Cognitive and Brain Processes in Young Adults with a History of Childhood Interpersonal Trauma

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COGNITIVE AND BRAIN PROCESSES IN YOUNG ADULTS
WITH A HISTORY OF CHILDHOOD INTERPERSONAL TRAUMA

by

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Multiple studies have demonstrated that childhood interpersonal trauma, a traumatic event purposefully perpetrated by one person against another, is associated with many negative factors in young adulthood. Although many studies have demonstrated that cognitive processes may be affected by a history of childhood interpersonal trauma, few studies have examined the neural underpinnings of these effects. Development of the prefrontal cortex is now considered to continue into the mid-20’s, with these regions of the brain being involved in cognitive control. Therefore, we investigated whether activation of networks recruited for cognitive control is altered in young women with a history of childhood interpersonal trauma. We specifically examined hypotheses that cognitive control networks related to inhibition and guiding attention in the face of distracting information would be altered in two different tasks. A total of 27 young women (age 22 – 30), 13 with a history of childhood interpersonal trauma and 14 with no history of trauma, completed a working memory task and a modified Stroop task while in an fMRI scanner. For the purposes of this study, childhood interpersonal trauma consisted of childhood physical or sexual abuse and/or assault occurring before the age of 17. Results of this study suggest alterations in cognitive control mechanisms underlying both inhibiting and maintaining previous representations in working memory in women with a history of childhood interpersonal trauma. Additionally, it suggests women with a history of childhood interpersonal trauma have difficulty maintaining an internally-generated task-set and attend to and process information in
the environment to help reinforce task-relevant processing. Alterations in these processes were associated with symptom severity. These findings support the proposal that trauma-exposed individuals demonstrate enhanced attentional allocation to environmental stimuli in order to guide cognitive control of attention, as well as decreased inhibitory networks supporting inhibition of information that is no longer task-relevant. The impact of limitations and how they might affect interpretations are also explored.
To my husband, Dragos

For believing in me, supporting me, and reminding me of my own strength, even when I could not find it in myself.
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CHAPTER 1

INTRODUCTION

Overview

Trauma exposure and its sequelae greatly impact many individuals. The National Comorbidity Study found that approximately 51% of women and 61% of men in community samples across the United States experienced at least one trauma in their life. Furthermore, of those respondents reporting trauma exposure, 56.3% of trauma-exposed men and 48.6% of trauma-exposed women reported experiencing two or more traumas in their life (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). The Diagnostic and Statistical Manual, 4th Edition, Text Revision (DSM-IV-TR) defines a traumatic event as a:

personal experience of an event that involves actual or threatened death or serious injury, or other threat to one's physical integrity; or witnessing an event that involves death, injury, or a threat to the physical integrity of another person; or learning about an unexpected or violent death, serious harm, or threat of death or injury experienced by a family member or other close associate (American Psychiatric Association, 2000, pg. 463).

Children and teenagers are at an elevated risk of exposure when compared to adults (Duke & Vasterling, 2005). Trauma exposure in childhood and adolescence is frequently comprised of interpersonal trauma, which is a traumatic event purposefully perpetrated by one or more individuals against another individual. Examples of interpersonal trauma include sexual abuse or assault, physical abuse or assault, and intimate partner violence. Childhood interpersonal trauma (CIT) refers to an interpersonal trauma that has occurred prior to the age of 18. Given that approximately 905,000 estimated cases of child abuse and trauma are reported in a year in the United States (Department of Health and Human Services, 2006), childhood abuse and trauma, and its subsequent consequences, affect a substantial portion of young adults in this country.
In children, CIT is associated with alterations in cognitive processing (for review, see DePrince, Weinzierl, & Combs, 2009) and emotion regulation (Pollak, Cicchetti, Hornung, & Reed, 2000; Pollak, Vardi, Bechner, & Curtin, 2005), as well as functional impairments, such as decreased school achievement (Shonk & Cicchetti, 2001). Negative associations with CIT are not limited to childhood and can continue into adulthood. Multiple studies have demonstrated that CIT is associated with negative factors in young adulthood, including psychopathology (Edwards, Holden, Felitti, & Anda, 2003), emotional dysregulation (Teicher, Samson, Polcari, & McGreenerney, 2006), and cognitive deficits (Navalta, Polcari, Webster, Boghossian, & Teicher, 2006).

One specific area of cognitive functioning that appears to be disrupted in people with CIT, both in childhood (Beers & De Bellis, 2002) and adulthood (Navalta et al., 2006), is cognitive control. Behavioral studies have found that cognitive control of attention (e.g., Foa, Feske, Murdock, Kozak, & McCarthy, 1991) and working memory (Stein, Kennedy, & Twamley, 2002), as well as an aspect of cognitive control, inhibition (Jenkins et al., 2000), is affected in individuals exposed to interpersonal trauma. Not only do behavioral studies suggest interpersonal trauma is associated with altered cognitive control, but neuroimaging studies have also demonstrated alterations in cognitive control of neutral (e.g., Falconer et al., 2008) and emotional (e.g., Bremner et al., 2004) information in adults with a history of trauma. A smaller body of literature has examined cognitive control in children and adolescents with a history of CIT, with the studies to date reflecting similar findings as adult studies.

In summary, although many studies have demonstrated that cognitive control is affected in individuals with a history of CIT, a limited number of studies have examined the neural underpinnings of these effects. This study examines whether a history of CIT is associated with
changes in cognitive and neural functioning in young adulthood. By understanding affected
cognitive and neural processes in individuals exposed to CIT, it may be possible to devise more
specific targets for therapeutic intervention. Following is a review of literature relevant to
understanding the interface of cognitive control and trauma exposure. Cognitive control is
reviewed initially in order to set a foundation for further reviewed findings, followed by a review
of the cognitive processes, brain processes, and brain structures affected in trauma-exposed
individuals.

**COGNITIVE CONTROL**

Cognitive control refers to brain processes involved in biasing task-relevant responding,
which results in the modulation of various types of input and output, including sensory, memory,
and emotional domains (Miller & Cohen, 2001). It allows individuals to guide behavior towards
a goal, especially in the face of distracting information and when the situation is novel (Banich &
Compton, 2011). Additionally, cognitive control involves overriding prepotent or automatic
responding and behaviors (Miller, 2000). A network of brain regions in the PFC has been
implicated in cognitive control (M. T. Banich & Compton, 2011; Earl K. Miller & Cohen, 2001),
in part because of its anatomical connectivity (see Miller & Cohen, 2001). Below is a brief
review of some of the neuroimaging findings related to the cognitive control of attention and
working memory. Inhibition is also reviewed, as it is likely a process involved in multiple
aspects of cognitive control (Banich et al., 2009).

*Attention*

Models of attentional control distinguish between two types of mechanisms: bottom-up
mechanisms in which characteristics of environmental information make them more salient and
allow them to capture attention, either because of perceptual characteristics or because of learning; and top-down control mechanisms, in which an individual uses categories or concepts to bias towards information that is task relevant (Banich & Compton, 2011). Furthermore, these two types of attentional control are thought to be imposed by different neural systems, with bottom-up processing associated with a posterior right-hemisphere system and top-down processing with a frontal system that imposes a top-down attentional set (Banich et al., 2000a, 2000b; Botvinick et al., 2001; Milham et al., 2001). The anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and posterior parietal regions have all been identified in healthy controls as being involved in a network of prefrontal brain structures important for guiding attention to relevant information in the face of distracting information (Banich et al., 2000a, 2000b; Botvinick et al., 2001; Brown et al., 1999; Bush et al., 1998; Carter, Mintun, & Cohen, 1995; Carter et al., 1998; Milham et al., 2001; Taylor, Kornblum, Lauber, Minoshima, & Koeppe, 1997). Activation of the DLPFC is thought to be related to maintaining and imposing an attentional-set that guides attention towards task-relevant information (Banich, 2009; Banich et al., 2000, 2009; MacDonald et al., 2000; Silton et al., 2010), with activation being greater in the DLPFC when it is more difficult to direct attention to task-relevant processes (Banich et al., 2000a). The DLPFC has been found to be recruited for the maintenance of attentional sets for both neutral and emotional information (see Compton, 2003). On the other hand, the ACC has been suggested to be involved in response selection and evaluation (Banich, 2009; Banich et al., 2009) or conflict monitoring and resolution (for review, see Botvinick et al., 2001). Therefore, a general conceptualization has been that the DLPFC maintains an attentional set for task-relevant processes and behavior, whereas the ACC is recruited when additional resources may be needed because of a higher chance of making an error or greater conflict (Badre & Wagner, 2004;
Banich, 2009; Barch et al., 2001; Miller & Cohen, 2001; Silton et al., 2010). Activation of the ACC may lead to further recruitment of the DLPFC and other regions necessary for cognitive control (Kerns et al., 2004; MacDonald et al., 2000; Milham et al., 2003).

Multiple models of cognitive control have been proposed, with some of the models directly relating to attentional control. One model elaborating on the general roles of the DLPFC and ACC presented above is the Cascade of Control model (Banich, 2009; Milham & Banich, 2005; Milham, Banich, & Barad, 2003). The Cascade of Control model proposes that the role of the DLPFC in maintaining an attentional set can be broken down by regions, with posterior DLPFC (pDLPFC; BA 6, 8, and 9) biasing posterior processing regions of the brain towards task-relevant processes and mid-DLPFC (mDLPFC; BA 9, 9/46) biasing ventrolateral PFC and dorsal ACC (dACC) towards task-relevant representations. Similarly, the ACC can be broken down into subregions as well, with more dACC directing task-relevant response selection and ventral ACC involved in response evaluation. Based on feedback from the ventral ACC to the pDLPFC, cognitive control is increased if processing is not sufficiently biased towards task-relevant processes. This model will serve as the foundation for conceptualizing and interpreting previous neuroimaging data on cognitive control in trauma-exposed individuals as well as the results of the current study.

Working Memory

Working memory “refers to the ability to keep information active for further use, while allowing it to be prioritized, modified and protected from interference” (Bledowski, Kaiser, & Rahm, 2010, pg. 172). Multiple models have been proposed to explain the involvement of various subregions of the PFC in working memory (for review, see Bledowski, Kaiser, & Rahm, 2010 and Wager & Smith, 2003). Some people have suggested that the PFC is functionally
organized by the type of material being processed, with dorsolateral regions being more involved in processing spatial information and ventral regions being more involved in processing non-spatial information (Goldman-Rakic, 1993, 1995; Smith & Jonides, 1999). Further implications have been made about lateralization for the type of information in working memory. Some have suggested verbal working memory is left-lateralized (Smith & Jonides, 1999). However, others have proposed spatial working memory is right-lateralized and object working memory is left-lateralized (Smith et al., 1995). In contrast, some have suggested that distinctions in functional regions are more linked with executive processes, not content. Some have proposed the ventrolateral PFC is involved in low-level encoding for and retrieval from simple storage, whereas the DLPFC is more involved in encoding and retrieval that requires response monitoring and manipulation (D’Esposito et al., 1998; Owen, 1997, 2000). Duncan & Owen (2000) have further suggested that although the dACC may be involved in working memory maintenance, most of the mPFC is not.

A meta-analysis by Wager and Smith (2003) examined neuroimaging studies of working memory on the basis of the content (verbal, spatial, or object) and executive processes (updating, manipulation, maintenance of order, and selective attention) involved in working memory. Differences for content were mainly seen in the parietal cortex, whereas dissociations in activation for executive processes were prominent in the PFC and were also present in the parietal cortex. Overall, they found bilateral superior frontal sulcus and DLPFC demonstrated the greatest specialization for updating and maintenance of temporal order, whereas manipulation produced the greatest specialization in right IFG (rIFG) and anterior frontal cortex. Another study directly comparing activation of PFC regions during updating across several tasks found the superior frontal sulcus and DLPFC were involved in updating tasks (Collette et al., 2005).
Wager & Smith (2003) highlight that although activation of the superior frontal sulcus is often thought to be related only to eye and motor movements, the findings from this meta-analysis are consistent with other findings that the superior frontal sulcus is involved in working memory. Selective attention was the only process that predicted activation in the mPFC, including the ACC. In contrast, the precuneus, a region of superior parietal cortex, was the only region to show activation across all executive processes. This is consistent with findings from another study that systematically examined three executive processes (Collette et al., 2005). Wager & Smith’s (2003) findings are consistent with the Cascade of Control model (Banich, 2009; Milham & Banich, 2005; Milham, Banich, & Barad, 2003), suggesting that mDLPFC and pDLPFC are involved in a task-related selection bias and that the parietal cortex is involved in implementing that bias. Additionally, the mPFC was only differentially activated for selective attention, which arguably could require the recruitment of increased cognitive control and inhibition of task-irrelevant information.

Inhibition

There is a growing body of literature on the neural networks underlying inhibition. Paradigms directly tapping motoric inhibition, through tasks such as the Stop-Signal task, have consistently found rIFG, mPFC, and DLPFC are recruited when actions are inhibited (Aron et al., 2004; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Garavan, Ross, & Stein, 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Menon, Adelman, White, Glover, & Reiss, 2001). Based on the evidence to date, two types of motor inhibition have been identified, global inhibition and selective inhibition. Global inhibition involves inhibiting all motor responding, whereas selective inhibition involves inhibiting a specific motor response (Aron & Verbruggen, 2008). Similarly, other inhibition tasks have found that inhibition of irrelevant
information during selective attention tasks (Clark, Fannon, Lai, Benson, & Bauer, 2000; Kirino, Belger, Goldman-Rakic, & McCarthy, 2000; McCarthy, Luby, Gore, & Goldman-Rakic, 1997; Menon, Ford, Kim, Glover, & Pfefferbaum, 1997; Yoshiura et al., 1999) and distractor information during working memory tasks (Clapp, Ruebens, & Gazzaley, 2010; Dolcos, Miller, Kragel, Jha, & McCarthy, 2007; Jha, Fabian, & Aguirre, 2004; Toepper et al., 2010; Sakai, Rowe, & Passingham, 2002) is associated with rIFG, mPFC, and DLPFC activation. Additionally, adaptations of the Go/No-Go task to a paradigm tapping inhibition of information to be stored in long-term memory, the Think/No-Think task (Anderson & Green, 2001), have found increased DLPFC and rIFG are associated with successful inhibition of items (Anderson & Green, 2001; Depue et al., 2007). More importantly, successful inhibition was also associated with decreased activation of visual processing regions and the hippocampus, suggesting that processing of irrelevant task information may be suppressed (Depue et al., 2007). Activation of the DLPFC and rIFG during inhibition tasks is consistent with the posited role of the mDLPFC in biasing ventrolateral PFC towards task-relevant representations, which may include inhibiting task-irrelevant representations. Consistent with this conclusion, a study of three aspects of executive functioning found that inhibition did not demonstrate a unique pattern of activation compared to shifting and updating (Collette et al., 2005), suggesting it may be a process underlying cognitive control more generally.

Summary

In summary, DLPFC, ACC, and rIFG have been implicated in models of cognitive control. The DLPFC has most consistently been implicated in active maintenance of task relevant attentional sets. According to the model proposed for use in this study, the Cascade of Control model, the DLPFC biases posterior regions to task-relevant processes and ventral frontal
regions to task-relevant representations. The ACC is involved in response selection and evaluation. This model is consistent with imaging findings examining attentional control, cognitive control of working memory, and inhibition.

ALTERED COGNITIVE PROCESSES

Most of the research on altered cognitive processes in trauma-exposed individuals has been conducted with individuals who meet criteria for Posttraumatic Stress Disorder (PTSD). Behavioral data suggests that two main cognitive processes compromised in PTSD are memory (McNally, 1997) and attention (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; Mathews & MacLeod, 2002). Although much of the available research has focused on participants with PTSD, emerging evidence points to compromised attention (DePrince et al., 2009; Navalta et al., 2006) and memory (El-Hage, Gaillard, Isingrini, & Belzung, 2006; Stein, Kennedy, & Twamley, 2002) following interpersonal trauma in the absence of PTSD. Behavioral studies of memory, attention, and inhibition are reviewed below because alterations in neural systems associated with attention (e.g., Bremner et al., 2004), memory (e.g., Morey et al., 2009), and inhibition (e.g., Falconer et al., 2008) have been demonstrated in trauma-exposed individuals and will be discussed at greater length later.

Attention

An attentional bias is a process by which detection of specific types of stimuli in the environment causes cognitive resources to be redirected without direct awareness. Resources are limited and therefore the increased allocation of available resources to attentional processes occurs at the expense of other cognitive processes (Constans, 2006). All individuals, regardless of current emotional state, direct attention towards strong threat stimuli (Mogg & Bradley, 1998).
However, the attentional deficits observed in both children and adults with a history of trauma have been linked to hypervigilance and an attentional bias to even mild threat information (Becker-Blease, Freyd, & Pears, 2004; Brewin & Holmes, 2003; Dalgleish, Moradi, Taghavi, Neshat-Doost, & Yule, 2001; Mathews & MacLeod, 1994; McNally, Kaspi, Reimann, & Zeitlin, 1990; Pollak, Cicchetti, Hornung, & Reed, 2000; Pollak, Vardi, Bechner, & Curtin, 2005). Constant attention directed towards mild threat in the environment results in the increased salience of non-threatening stimuli, leading to chronic levels of hyperarousal (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002; Mathews & MacLeod, 2002).

There is a robust body of literature demonstrating this phenomenon through the use of the emotional Stroop task. The emotional Stroop task, a variant of the classic Stroop task (Stroop, 1935), requires individuals to attend to a word’s ink color while ignoring the meaning of emotional (e.g., disgust, threat, positive) or neutral words. Adults and children who have a history of trauma, whether or not they meet clinical criteria for PTSD, are slower at naming the color of words related to the trauma they have experienced as compared to words un-related to their trauma (Bryant & Harvey, 1995; Buckley, Blanchard, & Hickling, 2002; Cassidy, McNally, & Zeitlin, 1992; Constans, McClosky, Vasterling, Brailey, & Mathews, 2004; Foa, Feske, Murdock, Kozak, & McCarthy, 1991; McNally, Amir, & Lipke, 1996; McNally, English, & Lipke, 1993; McNally, Kaspi, Reimann, & Zeitlin, 1990; Moradi, Taghavi, Doost, Yule, & Dalgleish, 1999; Vrana, Roodman, & Beckman, 1995). These effects are robust across different media and modalities (Constans, 2006) as well as type of trauma (Constans et al., 2004; Foa et al., 1991; McNally, 2003), with the greatest effects being found in women who have been raped (Foa et al., 1991). Moreover, deficits are positively correlated with PTSD symptom severity (McNally, Clancy, Schacter, & Pitman, 2000). In addition, individuals with PTSD demonstrate
an attentional bias to threat information when completing the dot-probe task, which is also positively associated with PTSD symptoms (Bryant & Harvey, 1997; Dalgleish et al., 2001; Elsesser, Sartory, & Tackenberg, 2004). However, it has been shown that this attentional bias to threat may not emerge until several months post-trauma (Elsesser, Sartory, & Tackenberg, 2005).

Not only is attention to threat altered in individuals with a history of trauma, but attention to neutral information is also altered. Studies have found children and adults with a history of trauma demonstrate both selective and divided attention deficits for both auditory and visual information (Beers & De Bellis, 2002; Freyd & DePrince, 2001; Jenkins, Langlais, Delis, & Cohen, 2000; McFarlane, Weber, & Clark, 1993; Vasterling, Brailey, Constans, & Sutker, 1998; Vasterling et al., 2002). Although some studies have found poorer performance on the classic Stroop task in individuals with PTSD (e.g., Lagarde, Doyon, & Brunet, 2010; Litz et al., 1996), other studies have not found differences in performance (e.g., Bremner, et al., 2004; McNally et al., 1996). Studies examining continuous performance measures have found that people with PTSD demonstrate deficits (for review, see Aupperle et al., 2011). Despite demonstrated deficits in selective attention, trauma-exposed individuals both with and without PTSD do not demonstrate altered alerting or orienting (Leskin & White, 2007). Attentional deficits haven been found in individuals with PTSD even after controlling for depression, alcohol abuse, IQ, and learning disabilities (Brandes et al., 2002; Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; Samuelson et al., 2006). It should be noted that some studies have used forward digit span as a measure for attention, either as the only sustained attentional measure or in conjunction with other measures (e.g., Jenkins et al., 2000; Samuelson et al., 2006). Although these measures may capture aspects of attention, they have traditionally been considered measures of one’s ability to maintain information in working memory. Therefore, some of these studies could also be
interpreted as suggesting alterations in not only attention, but also maintenance of information in working memory.

Memory

Multiple studies demonstrate emotional memories are more vivid and persistent than non-emotional memories. As a result of increased vividness at the time of the event, emotional memories are better encoded and consolidated into long-term memory (Phelps, 2004). People with PTSD specifically demonstrate a stronger bias for enhanced recall of trauma-related materials. Concordant with studies of emotional memory in general, they are not just more likely to recall trauma-related material, but memories of this material or actual events are often vivid and long-lasting (Brewin & Holmes, 2003). Experimental tasks have demonstrated adults with PTSD have greater explicit and implicit memory for trauma related as compared to non-trauma related material (for review, see McNally, 1997). Not only do adults with PTSD demonstrate increased recall of trauma related material, but they also exhibit difficulty forgetting trauma material. In a study by McNally and colleagues (1998), women with PTSD resulting from a history of childhood sexual abuse exhibited deficits in recalling positive and neutral words, but not trauma words, in a directed forgetting task. Paradoxically, it has been found that increased recall of trauma related material is coupled with difficulty in retrieving autobiographical memories of the trauma (Buckley, Blanchard, & Neill, 2000). Clinicians note observations of clients with PTSD reporting confusion, disorganization, and forgetting of the trauma memory, although they simultaneously report such memories are vivid and persistent (Herman, 1992). Multiple studies have demonstrated an association between trauma history and over general memory, such that more severe trauma history is predictive of more over general memory of the trauma (Kuyken & Brewin, 1995; McNally, Lasko, Macklin, & Pitman, 1995; McNally, Litz,
Prassas, Shin, & Weathers, 1994). Furthermore, people with PTSD are more physiologically responsive to autobiographical trauma scripts than generic trauma scripts (McNally et al., 1998).

Behavioral studies of individuals who have experienced trauma have also found deficits in episodic and short-term memory for non-emotional information (for review see, Buckley et al., 2000; Gilbertson et al., 2001; Golier et al., 2002; LaGarde et al., 2010; Wessel, Merckelbach, & Dekkers, 2002). Associations between trauma and working memory have been receiving increasing attention in the literature. Studies show that individuals with PTSD demonstrate deficits on verbal working memory tasks (Gilbertson et al., 2001; LaGarde et al., 2010; Koso & Hansen, 2006; Samuelson et al., 2006; Vasterling et al., 1998, 2002). However, many studies have not found deficits on visual working memory tasks (see Aupperle, Melrose, Stein, & Paulus, 2011). It has been shown that deficits in working memory positively correlate with PTSD symptoms (Burriss, Ayers, Ginsberg, & Powell, 2008). Some studies have found that introducing emotional distractors in working memory tasks or provoking symptoms prior to completing tasks does not differentially influence working memory in people with PTSD (Jelinek et al., 2008; Morey et al., 2009, but see Mueller-Pfeiffer, 2010). This suggests that working memory deficits may not be the direct result of intrusive memories, but rather a more pervasive cognitive deficit in people with PTSD (Jelinek et al., 2008). Working memory deficits observed in trauma-exposed individuals remain after controlling for depression and alcohol abuse (Brandes et al., 2002; Gilbertson et al., 2001). However, one study found that decreased encoding of verbal information in individuals with PTSD was most likely related to comorbid depressive symptoms, not trauma symptoms (Johnsen, Kanagaratnam, & Asbjornsen, 2007). Therefore, it is possible that depression and PTSD symptoms contribute to memory deficits observed in people with
PTSD, but that trauma symptoms may underlay more core working memory deficits whereas depression contributes to difficulties with encoding and learning.

Although some studies have found that only individuals with PTSD, as compared to trauma-exposed controls, demonstrate working memory deficits (Gilbertson et al., 2001; LaGarde et al., 2010; Samuelson et al., 2006), other studies have found working memory deficits regardless of PTSD. For example, one study found women with a history of interpersonal violence performed more poorly on verbal working memory tasks than women with no history of interpersonal violence, regardless of PTSD status (Stein et al., 2002). Additionally, psychiatric outpatients with histories of trauma show deficits in working memory relative to non-exposed outpatients (El-Hage et al., 2006).

Inhibition

Another aspect of cognitive control highly related to attention and working memory that has been found to be disrupted in trauma-exposed children and adults is inhibition (Carrion et al., 2008; Casada & Roache, 2005, 2006; Falconer et al., 2008; Jenkins et al., 2000; Koso & Hansen, 2006; Leskin & White, 2007; Shucard, McCabe, & Szymanski, 2008). Trauma-exposed children and adults demonstrate deficits on tasks tapping motoric inhibition, including Go/No-Go tasks (Carrion et al., 2008; Falconer et al., 2008; Shucard et al., 2008), attention network tasks (Jenkins et al., 2000; Leskin & White, 2007), and the Stop-Signal task (Casada & Roache, 2005, 2006). Furthermore, inhibitory deficits have been associated with altered event-related potential (ERP) patterns (Shucard et al., 2008), physiological responding (Casada & Roache, 2006), and PTSD symptoms (Leskin & White, 2007). On continuous performance measures, individuals with PTSD demonstrate greater errors of commission to distractor stimuli than errors of omission, which has been suggested to reflect greater difficulty inhibiting automatic responses (Aupperle et
al., 2011). A recent review by Aupperle and colleagues (2011) suggests that deficits in attentional control, such as ignoring irrelevant information during the Stroop task, and working memory, such as struggling to maintain task-relevant information, may reflect a core deficit in inhibitory networks in individuals with PTSD.

**Summary**

In summary, trauma-exposed individuals demonstrate deficits in the cognitive control of memory and attention. Not only is the processing of emotional, especially threat, information altered, but the processing of neutral information is also altered. Given demonstrated deficits in inhibition, it has been suggested that alterations in these various cognitive processes may reflect a core deficit in inhibitory networks.

**AFFECTED BRAIN PROCESSES**

Many neuroimaging studies have examined alterations in the processing of emotional stimuli, especially threat stimuli, in trauma-exposed individuals. These studies have identified hyperactivation of various limbic regions, such as the amygdala, and hypoactivation of frontal regions, including the orbital frontal cortex. This consistent pattern of activation has been related to the hyperarousal generally seen in trauma-exposed individuals. Specifically, it has been interpreted as representing an over activation of bottom-up processing coupled with an under activation of regions involved in dampening limbic responding through feedback loops. However, a relatively smaller body of work has examined how neural mechanisms of cognitive control are disrupted as a result of trauma. In general, these studies suggest alteration in functioning in aspects of the prefrontal cortex implicated in top-down control, including inferior frontal and medial regions.
Threat Responding and Attention

As reviewed earlier, trauma-exposed individuals demonstrate an attentional bias to threat. Although the limbic system as a whole has been implicated in responding to threat, there is a large body of literature that has found the amygdala is a key structure involved in threat detection and vigilance in all individuals. Increased amygdala activation has been found in response to fear faces, threatening pictures, during the acquisition of fear conditioning, and observational fear conditioning (for review, see Shin & Liberzon, 2010). Individuals with PTSD demonstrate enhanced amygdala activation to fear-related stimuli, including fearful faces and trauma related words (Davis & Whalen, 2001; Protopopescu et al., 2005; Rauch et al., 2000; Shin et al., 2004, 2005; Williams et al., 2006). The degree of amygdala hyperactivation in response to trauma cues in individuals with PTSD is linked to symptom severity (Pissiota et al., 2002; Fredrikson & Furmark, 2003; Shin et al., 2004). Increased amygdala activation in individuals with PTSD has also been observed in response to fear stimuli when it is presented below perceptual awareness, including using backward masked stimuli (Armony, Corbo, Clément, & Brunei, 2005; Rauch et al., 2000) and in fear conditioning (Bremner et al., 2005). Furthermore, PTSD symptoms are positively associated with greater processing of backward masked fearful than happy faces (Armony et al., 2005; Rauch et al., 2000). Not only is greater amygdala activation observed in individuals with PTSD in response to fear, it has also been found at rest (Chung et al., 2006; Semple et al., 2000) and when completing neutral attention and memory tasks (Bryant et al., 2005; Shin et al., 2004). It is thought that this increased amygdala activation is part of the larger neural system that leads to hypervigilance to threat seen in people with PTSD. In further support of the amygdala’s implication in PTSD symptomatology, response to cognitive behavioral therapy (CBT) is associated with decreased amygdala activation (Felmingham et al., 2007; Peres
et al., 2007) and predictive of CBT treatment outcome (Bryant et al., 2008) in individuals with PTSD.

In addition to the amygdala, various regions of the mPFC demonstrate altered activation in individuals with PTSD. In contrast to the amygdala, studies have found decreased activation of the mPFC in adults and adolescents with PTSD compared to individuals without PTSD during presentation of trauma-related or fearful stimuli, including the rostral anterior cingulate cortex (rACC; Bremner, et al., 1999; Hou et al., 2007; Shin et al., 2005; Williams et al., 2006; Yang, Wu, Hsu, & Ker, 2004) and ventral aspects of the medial prefrontal cortex (Hou et al., 2007; Rauch et al., 2000; Shin et al., 2005; Williams et al., 2006). A meta-analysis by Etkin & Wager (2007) found decreased mPFC, in both ventral vmPFC and rACC, in individuals with PTSD. In contrast to amygdala activation, mPFC activation is negatively correlated with PTSD symptoms (Shin et al., 2004, 2005; Williams et al., 2006) and demonstrates decreased activation at rest (Semple et al., 2000). Furthermore, Shin and colleagues (2005) have found that increased amygdala activation to fearful stimuli in people with PTSD is functionally associated with decreased mPFC activity. This is consistent with animal and human studies demonstrating direct connectivity between the mPFC and amygdala, with the mPFC working through a negative feedback loop to inhibit amygdala responding (Beauregard et al., 2001; Hariri et al., 2000; Nakamura et al., 1999; Shin & Liberson, 2010; except see Rauch et al., 2000). Additionally, Johnstone and colleagues (2007) have further suggested that the mPFC mediates the relationship between lateral prefrontal areas and control over the amygdala. Commensurate with this model, studies have found increased activation of dACC in individuals with PTSD in response to fear (Bremner et al., 2005; Felmingham et al., 2009). A recent twin study by Shin and colleagues (2009) found higher levels of glucose metabolism in dACC in men with PTSD and their
A monozygotic twin who was not trauma-exposed. Furthermore, metabolic activity in the dACC of the un-exposed twin was positively correlated with PTSD symptom severity in the exposed twin. These results suggest that increased dACC activity at baseline may be a risk-factor for the development of PTSD subsequent to trauma exposure.

A growing body of literature has begun to examine the neural bases of cognitive control in individuals with PTSD. Similar to some of the reviewed behavioral studies on attentional control, some imaging studies have employed variants of the emotional Stroop task to explore cognitive control of attention in the face of irrelevant trauma-related and neutral information. Commensurate with other findings of trauma-related and fear stimuli in individuals with PTSD, imaging studies of emotional Stroop tasks have found decreased mPFC, including rACC and vmPFC, and increased dACC activation in individuals with PTSD compared to trauma controls (Bremner et al., 2004; Shin et al., 2001). Imaging studies of the classic color Stroop have found individuals with PTSD show less activation of visual processing regions and parietal cortex but greater activation in superior temporal regions and orbitofrontal cortex than trauma controls (Bremner et al., 2004). The oddball task has also been used to examine cognitive control of attention for both trauma-related and neutral information. In contrast to the Stroop findings, individuals with PTSD demonstrate greater mPFC activation during both an emotional and neutral oddball task (Bryant et al., 2005; Pannu Hayes et al., 2009), which is positively correlated with PTSD symptoms (Pannu Hayes et al., 2009). However, greater activation in the dACC and middle frontal gyrus (MFG) was observed in individuals with PTSD (Bryant et al., 2005; Pannu Hayes et al., 2009). See discussion of oddball tasks under the Inhibition heading.

Memory
In order to study the neural mechanisms involved in the recall of traumatic memories as well as re-experiencing (including flashbacks) of the trauma, script-driven paradigms have been frequently employed in fMRI and PET research (Lanius et al., 2001, 2004; Osuch et al., 2001; Shin et al., 2004). In a typical script-driven paradigm, each participant constructs an autobiographical narrative of a traumatic experience, which is then read aloud with instructions to recall the specific memory in the script and to remember sensory details of the experience. It has been verified by participants that this paradigm does induce PTSD symptoms. Findings for script-driven studies have been fairly heterogeneous, which Lanius and colleagues (2006) have suggested may be due to the fact that some participants experience predominantly hyperarousal/re-experiencing symptoms whereas others experience predominantly dissociative symptoms during the trauma narrative. However, it has been rather consistently found that individuals with PTSD demonstrated decreased activation or blood flow in mPFC and increased activation or blood flow in the amygdala (Shin & Liberzon, 2010), as well as decrease activation in the IFG (Lanius et al., 2006). This pattern may better reflect hyperarousal/re-experiencing symptoms than dissociative symptoms, as approximately 70% of participants subjectively report experiencing hyperarousal/re-experiencing symptoms during script-driven imagery (Lanius et al., 2006). Functional connectivity studies have found amygdala activation is negatively correlated with mPFC activation (Shin et al., 2004) and that the amygdala has direct influences on visual cortex, rACC, and dACC (Gilboa et al., 2004) during script-driven imagery in individuals with PTSD. In addition, one functional connectivity study found greater connectivity between the right dACC and visual cortex in individuals with PTSD than trauma controls, whereas trauma controls demonstrated greater connectivity between the right dACC and the left dACC and DLPFC than individuals with PTSD (Lanius et al., 2004). Although the majority of PTSD
participants report hyperarousal/re-experiencing during the trauma script, approximately 30% of
participants dissociate when they are listening to the trauma script (Lanius et al., 2006).
Participants who dissociate demonstrate a different, and at times opposite, pattern of activation
during script-driven imagery, including increased activation of the dACC, rACC, IFG, and visual
cortex (Lanius et al., 2002, 2006).

Besides retrieval of long-term, autobiographical memories, studies have also examined
encoding and short-term memory for both neutral and emotional information. A study using a
declarative memory task, using neutral and emotional word pairs, found individuals with PTSD
compared to controls demonstrated decreased activation of mPFC and hippocampus, and
increased activation in posterior cingulate, MFG, and visual cortex during retrieval of deeply
encoded emotional word pairs compared to shallowly and deeply encoded neutral word pairs. No
differences were found for retrieval of the neutral word pairs (Bremner et al., 2003). Another
study of declarative memory using neutral word pairs found increased activation of right
DLPFC, parahippocampus, and temporal regions, along with decreased activation of mPFC, IFG,
left MFG, and precuneus during encoding (Geuze, Vermetten, Ruf, Kloet, & Westenberg, 2008).
In contrast to the study by Bremner and colleagues (2003) that did not find any differences of
neutral word pairs, in this study individuals with PTSD demonstrated decreased activation during
retrieval included the IFG, DLPFC, hippocampus/parahippocampus, and temporal regions
(Geuze et al., 2008). This difference could be due to the fact that in comparing individuals with
PTSD and trauma-exposed controls for neutral retrieval, the only comparison reported by
Bremner and colleagues (2003) was a contrast between deeply and shallowly encoded neutral
words. No contrast between neutral and emotional words collapsing across encoding conditions
was reported. In further support of disruptions in memory for both emotional and neutral stimuli,
one study examining encoding and delayed recognition of neutral and fearful faces found that individuals with PTSD demonstrated a negative association between activation of mPFC for forgotten items, across both neutral and fearful faces, and symptom severity. However, there was no association between activation of the mPFC for remembered items and symptom severity (Dickie, Brunet, Akerib, & Armony, 2008).

Working memory has also been explored in trauma-exposed individuals using imaging. Studies using a fixed target vs. variable target task to explore working memory have found decreased activation of the DLPFC, IFG, and rACC, and increased activation of inferior parietal cortex in individuals with PTSD compared to controls during updating (Clark et al., 2003; Moores et al., 2008; Shaw et al., 2002). One of these studies (Moores et al., 2008) used a similar paradigm that additionally included the ability to compare maintenance to baseline activation. Moores et al. (2008) found no significant difference between individuals with PTSD and controls, but did find a trend for increased activation in the DLPFC and IFG in individuals with PTSD compared to controls during maintenance. Moores and colleagues (2008) suggest that individuals with PTSD may recruit updating networks during maintenance and that decreased activation observed in previous studies actually reflects use of similar strategies for updating and maintenance in individuals with PTSD as compared to controls who use different strategies. One study (Morey et al., 2009) has examined the impact of trauma-related as compared to neutral distracting information on working memory. Overall, individuals with PTSD demonstrated poorer working memory when distractor images were presented briefly between stimulus presentation and recognition regardless of whether the distractors were trauma-related or neutral, whereas controls only demonstrated poorer working memory performance when the distractors were trauma-related. Consistent with this behavioral finding, individuals with PTSD
demonstrated decreased DLPFC during the working memory task regardless of distractor type, whereas controls only demonstrated decreased DLPFC activation when a trauma-related distractor was present. Additionally, individuals with PTSD demonstrated greater MFG activation to trauma-related than neutral distractors (Morey et al., 2009).

**Inhibition**

Two studies to date have been performed directly examining inhibition in trauma-exposed individuals. Both of these studies have employed a Go/No-Go task, in which a majority of trials require a response, while a minority of trials require inhibition of that response. Adults with PTSD demonstrate less activation than controls of rIFG (Falconer et al., 2008), a region implicated in inhibitory aspects of cognitive control (Aron, Robbins & Poldrack, 2004). Lesser activation of the rIFG, as well as the DLPFC and mPFC, during inhibitory processing is associated with greater severity of PTSD symptoms (Falconer et al., 2008). Children with a history of trauma exposure demonstrated decreased DLPFC activation and increased mPFC when inhibiting (Carrion et al., 2008). Although both studies demonstrate decreased DLPFC during inhibition, patterns of mPFC activation differ across the two studies. This could be due to one of two things. First, the brain develops ventral to dorsal; therefore mPFC regions are more developed than the DLPFC in children and adolescents (Paus et al., 1999; Toga, Thompson, & Sowell, 2006). As a result, children might demonstrate heightened mPFC activation to compensate for less DLPFC activation. Additionally, Falconer and colleagues (2008) found that behaviorally individuals with PTSD demonstrated poorer inhibition on the Go/No-Go task, whereas Carrion and colleagues (2008) did not find any differences in performance between the trauma-exposed youth and controls. Therefore, the difference in activation patterns between the
two studies likely reflects either differences in brain development or behavioral task performance, which could also be a reflection of age.

Although there have only been two direct studies of inhibition, many of the studies reviewed earlier examining cognitive control of attention and working memory likely involve some aspect of inhibition. For example, the Stroop task requires the inhibition of irrelevant, and sometimes competing, information in addition to attending to relevant information. Under the review of attention, some studies using oddball tasks were presented (e.g., Bryant et al., 2005; Pannu Hayes et al., 2009). Oddball tasks require attention, but they also require inhibition of prepotent responding. As such, individuals with greater PTSD symptoms demonstrate less IFG activation than those with fewer symptoms on an emotional oddball task (Pannu Hayes et al., 2009). Working memory tasks presented (e.g., Clark et al., 2003; Moores et al., 2008; Morey et al., 2009; Shaw et al., 2002) may require the recruitment of inhibitory networks in order to inhibit intruding information, and also to inhibit old information that is no longer relevant during updating. This is consistent with results reviewed earlier relating to cognitive control and inhibition. Aupperle and colleagues (2011) have suggested that individuals with PTSD may demonstrate a “combination of enhanced ‘emotional’ processing networks that serve to enhance attention towards specific stimuli and decreased ‘inhibitory’ networks meant to disengage attention and redirect it” (pg. 5). Given that deficits in the cognitive control of attention, working memory, and inhibition have been noted in trauma-exposed individuals with both emotional and neutral stimuli, it is possible that increased attentional allocation and decreased inhibition affect multiple aspects of cognitive processing.

Summary
In summary, neuroimaging studies demonstrate decreased ACC, DLPFC, MFG, and mPFC activation in people with a history of trauma when they must recruit cognitive control, specifically related to attention, working memory, and inhibition. These findings are consistent with the Cascade of Control Model (Banich, 2009; Milham & Banich, 2005; Milham, Banich, & Barad, 2003) proposing pDLPFC and mDLPFC are recruited in order to direct attention towards task-relevant processes and representations. Decreased DLPFC activation during tasks that require cognitive control of attention and working memory suggests trauma-exposed individuals cannot attend to task-relevant processes as well. This is further supported by noted increases in visual processing and temporal areas in trauma-exposed individuals, suggesting they are attending more to irrelevant information. Decreased mPFC and IFG may reflect difficulties inhibiting task-irrelevant representations and selecting the correct response.

**AFFECTED BRAIN STRUCTURES**

In addition to demonstrating functional differences in activation patterns in areas related to cognitive control and memory, trauma-exposed individuals also demonstrate structural changes in volume and connectivity in these regions. The convergence of findings from functional and structural neuroimaging further supports specific disrupted networks in individuals with PTSD. Additionally, data from structural studies provides us with a better foundation when attempting to parse predisposing risk factors for the development of PTSD or PTSD symptoms from the impact of trauma-exposure or PTSD. Although resting state data (e.g., Semple et al., 2000) and some limited functional twin studies (e.g., Shin et al., 2009) have begun to address the question of predisposition vs. consequence, our knowledge of structural brain development exceeds are knowledge of functional development. Therefore, structural data can
serve as a tool to help identify potential areas of interest as well as allow us to consider the impact of brain development on potential functional patterns of activation. Below, findings from structural studies of trauma-exposed individuals related to regions of interest for this study are briefly reviewed.

*Frontal Regions*

Studies of adults with a history of trauma demonstrate alterations in the brain anatomy of multiple frontal regions often involved in cognitive control. One finding has been decreased volume of the ACC, with studies finding both decreased subgenual ACC volume (Rauch et al., 2003; Bryant et al., 2008; Kasai et al., 2008) and dorsal ACC volume (Yamasue et al., 2003; Kitayama et al., 2006) in people with PTSD. These findings are further supported by a meta-analysis that demonstrated decreased ACC volume in adults with PTSD (Karl et al., 2006). Furthermore, decreased dACC volume has been negatively associated with PTSD symptom severity (Yamasue et al., 2003) and decreased rACC has been negatively associated with treatment response to cognitive behavior therapy (Bryant et al., 2008). In addition to reduced volume, studies employing diffusion tensor imaging (DTI) have found alterations in the white matter integrity of the rACC, dACC, mPFC, and parietal regions (Abe et al., 2006; Schuff et al., 2011). A twin study performed by Kasai and colleagues (2008) found that decreased rACC volume was found only in the monozygotic twin with PTSD and not in the un-exposed twin. This suggests that decreased rACC volume may be acquired as a result of PTSD, rather than being a vulnerability factor for the development of PTSD. This is in contrast to the previously reviewed study by Shin and colleagues (2009) suggesting increased glucose metabolism in the dACC at rest may be a familial risk factor for PTSD. Therefore, structural changes may be
isolated to specific parts of brain regions or structural and functional changes may not offer similar risk factors.

In addition to decreased ACC volume, research has demonstrated decreased corpus callosum (CC) volume in both children (De Bellis et al., 1999; 2002; Jackowski et al., 2008; Teicher et al., 2004;) and adults (Choi et al., 2009; Villarreal et al., 2004) with a history of trauma, with both sets of findings being confirmed by a recent meta-analysis (Jackowski et al., 2009). In regards to pediatric samples, it has been found that decreased CC volume is most prominent in the midbody and poster portions of the CC (see Jackowski et al., 2009). Furthermore, decreased white matter tract integrity has been found in both pediatric samples (Jackowski et al., 2008) and young adults with a history of CIT (Choi et al., 2009). Given the age at which the CC develops, usually between 6 months and three years, and findings indicating that a history of childhood abuse in pediatric samples, regardless of PTSD diagnosis, is associated with decreased CC (see review in Jackowski et al., 2009), it is likely that the CC is a target structure in understanding the impact of CIT on brain development.

Despite the fact that overall reductions in grey matter volume have not been found in individuals with PTSD (see review in Jackowski et al., 2009; Rauch et al., 2003), studies have found decreased frontal volumes in pediatric PTSD (Carrion et al., 2001; DeBellis et al., 1999, 2000, 2002), including decreased volume in mid-inferior and medial prefrontal regions (Richert et al., 2006). A developmental study (Andersen et al., 2008) examining sensitive periods for effects of sexual abuse during childhood found that young adults who had experienced sexual abuse between the ages of 14 – 16 years were most likely to demonstrate attenuated frontal cortex volume. Furthermore, CC volume reductions were most likely to result if individuals had experienced sexual abuse between the ages of 9 – 10 years. There is some evidence of decreased
frontal volume in adults as well. A study of women with a history of intimate partner violence revealed smaller frontal grey matter volume, regardless of whether or not they met criteria for PTSD (Fennema-Notestine, Stein, Kennedy, Archibald, & Jernigan, 2002).

Limbic and Temporal Regions

Although there is a large and rather consistent body of literature demonstrating increased amygdala responding in trauma-exposed individuals, relatively little research has examined the structure of the amygdala in the context of trauma-exposure. The literature to date is relatively inconsistent, with some studies suggesting smaller amygdala volume in adults with PTSD, but multiple other studies failing to find volumetric differences (for review, see Shin & Liberzon, 2010). A meta-analysis by Woon and Hedges (2008) exploring amygdala volume in both adults and children with childhood-maltreatment related PTSD did not find any volumetric differences for the amygdala in either child or adult populations. Additionally, findings examining receptor binding in the amygdala have also been mixed (for review, see Shin & Liberzon, 2010). Therefore, at this time, more studies than not suggest trauma-exposed individuals do not demonstrate altered amygdala volume. However, it is not clear if the structure or integrity of the amygdala is altered in trauma-exposed individuals. Given findings of altered functional connectivity between the amygdala and mPFC in individuals with PTSD (Shin et al., 2004, 2005) and limited studies on receptor-binding, structural alterations related to amygdala functioning in individuals with PTSD are more likely related to connectivity or receptor-binding than volume.

Multiple functional MRI studies have demonstrated decreased hippocampal volume in adults with PTSD compared to non-trauma exposed controls (Bremner et al., 1995a, 1997, 2003; Gurvits et al., 1996; Shin et al., 2004b; Wang et al., 2010; Woon & Hedges, 2008; except see
Pederson et al., 2004). Furthermore, studies have found that hippocampal volume is negatively correlated with symptom severity (Gilbertson et al., 2002; Karl et al., 2006; Villarreal et al., 2002; Woon & Hedges, 2007). One study comparing adults with PTSD as a result of childhood abuse and adults exposed to childhood abuse but with no PTSD did not demonstrate significant differences in hippocampal volume but both demonstrate reduced hippocampal volume (Stein, Koverola, Hanna, Torchia, & McClarty, 1997). Additionally, a meta-analysis (Karl et al., 2006) found decreased bilateral hippocampal volume when people with PTSD were compared to healthy controls as well as when they were compared to trauma-exposed individuals with no PTSD, but also found decreased left hippocampal volume when trauma-exposed individuals with no PTSD were compared to healthy controls. Therefore, findings generally support the conclusion that individuals with PTSD demonstrate decreased hippocampal volume. However, it is not clear from the findings to date whether decreased hippocampal volume is associated with just PTSD or trauma-exposure more generally.

In contrast to the adult literature, MRI studies have demonstrated no change in hippocampal volume in pediatric PTSD (Carrion et al., 2001; De Bellis et al., 1999; 2002; Tupler & De Bellis, 2006). A meta-analysis by Woon & Hedges (2008) examining hippocampal volume in adults and children with maltreatment-related PTSD compared to non-trauma exposed controls found that adults with PTSD demonstrated decreased bilateral hippocampal volume and decreased hippocampal asymmetry (adults normally demonstrate greater left than right hippocampal volume). However, children with PTSD did not demonstrate decreased hippocampal volume. Woon and Hedges (2008) suggest that alterations in hippocampal volume therefore develop some time after childhood trauma-exposure or resultant PTSD. Consistent with this conclusion, Carrion and colleagues (2007) found that severity of trauma symptoms as a
result of childhood trauma and cortisol levels predicted hippocampal volume 12-18 months later. However, two longitudinal studies examining hippocampal volume changes in people directly post-trauma and then six months and two years later found no significant decreases in hippocampal volume between people who developed PTSD and those who did not (Bonne et al., 2001; DeBellis et al., 2001). Additionally, a twin study found that in monozygotic twins discordant for trauma-exposure, smaller hippocampal volume was found in both the trauma-exposed and non-exposed twins and symptom severity of the trauma-exposed twin was correlated with their and their non-exposed twin’s hippocampal volume (Gilbertson et al., 2002).

One potential explanation for these discordant findings is that the age or ages over which a trauma was experienced could contribute to alterations in hippocampal volume. One study found that young adults with a history of childhood sexual abuse demonstrated decreased hippocampal volume, but only if the abuse occurred between 3-5 years or 11-13 years (Andersen et al., 2008). Additionally, the meta-analysis by Woon & Hedges (2008) included adults and children with PTSD resulting from childhood abuse or maltreatment, as do all the structural studies of children with trauma-exposure. In contrast, adult PTSD studies are a mix of individuals with PTSD resulting from combat exposure and childhood abuse. For example, the twin study by Gilbertson and colleagues (2002), which most directly contradicts the finding of Woon & Hedges (2008), was comprised of twins with and without combat-exposure during adulthood. Therefore, whether smaller hippocampal volume is a risk factor for or consequence of trauma-exposure or PTSD is still unclear. However, it is possible that factors such as age of trauma exposure and brain development may impact whether hippocampal volume is a risk factor or consequence.

Summary
Overall, studies of structural changes have demonstrated alterations in the ACC, CC, prefrontal cortex, and hippocampus in trauma-exposed individuals. Many of the regions reviewed have been implicated in the earlier reviewed functional studies of altered cognitive control in trauma-exposed individuals. However, based on the literature to date, it is not entirely clear whether some of the changes are risk factors for or consequence of trauma exposure.

CURRENT STUDY

Overview

The current study is designed to examine alterations in cognitive control mechanisms, specifically related to attention and working memory, in individuals exposed to CIT. In order to examine the cognitive control of attention in individuals exposed to CIT, we used a hybrid (event-related trials interspersed among blocked trials) Stroop paradigm with emotional and neutral stimuli. Emotional stimuli include trauma-related words (e.g., abuse) and positive words (e.g., happy), and neutral stimuli consisting of non-color neutral words (e.g., add) and color words. There are three blocks of trials containing specific target words that cause interference, namely trauma-related (threat block), positive (positive block), or color words incongruent with ink color (incongruent block). Interspersed within these blocks are non-color neutral words. This paradigm allows us to dissociate alterations in maintenance of a top-down, task-relevant attentional set (blocked trials) from transient recruitment of additional cognitive control (event-related trials) in both the face of emotional and neutral interference. To date, studies of trauma-exposed individuals have not examined this dissociation in cognitive control. Additionally, we employed a recently developed paradigm for examining the manipulation of neutral information in working memory in trauma-exposed individuals. The small number of previously conducted
neuroimaging studies examining working memory in trauma-exposed individuals have mainly looked at maintenance and updating. Our paradigm allows us to examine separately maintenance, updating, and inhibition of information in working memory. Inhibition has been suggested to be a potential executive process in working memory, with alterations in inhibitory processing being suggested to underlie many of the alterations in cognitive processing observed in trauma-exposed individuals. Therefore, this study offers the ability to directly compare these processes, which has not been done to date. Furthermore, it allows us to distinguish between global and selective inhibition, two types of inhibition that have been proposed to exist in motoric inhibition.

Neuroimaging studies of emotional processing in trauma-exposed individuals have used a mix of individuals with PTSD, trauma-exposed controls, and healthy controls, whereas most of the neuroimaging studies to date examining altered cognitive processing of neutral information have used individuals with PTSD and healthy controls. Therefore, it is not possible to determine if cognitive control is altered only in people with PTSD or more generally in trauma exposed individuals. The current study, in contrast, examines individuals with trauma-exposure, regardless of whether they meet criteria for PTSD. Given that many individuals who experience trauma demonstrate PTSD symptoms, even if they do not meet full criteria for PTSD, it is possible that trauma-exposure is associated with alterations in cognitive processing even if full criteria for PTSD are not met. Cognitive control was examined in a sample of young adults (22-30) exposed to interpersonal trauma (e.g., sexual or physical abuse) during childhood and adolescence (<17 years of age). A sample restricted to young adulthood was selected because by this age most aspects of brain development have reached maturity (Sowell et al., 2003).
Therefore, we can determine if trauma-exposure during childhood and adolescence is associated with altered cognitive control in adults once development of the PFC is complete.

**Predictions**

For the working memory task, we predict that both individuals with and without a history of CIT will comply with task instructions, and hence demonstrate a pattern of activation similar to that seen in the first study using this paradigm (Banich, Mackiewicz Seghete, and Chatham, in prep). Across individuals there should be more activity in visual cortex when maintaining and updating information compared to globally or selectively inhibiting information. Based on prior work implicating regions of mDLPFC as important for controlling the contents of working memory (Banich, 2009; Depue, Curran, & Banich, 2007; Milham, Banich, & Barad, 2003) and results indicating compromise of cognitive control even for emotionally-neutral information in individuals with a history of interpersonal trauma (e.g., Moores et al., 2008), we predict that young adults with a history of CIT will demonstrate less activation of mDLPFC than young adults with no history of CIT when attempting to globally or selectively inhibit information that is being held in working memory. In addition, since the rIFG has also been associated with inhibition (e.g., Aron, Robbins & Poldrack, 2004), and this region has shown less activation in motor tasks in adults with a history of childhood trauma (Falconer et al., 2008), we expect to observe less activity in rIFG in young adults with a history of CIT than young adults with no history of CIT when inhibiting information in working memory. We also expect greater activity in visual processing regions in young adults with a history of CIT than young adults with no history of CIT when they are either globally or selectively inhibiting information, which would provide additional evidence that they have difficulty controlling such information.
Additionally, we predict that there will be differences in the cognitive control of attention in young adults with a history of CIT compared to young adults without a history of CIT as measured by the emotional and classic Stroop task. Based on previous findings of individuals exposed to interpersonal trauma demonstrating more interference when completing an emotional Stroop task using threat-related words (e.g., Foa et al., 1991), young adults with a history of CIT should show significantly more interference for trauma-related than positive or neutral words. However, we do not expect more interference for positive than neutral words, as previous studies have found individuals with a history of trauma do not demonstrate greater interference for positive than neutral words during an emotional Stroop task (e.g., Cassiday et al., 1992; McNally et al., 1990). This difference could be due in part to the fact that individuals with a history of trauma demonstrate blunted responding to positive stimuli (Kashdan et al., 2006), and therefore it may not be perceived as conflicting information. Furthermore, we expect regions involved in cognitive control to be altered in young adults with a history of CIT compared to young adults with no history of CIT. Based on previous studies of adults with PTSD (Bremner et al., 2004; Shin et al., 2001) and our prior studies with the Stroop task (e.g., Banich et al., 2000), we predict that young adults with a history of CIT will demonstrate reductions in activity in DLPFC, along with increased activity in anterior cingulate cortex for threat blocks as compared to neutral blocks. The reduction in DLPFC would be consistent with a poorer ability to maintain top-down control towards the correct attentional set, while the increased ACC activity would be consistent with greater demands at late-stages of attentional control (Banich, 2009; Milham & Banich, 2005). Furthermore, we expect that the decrease in activity in DLFPC in young adults with a history of CIT will be associated with increased activity in brain regions that are involved in processing the task-irrelevant word. A similar but attenuated effect is expected for the positive
word blocks, which would be consistent with the idea that these control mechanisms are altered in young adults with a history of CIT whenever there is emotionally-salient information in the environment. Although studies have found blunted emotional responding to positive stimuli, this has been attributed to individuals with a history of trauma interpreting positive stimuli more negatively than individuals with no trauma history and this is associated with altered activation patterns (Frewen et al., 2010). Therefore, differences may be found in cognitive control of this emotional information despite a lack of behavioral differences on performance. Given the inconsistent findings on the classic Stroop task, the incongruent block will allow us to test two competing theories. If an overall ability to maintain a task-relevant attentional set is altered in trauma-exposed individuals, we should see less DLPFC activation for the incongruent block in young adults with a history of CIT than young adults with no history of CIT. However, if an inability to maintain a task-relevant attentional set is only altered for the processing of emotional information, there should be no difference in DLPFC activation between young adults with a history of CIT compared to young adults with no history of CIT. If, as predicted, young adults with a history of CIT will have difficulty imposing an attentional set across a block of threat trials, the difference between threat and neutral trials within the threat block will be increased compared to young adults with no history of CIT. Once again, a similar, but attenuated group difference is expected for the positively-valenced block.

For the Stroop task, we also predict young adults with a history of CIT will exhibit more activation of the amygdala during the threat block than young adults with no history of CIT. Furthermore, we predict that the response to the emotionally threatening information will be more transient for the young adults with no history of CIT and more sustained for young adults with a history of CIT. Consequently, for the young adults with no history of CIT, we expect
differentiation of neural response across trial types in the threat block (e.g., neutral, threatening), which will be absent or reduced for young adults with a history of CIT.

Given previous findings that regions of the PFC are associated with severity of PTSD symptoms (e.g., Shin et al., 2005), we predict that decreased activation of DLPFC regions involved in cognitive control of attention during the emotional Stroop task will be associated with intrusive symptoms (Cluster B) in young adults with a history of CIT. A similar effect should also be observed for control over the working memory task. Additionally, we predict increased mPFC activation during the Stroop task will be associated with hyperarousal symptoms, which include hypervigilance (Cluster D). Furthermore, we predict decreased rIFG activation, seen when attempting to selectively inhibit information in working memory, will be negatively associated with intrusive symptoms (Cluster B) in young adults with a history of CIT.
CHAPTER 2

METHODS

Participants

Participants were women between the ages of 22 and 30 who responded to flyers and electronic announcements posted at community agencies (e.g., mental health clinics, social services agencies) and through web-based list-serves in the Denver Metro area. Only women were recruited for the study because of gender differences in exposure to CIT. Relative to males, females are more likely to report exposure to child sexual abuse (Finkelhor, et al., 1990; Goldberg & Freyd, 2006; Tolin & Foa, 2006) and/or interpersonal traumas perpetrated by close others (either physical or sexual; Goldberg & Freyd, 2006). In addition to reporting closer victim-perpetrator relationships, females (compared to males) also report earlier onset and longer duration of abuse (Dhaliwal et al., 1996). Thus, if we had recruited both males and females, they would likely differ on characteristics of the CIT experience that may be important to neurocognitive development (e.g., closeness of the victim-perpetrator relationship, age of onset). All participants were right-handed, native English speakers, and reported no history of brain injury, neurological disease, or psychotic symptoms, and no MR contraindications. All participants gave informed, written consent and were compensated monetarily. The study was approved by the Colorado Multiple Institutional Review Board at the University of Colorado.

Participants were categorized into one of two groups, women exposed to CIT (trauma group) and women with no history of CIT (control group). Criteria for inclusion in the trauma group included experiencing physical or sexual abuse or assault prior to the age of 17. Physical abuse or assault was defined as another individual purposefully injuring the participant with the individual’s body, an object, or a weapon. Sexual abuse or assault was defined as any attempted
or completed forced sexual contact (e.g., molestation, rape). Exclusion included experiencing current interpersonal trauma (e.g., intimate partner violence). Criteria for inclusion in the control group included no history of interpersonal trauma. For both the CIT and control group, an individual could have experienced a non-interpersonal trauma (e.g., car accident) and still be included in the group, as long as they denied Criteria A for PTSD. 32 women were eligible for the behavioral session based on the telephone screen. Of those 32 women, 29 women met criteria for either the trauma or control group and were eligible for the study. Of those four women not eligible, three were women who reported childhood trauma that did not meet our criteria for CIT in this study and one woman reported interpersonal trauma only after the age of 17. One woman who was eligible for the study and met criteria for the trauma group discontinued during the MRI scan because she was claustrophobic. Final sample size was 13 participants in the trauma group and 14 participants in the control group. Of the final 27 participants, 17 self-identified as Caucasian, 2 self-identified as Hispanic or Latina, and 8 self-identified as Biracial or Other.

MEASURES

Demographic Information

Participants provided information on their age, race, occupation, education, and parental education. Current socioeconomic status was determined using education and occupation information in order to calculate the Hollingshead Index of Social Position (ISP; Hollingshead & Redlich, 1958). Education is scored on a scale of 1 to 7, with lower numbers representing higher levels of education (e.g., 1 = professional or graduate degree, 7 = less than seven years of school). Occupation is also scored on a scale of 1 to 7, with higher numbers representing more executive and professional level work and lower numbers representing skilled and unskilled labor positions (e.g., 1 = higher executives and major professionals, 7 = unskilled employees). The ISP is calculated by summing the education score weighted by a factor of four with the
occupation score weighted by a factor of seven. Parental education was used as a proxy for parental socioeconomic status. Given that parental occupation could have changed over the course of the participant’s childhood and that participants may not have been fully aware of their parents’ occupations, education was seen as a more appropriate proxy for socioeconomic status during childhood than the ISP.

**Intelligence**

Intelligence was measured using the Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999). We used the WASI two subtest format, which includes the Vocabulary and Matrix Reasoning subtests, to calculate a full scale intellectual quotient (FSIQ) for each participant. The WASI two subtest format FSIQ correlates 0.87 with the Wechsler Adult Intelligence Scale, 3rd Edition FSIQ. Intelligence was measured to ensure that there were no group differences and to ensure that any differences in performance on cognitive control tasks were not caused by underlying differences in overall cognitive ability.

**Trauma History**

Interpersonal trauma exposure was assessed using a two-stage interview strategy adapted from the National Crime Victims Survey (see Fisher & Cullen, 2000). In the first stage, participants were asked a series of behaviorally-defined screening questions designed to cue memory for relevant incidents. In the second stage, participants who answer “yes” to any screening questions were asked a series of detailed questions about the incident(s), including characteristics of the victim-offender relationship, age of onset, and duration.

Additionally, the Trauma History Questionnaire (THQ; Green, 1996) was used to control for exposure to other potentially traumatic events. The THQ includes 24 items that tap a range of
potentially traumatic events, including crime-related events and non-interpersonal disasters/traumas. Participants indicated whether each item happened to them, and if so, the number of times and approximate age(s) of occurrence. Although this questionnaire is typically administered as a self-report measure, we had a clinician administer the questionnaire verbally. By administering the questionnaire in this format, the clinician was able to directly ascertain whether participant met Criteria A for PTSD for any non-interpersonal traumas.

Posttraumatic Stress Disorder

Participants in the CIT group completed the Posttraumatic Diagnostic Scale (PTDS; Foa, Cashman, Jaycox, & Perry, 1997). The PTDS is a 49-item self-report measure based on the DSM-IV (American Psychiatric Association, 1994) criteria for PTSD that yields a diagnosis of PTSD as well as PTSD symptom severity. This measure is unique among PTSD symptom self-reports in that Criterion A (traumatic event and response to the event) is assessed. It measures PTSD symptom severity over the past month for intrusive recollections (Cluster B), avoidance/numbing (Cluster C), and hyperarousal (Cluster D). Symptom severity is rated on a scale from 0 to 3, with higher numbers representing greater severity (0 = not at all or only 1 time; 1 = once a week or less; 2 = 2-4 times a week; 3 = 5 or more times a week). Whether or not symptoms have interfered with various areas of functioning (e.g., work, relationships with friends) over the past month is determined with a yes/no response. The PTDS also assesses for duration of symptoms using three categories (less than 1 month; 1 to 3 months; and more than 3 months) and onset of symptoms post-trauma using two categories (less than 6 months; 6 or more months). For each participant, total symptom severity was calculated by summing across all symptoms, and symptom severity for each of the symptom clusters was calculated by summing ratings for each item in that cluster. Whether or not a participant met full criteria for PTSD was
also determined. When compared to administration of the Structured Clinical Interview for DSM-IV Disorders (SCID) in order to determine PTSD diagnosis, the PTDS has a kappa of 0.65, sensitivity of 0.89, and specificity of 0.75 (Foa et al., 1997). This measure was used in place of a clinician-administered diagnostic tool because it is effective in screening for PTSD (Foa et al., 1997), which was the purpose of its use in this study.

*Parental Conflict*

Individuals exposed to CIT may have experienced different levels of conflict between parents as children and adolescents. Therefore, a version of the Children’s Perception of Interparental Conflict Scale (CPICS; Grych, Seid, & Finchman, 1992) that has been adapted for use with late adolescents was used (Bickham & Fiese, 1997) in order to retrospectively measure perceived parental conflict during childhood. Participants rated 51 items on a 3–point scale (1 = True, 2 = Sort of True, or 3 = False) describing parental conflict (e.g., I never saw my parents arguing or disagreeing). The CPICS has three factors, Conflict Properties, Threat, and Self-Blame. The conflict properties factor measures the intensity, frequency, and aspects of resolution for conflict, with higher scores indicating more intense and frequent conflicts with less resolution. The threat factor measures the degree of perceived threat to self and ability to cope with the conflict, with higher scores indicating greater perceived threat and less ability to cope with the conflict. The self-blame factor measures the degree to which the participant perceived themselves to be at blame for the conflict, with higher scores representing more self-blame. Each subscale was calculated by summing the items for the scale (some items reversed).

*Depression*
The self-report Beck Depression Inventory - II (BDI-II; Beck, Steer, & Brown, 1996) provided a 4 point measure (from 0 to 3) on 21 depressive symptoms (e.g., Sadness) that participants might have experienced over the past two weeks. Scores represent the sum of an individual’s response to all 21 items. Higher scores indicate greater levels of depressive symptoms. Depression was measured because previous studies have found that some of the changes in cognitive processing observed in people with trauma exposure can be better accounted for by levels of depression rather than trauma response (e.g., Johnsen, Kanagaratnam, & Asbjørnsen, 2008).

fMRI TASKS

Working Memory

Participants performed a task that required them to manipulate visual information in working memory. 16 familiar pictures (e.g., penguin), eight in black and white and eight in color, were used in the task. A picture was presented for four seconds, followed by a black screen with two words indicating the instructions for that trial presented for four seconds. During this time the participant was to engage in the instructed cognitive manipulation (See Figure 1). In three of the conditions the two words in the instruction were the same (Maintain, Clear, and Suppress), and for the Replace condition the two words were different (Switch “Stimuli”). In the Maintain condition, participants were instructed to maintain the image of the picture in their mind. In the Replace condition, participants were instructed to clear the image of the picture they had just seen and replace it with the picture associated with the words presented on the instruction screen. In the Clear condition, participants were instructed to clear their mind of everything. In the Suppress condition, participants were instructed to suppress just the image they had recently seen, without using a strategy of replacing it with another image. This condition was described to
Figure 1. Working memory paradigm. Individuals saw an item for four seconds and then immediately afterwards were asked to perform a mental manipulation on that item (Maintain, Replace, Suppress or Clear) for the next four seconds. Fixation trials were distributed logarithmically between these eight second epochs to provide a baseline for comparison.
participants as being similar to “suppressing a cough.” The Clear and Suppress conditions were further delineated to participants, with the instruction that in the Suppress condition you are suppressing a particular image, whereas in the clear condition you are clearing your mind of not only that image, but everything. Each picture was presented once per condition, for a total of 64 experimental trials. There were 32 fixation trials (a white cross centered on a black screen), ranging from 2 to 16 seconds, logarithmically and randomly distributed. Trial and fixation order was optimized using OptSeq2 (Dale, 1999). There was 20 seconds of fixation baseline at the beginning of the scan.

Stroop

While in the scanner, participants performed a modified version of the Stroop task (Stroop, 1935). Participants responded via a button press to the ink color (red, blue, yellow, or green) in which a word was printed. There were four types of trials, defined by the type of word: incongruent, neutral, threat, and positive. Neutral trials consisted of neutral, non-color words (e.g., add), incongruent trials consisted of color words in a different color ink (e.g., “red” in blue ink), threat words consisted of trauma-specific words (e.g., abuse), and positive words consisted of positively-valenced words (e.g., joy) not related to physical or emotional safety. The four ink colors used served as the incongruent words. Threat words were selected from a previous study using trauma-related threat words (Bremner et al., 2001). Positive words were selected from the normed words on the Affective Norms for English Words (ANEW; Bradley & Lang, 1999), and matched the threat words in arousal, to the degree possible. It was also confirmed that the valence of positive words, threat words, neutral words, and incongruent words were within positive, negative, and neutral ranges, respectively. Words across type were matched in length. Given that many of the emotional words, especially the threat words, are not used with the same
frequency as color words and the neutral words, it was not possible to match words across type on frequency.

A hybrid design was used in order to examine both sustained and transient neural responses. The hybrid design consists of blocks of trials that measure sustained activity and event-related trials within these blocks that measure transient activity (See Figure 2). Each block consists of block-specific trials (threat, positive, or incongruent) and neutral frequent trials that occur in all blocks. In all the blocks, block-specific and neutral frequent trials were presented for 2 seconds. There were 4 repetitions of each block type (threat, positive, incongruent) for a total of 12 Stroop blocks, which were followed by fixation blocks (total=11). Each block contained eight target trials and eight neutral frequent trials randomly distributed across the block, resulting in a total of 32 trials for each trial type. Each trial block was 32 seconds in length and each fixation block was 32 seconds in length. Block order was randomly distributed. Across subjects, block type for the first block was counter-balanced within group. There was 20 seconds of fixation baseline at the beginning of the scan. See Figure 2.

Data Acquisition

Functional images were acquired with a GE (Waukesha, Wisconsin) Signa 3T MRI scanner with a T2*-weighted gradient-echo, echo-planar imaging (TR = 2000 msec, TE = 32 msec, flip angle = 77°, 29 Axial slices, thickness = 4 mm, gap = 0 mm, 64 x 64 in-plane resolution, in-plane FOV = 22 cm). A high-resolution T1-weighted anatomical scan was collected for each participant to localize functional activity.
Figure 2. Hybrid Stroop paradigm. There were 24 total blocks, with each block lasting 32 seconds. 12 of the blocks were experimental blocks, with four blocks of each type of experimental block (incongruent, positive, threat). Each experimental block consisted of eight target trials (incongruent, positive, or threat) and eight neutral trials, each presented for two seconds. 12 blocks consisted of fixation.
PROCEDURES

Potential participants completed a phone interview that screened for inclusion criteria using a set of questions to rule out individuals who would not be eligible and MR contraindications. If the potential participant met all of the inclusion criteria and none of the exclusion criteria, they were invited to the first session. At the beginning of the session, participants provided written consent. During the first session, a clinician administered the two-stage trauma interview, THQ, and WASI. Then the participant completed a computerized battery of questionnaires, including the BDI-II and CPICS. Women who endorsed a trauma history also completed the PTDS. Other behavioral measures and questionnaires were completed, although not reported here. After completion of the first session, the examiner determined whether or not a participant met full criteria for either the CIT or control group. If a participant met criteria for either group, she was invited to come back for the MR session. All participants reporting any trauma history were provided with a list of resources related to trauma exposure.

The second session was the MR session. Prior to entering the scanner, participants were shown all of the words that would be used in the Stroop task and rated each word for valence and arousal. Valence and arousal were each rated on a 7-point scale from 1 to 7. Higher ratings reflect more negative valence and higher arousal. Additionally, participants rated each of the 16 pictures used in the working memory task on two dimensions using a 7-point scale from 1 to 7, familiarity of the content in general and familiarity of the content in that particular modality (black and white or color). Higher ratings on either dimension reflect greater familiarity. Following picture ratings, participants learned paired associations between the stimuli and words that described the stimuli (e.g., picture of a peacock paired with the word “peacock”). They were then tested on these paired associations until they correctly recognized all 16 word-stimuli pairs.
Instructions for the Stroop task and working memory task were provided at this and participants were shown examples of the task, using novel stimuli.

The scanning session began with an anatomical scan. Participants then completed the working memory task. The working memory task was comprised of one function scan with 338 volumes. The working memory task always preceded the Stroop task, as there were concerns that exposure to trauma-related words could interfere with the processing of neutral information during the working memory task. After the working memory task, participants completed practice trials for the Stroop. Practice trials consisted of X’s in the four different colors. Participants were to respond to the colors using a button box. This served as practice to familiarize the participants with using the button box in the scanner. Participants then completed the Stroop task, making responses via a button box. The Stroop task consisted of one functional scan with 400 volumes. Stimuli were programmed using E-Prime software (Psychology Software Tools, Inc.) and presented via a pair of stereoscopic, MRI-compatible goggles. Participants were given earplugs to dampen scanner noise and head movement was restricted through the use of an air pillow conformed to each participant's head.

After scanning, participants completed a post-scan interview. The post-scan interview consisted of questions asking participants about their experience in the scanner, for example whether or not they fell asleep or drifted off during the task, and what they did during each of the conditions. This interview served mainly to verify that participants were attending during the task and had followed/understood the task instructions. No participants had to be dropped because of their responses.

ANALYSES

Image Preprocessing
Image preprocessing was conducted with the FMIRB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/index.html). Images were motion corrected with MCFLIRT, and brain tissue was extracted with BET to remove all non-brain tissue from the images. Prior to statistical analysis, images were spatially smoothed with a Gaussian kernel (FWHM = 8 mm), mean-based intensity normalized, high-pass temporal filtered with a cut-off period of 100 seconds to remove low-frequency noise, slice time corrected, and intensity-normalized to allow valid analyses across participants. Seven volumes (all fixations) were dropped from the beginning of each functional run to ensure steady-state magnetization.

**Statistical Analyses**

Statistical analyses were conducted with FMIRB’s improved linear model. Analyses on the blood oxygen level dependent (BOLD) time series were run separately for each individual participant for each task, using event-related analyses for the working memory task and separate blocked and even-related analyses for the Stroop task. Time series were convolved using a double-gamma hemodynamic response function. For comparisons across individuals, parameter and variance estimates for each participant were registered to Montreal Neurological Institute standard stereotaxic space (MNI152) with the two-stage registration procedure implemented in FMIRB’s Linear Image Registration Tool. The FMIRB’s Local Analysis of Mixed Effects (FLAME) was used to model the mixed-effects variance for each contrast of interest, taking into account both fixed effects and random effects. The working memory task, Stroop block effect, and Stroop event-related effects were modeled within separate GLMs.

For the working memory task, four regressors corresponding to the four trial types were modeled in a single GLM: Maintain, Replace, Suppress, and Clear. For each regressor, a double-gamma response function was convolved at the onset of each trial. For the Stroop task, separate
GLMs were run to explore block effects and event-related effects. To examine block effects, separate regressors for each block type (incongruent, positive, and threat) was modeled in a single GLM with the onset of each initial correct trial in a string of correct trials. Additionally, three separate regressors were modeled to account for error trials within each block type. In order to ensure that blocked effects were independent of these error trials, each blocked regressor was orthogonalized with respect to the corresponding error regressor. In order to examine event-related effects, seven regressors corresponding to the trial types were modeled in a single GLM: incongruent trials, neutral trials within incongruent blocks, positive trials, neutral trials within positive blocks, threat trials, neutral trials within threat blocks, and error trials. For each regressor, a double-gamma response function was convolved at the onset of each trial. Within FLAME, group difference analyses for each contrast of interest were computed using two-sample t-tests. Higher-level whole brain correlation analyses between working memory and Stroop interference estimates (parameter estimates for the contrasts of interest), separately, and total severity for each of the three PTSD symptom clusters (intrusive recollections, avoidance/numbing, and hyperarousal) as measured by the PTDS were conducted.

fMRI Statistical Tables

A variety of criteria were used to convert whole-brain fMRI statistical image maps into fMRI statistical tables (see Tables 4 - 10). In order to minimize Type I errors, statistical maps were subjected to Monte Carlo permutation simulations using the AlphaSim toolbox (Ward, 2000). For the working memory task, activity clusters were considered significant, corrected for family wise error rate at $p < 0.05$, if they exceeded a voxel wise threshold of $p < 0.005$ and a cluster wise threshold of 103 contiguous voxels. A slightly lower threshold was used for the Stroop task because of less usable data for this task, described later. For the Stroop task, activity
clusters were considered significant, corrected for a family wise error rate at $p < 0.05$, if they exceeded a voxel wise threshold of $p < 0.025$ and a cluster wise threshold of 154 contiguous voxels. The peak x,y,z coordinate in Montreal Neurological Institute (MNI) space was extracted from each significant cluster and listed in the fMRI table, as well as the number of voxels comprising each cluster and the z-value corresponding to the control group, trauma group, and group difference maps, as appropriate. In some cases, a significant cluster comprised a large number of voxels and spanned distant brain regions. In such cases, the larger cluster was subjected to increasingly stricter voxel-wise thresholds and increasingly smaller cluster-wise thresholds (in accordance with AlphaSim) until it partitioned into smaller clusters. The peak coordinates from these smaller clusters are listed in the table.
CHAPTER 3

RESULTS

All ANOVAs and MANOVAs were performed using an alpha of 0.05 and are two-tailed. All statistical analyses for behavioral data were performed using SPSS (2006).

Demographics

In order to ensure the trauma group and control group were matched on age, a one-way (Group: Trauma, Control) ANOVA for age was performed. There was no Main Effect of Group, $F(1, 27) = 0.47, p = 0.50$. See Table 1 for means and standard deviations.

A one-way (Group: Trauma, Control) ANOVA for SES was performed, using the Hollingshead as a proxy for current SES. There was no main effect of Group, $F(1, 27) = 0.58, p = 0.45$. Means and standard deviations are reported in Table 1. Given that some participants in the sample reported they were students, a one-way (Group: Trauma, Control) ANOVA was performed for education, using the Hollingshead classification for education, to ensure SES was not confounded in a group because of student occupation status. There was no Main Effect for education, $F(1, 27) = 1.45, p = 0.24$. Means and standard deviations are reported in Table 1.

Additionally, childhood SES was explored using father’s and mother’s highest level of education as a proxy, using the Hollingshead classification for education. A one-way (Group: Trauma, Control) MANOVA for mother education and father education was performed. There was a Main Effect of Group for father education, $F(1, 27) = 6.18, p = 0.020$, with the Trauma group having lower father education ($M = 3.31, SD = 1.44$) than the Control group ($M = 2.07, SD = 1.14$). There was no Main Effect of Group for mother education, $F(1, 27) = 2.50, p = 0.13$. Means and standard deviations reported in Table 1.
<table>
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<th>Variable</th>
<th>Trauma Group</th>
<th>Control Group</th>
<th>F</th>
<th>P</th>
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<tr>
<td>Age</td>
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<td>IQ</td>
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<td>117.21 (8.1)</td>
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<td>0.92</td>
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<td>SES</td>
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<td>37.29 (12.89)</td>
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<td>Education</td>
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<td>1.57 (0.51)</td>
<td>1.45</td>
<td>0.24</td>
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<td>Father Education</td>
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<td>2.07 (1.14)</td>
<td>6.18</td>
<td>0.020</td>
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<td>Mother Education</td>
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<td>BDI–II</td>
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<td>3.46 (4.68)</td>
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<td>Conflict Properties</td>
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<td>32.69 (10.38)</td>
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<td>Threat</td>
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<td>18.23 (4.44)</td>
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<td>Blame</td>
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<td>9.69 (1.93)</td>
<td>3.22b</td>
<td>0.085</td>
</tr>
</tbody>
</table>

**Table 1.** Means and standard deviations for demographic and individual differences variables. N = 27 (trauma group = 13, control group = 14). Means are presented for each group, with standard deviation in parentheses. For all F values, except where otherwise indicated, d.f. = 1, 27. α N = 13 for trauma group, d.f. = 1, 26. β N = 13 for control group, d.f. = 1, 26. IQ = Intelligence Quotient, measured by the WASI. SES = Socioeconomic Status, measured by the Hollingshead. All measures of education use the Hollingshead education scale. BDI–II = total score on Beck Depression Inventory – II. CPICS = total scale scores for the Children’s Perception of Interparental Conflict Scale.
Given that the trauma and control groups demonstrated no significant differences between groups for age, education, or current SES, these variables were not used as covariates in any subsequent analyses. Since parent education was being used only as a proxy for childhood SES and there was a group difference for father education but not mother education, parental education was not used as a covariate in any analyses.

**Intelligence**

To examine whether IQ was a potentially confounding variable, a one-way (Group: Trauma, Control) ANOVA for IQ was conducted. Data was missing for one participant in the trauma group. There was no Main Effect of Group, $F(1, 26) = 0.11, p = 0.92$. Means and standard deviations are reported in Table 1. Therefore, IQ was not used as a covariate or considered to be significantly affecting the interpretation of the results.

**Trauma**

Based on the trauma interview and THQ administration, we examined each participant’s response for the endorsement of CIT and non-interpersonal trauma during childhood (before age 17). Information about childhood trauma history for both groups is reported in Table 2. All participants in the trauma group, and no participants in the control group, endorsed experiencing physical abuse/assault and/or sexual abuse/assault. Physical abuse/assault included the participant being purposefully attacked by another person with an object or the person’s body, regardless of the degree of injury. Sexual abuse/assault included forced viewing of sexually-explicit material or individuals, molestation, and rape. Three participants, two in the trauma group and one in the control group, endorsed experiencing a non-interpersonal trauma. Non-interpersonal traumas endorsed by participants included being in a car accident or natural disaster. All three participants who reported a non-interpersonal trauma denied Criteria A for
Table 2. Types of childhood traumas experienced by participants in each group. N = 27 women (N = 13 for Trauma group, N = 14 for Control group). Numbers represent the number of participants who endorsed experiencing the type of trauma prior to the age of 17, and percentages in parentheses represent the percentage of the sample in the group endorsing the childhood trauma. Non-interpersonal trauma consisted of a car accident or natural disaster. Witnessing or hearing about a traumatic event could be any type of event, either interpersonal or non-interpersonal.

<table>
<thead>
<tr>
<th>Trauma Type</th>
<th>Trauma Group</th>
<th>Control Group</th>
<th>P (Fisher’s Exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpersonal</td>
<td>13 (100%)</td>
<td>0 (0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical Abuse/Assault</td>
<td>5 (38%)</td>
<td>0 (0%)</td>
<td>--</td>
</tr>
<tr>
<td>Sexual Abuse/Assault</td>
<td>4 (31%)</td>
<td>0 (0%)</td>
<td>--</td>
</tr>
<tr>
<td>Both Physical and Sexual Abuse/Assault</td>
<td>4 (31%)</td>
<td>0 (0%)</td>
<td>--</td>
</tr>
<tr>
<td>Non-interpersonal</td>
<td>2 (15%)</td>
<td>1 (7%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Witness</td>
<td>5 (38%)</td>
<td>0 (0%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Hear About</td>
<td>7 (54%)</td>
<td>3 (21%)</td>
<td>0.12</td>
</tr>
</tbody>
</table>
PTSD. Based on Fisher’s Exact Test, there was no significant difference in the number of non-interpersonal traumas experienced between the two groups, $p = 0.60$. Information on whether participants had witnessed or heard about a traumatic event during childhood (before age 17) was also collected. Based on Fisher’s Exact Test, the trauma group reported witnessing significantly more traumatic events than the control group, $p = 0.016$. No participants in the control group reported witnessing a traumatic event. For the trauma group, 5 out of 13 (38%) participants reported witnessing a traumatic event. Qualitative examination revealed that the perpetrator of their traumatic event, or one of their traumatic events, was the same perpetrator of the witnessed traumatic event. Based on Fisher’s Exact Test, there was no significant difference between the number of participants hearing about traumatic events between the groups, $p = 0.12$. The three participants in the control group endorsing hearing about traumatic events denied Criteria A for PTSD. Similar to witnessing traumatic events for participants in the trauma group, at least one of the events they heard about was in some way related to their own trauma or perpetrator.

**PTSD**

Of the 13 participants in the trauma group, 10 participants (77%) met criteria for PTSD based on their responses to the PTDS. Each participant, regardless of PTSD status, reported experiencing some PTSD symptoms, with the lowest number being four. Means and standard deviations for symptom counts and severity are reported in Table 3.

**Depression**

Data from the BDI-II for one participant in the control group was not available because of technical error. A one-way (Group: Trauma, Control) ANOVA for Depression, operationalized as total BDI-II score, was performed. As expected, there was a Main Effect for
**Table 3.** Means and standard deviations for PTSD symptoms and criteria in the trauma group. N = 13. Variables measured using the PTDS. Means are presented with standard deviation in parentheses. In parentheses after the symptom cluster names is the number of symptoms required out of the total number of possible symptoms in that cluster in order to meet DSM-IV-TR criteria for PTSD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full PTSD Criteria</td>
<td>10 (77%)</td>
<td>---</td>
</tr>
<tr>
<td>Total Symptoms</td>
<td>12.08 (3.57)</td>
<td>17.23 (11.28)</td>
</tr>
<tr>
<td>Intrusive Recollections (1 of 5)</td>
<td>3.31 (1.60)</td>
<td>5.77 (3.96)</td>
</tr>
<tr>
<td>Avoidant/Numbing (3 of 7)</td>
<td>4.92 (1.71)</td>
<td>8.54 (4.82)</td>
</tr>
<tr>
<td>Hyperarousal (2 of 5)</td>
<td>3.85 (1.14)</td>
<td>8.62 (5.52)</td>
</tr>
</tbody>
</table>
Group, $F(1, 26) = 11.54, p = 0.002$, with the trauma group ($M = 14.46, SD = 10.70$) endorsing more depressive symptoms than the control group ($M = 3.46, SD = 4.68$). See Table 1.

Parental Conflict

Data from the BDI-II for one participant in the control group was not available because of technical error. A one-way (Group: Trauma, Control) MANOVA was performed for the three factors of childhood parental conflict measured by the CPICS: conflict properties, threat, and self-blame. There was a Main Effect for threat, $F(1, 26) = 7.50, p = 0.011$, with the trauma group ($M = 24.62, SD = 7.14$) reporting greater levels of perceived threat during interparental conflict than the control group ($M = 18.23, SD = 4.44$). There was a trend towards a Main Effect of Group for conflict properties, $F(1, 26) = 3.31, p = 0.081$, with the trauma group ($M = 41.15, SD = 13.18$) reporting more intense, frequent, and poorly resolved interparental conflicts than the control group ($M = 32.69, SD = 10.38$). There was also a trend towards a Main Effect of Group for self-blame, $F(1, 26) = 3.22, p = 0.085$, with the trauma group ($M = 10.85, SD = 1.28$) reporting more self-blame for interparental conflict than the control group ($M = 9.69, SD = 1.9$). See Table 1.

WORKING MEMORY TASK

Performance of Task Demands (Maintain & Replace > Clear & Suppress)

The first set of analyses was run to determine whether individuals complied with task demands. One of the advantages of using neuroimaging for the current study is that we can utilize activity in sensory processing areas to confirm that manipulations of mental representations are occurring. If this is indeed the case, then greater activity in visual processing regions should be observed when individuals must keep a representation in mind, such as is
required for Maintain and Replace, as compared to when they must clear a representation, such as is required for Clear and Suppress. Furthermore, activity for Clear and Suppress, independently, should not be significantly above baseline ($z < 1.96$).

Activation for Maintain and Replace was contrasted with activation for Clear and Suppress separately for each group. For both groups, greater activation was seen in the ventral visual processing stream for Maintain and Replace compared to Clear and Suppress. For the control group, the inferior temporal gyrus (BA 20) was significantly activated for Maintain and Replace. Additionally, the fusiform gyrus (BA 37) demonstrated activation that was significantly above baseline for all four conditions, but activation was significantly greater for Maintain and Replace than Clear and Suppress. Similarly, the trauma group demonstrated significant activation in the fusiform gyrus (BA 37) and middle temporal gyrus (BA 21). A direct contrast of the two groups revealed no group differences in posterior regions of the brain. Therefore, these results suggest that both the control group and trauma group were able to comply with task demands for maintaining and replacing information in working memory. However, as is evident from Figure 3, activation was less robust in visual processing regions for the trauma group than control group. See Table 4 and Figure 3.

**No Information in Working Memory (Clear & Suppress > Maintain and Replace)**

Clear and Suppress were compared to Maintain and Replace separately for each group. This contrast was designed to reveal those regions that are involved when the contents of working memory must be removed and leave it blank, either by suppressing the current item or clearing all information from working memory. In order for a region to meet criteria for this contrast, activation for Clear and Suppress had to be significantly above baseline and activation for Clear and Suppress could not be significantly above baseline ($z < 1.96$). Regions that
<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>Max z</th>
<th># Voxels</th>
<th>x</th>
<th>y</th>
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</tr>
<tr>
<td>Middle Temporal Gyrus (L)*</td>
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<td>-6</td>
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<td>3.57</td>
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<td><strong>Trauma &gt; Control</strong></td>
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</table>

**Table 4.** Regions showing more activation when specific information is held in working memory than when no specific information is held in working memory (Maintain and Replace > Clear and Suppress). All regions met a voxel wise threshold of $z = 2.8$, $p < 0.005$, with a cluster wise correction of $p < 0.05$, 103 voxels. The z score presented represents peak activation in the cluster. R = right. L = left. BA = Brodmann’s area. All coordinates presented in MNI space. N = 26 (control group = 14, trauma group = 13). Note: * = Activity for maintain and replace, independently, was significantly greater than fixation baseline ($z > 1.96$), whereas for suppress and clear, independently, it was not ($1.96 > z > -1.96$). # = Activity for all conditions was significantly above fixation ($z > 1.96$), but more so for maintain and replace than suppress and clear.
Figure 3. Activity in sensory regions confirming compliance with task demands (Maintain and Replace > Clear and Suppress). All activity represents greater activation for Maintain and Replace than Clear and Suppress. Activation for both groups is shown, with activation in red representing the control group and activation in blue representing the trauma group. Plots represent percent signal change for each condition compared to fixation baseline for peak activation in the contrast of Maintain and Replace compared to Clear and Suppress. A) Greater activation in left fusiform gyrus (BA 37) for the control group. B) Greater activation in right fusiform gyrus (BA 37) for the trauma group. All regions met a voxel wise threshold of $z = 2.8$, $p < 0.005$, with a cluster wise correction of $p < 0.05$, 103 voxels. N = 27 (trauma group = 13, control group = 14). Coordinates are presented in MNI space.
exhibited greater activation for this contrast are those that have been previously identified as being involved in cognitive control.

For the control group, no regions met the above criteria. However, three regions showed activity that was above baseline for all four conditions, but significantly greater for Clear and Suppress than Maintain and Replace: anterior middle frontal gyrus (BA 10), superior frontal gyrus (BA 6), and a portion of right IFG (BA 44) extending into insula (BA 13). rIFG has been implicated in studies of inhibition (e.g., Aron et al., 2004), which is consistent with both clear and suppress requiring the inhibition of information in working memory. Anterior frontal gyrus has been implicated in task switching (e.g., Monsell, 2003), and has also been found to activate along with rIFG in studies of inhibition (Dreher & Berman, 2002). The trauma group also demonstrated activation of the rIFG (BA 44), but did not demonstrate significant activation of any other frontal regions. In contrast to the control group, the trauma group demonstrated greater activation of a posterior visual processing region for Suppress and Clear. This suggests that during both Clear and Suppress, there was some information being held in working memory. A direct comparison of the two groups for this contrast revealed no group differences. In sum, the control group activated a more robust group of frontal regions involved in cognitive control than the trauma group and the trauma group demonstrated activation of one visual processing region, but there were no significant differences in activation. See Table 5 and Figure 4.

*Information in Working Memory (Maintain & Replace > Clear & Suppress)*

We then examined the reverse contrast, identifying regions showing significantly more activity when information must be held in working memory as compared to when it should not. In order for a region to meet criteria for this contrast, activation for Maintain and Replace had to
<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>Max z</th>
<th># Voxels</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Inferior Frontal Gyrus/Insula (R)#</td>
<td>44/13</td>
<td>4.21</td>
<td>763</td>
<td>50</td>
<td>14</td>
<td>4</td>
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<tr>
<td>Superior Frontal Gyrus (R)#</td>
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<td>3.59</td>
<td>213</td>
<td>14</td>
<td>12</td>
<td>58</td>
</tr>
<tr>
<td>Middle Frontal Gyrus (L)#</td>
<td>10</td>
<td>3.8</td>
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<td>-30</td>
<td>52</td>
<td>6</td>
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<tr>
<td><strong>Trauma Group</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td>Inferior Frontal Gyrus/Insula (R)#</td>
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<td>-78</td>
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</tbody>
</table>

**Control > Trauma**

No regions noted

**Trauma > Control**

No regions noted

**Table 5.** Regions showing greater activation when there is no information in working memory than when information is in working memory (Clear & Suppress > Maintain & Switch). All regions met a voxel wise threshold of $z = 2.8$, $p < 0.005$, with a cluster wise correction of $p < 0.05$, 103 voxels. The $z$ score presented represents peak activation in the cluster. $R =$ right. $L =$ left. BA = Brodmann’s area. All coordinates presented in MNI space. N = 27 (control group = 14, trauma group = 13). Note: # = Activity for all conditions was significantly above fixation ($z > 1.96$), but more so for Clear and Suppress than Maintain and Replace.
Figure 4. Regions that are activated when one must remove information from working memory (Clear and Suppress > Maintain and Replace). All activity represents greater activation for Clear and Suppress than Maintain and Replace. Both groups are shown, with activation in red representing the control group and activation in blue representing the trauma group. A) Activation was observed for both groups in the rIFG (BA 47) extending into the right insula (BA 13). B) The control group demonstrated activation in an additional frontal region, anterior DLPFC (BA 10). Some regions are present in these figures but not reported in the tables, as these regions were significant for the contrast but did not meet criteria. aDLPFC = anterior DLPFC. Ins = insula. IFG = inferior frontal gyrus. All regions met a voxel wise threshold of $z = 2.8$, $p < 0.005$, with a cluster wise correction of $p < 0.05$, 103 voxels. $N = 27$ (trauma group = 13, control group = 14). Coordinates are presented in MNI space.
be significantly above baseline and activation for Clear and Suppress could not be significantly above base line (Z<1.96).

In addition to activation observed in both groups for regions in the ventral visual processing stream, the control group demonstrated greater activation for Maintain and Replace than Clear and Suppress in the precuneus (BA 7). The precuneus is thought to aid in guiding attention and mental imagery (Cavanna & Trimble, 2006), which would be consistent with selectively attending to and maintaining a specified mental image. Of note, there was no significant activation in frontal regions for either group, consistent with suggestions that frontal regions are not required for maintaining representations in working memory, except under conditions in which information must be buffered from distracting or competing information (e.g. D’Esposito, Cooney, Gazzaley, Gibbs, & Postle, 2006). Rather, there was extensive activation in the ventral visual processing stream bilaterally and parietal regions thought to support maintenance of information in working memory. Although a direct comparison of the two groups for this contrast revealed no significant differences, the lack of parietal activation in the trauma group suggests they may be under recruiting more posterior regions associated with maintenance of information in working memory. See Table 4.

*Inhibition of a Specific Memory Representation Compared to No Inhibition (Suppress & Replace > Clear & Maintain)*

For both Suppress and Replace, the item that was previously being processed must be specifically inhibited. Suppress and Replace were compared to Maintain and Clear, in which no such specific inhibition is required. In order for a region to meet criteria for this contrast, activation for Suppress and Replace had to be significantly above baseline and activation for Maintain and Clear could not be significantly above baseline (z < 1.96). For the control group,
one frontal region met this criteria: right posterior DLPFC (BA 8). Two frontal regions were activated above baseline for all four conditions, but significantly more for Suppress and Replace: left mid-DLPFC (BA 9/46) and rIFG (47) spreading into insula (BA 13). Activation of the left mid-DLPFC may reflect that the task-relevant representation shifts, with a new representation for Replace and removing a previous representation for Suppress. Additionally, rIFG activation could reflect inhibition of the previous representation. This region is different from the region of the rIFG observed for both Suppress and Clear. The caudate and brain stem were also activated significantly above baseline for Suppress and Replace but not Maintain and Clear in the control group. The caudate, a part of the basal ganglia, has also been implicated in inhibitory processes, including processes related to working memory (Cropley et al., 2006). The trauma group demonstrated similar activation to the control group in left mid-DLPFC (BA 9/46), with significant above baseline activation for Suppress and Replace but not Maintain and Clear. A direct comparison of the two groups demonstrated more activation in right posterior DLPFC (BA 8) for the control group than trauma group, suggesting the trauma group has more difficulty with biasing towards task-relevant processes. See Table 6 and Figure 5.

No Inhibition of a Specific Memory Representation (Maintain & Clear > Suppress and Replace)

For both the control group and trauma group, no regions met criteria for this contrast separately, and a direct contrast of the two groups revealed no significant differences in activation between the groups.

Activation Specific to a Given Condition

In this portion of the analyses we examined which regions showed activation that was greater for a specific condition as compared to all the other conditions. Furthermore, we required that the condition of interest show activity that was significantly above fixation ($z > 1.96$), but
<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>Max z</th>
<th># Voxels</th>
<th>x</th>
<th>y</th>
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<td><strong>Control Group</strong></td>
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<td>Multiple Frontal Regions</td>
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**Table 6.** Regions showing greater activation when a specific item in working memory must be inhibited than when no specific information must be inhibited (Suppress and Replace > Maintain and Clear). All regions met a voxel wise threshold of $z = 2.8, p < 0.005$, with a cluster wise correction of $p < 0.05$, 103 voxels. The $z$ score presented represents peak activation in the cluster. R = right. L = left. BA = Brodmann’s area. All coordinates presented in MNI space. N = 27 (control group = 14, trauma group = 13). Note: * = Activity for Suppress and Replace, independently, was significantly greater than fixation baseline ($z > 1.96$), whereas for Maintain and Clear, independently, it was not ($1.96 > z > -1.96$). # = Activity for all conditions was significantly above fixation ($z > 1.96$), but more so for Suppress and Replace than Maintain and Clear.
Figure 5. Group difference in removing something from working memory (Suppress and Replace > Maintain and Clear). A) Activation in red represents greater activation by the trauma group than control group in right middle frontal gyrus. All regions met a voxel wise threshold of $z = 2.8$, $p < 0.005$, with a cluster wise correction of $p < 0.05$, 103 voxels. $N = 27$ (trauma group = 13, control group = 14). MFG = middle frontal gyrus. Coordinates are presented in MNI space.
that none of the other conditions did so ($z < 1.96$), while for the reverse contrast all conditions except the condition of interest exhibited activity that was significantly above fixation.

Maintain. Consistent with the idea that parietal regions are important for holding information on-line for use in working memory, inferior parietal regions, including the supramarginal gyrus (BA 40), showed more activity for Maintain than all the other conditions for the control group. Conversely, whereas all other regions showed significant activation for anterior DLPFC, the Maintain condition did not. This is consistent with the role of this region in task-switching, as Maintain is the only condition in which the task-set does not significantly change after viewing the image. In contrast, the trauma group did not show greater activation for maintain compared to the other three conditions, but did show greater activation of bilateral IFG (BA 47), medial frontal gyrus (BA 6), and precuneus/cuneus for the other three conditions compared to Maintain. Given the role of rIFG in inhibition, this suggests the trauma group was inhibiting information during the other three conditions, which is consistent with task demands. However, this region was activated for all three conditions in the trauma group, whereas it showed specific activation for Replace in the control group. Additionally, the lack of activation for the precuneus in the Maintain condition is in contrast to the control group demonstrating greater activation of this region for both Maintain and Replace. A direct comparison of the two groups revealed differential activation in a region of the superior frontal gyrus (BA 6) for the control group compared to the trauma group. Specifically, the control group did not demonstrate significant activation for any of the conditions independently in this region, whereas the trauma group demonstrated significant activation below baseline for Maintain and non-significant activation of the other three conditions. This is consistent with previous research demonstrating
altered maintenance networks in trauma-exposed individuals (Shaw et al., 2009; Moores et al., 2008). See Table 7 and Figure 6.

*Replace.* For the control group, one frontal region was activated more for Replace than the other conditions, rIFG (BA 47). The rIFG has been implicated in inhibiting automatic and prepotent responding, and is consistent with this condition requiring the inhibition of a current representation prior to updating with a new image. The control group also demonstrated significant activation for Replace in the posterior cingulate (BA 31), middle temporal gyrus (BA 39), and parahippocampal gyrus (BA 36). The parahippocampal gyrus has been shown previously to become active when information must be retrieved again from memory in the face of other information having just been in working memory (Sakai, Rowe, & Passingham, 2002). As such, this pattern is consistent with the idea that a specific item learned from earlier in the experiment was being placed in working memory. The trauma group demonstrated a different pattern of frontal activation, activating mid-DLPFC for Replace and not the other conditions. It should be noted this region was on the right side, whereas activation of this region for the contrast of Replace and Suppress compared to Maintain and Clear was on the left side for both groups. However, they did not demonstrate any parahippocampal activation. A direct comparison of the two groups revealed no significant differences for Replace, suggesting the trauma group may under recruit, but not significantly, similar brain regions to the control group when updating information in working memory. See Table 7 and Figure 6.

*Clear.* A group difference was found in activation of middle temporal gyrus (BA 21), with controls activating this region for all other conditions except Clear and the trauma group activating it only for Clear. This region of the temporal cortex is involved in semantic processing, including semantic processing related to episodic memory (Svoboda, McKinnon, &
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Table 7. Regions showing activation specific to an individual condition for the working memory task. All regions met a voxel wise threshold of $z = 2.8$, $p < 0.005$, with a cluster wise correction of $p < 0.05$, 103 voxels. The $z$ score presented represents peak activation in the cluster. R = right. L = left. BA = Brodmann’s area. All coordinates presented in MNI space. N = 27 (control group $= 14$, trauma group $= 13$). For a Specific Condition > Other, the contrast of that condition compared to the others was significant, (e.g. Maintain > Replace + Suppress + Clear) and the activity for a given condition was significantly above fixation, (e.g. Maintain) which was not the case for the other conditions. Likewise, for Other > Specific Condition, that contrast was significant, and activity compared to baseline was significant for all conditions other than the specific condition (e.g. Maintain). * = Activity in trauma group was significantly below baseline ($z < -1.96$) for the specified condition and non-significant for the other three conditions, whereas the control group demonstrated non-significant activation across conditions.
Figure 6. Group differences in regions showing activation for only one condition. A) Activation for Maintain compared to other three conditions, with suppressed activation of medial frontal gyrus (BA 6) in the trauma group compared to non-significant activation in the control group in green. B) Activation for Clear compared to the other three conditions, with greater activation of middle temporal gyrus (BA 22) for the trauma group compared to the control group. All regions met a voxel wise threshold of $z = 2.8$, $p < 0.005$, with a cluster wise correction of $p < 0.05$, 103 voxels. N = 27 (trauma group = 13, control group = 14). MTG = middle temporal gyrus. Coordinates are presented in MNI space.
Levine, 2006). Therefore, this suggests that during Clear, the control group was able to clear their mind of aspects of semantic processing, including that related to episodic memory, whereas the trauma group engaged in these types of processing while attempting to clear working memory. The control group demonstrated activation in the precentral gyrus (BA 6) for Clear compared to non-significant activation for the other three conditions. Of note, the region activated by the control group for Clear was a region the trauma group demonstrated suppressed activation for during Maintain. In contrast, the trauma group activated multiple regions for clear and not the other conditions: right anterior DLPFC (BA 10), right precentral gyrus (BA 6), and supramarginal gyrus (BA 40). In addition to frontal regions related to task switching, the trauma group recruited a number of parietal and temporal regions supporting higher order processing of information. This suggests they are not able to engage in clearing the contents of working memory as effectively as the control group. See Table 7 and Figure 6.

*Suppress.* Neither the control group nor the trauma group demonstrated any regions with differential activation specific to Suppress. This suggests mechanisms tapped by the Suppress condition are not unique, and overlap to at least some degree with mechanisms in the other conditions.

*Activation Associated with Trauma Symptoms*

In this set of analyses, we examined whether reported severity of trauma symptoms in the trauma group was related to activation on this task. Total symptom severity was positively correlated with each of the three symptom clusters, intrusive recollections, avoidance/numbing, hyperarousal (0.72, 0.91, and 0.68, respectively), whole brain analyses for all three symptom clusters individually revealed the same patterns. Therefore, only total symptom severity was used as a regression.
Although different contrasts yielded associations with different brain regions, some general trends were observed. Activation in cognitive control regions, including DLFPC and medial frontal regions, was less for women with more severe symptoms when they needed to remove information in working memory and leave it blank. Of note, all of the regions were left-sided, with left-sided regions more frequently being implicated in cognitive control than similar right-sided regions. Ventral medial prefrontal cortex (BA 10) was one of the regions in this network, which is similar to other findings of decreased ventral medial prefrontal cortex in trauma-exposed individuals (e.g., Shin et al., 2004). Therefore, this suggests that greater trauma symptoms are associated with less use of cognitive control regions to remove information from working memory. In contrast, when the trauma group needed to inhibit a specific representation, greater symptom severity was associated with greater activation of a large region of the DLPFC. This region overlaps with a region showing greater activation for Suppress and Replace than Maintain and Clear for the trauma group as well as the control group. However, this association was primarily driven by activation in the Replace condition. Although this would seem inconsistent with the negative association between activation of cognitive control regions with symptom severity when clearing the contents of working memory, it is possible this finding is related to properties of the task design. The Replace condition is the only condition where the representation that should be manipulated is on the screen, in addition to the instructions. Therefore, a reminder in the environment of the task-relevant representation may support increased recruitment of frontal regions that are necessary when there is competing or distracting information in working memory (D’Esposito et al., 2006). Similarly, greater activation of dorsal ACC was associated with increased symptom severity, which is consistent with findings of
greater dorsal ACC activation for trauma-exposed individuals when completing interference tasks (e.g., Bremner et al., 2005). See Table 8 and Figure 7.

Additionally, two regions of left mid to anterior DLPFC for Maintain were associated with symptom severity. These regions are similar to regions for the control group that demonstrated greater activation for all three conditions other than Maintain. This is consistent with our other findings and proposals that maintenance of information in working memory is not only altered, but may also be associated with the recruitment of updating mechanisms during maintenance (Shaw et al., 2009; Moores et al., 2008), in trauma-exposed individuals. See Table 8.
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Table 8. *Regions that show a significant relationship with total severity of trauma symptoms.* All regions met a voxel wise threshold of $z = 2.8$, $p < 0.005$, with a cluster wise correction of $p < 0.05$, 103 voxels. R = right. L = left. BA = Brodmann’s area. All coordinates presented in MNI space. $N = 27$ (control group = 14, trauma group = 13).

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Figure 7. Brain regions associated with trauma symptoms for the working memory task. Whole-brain regression of total severity of trauma symptoms on contrasts of interest. A) Region of DLPFC activated for Suppress and Replace more than Clear and Maintain demonstrating a positive association with trauma symptoms, shown in blue. B) Region of posterior cingulate cortex and ventral medial PFC (above) activated more for Clear and Suppress than Maintain and Replace demonstrating a negative association with trauma symptoms, shown in red. Region of superior frontal gyrus (below) activated more for Clear and Suppress than Maintain and Replace demonstrating a negative association with trauma symptoms, shown in red. All regions met a voxel wise threshold of $z = 2.8$, $p < 0.005$, with a cluster wise correction of $p < 0.05$, 103 voxels. $N = 27$ (trauma group = 13, control group = 14). DLPFC = dorsolateral prefrontal cortex. pCC = posterior cingulate cortex. vmPFC = ventral medial prefrontal cortex. SFG = superior frontal gyrus. Coordinates are presented in MNI space.
STROOP TASK

Two participants, one from the trauma group and one from the control group, had movement greater than 2 mm for the Stroop functional scan. Therefore, they were not included in the Stroop analyses. Additionally, one participant in the trauma group had low accuracy, with one block having accuracy below 60%. This resulted in an insufficient number of trials and useable block data and therefore she was not included in the Stroop analyses. Final sample size for the Stroop task was 24 (control group =13, trauma group = 11).

Behavioral Data

A 3 (Block: Incongruent, Positive, Threat) x 2 (Group: Control, Trauma) Repeated Measures ANOVA was run for reaction time (RT) to examine differences in RT between groups at the block level. Average RT was calculated only for correct trials. There was a Main Effect for Block, $F(2,24) = 29.13, p < 0.001$. Follow up Simple Main Effects analyses revealed longer RT’s (ms) for incongruent blocks (Control: M = 750.10, SD = 84.33; Trauma = 817.44, SD = 91.34) than either positive blocks (Control: M = 682.40, SD = 79.28; Trauma = 749.38, SD = 113.14) or threat blocks (Control: M = 701.55, SD = 65.43; Trauma = 755.57, SD = 107.84), all $p$’s ≤ 0.001. There was no difference between RT’s for the positive and threat blocks. There was also a trend towards a Main Effect for Group, $F(1,24) = 3.14, p = 0.090$, with the trauma group showing overall longer RT’s than the control group. The Block x Group interaction was not significant.

A 3 (Block: Incongruent, Positive, Threat) x 2 (Group: Control, Trauma) Repeated Measures ANOVA was run for interference within block to examine differences in interference between groups within blocks. Interference is the percentage increase in interference for the target trials compared to the neutral trials within block, and is calculated as follows: (target trial
RT – neutral RT)/neutral RT. Similar to the block effects, there was a Main Effect of Block, $F(2,24) = 22.31, p < 0.001$. Follow up Simple Main Effects analyses revealed both groups demonstrated greater interference within the incongruent blocks (Control: $M = 0.14$, $SD = 0.11$; Trauma = $0.19$, $SD = 0.12$) compared to the positive blocks (Control: $M = 0.001$, $SE = 0.078$; Trauma = $0.016$, $SD = 0.076$) and threat blocks (Control: $M = -0.0002$, $SD = 0.067$; Trauma = $0.029$, $SD = 0.064$), all $p$’s ≤ 0.002. There was no Main Effect for Group, $F(1,24) = 2.44, p = 0.13$, or Block x Group Interaction, $F(2,24) = 0.18, p = 0.84$.

Additionally, a 3 (Block: Incongruent, Positive, Threat) x 2 (Group: Control, Trauma) Repeated Measures ANOVA was run for accuracy across the blocks to examine whether there were differences between groups across blocks. There was no Main Effect for Block, $F(2,24) = 1.01, p = 0.37$, or Group, $F(1,24) = 0.083, p = 0.78$. There also was no Block x Group Interaction, $F(2,24) = 0.025, p = 0.98$. Across groups and blocks, average accuracy ranged from 97% to 98%. Within block accuracy was compared using paired $t$-tests. There was no difference in accuracy between target trials and neutral trials within block for any of the three blocks, all $p$’s > 0.16. Accuracy across trials and groups ranged from 96% to 98%. Therefore, there were no differences in accuracy across blocks or between groups and accuracy rates suggest participants were able to successfully complete the task.

**Blocked Analyses**

*Conditions vs. Fixation.* Although task blocks vary in their demands for cognitive control, all blocks encourage sustained, top-down biasing of attention towards task-relevant goals (color identification) and away from task-irrelevant processes (word reading). Thus, one might expect that alterations in neural mechanisms for maintaining a proactive, top-down attentional set might manifest itself during all block types compared to fixation.
To examine the effect of group associated with proactive maintenance of task goals, we first performed a contrast of task blocks versus fixation baseline blocks separately for each block type (incongruent, positive, threat) and group separately. For each of the three contrasts, both groups activated several frontal and parietal brain regions implicated in top-down control, including regions at or near the middle and inferior frontal gyrus, ACC, anterior inferior parietal cortex, superior parietal cortex, and precuneus. Additionally, regions in the thalamus and cerebellum were also activated. A direct contrast of the two groups for each of the blocks separately only revealed differences for the incongruent block. Specifically, the control group recruited the precuneus when maintaining a top-down attentional set, but the trauma group did not. This finding is similar to the trauma group not recruiting this region when maintaining information in working memory, whereas the control group did. This could be reflective of a general difficulty with parietal regions supporting implementation of sustained, task-relevant processes. The lack of group differences in frontal regions may be due to insufficient power resulting from a decreased sample size for this task. See Table 9 and Figure 8.

*Differences Between Conditions:* The next objective was to examine differences in blocked activity for the Stroop related to the type of interference. The contrast between positive and threat blocks with the incongruent block isolates differences between biasing attention away from emotional task-irrelevant information and neutral task-irrelevant information. All three blocks have increased demands to bias attention towards task-relevant processes (color information) and away from task-irrelevant processes (word reading). They have two attentional priorities, with one of the priorities, attending to the ink color, being the same for both. However, the second attentional priority is different for the blocks. For the incongruent block, an additional, neutral source of color information competes for attentional priority, whereas for the
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**Table 9. Differences in activation across blocks for Stroop task.** All regions met a voxel wise threshold of \( z = 2.58, p < 0.005 \), with a cluster wise correction of \( p < 0.05 \), 154 voxels. The \( z \) score presented represents peak activation in the cluster. R = right. L = left. BA = Brodmann’s area. All coordinates presented in MNI space. \( N = 24 \) (control group = 13, trauma group = 11). * = Significant suppression of activation below baseline for incongruent blocks.
Figure 8. Group differences in blocked Stroop activation. Greater activation in the precuneus for the control group than trauma group for the blocked contrast of the incongruent blocks compared to fixation blocks, shown in red. All regions met a voxel wise threshold of $z = 2.58$, $p < 0.025$, with a cluster wise correction of $p < 0.05$, 154 voxels. $N = 24$ (trauma group = 11, control group = 13). PreC = precuneus. Coordinates are presented in MNI space.
positive and threat blocks emotional information competes for attentional priority. For the control group, activation of the posterior cingulate was suppressed below baseline for the incongruent block and above baseline for the positive and threat blocks. In contrast, the fusiform gyrus was significantly activated for the incongruent block but not the positive and threat blocks. This suggests that top-down control was more efficient and able to bias processing towards the task-relevant process and decrease default mode processing for the incongruent blocks. The trauma group did not demonstrate any differences. A contrast of positive and incongruent blocks compared to threat blocks was performed in order to examine if there was any differential activation for the threat blocks. The trauma group demonstrated significant activation of a region of fusiform gyrus for incongruent and positive blocks than the threat blocks, suggesting they were not able to bias processing towards the task-relevant process as well when a competing attentional demand was trauma-related. The control group did not show any differences. See Table 9.

Additionally, we contrasted the incongruent blocks with positive and threat blocks separately in order to determine whether the type of emotional information competing for attentional priority affected processes biasing attention. The control group demonstrated suppressed activation of medial frontal cortex (BA 9) for the two emotional blocks separately compared to the incongruent block. Medial prefrontal cortex, including BA 9, has been implicated in experiencing emotion (e.g., Lane et al., 1997). Therefore, the control group may be proactively dampening emotional processing, which it task-irrelevant. There was also greater recruitment of fusiform gyrus (BA 37) for the incongruent block than positive block. This suggests that for the controls, they were better able to bias task-relevant processing in the face of conflicting color information than positive, emotional information. No differences were observed
for either group between the incongruent and threat blocks. Taken with the previous block analyses, these results suggest that the trauma group demonstrated more difficulty biasing attention towards task-relevant processing in the face of trauma-related information, whereas the control group demonstrated more difficulty biasing attention towards task-relevant processing in the face of positive information. Additionally, the control group engaged proactive control focused on dampening emotional, task-irrelevant processing during the emotional blocks. See Table 9.

In contrast to the control group, the trauma group only demonstrated differential activation for one contrast. Given that direct comparisons of the two groups did not reveal any differences, the lack of differences seen in the trauma group is more likely a reflection of insufficient power.

**Individual Trial Analyses:**

In order to examine differences in reactive control mechanisms, which are thought to be activated after a stimulus is presented, we examined differences in activation between target trials (incongruent, positive, threat) and neutral trials within block. For the control group, no regions related to reactive control were activated more for the incongruent trials than incongruent neutral trials. Rather, mid-DLPFC was activated more for incongruent than incongruent neutral trials. This suggests that individuals in the control group were activating top-down control mechanisms in order to maintain attention of the task-relevant information. Greater activation of the fusiform gyrus was also observed for the incongruent than neutral incongruent trials, suggesting enhanced processing of the ink color information. Similar to the control group, the trauma group also activated mid-DLPFC more for incongruent than neutral incongruent words. The presence of the incongruent trials has been suggested to provide environmental support for
the task that should be maintained (Kane & Engle, 2003), and therefore greater activation of mid-DLPFC and task-relevant processes, at least in the control group, is consistent with this proposal. However, the trauma group also activated the inferior parietal lobule and left inferior frontal gyrus (BA 45) more for incongruent than neutral incongruent trials. The left IFG is thought to be involved in selecting task-relevant representations from competing representations. Additionally, they activate regions related to word reading. This would be consistent with the trauma group needing to select the relevant color information from two sources of color information, suggesting they are implementing additional reactive mechanisms to inhibit prepotent responding. For the threat words compared to the neutral threat words, the control group demonstrated greater activation of the left IFG. As described earlier, this suggests they are choosing from two representations, as would be expected when faced with attention capturing threat information and task-relevant information. In contrast, the trauma group demonstrated greater activation of one medial frontal region (BA 8) for threat than neutral threat words, which suggests they are recruiting mechanisms related to emotional responding. No differences were found between the positive and neutral positive words for either group. A direct comparison between groups of trial types within the three blocks, separately, revealed no group differences. This is again thought to be because of insufficient power to detect group differences. It should also be noted that differences in activation of limbic regions, such as the amygdala, that were predicted to be present were not for the individual or blocked analyses. Insufficient power would inordinately affect the ability to test for activation in these regions, as they are much smaller in volume than other regions examined in this study and therefore require more power to detect differences. Inclusion of additional participants will make it possible to examine these differences, especially in limbic regions, adequately. See Table 10 and Figure 9.
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**Table 10. Differences in activation within blocks for Stroop task.** All regions met a voxel wise threshold of $z = 2.58$, $p < 0.005$, with a cluster wise correction of $p < 0.05$, 154 voxels. The $z$ score presented represents peak activation in the cluster. $R =$ right. $L =$ left. BA = Brodmann’s area. All coordinates presented in MNI space. N = 24 (control group = 13, trauma group = 11).
Figure 9. Event-related Stroop activation. Activation for both groups for the contrast of incongruent trials greater than neutral trials within the incongruent block. Control group is shown in red and trauma group is shown in blue. A) Both groups demonstrate greater activation of DLPFC for incongruent than neutral trials, with controls showing more left-sided activation. B) Trauma group demonstrated activation of inferior parietal lobule, while control group demonstrated activation of fusiform gyrus. All regions met a voxel wise threshold of $z = 2.58$, $p < 0.025$, with a cluster wise correction of $p < 0.05$, 154 voxels. N = 24 (trauma group = 11, control group = 13). R = right. L = left. DLPFC = dorsolateral prefrontal cortex. IPL = inferior parietal lobule. FG = fusiform gyrus. Coordinates are presented in MNI space.
Activation Associated with Trauma Symptoms

In this set of analyses, we examined whether reported severity of trauma symptoms in the trauma group was related to activation for the top-down and more transient aspects of cognitive control. Initially, symptom severity for each symptom cluster (intrusive recollections, avoidance/numbing, and hyperarousal) was used as a regressor for a whole brain search with the blocked and event-related contrasts of interest. However, similar to the working memory task, whole brain analyses for all three symptom clusters individually revealed the exact same patterns. Therefore, the results are presented for total symptom severity.

No regions demonstrated an association with symptom severity for any of the blocked contrasts of interest. There were associations between symptom severity and activity in the blocks compared separately to fixation, but nothing for the contrasts of interest. Given the low level of activation demonstrated in general for the trauma group on the blocked analyses, it is not surprising that associations were not found. For the event-related analyses, associations were found for one contrast, incongruent trials compared to neutral incongruent trials. For this contrast, greater symptom severity was associated with increased activation in a region found for the initial contrast, right posterior to mid-DLPFC (BA 9/46). Although overlapping, the region identified in the whole brain regression extends more posteriorly than the region identified in the contrast. Activation in another region, left angular gyrus/lateral occipital cortex, was also found to be positively associated with symptom severity. This region overlaps some with the region of inferior parietal lobule (BA 40) that was found to be activated in this contrast as well. Therefore, trauma symptomatology is associated with greater engagement in word reading and additional recruitment of top-down mechanisms. As discussed earlier, the presence of the incongruent trials has been suggested to provide environmental support for the task that should be maintained.
(Kane & Engle, 2003), and therefore may serve to decrease the difference in activation on the two types of trials. This suggests that trauma-exposed individuals are processing the salient word, which serves as a reminder of the task-relevant processes and therefore increases the recruitment of regions related to biasing towards the task-relevant process. See Figure 10.
Figure 10. Brain regions associated with trauma symptoms for transient cognitive control in the Stroop task. A) Region of right DLPFC (BA 9) activated more for incongruent trials than neutral trials within the incongruent block demonstrating a positive association with trauma symptoms, shown in blue. B) Activation in left inferior parietal lobule (BA 40) greater for incongruent trials than neutral trials within the incongruent block demonstrating a positive association with trauma symptoms, shown in blue. All regions met a voxel wise threshold of $z = 2.58$, $p < 0.025$, with a cluster wise correction of $p < 0.05$, 154 voxels. $N = 24$ (trauma group = 11, control group = 13). DLPFC = dorsolateral prefrontal cortex. IPL = inferior parietal lobule. Coordinates are presented in MNI space.
CHAPTER 4

DISCUSSION

Working Memory Task

The present study used the power of neuroimaging to examine the nature of cognitive control mechanisms that act on representations in working memory in two groups, a group of women with a history of CIT and a group of women with no history of trauma. Our paradigm provided evidence, via patterns of activation in posterior cortex, that women in both groups were able to comply with task demands and suppress or clear their mind of thoughts being held in working memory. Generally speaking, patterns in the control group replicated our previous findings using this paradigm with a healthy control sample (Banich, Mackiewicz Seghete, & Chatham, in prep). Women with a history of CIT demonstrated activation overall that was less robust than women with no history of trauma, suggesting the task might be more difficult for them. The results suggest some processes in working memory may be altered in women with a history of CIT, and that some alterations are associated with trauma symptoms.

Task Difficulty. Although women in both groups were able to comply with task demands, as evidenced by greater posterior activation when a representation needed to be held in working memory, women with a history of CIT did not demonstrate activation as robust as women with no history of trauma in visual processing regions. Furthermore, women with no history of trauma recruited the precuneus while holding a representation in working memory, which is a region that has been implicated as mediating control over the focus of attention (Bledowski et al. 2009, 2010; Wager & Smith, 2003). Greater activation of parietal regions involved in guiding attention, as opposed to the lack of significant activation in frontal regions, suggests attending to and
maintaining a representation in working memory is not largely driven by cognitive control mechanisms and is consistent with previous findings (e.g., D’Esposito et al., 2006). Although the precuneus was the only region that demonstrated differential activation when the two groups were examined separately, direct comparison of the two groups revealed no significant differences. The less robust activation for the women with a history of CIT coupled with the lack of significant group differences suggests that simply holding a representation in working memory is more difficult for the women with a history of CIT than the women with no history of trauma, and hence the task itself is more difficult for the women with a history of CIT. As such, the current sample may not be sufficient to detect group differences. Although originally it was thought the sample sizes would provide sufficient power, based on previous studies of group differences in working memory in trauma-exposed individuals compared to controls (e.g., Shaw et al., 2009; Moores et al., 2008), this may not be the case if the task proves more difficult for one group than another. This limitation will be discussed in further detail later.

Cognitive Control of Information in Working Memory. The results show that for both groups suppressing and clearing the contents of working memory involved an active cognitive control mechanism, above and beyond any needed to maintain or replace the current representation being held in working memory. Although we had conceptualized these processes as being specifically related to inhibition, a number of findings suggest inhibition as well as other mechanisms may be occurring. For the control group, these two processes engaged the right IFG, which has been implicated in inhibition (Aron et al., 2003, 2004; Garavan et al., 1999). Although there were no significant group differences, the trauma group demonstrated less robust activation of the rIFG than the control group. Additionally, there was significant activation in a region of the visual processing stream only for women with a history of CIT, suggesting they were not
suppressing visual processing as much. Consistent with this pattern, previous imaging studies of trauma-exposed individuals have found decreased activation in the rIFG when they must exert inhibitory control (Falconer et al., 2008; Shucard et al., 2008). In addition to rIFG, the control group demonstrated activation of the anterior DLPFC (BA 10) and caudal superior frontal sulcus (SFS; BA 6/8) when suppressing and clearing the contents of working memory, but not when maintaining or replacing the contents. Anterior DLPFC has been observed in other studies to be involved in task switching, creating a task set, and with the creation of abstract goals (for review, see Monsell, 2003). Studies have found activation of both the DLPFC and rIFG when switching tasks (Dove et al., 2000; Dreher & Berman, 2002). Taken together, this suggests that the main mechanism of the Suppress and Clear conditions is to switch the task-set to inhibiting something. Activation of caudal SFS (BA 6/8) when information needs to be removed from working memory, and not when it needs to be maintained or updated, is inconsistent with proposals that this region is involved with updating information in working memory (Bledowski et al., 2009, 2010). If this region was involved in updating, it would not be activated as much for Maintain as Replace. Rather, it is more consistent with findings that BA 6/8 is often involved in setting the parameters for stimulus-response mappings (Badre & D’Esposito, 2009). It may be that these regions provide a general updating with regards to the nature of the response that is related to the contents of working memory (e.g., empty the contents of working memory when they have been previously occupied). Although there were no significant group differences, only the control group demonstrated significantly greater activation of anterior DLPFC and caudal SFS and the trauma group demonstrated less robust activation of rIFG. Furthermore, under recruitment of multiple cognitive control regions when switching to inhibiting the contents of working memory was associated with increased trauma symptoms. A region of vmPFC and ventral ACC were
among these regions, which have shown similar associations in other studies (Bremner et al., 2004; Etkin & Wager, 2007; Shin et al., 2001). Studies demonstrating decreased vmPFC activity have often used emotional paradigms, including trauma-driven scripts and exposure to fear stimuli. Given the strong connectivity of the amygdala, which is hyperactivated in trauma-exposed individuals, with vmPFC, it has been proposed hypoactivation of the vmPFC is related to decreased regulation of emotional responding. Our findings extend this body of literature further, suggesting that decreased activation of the vmPFC may be linked with a more general deficit in cognitive control. Therefore women with a history of CIT demonstrate an under recruitment of cognitive control regions when they must switch a task-set to inhibiting, and associations with symptoms in regions of medial PFC are related to this more general deficit in switching to inhibiting.

Inhibitory control over working memory. One aspect of cognitive control that demonstrated significant group differences was when a specific representation in working memory had to be inhibited, with women with no history of trauma demonstrating greater activation of posterior DLPFC (BA 8) than women with a history of CIT. As described earlier in our discussion of the Cascade of Control Model (Banich, 2009; Milham & Banich, 2005; Milham et al., 2003), posterior DLPFC is involved in biasing towards task-relevant processes. This finding is consistent with that proposal, as in the Suppress and Replace condition individuals are biasing processing towards inhibiting a specific representation, whereas in Maintain and Clear there is no shared task-relevant process. An alternative explanation would be that Suppress actually occurs by replacing the previous item with another item, similar to Replace, and therefore the shared task-relevant process is updating with a new representation. Others have proposed this model of inhibition (e.g., Collete et al., 2005). However, if
suppressing an item occurs by replacing it with something else, then the brain regions activated by the Suppress condition should be isomorphic with those of the Replace condition. In this study, that would mean there should only be significant regions activated by both Suppress and Replace and distinct regions should not be uniquely activated by Replace or Suppress. In this study, we found unique regions activated by both groups for Replace, but not for Suppress. This suggests that women with a history of CIT had difficulty biasing processing towards inhibiting a specific representation.

Although in the left hemisphere, and not the right like the prior region, a region of posterior to mid-DLPFC was positively associated with symptom severity in women with a history of CIT. This association seemed to be driven by the Replace condition, which is unique among the four conditions in that the instructions remaining on the screen during the mental manipulation include the name of the task-relevant representation. Although the other conditions do have instructions reminding the participants of the task, they do not have a reminder of what should be done with specific representations. Therefore, it is possible that women with a history of trauma are more focused on information in the environment and reminders from the environment aid in recruiting regions involved in updating representations in the face of competing information (D’Esposito et al., 2006). Consistent with this explanation, greater activation in word-reading areas was also positively associated with trauma symptoms. This is similar to the pattern observed for the incongruent and neutral trials within the incongruent block of the Stroop task, such that reminders from the environment were processed on the incongruent trials and top-down control intensified. Thus, these findings suggest women with a history of CIT use remind
The Replace condition engaged mechanisms above and beyond those required for the other three conditions, including Suppress, for both groups. Although a direct contrast between the two groups did not reveal any significant differences, a pattern of differences could be seen when looking at analyses run separately for each group. Only the control group demonstrated significant recruitment of portions of the parahippocampal gyrus. This region has been shown to be activated during recollection of associations (Eichenbaum, Yonelinas, & Ranganath 2007) and is therefore consistent with retrieval of another item to replace the one currently in working memory. This further supports the suggestion that individuals complied with tasks demands, with the task being more difficult for women with a history of CIT than women with no history of trauma. Additionally, although both groups activated frontal regions, the women with a history of CIT activated posterior to mid-DLPFC, whereas women with no history of trauma activated rIFG (BA 47). This region of rIFG is different from the region demonstrating activation when clearing information from working memory. Research to date has implicated rIFG in inhibition, but has not clearly delineated the role of the three sub-regions of the rIFG, pars orbitalis (BA 47), pars opercularis (BA 44), and pars triangularis (BA 45). Therefore, it is possible that this region is involved more than the other two when one of two specific, competing representations must be inhibited. Further analysis using anatomical ROI’s for the subregions is necessary to delineate the role each region plays in the processes discussed. Additionally, the control group activated a network of posterior cingulate and middle temporal gyrus, which has been implicated in memory retrieval and hence is consistent with parahippocampal activation suggesting retrieval of another formerly learned item.

Neither group demonstrated unique activation for clearing a specific representation from working memory, suggesting that the mechanisms involved in this task are shared with other
processes. However, results suggest that clearing everything from working memory has unique mechanisms, and these differ between groups. There was a group difference for a region of middle temporal gyrus, with women with no history of CIT activating this region for all other conditions except Clear and women with a history of CIT activating it only for Clear. Middle temporal gyrus has been implicated in semantic processing, including semantic retrieval of episodic memories (Svoboda et al., 2006). Therefore, women with a history of CIT are potentially engaged in semantic processing or retrieval of episodic memories when they are instructed to clear the contents of working memory. This would be consistent with intrusive trauma symptoms, both of memories and unwanted thoughts. Women with a history of CIT engaged superior frontal cortex (BA 6) uniquely for clear, whereas the control group did not. In contrast, the control group actually activated this region for Maintain and Replace. This suggests that women with a history of CIT recruit a mechanism involved in clearing the entire contents of working memory when they should be maintaining a representation. It has been previously suggested that trauma-exposed individuals recruit altered mechanisms for maintenance and updating of information in working memory, specifically suggesting they need to continually update working memory and that this may be reflective of trauma-exposed individuals displaying difficulties with retaining goal-relevant information (Moores et al., 2008; Shaw et al., 2009). Taken with our findings, this suggests that individuals are clearing information out of working memory, and then it needs to be updated with task-relevant information. This could be associated with their less robust activation when holding a representation in working memory.

*Maintaining a representation.* Women with a history of CIT showed suppressed activation of dorsal medial frontal cortex (BA 6) when maintaining a previous representation in working memory, whereas women with no history of trauma did not show significant activation
or suppression for this region in any condition. Additionally, regions of DLFPC that women with no history of trauma recruited for all other tasks except maintaining a previous representation in working memory was associated with symptom severity in women with a history of CIT, such that it was recruited more in women with more severe symptoms. Furthermore, they demonstrated suppressed activation of parietal regions involved in selective attention and biasing processes, whereas women with a history of no trauma demonstrated activation of this region while selectively holding a representation in working memory. Women with no history of CIT also demonstrated greater activation of other parietal processing regions when maintaining a previous representation. Taken together, these findings suggest that women with a history of CIT demonstrate altered patterns of activation when maintaining a previously seen representation in working memory. These findings are consistent with previous findings examining maintenance of information in working memory in trauma-exposed individuals and the suggestion that mechanisms related to maintenance of information in working memory contributed significantly to working memory problems in trauma-exposed individuals (Moores et al., 2008; Shaw et al., 2009;).

Summary. In summary, both women with a history of CIT and women with no history of trauma were able to comply with task demands, although the task as a whole was likely more difficult for the women with a history of CIT. Women with a history of CIT demonstrated a pattern of hypoactive cognitive control regions that extends previous findings to suggest a more general deficit in switching task-sets to inhibiting the contents of working memory. Similarly, women with a history of CIT did not recruit cognitive control regions, which the control group did, that aided in the suppression of specific representations. Other working memory processes affected in women with a history of CIT included maintaining previous representations in
working memory, for which they actually recruited regions related to clearing the entire contents of working memory. Additionally, women with a history of trauma may use reminders in the environment to aide in updating task-relevant representations. Taken together, this data suggests women with a history of CIT demonstrate deficits in setting a task-set to inhibit the contents of working memory and are better able to maintain representations in working memory when there are external reminders of the representation.

**Stroop Task**

Overall, no differences in performance on the Stroop task between women with a history of CIT and women with no history of trauma were found. Additionally, findings were not very robust for this task, with only one significant group difference in activation being found for either the blocked or event-related analyses. Previous studies have found both behavioral and brain activation differences, so this seems inconsistent with the literature. Therefore, given the smaller number of participants with usable data for this task, we believe that sample size significantly impacts the findings. Some of the findings are discussed below, but are believed to only provide some suggestions of what patterns might emerge once a larger sample is collected.

**Proactive Cognitive Control.** There was one group difference found between women with no history of CIT and women with a history of CIT when examining maintenance of a top-down, task-relevant attentional set, namely greater activation of the precuneus in women with no history of trauma than women with a history of CIT during the incongruent block. This region was also under recruited by women with a history of CIT when they had to hold a representation in working memory. The precuneus has been implicated in multiple functions, with many of these functions being related to mental imagery and strategies. This includes internally-guided attention, manipulation of mental images, and retrieval of episodic memories (Cavanna &
Trimble, 2006). Both tasks are similar in that they require internally-guided attention, with the maintain condition of the working memory task requiring individuals to direct attention to a held mental image and the incongruent block of the Stroop task requiring individuals to guide attention to the task-relevant color information. Although all conditions of both tasks require some degree of internally-guided attention, maintain compared to all three conditions and blocked incongruent Stroop activity compared to event-related Stroop activity share that a task-set is consistently being maintained, in the absences of any form of updating (e.g., switching representations, being reminded of the task-set on incongruent trials), and therefore attention needs to be continually guided to maintain task-relevant processing. Taken together, this suggests that women with a history of CIT have difficulty guiding attention to sustained task-relevant processes.

Women with a history of CIT demonstrated few significant differences between any of the blocks. In contrast, women with no history of trauma demonstrated different patterns of activation across the blocks. In general, brain regions demonstrating differential activation across the blocks for women with no history of trauma are lateral frontal regions and parietal regions that have been previously implicated in top-down cognitive control, as well as posterior regions related to word-reading and visual processing. Given that women with no history of trauma showed differential activation of cognitive control and sensory processing regions in response to the task, the lack of differential activation in the women with a history of CIT is not thought to be due to the paradigm itself. Furthermore, given there were no differences in performance or accuracy, the lack of differences is not a reflection of task difficulty. An explanation for the observed pattern could be that women with a history of CIT did not engage in top-down attentional control. However, activation in top-down control regions was observed for both
groups when comparing the individual conditions to fixation, suggesting women with a history of CIT were able to engage top-down control mechanisms. As mentioned previously, this could be due to limited power to detect differences within the group. On the other hand, this could support the proposal that trauma-exposed individuals have a more global deficit implementing top-down cognitive control biasing towards task-relevant information in the face of task-irrelevant information in the environment. The inclusion of additional participants is necessary to further tease apart the underlying cause of this lack of differential activation.

*Transient cognitive control.* For both groups, incongruent and threat trials required the recruitment of additional cognitive control above and beyond that implemented to maintain a top-down attentional set. Incongruent trials recruited greater activation of posterior DLPFC (BA 9), spanning into more mid-DLPFC (BA 9/46). According to the Cascade of Control model this region is involved in biasing towards task-relevant processing, and recruitment suggests a greater need to bias towards task-relevant processing since there are two types of color information. This region was activated for the block, but activation is likely ramped up when an incongruent, as opposed to neutral word, is seen. Women with no history of trauma also demonstrated greater activation of color-processing regions, suggesting they are successfully biasing processing towards ink color and not the word. This is consistent with previous studies finding greater activation of the above regions in trauma controls compared to trauma-exposed women (Bremner et al., 2004). In contrast, women with a history of CIT demonstrated increased activation of inferior parietal cortex, suggesting that they are engaging in word reading, the task-irrelevant process. This is not consistent with previous studies (Bremner et al., 2004). However, previous studies have used block designs consisting of one trial type. Therefore, trauma-exposed individuals may recruit parietal regions more transiently because they are not activated as much
for the duration of the block. Consistent with this explanation, activation in these regions of DLPFC and inferior parietal cortex were positively associated with symptom severity. This is consistent with difficulty internally-directing attention towards a task-set, as this is the only contrast where the target trials actually serve as a reminder of task demands. It has been argued that the conflict inherent in the incongruent trials forces individuals to think about whether they should be identifying the color name by ink or the word, reinforcing the top-down attentional set towards ink color identification. Thus, the presence of the incongruent trials provides environmental support for the task that should be maintained (Kane & Engle, 2003). This suggests that trauma-exposed individuals are better able to use information in their environment to support a top-down attentional set. Our findings from the working memory task also support this explanation. Hypervigilance is one symptom related to using information in the environment to support the top-down attentional set of “be aware of threat.” Additionally, women with a history of CIT activate left IFG (BA 45). Left IFG is involved in word generation and selection from competing semantic representations. There are multiple potential explanations for this finding, including verbalizing what is to be attended to (e.g., “ink color), internally verbalizing the word or the ink color, or choosing from two competing semantic representations of the color. Any of these explanations suggest women with a history of CIT are attending to the salient information and using that information to maintain or bias towards task-relevant goals. Therefore, these patterns suggest women with a history of CIT may use salient reminders in the environment to bias attention or to maintain internally-generated top-down attentional sets.

In contrast to the incongruent trials, women with no history of trauma demonstrated greater activation of left IFG (BA 45) for threat trials than neutral trials in the threat block. One explanation is that activation could be a reflection of verbalizing the threat words, which
compete for attention. Alternatively, as just suggested, this region may be recruited to aid in inhibition (Aron et al., 2004) of the irrelevant, yet attention-capturing, threat words. Both explanations would be consistent with a study by Morey and colleagues (2009) demonstrating threat distractors, as compared to neutral distractors, are associated with greater working memory interference for individuals with no trauma history but not for trauma-exposed individuals. Women with a history of CIT demonstrated greater activation of dorsal medial prefrontal cortex (BA 8) for the threat words than neutral words in the threat block. Dorsal medial prefrontal cortex is related to responding to emotional stimuli (e.g., Lane et al., 1997), making attributions about one’s own emotional state (e.g., Paradiso et al., 1999), and reappraising negative emotions (e.g., Ochsner, Bunge, Gross, & Gabrieli, 2002). Therefore, women with a history of CIT may be having a transient response to the emotional content of the word, despite a top-down attentional set to attend to the ink color and not the threat word. This is in contrast to the women with no history of trauma who demonstrated decreased activation in medial prefrontal cortex as part of top-down control across both emotional blocks.

In summary, some patterns related to top-down cognitive control and transient, reactive cognitive control are suggested by the results. Women with a history of CIT demonstrate more difficulty internally guiding attention and use information in the environment to further recruit mechanisms of top-down control, which is consistent with findings from the working memory task and associated with trauma symptoms. When maintaining a task-set biased away from threat-related information, women with a history of CIT are more likely to process the threat information, whereas women with no history of trauma engaged top-down control to dampen processing emotional stimuli.
Limitations and Considerations

Perhaps the biggest limitation to this study is the sample size. Although previous studies have demonstrated significant differences for both working memory (e.g., Moores et al., 2008) and Stroop (e.g., Bremner et al., 2004) tasks with similar sample sizes, the presence of different patterns of activation for the groups separately but relatively few group differences suggests there is not sufficient power to detect group differences. This is especially true for the Stroop task given that more participants did not have usable data for this task because of movement. With the Stroop task, our ability to detect difference in activation of small volume structures, such as the amygdala, are particularly affected. Additionally, based on posterior activation patterns, it is possible that the working memory task was more difficult for women with a history of CIT than for women with no history of trauma. If this is the case, a larger sample is required because overall activation for the women with a history of CIT may be lower. Therefore, increasing the number of participants per group will allow us to more definitively establish for which processes there are significant group differences as compared to under-recruitment by one group that is not significantly different from the other group. This will allow us to draw more definitive conclusions from the data.

Given that both groups displayed relatively high and equal levels of education and SES, this is a relatively high functioning group of trauma-exposed women. For example, it has been reported that women with a history of childhood sexual abuse are less likely to complete high school (Tolin & Foa, 2006), whereas our sample on average had at least a college degree. Approximately 75% of the women with a history of CIT met criteria for PTSD, suggesting they are experiencing distressing and/or impairing symptoms, yet by more gross measures of functioning they are doing well. Additionally, both groups of women had on average above
average IQ’s, and pre-morbid cognitive functioning is a protective factor after trauma-exposure (Vasterling et al., 2002). Therefore, group differences may be less pronounced because alterations in processing may be more subtle between these two groups of women, or women with a history of CIT in this study are better able to compensate for alterations in processing. Alternatively, it is possible that fewer differences exist, as alterations in cognitive control may be linked to functioning. This may be a group of women that is relatively resilient in the face of trauma and/or psychopathology. Again, a larger sample will help us to better delineate which of these explanations is more accurate.

There are some confounding factors that may also be present and affect the results, including PTSD status, depression, family factors, and witnessing trauma in the home during childhood. In our sample of trauma-exposed women, approximately 75% met criteria for PTSD and 25% did not. It is possible that PTSD status affects the results. However, examination of the data including only women with PTSD compared to women with no history of trauma produced a similar pattern of results as those reported here. It will be necessary in future analyses to directly control for PTSD status. Additionally, there were group differences in reported depressive symptoms. Although there were differences, the average BDI-II score for women with no history of trauma was within normal limits and the average score for women with a history of CIT was in the mild range. This study was focused on the sequelae of exposure to CIT, which includes depression and depressive symptoms. Furthermore, there is overlap between PTSD symptoms and depression (e.g., less sleep than usual on the BDI-II could correspond to middle of the night waking seen in depression or middle of the night waking/fear of going to sleep because of nightmares related to traumatic event). Some frontal regions that have shown aberrant activation in depression include DLPFC, which was seen in this study, and rACC,
which was not seen in this study (Nitschke & Mackiewicz, 2006). As discussed in the introduction, studies examining selective attention and working memory (e.g., Brandes et al., 2002; Gilbertson et al., 2001; Samuelson et al., 200) have found deficits even after controlling for depression. When differences in working memory have been found after controlling for depression, depression was associated mainly with learning and encoding (Johnsen et al., 2007). This study does not involve learning and/or encoding to the extent it does in other working memory studies. Regardless, future analyses should include depression as a covariate, but this should be done once a larger sample is collected. Both the trauma interview and results of the CPICS reveal women with a history of CIT report higher levels of threat related to parental conflict and witnessing domestic violence (referring to either a caregiver or sibling being emotionally or physically abused). Studies have shown that witnessing intimate partner violence does impact children cognitively (Teicher et al., 2006). In the future, it will be important to include groups of participant that have witnessed but not experienced trauma. Unfortunately, we did not have the ability to recruit such a sample for this study.

Lastly, it is also important to note this study does not imply causality between trauma exposure and altered cognitive control mechanisms. Given that approximately 75% of the sample met criteria for PTSD, the observed differences could either be the result of trauma and/or the development of PTSD or risk factors for the development of long-lasting trauma symptoms. We designed this study specifically to examine trauma-exposure during the time period that frontal brain regions, which are involved in cognitive control and implicated in this study, are continuing to develop, and therefore development and exposure likely impact trauma symptoms. However, without a longitudinal design, we cannot know the degree to which these cognitive control regions are risk factors for trauma symptomatology or the result of trauma-exposure. This
study provides a better understanding of what some cognitive control mechanisms may look like in adults with childhood trauma-exposure, and working backwards towards childhood will give us a better understanding of how changes unfold over development.

Conclusion

In conclusion, this study suggests alterations in cognitive control mechanisms underlying both inhibiting and maintaining previous representations in working memory in women with a history of CIT. Additionally, it suggests women with a history of CIT have difficulty maintaining an internally-generated task-set and attend to and process information in the environment to help reinforce task-relevant processing. Alterations in these processes were associated with symptom severity, suggesting that these deficits are related to trauma symptoms. They are consistent with previous findings of altered working memory maintenance and inhibitory networks in trauma-exposed individuals. These findings support the proposal that trauma-exposed individuals demonstrate enhanced attentional allocation to of environmental stimuli in order to guide cognitive control of attention, as well as decreased inhibitory networks supporting inhibition of information that is no longer task-relevant.
CHAPTER 5

REFERENCES


