs, charges, and revenues for hospital diagnostic imaging procedures: Differences by modality and hospital

characteristics. *Journal of the American College of Radiology, 2*(6), 511-519.
Slobounov, S., Sebastianelli, W., & Hallett, M. (2012). Residual brain dysfunction observed one year post-mild traumatic brain injury: Combined EEG and balance study. *Clinical Neurophysiology, 123*(9), 1755-1761.
Slobounov, S., Slobounov, E., Sebastianelli, W., Cao, C., & Newell, K. (2007). Differential rate of recovery in athletes after first and second concussion episodes. *Neurosurgery, 61*(2), 338-344.
Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science, 283*(5408), 1657-1661.
Smits, M., Houston, G. C., Dippel, D. W., Wielopolski, P. A., Vernooij, M. W., Koudstaal, P. J., . . . van der Lugt, A. (2011). Microstructural brain injury in post-concussion syndrome after minor head injury. *Neuroradiology, 53*(8), 553-563. doi: 10.1007/s00234-010-0774-6
Sommer, M. A., & Wurtz, R. H. (2004). What the Brain Stem Tells the Frontal Cortex. I. Oculomotor Signals Sent From Superior Colliculus to Frontal Eye Field Via Mediodorsal Thalamus. *Journal of Neurophysiology, 91*(3), 1381-1402.
Spering, M., Schütz, A. C., Braun, D. I., & Gegenfurtner, K. R. (2011). Keep your eyes on the ball: smooth pursuit eye movements enhance prediction of visual motion. *Journal of Neurophysiology, 105*(4), 1756-1767.
SR Research Ltd. (2008). *EyeLink® User Manual*. Mississauga, Ontario, Canada.
Stuart, B., Mandleco, B., Wilshaw, R., Beckstrand, R. L., & Heaston, S. (2012). Mild Traumatic Brain Injury: Are ED Providers Identifying Which Patients Are at Risk? *Journal of Emergency Nursing, 38*(5), 435-442.
Suh, M., Kolster, R., Sarkar, R., McCandliss, B., & Ghajar, J. (2006). Deficits in predictive smooth pursuit after mild traumatic brain injury. *Neuroscience Letters, 401*(1–2), 108-113.
Tabachnick, B. (2001). Logistic Regression *Using multivariate statistics* (pp. 517-575). Needham Heigts, MA: Allyn & Bacon.
Tanaka, M. (2005). Involvement of the Central Thalamus in the Control of Smooth Pursuit Eye Movements. *The Journal of Neuroscience, 25*(25), 5866-5876.
Tanaka, M. (2006). Inactivation of the central thalamus delays self-timed saccades. *Nature Neuroscience, 9*(1), 20-22.
Tanaka, M., & Lisberger, S. G. (2002). Enhancement of multiple components of pursuit eye movement by microstimulation in the arcuate frontal pursuit area in monkeys. *Journal of Neurophysiology, 87*(2), 802-818.
Tay, S. Y., Ang, B. T., Lau, X. Y., Meyyappan, A., & Collinson, S. L. (2010). Chronic impairment of prospective memory after mild traumatic brain injury. *Journal of Neurotrauma, 27*(1), 77-83.
Theeler, B. J., & Erickson, J. C. (2009). Mild head trauma and chronic headaches in returning us soldiers. *Headache, 49*(4), 529-534.

Theeler, B. J., Flynn, F. G., & Erickson, J. C. (2010). Headaches after concussion in US soldiers returning from Iraq or Afghanistan. *Headache, 50*(8), 1262-1272.

Thiessen, M. L., & Woolridge, D. P. (2006). Pediatric Minor Closed Head Injury. *Pediatric Clinics of North America, 53*(1), 1-26.

Thurman D, G. J. (1999). TRends in hospitalization associated with traumatic brain injury. *JAMA: The Journal of the American Medical Association, 282*(10), 954-957.

Tychsen, L., & Lisberger, S. G. (1986). Visual motion processing for the initiation of smooth-pursuit eye movements in humans. *Journal of Neurophysiology, 56*(4), 953-968.

Vagnozzi, R., Signoretti, S., Cristofori, L., Alessandrini, F., Floris, R., Isgró, E., . . . Lazzarino, G. (2010). Assessment of metabolic brain damage and recovery following mild traumatic brain injury: A multicentre, proton magnetic resonance spectroscopic study in concussed patients. *Brain, 133*(11), 3232-3242.

Van Horn, M. R., & Cullen, K. E. (2012). Coding of Microsaccades in Three-Dimensional Space by Premotor Saccadic Neurons. *The Journal of Neuroscience, 32*(6), 1974-1980.

Vanderploeg, R. D., Curtiss, G., Luis, C. A., & Salazar, A. M. (2007). Long-term morbidities following self-reported mild traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology, 29*(6), 585-598.

Villemure, R., Nolin, P., & Le Sage, N. (2011). Self-reported symptoms during post-mild traumatic brain injury in acute phase: Influence of interviewing method. *Brain Injury, 25*(1), 53-64.

Warner, R. (2013). *Applied Statistics: From Bivariate Through Multivariate Techniques* (second ed.). Thousands Oaks, California, USA: SAGE.

White, B. J., Stritzke, M., & Gegenfurtner, Karl R. (2008). Saccadic Facilitation in Natural Backgrounds. *Current Biology, 18*(2), 124-128.

Wilde, E. A., McCauley, S. R., Hunter, J. V., Bigler, E. D., Chu, Z., Wang, Z. J., . . . Levin, H. S. (2008). Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology, 70*(12), 948-955.

Wolf, J. A., Stys, P. K., Lusardi, T., Meaney, D., & Smith, D. H. (2001). Traumatic Axonal Injury Induces Calcium Influx Modulated by Tetrodotoxin-Sensitive Sodium Channels. *The Journal of Neuroscience, 21*(6), 1923-1930.

Woolfson, M. M., & Woolfson, M. S. (2007). Auto- and cross-correlation functions *Mathematics for physics* (pp. 541-570). New York: Oxford University Press.

Wyatt, H. J. (2010). The human pupil and the use of video-based eyetrackers. *Vision Research, 50*(19), 1982-1988.

Yamamoto, J., Ikeda, A., Satow, T., Matsuhashi, M., Baba, K., Yamane, F., . . . Shibasaki, H. (2004). Human eye fields in the frontal lobe as studied by epicortical recording of movement-related cortical potentials. *Brain, 127*(Pt 4), 873-887.

Yang, Z., Yeo, R. A., Pena, A., Ling, J. M., Klimaj, S., Campbell, R., . . . Mayer, A. R. (2012). An fMRI study of auditory orienting and inhibition of return in pediatric mild traumatic brain injury. *Journal of Neurotrauma, 29*(12), 2124-2136.

Yeates, K. O., & Taylor, H. G. (2005). Neurobehavioural outcomes of mild head injury in children and adolescents. *Pediatric Rehabilitation, 8*(1), 5-16.

Yeo, R. A., Gasparovic, C., Merideth, F., Ruhl, D., Doezema, D., & Mayer, A. R. (2011). A longitudinal proton magnetic resonance spectroscopy study of mild traumatic brain injury. *Journal of Neurotrauma, 28*(1), 1-11.

Yoshino, A., Hovda, D., Kawamata, T., Katayama, Y., & Becker, D. (1991). Dynamic changes in local cerebral glucose utilization following cerebral conclusion in rats: evidence of a hyper- and subsequent hypometabolic state. *Brain Research, 561*(1), 106-119.

Zafonte, R. (2011). Diagnosis and Management of Sports-Related Concussion. *JAMA: The Journal of the American Medical Association, 306*(1), 79-86.

Zaksas, D., & Pasternak, T. (2006). Directional Signals in the Prefrontal Cortex and in Area MT during a Working Memory for Visual Motion Task. *The Journal of Neuroscience, 26*(45), 11726-11742.

Zetterberg, H., Smith, D. H., & Blennow, K. (2013). Biomarkers of mild traumatic brain injury in cerebrospinal fluid and blood. *Nature Reviews Neurology, 9*(4), 201-210.

Zhang, L., Yang, K. H., & King, A. I. (2004). A Proposed Injury Threshold for Mild Traumatic Brain Injury. *Journal of Biomechanical Engineering, 126*(2), 226-236.

Zohar, O., Schreiber, S., Getslev, V., Schwartz, J. P., Mullins, P. G., & Pick, C. G. (2003). Closed-head minimal traumatic brain injury produces long-term cognitive deficits in mice. *Neuroscience, 118*(4), 949-955.