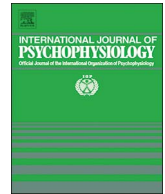




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## Registered Reports

## An Emotional Go/No-Go fMRI study in adolescents with depressive symptoms following concussion

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## ABSTRACT

**Background:** Following concussion, adolescents may experience both poor inhibitory control and increased depressive symptoms. fMRI research suggests that adolescents with major depressive disorder have abnormal physiological responses in the frontostriatal pathway, and exhibit poorer inhibitory control in the presence of negatively-aroused images. The scarcity of information surrounding depression following concussion in adolescents makes it difficult to identify patients at risk of depression after injury. This is the first study to examine neural activity patterns in adolescents with post-concussive depressive symptoms.

**Purpose:** To explore the effect of depressive symptoms on inhibitory control in adolescents with concussion in the presence of emotional stimuli using fMRI.

**Methods:** Using a prospective cohort design, 30 adolescents diagnosed with concussion between 10 and 17 years were recruited. The Children's Depression Inventory questionnaire was used to divide participants into two groups: average or elevated levels of depressive symptoms. Participants completed an Emotional Go/No-Go task involving angry or neutral faces in a 3Telsa MRI scanner.

**Results:** Eleven participants had elevated depressive symptoms, of which 72% were hit in the occipital region of the head at the time of injury. fMRI results from the Emotional Go/No-Go task revealed activity patterns in the overall sample. Faces activated regions associated with both facial and cognitive processing. However, frontal regions that are usually associated with inhibitory control were not activated. Adolescents with elevated levels of depressive symptoms engaged more frontal lobe regions during the task than the average group. They also showed a trend towards worse symptoms following MRI scanning.

**Conclusions:** Adolescents with elevated depressive symptoms engaged brain regions subserving evaluative processing of social interactions. This finding provides insight into the role the environment plays in contributing to the cognitive demands placed on adolescents recovering from concussion.

## 1. Introduction

Concussion is a major cause for disability in adolescence and often contributes to an array of cognitive and emotional difficulties during development. While past research has focused primarily on concussions in adulthood, the incidence of concussion in children and adolescents is increasing (Macpherson et al., 2014). A Canadian survey conducted between 2009 and 2010 found that youth ages 12 to 19 years accounted for 30% of brain injuries (Billette and Janz, 2011). The increasing rate of pediatric concussions treated in Ontario emergency room departments and doctor's offices between the years 2003 and 2010 (Macpherson et al., 2014) might imply greater vulnerability in youth.

Adolescents, in particular, show heightened susceptibility to the negative consequences of concussion in comparison to adults and children (Baillargeon et al., 2012; Chrisman and Richardson, 2014; Zuckerman et al., 2012).

Adolescence marks a critical period in development during which time the brain is most sensitive to its environment (Sisk and Zehr, 2005). Thus, developmental neurobiological processes during adolescence are hypothesized to contribute to this vulnerability. For instance, structural properties of the brain undergo rapid development. This includes the myelination of corpus callosum (Reeves et al., 2005) and frontal lobe (Sowell et al., 1999), and the thickening of white and grey matter of the brain (Barnea-Goraly, 2005; Giedd et al., 1999). Injury

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during this time could alter neurochemical processes (Giza et al., 2005; Giza and Hovda, 2001) and disrupt the consolidation of important neuronal networks such as those related to executive functioning and emotion processing (Anderson et al., 2011).

Of great concern for adolescents with concussion is the prevalence of depression following injury. The adult concussion literature cites heightened risk of depression up to 9 years following concussion for professional football athletes (Kerr et al., 2012). Children and adolescents with a history of concussion are 3.3 times more likely to experience depression their lifetime even when controlling for age, sex, parental mental health, and socioeconomic status (Chrisman and Richardson, 2014). In the general population of children and adolescents, the incidence of depression falls between 5 and 11% (Haarasilta et al., 2001; Kessler et al., 2012; Richardson et al., 2010). Following concussion, that rate increases to approximately 22% (Stazyk et al., 2017). The scarcity of information surrounding depression following concussion in youth makes it difficult to identify patients at risk of depression after injury.

The body of literature on psychiatric illness provides insights to cognitive dysfunctions that might follow adolescents who exhibit depressive symptoms after a concussion. Tests of cognitive control (or inhibitory control) offer a measure of frontal lobe functioning in adolescents who are diagnosed with major depressive disorder (MDD), showing that they perform more poorly compared to healthy controls (Lim et al., 2013; Nilsson et al., 2016; Tavittian et al., 2014). Inhibitory control is of particular interest in clinically depressed populations as performance is dependent on the emotional context (Lamm et al., 2012). In fact, neural activity in regions that govern inhibitory control processes including the dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate cortex (dACC), and orbitofrontal cortex (OFC) varies in response to changes in the emotional context (Dichter et al., 2009; Durston et al., 2002; Lamm et al., 2012). Functional magnetic resonance imaging (fMRI) studies show that adolescents with MDD have abnormal physiological responses in the frontostriatal pathway and suggest deficits in frontal lobe functioning (Langenecker et al., 2007; Rogers et al., 1998; Shah et al., 2002). Pathology in these underlying neural regions translates into behavioural deficits on inhibitory control tasks for patients with MDD compared to controls. Modifying traditional inhibitory control tasks such as the Go/No-Go task to incorporate emotion-related images has allowed us to experimentally change and assess the impact of the implicit emotional context in which inhibitory control is exercised. Adolescents with MDD exhibit poorer inhibitory control in the presence of negatively-charged images which has been attributed to an attentional bias for negative stimuli (Dichter et al., 2009; Erickson et al., 2005; Gotlib et al., 2004) or a failure to maintain goal-directed behaviour (Colich et al., 2016; Eysenck et al., 2007), which is often noted in other psychiatric illnesses as well (Derakshan et al., 2009; Harrison et al., 2010; Macleod et al., 1986).

Thus far, few studies have explored the impact post-concussive depressive symptoms on cognitive performance and neural activity. Kontos et al. (2012) found an inverse relationship between neurocognitive performance and depressive symptoms in children and youth with concussion, but sampled participants who were below the clinical threshold for depression on the depression-screening tool. Chen et al. (2008) compared non-injured adults to adults experiencing no depression, mild depression, or moderate depression after concussion on a working memory task. While behavioural performance did not differ significantly between the groups, the 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. In areas that are normally deactivated during working memory tasks, the mildly and moderately depressed individuals showed greater activation. By contrast, the DLPFC, which is implicated in several cognitive tasks including working memory and spatial memory, it was negatively correlated with depression in this sample.

This study exemplifies a potential difference between MDD and post-concussive depressive symptoms. Adolescents with MDD often demonstrate hyperactivity in regions corresponding to the cognitive task such as the prefrontal cortex (Fitzgerald et al., 2008; Langenecker et al., 2007), thalamus (Fitzgerald et al., 2008), ACC (Harvey et al., 2005; Langenecker et al., 2007), and insula (Langenecker et al., 2007), suggesting that patients with MDD need to recruit additional resources to complete the task. Following a concussion, Chen et al. (2008) found that adults with mild and moderate depressive symptoms displayed deactivation in brain areas associated with the task. This might imply that post-concussive depressive symptoms have different neurofunctional manifestations relative to clinical depression.

The main objective of the current study was to determine how adolescents with depressive symptoms might present differently in brain activity patterns compared to those without depressive symptoms following concussion. In addition, we would like to explore how the location of impact might be related to the emergence of depressive symptoms.

The Emotional Go/No-Go task was used in this study to measure the neurophysiological response to emotion-related images during inhibitory control processes. The Emotional Go/No-Go task has been tested in children and adolescents with mild to moderate traumatic brain injury in the past to show abnormal activity in the ACC and motor regions (Tlustos et al., 2015), but has yet to be assessed specifically in adolescents with depressive symptoms following concussion. Based on the study conducted by Chen et al. (2008), it was hypothesized that adolescents with depressive symptoms following concussion would display abnormal brain activity in areas normally associated with inhibitory control including the DLPFC, ACC and OFC. Relative to neutral stimuli (*i.e.* neutral faces), negatively-charged stimuli (*i.e.* angry faces) are expected to yield abnormalities in emotion-related brain regions for adolescents with depressive symptoms compared to adolescents with normal levels of depressive symptoms.

Since concussions are known as global rather than focal injuries (McCrory et al., 2013), the location of impact is not commonly reported in concussion studies with respect to its effects on post-concussive symptoms. However, based on reports of frontostriatal disruptions in the MDD literature (Furman et al., 2011; Rogers et al., 1998; Shah et al., 2002), we decided to investigate if location of injury might be indicative of depressive symptoms. We predicted that adolescents with depressive symptoms would be more likely to report the frontal region of the head (*i.e.*, forehead) as the primary site of impact.

## 2. Materials and methods

### 2.1. Design

The data presented in this study was collected from a study that took place at *CanChild* Centre for Disability Research at McMaster University. Only the participants who agreed to take part in the brain-imaging component of the 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.

### 2.2. Participants

Adolescents between the ages of 10 and 17 years currently experiencing a concussion with a confirmed diagnosis by a physician were invited to participate. All participants had to be symptomatic at the time of recruitment (5.9 days since injury on average). Participants with a prior concussion were not excluded. They were recruited from a number of health facilities including the McMaster University Children's Hospital, rehabilitation clinics, physicians' offices, or by self-referral from the *CanChild* website. Exclusion criteria included (1) a diagnosis of a severe developmental delay or a neurological disorder, (2) a severe injury requiring resuscitation, surgery, or admission to the

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