DEPRESSIVE SYMPTOMS AND EXECUTIVE FUNCTION IN ADOLESCENTS AFTER CONCUSSION

THE STORM YOU CANNOT SEE: EXPLORING THE BIOLOGICAL AND CLINICAL EFFECT OF DEPRESSIVE SYMPTOMS ON EXECUTIVE FUNCTION IN ADOLESCENTS AFTER CONCUSSION

By

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Thesis Abstract

Concussions impact the cognitive abilities and emotional wellbeing of adolescents. More specifically, adolescents exhibit signs of executive dysfunction and depressive symptoms following concussion. Evidence suggests a link between cognitive performance and depressive symptoms in concussed populations; however, concussion research has focused mostly on cognitive deficits and emotional dysregulation in singularity, rather than as an integrated system. Therefore, the purpose of this thesis is to explore the clinical and biological relationship between depressive symptoms and executive dysfunction following mild traumatic brain injury (mTBI) or concussion in pediatric populations.

Chapter 1 provides an overview of the literature surrounding children and youth with concussive injury as it pertains to executive dysfunction and depressive symptoms. Chapter 2 describes the clinical nature of the relationship between depressive symptoms and executive dysfunction. The results demonstrate that individuals with elevated depressive symptoms had comparable performance to individuals with normal levels of depressive symptoms on executive function scores. This included their performance on an inhibitory control task in which emotional distractors were presented. Regardless of levels of depressive symptoms, adolescents with concussive injury displayed impaired executive functioning compared to normative data, which emphasizes the importance of evaluating executive function following concussion.

Chapter 3 involves the use of functional brain imaging to explore the physiological differences between adolescents with average and elevated depressive symptoms on emotion-mediated inhibitory control processes. The group as whole did not display activity in the frontostriatal regions that are associated with inhibitory control, which suggests a potential impairment in this network. Adolescents with elevated depressive symptoms displayed fewer

areas of activity compared to adolescents with average levels of depressive symptoms. As a number of individuals (particularly those with elevated depressive symptoms) were injured in the occipital region of the skull, the coup-contrecoup impact may have resulted in frontal lobe injury.

Faces were used to evoke emotional processing throughout the inhibitory control task. The results revealed that adolescents with elevated depressive symptoms were more likely to engage in brain regions subserving evaluative processing of social interactions. This might suggest that depressive symptoms display differences in physiology when emotional stimuli are present. These findings provide insight into the role the environment plays in contributing to the cognitive demands placed on adolescents recovering from concussion.

Chapter 4 reviews the key messages derived from these results and describes their clinical relevance. This exploration may lead to a more holistic understanding of concussion and a better approach to injury management, particularly for adolescents who express higher levels of depressive symptoms following concussion.

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Dedicated to my siblings:
Larissa, Stephanie, Mathias & Elizabeth,
With whom I first learned the art of defense

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CHAPTER 1:

INTRODUCTION

Overview

There is growing concern for children and youth experiencing concussion as the negative consequences of concussive injury become more apparent and as the incidence for concussion increases (Lincoln et al., 2011). Concussions, also known as mild traumatic brain injuries (mTBIs), are very common in youth. For the purposes of this thesis, these injuries will be referred to as concussions. Concussions constitute 87-90% of reported traumatic brain injuries in youth (McKinlay et al., 2008; Yue et al., 2016). Research has shown that between the years 2003 to 2010, the rate of pediatric concussions treated in Ontario emergency rooms and physicians' offices per 100 000 increased from 340.5 to 601.3 (Macpherson, Fridman, Scolnik, Corallo, & Guttmann, 2014). However, reports show that 30-50% of concussions in adolescents are unreported and are, therefore, untreated (McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004; Meehan, et al., 2013). This suggests that the incidence of concussions in youth are higher than those reported.

Cognitive difficulties and emotional problems are among the symptom sequelae affecting adolescents with concussion (Eisenberg, Andrea, Meehan, & Mannix, 2013; McCrory et al., 2013). Thus far, concussion studies have focused mostly on cognitive deficits and emotional dysregulation in singularity, rather than as an integrated system. As research suggests a complex biological relationship between cognition and emotion (Gray, 2004; Padmala & Pessoa, 2010; Schmeichel & Tang, 2015), exploring the relationship between cognitive and emotional symptoms of concussion may hold importance for recovery. Currently, it is unclear if these two

symptoms emerge simultaneously as a result of damage to shared functional brain regions, or if symptoms arise through separate mechanisms (Chen, Johnston, Petrides, & Ptito, 2008; Mainwaring, Hutchison, Bisschop, Comper, & Richards, 2010). This exploration may lead to a more holistic understanding of concussion and a better approach to injury management. Therefore, the following dissertation aims to explore the clinical and biological relationship between cognitive and emotional symptoms in adolescents with concussive injury with a particular focus on executive function and depression.

This exploration of executive function and depression following concussion is presented in two sections: Chapter 2 investigates depressive symptoms as a modulator of cognitive processes after concussion using the Go / No-Go test as a measure of inhibitory cognitive processes and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) as a measure of executive function. This focuses on the behavioural or clinical consequences of concussion. Chapter 3 further examines how depressive symptoms affects the engagement of functional brain regions during the Go / No-Go test, addressing the biological underpinnings of executive function and depressive symptoms.

The current chapter provides a review of the evidence and theory related to the relationship between cognition and emotional dysfunction and how this may be impacted by concussion. In addition, this chapter will explore the neurobiological and neurochemical processes in the brain following a concussion and the literature surrounding the emergence of depressive symptoms and cognitive dysfunction.

Concussion and Youth

There is a growing body of evidence focusing on concussion in children and youth. Youth have been shown to have symptoms and post-concussive syndrome similar to adults yet have slower recovery (Field, Collins, Lovell, & Maroon, 2003; Nelson et al., 2016; Zemek et al., 2016; Zuckerman et al., 2012). In studying the pediatric population, researchers have found that prevalence, cause, and recovery are affected by factors such as age and gender (Willer, Dumas, Hutson, & Leddy, 2004). Studies found that males were more likely to be diagnosed with concussion (Macpherson, Fridman, Scolnik, Corallo, & Guttmann, 2014; Marar, McIlvain, Fields, & Comstock, 2012). However, studies on sport-related concussions report that females were more likely to be injured during sports, especially in sports that had the same rules between both genders (Lincoln et al., 2011; Marar et al., 2012). Females are also more likely to report post-concussive symptoms and have prolonged recovery times (Eisenberg et al., 2013; Zemek et al., 2016). Reporting biases have not yet been ruled out as a possible reason for this discrepancy (Marar et al., 2012).

There are number of common causes of injury in youth. Falls constitute the majority (34-50%) of concussion cases in youth seen in the emergency department (Barlow et al., 2010; Macpherson et al., 2014; Zemek et al., 2016), a rate which increases to 75% when examining falls during sport-related activities (Willer et al., 2004). Moreover, sport-related concussions overall account for 25-67% of concussions in youth (Bakhos, Lockhart, Myers, & Linakis, 2010; Barlow et al., 2010; Zemek et al., 2016). A prospective longitudinal study found that the incidence rate of sport-related concussions was 0.24 per 1000 in 2008, but had been increasing since 1997 (Lincoln et al., 2011). Cause of injury also shows patterns related to age. Younger children are more likely to sustain a concussion from falls (Barlow et al., 2010; Willer et al.,

2004); older adolescents during full-contact sport activities (Bakhos et al., 2010; Willer et al., 2004). Motor vehicle accidents are also prevalent among youth (Babcock et al., 2013; Macpherson et al., 2014).

The following section discusses the diagnosis and recovery of concussion and highlights the neurobiological changes that occur in the adolescent brain. This thesis categorizes adolescents and pre-adolescents as individuals between 10 and 18 years of age.

Concussion Diagnosis and Identification

According to the 2013 Concussion Consensus Statement, concussion is the result of a direct or indirect blunt blow to the head or other body part that delivers a force to the brain that may induce neuropathological changes in the brain (McCrory et al, 2013). Individuals with concussive injury often present symptoms across four domains: somatic, cognitive, emotional, and sleep-related (Choe & Giza, 2015; Eisenberg, Meehan, & Mannix, 2014; McCrory et al., 2013).

Somatic symptoms:

- nausea
- headaches
- poor coordination
- sensitivity to light and noise

Cognitive symptoms:

- difficulty concentrating
- slower reaction times
- poor memory or amnesia

- feeling mentally foggy

Emotional symptoms:

- increased emotionality
- irritability
- anxiety
- depression

Sleep-related symptoms:

- difficulty falling asleep
- waking up in throughout the night
- restlessness
- sleeping too much or too little

Diagnostic procedures for concussion focus primarily on functional abnormalities as structural abnormalities are not detectable in standard clinical brain scans (McCrory et al., 2013). As such, defining objective standards for concussion diagnosis are difficult (Choe & Giza, 2015) and reliant on clinical assessment and symptom-reporting (Alla, Sullivan, & McCrory, 2012; Choe & Giza, 2015; Iverson et al., 2015; McCrory et al., 2013).

Although these neurological dysfunctions are described to be transient and self-resolving within 7 to 10 days by the International Consensus Statement (McCrory et al., 2013), determining recovery is yet another clinical challenge in concussion research (Alla et al., 2012; Iverson et al., 2015). Indeed, the length of recovery varies from patient to patient as a number of factors contribute to the complexity of recovery, such as number of previous concussions, history of psychiatric illness, and severity of concussion (McCrory et al., 2013).

Moreover, youth are more likely to exhibit longer lasting symptoms compared to adults (McCrory et al., 2013; Zemek et al., 2016). Approximately 25-30% of pediatric concussion cases show persisting symptoms 4 weeks after injury (Barlow et al., 2010; Eisenberg et al., 2014; Zemek et al., 2016). Where adults demonstrate normal cognitive performance despite abnormal brain activity (Chen et al., 2008), youth exhibit abnormalities in both cognitive performance and brain patterns (Keightley et al., 2014). However, asymptomatic adults and adolescents have been shown to have persistent abnormal brain physiology (Breedlove et al., 2012). It is suggested that the absence of somatic symptoms forms the basis for perceived recovery in adolescents (Sandel, Lovell, Kegel, Collins, & Kontos, 2013).

In addition to contrasting adults and youth, studies have shown recovery differences in between children and adolescents. Anderson et al. (2005) found that concussion had a higher impact on cognitive performance in younger children (aged 3-7 years) than older, pre-adolescent children (aged 8-12 years). Yet Baillargeon et al. (2012) found that adolescents, (aged 13-16 years) scored more poorly than both children and adults on neuropsychological and electrophysiological tests (Baillargeon, Lassonde, Leclerc, & Ellemberg, 2012). Similarly, Eisenberg and colleges reported that adolescents over the age of 13 years had longer recovery times compared to younger children (Eisenberg et al., 2013). Despite these inconsistencies, these studies collectively suggest the vulnerability of youth to the effects of concussion.

The Neurobiology of Concussion

The impact of concussions on youth can be understood through the biological changes in the brain that are undetectable by routine medical imaging scans. Animal studies have shown that when a concussion occurs, the impact causes the brain to move within the skull and to hit the

walls of the skull, leading to surface contusions and axonal shearing. This stretching and shearing of the neuronal axons disassembles the cellular membrane of the axon, triggering a cascade of neurochemical changes (see Giza et al., 2001 for review).

The efflux of potassium and influx of sodium across the membrane offset the resting membrane potential and drive depolarization (neuronal firing). Nonspecific releases of excitatory neurotransmitter glutamate ensue (Katayama et al, 1990). This sudden increase in glutamate and ionic flux drives metabolic processes in the brain to restore homeostasis. This requires energy; thus glucose metabolism (through glycolysis) is increased. Resultantly, the brain is in a global hyperactive and hypermetabolic state. However, hyperglycolysis causes an influx of calcium, leading to the impairment of oxidative phosphorylation in the mitochondria that is needed for the production of energy. A simultaneous reduction in cerebral blood flow means that the demand for metabolic resources is not met. This imbalance, or mismatch, between the demand for energy and the supply of resources renders the brain in a state of vulnerability (*Figure 1*; Giza & Hovda, 2001). Along with the disassembly of the cell membrane and swelling of the axons, these metabolic changes drive a cascade of neurological dysfunctions (Farkas, 2006; Giza & Hovda, 2001).

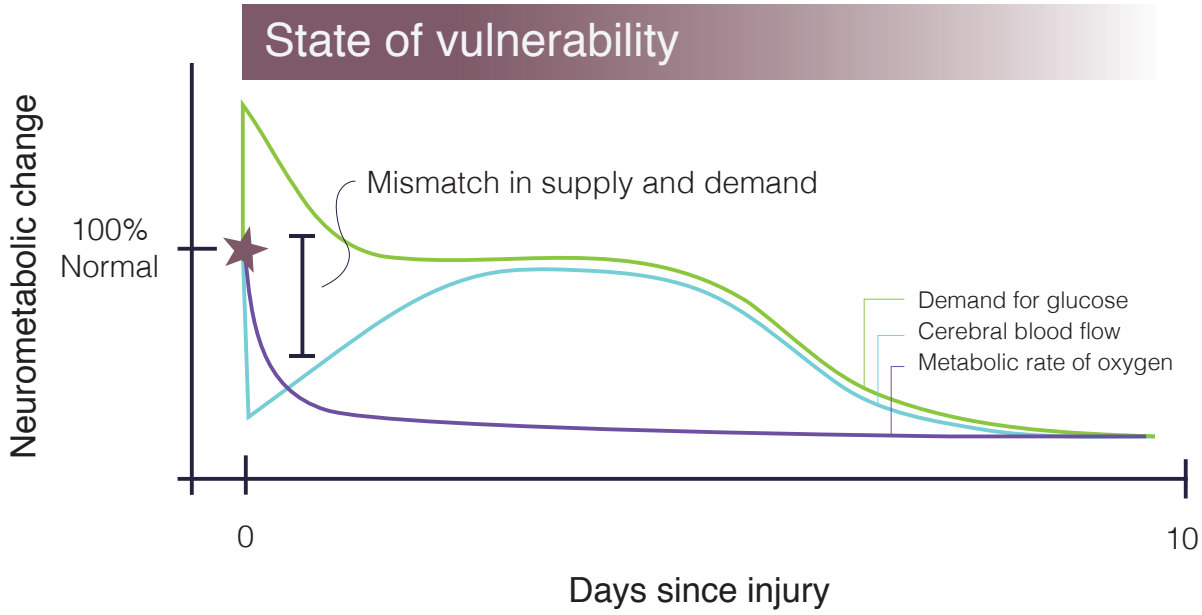

Figure 1. A period of vulnerability follows a concussion as there is a mismatch in the demand for energy (glucose) and the supply of oxygen and cerebral blood flow. Adapted from Giza, C., & Hovda, D. (2001). The neurometabolic cascade of concussion. Journal of Athletic Training, 36(3), 228-235.

Decreased metabolic levels of glutamate and N-acetylaspartate (a marker for neuronal health) are correlated with reports of post-concussive symptoms (Henry, Tremblay, Boulanger, Ellemberg, & Lassonde, 2010). This might explain why children report new or worsening symptoms days after injury (Eisenberg et al., 2014; Hartings et al., 2009). Moreover, the vulnerable state during the acute phase of concussion makes the brain susceptible to repeat injury. Further injury can cause irreversible damage to the neurons, and even neuronal death (Farkas, 2006; Giza & Hovda, 2001).

While this research is largely based on animal models and the pathophysiology of concussion is not fully understood, these alterations to the neurochemical stability of the brain are shown in brain imaging studies in humans. One study used a method to quantify cerebral

blood flow in adolescents and found that cerebral blood flow was indeed reduced after concussion although structural and metabolic changes were not seen (Maugans, Farley, Altaye, Leach, & Cecil, 2012). Altered levels in cerebral blood flow are detectable in imaging studies, but also hinder the ability to study function. Functional magnetic resonance imaging (fMRI) studies use the blood-oxygen level dependent (BOLD) effect to acquire information about brain activity. With alterations in cerebral blood flow and neurochemical releases, adolescents with concussion show abnormal connectivity in resting state networks – i.e. when the brain is not working on any particular task (Borich, Babul, Yuan, Boyd, & Virji-Babul, 2014; K. Zhang et al., 2012; Zhou et al., 2012). Other studies have demonstrated these physiological changes during cognitive tasks as well (Chen et al., 2008; Dettwiler et al., 2014; Keightley et al., 2014). This suggests that fMRI findings are in accordance with metabolic changes and that fMRI can be used to study the functional consequences of these changes.

Age influences neuronal vulnerability to these biological changes. As developmental age is a reflection of cortical maturity, physical trauma can be more disruptive during childhood and adolescence because the brain is still developing (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005; Anderson et al., 2011). Structural imaging has shown that axonal maturation occurs throughout childhood and adolescence with developmental changes occurring in the prefrontal cortex, internal capsule, basal ganglia, and thalamus (Barnea-Goraly, 2005) Similarly, the process of myelination (the formation of a fatty sheath around the axon of a neuron for improved signal transduction) continues into adulthood (Hayakawa & Matsuda, 1990). The unmyelinated axons are, therefore, vulnerable to trauma (Reeves, Phillips, & Povlishock, 2005). Therefore, children and adolescents are more likely to exhibit prolonged symptoms compared to

adults (McCrory et al., 2013). Taken together, the effects of concussion and the vulnerability of the adolescent brain can lead to serious consequences.

Concussion and Cognition

Poor concentration, slowed reaction times, difficulty thinking clearly, and loss of memory are hallmark signs of concussion. They are among a number of cognitive symptoms that emerge immediately following concussion and take the longest to dissipate in youth (Eisenberg et al., 2014). These cognitive symptoms may be reflective of the physical trauma to the frontal lobe connectivity and white and grey matter density following concussion (Giza, Griesbach, & Hovda, 2005). Incorporating neurocognitive testing in concussion assessment is beneficial in determining the scope of the injury. Common neuropsychological tests show that children and adolescents with concussion perform significantly worse on a number cognitive domains including working memory, verbal fluency, and delayed recall compared to healthy controls (Keightley et al., 2014); however, inconsistent findings challenge the ability of these clinical tests to detect changes in neurocognitive function following concussion (Kontos, Sufrinko, Womble, & Kegel, 2016; Nelson et al., 2016).

Computerized neurocognitive tests have been developed specifically to detect cognitive deficits in concussion populations. Although these tests alone are not diagnostic, the brevity of these tests and computerize scoring tools are advantageous in clinical and research settings (Kontos et al., 2016) and assist in baseline testing of athletes (Reynolds, Fazio, Sandel, Schatz, & Henry, 2016; Zuckerman et al., 2012). ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing) is a widely used neurocognitive test for concussion (Lovell, Collins, Podell, Powell, & Maroon, 2000). Using a series of computerized modules, it assesses verbal memory,

visual memory, visual motor speed, reaction time, and impulse control. Processing speed, reaction time, and accuracy rates are also incorporated in computerized neurocognitive tests to assess executive function, which has been shown to be impaired following concussion (Howell, Osternig, Van Donkelaar, Mayr, & Chou, 2013; Mangeot, Armstrong, Colvin, Yeates, & Taylor, 2002).

Executive Function & Inhibitory Control in Concussion

Cognitive tasks involving executive function has been an area of concern for adolescents with concussive injury (Howell et al., 2013; Karr, Garcia-Barrera, & Areshenkoff, 2014; Mangeot et al., 2002). Executive functions are tasks of the frontal lobe characterized by three cognitive processes – cognitive flexibility, working memory, and inhibition – that collectively serve to control and self-regulate behaviour (Miyake et al., 2000). Executive functions allow physical and mental demands to be met in the attainment of new skills in sports, school, and social interactions (Diamond, 2013). It has also been implicated in the regulation of emotions and psychiatric disorders (Davidovich et al., 2016). Cortical thickening and maturation of the fronto-striatal networks through childhood and adolescence parallels the development of executive functioning (Barnea-Goraly, 2005; Casey et al., 1997; Durston et al., 2002). Thus, older adolescents typically outperform younger children on tasks of executive function (Durston et al., 2002).

Although the three executive functions are interdependent processes, this dissertation focuses on inhibition, which describes both behavioural inhibition and cognitive inhibition. Behavioural inhibition involves withholding a prepotent behaviour (Miyake et al., 2000). Clinically, this is understood as the ability to resist an automated response or control impulses.

Cognitive inhibition refers to the ability to ignore internal or external distractors by suppressing interfering thoughts or selectively attending to stimuli in the environment (Diamond, 2013).

Measuring Inhibitory Control Processes

Inhibitory control tasks, such as the Stroop task, are often used in clinical populations as a measure of executive dysfunction. Results regarding deficits in inhibitory control are mixed (Nelson et al., 2016; Saluja, Chen, Gagnon, Keightley, & Ptito, 2015; Sinopoli et al., 2014), which suggests that the Stroop task may not be sensitive to changes due to concussion.

Another such task of inhibitory control is the Go/No-Go task (Durston et al., 2002). The Go/No-Go has been implemented in brain imaging research as it has been developed to detect changes in the physiological response of the brain to behavioural inhibition that cannot be captured by computerized neurocognitive tests. It requires the participant to respond (by pressing a button) when a target stimulus appears on the screen (Go trial), and withhold that response when a non-target stimulus appear on the screen (No-Go trial). The button-pressing response is habituated during Go blocks in which every trial presents the target stimulus and requires a response. No-Go blocks intermingle Go trials (target stimulus presented) and No-Go trials (non-target stimulus presented), thereby requiring inhibitory control to avoid errors. Response times are measured during Go trials on both Go blocks and No-Go blocks. The difference between the response times and accuracy rates during the Go blocks and No-Go blocks determines performance on this task.

It has been adapted to incorporate cognitive inhibitory control processes with the use of emotionally-charged stimuli. Emotionally-charged stimuli (i.e., an angry face) are implicitly and automatically registered in the brain and elicit a visceral response. In the Emotional Go/No-Go

task, emotional stimuli are irrelevant to the task goal (which is to respond to the target object) and require disengaging attention from the emotional stimuli or suppressing an emotional response to the stimuli. Areas of the brain associated with behavioural inhibition include the dorsal lateral prefrontal cortex (DLPFC), ventral prefrontal cortex, anterior cingulate cortex, and the orbitofrontal cortex (Chevrier, Noseworthy, & Schachar, 2007; Elliott, Rubinsztein, Sahakian, & Dolan, 2000; Kerestes et al., 2012). Individuals with anxiety and depression perform more poorly in comparison to healthy controls when emotional stimuli are present in the Go/No-Go task due to the selective bias towards negative stimuli (Kerestes et al., 2012; Tavitian et al., 2014).

Emotional and Inhibitory Processing in Concussion

Deficits in inhibitory control are often noted after concussions. Moore et al. (2016) found that preadolescents (ages 8-10 years) with concussion were more likely to incorrectly respond to non-target stimuli (i.e. errors of commission) than healthy controls. Those who were injured at a younger age were more likely to make these errors (Moore et al., 2016). A study on adults found differences in emotional and inhibitory processing in concussion populations. Using an adapted version of the Go/No-Go, participants were asked to respond to the colour on the screen, irrespective of the object on the screen (a spider for the threat condition; a flower for the neutral condition). Researchers conclude that adults with concussion had increased attention towards negative stimuli (Mäki-Marttunen et al., 2014).

Tlusto and colleges conducted a pediatric study to investigate the long-term effects of traumatic brain injury (TBI) on facial processing in an inhibitory control task. The sample included 10 TBI participants of varying severity – 7 of which had mild TBI, but all were

classified as having "complicated" injuries as a result of abnormal brain imaging. Compared to healthy controls, the TBI group showed trends for slightly longer reaction times, but accuracy rates and reaction times were not significantly different between the groups. Imaging results indicated that TBI participants displayed less activity overall compared to controls during No-Go blocks particularly in the medial prefrontal and parietal regions (Tlusto, Peter Chiu, Walz, & Wade, 2015). This study did not account for the differential effects of depressive symptoms on socio-emotional processing. Currently, no research has been done to examine how emotional stimuli modulate inhibitory processes in adolescents with concussion who are experiencing depressive symptoms.

Concussion and Depression

In recent years, the association between mental illness and a history of a brain-related injury has garnered concern as clinical studies show that patients are more likely to display new or worsening psychiatric symptoms after head injury (Ellis et al., 2015; Kreutzer, Seel, Gourley, & Jeffrey S. Kreutzer, 2001; E. L. Moore, Terryberry-Spohr, & Hope, 2006). Symptoms such as irritability, sadness, anxiety, and depression are all common symptoms of concussion (Choe & Giza, 2015; McCrory et al., 2013). Although anxiety is often comorbid with depression (Schoenhuber & Gentilini, 1988), this dissertation focuses on depression.

Patients diagnosed with clinical depression (or major depressive disorder, MDD) tend to display poorer psychological, psychosocial and cognitive functioning. Adolescents with clinical depression are less likely to obtain higher education, secure long-term careers, and maintain healthy relationships as adults (McLeod, Horwood, & Fergusson, 2016). Cognitive performance of depressed adolescents has been found to be worse than healthy controls on a number of

cognitive domains including executive function and inhibitory control (Lim et al., 2013; Nilsson et al., 2016; Tavitian et al., 2014).

Similarities in neurocognitive and psychosocial outcomes between post-concussive depression and clinical depression emphasize the importance in understanding these depressive symptoms after concussion (Rapoport, Mccullagh, Streiner, & Feinstein, 2003). Currently, the International Consensus Statement considers pre-existing psychiatric conditions such as depression to be modifying factors of recovery (McCrory et al., 2013). Research indicates that patients displaying depressive symptoms following concussion tend to report more symptoms and have longer recovery times (Kumar et al., 2014, Stazyk et al., in press). These poor functional outcomes are concerning and wanting of a better understanding.

A disproportionate number of patients with TBI are diagnosed with depression or display depressive symptoms. Kreutzer, Seel, and Gourley (2001) found that 42% of 722 adults with TBI had a depression diagnosis. Similarly, Jorge and colleges found that 33% of TBI patients in their sample were diagnosed with depression by psychiatrists, which is a stark contrast to the 8% of trauma control patients with the same diagnosis. Although this sample consisted of mild, moderate, and severe TBI, 46.7% of the TBI patients with depression in this sample had mTBI (Jorge et al., 2004). Like adults, TBI youth exhibit elevated prevalence of depression in comparison to healthy populations. In the general population of children and adolescents, the incidence of depression falls between 5-11% (Haarasilta, Marttunen, Kaprio, & Aro, 2001; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; Richardson, Russo, Lozano, McCauley, & Katon, 2010). In populations with concussion, that rate increases to approximately 22% (Stazyk et al., in press).

Concussion increases risk for depression both immediately after injury as well as later in life. A retrospective study found that youth (ages 12 to 17) who have had a concussion are 3.3-times more likely to develop depression during their lifetime than those without a history of head injury (Chrisman & Richardson, 2014). Older adolescents (ages 14 to 17) are 1.5-times more likely than their younger adolescent counterparts, which suggests that developmental stage at the time of injury might influence the presentation of post-concussive symptoms (Chrisman & Richardson, 2014). In retired football players, a nine-year risk of depression followed players with a history of concussion (Kerr, Marshall, Harding, & Guskiewicz, 2012). A dose-response linear relationship between the number of self-reported concussion and depression diagnoses shows that the risk of depression increases with increasing numbers of concussion (Kerr et al., 2012; Pryor, Larson, & Debeliso, 2016). Other risk factors for depression after concussion (i.e. female sex, prior history of depression) further increase this risk (Chrisman & Richardson, 2014, Stacyk et al., in press). Adolescents with subsyndromal depressive symptoms are also at higher risk of developing MDD in adulthood (Fergusson, Horwood, Ridder, & Beautrais, 2005; McLeod et al., 2016), but further investigation is required to determine if subsyndromal depressive symptoms following concussion increases risk of clinical depression.

Identifying Depression

According to the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013), subjective or observational reports of a patient's depressed mood or loss of interest in enjoyable activities as well as the inability to carry out daily functions for longer than 2 weeks constitute a clinical depression diagnosis (Uher, Payne, Pavlova, & Perlis, 2014). The process of diagnosing clinical depression requires a careful and

informed assessment because depressive-like symptoms are common in the gamut of everyday emotions and are present in non-depressed individuals. In fact, a cross-national study found that 52.3% of individuals from high-income countries report at least one emotional symptom related to depression, but only 14.6% met the criteria for clinical depression (Bromet et al., 2011). When identifying clinical depression in children and adolescents, depressive symptoms are often mistaken for normative behaviours of adolescents or are co-morbid with other psychiatric conditions (Rao & Chen, 2009). Richardson et al. (2010) found that only 22% of youth with clinical depression between 11-17 years have been recognized. This low rate of detection could be further compromised by post-concussive symptoms, which suggests the importance of measuring depression in concussion patients with concussion.

Although an assessment by a psychiatrist is the most effective method of diagnosing depression, the use of self-report questionnaires to identify depressive symptoms are common in clinical settings (Williams, Cordes, Ramirez, & Pignone, 2002). Opting for self-report questionnaires is desirable for brevity and symptom monitoring purposes (Williams et al., 2002) as well as quick identification of those with subsyndromal depressive symptoms (characterized by minor depression that is not severe enough for a clinical diagnosis) who display similar psychosocial and functional impairments (Fergusson et al., 2005; McLeod et al., 2016). Researchers also use clinical screening tools as a method of identifying patients with elevated levels of depression in clinical populations like concussion populations, which best mimics clinical practices (Williams et al., 2002). The Children's Depression Inventory-2 (Kovacs, 2011) is a clinical screening tool comprised of 28 questions to assess symptoms related to depression as well as the severity of these symptoms. Although it is not diagnostic, it is useful in surveying the

extent of emotional distress in a large sample and can capture individuals in the subsyndromal level, as indicated by a *high average* classification on the screening tool.

The overlapping symptoms between concussion and depression (such as irritability, sadness, emotionality), however, can mask the depressive symptoms in patients with concussion and make depressive symptoms difficult to detect (Broshek, De Marco, & Freeman, 2015). This is possibly due to the lack of symptom reporting (Chrisman, Quitiquit, & Rivara, 2013), or the misattribution of psychological symptoms to the injury recovery process (Broshek et al., 2015; Mittenberg, DiGiulio, Perrin, & Bass, 1992). Moreover, studies report that depressive symptoms can emerge after the initial assessment of concussion (Eisenberg et al., 2014; Jorge et al., 2004). In one study, only half of the TBI patients with depression were diagnosed with depression immediately following injury. The other half developed depression 3 months after injury (Jorge et al., 2004). Therefore, monitoring depressive symptoms throughout concussion recovery can aid in the detection of depressive symptoms.

The Biology of Depression

Researchers turn to MRI to capture the biological nature of depression in order to understand these functional outcomes. Overall, the functional neural substrates of depressed adolescents differ from healthy controls. Particular abnormalities exist in emotion-regulating networks during resting state analyses between the prefrontal-limbic-thalamic regions (Connolly et al., 2013; Wang, Hermens, Hickie, & Lagopoulos, 2012). Cognitive tasks also render abnormal neural activation for depressed patients. In adults, depression is associated with abnormal activation levels in the dorsal lateral prefrontal cortex (DLPFC) during inhibitory control tasks that involve emotional appraisal (Arnsten & Rubia, 2012; Grimm et al., 2008;

Kerestes et al., 2012). Adolescents yield similar results (Arnsten & Rubia, 2012; Colich, Foland-Ross, Eggleston, Singh, & Gotlib, 2016).

To date, only one study has investigated the functional neural correlates in concussion patients with depressive symptoms. Chen et al. (2008) looked at concussion patients of differing depression severity and compared them to non-depressed concussion patients as well as non-injury controls. The depressed concussion patients displayed reduced activation in the insular cortex, dorsal anterior cingulate cortex, and DLPFC during a working memory task. Chen et al. posit that depressive symptoms that emerge after concussion have neurobiological underpinnings. Youth were not examined in this study. Kontos and colleges noted that adolescents with depressive symptoms after concussion were more likely to perform poorly on executive function (Kontos, Covassin, Elbin, & Parker, 2012), which supports a link between post-concussive depressive symptoms and executive dysfunction.

Theoretical Framework

As the outcomes of brain injury are complex, the following theories offer insight as well as guidance in research hypotheses and methodology. Individually, they help to explain aspects of the biological, psychological and cognitive nature of concussion, but together they illustrate the interrelatedness between cognitive function and depressive symptoms following concussion in adolescents.

Cognitive Reserve Theory

There is a widespread variability in the functional consequences following brain injury. *Cognitive reserve theory* explains why some individuals exhibit certain symptoms while other do

not. It proposes a dynamic resiliency to brain injury. It hypothesizes that individualistic differences in symptomology and severity arise following brain injury because of differences in the ability to recruit alternative cognitive networks. This theory speculates that cognitive efficiency enables the brain to cope with increased task difficulty and compensate for brain-damaged areas. This concept of compensation applies to the functional abilities of the brain. In other words, it describes ability to flexibly engage other brain networks or cognitive strategies to support physiological deficits.

When neurological damage occurs, functional deficits are expected to emerge. However, patients with concussion often demonstrate comparable performance on cognitive tests in comparison to healthy controls, but engage brain networks not normally used during that particular task (Chen et al., 2008; Keightley, Chen, & Ptito, 2012). According to cognitive reserve theory, this demonstrates the engagement of compensatory mechanisms to maintain performance in the event of brain injury. Youth often exhibit poor behavioural performance and abnormal brain activation (Keightley et al., 2012; Keightley et al., 2014). This supports the notion of cognitive efficiency. Children are less efficient at the engagement of alternative cognitive networks that would benefit performance outcomes.

The Integration of Emotion and Cognition

Emotion and cognition have important effects on behaviour. Researchers have continued to investigate the relationship between emotion and cognition so as to model its impact on behaviour. Emotional information (i.e. facial expressions) is processed automatically; an adaptive feature that allows for rapid processing of important stimuli in the environment (i.e. threat-related cues). The *arousal-biased theory* (Mather & Sutherland, 2011) proposes a

framework in which cognition and emotion compete to direct attention. It builds upon the concepts from the biased competition theory, which posits that stimuli in the environment compete for neural representation in the visual field. Top-down processing directs attention towards goal-related stimuli (Beck & Kastner, 2010). The arousal-biased theory accommodates the effect of cognition on emotional processing as well. It postulates that arousal maintains goals by amplifying perception of goal-related stimuli, and suppresses perception of irrelevant stimuli. Although more recent research has continued to develop the concepts related to this theory, it provides insight for current concussion research.

Prior beliefs about the underlying bottom-up influence emotion has over behaviour has seen increasingly more contention (Gray, 2004; Pourtois, Schettino, & Vuilleumier, 2013). However, a unified theory supporting the integrated approach of emotion and cognition is still lacking.

Studies have demonstrated that emotion can indeed be subject to top-down influences, or goal-directed behaviour (see review: Pessoa, 2009). New models posit that emotion and cognition are different functions that stem from overlapping neural networks (Pourtois et al., 2013). Thus, brain trauma can simultaneously alter the functionality of both.

As the association between depressive symptoms and cognitive dysfunction following concussion has been noted in both adult and pediatric populations (Chen et al., 2008; Kontos et al., 2012), it is reasonable to hypothesize a theoretical interaction between the two concussive symptoms.

Research Question and Objectives

The overall purpose of this dissertation is to explore the clinical and biological relationship between depressive symptoms and executive dysfunction following mild traumatic brain injury (mTBI) or concussion in pediatric populations. To achieve this purpose, the following questions were explored:

1. How does performance on executive function compare between adolescents with elevated depressive symptoms and adolescents without depressive symptoms following concussion?
2. What are the functional neural pathways involved in the inhibitory control processing of emotional information in adolescents with depressive symptoms after concussion?

It is hypothesized that depressive symptoms and executive dysfunction resulting from concussion are clinically and physiologically related. More specifically, adolescents with elevated levels of depression are hypothesized to exhibit greater executive dysfunction and display more activity along the fronto-striatal circuitry of the brain.

To address the lack of understanding for the nature of depression in the adolescent brain that has sustained concussion, the following objectives will also be addressed in this thesis:

1. To explore how concussion populations with elevated depressive symptoms differ clinically (symptoms) and biologically (fMRI) from those without depressive symptoms;
2. To investigate the effects of implicit emotional processing on inhibitory control in adolescents with concussion.

In doing so, this thesis may contribute to our understanding of the affective and cognitive sequelae of concussion, highlight differences between individuals with elevated and average levels of depression, and inform clinical decisions regarding the return to school and physical activity through a greater understanding of the recovery of individuals with depression following concussion.

This is a cross-sectional study which is part of a larger longitudinal prospective cohort. The study was approved by the Hamilton Integrated Research Ethics Board (HiREB #14-376). The results of this cross-sectional study are presented in the following two chapters. Chapter 2 focuses on cognitive outcomes of ImPACT and the Emotional Go/No-Go task. Chapter 3 delves into the neural substrates of inhibitory processes. A summary and discussion follows in Chapter 4 to consolidate findings, relay the clinical implications of this work, and suggest directions for future research.

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CHAPTER 2:

EMOTION-MEDIATED EXECUTIVE FUNCTION IN ADOLESCENTS WITH POST-CONCUSSIVE DEPRESSIVE SYMPTOMS

Abstract

Background: Both deficits in executive functioning and elevated depressive symptoms are noted in adolescents following concussion. Evidence suggests a link between cognitive performance and emotional regulation in both healthy and concussed populations. The impact of emotional stimuli on executive control performance has yet to be explored in individuals with concussion who are displaying depressive symptoms.

Purpose: To explore the effect of depressive symptoms on executive function in youth with concussion in the presence of emotional stimuli.

Methods: Adolescents (10-17 years) completed a depression screening form (Children's Depression Inventory-2; CDI 2) to assess levels of depressive symptoms. Individuals with CDI T-scores above 1.0 STD from the population mean were categorized as the Elevated group. Individuals with normal levels of depressive symptoms were categorized as the Average group. Both groups completed a neurocognitive test (ImPACT) and an Emotional Go/No-Go task (involving neutral and angry faces) to assess executive functioning including inhibitory control.

Results: Of the 30 participants, 36.7% (n=11) had elevated depressive symptoms following concussion, as per the CDI 2. Post-concussive symptoms relating to depressive symptoms included: irritability, emotionality, sadness, and nervousness. The results showed that the behavioural performance on visual memory, verbal memory, reaction time, processing speed, and inhibitory control were not statistically different between groups. However, the normative data from ImPACT revealed that the group as a whole had impaired performance on reaction time and processing speed. The Emotional Go/No-Go demonstrated that adolescents overall performed comparably on inhibitory control tasks regardless of the emotion given on the face. Angry faces showed a trend towards significance, demonstrating a potential to facilitate behavioural performance.

Conclusions: After concussive injury, adolescents with normal and elevated levels of depression perform comparably on executive function including inhibitory control. Therefore, the presence of depressive symptoms is not indicative of poorer performance on executive function. A potential threat-related bias in attention demonstrated in this sample corroborates findings in previous studies.

Introduction

Concussions account for 13.2% of all injuries reported in the United States (Marar et al., 2012). The 2013 Concussion Consensus Statement describes mild traumatic brain injury, commonly known as concussion, as a pathological process that results from biomechanical forces to the brain may lead to clinical and neurological dysfunctions (McCrory et al., 2013). Symptoms can range from headaches to sleep disturbances, difficulty concentrating to anxiety and depression. By the definition provided by the 2013 Consensus Statement, these post-concussion impairments are transient and self-resolving, but a number of symptoms have a long-lasting impact on individuals with concussion (Ahman, Saveman, Styrke, Björnstig, & Stålnacke, 2013; Eisenberg et al., 2014). Cognitive deficits (Anderson et al., 2005) and depression (S. P. D. Chrisman & Richardson, 2014) are among a few of the post-concussion symptoms affecting youth that can continue to debilitate them in adulthood. As evidence suggests a link between cognitive performance and emotional regulation in both healthy and concussed populations (Kontos et al., 2012; Tavitian et al., 2014), the focus of this study will be to explore that clinical relationship as they pertain to adolescents with concussion. Specifically, executive function in adolescents following concussion is explored as it holds clinical relevance for maintaining goals and academic performance (Liew, McTigue, Barrois, & Hughes, 2008; Passolunghi & Siegel, 2001).

Cognitive performance is an area of concern for adolescents with concussive injury, particularly in executive function (Howell et al., 2013; Karr et al., 2014; Mangeot et al., 2002; D. R. Moore et al., 2016). Executive functions are a set of skills that govern higher-order cognitive abilities such as planning, reasoning and decision-making (Diamond, 2013; Miyake et al., 2000). Poor executive functioning in adolescents with concussion is characterized by worse reaction

times and accuracy rates and has been shown in working memory, selective attention, processing speed and inhibitory control tasks (Brooks et al., 2016; Howell et al., 2013; D. R. Moore et al., 2016). Computerized tools such as Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) have been developed to detect neurocognitive deficits after concussion and facilitate the assessment of multiple cognitive domains including executive function.

Inhibitory control is one of the executive functions that is impaired after head injury. It describes the ability to withhold or suppress a response to an environmental cue (Miyake et al., 2000). This ability to control impulses and regulate one's own behaviours has been linked with better school performance in children (Liew et al., 2008), thus a behavioural measures have been designed to test inhibitory control. The Go/No-Go paradigm was designed to create a habituated response for a particular ("go") stimulus. The responder would later need to inhibit or withhold the habituated response when a predetermined ("no-go") stimulus is given (Casey et al., 1997). Moore et al. (2016) used a Go/No-Go paradigm to assess inhibitory control in concussed adolescents. They found a higher rate of errors in the concussion group relative to the control group, suggesting poorer impulse control tendencies in children with history of brain injury. Other researchers have investigated the effects of emotional processing on inhibitory control in brain-injured populations, but the findings are mixed. Maki-Mattuen et al. (2014) included emotional distractors in the Go/No-Go task and found a negativity-bias in concussion participants, as evidenced by faster reaction times when responding to threat-related stimuli (Mäki-Marttunen et al., 2014). In a similar socio-emotional task, Tlusto et al. used facial expressions (happy, sad, neutral) as emotional distractors during their Go/No-Go task. Unlike Maki-Mattuen et al., they found that the effect of the different facial conditions did not yield a significant outcome. However, they found that inhibitory control in brain-injured participants

had a tendency for slower reaction times. (Tlusto et al., 2015). Despite the ambiguity related to the influence of emotions, both of these suggest deficits in inhibitory processes and, more generally, in executive function.

Deficits in executive function have demonstrated a link to poor emotion regulation, as shown in psychiatric populations. In fact, clinically depressed populations have difficulties with inhibitory control in the presence of interfering emotional stimuli (Kerestes et al., 2012; Tavitian et al., 2014), which is similar to the Maki-Mattuen et al. findings in concussion populations.

Psychiatric conditions like depression complicate concussion recovery because of shared symptoms such as fatigue, feeling slowed down, and sleep disturbances (Iverson, 2006). As a result, the International Consensus Statement recognizes that pre-existing psychiatric conditions modify recovery (McCrory et al., 2013; Solomon, Kuhn, & Zuckerman, 2016). However, youth with a history of brain injury are being diagnosed with depression at a disproportionate rate to non-injured populations (S. P. D. Chrisman & Richardson, 2014; Schoenhuber & Gentilini, 1988). Youth with concussion are 3.3 times more likely to be diagnosed with depression later in life (S. P. D. Chrisman & Richardson, 2014). Several risk factors contributing to this increased risk for depression post-concussion include age (S. P. D. Chrisman & Richardson, 2014), gender (Stazyk et al., in press) and number of previous concussions (Kerr et al., 2012; Pryor et al., 2016). The resulting psychosocial profiles of youth with post-concussive depression is similar to that of individuals with clinical depression (McLeod et al., 2016; Rapoport et al., 2003); however, post-concussive depressive symptoms remains largely unexplored.

Both executive dysfunction and depression interfere with the youth returning to full participation in their school, sport, and social and leisure activities (Iverson et al., 2015). To date, the literature demonstrating the effects of depressive symptoms and cognitive performance have

been done primarily on adults and the findings are inconclusive. In one study, Chen et al. noted trends for slower reaction times and poorer accuracy in working memory between healthy controls, concussion patients with mild depression, and concussion patients with moderate depression (Chen et al., 2008). Another study explored post-traumatic stress, depression, and pain and found that acute post-traumatic stress, but not depression, correlated with greater error rates in adults with concussion (Massey, Meares, Batchelor, & Bryant, 2015). Thus far, only one study investigated the effects of depressive symptoms in adolescents. Kontos et al. (2012) found that individuals that had higher depressive symptoms based on a self-report questionnaire were more likely to perform worse on the neurocognitive test ImPACT, which supports a link between depressive and cognitive symptoms after concussion. The impact of emotional stimuli on executive control performance has yet to be explored in individuals with concussion who are displaying depressive symptoms.

To address this lack of knowledge, the following study employed (1) a clinical depression-screening tool, (2) an Emotional Go/No-Go paradigm to measure emotion-mediated inhibitory control and (3) a concussion-specific computerized neurocognitive test. The overall purpose of this study is to explore the implications of depressive symptoms on executive function in youth with concussion in the presence of emotional stimuli. Secondary objectives include (1) examining cognitive performance in relation to normative data and (2) comparing post-concussive symptoms between those with elevated and average levels of depressive symptoms.

It was hypothesized that individuals indicating higher levels of depressive symptoms will show worse performance on both the neurocognitive test and the emotional inhibitory control task compared to individuals with average levels of depressive symptoms. Negatively-charged

emotional stimuli will further compromise their performance, as was demonstrated in studies involving psychiatric populations (Kerestes et al., 2012; Tavitian et al., 2014).

Methods

Design

The current study is a cross-sectional investigation of depressive symptoms and executive functioning in adolescents with concussion. The data collected was part of a longitudinal prospective cohort study at *CanChild* Centre for Disability Research at McMaster University. Participants who consented to participate in an fMRI component of the study comprised the sample of the current study. The study has been approved by the Hamilton Integrated Research Ethics Board (HiREB #14-367).

Participants

Participants between the ages 10-17 years with a concussion diagnosis were recruited from the McMaster University Children's Hospital emergency department, community rehabilitation clinics, community physician's referral, or by self-referral. Participants were excluded in the event of (1) a prior diagnosis of a severe developmental delay, (2) a severe injury requiring resuscitation, surgery, or admission to the critical care unit, or (3) a participant that is asymptomatic.

Procedures

Eligible adolescents were invited to participate in two in-person visits. Demographic information regarding past medical history, age, sex and injury specifics was collected over the

phone prior to the first in-person visit. The first visit took place in a testing room at McMaster University where participants completed the Post-Concussion Symptom Scale (PCSS; Lovell et al., 2006), Children's Depression Inventory (CDI 2; Kovacs, 2011), and Immediate Post-Concussion Assessment and Cognitive Test (ImPACT; Lovell, Collins, Podell, Powell, & Maroon, 2000), all of which were administered by a trained research assistant. A second visit was required to obtain fMRI data at St. Joseph's Hospital in the Imaging Research Centre. During this visit, the Emotional Go/No-Go task was administered while participants were in a 3T GE MRI scanner.

Measures

Concussion Symptoms – PCSS. The Post-Concussion Symptom Scale (PCSS) is a 22-item self-report survey that takes inventory of the symptoms and the severity of symptoms of concussion. Symptoms are measured on a 7-point Likert scale where 0 indicates the absence of a symptom, and a 6 indicates the greatest severity of a symptom. Symptoms were rated based on the past two days.

Depression – CDI 2. The Children's Depression Inventory (CDI) is a 28-item self-report questionnaire commonly used in clinical settings to screen for depressive symptoms in children and adolescents ages 7-17 years. It is not a diagnostic assessment, but provides an inventory of depressive symptoms and the extent to which these symptoms are experienced. The items are reflective of symptoms of major depressive disorder and dysthymic disorder in the DSM-IV. Each item consists of three statements, each representing a level of severity that is scored from 0 (none) to 2 (definite) and is based on experiences within the past two weeks. Higher scores

indicate that a child is more symptomatic. This measure is standardized and allows for comparisons across age and sex. This measure has been shown to be valid (Timbremont, Braet, & Dreessen, 2004) and reliable (Saylor, Finch, Spirito, & Bennett, 1984). T-scores can be derived to allow for the classification of depressive symptoms into four categories: *average or lower* (T-scores 0-59), *high average* (T-scores 60-64), *elevated* (T-scores 65-69), *very elevated* symptoms (T-scores >70). The CDI provides a recommended clinically significant threshold (T=65) to signify elevated depressive symptoms, but suggests that lowering the cut-off point is acceptable for homogeneous clinical populations.

In this study, a threshold T-score of 60 was chosen to encompass individuals in the *high average* category. These individuals fall into a subthreshold, or subsydromal, level of depression. According to the CDI manual, the range is an ambiguous area because individuals who should score in the *average and lower* and the *elevated* or *very elevated* ranges are equally likely to fall into *high average*. In lowering the threshold for what scores constitute Elevated levels of depressive symptoms, the sensitivity of the measure to detect depressive symptoms is increased. It allows for subsydromal participants to be categorized as Elevated depression participants, who have been noted in the literature to be functionally similar to depression patients (Fergusson et al., 2005; McLeod et al., 2016).

Neurocognitive performance – ImPACT. The Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) is a 25-minuted computerized neurocognitive test designed to assess cognitive performance in individuals with concussion. The test battery includes a series of modules to five composite scores: verbal memory, visual memory, reaction time, visual motor speed (or processing speed), and cognitive efficiency (a measure of speed and accuracy). It has

shown to be valid (Maerlender et al., 2010; Melorose, Perroy, & Careas, 2015) and reliable (Schatz & Ferris, 2013; Schatz, Pardini, Lovell, Collins, & Podell, 2006). ImPACT has aged and gendered norms and corresponding classification ranges to describe performance.

Inhibitory control - Emotional Go/No-Go task. The Emotional Go/No-Go task has been adapted from the classic Go/No-Go paradigm (Casey et al., 1997) to measure inhibitory control. It involves a behavioural response (a button press) when a Go stimulus is shown on a screen (a circle) and a withheld response (no button press) when a No-Go stimulus is shown (a square). For each correct button press given for circles, the circle will turn grey. For each button press given for squares for which the response should have been withheld, the square will turn red (an error). In Go blocks (the habituation condition), all trials are Go trials (circles) and are presented before No-Go blocks to habituate the button pressing response. In No-Go blocks (the inhibition condition), trials are intermingled with Go trials (circles) and No-Go trials (squares). Each block contains 14 trials. An emotional component (faces) is incorporated to assess the social and emotional effect on inhibition. The faces are task-irrelevant, requiring that the participant elicit mental inhibitory control to ignore the emotional stimuli in order to focus on the task-relevant information (the circles and squares). One face appears at each trial and is either Neutral or Angry in expression. They are displayed 250-550 ms before the shapes (circles/squares) appear, as shown in Figure 2.

The task was designed in experimental software E-prime with four cycles of four blocks each for a total of 224 trials in a single run. One cycle is comprised of the following blocks in order: 1) *NeutralGo*: a Go block during which all faces are neutral, 2) *NeutralNoGo*: a No-Go block during which all faces are neutral, 3) *AngryGo*: a Go block during which all faces are

angry, 4) *AngryNoGo*: a No-Go block during which all faces are angry. Rest periods are given briefly in between each block, and longer rest periods are given after blocks 1 and 3. Three different runs were programed with a different cycle order. Each participant completes two randomly chosen runs of this task.

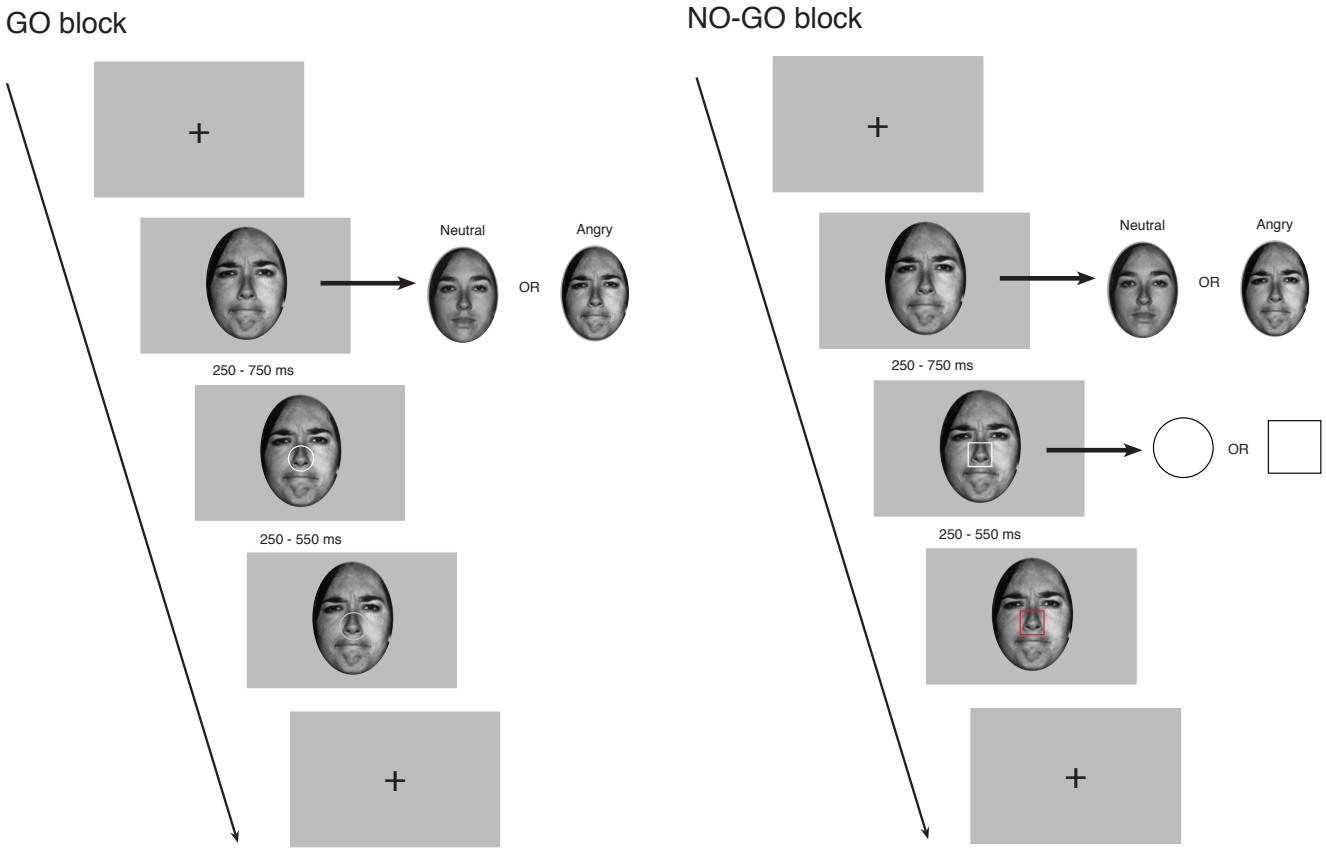

Figure 2. The Emotional Go/No-Go task is comprised of Go blocks (in which all trials are circles) and No-Go blocks (in which trials may have circles or squares). Before the presentation of the circle or square, a face that is either neutral or angry in expression will appear and will remain on the screen when the shape appears.

Data Analysis

Descriptive statistics were computed from the demographic information collected from questionnaires. Participants were grouped based on T-score on the CDI. Individuals below T=60 were categorized as having Average levels of depressive symptoms. Individuals scoring T=60 or higher had Elevated levels of depressive symptoms. Mann-Whitney U tests were conducted to determine between-group differences since the sample was not normally distributed and contained a low N value in each group. Neurocognitive scores were generated by ImPACT. Performance classifications on ImPACT were determined by normative data collected by Iverson, Lovell, and Collins (2003).

For the Emotional Go/No-Go task, responses that were faster than 200 ms or longer than 1000 ms were removed. While shapes can be detected quicker than 200 ms, the ability to discriminate between shapes requires more time (Elder & Zucker, 1993). Responses longer than 1000 ms exceed the length of the trial. Mixed factor analysis of variance tests were conducted to ascertain the main effects of depression (Average/Elevated) and trial type (Angry/Neutral faces) for each block (Go/No-Go) for both reaction time and accuracy.

Results

Participants

30 participants diagnosed with concussion agreed to participate in the fMRI component of the longitudinal study which included the Emotional Go/No-Go task. *Table 1* depicts the spread of the scores based on the CDI-2 classification. The division of participants into two study groups (Average or Elevated) is also reported. Of the total sample, 63.3% (n = 19) of participants were in the Average depression group, 36.7% (n = 11) in the Elevated group. Participant age

ranged from 10 to 17 years (M = 13.77, SD = 2.59y), of which 10 were male and 20 were female *(Table 2)*. At the time of the first in-person visit, participants were within 0 to 6-months of injury, although the spread of sample was highly variable. The median time since injury was 4.6 weeks. The number of weeks since injury was slightly longer for the Elevated group but the difference was not significant (p = 0.39). Groups were balanced in age (p = 0.5) and sex proportions (p = 0.7) such that the ratio of males to females did not differ significantly between groups. Symptom score accounting for number of symptoms and severity of symptoms showed that the Elevated group reported greater symptoms (M = 42.1, SD = 24.6) than the Average group (M = 28.1, SD = 21.2), but the difference was not significant (p = 0.16).

Table 1
Depression Levels & Study Groups

CDI Categories	T-score	Study Groups	n (%)
Average or Lower	0-59	Average	19 (63.3)
High Average	60-64	Elevated	2 (6.7)
Elevated	65-69	Elevated	7 (23.3)
Very Elevated	≥70	Elevated	2 (6.7)

Table 2
Descriptive Characteristics of the Study Sample

Variable		Level of Depressive Symptoms		*p*-value
	Total sample	Average	Elevated	
N (%)	30	19 (63.3)	11 (36.7)	
Sex *n (%)*				
Male	10 (33.3)	7 (36.8%)	3 (27.3%)	0.7
Female	20 (66.6)	12 (63.1%)	8 (72.7%)	
Age (years) *M (SD)*	13.77 (2.59)	13.5 (2.59)	14.2 (2.63)	
Time since injury (days) *M (SD)*				
Visit 1	5.9 (8.0)	4.9 (6.1)	7.8 (9.7)	0.5
Visit 2	8.2 (8.1)	7.5 (7.5)	9.3 (9.3)	0.39
Time between Visit 1 & 2	2.2 (3.3)	2.6 (4.2)	1.6 (1.0)	0.57
Prior diagnoses *n (%)*				
Anxiety or depression	3 (10)	2 (10.5)	1 (9.1)	
Other psychiatric conditions	0	0	0	
Sleeping disorder	0	0	0	
Learning disability	1 (9.1)	1 (9.1)	0	
History of concussive injury				
Number of participants with past concussions *n (%)*	12 (40)	8 (42.1)	4 (36.4)	
Number of past concussions *M (SD) Range*	0.87 (1.04) range:0-4	0.84 (0.89) range 0-3	0.91 (1.3) range 0-4	
PCSS *M (SD) n=27*				
Total PCSS score (max score: 120)	33.3 (23.1)	28.2 (21.2)	42.1 (24.5)	0.16
PCSS score of depressive symptoms				
5 symptoms (including fatigue; max score 30)	9.0 (7.7)	7.1 (7.1)	12.2 (8.2)	0.07
4 symptoms (excluding fatigue; max score 24)	6.5 (6.6)	4.7 (5.9)	9.7 (6.7)	0.023*
Number of depressive symptoms endorsed on PCSS				
5 symptoms (including fatigue)	3.2 (1.6)	2.6 (1.6)	4.2 (0.9)	0.006**
4 symptoms (excluding fatigue)	2.5 (1.5)	1.9 (1.5)	3.6 (0.67)	0.002**
PCSS score by item (max score 6 for each item)				
Fatigue	2.3 (1.8)	2.2 (1.8)	2.5 (1.9)	0.69
Irritability	1.9 (1.9)	1.3 (1.7)	2.9 (1.7)	0.02*

Sadness	1.6 (2.0)	1.3 (1.9)	2.3 (2.0)	0.12
Nervousness	1.3 (1.7)	0.89 (1.6)	2.1 (1.5)	0.001**
Emotionality	1.6 (1.8)	1.2 (1.7)	2.4 (1.7)	0.024*

*$p < 0.05$. ** $p < 0.001$

Depressive symptoms on the PCSS

The mean symptom score on the PCSS was 33.3 (*SD* = 23.1). The Average depression group reported fewer symptoms (*M* = 28.2, *SD* = 21.2) than the Elevated depression group (*M* = 42.1, *SD* = 4.5) but the difference was not significant ($p = 0.16$). There were five PCSS items that were identified as depressive symptoms: *fatigue*, *irritability*, *sadness*, *nervousness*, and *emotionality*. As shown in *Table 2*, 25 participants endorsed at least one depressive symptom on the PCSS. The two participants who endorsed none of the depressive symptoms were from the Average group. The results show that the variability in symptom severity is consistent throughout the sample on all measures. The Elevated group reported significantly more depressive symptoms overall than the Average group ($p = 0.006$) and there was a trend for the Elevated group to have a higher PCSS score for depressive symptoms ($p = 0.069$).

A comparison between the mean PCSS score between groups revealed significant differences in reports of irritability ($p = 0.019$), nervousness ($p = 0.009$), and emotionality ($p = 0.024$). There was no statistical difference in the average severity of sadness between the two groups. However, sadness was only reported in 47.3% of the individuals in the Average group, whereas 81.8% of participants reported it in the Elevated group. A Fisher's exact test was conducted and showed that a higher proportion of participants in the Elevated group reported feeling sad compared to the Average group ($p=0.023$, *OR* = 10.301). In examining fatigue, both groups scored comparably (Average: *M* = 2.2, *SD* =1.8; Elevated: *M* = 2.5, *SD* = 1.9; $p = 0.69$), with 78.9% individuals reporting fatigue from the Average group, and 72.7% from the Elevated group. A Fisher's exact test found that the proportion of participants reporting fatigue in each group was the same ($p = 1.0$, *OR* = 0.978).

A further analysis was done on the number of depressive symptoms endorsed and the severity of the depressive symptoms endorsed without including scores on fatigue since fatigue is a common symptom of concussion. The mean severity score for the four other depressive symptoms (irritability, sadness, nervousness, emotionality) for the Elevated depression group was significantly higher than that of the Average depression group ($p = 0.023$). Similarly, the Elevated group endorsed a higher number of depressive symptoms than the Average group ($p = 0.002$).

ImPACT

The mean composite scores from ImPACT testing are shown in Table 3. Mann-Whitney U tests were conducted between groups revealed no significant differences between groups. Between-group differences do not account for performance in comparison to normative data, thus Table 4 provides a summary of the results as classified by ImPACT based on percentile rank. Scores that were classified as "superior" or "very superior" were collapsed and labeled *above average*. "Impaired" and "borderline" classifications were denoted *below average*. High percentages of individuals from the overall group of participants were below average in visual motor speed (50%) and reaction time (56.7%). 22 participants (73.3%) had Cognitive Efficiency Index scores below the average score. 10 participants (30%) were severely below average.

Table 3
Neurocognitive performance based on ImPACT composite scores

Composite Score N=30	Total Sample *M (SD)* n = 30	Depression Level Average *M (SD)* n = 19	Depression Level Elevated *M (SD)* n = 11	*p*-value
Verbal Memory	81.13 (13.16)	82.79 (14.98)	78.27 (9.16)	0.29
Visual Memory	68.6 (13.67)	70.37 (15.92)	65.55 (8.30)	0.25
Visual Motor Speed	28.31 (6.24)	28.37 (7.12)	28.21 (4.67)	0.9
Reaction Time*	0.76 (0.14)	0.77 (0.17)	0.72 (0.06)	0.39
Impulse Control*	11.77 (13.81)	12.36 (16.65)	10.73 (7.21)	0.65
Cognitive Efficiency Index	0.24 (0.21)	0.23 (0.25)	0.26 (0.12)	0.97

* lower scores indicate better reaction time

Table 4
Collapsed performance classifications for each ImPACT composite score

Composite Score N=30	Performance Classification *n (%)* Impaired $< 10^{th}$ percentile	Average 10^{th}-90^{th} percentile	Supervisor $> 90^{th}$ percentile
Verbal Memory	10 (33.3)	17 (56.7%)	3 (10%)
Visual Memory	7 (23.3%)	22 (73.3%)	1 (3.3%)
Visual Motor Speed	15 (50%)	15 (50%)	0
Reaction Time	17 (56.7%)	13 (43.3%)	0

Emotional Go/No-Go – response times

Go vs. No-Go blocks: Response times for the Emotional Go/No-Go are displayed in Table 5. A Mann-Whitney U test of independent groups was conducted to compare response times between Go and No-Go blocks. The results revealed that Go blocks (M = 322.68, SD = 116.3) yielded significantly faster response times compared to No-Go blocks (M = 335.21, SD = 105.89), in which inhibitory control was required ($p < 0.001$).

Go blocks (including both Neutral and Angry faces): Response times for the Emotional Go/No-Go are depicted in *Figure 3*. The mean response times were submitted to a mixed factor ANOVA (*Table 6*) that treated depression (Elevated/Average) as a between-subject variable and trial type (NeutralGo/AngryGo) as a within-subject variable. The interaction

between depression level and block type was not significant ($p = 0.39$). However, the analysis indicated a main effect of the depression ($F(1,26) = 4.38$, $p = 0.046$), signifying that the *Elevated* group had significantly faster responses compared to the Average group. The main effect for block type was not significant ($p = 0.82$), indicating that response times were not significantly different between NeutralGo blocks and AngryGo blocks.

No-Go blocks (including both Neutral and Angry faces): Reaction times for No-Go blocks are shown in *Figure 4*. The mean response times were submitted to a mixed factor ANOVA (*Table 7*) that treated depression (Elevated/Average) as a between-subject variable and block type (NeutralNoGo/AngryNoGo) as a within-subject variable. The interaction between depression level and block type was not significant ($p = 0.39$), indicating that the means of the Average group and the Elevated group were not different. The main effects of depression ($p = 0.25$) and block type ($p = 0.76$) were not significant, meaning that the response times between the NeutralNoGo and AngryNoGo blocks were not statistically different.

Table 5
Response Times on the Emotional Go/No-Go

Block Type		Depression Level		
	Total Sample *M (SD)* N = 30	Average *M (SD)* n = 19	Elevated *M (SD)* n = 11	p-value
Neutral Go	323.02 (115.94)	335.16 (119.69)	302.80 (106.49)	0.09
Angry Go	322.36 (116.67)	331.85 (119.67)	304.31 (108.57)	0.15
Neutral NoGo	334.14 (104.85)	340.76 (109.01)	322.42 (96.05)	0.73
Angry NoGo	336.23 (106.91)	343.77 (109.24)	322.37 (101.13)	0.58

Note: Mann-Whitney U tests were conducted between the Average and Elevated response times.

Table 6
Mixed Factorial ANOVA for Response Times on Go Blocks

Source	Df	SS	MS	F	p
Between-subjects					
Block Type	1	7515	7515	0.05	0.818
Depression	1	606754	606754	4.38	0.046 *
Depression x Block Type	1	178426	178426	1.29	0.267
Residuals	26	3599848	138456		
Within-subjects					
Block Type	1	2285	2285	0.23	0.64
Depression x Block Type	1	295	295	0.03	0.87
Residuals	28	283790	10135		

Note: Significance is determined as $p<0.05$

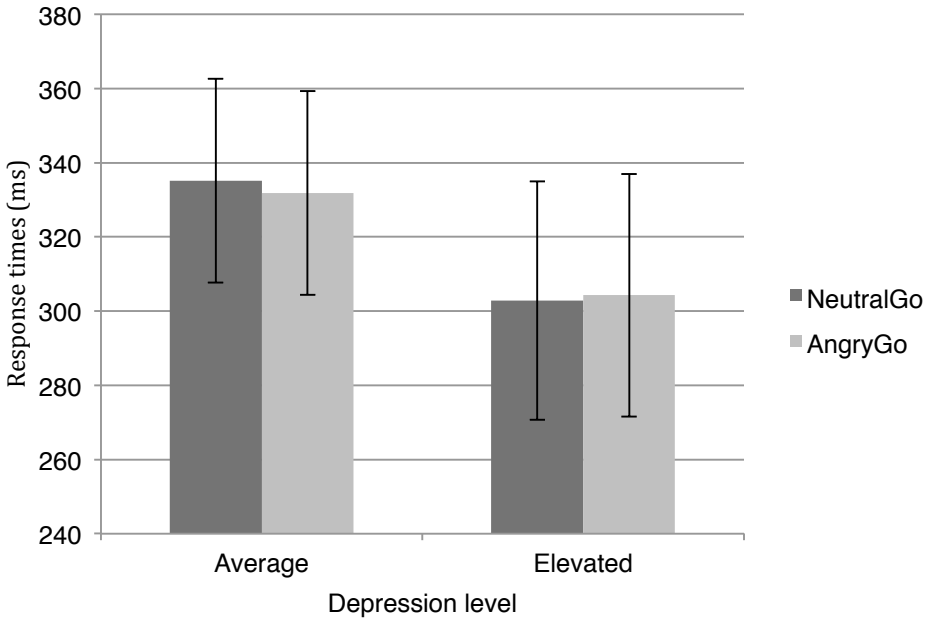

Figure 3. Response times for by depression for each trial type on Go blocks

Table 7
Mixed Factorial ANOVA for Response Times on No-Go Blocks

Source	Df	SS	MS	F	p
Between-subjects					
Block Type	1	17305	17305	0.10	0.76
Depression	1	240005	240005	1.37	0.25
Depression x Block Type	1	135865	135865	0.78	0.39
Residuals	26	4550826	175032		
Within-subjects					
Block Type	1	2285	2285	0.23	0.64
Depression x Block Type	1	295	295	0.03	0.87
Residuals	28	283790	10135		

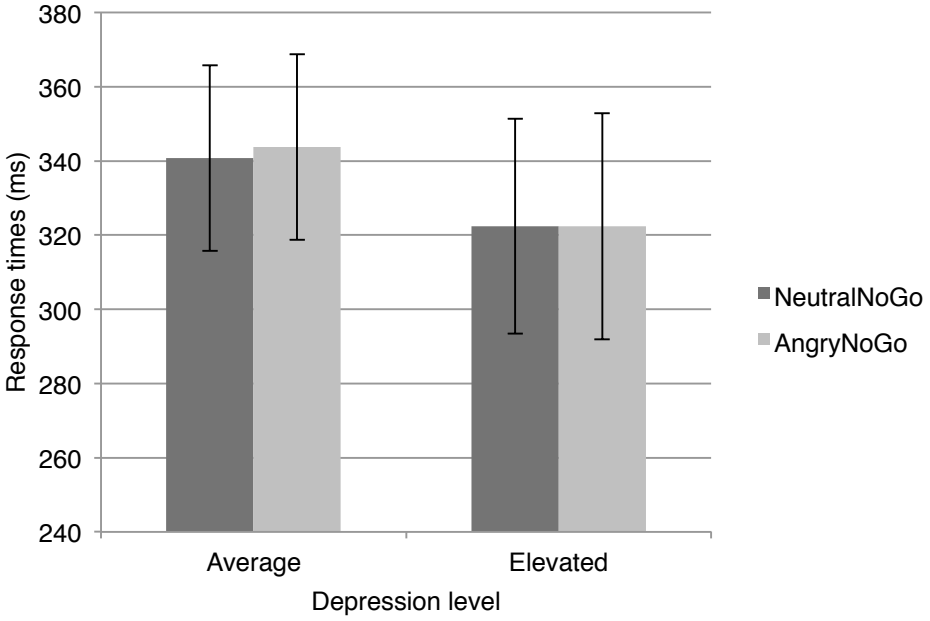

Figure 4. Response times for by depression for each trial type on No-Go blocks

Emotional Go/No-Go – accuracy rates

Go vs. No-Go blocks: A Mann-Whitney U test was conducted to determine the effect of the Go vs. No-Go blocks. It revealed that accuracy was not significantly different between Go (M = 79.24, SD = 16.15) and No-Go blocks (M = 82.39, SD = 10.45, p = 0.69). *Table 8* shows the accuracy rates for each of the block types.

Go block (including both Neutral and Angry faces): *Figure 5* displays accuracy on Go blocks. The mean number of correct responses in Go blocks was submitted to a mixed factor ANOVA (*Table 9*) that treated depression (Elevated/Average) as a between-subject variable and block type (NeutralGo/AngryGo) as a within-subject variable. The results revealed that there was no main effect of depression (F(1, 28) = 0.4, p = 0.53) or block type (F(1, 28) = 3.30, p = 0.08) within Go blocks. The effect of the block type was trending towards significance, meaning which might indicate that there were more correct trials for AngryGo blocks than NeutralGo blocks.

No-Go block (including both Neutral and Angry faces): *Figure 6* displays accuracy on No-Go blocks. The mean number of correct responses in No-Go blocks was submitted to a mixed factor ANOVA (*Table 10*) that treated depression (Elevated/Average) as a between-subject variable and trial type (Neutral/Angry) as a within-subject variable. Again, there was no main effect of depression (F(1,28) = 0.12, p = 73) or block type (F(1,28) = 0.03, p = 0.86) within No-Go blocks.

Table 8
Accuracy Rates on the Emotional Go/No-Go

Block Type		Depression Level	
	Total sample M (SD) N = 30	Average *M (SD)* n = 19	Elevated *M (SD)* n = 11
Neutral Go	78.33 (15.67)	76.50 (16.61)	81.78 (14.64)
Angry Go	80.04 (16.66)	79.14 (17.38)	81.61 (16.01)
Neutral NoGo	82.32 (10.73)	82.90 (11.86)	81.35 (8.88)
Angry NoGo	82.45 (10.34)	82.90 (11.17)	81.67 (9.32)

Table 9
Mixed Factorial ANOVA for Accuracy Rates on Go Blocks

Source	Df	SS	MS	F	p
Between-subjects					
Depression	1	0.021	0.0209	0.4	0.53
Residuals	28	1.478	0.0528		
Within-subjects					
Block Type	1	0.0039	0.00385	3.30	0.08
Depression x Block Type	1	0.0027	0.00274	2.35	0.14
Residuals	28	0.0327	0.00117		

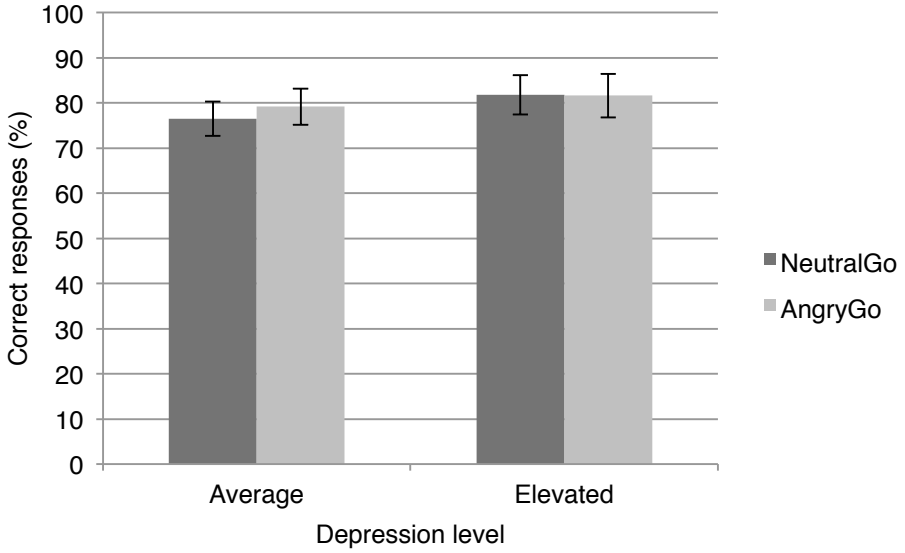

Figure 5. Accuracy rates for by depression for each trial type on Go blocks

Table 10
Mixed Factorial ANOVA for Accuracy Rates on No-Go Blocks

Source	Df	SS	MS	F	p
Between-subjects					
Depression	1	0.003	0.00268	0.12	0.73
Residuals	28	0.624	0.02227		
Within-subjects					
Block Type	1	0.00002	0.000021	0.03	0.86
Depression x Block Type	1	0.00004	0.000037	0.06	0.81
Residuals	28	0.01788	0.000639		

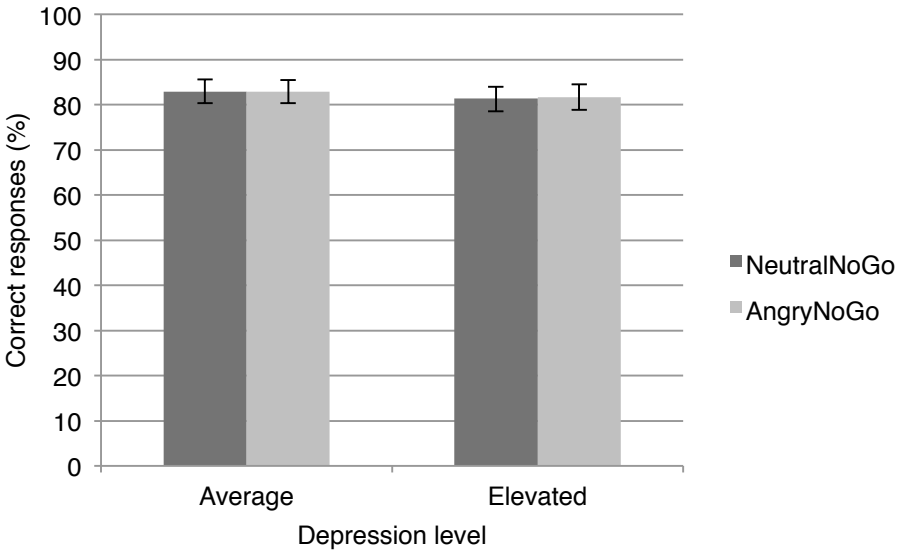

Figure 6. Accuracy rates for by depression for each trial type on No-Go blocks

Discussion

The purpose of this study was to examine executive function in adolescents with concussion who are experiencing depressive symptoms. This is the first study to examine adolescents with elevated levels of depressive symptoms as compared to those who report average (normal) levels of depressive symptoms. The results suggest that depressive symptoms following a concussion are not necessarily indicative of greater difficulties in executive function. Participants who reported clinical signs of depression did not differ statistically from the individuals who reported normal levels of depressive symptoms on neurocognitive performance as well as inhibitory control.

The study used a clinical screening tool to differentiate participants based on self-reported extent symptoms of depression. The sample reported that 36.7% (n = 11) of participants had elevated levels of depressive symptoms on the CDI 2. This rate is slightly higher than the 22% rate reported in previous literature (Stazyk et al., in press), but it is indicative of the disproportionately high rates of depression following concussion in comparison to the 5-11% noted in the general public (Haarasilta et al., 2001; Kessler et al., 2012; Richardson et al., 2010).

Ratings on the PCSS varied greatly and the mean symptom scores did not differ significantly between the Elevated depression and Average depression groups. Five items on the PCSS were flagged as depression-related (fatigue, irritability, sadness, nervousness, and emotionality). In concordance with CDI depression reporting, the Elevated group was more likely to endorse these symptoms and with greater severity. This was in agreement with the hypothesis that individuals indicating higher levels of depressive symptoms on the depression-screening tool would also report a higher severity of depression-related symptoms on the concussion symptom scale. Sadness and fatigue did not show statistical significance when

comparing the two groups. This could be interpreted as an example of overlapping symptoms of depression and concussion, which makes it difficult for researchers and clinicians to determine if a patient is demonstrating signs of depression (Iverson, 2006). Although the mean ratings of sadness were not statistically different between groups, the sheer numbers of participants from the Elevated group reported sadness compared to the Average group was, in fact, statistically higher. This may mean that sadness is another common symptom of concussion that can be experienced by a large number of individuals after a concussion, but not all individuals will display clinical levels of depression.

The lack of between-group differences in both the severity of fatigue and the proportions of individuals reporting fatigue shows that levels of fatigue are the same regardless of the experience of levels of depressive symptoms. This is evidence that fatigue after a concussion may be the result of the concussion rather than a "red flag" for depression. On the other hand, fatigue, in combination with raised levels of irritability, nervousness, and emotionality, may be indicative of overall elevated levels of depressive symptoms in an adolescent with concussion, as suggested by this study.

Computerized neurocognitive testing, ImPACT, was chosen for its sensitivity to concussive injuries on multiple cognitive domains, including executive function. The results from ImPACT revealed that the neurocognitive performance between groups did not differ statistically even though the Elevated group had lower mean values on five of the six composite scores: verbal memory, visual memory, visual motor speed, impulse control, and cognitive efficiency. In a similar study, Kontos et al. (2012) investigated correlations between neurocognitive performance and depressive symptoms in adolescents with concussion. They found that higher depression scores were associated with lower verbal and visual memory scores.

However, their sample reported very low levels of depression overall; at least 96% of participants reported minimal to no depressive symptoms at any of four study time points. Given that their sample comprised of mostly non-depressed individuals, their findings showed statistical but not clinical significance. Chen et al. (2008) divided their sample of adults with concussion into mild, moderate, and no depressive symptoms and tested working memory performance. Like the current study, they found numerical trends for mild and moderate depressed participants to have slower reaction times and poorer accuracy, but the difference was not statistically different between groups. This indicates that performance deficits in individuals with depressive symptoms following concussion may be too minute to detect, or non-existent on behavioural cognitive tasks.

In addition, the Chen et al. study illustrates a difference between youth and adult neurocognitive performance. When comparing the total sample of concussed adults to healthy controls, Chen et al. found that participants in both groups performed equally well. The current study found that the performance of the total sample of concussed adolescents was not on par with normative data. The majority of participants performed within the 10^{th} to 90^{th} percentile on verbal memory and visual memory. However, about 23-33% of participants were below the 10^{th} percentile rank, which suggests that distribution of scores is shifted towards lower performance scores. Visual motor speed and reaction time results showed that at least half of the participants had impaired performance ($< 10^{th}$ percentile). Likewise, 73.3% had below average cognitive efficiency index scores, and 10% were severely below average. Therefore, unlike adults, adolescents with concussion are more likely to exhibit deficits on neurocognitive performance as well as executive functioning, a finding that has been previously supported in the literature (Baillargeon et al., 2012; Kontos et al., 2012; Nelson et al., 2016)

The Emotional Go/No-Go task was used as another measure of executive function, and more specifically, inhibitory control. It involves both behavioural and cognitive inhibitory control mechanisms to which it was hypothesized that the Elevated depression group would perform worse. This hypothesis stems from research on patients with psychiatric conditions like major depressive disorder who, researchers propose, exhibit threat-related biases in attention and therefore have difficulties with inhibiting the threatening stimuli (Erickson et al., 2005; Kerestes et al., 2012). The participants from the current study scored in the *high average* range on the CDI grouped together in the Elevated depressive symptoms group on the basis that children who are at risk for depression also display deficits in executive function in the presence of negative stimuli (Joormann, Talbot, & Gotlib, 2007). Enhanced attention for emotionally charged stimuli has also been noted in concussion populations (Mäki-Marttunen et al., 2014; Tlusto et al., 2015).

The results revealed that the facial expressions (Neutral or Angry) did not have an effect on response times or accuracy for either of the groups. When examining the Go blocks, the Elevated group was significantly faster than the Average group, even though both groups had comparable accuracy rates. On blocks where inhibitory control was required (No-Go blocks), response times between the Elevated and Average groups were not different.

These findings are contrary to the investigators' hypothesis. First, the results show that individuals with higher depression levels performed comparably to those with normal levels of depression in inhibitory control. This was also in concordance with ImPACT results, which revealed that the groups did not differ in reaction time, visual motor (processing) speed, or cognitive efficiency, but performed poorly with respect to the norm. Second, the social-affective aspect of the Emotional Go/No-Go task (the neutral or angry facial expressions) did not have an effect on performance, regardless of depression or block type. This highlights a limitation of the

task. Participants were shown the same facial expressions (neutral or angry) for the full block, rather than intermixing the facial expressions and, as such, the participants may have been customized to the effect of face. Thus, the expected effect may be only noticeable within the first few trials of each block because the participant is unsure of the forthcoming facial expression.

Limitations

The current study is limited by the high variability among participants, and a small and uneven sample size. Moreover, the study is reliant on honest and unbiased self-report measures to capture both depressive and post-concussive symptoms. An in-depth assessment of the functional and clinical deficits of the depressive symptoms was not conducted, thus participants in the Elevated depression group were not diagnosed with clinical depression. Similarly, family history of depression was not investigated so adolescents who were at-risk of depression prior to concussion could not be identified. Lastly, participants were recruited as assessed at different time points during recovery. Although all participants were symptomatic at the time of recruitment, this study did not control for the variability in the emergence of depressive symptoms.

Conclusion

This is the first study to investigate the implications of depressive symptoms on executive performance and emotional processing in adolescents with concussions. In this study, the results demonstrate that after concussive injury, adolescents with normal and elevated levels of depression perform comparably on executive function including inhibitory control. The emotion of the faces did not influence performance, although a trend suggests that angry faces draw more

attention. Therefore, the presence of depressive symptoms is not indicative of poorer performance on executive function.

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CHAPTER 3:

THE NEUROPHYSIOLOGICAL IMPACT OF EMOTION ON INHIBITORY CONTROL IN ADOLESCENTS WITH DEPRESSIVE SYMPTOMS AFTER CONCUSSION

Abstract

Background: Following concussion, adolescents may experience both poor inhibitory control and increased depressive symptoms. Studies have shown that brain activity in adolescents with concussion deviates from that of uninjured controls. Despite the gravity of depressive symptoms on quality of life in youth after concussion**,** very little research has been done to show how concussed adolescents with depressive symptoms might present in brain pathology during cognitive tasks.

Purpose: to determine how adolescents with depressive symptoms might present differently in brain activity patterns than those without depressive symptoms after concussion, particularly in the presence of distracting emotional images while engaging inhibitory control processes.

Methods: Adolescents diagnosed with concussion between 10-17 years were recruited. Levels of depressive symptoms were collected using the Children's Depression Inventory (CDI) self-report questionnaire. Participants were divided into two groups based on T-scores from the CDI: Elevated and Average. They completed an Emotional Go/No-Go task involving neutral and angry faces as emotional distractors in an fMRI scanner. Group comparisons were conducted to analyze differential areas of brain activity during emotion-mediated cognitive processing (Go>No-Go; No-Go>Go) and emotional processing (Neutral>Angry; Angry>Neutral).

Results: *Adolescents with concussion:* Fewer areas of activity were seen during the inhibitory condition (No-Go blocks) compared to the habituation condition (Go blocks). Emotion-mediated inhibitory control activates areas including the right caudate, left occipital fusiform gyrus, bilateral hippocampus, and bilateral anterior cingulate cortex The emotional stimuli yielded activity in the thalamus, pallidum, insula, and putamen were seen in the right hemisphere, while the fusiform gyrus, lateral prefrontal cortex, middle frontal cortex, and precentral gyrus. Adolescents with post-concussive depressive symptoms: Lowering the threshold to Z=2.0, threshold cluster= 0.05 revealed activity in the lateral frontal gyrus, superior frontal gyrus, and left inferior parietal lobe in the Elevated group. Regions associated with Angry>Neutral contrast were minimal, both groups exhibiting little activity at Z=2.0.

Conclusions: The findings show that engaging in inhibitory control processes results in fewer areas of brain activity in comparison to simple, automated tasks in adolescents with concussive injury. Frontal regions that are usually associated with inhibitory control were not activated, which suggests that an impairment in the frontal networks. Location of injury may have been a contributing factor to this finding. Faces activated regions associated with both facial and cognitive processing. Adolescents with elevated levels of depressive symptoms were more likely to engage frontal regions that subserve evaluative processes.

Introduction

Adolescents have shown greater vulnerability to the negative consequences of concussion in comparison to adults and children (Baillargeon et al., 2012; Zuckerman et al., 2012). A Canadian survey completed in 2009 to 2010 found that 30% brain injuries were in youth ages 12 to 19 years, exceeding that of adults including seniors (Billette & Janz, 2011). Likewise, Ontario emergency room departments and doctors offices saw an increase in the number of pediatric concussions from 340.5 to 601.3 per 100 000 between the years 2003 and 2010 (Macpherson et al., 2014). Following concussion, adolescents may experience somatic symptoms (such as headaches, balance problems, blurry vision), cognitive deficits (such as difficulty remembering, slower reaction times, trouble concentrating), mood disturbances (such as anxiety, depression, irritability), or disrupted sleeping patterns (Eisenberg et al., 2014; McCrory et al., 2013). Mood disturbances and cognitive deficits are among the longest lasting symptoms (Chrisman & Richardson, 2014; Eisenberg et al., 2014), but the underlying pathophysiology remains unexplored in adolescents.

A number of neurobiological processes have been hypothesized to contribute to the vulnerability of adolescent brains to the consequences of concussion. One factor involves the rapid development of structural properties across adolescence such as the myelination of the corpus callosum (Reeves et al., 2005) and frontal lobe (Sowell et al., 1999), and thickening of white and grey matter of the brain (Barnea-Goraly, 2005; Giedd et al., 1999). The neurochemical cascade that is triggered in the brain when a concussion occurs can negatively impact these developmental processes, all of which may have consequences on function. Moreover, adolescence marks critical periods in development during which the brain is most sensitive to its

environment (Sisk & Zehr, 2005). Injury during this time could alter the consolidation of neuronal networks (Anderson et al., 2011).

Functional magnetic resonance imaging (fMRI) has been used to observe the pathophysiology in adolescents following concussion. It has enabled researchers to identify abnormalities in function after concussion, determine underlying neural mechanisms of symptoms, and understand behavioural outcomes on neurocognitive and neuropsychological tests. Brain imaging in concussion research has furthered the understanding of how the injury has altered neuronal connectivity when the brain is at rest and when the brain is carrying out purposeful activity. In the absence of any particular task, the brain at rest shows functionally different activity patterns in both adolescents and adults with concussion compared to age-matched controls (Borich et al., 2014; Stevens et al., 2012; Zhou et al., 2012). Researchers have therefore taken interest in the functional connectivity of the brain when there are task demands. Although the majority of this research has been done on adults, altered functional activation patterns during cognitive activity have also been noted in adolescents as well (Breedlove et al., 2012; Michelle L Keightley et al., 2014; Saluja et al., 2015; Sinopoli et al., 2014).

Executive function has been of interest to concussion researchers since the development of executive processes (inhibition, working memory, cognitive flexibility) parallels neuronal development and occurs across adolescence (Durston et al., 2002; Yurgelun-Todd, 2007). Recent studies have shown that brain activity in adolescents with concussion deviates from that of uninjured controls. Keightley et al. (2014) found that adolescents with concussion performed worse than healthy controls on working memory tasks and displayed hypoactivity in the dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (dACC) in comparison, areas that are highly associated with executive function. Sinpoli et al. (2014) used a

combined working memory and motor response task to measure brain activity during dual-task performance. They found that adolescents with concussion were less likely to engage the appropriate brain regions for the task (namely the DLPFC and the posterior parietal lobe). Other cognitive tasks like navigation memory have been examined with results reflecting normal behavioural performance, but reduced activation in brain areas associated with the task and increased engagement of areas external to the task (Saluja et al., 2015). Collectively, these studies suggest that adolescents with concussions display reduced activation of the task-specific brain regions, but engage other areas of the brain that are normally unrelated to the task in order to meet the demands of the task.

This recruitment of alternative brain regions during cognitive tasks is a pattern seen in individuals with psychiatric illnesses (Colich et al., 2016; Kerestes et al., 2012); however, very little research has been done to show how concussed adolescents with depressive symptoms might present in brain pathology. Despite the gravity of depressive symptoms on quality of life in youth after concussion (Stazyk et al., in press), the extent of this research has been done on adults. Chen, Johnston, Petrides, and Ptito (2008) compared adults experiencing mild, moderate, or depression after concussion to non-injured adults on a working memory task. While reaction times and accuracy rates did not differ significantly between the groups, blood-oxygen level dependent (BOLD) response for areas associated with the task was reduced in the mild depressed group and even further reduced in the moderately depressed group. These areas included the DLPFC, dACC, insular cortex, striatum, and thalamus. Chen and colleges also indicated the deactivation of regions not normally associated with working memory in the comparison groups (healthy controls and concussed adults without depression). The mildly and moderately depressed groups, however, showed greater activity in regions not associated with the task.

Although the DLPFC is implicated in several cognitive tasks including working memory and navigational memory, it was negatively correlated with depression in this sample.

Adolescents differ functionally and developmentally from adults. As the emergence of depressive symptoms may be indicative of brain function and recovery patterns, an examination of the neural correlates of depressive symptoms during a cognitive inhibition task was conducted in the current study. Thus far, only one study has examined the neural correlates of adolescents with concussion during emotion-mediated inhibitory control. It was found that adolescents with brain injury did not exhibit significant brain activity in areas that are normally associated with emotional processing where healthy controls did during the task, suggesting that emotional processing has a greater impact on inhibitory control following brain injury (Tlusto et al., 2015). The physiological differences in individuals expressing higher levels of depressive symptoms were not investigated. The main objective of the current study was to determine how adolescents with depressive symptoms might present differently in brain activity patterns than those without depressive symptoms after concussion, particularly in the presence of distracting emotional images while engaging inhibitory control processes. Secondary objectives include 1) determining the effects of MRI scanning on post-concussive symptomology and 2) exploring how location of injury might be reflective of physiological differences in adolescents with elevated depressive symptoms after concussion.

It was hypothesized that abnormalities in areas associated with cognitive inhibition would be observed, particularly in the DLPFC and the ACC, both of which are implicated in cognitive tasks and monitoring attention. An Emotional Go/No-Go task was used in this study to measure the neurophysiological response to emotion-related images during inhibitory control processes. The fMRI results were hypothesized to demonstrate disrupted emotional processing activity for

adolescents experiencing depressive symptoms following concussion relative to those who are not experiencing depression.

Methods

Design

The data presented in this study was collected from a longitudinal prospective study that is taking place at *CanChild* Centre for Disability Research. Participants who had agreed to take part in the brain imaging component of the longitudinal study were included in the current analysis. The current study is cross-sectional in design and has been approved by the Hamilton Integrated Research Ethics Board.

Participants

Adolescents who had been diagnosed by a physician with concussion between the ages of 10 and 17 years were invited to participate. They were recruited from a number of health facilities including the McMaster University Children's Hospital, rehabilitation clinics, physician's offices, or by self-referral from CanChild website. Exclusion criteria included (1) a diagnosis of a severe developmental delay, (2) a severe injury requiring resuscitation, surgery, or admission to the critical care unit, or (3) a participant that is asymptomatic.

Procedures

Data was collected over two visits that were scheduled to be as close in time as participants' schedules allowed. Visit 1 took place in an assessment room at McMaster University, where information regarding demographics, injury specifics, depressive symptoms,

and post-concussive symptoms was collected. Visit 2 took place at St. Joseph's Hospital in the Imaging Research Centre. There, the participants completed an Emotional Go/No-Go task while in an fMRI scanner. Although the Emotional Go/No-Go task took 20 minutes to complete, participants were in the scanner for approximately one hour to accommodate for routine scans (described below) and other scans relevant for the longitudinal study. Post-concussive symptoms before and after scanning took place was also collect during Visit 2 to determine if exposure to loud noises during MRI scanning would worsen symptoms.

MRI Data Acquisition

Participants were scanned in a 3-Tesla GE MRI scanner using a 32-channel RF receiver coil. 3-plane localizer and calibration scans were completed. Then the 3D T1-weighted anatomical images were acquired (TE = 4.25; TR = 11.36; flip angle = 12^{o}; image matrix: 256x256 with 1 mm slice thickness; FOV = 25.6 cm with 1 mm isotropic acquisition). Functional images of the resting state was taken, followed by functional BOLD scan for the Emotional Go/No-Go paradigm (TE = 35 ms; TR = 2000 ms; flip angle = 90^{o}; image matrix: 64x64 with 1 mm slice thickness; EPI sequence with FOV = 22 cm; 180 temporal points). Four disabled data acquisitions were acquired prior to the start of the scan and were later discarded. The scan time for this a single run was 10 minutes, which was repeated for the second run for a total of 20 minutes.

Measures

Concussion Symptoms – PCSS. The Post-Concussion Symptom Scale (PCSS; Lovell et al., 2006) consists of a list of somatic, emotional, cognitive, and sleep-related symptoms of

concussion. There are a total of 22 symptoms that are rated on a 7-point scale from 0 (absence of symptom) to 6 (extremely severe symptom).

Depression - CDI 2. The Children's Depression Inventory (CDI; Kovacs, 2011) consists of 28 symptoms that are indicative of depression as defined by the DSM-IV. It is designed to capture the extent of depressive symptoms in children and adolescents between 7 and 17 years. Each item contains three statements with graded severity: 0 (none) to 2 (definite). Responders are instructor to indicate symptoms from the most recent two weeks. Scores are normalized by age and sex and can be categorized as Average or Lower (*T*-scores 0-59), High Average (*T*-scores 60-64), Elevated (*T*-scores 65-69), Very Elevated symptoms (T-scores > 70). A lower cut-off point for depression ($T = 60$) was chosen for this study, which encompasses individuals who score at least 1.0 standard deviations from the mean.

Inhibitory control - Emotional Go/No-Go task. The Emotional Go/No-Go task is an inhibitory control task, adapted from the classic Go/No-Go paradigm (Casey et al., 1997). Participants are expected to respond to a "go" stimulus (a circle) and refrain from responding when presented with a "no-go" stimulus (a square). Trials involving the target stimulus are Go trials, where trials involving the foil stimulus are No-Go trials. The response to a Go trial is given by a pressing a button on a button box with the index finger of the dominant hand. Go blocks consist of only Go trials. No-Go blocks involve both No-Go trials (squares) and Go trials (circles). This automatizes button pressing such that inhibitory control must be exercised to avoid errors in the No-Go block. Blocks alternate between Go and No-Go blocks. Emotional distractors are presented at every trial. These include angry or neutral facial expressions, which

are shown on the screen 250-550 ms prior to the presentation of the shapes (circles/squares). Participants are instructed to respond only to the shapes, not the faces. Again, the blocks alternate between Neutral and Angry blocks. When a correct response is given for a circle, the circle will turn grey. If the participant fails to inhibit a response for a square, the square will turn red to remind the participant not to press for the squares, as shown in Figure 7.

Each block has 14 trials for a total of 224 trials in one run. Each task run has four cycles of four blocks each designed in experimental software E-prime in the following order: 1) *NeutralGo*: a Go block during which all faces are neutral, 2) *NeutralNoGo*: a No-Go block during which all faces are neutral, 3) *AngryGo*: a Go block during which all faces are angry, 4) *AngryNoGo*: a No-Go block during which all faces are angry. Rests periods are given after block 1 and 3, during which a fixation cross is presented on the screen. There are three versions of the task to counterbalance the order in which the faces appear.

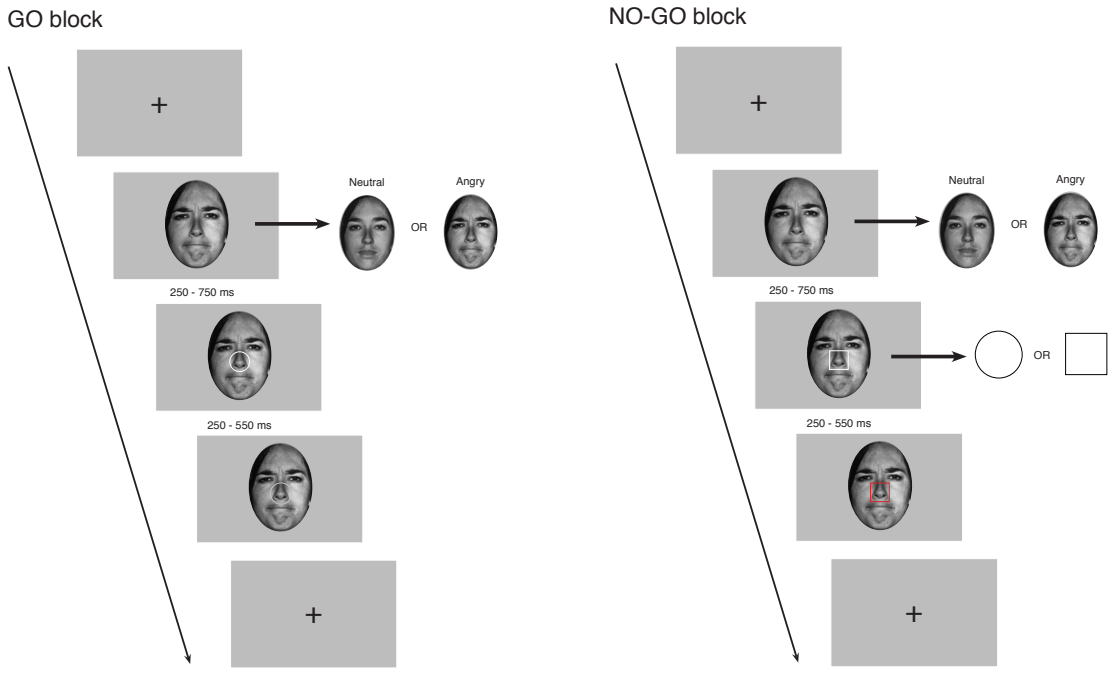

Figure 7. The Emotional Go/No-Go task is comprised of Go blocks (in which all trials are circles) and No-Go blocks (in which trials may have circles or squares). Before the presentation of the circle or square, a face that is either neutral or angry in expression will appear and will remain on the screen when the shape appears.

Data Analysis

Descriptive statistics were computed from demographic questionnaires and symptom surveys (CDI and PCSS). Participants were grouped based on T-score on the CDI. Individuals below T=60 were categorized as having Average levels of depressive symptoms. Individuals scoring T=60 or higher had Elevated levels of depressive symptoms. Mann-Whitney U tests were conducted to determine between-group differences since the sample was not normally distributed and contained a low N value in each group.

For the Emotional Go/No-Go task, responses that were faster than 200 ms or longer than 1000 ms were removed. While shapes can be detected quicker than 200 ms, the ability to discriminate between shapes requires more time (Elder & Zucker, 1993). Responses longer than 1000 ms exceed the length of the trial. Mixed factor analysis of variance tests were conducted to ascertain the main effects of depression (Average/Elevated) and face type (Angry/Neutral) for each condition (Go/No-Go) on reaction time and accuracy.

fMRI Analysis

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration of the high-resolution structural to standard space was carried out using FLIRT (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002). The following pre-statistics processing was applied: motion correction using MCFLIRT (Jenkinson et al., 2002); slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 6.0 mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; highpass temporal

filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 102.5 s). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). The time-series model included six regressors, each representing the block (Go/No-Go), emotion (Neutral/Angry), and block type (Go/No-Go), with gamma convolution. A temporal derivative and temporal filtering were applied. Four contrasts were derived: Go > No-Go, Go > No-Go, Neutral > Angry, Angry > Neutral. *Z* (Gaussianised T/F)-statistic images were thresholded at $p = 0.05$ (uncorrected) at first-level (single run) analysis.

Second-level analysis, which averaged contrast images of two single runs within-subject, was carried out using a fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects; Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004; Woolrich, 2008). Group-level analysis was carried out on all subjects using FLAME stage 1 (Beckmann, Jenkinson, & Smith, 2003; Woolrich et al., 2004; Woolrich, 2008). *Z*-statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$ (Worsley, 2001). Between-group analysis was carried out using FLAME stage 1 (Beckmann, Jenkinson, & Smith, 2003; Woolrich et al., 2004; Woolrich, 2008). Again, *Z* (Gaussianised T/F)-statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$ (Worsley, 2001).

fMRI Contrasts

To isolate areas of activity pertaining to the cognitive (Go and No-Go blocks) and emotional (Neutral and Angry blocks), four contrasts were conducted: Go>No-Go, No-Go>Go,

Neutral>Angry, Angry>Neutral. In each contrast, the mean activation image was subtracted from one another. For example, in the No-Go>Go contrast, the mean image for all Go blocks was subtracted from the mean image of the No-Go blocks. The resulting image contains areas related to No-Go blocks only (Figure 8).

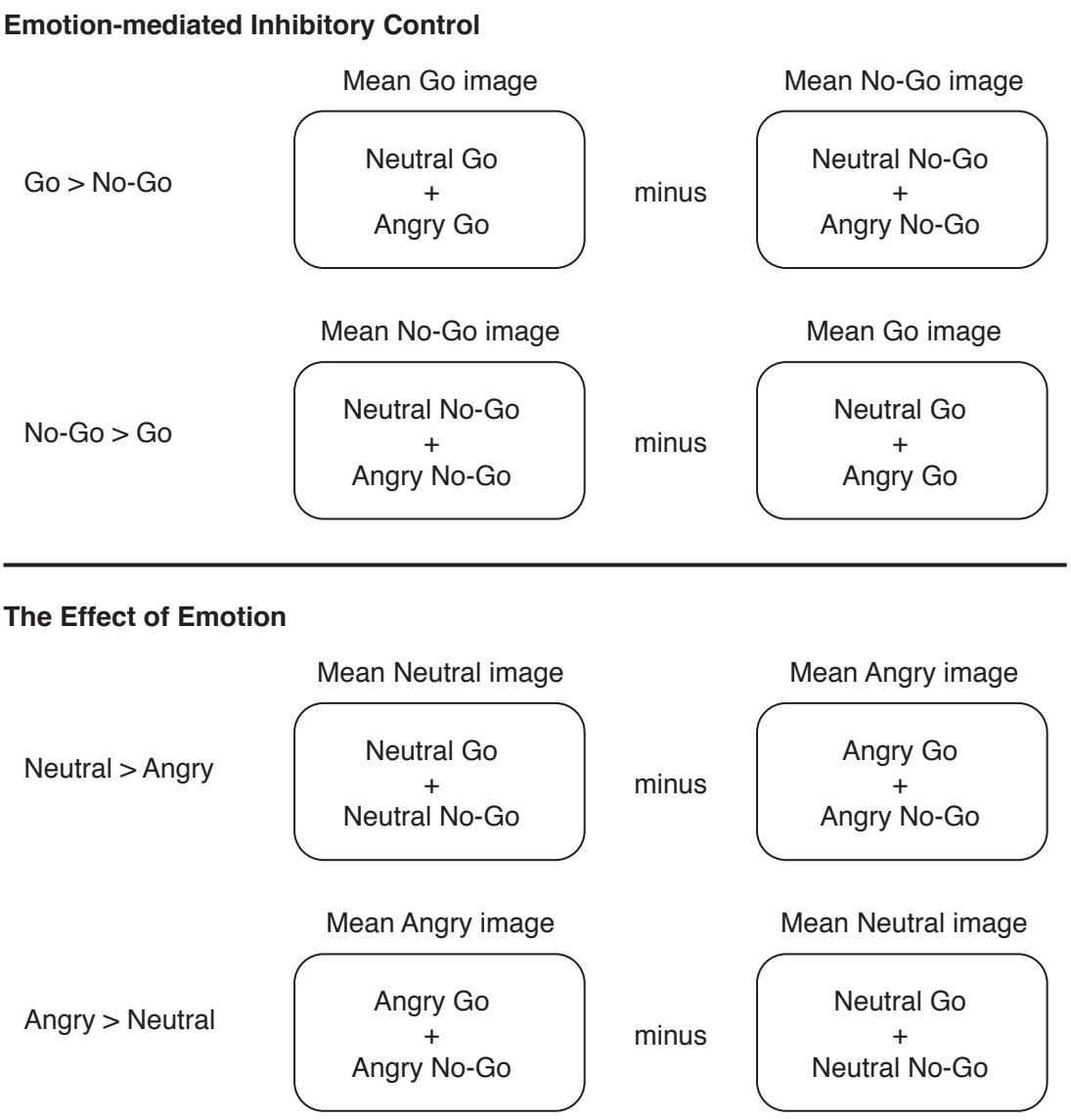

Figure 8. Four contrasts were conducted on the fMRI data collected from the Emotional Go/No-Go task. The resulting image from each contrast was used to determine regions of activity related to each contrast.

Results

Participants

Participants who had agreed to take part in the MRI portion of the longitudinal study from which this data was collected comprised the sample of this study. 30 adolescents between the ages of 10 and 17 years who were diagnosed with concussion by a physician were recruited. The sample was divided into two groups based on their T-score on the CDI 2, shown in *Table 11*. The Elevated depression group consisted of 11 participants (36.7%) who had a T-score of 60 or above. The Average depression group consisted of the remaining 19 participants (63.3%) had a *T*-score of 59 or lower.

Demographic information is depicted in *Table 12*. The mean age of the total sample was 13.7 years. The Elevated group was slightly older (M = 14.2, SD = 2.63) than the Average group (M = 13.5, SD = 2.59), but this was not statistically significant (p = 0.5). The ratio of females to males was 2:1 overall (20 females, 10 males). The Average group had 7 males and 12 females and the Elevated group had 3 males and 8 females. A Fisher's exact test determined that these sex proportions were balanced between groups (p = 0.7). Twelve participants had a previous diagnosis of concussion. Three participants had a previous diagnosis of depression and/or anxiety, 2 whom scored within the Average depression range and 1 whom scored in the Elevated depression range. Time-of-injury to time-of-assessment (reported in weeks) varied from 1 to 6 months. This was not statistically significant between the two groups at visits 1 or 2.

Location of Injury

Participants indicated the following locations of injury: temporal, frontal, occipital, parietal, and face and other body part. The occipital region of the skull was the most common

site of impact (43.3%), followed by the temporal region (16.7%), and the frontal region (16.7%). *Table 12* depicts the proportion of injuries by location. A Fisher's exact test was conducted to compare the proportion of occipital region to other locations between the two groups. The results demonstrate that the proportions of occipital injuries to all other locations between groups is statistically different ($p = 0.02$), indicating that Elevated group was significantly more likely to have been injured in the occipital lobe.

Table 11
Depression Levels & Study Groups

CDI Categories	T-score	Study Groups	n (%)
Average or Lower	0-59	Average	19 (63.3)
High Average	60-64	Elevated	2 (6.7)
Elevated	65-69	Elevated	7 (23.3)
Very Elevated	≥70	Elevated	2 (6.7)

Table 12
Descriptive Characteristics of the Study Sample

Variable		Levels of Depressive Symptoms		
	Total sample	Average	Elevated	*p*-value
N (%)	30	19 (63.3)	11 (36.7)	
Sex *n (%)*				
Male	10 (33.3)	7 (36.8%)	3 (27.3%)	0.7
Female	20 (66.6)	12 (63.1%)	8 (72.7%)	
Age (years) *M (SD)*	13.8 (2.59)	13.5 (2.59)	14.2 (2.63)	0.5
Time since injury (days) *M (SD)*				
Visit 1 (weeks)	5.9 (8.0)	4.9 (6.1)	7.8 (9.7)	0.5
Visit 2 (weeks)	8.2 (8.1)	7.5 (7.5)	9.3 (9.3)	0.39
Time between Visit 1 & 2	2.2 (3.3)	2.6 (4.2)	1.6 (1.0)	0.57
Prior diagnoses *n (%)*				
Anxiety or depression	3 (10)	2 (10.5)	1 (9.1)	
Other psychiatric conditions	0	0	0	
Sleeping disorder	0	0	0	
Learning disability	1	1 (9.1)	0	
History of concussive injury				
Number of participants with past concussions *n (%)*	12	8 (42.1)	4 (36.4)	0.88
Number of past concussions *M (SD) Range*	0.87 (1.04) range:0-4	0.84 (0.89) range 0-3	0.91 (1.3) range 0-4	
Location of injury *n (%)*				
Frontal region	5 (16.7)	4 (13.3)	1 (9)	
Temporal region	5 (16.7)	4 (13.3)	1 (9)	
Parietal region	3 (10)	3 (15)	0	
Occipital region	13 (43.4)	5 (26)	8 (72)	
Face	3 (10)	3 (15)	0	
Other	1 (3.3)	0	1 (9)	

PCSS

An inventory of symptoms was recorded using the PCSS before entering the MRI and after completing the scan. This scale was implemented after the first three participants had been scanner, thus only 27 participants were surveyed. The mean PCSS score of all participants prior to and after the MRI scanning session. PCSS scores did not differ significantly between groups before scanning (M = 20.9, SD = 22.7) or after scanning (M = 26.2, SD = 28.9) for the group as a whole (p = 0.50). When the sample was examined by group, the Elevated group had a higher mean score both before and after the MRI scan (before: M = 22.0, SD = 21.3; after: M = 35.8, SD = 34.8; p = 0.41) compared to the Average group (before: M = 20.2, SD = 24.3; after: M = 19.6, SD = 22.9; p = 0.98), although the difference between the groups was not significant (before: p = 0.52; after: p = 0.11). The mean PCSS scores were submitted to a mixed factor ANOVA (*Table 13*) that treated depression (Elevated/Average) as a between-subject variable and time of survey (Before or After the MRI) as a within-subject variable. Interaction effects between groups and PCSS scores before and after the MRI are not significant (p = 0.066), but show a trend for the Elevated group to report greater symptoms after the MRI as shown in *Figure 9*.

Table 13
Mixed Factorial ANOVA for Post-Concussive Symptoms Before and After MRI scanning

Source	Df	SS	MS	F	p
Between-subjects					
Depression	1	1064	1064	0.92	0.35
Residuals	25	28907	1156		
Within-subjects					
Time (before or after)	1	373	373	2.03	0.167
Depression x Time	1	690	680	3.70	0.066
Residuals	25	4597	184		

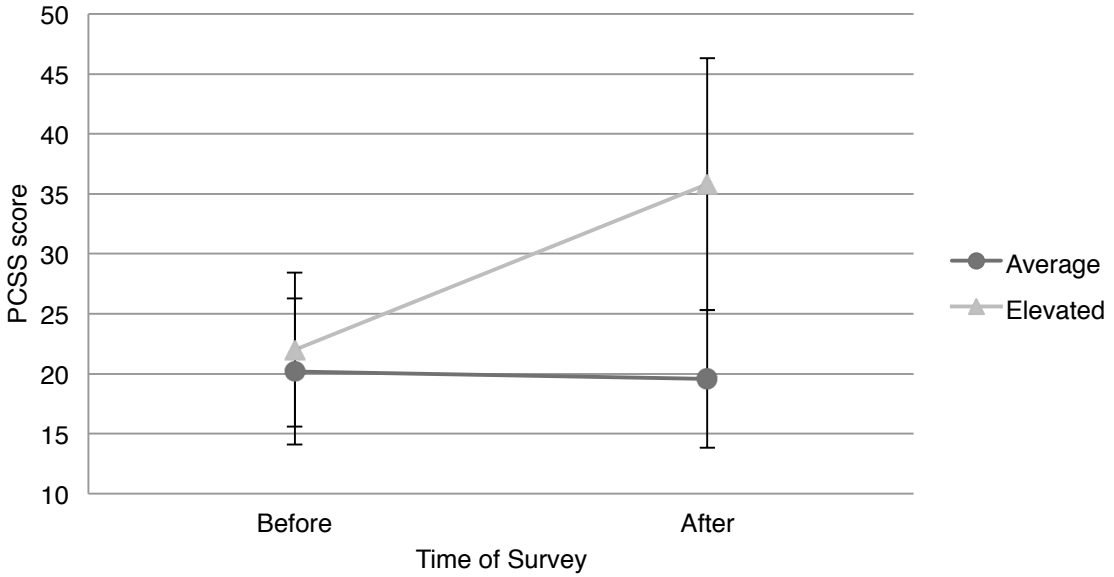

Figure 9. PCSS scores before and after MRI scanning. The interaction effect was not significant (p=0.07) but demonstrated a trend for higher symptom scores in the Elevated group post-MRI scanning.

Emotional Go/No-Go – Behavioural results

Response times. Go blocks and No-Go blocks were each analyzed using a factor ANOVA with depression (Average/Elevated) as the between-subjects variable and block type (Neutral/Angry) as the within-subjects variable. In both Go and No-Go blocks, the results revealed that there was no effect of the block type on response time (Go blocks: $p = 0.82$; No-Go blocks: $p = 0.76$), thus the faces had no effect on response times for either group. The analysis Go blocks revealed that the main effect of depression was significant ($F(1,26) = 4.38$, $p = 0.046$) such that the Elevated depression group had significantly faster response times compared to the Average group on Go blocks. The analysis for No-Go blocks showed that there was no main effect of depression, thus the Average and Elevated groups performed comparably on No-Go blocks. The interaction effects between depression and block type were not significant for either Go blocks or No-Go blocks.

Accuracy. Accuracy rates Go blocks (Table 6) and No-Go blocks were each analyzed using a factor ANOVA with depression (Average/Elevated) as the between-subjects variable and block type (Neutral/Angry) as the within-subjects variable. The analyses revealed similar findings on both Go and No-Go blocks. Again, there were no significant interaction effects between depression and block type (Go blocks: $p = 0.14$; No-Go blocks: $p = 0.81$). The main effect of depression was also not significant either (Go blocks: $p = 0.53$; No-Go blocks: $p = 0.73$), indicating both groups performed comparably in accuracy rates. There was no main effect of block type on either of the Go blocks or No-Go blocks (Go blocks: $p = 0.08$; No-Go blocks: $p = 0.86$); however, there was a slight trend on Go blocks, suggesting that AngryGo blocks yield more correct trials than NeutralGo blocks.

Emotional Go/No-Go – fMRI results

Total sample. The following areas represent threshold-level regions of activity that are visible in response to response inhibition and the social emotional context for the overall sample (*Table 9*). Successful No-Go trials were extracted to determine areas of related to response inhibition. These areas include the right caudate, left occipital fusiform gyrus, bilateral hippocampus, and bilateral anterior cingulate cortex (ACC). The Go > No-Go contrast demonstrates activity solely related to stimulus responding when inhibitory control is not required. Bilateral activity in the thalamus, orbitofrontal cortex (OFC), ACC, and superior frontal gyrus was activated. In comparing these two contrasts, the response inhibition contrast (No-Go > Go) was associated with less diffuse activity compared to the Go > No-Go contrast, but also a lack of activity in areas associated with behavioural inhibition in the frontal regions such as the dorsolateral prefrontal cortex or inferior frontal cortex.

The effect of the facial processing was examined in two contrasts to examine the differential processing of the facial expressions. The Neutral > Angry contrast exhibited a lateralized activity in a number of areas, as shown in *Figure 10*. The thalamus, pallidum, insula, and putamen were seen in the right hemisphere, while the fusiform gyrus, lateral prefrontal cortex, middle frontal cortex, and precentral gyrus were seen on the left. The ACC was bilaterally activated. The Angry > Neutral contrast yielded no above-threshold levels of activity. An exploratory analysis was conducted to determine areas below threshold ($Z = 2.0$, *cluster threshold* = 0.05). Minimal activity was seen in the left fusiform gyrus, likely related to facial processing, and left precentral gyrus, which is associated with motor response. Diffuse areas of white matter areas were also noted in left temporal regions. Limbic midline structures associated with emotion such as the amygdala or cingulate cortex were not seen at this threshold.

Group differences. The analysis was unable to detect differences between Average and Elevated groups in both response inhibition contrasts and emotion processing contrasts at threshold levels. The threshold was relaxed to $Z = 2.0$, *cluster threshold* = 0.05, but only subtle differences were noticeable. The mean activity patterns for each group were analyzed separately. *Table 13* provides a comparison between the regions of activity in Elevated and Average depression groups. In the No-Go > Go contrast, the Average depression group displayed activity in the left occipital fusiform gyrus, but no activity was seen in the Elevated group mean at threshold levels. Lowering the threshold to $Z = 2.0$, cluster threshold=0.05, the left fusiform gyrus, the brain stem, and diffuse white matter clusters in the temporal region emerged in the Elevated group. The Go > No-Go contrast revealed similar activity between the two groups, which might be the reason for the lack of differential activity seen in this contrast. The thalamus, OFC, ACC, and inferior frontal gyrus (IFG) were common for both groups. A few differences were noted: the Average group had the addition of the left pallidum and left insula, while the Elevated group activated the left superior frontal gyrus and bilateral paracingulate cortex (PCC). The Elevated group also had greater activity in the OFC, as shown in *Figure 10*.

When examining neural activity in response to the faces, threshold-levels of activity were not present in the Elevated depression group for either of the two social emotional contrasts. Thresholds were lowered to examine subthreshold regions of activity ($Z = 2.0$, *cluster threshold* = 0.05). The Neutral > Angry contrast (*Figure 11*) revealed that the only common region between the two groups was the occipital fusiform gyrus. The Average depression group displayed activity in the right hippocampus, right insula, and bilaterally in pallidum, OFC, caudate, and putamen. The Elevated group displayed activity in the lateral frontal gyrus, superior

frontal gyrus, and left inferior parietal lobe. Regions associated with Angry > Neutral contrast were minimal, both groups exhibiting little activity at $Z = 2.0$.

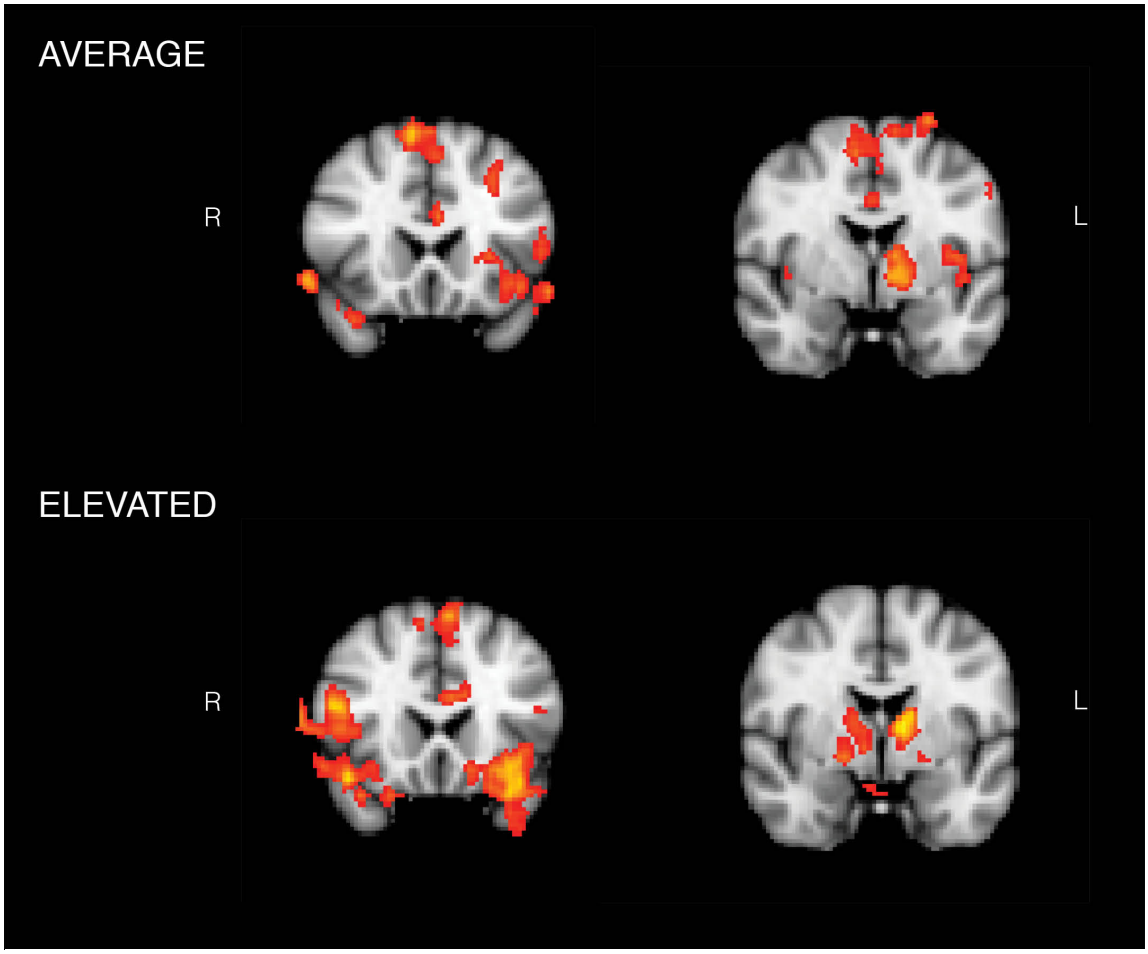

Figure 10. The results from the Go>No-Go contrast revealed that the Average group had the addition of the left pallidum and left insula, while the Elevated group activated the left superior frontal gyrus and bilateral paracingulate cortex, and greater orbitofrontal cortex activity. (Z=2.3, cluster threshold=0.05)

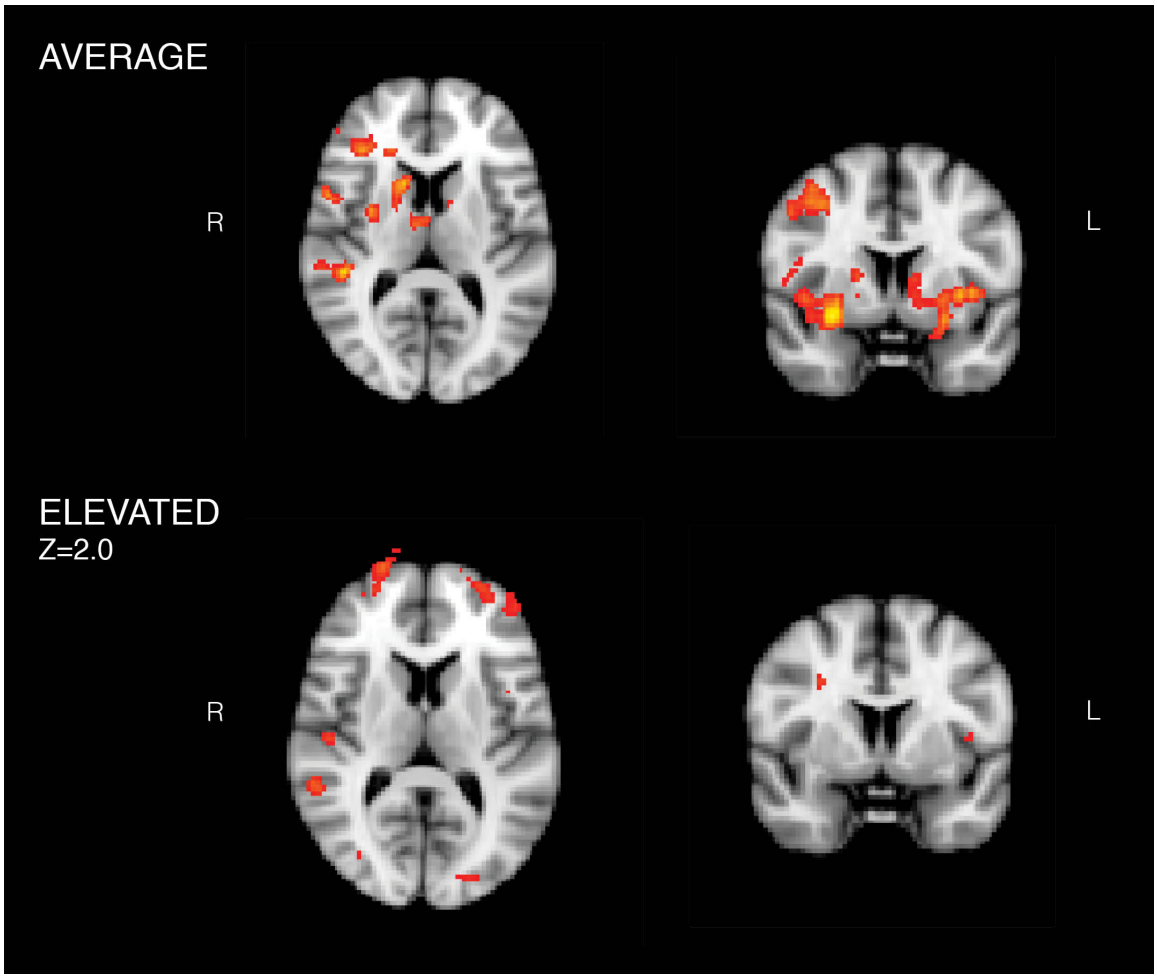

Figure 11. The Neutral>Angry contrast revealed that the Average group (Z=2.3, cluster threshold=0.05) had more areas of activity in comparison to the Elevated group. The areas depicted for the Elevated group were at subthreshold levels (Z=2.0, cluster threshold=0.05).

Table 14

Regions displaying activity during each contrast of the Emotional Go/No-Go task

Contrast	Total Sample		Level of Depressive Symptoms			
			Average		Elevated	
	Region	Hemisphere	Region	Hemisphere	Region	Hemisphere
Go > No-Go						
	Thalamus	L/R	Thalamus	L	Thalamus	L/R
	Orbitofrontal cortex	L/R	Orbitofrontal cortex	L	Orbitofrontal cortex	L/R
	Anterior cingulate cortex	L/R	Anterior cingulate cortex	L/R	Anterior cingulate cortex	L
	Inferior frontal gyrus	L/R	Inferior frontal gyrus	L/R	Inferior frontal gyrus	L/R
	Superior frontal gyrus	L/R	Insula	L/R	Superior frontal gyrus	L
			Pallidum	L	Paracingulate gyrus	L/R
No-Go > Go						
	Occipital fusiform gyrus	L	Occipital fusiform gyrus	L	Occipital fusiform gyrus*	L
	Lingual gyrus	L/R	Lateral occipital cortex	L	Brain stem*	L/R
	Cuneus	R				
	Lateral occipital cortex	L/R				
Neutral > Angry						
	Occipital fusiform gyrus	L	Occipital fusiform gyrus	L/R	Occipital fusiform gyrus*	L
	Pallidum	R	Pallidum	L/R	Superior frontal gyrus*	L/R
	Insula	R	Insula	R	Inferior parietal lobule*	L
	Putamen	R	Putamen	L/R	Lateral frontal cortex*	L/R
	Anterior cingulate cortex	L/R	Orbitofrontal cortex	L/R		
	Thalamus	R	Hippocampus	R		
	Lateral prefrontal cortex	L	Caudate	L/R		
	Middle frontal gyrus	L	Middle frontal gyrus	R		
	Precentral gyrus	L				
Angry > Neutral						
	Occipital fusiform gyrus*	L				
	Precentral gyrus*	L				

Note: The asterisk (*) denotes areas activated at $Z = 2.0$, *cluster threshold* = 0.05.

Discussion

The purpose of this study was to explore the physiological and behavioural effects of emotionally-mediated inhibitory control in adolescents following concussion. While the simultaneous processing of emotional and cognitive information in concussion populations has been explored in the past in both adults and adolescents with concussion (Mäki-Marttunen et al., 2014; Tlusto et al., 2015), this study sought to differentiate performance between adolescents with post-concussive injury experiencing elevated levels of depressive symptoms and those with average or normal levels of depressive symptoms. Overall, the results show subtle differences in cognitive and physiological outcomes between individuals experiencing depressive symptoms and those who are not.

Behavioural performance

Following concussion, adolescents display difficulties with directing attention and controlling behaviour (Howell et al., 2013; Karr et al., 2014; D. R. Moore et al., 2016). In the current study, a Emotional Go/No-Go task similar to the one used by Tlusto et al. (2015) was employed to investigate response inhibition in the presence of emotionally-charged stimuli. The behavioural results indicated that individuals with elevated depressive scores had faster response times during Go blocks than those with normal levels. Since the development of attentional control and executive functioning spans the length of adolescence and mirrors cortical development in the brain, older adolescence tend to have faster response times (Durston et al., 2002; Yurgelun-Todd, 2007). As such, the faster response times presented by Elevated group in the Go condition could be due in part to their slightly older age (13.5 years for the Average

group; 14.2 years for the Elevated group). On the other hand, response times for No-Go blocks, however, did not differ significantly between groups.

Incorporating emotion-laden images in a cognitive task allows for the dual processing of emotion and cognition to be investigated. The emotions of the faces had no effect on response times, but had a trending (not significant) effect on accuracy rates. Angry faces produced slightly more correct trials in Go blocks, an effect that has the potential to show significance with a larger sample size. A study done by Maki-Marttunen et al. (2015) showed that patients with concussions had an enhanced attention for threat-related stimuli. The relevance of the stimulus to the given task played a crucial role in performance, however. Their results suggest that orienting attention towards threat-related stimuli benefited response times when the stimulus was relevant to the task, but hindered performance when it was irrelevant to the task. In the current study, the angry faces (the threat-related stimuli) were irrelevant to the task, but it is possible that the presence of threat heightened attention for the AngryGo block overall. Therefore, there is potentially a threat-related bias in attention in adolescents with concussive injury.

Brain activity patterns

To determine the physiological response of inhibitory control and emotional processing in adolescents following concussion, four BOLD contrasts were analyzed. These contrasts allow for areas associated with particular neural correlates to be identified. For instance, contrasting No-Go activation against resting state should provide activity related to inhibitory control as well as activity for motor responses. In the No-Go>Go contrast, the areas related to motor responding during the Go blocks are subtracted out, allowing for block-specific activity to be isolated. In doing so, researchers can determine the effect of each block type.

Emotion-mediated inhibitory control. When examining patterns of activity for the overall sample of adolescents, the response inhibition contrast (No-Go > Go) displayed fewer areas of activity in comparison to the Go > No-Go contrast. In particular, the response inhibition contrast yielded activity in lateral occipital cortex, fusiform gyrus, cuneus, and lingual gyrus. The lateral occipital cortex and fusiform gyrus are part of the lateral occipital complex, known for object perception and recognition (Grill-Spector et al., 1999). This process is pertinent in identifying the target object (circle) from the foil object (square) and for success in the No-Go block. The expected activity in the prefrontal cortex during No-Go blocks (Casey et al., 1997; Durston et al., 2002) was not seen in this sample, suggesting possible disruptions in the frontal networks during inhibitory control in adolescents with concussion.

On the other hand, Go blocks activated brain regions involved in integrating information. The analysis found both left and right activity in the thalamus, OFC, and ACC, areas which have documented involvement in response inhibition literature (Bokura, Yamaguchi, & Kobayashi, 2001; Casey et al., 1997). The thalamus is involved in the integrating sensory information and maintaining arousal (Portas et al., 1998), while the OFC and ACC are involved in monitoring responses and error detection (Chevrier et al., 2007; Schoenbaum, Roesch, Stalnaker, Takahashi, & Yuji, 2009). The literature also suggests that ACC participates in suppressing the irrelevant information (Bokura et al., 2001), and in the dual processing of emotional and cognitive information (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). However, the areas displayed in this contrast (such as the thalamus, OFC, inferior frontal gyrus, and insula) are also associated with automatic processing and the habituation (Jansma, Ramsey, Slagter, & Kahn, 1985; Levitin et al., 2003; Raffone et al., 2014). Automatizing the behavioural response was the purpose of the Go blocks.

The Effect of the Emotion. The emotion-related contrasts revealed higher levels of activity for neutral faces compared to angry faces. In fact, the Angry > Neutral contrast was unable to demonstrate threshold-levels of activity. The Neutral > Angry contrast demonstrated activity in regions associated with the salience network (insula and ACC), as well as motor responses (precentral and middle frontal gyrus) and motor control (pallidum, putamen). These findings are aligned with other studies investigating the impact of emotional stimuli on response inhibition (Luo et al., 2014; Tlusto et al., 2015). This demonstrates the dual processing of cognitive and emotion-related information when adolescents with concussion are presented with emotional stimuli during inhibitory control tasks.

Group differences. Group differences based on levels of depressive symptoms were subsequently analyzed and revealed that the four contrasts were unable to show threshold-levels of differential activity. However, an exploratory analysis showed that the Average and Elevated groups are engaging different brain regions during the Emotional Go/No-Go task. Brain activity followed similar trends to the total sample analysis (greater activity for Go blocks and Neutral blocks compared to No-Go and Angry blocks), but the Elevated group displayed less activity relate to the Average group. In the No-Go > Go contrast, the Elevated group had subthreshold activity in the occipital fusiform gyrus and brain stem, while the Average group exhibited threshold-levels of activity in the occipital fusiform gyrus as well as the lateral occipital cortex. As previously mentioned, the fusiform gyrus and lateral occipital cortex are associated with shape recognition, which is necessary for differentiating the “go” stimulus from the “no-go”

stimulus. One might speculate whether location of injury affected functional activity in these regions in the Elevated group as 72% of the Elevated group hit the occipital region of the skull.

Some of the main differences between groups in the Go > No-Go contrast involved activity of the left superior frontal gyrus and paracingulate gyrus in the Elevated group. As the No-Go blocks require higher cognitive demands compared to Go blocks, further investigation is required to understand there were fewer areas of activity during No-Go blocks compared to Go-blocks.

Unlike the Go and No-Go contrasts, the emotion-related contrasts yielded dissimilar findings between the two groups. Overall, there was more activity for neutral faces than for angry faces, but in different regions. For neutral faces, there were significantly higher levels of activity in the midline structures (pallidum, caudate, OFC, putamen, hippocampus) in the Average group, whereas the Elevated group displayed frontal and parietal activity. These suggest that the Elevated group was engaging in more evaluative processes when presented with emotion-related information. The regions activated in the Average group are associated with the basal ganglia, which is important for executive functioning as it is involved in the selection of a behavioural response (Graybiel, Aosaki, Flaherty, & Kimura, 1994; Rieger et al., 2013), which is an appropriate response given that participants were instructed to withhold a from pressing the button when the face appears and wait for the shape.

Similar to the findings in this study, past research shows that clinically depressed populations display greater activity in frontal regions relative to healthy controls for emotion-related stimuli (Dichter, Felder, & Smoski, 2009; Langenecker et al., 2007). While the activity of the frontal lobe regions in the Elevated group were not significantly higher than the Average group, Dichter et al. (2009) suggest that individuals experiencing depression require more frontal

activity to disengage from emotion-related stimuli. Therefore, adolescents experiencing depressive symptoms after concussion may also demonstrate impairments in managing affective information.

MRI scanning on post-concussive symptoms

A concern surrounding MRI scanning is the effect of loud noises on post-concussive symptoms. The results from the PCSS showed that the overall sample showed that symptoms did not differ significantly as a result of the MRI scanning. However, MRI scanning may worsen post-concussive symptoms for individuals with elevated depression scores. It suggests that the Elevated group may be more sensitivity to sensory stimulation.

Location of injury

A survey of the location of injury found that the occipital region was the main point of impact for a number of participants, which was statistically higher in participants with elevated depression scores. The site of injury is not the only recipient of the peak impact following a concussion. The rebounding effect of the brain (the coup-contrecoup phenomenon) can, in turn, cause the opposite side of the brain to hit the inside of the skull (Drew & Drew, 2004; L. Zhang, Yang, & King, 2004). Therefore, occipital region injury can lead to frontal lobe injury. Frontal lobe dysfunction has been shown in psychiatric populations (Baxter et al., 1989; Drevets et al., 1997); however, it remains inconclusive whether occipital lobe injuries lead to higher rates of depression following concussion. However, frontal lobe injury could explain the lack of activity in this region during the inhibitory control condition of the Emotional Go/No-Go.

Limitations

The current study did not detect differences between groups or in response to different emotions. The processing of emotion-related information, particularly faces, occurs rapidly and it can occur without awareness (Crouzet, Kirchner, & Thorpe, 2010; Pessoa, 2005). Since the Emotional Go/No-Go paradigm used in this study shows the faces 250-550 ms prior to the relevant objects (the circles and squares), it is possible that evaluation the threatening stimuli had already occurred before the engaging in response inhibition. Thus, the emotion displayed on the faces may not affect responses to the shapes.

Moreover, the sample was relatively small in size and high in variability. One contributing factor to variability was the large age range of the participants. Adolescent years mark a period of rapid neuronal growth and, as such, the effects of concussion on inhibitory control may vary by age. In addition, the trauma may have induced greater variability in functionality among participants, which would reduce the likelihood of identifying differences between groups.

Yet another factor is motion in the MRI scanner. Since both temporal and spatial resolution is important for imaging analysis, scanning children poses difficulty because they are required to remain still for the duration of the scan. A number of participants had shifted between 4-8 mm, which creates a lot of noise in the sample. An analysis that eliminated scans that had movement over 5 mm was conducted, but group differences were still not significant. Therefore, a combination of factors is likely to contribute to the lack of group differences in this study.

The processing of emotion-related information, particularly faces, occurs rapidly and it can occur without awareness (Crouzet et al., 2010; Pessoa, 2005). One study found that neural responses to angry faces can occur within 30 ms of stimulus presentation (Morris, Ohman, &

Dolan, 1998). The Emotional Go/No-Go paradigm used in this study shows the faces 250-550 ms prior to the relevant objects (the circles and squares). It is possible that evaluation the threatening stimuli had already occurred before the engaging in response inhibition; thus, the effect of the emotion on the faces may not have affected performance.

Conclusion

Engaging in inhibitory control processes results in fewer areas of brain activity in comparison to simple, automated tasks in adolescents with concussive injury. Frontal regions that are usually associated with inhibitory control were not activated, which suggests that an impairment in the frontal networks. These findings suggest that differences in emotion-mediated inhibitory control between individuals with elevated and normal levels of depressive symptoms are not expressed behaviourally, but display physiological differences in the allocation of cognitive resources.

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CHAPTER 4:

DISCUSSION & CLINICAL RELEVANCE

Overview

The cognitive and emotional sequelae that follow a concussion are the result of a trauma-induced neurochemical cascade in the brain, termed a "neurotransmitter storm" (Giza & Hovda, 2001). Much like this neurotransmitter storm, both the cognitive and emotional consequences of a concussion are not often visible, yet they affect the individual with concussion profoundly. Grasping an understanding of these symptoms holds clinical relevance to the recovery of concussion. The current findings contribute to the body of knowledge surrounding the link between concussion and depressive symptoms and the relationship between depressive symptoms and poor executive functioning. The main purpose of this thesis was to explore the link between post-concussive depressive symptoms and executive dysfunction in adolescents with a particular focus on the effect of emotional cues on inhibitory executive control.

The following provides a summary of the results from a sample of adolescents aged 10 to 17 years who had been diagnosed with concussion. The key messages derived from the findings relay information relevant to 1) adolescents with concussion, 2) adolescents with concussion experiencing depressive symptoms, 3) executive dysfunction following concussion, 4) the link between post-concussive depressive symptoms and executive dysfunction in adolescents.

Post-Concussive Depressive Symptoms

The research presented in Chapters 2 and 3 used the Children's Depression Inventory (CDI) as a measure of the extent to which depressive symptoms impeded daily function in

adolescents following concussion. Scores on the CDI were used to determine if a participant exhibited elevated or normal levels of depressive symptoms. Of 30 participants, 36.7% (n=11) reported elevated levels of depression (T-score ≥60) and comprised the Elevated symptoms group. The other 63.3% (n=19) scored within normal levels of depressive symptoms and thus comprised the Average symptoms group. This rate of elevated levels of depressive symptoms is similar to the 22% reported by Stazyk et al. (in press), which is much higher than the 5-11% rate reported in the general population (Haarasilta et al., 2001; Kessler et al., 2012; Richardson et al., 2010).

Pre-existing factors that increase the susceptibility of adolescents to depressive symptoms were not examined as this was not the primary research goal. In the general population, females have been shown to report depression at a higher rate (Bromet et al., 2011; Haarasilta et al., 2001). Although the sex proportions were not statistically different in the current study sample as shown in Chapter 2, the study sample comprised of twice as many females than there were males. Therefore, it is unclear if sex played a role in the high rate of elevated levels of depressive symptoms in this sample.

The Post-Concussive Symptom Scale (PCSS), a self-report measure of concussion symptom frequency and severity, includes common emotional symptoms that arise following a concussion. Past research has shown that individuals who report higher depressive symptoms are also more likely to report more post-concussive symptoms (Kumar et al., 2014; Stazyk et al., in press). Unlike previous findings, the results from the PCSS from the current study showed that the Elevated group had a higher mean PCSS score, but it was not significantly different from the Average group. This suggests that levels of depressive symptoms may be independent of

concussion symptom severity. However, the high variability in symptom reporting on the PCSS might account for the lack of difference in PCSS score between the two groups.

By examining specific items on the PCSS that are related to depression (fatigue, irritability, sadness, nervousness, emotionality), between-group differences in symptom reporting are detectable. The Elevated group reported a statistically higher number of depressive symptoms and with greater severity, particularly in irritability, nervousness, and emotionality. This demonstrates that particular post-concussive symptom ratings may be more indicative of depression than the overall PCSS score. Irritability, nervousness, and emotionality are overlapping symptoms of depression and concussion and may help to identify individuals who might be at risk for depression. It is, therefore, important for clinicians to take note when an adolescent with a concussion scores high on these depressive symptoms on the PCSS as they may be indicative of greater emotional distress.

In addition to symptom profiles, the site of impact has shed some insight on post-concussive depressive symptoms. An examination of the first site of impact revealed that 13 participants (43.3%) were injured on the occipital region of the head, 8 of whom belonged to the Elevated depression group. The number of injuries to the occipital region of the skull was significantly higher for individuals with elevated depressive symptoms. While it is possible that individuals who injured the back of the head may have sustained a harder hit, a rebounding force known as the coup-contrecoup (Drew & Drew, 2004; L. Zhang et al., 2004) originating from the occipital region may have caused additional injury to the frontal region. Frontal lobe dysfunction has been linked with depression in the past literature (Baxter, et al., 1989; Colich, Foland-Ross, Eggleston, Singh, & Gotlib, 2015). As this is the first study to identify that a potential link between location of injury and the emergence of depressive symptoms, the mechanism through

which an occipital region injury could lead to depressive symptoms is unexplored. An investigation of this link could help to determine adolescents at risk of depressive symptoms following concussion.

Executive Function After Concussion

The concussion-specific neurocognitive test, ImPACT, described in Chapter 2 evaluated multiple domains of cognition and incorporates measures of executive function. There were no differences between the depression groups on any the composite scores including those measuring executive function: impulse control, reaction time, visual motor speed (or processing speed). There was however evidence of poor executive functioning in the total sample. Specifically, a higher percentage of individuals scored under the 10^{th} percentile range in processing speed (50%) and reaction time (56%). Similarly, 73.3% fell below average on cognitive efficiency, a measure ImPACT uses to address the relationship between speed and accuracy during testing. These results contribute to the literature that demonstrates marked deficits in executive functioning and highlight the importance of assessing neurocognitive function post-concussion as it is informative of recovery.

Inhibitory Control in the Presence of Emotional Stimuli

The purpose of the data analyses described in Chapter 3 was twofold: to examine response inhibition in the presence of emotionally stimulating images, and to determine the impact of the emotional valence (angry / neutral) of the images on response inhibition using a psychological test called the Go/No-Go test. The Go/No-Go is a paradigm used to measure inhibitory control by creating an automatic behavioural response that, subsequently, requires

inhibiting. The Emotional Go/No-Go incorporated faces to prime the emotional context in which inhibitory control is exercised. This task assesses to the evaluation of threat and the ability to ignore emotional, task-irrelevant environmental cues.

Both the Average and Elevated groups were slower to respond to No-Go blocks than to Go blocks, as was expected with the engagement of higher cognitive demands with inhibitory processes in No-Go blocks (Logan, Schachar, & Tannock, 1997). However, accuracy rates were comparable between the two depression groups for both Go and No-Go blocks, suggesting that the delay in response times to No-Go blocks was in efforts to maintain accuracy. It was hypothesized that the Elevated group would perform more poorly on No-Go blocks than the Average group, a trend that is documented in the literature when comparing individuals who are clinically diagnosed with depression compared to healthy controls in inhibitory control (i.e. Gohier et al., 2009). The results from the Emotional Go/No-Go demonstrate that the Elevated group's response times and accuracy rates did not differ from that of the Average group's significantly. Therefore, emotional stability following concussion does not show a beahvioural relationship to task performance in response inhibition. This corroborates with the results from ImPACT that show that no significant differences between depression groups on impulse control. However, even when comparing adolescents with TBI to healthy controls, earlier findings that show that adolescents with TBI do not perform differently than healthy controls on measures of inhibitory control (Tlusto et al., 2015).

The MRI scanner monitored brain activity during the completion of the Emotional Go/No-Go task. Brain activity patterns in response to these cognitive processes reflect overall group level patterns as well as subtle between-group differences. Overall, the group displayed fewer areas of brain activity during the inhibitory condition (No-Go) compared to the habituation

condition (Go). In the inhibitory condition, the group as whole had activity in the lateral occipital cortex, which has been shown to be involved in object recognition (Grill-Spector et al., 1999), as well as facial recognition areas including the occipital fusiform gyrus, lingual gyrus, and cuneus. These areas that were activated during the inhibitory condition have also been associated with mediating social interactions (Luo et al., 2014; Saggar, Shelly, Lepage, Hoeft, & Reiss, 2014). As the faces are present when the "go" or "no-go" stimulus appears, these areas of activity suggest that there was a level of social processing taking place during the inhibitory condition that was not seen when participants simply had to respond during the Go blocks. Furthermore, the areas that are generally associated with inhibitory control such as the prefrontal cortex did not display significant activity in either group. When comparing the Average depression group to the Elevated in brain activity, the differences were not significant. However, the mean activation patterns for each of the groups revealed that the Average group had significant activity in the occipital fusiform gyrus and lateral occipital cortex whereas the Elevated group displayed no areas that reached significance. Although the groups displayed comparable behavioural performance during the inhibitory condition, these fMRI results suggest that differences in functional connectivity. Taken together, these are the modulatory effects of emotion processing on inhibitory control in adolescents following concussion. These results show that the adolescents in this sample were more likely to engage in areas related to facial appraisal than regions associated with cognitive control.

Contrary to the behavioural findings in the inhibitory condition, Go blocks yielded significant difference in performance between the Elevated and Average depression groups that indicated that the Elevated group was significantly quicker to respond. Go blocks were designed to habituate a response that would later be inhibited. In an evaluation of brain activation patterns

during Go blocks revealed that the two groups had similar areas of activity (i.e. thalamus, orbitofrontal cortex, anterior cingulate cortex, inferior frontal gyrus). The superior frontal gyrus and paracingulate gyrus were the only two regions that were activated in the Elevated group that was not displayed in the Average group. However, further research is needed to understand this facilitated performance in adolescents with higher depressive symptoms.

The Effects of Emotional Processing

The emotion of the faces (angry or neutral in expression) did not demonstrate a significant effect on performance. Response times and accuracy rates were not statistically different between angry and neutral faces for either of the two depression groups. However, a trend towards a significant effect of angry faces on accuracy ($p=0.07$) demonstrates a potential threeat-related influence on performance such that the emotion of the faces heightened arousal and, therefore, attention. Similar findings were shown in an adult study in which patients with concussion had faster response times in threat-related conditions compared to neutral conditions but only when the emotional stimuli were relevant to the task (Mäki-Marttunen et al., 2014). As the emotional stimuli were irrelevant to the task used in this thesis, the facilitated response times towards threat-related images might suggest that adolescents are worse at inhibiting irrelevant emotional information.

The fMRI results of the emotional aspects of the task found that the Average and Elevated groups engaged slightly different brain regions in response to the faces. While the differences did not reach statistical significance, the Elevated group displayed areas superior frontal gyrus, inferior parietal lobule, and lateral frontal cortex. These areas have been associated with mediating social interactions and evaluating faces (Akitsuki & Decety, 2009; Iacoboni et

al., 2004). The findings of past literature and the current study suggest that individuals with elevated depressive symptoms are more likely to allocate cognitive resources towards the appraisal of faces. Therefore, emotional stimuli activate cognitive regions individuals with depressive symptoms following concussion, which reflects the engagement evaluative processes in response to emotion-related images.

Clinical Significance

One of the primary goals of clinicians and other health professionals working with adolescents who have sustained a concussion is to support the adolescent in the return to daily activities in a timely manner while addressing safety measures to avoid the worsening of symptoms or a repeated injury. Attending school and participating in physical activity are important for their academic, physical, and psychosocial development. Both executive dysfunction and depression hinder the return to school and physical activity.

Executive function plays a pivotal role in academic performance throughout childhood and adolescences as it involves attentional systems, self-regulatory processes, and cognitive flexibility (Miyake et al., 2000). These executive functions work in concert to aid in the adaptability to new environments and in the achievement of new skills, both of which are essential for academic performance (Diamond, 2013; Miyake et al., 2000). Poor academic performance has been linked with deficits in executive functioning such as poor inhibitory control (Liew et al., 2008; Passolunghi & Siegel, 2001). As hypothesized by the cognitive reserve theory discussed in Chapter 1, concussion reduces the efficiency of brain networks such that adolescents with concussion are less able to adapt to meet task demands. Thus, symptoms are more likely to emerge. Research has shown that when children return to school too quickly

following a concussion, they are more likely to have prolonged symptoms (Brown et al., 2014). The current findings demonstrate that the use of concussion-sensitive assessments benefits in the detection of abnormal cognitive functioning. They contribute to the mounting evidence that the assessment of executive function following concussion is important in back-to-school decision-making.

Moreover, emotional responses can interrupt cognitive processing (Cohen & Henik, 2012; Derakshan, Smyth, & Eysenck, 2009; Ladouceur et al., 2009). It places greater demands on the cognitive control system to suppress attention towards emotional distractors. While a unified theory has yet to be developed, models derived from the literature support the integration of emotion and cognition. The arousal-biased theory is one of the theories rooted in this integrated approach. According to the arousal-biased theory, emotional context can influence cognitive performance, as shown by the negative effect of threatening images on reaction time. At the same time, the arousal-biased theory posits that top-down cognitive processing allows for the maintenance of goals by suppressing information that is irrelevant to the goal (Mather & Sutherland, 2011). As such, the influence of the emotional context is lessened. In terms of the arousal-biased theory, the results of the current study demonstrate that adolescents with concussion may display difficulties in suppressing attention for cues external to their goals.

Emotional cues, particularly those that are threatening, are present in everyday situations. Adolescents encounter them in competitive sports as well as in school settings where high demands for concentration are contended with inevitable emotional processing. While clinical assessments are important for capturing the behavioural aspects of concussive injury, function brain imaging provides insight into the neural underpinnings of behavioural outcomes. Through fMRI scanning, differences in the engagement of brain areas demonstrated how adolescents with

depressive symptoms differ from their counterparts. This might inform clinicians about how individuals with depressive symptoms following concussion react to emotional cues. Understanding how emotional cues affect function in adolescents following concussion provides insight into the role the environment plays in contributing to the cognitive demands placed on adolescents recovering from concussion.

In addition, the current work emphasizes the importance of assessing depressive symptoms in adolescents following concussion. As shown in Chapter 2, neurocognitive performance of individuals expressing depressive symptoms compared to those without depressive symptoms is not significant. Thus, differences in function for those with elevated depressive symptoms may not be detectable using clinical cognitive measures. Regardless of cognitive function, detecting abnormal depressive symptoms adolescents is indicative of poor emotional health. Adolescents who have been clinically diagnosed with depression, including those who display subthreshold levels of depression, are more likely to perform poorly in school, show poor social skills, and display behavioural issues (Fergusson et al., 2005; McLeod et al., 2016). The past literature in conjunction with the current findings emphasize that screening for depression in pediatric populations after concussion may provide clinical insight into concussion recovery as post-concussive depressive symptoms may be indicative of poorer psychosocial functioning and greater psychological distress following concussion (Rapoport et al., 2003). Thus, clinicians should continue to monitor depressive symptoms throughout concussion recovery in addition to cognitive assessments.

Conclusion

Adolescents with concussion perform worse on cognitive tests of reaction time and processing speed compared to healthy controls. Neurocognitive performance was comparable between the Average and Elevated depression groups. Nonetheless, concussions have an impact on neurocognitive performance. Concussion leads to marked deficits in executive functioning, but individuals with elevated depression levels do not exhibit greater difficulties in executive functioning than those with normal depression levels. In terms of brain activity levels, adolescents with concussion tend to display fewer areas of activity during demanding inhibitory control tasks, and more areas of activity during simple automated tasks. Adolescents with concussion who are experiencing depressive symptoms have comparable performance to adolescents who are not experiencing depressive symptoms in response inhibition in the presence of emotional stimuli, but display fewer areas of functional brain activity and a lack activity in the prefrontal regions. To that end, depressive symptoms and emotion-mediated inhibitory control demonstrate a physiological relation, which should be investigated further with a larger sample size.

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Appendix A: Ethics Approval Letter

Hamilton Health Sciences

McMaster University
Inspiring Innovation and Discovery

St. Joseph's Healthcare Hamilton

Hamilton Integrated Research Ethics Board (HIREB)
293 Wellington St. N., Suite 102, Hamilton, ON L8L 8E7
Telephone: 905-521-2100, Ext. 42013
Fax: 905-577-8378

June 23, 2014

PROJECT NUMBER: **14-376**

PROJECT TITLE: Safely Returning Children and Youth to Activity after Concussion

PRINCIPAL INVESTIGATOR: **Carol DeMatteo**

This will acknowledge receipt of your letter dated June 11, 2014 which enclosed revised copies of the Information/Consent Forms, Assent Form, Outstanding Signatures and the Application Form along with response to the additional queries of the Board for the above-named study. These issues were raised by the Hamilton Integrated Research Ethics Board at their meeting held on May 20, 2014. Based on this additional information, we wish to advise your study has been given ***final*** approval from the full HIREB.

The following documents have been approved on both ethical and scientific grounds:

- The submission
- Study Protocol
- Information/Consent Form - Parent version 2 dated May 29, 2014
- Information/Consent Form – Youth 16-18 Years version 1 dated May 29, 2014
- Assent for children and Adolescents 7-15 Years of Age version 2 dated May 29, 2014
- Recruitment Poster – Safely Returning Children and Youth to Activity After Concussion version 2 dated June 20, 2014
- Recruitment Poster (with Tear-Off tabs) – Safely Returning Children and Youth to Activity After Concussion version 2 dated June 20, 2014
- Recruitment Postcard version 1 dated April 17, 2014
- Concussion Management Guidelines Information Sheet for Returning to activity and School for Children and Youth
- Concussion Management Guidelines Brochure for Return to Activity for Children and Youth
- Concussion Management Guidelines Brochure for Return to School for Children and Youth
- Parent Perception of Guidelines Questionnaires version 1 dated April 11, 2014
- Child Perception of Guidelines Questionnaires version 1 dated April 11, 2014

The following documents have been acknowledged:

- CIHR Authorization of Funding Letter dated February 10, 2014

Please note attached you will find the Information/Consent Forms, Assent Form and Recruitment Posters with the HIREB approval affixed; all consent forms/assent forms/posters used in this study must be copies of the attached materials.

The Hamilton Integrated Research Ethics Board operates in compliance with and is constituted in accordance with the requirements of: The Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans; The International Conference on Harmonization of Good Clinical Practices; Part C Division 5 of the Food and Drug Regulations of Health Canada, and the provisions of the Ontario Personal Health Information Protection Act 2004 and its applicable Regulations; for studies conducted at St. Joseph's Hospital, HIREB complies with the health ethics guide of the Catholic Alliance of Canada

REB #: 14-376 -DeMatteo

We are pleased to issue final approval for the above-named study for a period of 12 months from the date of the HIREB meeting on May 20, 2014. Continuation beyond that date will require further review and renewal of HIREB approval. Any changes or revisions to the original submission must be submitted on an HIREB amendment form for review and approval by the Hamilton Integrated Research Ethics Board.

PLEASE QUOTE THE ABOVE-REFERENCE PROJECT NUMBER ON ALL FUTURE CORRESPONDENCE

Sincerely,

S. Salama

Suzette Salama, PhD.
Chair, Hamilton Integrated Research Ethics Board

Appendix B – Parent Consent Form

LETTER OF INFORMATION / CONSENT

Safely Returning Children and Youth to Activity after Concussion

Local Principal Investigator:
Prof. Carol DeMatteo, MSc OT(Reg)
School of Rehabilitation Science
McMaster University
Hamilton, Ontario, Canada
(905) 525-9140, ext. 27805
E-mail: dematteo@mcmaster.ca

Co-Investigators:
Dr S. Singh, Dr. L. Giglia, (McMaster Children's Hospital); Dr. M. Noseworthy, Dr N. Bock, Dr. J. Connolly; Dr. B. Timmons; Dr. M. Mazurek; Dr. G. Hall; Ms C. Cupido (McMaster University)

Funding Source: Canadian Institutes of Health Research

You and your child are being invited to participate in this research study being conducted by Carol DeMatteo, because your child has recently had a concussion. In order to decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits. This form gives detailed information about the research study, which will be discussed with you. Once you understand the study, you will be asked to sign this form if you and your child wish to participate.

What is the study about?

The decision regarding return to activity following Mild Traumatic Brain Injury (MTBI)/concussion is one of the most difficult and controversial areas in concussion management for adults and even more complicated for children and youth. Children who sustain a MTBI are being provided with management strategies and return to activity guidelines that have been designed for adult athletes. Children and teenagers are at high risk for repeat injuries within a short period of time as well as prolonged symptoms affecting their school and leisure participation. Experts agree that return to

activity (RTA) including return to School (RTS) decisions should be more conservative, cautious and individualized for children and youth.

Outcomes of the study will include: time to symptom resolution, repeat injuries, length of time to return to play and school and parents' and children's perception of the new guidelines. Electronic activity monitoring devices as well as APPS for symptom monitoring will be used to provide both compliance with guidelines and health information. In order to understand how children with different symptom resolution differ biologically, we will incorporate new EEG and MRI techniques never used with children with concussion on a small subsample of the children. The issue of returning to activity after MTBI is very important to the children and families of Canada. Protecting the brains of our children through increased knowledge and decision-making based on sound research is paramount.

What is the purpose of this study?

This study will determine if following these new RTA and RTS guidelines results in decreased duration of post-concussive symptoms and risk for subsequent head injuries in children and youth 5-18 years of age. This study will also use accepted measures of brain function (MRI with exercise and Neurovox® EEG) but never before used with children with concussion to help us learn about what is actually happening in the brain during the recovery period.

How will my child be involved in this study?

If you and your child consent to be a participant in the study, we will ask you to do the following things. As soon as you enter the study, you will be given and taught how to use the guidelines. The following are study activities that you and your child will be asked to complete:

- Your child will be asked to wear a pager-sized accelerometer called an Actigraph, which collects daily activity information.
- You will also be asked to keep a log, provided to you, of your child's cognitive activity.
- You will also be provided with a symptom-monitoring APP that will require completion every 2 days and will take 5 minutes to complete.
- Within one week of entering the study, a computerized neurocognitive test (ImPact), balance test, a children's depression questionnaire and a quality of life questionnaire will all be administered at McMaster University by an occupational therapist or research assistant. This will take approximately 45 minutes to one hour.
- These tests will be repeated when symptoms have ended and again 3 months after symptoms disappear.

Approximately 60 youth aged 10-18 will be randomly selected to receive a Magnetic Resonance Imaging (MRI) brain scan and a new type of electroencephalogram (EEG) of the

brain, to help us learn about what is happening in the brain during recovery from concussion. You can still be involved in the study and decline having these brain tests.

What will happen during the (MRI) scan and the EEG testing?

THE MRI
Your child will have 2 MRIs at St. Joseph's Healthcare Hamilton, the 1st one within 1 month of entering the study and the 2nd scan, three months after the symptoms have disappeared. During each scan, he or she will be scanned immediately before and after exercising on a stationary reclined cycle, especially designed for the MRI and already pilot tested by us in another research study. It will take 1 hour.

The Neurovox® EEG
The protocol can be completed quickly during the child's visit for the balance testing, as the equipment is portable and testing time is 1 hour. The EEG system uses dry electrodes attached to a cap that the child wears. He or she is then given age appropriate language questions while the brain activity is recorded.

What are the risks?

Some participants may experience worsening of post-concussion symptoms during the completion of the testing protocol due to physical or cognitive exertion (e.g. headache, dizziness, nausea, etc.). In the event of worsening post-concussion symptoms, all testing will be stopped immediately and resumed again only after a minimum period of 24 hours of rest and the resolution of symptoms. If symptoms do not resolve and/or you do not want to continue with the testing, there will be no negative consequences.

Some participants may feel anxious about their performance or testing in general. The research study team will explain the tests in detail and take special care to emphasize that their results will be completely confidential and not shared with anyone outside of the research team.

Some children may be claustrophobic and not able to undergo the MRI and they do not have to undergo this test.

What are the benefits for my child and our family and for society?

The potential benefits of children being carefully monitored to control their activity level and better follow the guidelines for restricted activity could quite possibly decrease their symptoms. Close monitoring will also alert the family, the child, school and the research team of any concerning symptoms and need for intervention. The following of the guidelines will prevent the child from returning to activity before they are ready and this can help to prevent further injury to a vulnerable recovering brain.

Concussion in children and youth is reaching epidemic proportions in our society with the increased participation and intensity of sport competition. We propose a new evidence-based guideline approach designed specifically for children 5-18 years. These guidelines have the potential to prevent repeat injuries and the problems such as depression, anxiety and school failure associated with chronic symptoms. This study will be the first to measure activity levels of concussed individuals during recovery to see if adherence to these child-specific guidelines does indeed prevent negative outcomes.

How many people will be in this study?

The study will involve 360 children and youth 5-18 years who have had a concussion, recruited from the Hamilton and surrounding regions. Only 60 of these children will receive the MRI and EEG scans of the brain. The study will end for each participant, 3 months after the concussion symptoms have disappeared. For most children they will be in the study for 3-6 months.

What if I change my mind about being in the study?

Your participation in this study is voluntary. You and your child may decide not to be in this study, or to be in the study now and then change your mind later. You and your child may leave the study at any time without affecting your care. You may also refuse to answer any questions and still remain in the study. Choosing not to participate in this study will in no way affect your care or treatment.

If you and your child decide to leave the study, the information that was collected before you and your child left the study will still be used, but you do have the option to remove it from the study.
If you choose to leave the study, you are still provided with the child post concussion guidelines to follow, as you and your physician deem necessary.

What information will be kept private?

All the information that we collect about your child will be kept private. Your data will not be shared with anyone except with your consent or as required by law. All personal information such as your name, address, phone number, OHIP number, family physician's name will be removed from the data and will be replaced with a number. A list linking the number with your name will be kept in a secure place, separate from your file. The data, with identifying information removed will be securely stored in a locked office in the research offices at CanChild, the Centre for Childhood Disability Research. No one but the study staff will know that it is your child who is in the study.

If the results of the study are published, your child's name will not be used. All data collected from all participants will be combined to form one large data set. As a result, individual participants will not be identified.

The information that is collected for the study will be kept in a locked and secure area by the researchers for 10 years. Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital.

Representatives of Hamilton Integrated Research Ethics Board may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines.

Will I be paid to participate in this study?

If you participate in the study, your child will receive a $20 generic gift card and you will be provided with parking vouchers for days of assessment visits to the university.

Questions about the Study

If you have questions or need more information about the study itself, please contact:

Local Principal Investigator	Research Coordinator at McMaster
Carol DeMatteo School of Rehabilitation Science McMaster University Hamilton, Ontario, Canada **(905) 525-9140 ext. 27805** **E-mail: dematteo@mcmaster.ca**	Chia-Yu Lin CanChild Centre for Childhood Disability Research McMaster University **905 5259140 ext 26842** **E-mail: concuss@mcmaster.ca**

CONSENT

Safely Returning Children and Youth to Activity After Concussion

Legally Authorized Representative:

I have read the preceding information thoroughly. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I understand that I will receive a signed copy of this form.

I give my permission for _____ to participate in this study. (Child's Name)

Name, Relationship to Participant	**Signature**	**Date**

Person obtaining consent:

I have discussed this study in detail with the participant. I believe the participant understands what is involved in this study.

Name, Role in Study	**Signature**	**Date**

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB). The HIREB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions regarding your rights as a research participant, please contact the office of HIREB at 905.521.2100 x 42013.

Appendix C – Youth Consent & Assent Forms

ASSENT FORM FOR CHILDREN AND ADOLESCENTS 7-15 YEARS OF AGE

Title of Study: Safely Returning Children and Youth to Activity after Concussion

Investigators:
Prof. Carol DeMatteo, School of Rehabilitation Science McMaster University
(905) 525-9140 ext. 27805; E-mail: dematteo@mcmaster.ca

Dr. S. Singh, Dr. L. Giglia, (McMaster Children's Hospital); Dr. M. Noseworthy, Dr N. Bock, Dr. J. Connolly; Dr. B. Timmons; Dr. M. Mazurek; Dr. G. Hall; Ms C. Cupido (McMaster University)

Funding Source: Canadian Institutes of Health Research

Why are we doing this study?
A research study is a way to learn more about people and what is the best way to help them. After a child or teenager has an injury to the brain sometimes called Mild Traumatic Brain Injury or Concussion, it is important to find out the best way to get them back to their everyday activities like sports and school. Children and teenagers from across southern Ontario will be participating in this study. We want to see if following the new guidelines for returning to activity and returning to school really do help children get better sooner.

Why am I being asked to be in the study?
We are inviting you to be part of this study because you recently had an injury to your brain called a concussion.

If I am in the study what will happen to me?

As soon as you enter the study, you will be given and taught how to use the guidelines. The following are study activities that you or your parents will be asked to complete:

1. You will be asked to wear an Actigraph. It is like an IPod, and it will measure how much, and how often you move.
2. You and parents will also be asked to keep a list. The list is of things that you do that make your brain think.
3. You will get an APP that measures your symptoms. You will need to check this every 2 days. This takes about 5 minutes to do.
4. You will do a brain functioning test called ImPact on the computer. You will do a balance test. We will ask questions about your symptoms and mood. We will do them at McMaster University. You will do these 2 more times – when your symptoms have ended and 3 months after that.

Some older children will be asked if they would have a brain scan called an MRI. Some older children will be asked if they would have a new type of EEG of the brain called Neurovox®. These tests will help us learn about what is happening in the brain during recovery from concussion. You can be involved in the study and say "no" to the brain tests.

What will happen during the MRI scan and the EEG testing?

THE MRI

- If selected and you want to participate you will have 2 MRIs at St Joseph's Hospital, the 1st one within 1 month of entering the study and the 2nd scan, three months after the symptoms have disappeared.
- During each scan, you will be scanned right before and right after exercising on a stationary lying down cycle, specially designed for the MRI. It will take 1 hour.

The Neurovox® EEG

- You will put on a cap with sensors attached to it. You are then asked some everyday questions while your brain activity is recorded on the EEG machine. This testing can be completed quickly during your visit for the balance testing.

Will I be hurt if I am in the study?

The study is safe. Sometimes children with concussion may have their post-concussion symptoms get worse during the testing because of exercise or having to

think harder (e.g. headache, dizziness, etc.). If your symptoms get worse, all testing will be stopped and you can try again, but only after resting for 24 hours. If symptoms do not go away and/or you do not want to continue with the testing, nothing bad will happen.

Some children may get an MRI, which sometimes causes people to be afraid of small spaces. If you feel you are not able to have the MRI then you do not have to have this test and again nothing bad will happen.

Will the study help me?
The study may help you learn more about concussion and returning to sports and school, safely, after a concussion. The study will help the doctors and therapists know which treatment works best for concussion symptoms. It will also help us decide when you are ready to go back to activity after a concussion. Following the guidelines will prevent you from returning to activity before you are ready. This can help to keep your brain safe and not get another injury. We really appreciate the time it will take you to answer our questions again and again and participate in the different parts of the study.

Do I have to be in this study?
You do not have to be in this study if you do not want to be. If you decide that you don't want to be in the study after we begin, that's OK too. Nobody will be angry or upset. We are also talking to your parents about the study and you should talk to them about it too.

What if I have questions?
You can ask questions at anytime if you do not understand any part of the study. If you have questions now or later, you can contact me or ask your parents to contact Carol DeMatteo at 905-525-9140, ext 27805.

What happens after the study?
When we are finished this study we will write a report about what we learned from collecting all of the information. This report will not include your name or that you were in the study.

This study has been reviewed by the Hamilton Integrated Research Ethics Board.

ASSENT FORM

Safely Returning Children and Youth to Activity After Concussion

The researcher explained this study to me. I have read and understand the information about this study about following the guidelines for children and teenagers with concussion.

If you decide that you want to be in this study, please print or write your name below.

I, _____(print or write your name) would like to be in this research study.

_____ Date of Assent

_____ Name of person who obtained consent

_____ Signature of person who obtained consent.

LETTER OF INFORMATION / CONSENT for Youth 16-18 years

Safely Returning Children and Youth to Activity after Concussion

Local Principal Investigator:
Prof. Carol DeMatteo, MSc OT(Reg)
School of Rehabilitation Science
McMaster University
Hamilton, Ontario, Canada
(905) 525-9140, ext. 27805
E-mail: dematteo@mcmaster.ca

Co-Investigators:
Dr. S. Singh, Dr. L. Giglia, (McMaster Children's Hospital); Dr. M. Noseworthy, Dr N. Bock, Dr. J. Connolly; Dr. B. Timmons; Dr. M. Mazurek; Dr. G. Hall; Ms. C. Cupido (McMaster University)

Funding Source: Canadian Institutes of Health Research

You are being invited to participate in this research study being conducted by Carol DeMatteo, because you have recently had a concussion. In order to decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits. This form gives detailed information about the research study, which will be discussed with you. Once you understand the study, you will be asked to sign this form if you wish to participate.

What is the study about?

The decision regarding return to activity following Mild Traumatic Brain Injury (MTBI)/concussion is one of the most difficult and controversial areas in concussion management for adults and even more complicated for children and youth. Children who sustain a MTBI are being provided with management strategies and return to activity guidelines that have been designed for adult athletes. Children and teenagers are at high risk for repeat injuries within a short period of time as well as prolonged symptoms affecting their school and leisure participation. Experts agree that return to activity (RTA) including return to school (RTS) decisions should be more conservative, cautious and individualized for children and youth.

Outcomes of the study will include: time to symptom resolution, repeat injuries, length of

time to return to play and school and parents' and children's perception of the new guidelines. Electronic activity monitoring devices as well as APPS for symptom monitoring will be used to provide both compliance with guidelines and health information. In order to understand how children with different symptom resolution differ biologically, we will incorporate new EEG and MRI techniques never used with youth with concussion on a small subsample of the youth. The issue of returning to activity after MTBI is very important to the children and families of Canada. Protecting the brains of children and youth through increased knowledge and decision-making based on sound research is paramount.

What is the purpose of this study?

This study will determine if following these new RTA and RTS guidelines results in decreased duration of post-concussive symptoms and risk for subsequent head injuries in children and youth 5-18 years of age. This study will also use accepted measures of brain function (MRI with exercise and Neurovox® EEG) but never before used with children with concussion to help us learn about what is actually happening in the brain during the recovery period.

How will I be involved in this study?

If you consent to be a participant in the study, we will ask you to do the following things. As soon as you enter the study, you will be given and taught how to use the guidelines. The following are study activities that you will be asked to complete:

- You will be asked to wear an iPod-sized accelerometer called an Actigraph, which collects daily activity information.
- You will also be asked to keep a log, provided to you, of your cognitive activity.
- You will also be provided with a symptom-monitoring APP that will require completion every 2 days and will take 5 minutes to complete.
- Within one week of entering the study, a computerized neurocognitive test (ImPact), balance test, a depression questionnaire and a quality of life questionnaire will all be administered at McMaster University by an occupational therapist or research assistant. This will take approximately 45 minutes to one hour.
- These tests will be repeated when symptoms have ended and again 3 months after symptoms disappear.

Approximately 60 youth aged 10-18 will be randomly selected to receive a Magnetic Resonance Imaging (MRI) brain scan and a new type of electroencephalogram (EEG) of the brain, to help us learn about what is happening in the brain during recovery from concussion. You can still be involved in the study and decline having these brain tests.

What will happen during the (MRI) scan and the EEG testing?

<u>THE MRI</u>

You will have 2 MRIs at St. Joseph's Healthcare Hamilton, the 1st one within 1 month of entering the study and the 2nd scan, three months after the symptoms have disappeared. During each scan, you will be scanned immediately before and after exercising on a stationary reclined cycle, especially designed for the MRI and already pilot tested by us in another research study. It will take 1 hour.

The Neurovox® EEG
The protocol can be completed quickly during your visit for the balance testing, as the equipment is portable and testing time is 1 hour. The EEG system uses dry electrodes attached to a cap that you wear. You will be asked questions while your brain activity is recorded.

What are the risks?

Some participants may experience worsening of post-concussion symptoms during the completion of the testing protocol due to physical or cognitive exertion (e.g. headache, dizziness, nausea, etc.). In the event of worsening post-concussion symptoms, all testing will be stopped immediately and resumed again only after a minimum period of 24 hours of rest and the resolution of symptoms. If symptoms do not resolve and/or you do not want to continue with the testing, there will be no negative consequences.

Some participants may feel anxious about their performance or testing in general. The research study team will explain the tests in detail and take special care to emphasize that your results will be completely confidential and not shared with anyone outside of the research team.

Some teens may be claustrophobic and not able to undergo the MRI and they do not have to undergo this test.

What are the benefits for me, my family and for society?

The potential benefits of being carefully monitored to control your activity level and better follow the guidelines for restricted activity could quite possibly decrease your symptoms. Close monitoring will also alert you, your family, your school and the research team of any concerning symptoms and need for intervention. The following of the guidelines will prevent you from returning to activity before you are ready and this can help to prevent further injury to your recovering brain.

Concussion in children and youth is reaching epidemic proportions in our society with the increased participation and intensity of sport competition. We propose a new evidence-based guideline approach designed specifically for children and youth 5-18 years. These guidelines have the potential to prevent repeat injuries and the problems such as depression, anxiety and school failure associated with chronic symptoms. This study will be the first to measure activity levels of concussed individuals during recovery to see if adherence to these child-specific guidelines does indeed prevent negative outcomes.

How many people will be in this study?

The study will involve 360 children and youth 5-18 years who have had a concussion, recruited from the Hamilton and surrounding regions. Only 60 of these youth will receive the MRI and EEG scans of the brain. The study will end for each participant, 3 months after the concussion symptoms have disappeared. For most children they will be in the study for 3-6 months.

What if I change my mind about being in the study?

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. You may leave the study at any time without affecting your care. You may also refuse to answer any questions and still remain in the study. Choosing not to participate in this study will in no way affect your care or treatment.

If you decide to leave the study, the information that was collected before you left the study will still be used, but you do have the option to remove it from the study.
If you choose to leave the study, you are still provided with the child post concussion guidelines to follow, as you and your physician deem necessary.

What information will be kept private?

All the information that we collect about you will be kept private. Your data will not be shared with anyone except with your consent or as required by law. All personal information such as your name, address, phone number, OHIP number, family physician's name will be removed from the data and will be replaced with a number. A list linking the number with your name will be kept in a secure place, separate from your file. The data, with identifying information removed will be securely stored in a locked office in the research offices at CanChild, the Centre for Childhood Disability Research. No one but the study staff will know that it is you who is in the study.

If the results of the study are published, your name will not be used. All data collected from all participants will be combined to form one large data set. As a result, individual participants will not be identified.

The information that is collected for the study will be kept in a locked and secure area by the researchers for 10 years. Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital.

Representatives of Hamilton Integrated Research Ethics Board may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines.

Will I be paid to participate in this study?

If you participate in the study, you will receive a $20 generic gift card and you will be provided with parking vouchers for days of assessment visits to the university.

Questions about the Study

If you have questions or need more information about the study itself, please contact:

Local Principal Investigator	Research Coordinator at McMaster
Carol DeMatteo School of Rehabilitation Science McMaster University Hamilton, Ontario, Canada **(905) 525-9140 ext. 27805** **E-mail: dematteo@mcmaster.ca**	Chia-Yu Lin CanChild Centre for Childhood Disability Research McMaster University **905 5259140 ext 26842** **E-mail: concuss@mcmaster.ca**

CONSENT

Safely Returning Children and Youth to Activity After Concussion

Legally Authorized Representative:

I have read the preceding information thoroughly. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I understand that I will receive a signed copy of this form.

I give my permission for _____ to participate in this study. (Child's Name)

Name, Relationship to Participant	**Signature**	**Date**

Person obtaining consent:

I have discussed this study in detail with the participant. I believe the participant understands what is involved in this study.

Name, Role in Study	**Signature**	**Date**

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB). The HIREB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions regarding your rights as a research participant, please contact the office of HIREB at 905.521.2100 x 42013.

Appendix D: Post-Concussive Symptom Scale

Please rate your symptoms from the past two days.

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

1	Headache	0	1	2	3	4	5	6
2	Nausea	0	1	2	3	4	5	6
3	Balance	0	1	2	3	4	5	6
4	Dizziness	0	1	2	3	4	5	6
5	Fatigue	0	1	2	3	4	5	6
6	Drowsiness	0	1	2	3	4	5	6
7	Sensitivity to light	0	1	2	3	4	5	6
8	Sensitivity to noise	0	1	2	3	4	5	6
9	Irritability	0	1	2	3	4	5	6
10	Sadness	0	1	2	3	4	5	6
11	Nervousness	0	1	2	3	4	5	6
12	Feeling more emotional	0	1	2	3	4	5	6
13	Feeling slowed down	0	1	2	3	4	5	6
14	Feeling mentally “foggy”	0	1	2	3	4	5	6
15	Difficulty concentrating	0	1	2	3	4	5	6
16	Difficulty remembering	0	1	2	3	4	5	6
17	Visual problems	0	1	2	3	4	5	6
18	Get confused with directions or tasks	0	1	2	3	4	5	6
19	Move in a clumsy manner	0	1	2	3	4	5	6
20	Answering questions more slowly than usual	0	1	2	3	4	5	6
21	Complains of neck pain	0	1	2	3	4	5	6
22	Complains of sleep problems	0	1	2	3	4	5	6

Appendix E: Children's Depression Inventory

By Maria Kovacs, Ph.D.

CDI 2 SELF-REPORT

Name/ID: _____ Date of Birth: ____/____/____ (Year / Month / Day)

Age:____ Grade: ____ Sex: Male Female (Circle one) Today's Date: ____/____/____ (Year / Month / Day)

Kids sometimes have different feelings and ideas.

This form lists the feelings and ideas in groups. From each group of three sentences, pick **one** sentence that describes you best for the **past two weeks**. After you pick a sentence from the first group, go on to the next group.

There is no right or wrong answer. Just pick the sentence that best describes the way you have been recently. Put a mark like this [X] next to your answer. Put the mark in the box next to the sentence that you pick.

Here is an example of how this form works. Try it. Put a mark next to the sentence that describes you best.

Example:
- ❑ I read books all the time.
- ❑ I read books once in a while.
- ❑ I never read books.

Remember, for each group, pick out the sentence that describes you best in the PAST TWO WEEKS.

Item 1 ❑ I am sad once in a while. ❑ I am sad many times. ❑ I am sad all the time.	**Item 6** ❑ I hate myself. ❑ I do not like myself. ❑ I like myself.
Item 2 ❑ Nothing will ever work out for me. ❑ I am not sure if things will work out for me. ❑ Things will work out for me O.K.	**Item 7** ❑ All bad things are my fault. ❑ Many bad things are my fault. ❑ Bad things are not usually my fault.
Item 3 ❑ I do most things O.K. ❑ I do many things wrong. ❑ I do everything wrong.	**Item 8** ❑ I do not think about killing myself. ❑ I think about killing myself but would not do it. ❑ I want to kill myself.
Item 4 ❑ I have fun in many things. ❑ I have fun in some things. ❑ Nothing is fun at all.	**Item 9** ❑ I feel like crying every day. ❑ I feel like crying many days. ❑ I feel like crying once in a while.
Item 5 ❑ I am important to my family. ❑ I am not sure if I am important to my family. ❑ My family is better off without me.	**Item 10** ❑ I feel cranky all the time. ❑ I feel cranky many times. ❑ I am almost never cranky.

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Remember, for each group, pick out the sentence that describes you best in the PAST TWO WEEKS.

Item 11 ❑ I like being with people. ❑ I do not like being with people many times. ❑ I do not want to be with people at all.	**Item 20** ❑ I never have fun at school. ❑ I have fun at school only once in a while. ❑ I have fun at school many times.
Item 12 ❑ I cannot make up my mind about things. ❑ It is hard to make up my mind about things. ❑ I make up my mind about things easily.	**Item 21** ❑ I have plenty of friends. ❑ I have some friends but I wish I had more. ❑ I do not have any friends.
Item 13 ❑ I look O.K. ❑ There are some bad things about my looks. ❑ I look ugly.	**Item 22** ❑ My schoolwork is alright. ❑ My schoolwork is not as good as before. ❑ I do very badly in subjects I used to be good in.
Item 14 ❑ I have to push myself all the time to do my schoolwork. ❑ I have to push myself many times to do my schoolwork. ❑ Doing schoolwork is not a big problem.	**Item 23** ❑ I can never be as good as other kids. ❑ I can be as good as other kids if I want to. ❑ I am just as good as other kids.
Item 15 ❑ I have trouble sleeping every night. ❑ I have trouble sleeping many nights. ❑ I sleep pretty well.	**Item 24** ❑ Nobody really loves me. ❑ I am not sure if anybody loves me. ❑ I am sure that somebody loves me.
Item 16 ❑ I am tired once in a while. ❑ I am tired many days. ❑ I am tired all the time.	**Item 25** ❑ It is easy for me to get along with friends. ❑ I get into arguments with friends many times. ❑ I get into arguments with friends all the time.
Item 17 ❑ Most days I do not feel like eating. ❑ Many days I do not feel like eating. ❑ I eat pretty well.	**Item 26** ❑ I fall asleep during the day all the time. ❑ I fall asleep during the day many times. ❑ I almost never fall asleep during the day.
Item 18 ❑ I do not worry about aches and pains. ❑ I worry about aches and pains many times. ❑ I worry about aches and pains all the time.	**Item 27** ❑ Most days I feel like I can't stop eating. ❑ Many days I feel like I can't stop eating. ❑ My eating is O.K.
Item 19 ❑ I do not feel alone. ❑ I feel alone many times. ❑ I feel alone all the time.	**Item 28** ❑ It is easy for me to remember things. ❑ It is a little hard to remember things. ❑ It is very hard to remember things.