I, Sarah J. Tlustos-Carter, hereby submit this original work as part of the requirements for the degree of Doctor of Philosophy in Psychology.

It is entitled:
Neural Substrates of Inhibitory and Socio-Emotional Processing in Adolescents with Traumatic Brain Injury

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Neural Substrates of Inhibitory and Socio-Emotional Processing in Adolescents with Traumatic Brain Injury

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ABSTRACT

A growing literature suggests that disturbances of emotional regulation and interpersonal difficulties are quite common in children with traumatic brain injury (TBI). Although estimates suggest that rates of TBI are highest for individuals between the ages of 15 and 24, very little research has investigated the cognitive and socio-emotional sequelae of TBI during this period. Significant brain maturation of the frontal and parietal lobes, purported to underlie the development of executive abilities including problem-solving, decision-making, and behavioral inhibition, occurs during adolescence. Recent research further suggests that developments within the “socio-emotional” brain system (e.g., amygdala, orbitofrontal cortex, insula, medial prefrontal cortex, and superior temporal cortex) during early adolescence and the more protracted development of “cognitive control” systems underlying executive functions (e.g., lateral prefrontal cortex, anterior cingulate, and parietal cortex) has implications for effective social decision-making and behavioral regulation during adolescence. The current study investigated the interaction between socio-emotional processing and inhibition in 10 adolescents with TBI, at least 12 months post injury, and 9 typically-developing (TD) adolescents. In an adaptation of the classic Go/No-Go paradigms of cognitive inhibition, participants saw photographs of adults displaying happy, sad, fearful, and angry emotional expressions. They were instructed to respond by button press (“go”) on pictures displaying happy, sad, or fearful, and withhold responding (“no-go”) on pictures displaying angry. The current study demonstrated that adolescents with TBI show similar patterns of neural activation while completing an emotionally-mediated inhibition paradigm as adults and adolescents in prior research. However, between-group differences in inhibition-related activation indicate that TD adolescents show higher levels of activation than adolescents with TBI within certain cognitive-control-related
brain regions, including medial prefrontal and parietal areas. Additionally, subtle group differences in task performance, indicating greater interference-susceptibility and more impulsive responding during the no-go blocks for the TBI group compared with the TD group indicate that participants with TBI may have failed to recognize errors and adjust their behavioral responding accordingly. These results suggest that adolescents with TBI may show inefficiencies in cognitive and neural processing. Given the protracted development of the cognitive-regulatory node, these between-group differences may suggest that TBI in adolescence interrupts development of fronto-parietal networks during a critical period of development, resulting in altered cognitive performance and patterns of activation. To the best of the author’s knowledge, the present study represents the first to investigate the interaction between emotional and cognitive-control processes in adolescents with TBI. It will be important to understand how these differences in activation relate to socio-emotional and behavioral outcomes after TBI in adolescence.
ACKNOWLEDGEMENTS

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CHAPTER I

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of acquired disability in children and adolescents and often results in deficits of cognition and behavior (Langlois, Rutland-Brown, & Thomas, 2006). Adolescents tend to engage in behaviors that increase their risk for accident, injury, or death (Casey, Jones, & Hare, 2008; CDC, 2010). Although estimates suggest that rates of TBI peak between the ages of approximately 15 and 24 (Bruns & Hauser, 2003; Langlois et al., 2006), very little research has investigated the cognitive and socio-emotional sequelae of TBI during this period. In fact, adolescents may be particularly susceptible to negative outcomes after TBI. Many of the same regions that are vulnerable to TBI undergo extended and continual development throughout childhood. The prefrontal cortex, temporal, and parietal lobes continue to increase in gray matter volumes into adolescence, peaking around the age of 12 for frontal and parietal regions and age 16 for temporal cortex. Similarly, white matter connections expand and increase in volume well into adolescence (Giedd et al., 1999). This is also a time when social relationships begin to shift, with increased reliance on and the importance of peer relationships, often accompanied by a decrease in family orientation and an increase in parent-child conflicts (Casey, Jones, & Hare, 2008; Nelson, Leibenluft, McClure, & Pine, 2005). Adolescents also display increased emotional reactivity (Casey et al., 2008). The interaction between emotional reactivity, developing brain, and dynamic social relationships in adolescence may impact risky decision making, higher incidence of affective disorder onset, and risky behaviors such as addiction during adolescence (Hessler & Katz, 2010).

A growing literature suggests that disturbances of emotional regulation and interpersonal difficulties are quite common in children after TBI (Yeates et al., 2007). Despite the important
implications for psychological adjustment and quality of life, relatively little is currently known about factors influencing adaptive and socio-emotional outcomes following childhood TBI. Studies have indicated that adults with TBI may experience blunted affect, decreased internal emotional experience, reduced emotion regulation, self-focused speech, insensitivity towards others, and inappropriate intimacy (Gouick & Gentleman, 2004). Children with TBI are often more impulsive, have less emotional awareness, reduced emotion regulation, and increases in externalizing behavior problems and new-onset psychiatric disorders, particularly in individuals with more severe TBI (Chapman et al., 2010; Ganesalingam, Sanson, Anderson, & Yeates, 2006; Warriner & Velikonja, 2006; Yeates et al., 2007). Furthermore, these difficulties tend to be more persistent and cause greater distress for the patient and their families than acquired cognitive deficits. Studies in children have documented little evidence for recovery of social function after TBI, and frequently outcomes worsen over time (Yeates, et al., 2004; Ganesalingam et al., 2006; Bornhofen & McDonald, 2008). However, very little is known about the impact of TBI in adolescence on socio-emotional functioning, despite this being a vulnerable period for the development of emotional disorders (Dahl, 2001; Nelson, Leibenluft, McClure, & Pine, 2005).

**Adolescent Brain Development**

Throughout childhood and adolescence, synaptogenesis and synaptic pruning result in an overall decrease in synaptic density that allows for “fine tuning” and strengthening of connections within frontal, temporal, and parietal lobes. Changes in cortical gray matter are regionally specific, such that prefrontal, parietal, and lateral temporal cortices mature at various rates throughout adolescence. Myelination also continues through adolescence, facilitating transmission speed in the frontal cortex from childhood to adolescence (Blakemore & Choudhury, 2006; Giedd et al., 1999). These changes are believed to enable the development of
more efficient cognitive processing and improved attention, processing speed, working memory, and executive functions (including problem-solving, decision making, and behavioral inhibition) during adolescence (Blakemore & Choudhury, 2006).

Recent research further suggests that developments within the “social-cognitive” or “socio-emotional” brain system, composed of regions important for emotional and social processing (e.g., amygdala, orbitofrontal cortex [OFC], insula, medial prefrontal cortex [mPFC], temporal-parietal junction [TPJ], and superior temporal cortex; Adolphs, 2001; Frith & Frith, 2001; Herba & Phillips, 2004; Phillips, Drevets, Rauch, & Lane, 2003) during early adolescence and the more protracted development of “cognitive control” systems underlying executive functions (e.g., lateral prefrontal cortex, anterior cingulate cortex [ACC], parietal cortex, and subcortical structures including basal ganglia and thalamus; Blakemore & Choudhury, 2006) have implications for effective social decision-making and behavioral regulation during adolescence (Casey, Jones, & Hare, 2008; Nelson, Leibenluft, McClure, & Pine, 2005; Steinberg, 2008). The social information processing network (SIPN), a model proposed by Nelson and colleagues (2005), defines these systems in terms of three “nodes” which are involved in the processing of social information: the social detection node, the affective processing node, and the cognitive regulatory node. According to this model, the detection node involves primarily occipital, inferior and anterior temporal brain regions, and the fusiform face area, and is involved in the identification or perception of stimuli as ‘social.’ This node is believed to be fully developed by around age five. The affective node (which closely corresponds to what others have referred to as the social-emotional network, above), composed of limbic regions including the amygdala, ventral striatum, and hypothalamus, is involved in tagging stimuli with emotional meaning and engaging in approach and avoidance behaviors such as
reward-seeking. This system is believed to undergo significant reorganization during adolescence, largely due to changes in the hormonal system with puberty, which can affect individuals’ responsiveness to social stimuli. Recent research has shown that levels of gonadal steroids, for example, influence sexual responsiveness and affective responses, social bonding, and social memory (Nelson, Leibenluft, McClure, & Pine, 2005). The cognitive-regulatory node (which closely corresponds to what others have referred to as the cognitive-control network, above), composed of prefrontal regions including dorsomedial, ventral, and dorsolateral prefrontal cortices, is believed to be involved in perceiving others’ mental states (theory of mind), inhibition and cognitive control, and goal-directed behavior. This system also undergoes functional changes during adolescence, however the changes in the prefrontal regions are more related to neuro-maturational factors such as increased myelination and pruning that occur throughout adolescence and into early adulthood. Whereas changes to the affective node occur fairly quickly and dramatically as a result of hormonal processes at the onset of puberty, the maturation and development of the prefrontal cortex underlying the cognitive-regulatory node are very slow and occur over many years based on environmental learning and exposure. Therefore, this mismatch between a highly responsive affective system and incompletely developed abilities to regulate, plan, and inhibit emotionally-driven responses makes adolescents vulnerable to making risky decisions, and for emotional and behavioral difficulties. With further development and life experience, these regions become more functionally connected, facilitating top-down control by prefrontal lobes and executive functions.

**Vulnerability of Social-Cognitive Neural Networks to TBI**

The socio-emotional and cognitive-control networks may be vulnerable to injury given that several of these regions included are commonly implicated in TBI (Wilde et al., 2005).
Frontal and temporal brain regions are particularly vulnerable to TBI due to proximity with bony protrusions within the skull cavity. Disruption by diffuse brain injury during development may interfere with the integration and connectivity of these regions. Further, immature brains are thought to be particularly vulnerable to insult, as developing neurons are more susceptible to excitotoxicity and hypoxic-ischemic injury than developed neurons and may also be more susceptible to cerebral blood flow dysregulation and edema (Wilde et al. 2005). Reduced whole-brain, prefrontal, and temporal regional tissue volumes have been found in children and adolescents with moderate to severe TBI, compared with typically developing children and adolescents, regardless of lesion location (Wilde et al., 2005). Reductions in gray matter were associated with focal injury, while white matter loss was related to both focal and diffuse injuries. Mechanically-induced trauma and shear injuries can have widespread impact on brain development and growth, and less-myelinated neurons of immature brains are more vulnerable to traumatic axonal injury (TAI). TAI disrupts the formation of white matter connections between regions (Wilde et al., 2006), potentially affecting brain regions far downstream from the actual injury locale. Wilde et al. (2007) also discovered decreased hippocampal, globus pallidus, and amygdala volumes after TBI in children, even where no focal subcortical lesions were present.

Children with this type of diffuse trauma to the socio-emotional and cognitive-control networks would be expected to have difficulties with a variety of aspects of social cognition and behavior. Recent research has found evidence for deficits in social problem-solving (Hanten et al., 2008; Yeates et al., 2004), self regulation (Ganesalingam, Sanson, Anderson, & Yeates, 2006), theory of mind (McDonald & Flanagan, 2004; Henry, Phillips, Crawford, Ietswaart, & Summers, 2006; Milders, Iestswaart, Crawford, & Currie, 2008), and emotion recognition and labeling (McDonald & Flanagan, 2004; Henry et al., 2006; Milders et al., 2008; Bornhofen &
McDonald, 2008; Green, Turner, & Thompson, 2004; Croker & McDonald, 2005; Ietswaart, Milders, Crawford, Currie, & Scott, 2008) in adults and children with TBI. Deficits in executive functions are also extremely common after TBI (Levin & Hanten, 2005), which can lead to inflexible thinking and impulsive behavioral responding. Some or all of these difficulties would be expected to lead to social, psychological, and behavioral problems (Warriner & Velikonja, 2006). Due to the dynamic nature of brain development, the nature and extent of socio-emotional impairment will depend not only on the location, extent, and severity of the injury, but also on the timing of the insult as it relates to brain maturation (Yeates et al., 2007).

Therefore, investigation into the functioning of socio-emotional and cognitive-control neural systems in adolescents may help elucidate the basis for social and psychological difficulties after TBI. Recent research using neuroimaging has revealed both functional and structural differences in individuals with TBI compared with healthy controls. Adolescents with TBI showed higher levels of brain activation while completing a perspective-taking paradigm and undergoing fMRI in social-cognitive areas (left lingual gyrus, posterior cingulate, cuneus and parahippocampal gyrus) compared with typically-developing adolescents (Newsome et al., 2010). The authors suggested that TAI disrupted fronto-parietal networks important for social cognition in individuals with TBI, leading to altered activation patterns. Hanten and colleagues (2011) found that adolescents with TBI showed impaired social problem-solving on a virtual reality paradigm, particularly with regard to defining problems and evaluating outcomes. Although this was not a functional brain imaging study, task performance was correlated with structural MRI findings. They found that task performance was differentially related to cortical thickness for participants with TBI compared with typically-developing adolescents in a variety of regions within the social-cognitive network, including the OFC, frontal pole, cuneus, and
temporal pole. These studies support the idea that TBI in adolescence may impact neural networks that support socio-emotional and cognitive-control functions.

*Studies on the Interaction Between Emotional Processing and Inhibition*

While the neural bases for cognitive control and for socio-emotional processing have been well studied independently, paradigms designed to investigate the interaction between emotion and cognitive control processes have just recently begun to emerge in the literature. Optimal decision making requires the integration of emotional and cognitive information (Bechara, Damasio, & Damasio, 2000; Shafritz, Collins, & Blumberg, 2006), and it is therefore important to determine how these processes interact in social contexts to guide behavior. Recent studies have used adaptations of the classic Go/No-Go paradigms of cognitive control that incorporate emotionally-provoking stimuli in order to investigate this interaction and approximate emotion regulation processes. However, most studies to date have investigated this in healthy adults, with very little research thus far in clinical populations.

Studies in healthy adults have shown evidence that emotional information modulates neural activity during inhibitory tasks, recruiting regions typically activated in traditional inhibition paradigms as well as regions known to be important for socio-emotional processing. Goldstein et al. (2007) used an emotional linguistic Go/No-Go to investigate emotional and inhibitory control processes in healthy adults using fMRI. The version of the task they generated used trials consisting of words intended to elicit either positive or negative emotions (e.g., “cheerful” to elicit positive emotions, and “worthless” to elicit negative emotions), as well as neutral words. Each emotion category was used as both “go” and “no-go” stimuli, counterbalanced across four runs. The investigators found common activations for emotionally modulated response inhibition across emotional conditions including fronto-limbic regions (e.g.,
OFC and amygdala). Greater activation was observed for the inhibition of negative emotions including medial OFC, dorsolateral prefrontal cortex (DLPFC), ACC, amygdala, paralimbic cortex, and parietal cortex. A similar study used a Go/No-Go task composed of words designed to elicit happy, sad, or neutral emotions (Elliott, Rubinsztein, Sahakian, & Dolan, 2000). They found that emotional words compared with neutral words elicited activation within hippocampal gyrus, right insula, and ACC. Additionally, they observed greater neural activation for happy opposed with sad targets (“go” responses) in the ventral ACC. The authors suggested that these regions may be important for the integration of emotional and cognitive information, and may have important implications for mood disorders. Shafritz, Collins, and Blumberg (2006) compared response inhibition in healthy adults during a traditional Go/No-Go composed of letters with one composed of happy and sad faces. They found that in both paradigms, inhibiting responses elicited brain regions typically associated with response inhibition (i.e., DLPFC, ACC, premotor cortex, dorsal striatum, and thalamus); however, the Emotional Go/No-Go additionally elicited activation in inferior frontal, inferior parietal, and anterior insular cortex. These authors concluded that response inhibition within an emotional context elicits a set of brain regions distinct from traditional cognitive control tasks that may be responsible for modulating emotional valence.

Similar paradigms have been used to investigate emotional and cognitive control processes within groups of adults with mood disorders compared with healthy controls. Studies have found abnormal responses within medial and ventral prefrontal cortex for adults with depression (Elliott, Rubinsztein, Sahakian, & Dolan, 2002) and mania (Elliott, Ogilvie, Rubinsztein, Caleron, Dolan, & Sahakian, 2004), along with a behavioral bias toward negative information in unipolar depression a converse bias toward positive emotion in participants with
mania. To the best of the author’s knowledge, there have been no studies investigating the neural response to emotionally-mediated inhibition in patients with TBI.

**Aims and Hypotheses**

**Aim 1**: To investigate the neural correlates of response inhibition within a socio-emotional context in adolescents with complicated-mild to severe TBI compared with typically developing adolescents. A functional magnetic resonance imaging (fMRI) experiment that requires inhibition of a response based on emotional cues will be used. **Hypothesis**: Adolescents with TBI will show differential levels of activation within socio-emotional and cognitive control systems than matched typically-developing control participants during the emotionally-mediated inhibition paradigm.

**Aim 2**: To explore the relationship between neural activation patterns during the emotional inhibition paradigm and behavioral measures of inhibition and executive ability. **Hypothesis**: Participants with greater levels of demonstrated and reported executive impairment will show differential recruitment of socio-emotional and cognitive-control systems than those participants with little or no executive impairment.
CHAPTER II

METHODS

Participants

Adolescents between the ages of 13 and 17 with confirmed complicated-mild, moderate, or severe traumatic brain injury were recruited to participate in this study from a pool of families that have participated in ongoing intervention research studies on adolescent TBI at Cincinnati Children’s Hospital Medical Center (CCHMC). All participants were required to be at least 12-months post-injury at time of assessment to ensure that acute recovery is complete. A control group of typically-developing adolescents with negative history for TBI or other neurological insult were recruited from the local community. Control participants were matched as closely as possible on age, gender, and maternal education. Exclusion criteria for both groups included significant developmental delay, significant psychiatric or behavior disturbance, and extreme vision or hearing impairments. All participants come from families where English is the primary language spoken in the home and met all MRI eligibility requirements. Both the ongoing intervention study and the current imaging study were approved by the Institutional Review Board at CCHMC.

A total of 31 children completed informed consent to participate in the study, and 19 (61%) yielded usable fMRI data (10 with TBI and 9 typically developing control participants). Of the 18 participants with TBI that consented to be enrolled in the study, 1 declined to complete the scan, fMRI data was lost for 1 participant due to equipment malfunction, and 6 were excluded due to excessive motion (see fMRI method below for details), leaving 10 with usable fMRI data. Of the 14 typically-developing control participants who consented to be enrolled in the study, 5 were excluded due to excessive motion, leaving 9 participants with usable fMRI
data. Those with usable fMRI data were significantly older at the time of assessment
\((M_{\text{usable}}=15.81, sd=1.05; M_{\text{excluded}}=14.37, sd=1.63; t[30]=3.05, p<0.01)\) than those who were
excluded due to unusable data. Age at injury approached significance \((M_{\text{usable}}=13.74, sd=1.02; M_{\text{excluded}}=12.27, sd=1.90; t[30]=2.08, p=0.055)\). However, they did not differ on time since injury
\((p=0.56)\). Those with usable fMRI data did not differ from those who were excluded in terms of
general cognitive ability, injury severity, or self- or parent-report of EF skills. Injury-related
characteristics of the current sample of adolescents with TBI are presented in Table 1.

Participants had a mean lowest GCS of 12.6 \((sd=3.84)\). Seven of 10 adolescents had complicated
mild TBI characterized by GCS scores of 13-15 with abnormal imaging. Two had moderate TBI
(GCS 9-12) and one had severe TBI (GCS ≤ 8), with no abnormalities on clinical CT or MRI at
the time of injury. The average time since injury was 1.8 years \((sd=0.48)\). Exploratory fMRI
analyses were conducted to determine whether inclusion of the one participant with severe TBI
would alter the pattern of results, and found that this was not the case. Therefore, this participant
was included in final analyses.

Table 1. Injury-related characteristics of the current sample of participants with TBI

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age at Assessment</th>
<th>Age at Injury</th>
<th>Time since Injury (years)</th>
<th>Sex</th>
<th>GCS</th>
<th>Imaging</th>
<th>Injury Classification</th>
<th>Mechanism of Injury</th>
</tr>
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<tr>
<td>TBI1</td>
<td>16.50</td>
<td>14.08</td>
<td>1.79</td>
<td>Male</td>
<td>15</td>
<td>Positive</td>
<td>Comp-Mild</td>
<td>Sport</td>
</tr>
<tr>
<td>TBI2</td>
<td>15.59</td>
<td>12.11</td>
<td>2.74</td>
<td>Female</td>
<td>13</td>
<td>Positive</td>
<td>Comp-Mild</td>
<td>Fall</td>
</tr>
<tr>
<td>TBI3</td>
<td>16.08</td>
<td>14.17</td>
<td>1.93</td>
<td>Female</td>
<td>11</td>
<td>Negative</td>
<td>Moderate</td>
<td>MVA</td>
</tr>
<tr>
<td>TBI4</td>
<td>17.00</td>
<td>14.92</td>
<td>2.11</td>
<td>Male</td>
<td>15</td>
<td>Positive</td>
<td>Comp-Mild</td>
<td>MVA</td>
</tr>
<tr>
<td>TBI5</td>
<td>16.00</td>
<td>14.00</td>
<td>1.98</td>
<td>Male</td>
<td>15</td>
<td>Positive</td>
<td>Comp-Mild</td>
<td>MVA</td>
</tr>
<tr>
<td>TBI6</td>
<td>16.08</td>
<td>14.92</td>
<td>1.14</td>
<td>Male</td>
<td>14</td>
<td>Positive</td>
<td>Comp-Mild</td>
<td>Sport</td>
</tr>
<tr>
<td>TBI7</td>
<td>16.17</td>
<td>14.02</td>
<td>2.00</td>
<td>Female</td>
<td>15</td>
<td>Positive</td>
<td>Comp-Mild</td>
<td>MVA</td>
</tr>
<tr>
<td>TBI8</td>
<td>16.08</td>
<td>14.02</td>
<td>1.88</td>
<td>Male</td>
<td>15</td>
<td>Positive</td>
<td>Comp-Mild</td>
<td>Fall</td>
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<tr>
<td>TBI9</td>
<td>14.83</td>
<td>13.10</td>
<td>1.10</td>
<td>Female</td>
<td>10</td>
<td>Negative</td>
<td>Moderate</td>
<td>MVA</td>
</tr>
<tr>
<td>TBI10</td>
<td>13.59</td>
<td>12.02</td>
<td>1.60</td>
<td>Male</td>
<td>3</td>
<td>Negative</td>
<td>Severe</td>
<td>Sport</td>
</tr>
</tbody>
</table>

Note. MVA = Motor vehicle accident
Procedure

Data were collected in one session, lasting approximately three to three and one half hours for each participant. After obtaining informed consent, participants completed a brief neuropsychological battery including an estimate of general cognitive ability, a measure of emotion labeling ability, and several measures of executive functioning. Participants then completed four paradigms measuring aspects of executive functioning, including the Emotional Go/No-Go described here, while undergoing fMRI scanning. Actual scanning time involved the acquisition of a high resolution anatomical scan, Diffusion Tensor Imaging, and four fMRI scans and lasted approximately 50 minutes. All participants were trained on paradigm instructions prior to entering the scanner.

Neuropsychological Measures

General Cognitive Ability. General cognitive ability was estimated using two measures that correlate highly with traditional intelligence tests. Single word reading skills, which have been used as a proxy for pre-injury cognitive functioning (Orme et al., 2004) were assessed using the Word Reading subtest of the Wide Range Achievement Test, Fourth Edition (WRAT-4). Receptive vocabulary was assessed using the Peabody Picture Vocabulary Test, Fourth Edition (PPVT-IV).

Executive Abilities.

Working Memory and Processing Speed. The Working Memory (WMI) and Processing Speed (PSI) Indices from the Weschler Intelligence Scale for Children, Fourth Edition (WISC-IV, Weschler 2003) were administered to assess domains of executive abilities known to be vulnerable to TBI.
**Inhibition.** The Color-Word Interference Test from the Delis-Kaplan Executive Function System (DKEFS, Delis et al., 2001) was used to assess verbal inhibition. On this Stroop-like test, participants are first timed while they read color words (i.e., “red,” “green,” and “blue;” *Word Reading Condition*) and then name small patches of color orally (*Color Naming Condition*) as quickly as possible. Participants are then presented color words that are printed in a font color that is different from the word (i.e., the word “red” is printed in blue ink) and asked to name the color of the ink (*Inhibition Condition*). The pre-potent tendency to read the word must be inhibited in order to correctly name the ink color.

**Behavioral Manifestations of Executive Abilities.** The Behavior Rating Inventory of Executive Function (BRIEF) rating scales provide ratings for behavioral manifestations of executive ability in every day contexts. Parent-report (BRIEF, Gioia et al., 2000) and self-report (BRIEF-SR, Guy et al., 2004) forms were administered. The BRIEF is summarized in terms of the Global Executive Composite (GEC), which provides an indication of overall executive functioning, and two composite scores, the Metacognitive Index (MI) and the Behavioral Regulation Index (BRI).

**Emotional Labeling.** The Diagnostic Assessment of Nonverbal Abilities (DANVA-2), Adult Faces subtest, was used to assess emotion labeling ability for basic emotions, including happy, sad, fearful, and angry. The subtest consists of 24 photographs of adults displaying emotional expressions (6 photographs for each of the four emotions). Overall emotion labeling accuracy (percent correct, collapsed across all emotion conditions) was used for a general measure of emotion recognition. Errors in labeling for each of the emotions were also recorded.

**Measure of Emotionally-Mediated Response Inhibition using fMRI.**

A modification of the classic “Go/No-Go” paradigm of behavioral inhibition was developed as a block-design fMRI experiment in order to integrate social and emotional information with
inhibitory control. The *Emotional Go/No-Go* paradigm consisted of five cycles of three block conditions, presented in the following order: 1) *Go blocks*, where all trials elicited a “go” response, 2) *Inhibit (“No-Go”) blocks*, where 50% of trials elicited a “go” response and 50% elicited a “no-go” response intermixed randomly, and 3) *Rest blocks* where participants were instructed to passively view a dynamic array of “Xs,” consisting of trials of one to five “Xs” presented in a horizontal row on the screen. Presentation of Go blocks prior to Inhibit blocks allowed for participants to develop a “go” response tendency, necessary for measuring inhibitory ability in Go/No-Go tasks. Go and Inhibit blocks each consisted of ten trials presented for two seconds each. Rest blocks lasted 12 seconds each. Response accuracy (percent correct and errors of omission and commission) and reaction time were recorded to serve as behavioral measures of inhibitory ability. Participants saw faces consisting of happy, sad, fearful, and angry emotional expressions and were instructed to “go” (i.e., press a button) on pictures displaying happy, sad, or fearful, and “no-go” (i.e., withhold responding) on pictures displaying angry. Emotional faces from the Penn Emotion Recognition Test were used as task stimuli. Stimuli were selected based on display of one of the four target emotions (happy, sad, fearful, and angry) at mild- and extreme-intensity, and to ensure ethnic variability in chosen stimuli. The frequency of the three “go” expressions were balanced across go-blocks to ensure roughly equal numbers of each emotion; fearful expression were used with less frequency than happy and sad, due to this being most similar in appearance to the target expression, angry. Angry was used for the inhibit condition because (1) research has shown that individuals with TBI may be impaired in their ability to recognize and respond to angry emotional expressions (Croker & McDonald, 2005; Green, Turner, & Thompson, 2004), and (2) recognition of anger appears to be particularly important in effective interpersonal communication. Stimulus administration and response
logging was accomplished using the experimental software E-Prime with magnet compatible goggles and a response system.

**fMRI Data Acquisition and Analysis**

Data were acquired on a 3T Phillips Achieva System MR scanner. A T1-weighted, three-dimensional MPRAGE whole-brain anatomical scan (TR/TE = 8.2/3.7ms, FOV = 25.2x25x18cm, matrix = 252x250, slice thickness = 1mm) lasting 6 minutes was acquired for the purposes of anatomical coregistration prior to the functional scans. A T2*-weighted, gradient-echo EPI sequence was used for each functional run / scan (EPI scan parameters: TR/TE=2000/30msec, FOV=24x24x16.4cm, matrix = 80x80, slice thickness = 4 mm, flip angle = 90 degree) utilizing a block design fMRI paradigm. Forty-one transverse slices were acquired at 142 time points. The total duration of each functional run was less than 5 minutes (284 seconds), consisting of an initial 12 second fixation period followed by five cycles of the three paradigm conditions in a fixed order (i.e., go, no-go, fixation). The initial four volumes (8 seconds) acquired at the beginning of the run were discarded prior to statistical post-processing of fMRI data to accommodate for T1 relaxation effects.

Following Schmithorst and Holland (2007), fMRI image post-processing was done using Cincinnati Children’s Image Processing Software (*CHIPS*), in-house software written in IDL™ (ITT visual information solutions). The EPI images were reconstructed by built-in software on the 3T Philips Scanner. The reconstructed EPI data were corrected for drift using quadratic baseline correction on a pixel-by-pixel basis (Hu et al., 1995; Le & Hu, 1996), co-registered to the initial reference volume to reduce the effects of motion artifacts using a pyramid iterative algorithm (Thevenaz, Ruttimann, & Unser, 1998), and transformed into Talairach coordinates using landmarks (anterior commissure, posterior commissure, inter-hemispheric plane, and
bounding volume) obtained from the T1-weighted anatomic images (Talairach & Tournoux, 1988), and using a linear affine transformation shown previously to be valid for individuals 5 to 18 years of age (Muzik & Chugani, 2000; Wilke, Schmithorst, & Holland, 2002). During the coregistration procedure, which produced one-point estimate of movement in 3-D space per time point, excessive motion was defined as a median voxel displacement of 3mm for > 10% of the EPI data set from Emotional Go/No-Go. This cut-off was selected to allow for inclusion of as many data sets as possible, while excluding poor data that were unusable even after motion correction.

For each participant, Pearson’s correlation maps were computed on a voxel-wise basis between EPI data and task reference function corresponding to the Go (20s), Inhibit (20s), and the Rest (12s) conditions using the motion correction parameter as a covariate. All task reference functions were constructed from the box-car reference convolved with a canonical hemodynamic response function. A 6s delay was applied to the reference function to allow for the canonical hemodynamic response to peak. Correlation coefficients on a voxel wide basis were transformed into z-score maps using Fisher’s z-transformation. Group analyses were performed on these z-maps from individual participants in the context of the random-effects General Linear Model (GLM). A post-processing filter (8mm FWHM) was then applied before significant regions of activation on a voxel-by-voxel basis were identified (Worsley & Friston, 1995), generating a statistical parameter map. A clustering threshold of 50 contiguous voxels was used unless otherwise stated to improve visualization of the parameter maps and to reduce the severity of the corrections that were made for multiple comparisons. Based on the method of Ledberg, Akerman, and Roland (1998), Monte Carlo simulations were used to estimate corrected p values and performed in the following manner. The spatial autocorrelations present in the fit residuals...
were used to estimate the intrinsic smoothness in the data. “Null” activation maps were
generated from spatially auto-correlated Gaussian noise generated using the previously found
smoothness estimates and post-processing parameters (e.g., threshold intensity, cluster size, and
exogenous spatial filtering). The simulations were repeated, and the corrected p values estimated
by computing the proportion of null maps with spurious activated clusters detected. Monte Carlo
simulation was performed to assure p < 0.001 after adjusting for multiple comparisons. For each
cluster, the Talairach coordinates of the pixel that showed the maximum Z value before
corrections and filtering (i.e., the maxima) is reported here.

All voxels from individual Z-maps were tested for significant difference from zero with
within-group analyses using a composite random effects GLM analysis, with a threshold set at Z
= 6.0 and cluster size = 50 (corrected for family-wise error at p < 0.001), unless otherwise stated.
Between-group GLM analyses were then conducted on the main contrast of interest (e.g., no-go
> go) to examine differential patterns of inhibition-related activation for adolescents with TBI
compared to typically-developing adolescents. Behavioral inhibitory performance (defined as the
inhibition-susceptibility score, described below) during the Emotional Go/No-Go paradigm was
entered into the GLM as a regressor to explore how individual differences in performance might
relate to group activation patterns. Additional exploratory analyses were also conducted using
neuropsychological measures of executive function, including the DKEFS Color-Word
Interference score, and the BRIEF GEC as regressors of interest.
CHAPTER III

RESULTS

Nine typically-developing (TD) adolescents (5 males, 4 females; age 13 to 17 yrs, $M=15.83$ yrs) with negative history for TBI or other neurological insult were compared with ten adolescents with confirmed moderate or severe traumatic brain injury (6 males, 4 females; age 13 to 17 yrs; $M=15.79$ yrs). Group characteristics on demographic, cognitive, and behavioral measures are presented in Table 2. Groups were comparable with respect to age, sex, family income, race, and parent education. Significant differences between groups were observed on the DKEFS Color-Word test, Word Reading and Inhibition conditions. Adolescents in the TD group showed numerically better performance on the WRAT and PPVT than the adolescents with TBI (with effect sizes indexed by Cohen’s $d = 0.86$ and $0.40$, respectively), but this difference did not reach statistical significance ($p > 0.09$). Groups were comparable on the WISC PSI and WMI. Adolescents with TBI had higher levels of parent-rated executive dysfunction on the BRIEF than the TD group, although this difference did not reach statistical significance, (Cohen’s $d$s in the medium to large ranges, $d_{GEC} = -0.79$, $d_{MI} = -0.91$, $d_{BRI} = -0.57$, all $p > 0.07$). It should be noted also that means for this measure in both groups were within the normal range. Adolescents with TBI tended to rate themselves as having greater difficulties with metacognition, such as mental set-shifting (Cohen’s $d_{MI} = -0.82$), although again this did not reach statistical significance ($p > 0.10$).

Table 2. Demographics and group characteristics on neuropsychological measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>TBI ($n=10$)</th>
<th>Control ($n=9$)</th>
<th>$t$/Chi square</th>
<th>$p$</th>
<th>Cohen’s $d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.79 (0.96)</td>
<td>15.83 (1.20)</td>
<td>-0.08</td>
<td>0.94</td>
<td>0.04</td>
</tr>
<tr>
<td>Male Sex (%)</td>
<td>6 (60%)</td>
<td>5 (56%)</td>
<td>0.04</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>Caucasian Race (%)</td>
<td>8 (80%)</td>
<td>8* (100%)</td>
<td>1.80</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Measure</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>t</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>-------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Right Handedness</td>
<td>10 (100%)</td>
<td>6 (75%)</td>
<td>2.81</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of ADHD(^\circ)</td>
<td>1 (10%)</td>
<td>2 (25%)</td>
<td>0.72</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Family Income(^\dagger)</td>
<td>6.40 (4.97)</td>
<td>9.00 (2.50)</td>
<td>-1.41</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Informant Education (&gt;) High School (%)</td>
<td>6 (60%)</td>
<td>6 (67%)</td>
<td>0.09</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>PPVT-4</td>
<td>102 (15.10)</td>
<td>107 (9.27)</td>
<td>-0.83</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>WRAT-4 Reading</td>
<td>100 (19.03)</td>
<td>115 (15.83)</td>
<td>-1.79</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>WISC-IV PSI</td>
<td>109 (15.34)</td>
<td>107 (9.98)</td>
<td>0.37</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>WISC-IV WMI</td>
<td>99 (10.78)</td>
<td>101 (13.14)</td>
<td>-0.45</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>DKEFS C-W: Word Reading</td>
<td>9.90 (2.51)</td>
<td>12.33 (1.73)</td>
<td>-2.43</td>
<td>0.03*</td>
<td></td>
</tr>
<tr>
<td>DKEFS C-W: Inhibit</td>
<td>9.20 (2.53)</td>
<td>11.67 (1.22)</td>
<td>-2.65</td>
<td>0.02*</td>
<td></td>
</tr>
<tr>
<td>BRIEF Parent GEC</td>
<td>51.50 (12.90)</td>
<td>43.33 (7.00)</td>
<td>1.69</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>BRIEF Parent MI</td>
<td>52.30 (12.19)</td>
<td>43.33 (6.91)</td>
<td>1.94</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>BRIEF Parent BRI</td>
<td>50.20 (11.93)</td>
<td>44.78 (6.20)</td>
<td>1.22</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>BRIEF Self Report GEC</td>
<td>53.30 (12.24)</td>
<td>49.89 (9.24)</td>
<td>0.68</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>BRIEF Self Report MI</td>
<td>55.60 (13.16)</td>
<td>46.67 (8.02)</td>
<td>1.76</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>BRIEF Self Report BRI</td>
<td>49.90 (10.93)</td>
<td>52.89 (12.64)</td>
<td>-0.55</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>DANVA Total Errors</td>
<td>5.00 (2.40)</td>
<td>5.11 (2.37)</td>
<td>-0.10</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>DANVA Happy Errors</td>
<td>0.11 (0.32)</td>
<td>0.33 (0.71)</td>
<td>-0.95</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>DANVA Sad Errors</td>
<td>1.10 (1.20)</td>
<td>1.22 (0.67)</td>
<td>-0.27</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>DANVA Angry Errors</td>
<td>2.60 (1.65)</td>
<td>1.67 (1.12)</td>
<td>1.43</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>DANVA Fearful Errors</td>
<td>1.20 (1.14)</td>
<td>1.89 (0.93)</td>
<td>-1.44</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Emotional Go-No-Go</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Go” RT</td>
<td>821.82 (114.78)</td>
<td>744.57 (64.96)</td>
<td>1.78</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>“No-Go” RT</td>
<td>845.26 (97.67)</td>
<td>820.36 (106.49)</td>
<td>0.53</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>“Go” RT sd</td>
<td>231.91 (64.00)</td>
<td>191.64 (45.69)</td>
<td>1.56</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>“No-Go” RT sd</td>
<td>279.53 (86.38)</td>
<td>263.22 (78.66)</td>
<td>0.43</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>“Go” (%Correct)</td>
<td>95.4 (2.83)</td>
<td>96.22 (2.11)</td>
<td>-0.71</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>“No-Go” (% Correct)</td>
<td>78.60 (6.74)</td>
<td>82.67 (4.0)</td>
<td>-1.58</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Interference Score (Go – No-Go)</td>
<td>16.80 (7.50)</td>
<td>13.56 (3.84)</td>
<td>1.17</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

* Significant at \(p<0.05\)

\(^\circ\) ADHD classification based on participant’s report of a prior diagnosis

\(^\dagger\) Data for child’s race is missing on 1 participant and was excluded from the analysis.

\(^\dagger\) Family income coded on 1-10 scale in $10,000 increments, where 1= <$20,000 and 10= $120,000
Emotional Go/No-Go: Behavioral and fMRI Results

Performance data for the Emotional Go/No-Go task were recorded during the fMRI scan. All participants showed higher accuracy for the Go condition than the Inhibit condition. There were no significant group differences in accuracy on the Emotional Go/No-Go task during either the Go or Inhibit conditions. The TBI group tended to have longer reaction times (RTs) and greater RT variability during Go blocks than the controls, though these differences were not statistically significant ($p_{RT}=0.09$, Cohen’s $d = -0.83$; $p_{RTvariability}=0.14$, Cohen’s $d = -0.72$); the same pattern was not observed for Inhibit blocks ($p_{RT}=0.60$, Cohen’s $d = -0.24$; $p_{RTvariability}=0.67$, Cohen’s $d = -0.20$). Further, RT differed significantly between the Go and Inhibit conditions for the TD group ($t=-4.27$, $p<0.01$), though this difference was not significant for the TBI group ($t=-1.01$, $p=0.34$). There was a significant main effect for RT condition (Go and No-Go; $F[1,17]=11.19$, $p<0.01$) reflecting longer RTs for the Inhibit condition than Go condition, but no main effect for group ($p=0.25$); the group x RT condition was non-significant ($p=0.10$), but demonstrated a medium-large effect size ($N^2=0.16$). In order to obtain an estimate of behavioral inhibitory ability during the Inhibit condition while accounting for performance accuracy related to other task-dependent factors (e.g., emotion discrimination ability), an interference-susceptibility score was calculated. For each participant, accuracy during the Inhibit condition was subtracted from accuracy during the Go condition to serve as an index of interference-susceptibility (i.e., in theory, participants who showed poor inhibition would show a high difference score). We chose to calculate interference-susceptibility on the basis of accuracy rather than RT because in this task both groups performed substantially below the ceiling ($<90\%$) in the Inhibit condition. The groups were not significantly different with regard to interference-susceptibility (16.80% difference for the TBI group and 13.56% difference for the
control group); however there was a medium effect size (Cohen’s $d = -0.54$). Groups were similar with regard to number of omission errors ($M=3.3$ for the TBI group and $M=4.4$ for the control group, $p=0.32$) and commission errors ($M=7.2$ for the TBI group and $M=8.6$ for the control group, $p=0.33$). When omission errors were made, groups showed similar patterns of errors for the various emotion types (43% happy, 39% sad, and 18% fearful for the TBI group; 40% happy, 37% sad, and 23% fearful for the control group).

Activation during the task blocks (Go and Inhibit) were each compared with the resting baseline in order to examine brain regions associated with each block condition (See Figure 1).

Figure 1. Brain activation z-map for the contrast Go > R (A) and the contrast No-Go > R (B) across the entire group of 19 participants. Images are in radiological convention, from $z= -29$ to $z=67$, with the following parameters: 8mm post-processing filter, $z$-threshold = 6.0, cluster threshold = 50.

Consistent with the visual nature of the task and the requirements of facial processing, participants showed greater “go” activation in cerebellum, fusiform gyrus, visual cortices, IFG, insula, and superior medial PFC the Go > Rest condition. For the No-Go > Rest contrast, participants showed greater “no-go” activation in the above regions, as well as within the amygdala (greater in right than left), dorsal striatum, thalamus, right superior temporal and TPJ regions, dorsal ACC, and within a broader extent of the inferior frontal gyrus, bilaterally.
Figure 2. Brain activation z-map for the entire group of 19 participants, showing only inhibition-related, positive activation (No-Go > Go). Images are in radiological convention, from $z = -29$ to $z = 67$, with the following parameters: 8mm post-processing filter, $z$-threshold = 10.0, cluster size threshold = 50.

Figure 2 shows the main contrast of interest, the composite Z-score map of brain regions that were significantly more active during the Inhibit condition compared to the Go condition in the entire sample of 19 participants. Inhibition-related activation (No-Go > Go) was observed bilaterally within superior and inferior parietal lobes, TPJ, supramarginal gyri, medial precuneus, PCC, parahippocampal gyri, fusiform gyri, insula, and cerebellum. Inhibition-related activation was also seen within left IFG, right superior and middle DLPFC, and right thalamus (see Table 3). Notably, we did not detect significant activation in midline frontal regions including the anterior cingulate (ACC).

Table 3. Regions showing inhibition-related activation (No-Go > Go) for all 19 participants. Talairach coordinates for the voxel with peak activation within each region of interest (ROI) are listed.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Brodmann Areas</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Peak Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Superior/Middle Prefrontal</td>
<td>6/9</td>
<td>38</td>
<td>9</td>
<td>39</td>
<td>4.02</td>
</tr>
<tr>
<td>R Dorsolateral Prefrontal</td>
<td>9/46</td>
<td>44</td>
<td>12</td>
<td>27</td>
<td>4.20</td>
</tr>
<tr>
<td>L Inferior Frontal</td>
<td>47</td>
<td>-38</td>
<td>21</td>
<td>-1</td>
<td>2.97</td>
</tr>
<tr>
<td>Middle Temporal/Angular Gyrus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(“Temporal-Parietal Junction”)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Within-group analyses of inhibition-related activation for the Control and TBI groups separately are displayed below in Figure 3. Both groups demonstrate roughly similar patterns of inhibition-related activation, although the Control group shows overall more widespread No-Go > Go activation. More importantly, there now appears to be significant differences in the mid-line frontal regions, with activation seen in the TD group and not in the TBI group. To confirm these impressions, between-group analyses were then conducted to directly examine group-related differences for inhibition-related activation.
Imaging of Inhibition and Emotion in TBI

Figure 3. Brain activation z-map for the group of Control participants (A) and TBI participants (B) individually. Only inhibition-related, positive activation (No-Go > Go) is shown. Images are in radiological convention, from z= -29 to z=67, with the following parameters: 8mm post-processing filter, z-threshold = 6.0, cluster threshold = 50. Note that the less stringent Z / cluster thresholds are used so that regional differences between groups is shown more clearly in the images; direct statistical comparison between groups are performed next.

With respect to group-related differences, there were no regions in which participants in the TBI group showed higher levels of inhibition-related activation. The participants in the Control group demonstrated greater inhibition-related activation than participants in the TBI group in medial superior frontal lobes (BA 8/9), right superior frontal/ACC and precentral gyrus (BA 6/32), medial precuneus (BA 7), and left postcentral gyrus and inferior parietal lobe (BA 40/3) (see Figure 4, Table 4).

Table 4. Regions showing group differences for inhibition-related activation (No-Go > Go). Talairach coordinates for the voxel with peak activation within each region of interest (ROI) are listed.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Brodmann Areas</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Peak Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control &gt; TBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial Frontal</td>
<td>9</td>
<td>-4.5</td>
<td>42</td>
<td>23</td>
<td>-5.67</td>
</tr>
<tr>
<td>Medial Frontal</td>
<td>8</td>
<td>16.5</td>
<td>27</td>
<td>39</td>
<td>-2.88</td>
</tr>
<tr>
<td>R Superior Frontal(ACC)/Precentral Gyrus</td>
<td>6/32</td>
<td>28.5</td>
<td>-9</td>
<td>51</td>
<td>-4.04</td>
</tr>
<tr>
<td>Medial Precuneus</td>
<td>7</td>
<td>-16.5</td>
<td>-60</td>
<td>43</td>
<td>-3.55</td>
</tr>
<tr>
<td>L Inferior Parietal/Postcentral Gyrus</td>
<td>40/3</td>
<td>-22.5</td>
<td>-30</td>
<td>59</td>
<td>-2.69</td>
</tr>
</tbody>
</table>
To examine whether between-group differences in the contrast between Inhibit and Go conditions were related more to group differences in Go-related activation alone (i.e., relative to the Rest condition as baseline), the above analyses were repeated for the Go > Rest contrast. At the same thresholds, analyses revealed no regions of significant differences in the Go > Rest contrast between groups. These results then do not support the notion that between-group activation differences in No-Go minus Go are artifactual, but support the idea that it is directly related to group differences in inhibition-related processes.

Correlational analyses were conducted to investigate the relationship, if any, between brain activation and behavioral inhibition ability, utilizing task performance (the interference-susceptibility score, described above), for all 19 participants. There were no regions that showed a significant correlation with interference-susceptibility, whether or not the effects of chronological age were controlled (all p > 0.05). Only when thresholds were made much less stringent (i.e., Z = 2.0, cluster size = 50) in exploratory analyses, did negative correlations
between interference susceptibility (i.e., *better inhibition*, as shown by a low difference score, associated with greater regional activation; or, alternatively, *poorer inhibition*, shown by a large difference score, associated with lower regional activation) and several isolated brain regions emerge (see Figure 5). However, to avoid Type II errors these are statistical thresholds that are not used typically in analyses of this type. Similarly, correlational analyses with out of scanner neuropsychological measures of inhibition (DKEFS Color-Word Interference score) and executive abilities (BRIEF GEC) revealed no regions of significant correlation between performance and brain activation at the more conventional threshold ($Z = 6.0$, cluster size $= 50$).

Figure 5. Statistical parametric map for the entire group of 19 participants, showing brain regions in which activation from the No-Go $>$ Go contrast was correlated with task performance (interference susceptibility score) at a very lenient threshold. Warm colors represent regions that demonstrated a positive correlation with task performance; cool colors represent regions showing a negative correlation with task performance. Images are in radiological convention, from $z = -29$ to $z = 67$, with the following parameters: 8mm post-processing filter, $z$-threshold $= 2.0$, clusterized threshold $= 50$. 
CHAPTER IV
DISCUSSION

Emotionally-Mediated Inhibition

The purpose of the present study was to investigate the neural correlates of emotionally-mediated response inhibition in adolescents with complicated-mild to severe TBI compared with typically developing adolescents using a novel Emotional Go/No-Go paradigm. Inhibition-related activation, shown in the No-Go > Go analysis for all participants, included regions important for cognitive control (left IFG, right DLPFC, bilateral inferior and superior parietal lobes, and right thalamus) and social cognition (bilateral TPJ and insula), as well as other regions including medial parietal lobes (PCC and precuneus) important for self-reflection and monitoring, medial temporal lobes (fusiform gyri and parahippocampal gyri) which are part of the “detection node,” and cerebellum. In contrast to prior studies (Elliott, Rubinsztein, Sahakian, & Dolan, 2000; Goldstein et al., 2007; Shafritz, Collins, & Blumberg, 2006), the No-Go > Go contrast did not show significant activation within many regions important for emotional processing, such as the OFC, ACC, mPFC, amygdala, and ventral striatum. The lack of activation in these regions with the current paradigm is likely related to the fact that it consisted of all emotional faces, whereas prior studies have embedded stimuli eliciting positive or negative emotions of interest within neutral stimuli. Investigations of Go and Inhibit conditions compared with the resting baseline revealed that both conditions recruited regions important for visual processing (visual association cortices, likely due to the heavy visual demands of processing faces compared with processing “Xs”), facial processing (fusiform gyrus), social cognition (superior temporal lobes), and attention/working memory (superior medial FC, bilateral IFG, insula). The Inhibit condition additionally recruited regions important for cognitive control (a
greater extent of the IFG and insula, dorsal striatum, and dorsal ACC) and emotional processing (amygdala). This suggests that the Inhibit condition, compared with rest, was supported by more regions important for emotion and inhibitory processing than the Go condition. However, the subtle differences in emotion areas between the two conditions were not robust enough to hold in the direct contrast (i.e., No-Go > Go). Instead, the No-Go > Go contrast indicates that regions within the cognitive-control network were more important for supporting inhibitory processes in the current paradigm. Overall, the results suggest that adolescents in the current study, with and without TBI, activated regions shown to be related to socio-emotional processing and cognitive control in prior studies of emotionally-mediated response inhibition in adults (Goldstein et al., 2007; Shafritz, Collins, & Blumberg, 2006). However, the inclusion of all emotional stimuli likely impacted the results such that less activation was observed within emotional brain regions. This also provides support for the Emotional Go/No-Go paradigm used in the current study as a measure of emotionally-mediated inhibition, similar to other paradigms in the literature.

*Group Differences in Emotionally-Mediated Inhibition*

Groups showed subtle differences in task performance on the Emotional Go/No-Go. Longer RT for both groups in Inhibit vs. Go conditions indicates that the paradigm induced an “inhibitory” mindset, as intended. However, the TBI group had slower RTs and greater RT variability (Cohen’s $d = -0.83$ and -0.72, respectively) during Go blocks only, such that participants with TBI had smaller differences in RT between Go and Inhibit conditions. This may suggest overall slower reaction times for the TBI group, coupled with less of an inhibitory mindset (faster, more impulsive responding or failure to detect errors) during Inhibit blocks. A medium-large effect size ($N^2=0.16$) for the group x RT condition (Go and No-Go) suggests important differences in the way the TBI and TD groups approached the task. However, groups
showed similar levels of omission and commission errors. Accuracy was lower for Inhibit blocks, compared with Go blocks for both groups (83% for TD group and 79% for TB group). Group differences on task accuracy were non-significant; however, the TBI group may have shown more interference in the Inhibit blocks, as shown by a medium effect size for the interference-susceptibility score (Cohen’s $d = -0.54$).

The results of the current study provide support for the primary hypothesis that adolescents with TBI would show differential levels of activation within socio-emotional and cognitive control systems than matched TD participants. Within-group analyses suggest that groups showed overall similar patterns of activation for emotionally-mediated inhibition, composed of regions in both cognitive-control and socio-emotional networks. However, TD adolescents had greater activation in specific regions within the cognitive-control network or cognitive-regulatory node, including dorsal medial FC (BA 9, 8) and dorsal ACC (BA 6/32), medial precuneus (BA 7), and left inferior parietal cortex (BA 40). Activation in dorsal medial FC regions has been observed in several studies of emotional and non-emotional cognitive-control paradigms, and is believed to be related to response inhibition, monitoring, and interference control (Badgaiyan & Posner, 1998; Goldstein et al., 2007; Rubia et al., 2001; Shafritz, Collins, Blumberg, 2006; Tlustos et al., 2011). Parietal regions are also commonly associated with cognitive-control paradigms, and are believed to be important for attentional and inhibitory control, response selection (Goldstein et al., 2007; Rubia et al., 2001; Shafritz, et al., 2006; Tlustos et al., 2011; Wagner et al., 2005), and self-reflection/self-monitoring (Johnson et al., 2006; Newsome et al., 2010). Given the protracted development of the cognitive-regulatory node, these between-group differences may suggest that TBI in adolescence interrupts development of fronto-parietal networks, resulting in altered patterns of activation. Additionally,
that differences were observed in cognitive control regions rather than socio-emotional regions has implications for neuropathology of emotional and behavioral regulation difficulties in various clinical populations. Prior studies using Emotional Go/No-Go paradigms revealed differences in activation in the affective node for adults with mood disorders compared to healthy adults. This suggest different neural substrates underlying socio-emotional outcomes for individuals with mood disorders and those with TBI.

Higher activation in the cognitive-regulatory node for TD adolescents is in contrast to recent brain imaging studies of executive functions in adults and adolescents with TBI (Kramer et al., 2008; McAllister et al., 2001; Newsome et al., 2010; Sanchez-Carrion et al., 2008; Tlustos et al., 2011) that have consistently found higher levels of activation in groups of participants with TBI compared with controls. Higher levels of activation were found in frontal and parietal regions in studies of inhibitory control in adolescents with TBI (Tlustos et al., 2011) and sustained attention in children with TBI (Kramer et al., 2008). A study of perspective-taking in adolescents with TBI also revealed higher levels of activation within posterior brain regions, including lingual gyrus and parahippocampal gyrus, PCC, and cuneus (Newsome et al., 2010). Increases in activation within brain regions are often thought to reflect increased processing load or “mental effort.” Many of these studies have suggested that the higher activation in TBI groups may reflect “compensatory” processes; however, the relationship between activation and processing load is one that is not completely understood. Other studies have revealed a more complicated relationship between levels of brain activation on executive functioning tasks, which may depend on task demands, task difficulty or “load,” injury severity, or time since injury. For example, Newsome et al. (2008) found that adolescents with TBI showed varying levels of brain activation during a working memory (WM) paradigm, depending on the specific task demands.
During maintenance portions of the task, typically-developing adolescents showed higher activation in frontal and parietal regions for high-load vs. low-load conditions; conversely, adolescents with TBI showed higher activation for high-load vs. low-load during encoding and retrieval portions of the task. The authors suggested that the “over-recruitment” of frontal regions during encoding and retrieval represent compensatory processes, whereas the opposite pattern during maintenance portions may reflect hypoactivation or “inefficiency” in processing during less active portions of the task. McAllister et al. (2001), found varying levels of activation in adults within one month after mild TBI depending on WM load during an N-back task. Adults with TBI showed heightened activation relative to healthy controls in moderate WM load conditions (2-back), but lower activation during high WM load conditions (4-back), suggesting that the task may have become too difficult for TBI participants during the high WM load condition. The observed hypoactivation may reflect disengagement of these regions as the participants mentally “give up.” The authors concluded that TBI altered participants’ ability to modulate WM processes after injury.

These results raise a couple of possibilities for interpreting the current results. Decreases in cognitive control regions for the TBI group may reflect overall difficulty level of the task, suggesting that the TBI group found the Emotional Go/No-Go paradigm too difficult and disengaged during Inhibit blocks. This interpretation would be consistent with behavioral performance indicating lower accuracy on Inhibit blocks and the indication of greater interference-susceptibility for TBI participants compared with TD participants. It is also possible that the TBI group processed the Emotional Go/No-Go stimuli in qualitatively different way than the TD group. For instance, decreased activation in the medial FC may reflect differences in groups’ error monitoring. Studies have implicated heightened activation in the medial FC as an
indication that individuals have detected that they made an error (Badgaiyan & Posner, 1998), and activation in this region has been shown to be associated with error-related negativities (ERNs) observed on EEG (Taylor, Stern, & Gehring, 2007). Thus, group differences observed in the current study may be related to better awareness or detection of errors within the TD group. This explanation may help explain the TBI groups’ relatively fast RTs during Inhibit blocks (compared with the TD group that showed a significant difference in RT between Go and Inhibit blocks). Slower RTs in Inhibit blocks often reflect participants’ attempts to slow down in order to avoid making errors. Thus, TBI participants’ failure to slow down may indicate that they failed to recognize that they were making errors to the same degree as the TD participants, and therefore did not recognize a need to engage cognitive control processes to the same degree.

Other studies have shown varying levels of activation for executive processes in TBI depending on injury severity or time since injury. Scheibel et al. (2009) showed higher levels of brain activation in regions important for attention and cognitive control associated with greater injury severity and better task performance, suggesting a compensatory effect after injury. Brain activation has also been shown to vary with time since injury. In a longitudinal study of adults with severe TBI, activation in right superior frontal areas initially showed reduced activation in adults with TBI compared to healthy controls, but activation increased in this area over a 6-month period such that the between-group differences were much attenuated and appeared to “normalize” (e.g., Sanchez-Carrion et al., 2008). These results highlight the complex relationship between task demands and activation levels in studies of participants with TBI. Thus, the implications of greater activation in the cognitive-regulatory node for TD adolescents compared with adolescents with TBI is not perfectly clear. However, altered activation does suggest that
TBI in adolescence may impact the development of fronto-parietal networks underlying cognitive control.

*Group Differences in Behavioral Measures of Inhibition, Affect Recognition, and Executive Abilities*

As indicated above, groups showed subtle differences in task performance on the Emotional Go/No-Go paradigm. Groups showed similar performance across most neuropsychological measures of cognitive ability, with indications for poorer executive abilities on certain measures. Groups showed significant differences on the DKEFS Color-Word test for Word Reading and Inhibition conditions, suggesting slower performance overall for adolescents with TBI. Medium-to-large effect sizes for parent-reported and self-reported executive dysfunction on the BRIEF were also evident, particularly for metacognitive abilities, such as mental set-shifting (Cohen’s $d = -0.79$ for Parent BRIEF, GEC; $d = -0.91$ for Parent BRIEF MI; $d = -0.82$ for Self Report BRIEF MI). Although groups did not show significant differences in affect recognition abilities on the DANVA, effect sizes for angry and fearful errors between groups were within the medium range (Cohen’s $d = 0.66$ and 0.66, respectively), indicating that adolescents with TBI made more angry errors, and TD adolescents made more fearful errors. However, groups did not demonstrate differences in errors by emotional expression on the Emotional Go/No-Go, suggesting that affect recognition difficulties did not significantly impact group differences in the current paradigm.

*Brain Activation and Behavioral Performance*

The secondary aim of the study was to explore the relationship between neural activation patterns during the emotionally-mediated inhibition paradigm and behavioral measures of inhibition and executive ability. In order to examine how individual differences in task
performance may have affected activation in the No-Go > Go contrast, correlations with the interference-susceptibility score were conducted. However, no regions demonstrated significant correlations with task performance. Similarly, despite group differences on neuropsychological measures of inhibition, processing speed, and parent-rated executive dysfunction, analyses failed to reveal significant correlations between brain activation and DKEFS Color-Word Interference score and Parent BRIEF, GEC. Therefore, there were no regions that were significantly correlated with behavioral measures of executive ability, failing to support the secondary hypothesis of the study that participants with greater levels of demonstrated and reported executive impairment would show differential recruitment of socio-emotional and cognitive-control systems than those participants with little or no executive impairment. This may suggest that injury-related factors may play a greater role in altered activation patterns, rather than individual differences in functional performance.

**Limitations**

The current study has several inherent limitations. Firstly, the small and heterogeneous sample and insufficient statistical power limits the generalizability of the current findings to the broader population. The sample was composed primarily of adolescents with complicated-mild injuries, with GCS scores of 13-15 with abnormalities on imaging; the one participant with severe TBI had no identified abnormalities on imaging. Neuroimaging studies on executive abilities after TBI have shown an important relationship between brain activation and injury severity (e.g., Scheibel et al., 2009). However, this could not be examined in the current study, as details regarding extent of brain injury, lesion location, and TAI are limited and the small sample prohibits further analyses based on injury details. Additionally, although most measures of cognitive performance fell within the average range overall, there was considerable variability
across participants. The effect size estimates (Cohen’s $d$) for some neuropsychological and behavioral measures, including certain estimates of overall cognitive ability, were in the “moderate” to “large” range, which suggests that statistically significant differences between groups may emerge with a larger sample size. Additionally, the paradigm used in the current study appears to be more difficult than paradigms used in prior studies, as indicated by lower accuracy for both TD and TBI groups for Inhibit conditions (83% for TD group and 79% for TB group, compared with 96.6% ± 0.5% for sad no-go and 96.3% ± 0.8% for happy no-go reported in Shafritz et al., 2006) than have previously been reported. Thus, subtle group differences in performance (accuracy and RT) may have affected the group differences observed in inhibition-related activation, confounding performance and neural response to some degree.

Implications and Directions for Future Research

To the best of the author’s knowledge, the present study represents the first to investigate the interaction between emotional and cognitive-control processes in adolescents with TBI. Individuals with TBI often show deficits in emotional and social cognition, as well as executive functions, all of which may have important implications for effective decision-making and socio-emotional functioning. The current study demonstrated that adolescents with TBI show similar patterns of neural activation while completing an emotionally-mediated inhibition paradigm as adults and adolescents in prior research. However, between-group differences in inhibition-related activation indicate that TD adolescents show higher levels of activation within certain cognitive-control-related brain regions, including medial prefrontal and parietal areas. These results suggest that adolescents with TBI may show inefficiencies in neural processing in these regions, perhaps as the result of alterations to the fronto-parietal networks from TBI during a critical period of development. However, the current study is preliminary, and further research is
needed to understand the impact of TBI on emotional and inhibitory processing. There is still surprising little research investigating the neural basis for social cognition and executive functions in adolescence, despite this being a critical period for the development of these systems. Cross-sectional and longitudinal studies will be important for better understanding how disruptions to networks during this critical period of development impacts both neural connectivity and the development of functional abilities. Further it will be important to understand how these differences in neural response are related to cognitive and socio-emotional outcomes after TBI in adolescence.
REFERENCES


Imaging of Inhibition and Emotion in TBI


