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NEURAL CORRELATES OF ATTENTION BIAS IN POSTTRAUMATIC STRESS
DISORDER: A fMRI STUDY

by

NEGAR FANI

Under the Direction of Erin B. Tone

ABSTRACT

Attention biases to trauma-related information contribute to symptom maintenance in Posttraumatic Stress Disorder (PTSD); this phenomenon has been observed through various behavioral studies, although findings from studies using a precise, direct bias task, the dot probe, have been mixed. PTSD neuroimaging studies have indicated atypical function in specific brain regions involved with attention bias; when viewing emotionally-salient cues or engaging in tasks that require attention, individuals with PTSD have demonstrated altered activity in brain regions implicated in cognitive control and attention allocation, including the medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (dlPFC) and amygdala. However, remarkably few PTSD neuroimaging studies have employed tasks that both measure attentional strategies being engaged *and* include emotionally-salient information.

In the current study of attention biases in highly traumatized African-American adults, a version of the dot probe task that includes stimuli that are both salient (threatening facial expressions) and relevant (photographs of African-American faces) was administered to 19 participants with and without PTSD during functional magnetic resonance imaging (fMRI). I hypothesized that: 1) individuals with PTSD would show a significantly greater attention bias to

threatening faces than traumatized controls; 2) PTSD symptoms would be associated with a significantly greater attentional bias toward threat expressed in African-American, but not Caucasian, faces; 3) PTSD symptoms would be significantly associated with abnormal activity in the mPFC, dlPFC, and amygdala during presentation of threatening faces.

Behavioral data did not provide evidence of attentional biases associated with PTSD. However, increased activation in the dlPFC and regions of the mPFC in response to threat cues was found in individuals with PTSD, relative to traumatized controls without PTSD; this may reflect hyper-engaged cognitive control, attention, and conflict monitoring resources in these individuals. Additionally, viewing threat in same-race, both not other-race, faces was associated with increased activation in the mPFC. These findings have important theoretical and treatment implications, suggesting that PTSD, particularly in those individuals who have experienced chronic or multiple types of trauma, may be characterized less by top-down “deficits” or failures, but by imbalanced neurobiological and cognitive systems that become over-engaged in order to “control” the emotional disruption caused by trauma-related triggers.

INDEX WORDS: Posttraumatic Stress Disorder, Attention bias, Trauma, fMRI, Amygdala, ACC, dlPFC, vmPFC, Race, Facial expression, Neuroimaging, Cognition

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DISORDER: AN fMRI STUDY

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NEGAR FANI

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

in the College of Arts and Sciences

Georgia State University

2011

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Negar Fani
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Chapter 1: Introduction

Posttraumatic Stress Disorder (PTSD) is a complex psychological disorder that may develop in response to perceived trauma. PTSD is characterized by three clusters of symptoms: re-experiencing of the traumatic event, avoidance of trauma-related stimuli and emotional numbing, and heightened levels of physiological arousal (American Psychiatric Association, 1994). Exposure to multiple traumatic events appears to increase risk for developing this disorder, particularly among individuals living in impoverished environments (Fincham, Altes, Stein, & Seedat, 2009; Liebschutz et al., 2007). Even so, U.S. epidemiological studies indicate that only a minority of traumatized individuals develop PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995).

Given these findings, PTSD researchers have made efforts to better understand factors that play a role in the disorder's development and maintenance. One factor that has garnered attention in the PTSD literature is cognitive processing style. Emotion processing theories (e.g., Foa and Kozak, 1986) suggest that PTSD is characterized by biases in information processing. Specifically, individuals with PTSD appear to treat incoming information differently than do peers without PTSD, in that they demonstrate a tendency to perceive mildly threatening or ostensibly benign stimuli as intensely threatening. It remains unclear, however, whether these biases are most prominent at earlier (i.e., attending and encoding) versus later (i.e., retrieving or interpreting) stages of cognitive processing. A large number of studies have found evidence of memory biases in PTSD (McNally, 1997; Moradi, Taghavi, Neshat-Doost, Yule, & Dalgleish, 2000; see Coles & Heimberg, 2002 for a review). Biases at earlier stages of information processing, such as attention, have also been observed in individuals with PTSD (Buckley, Blanchard, & Neill, 2000).

Although disruptions in attention to neutral stimuli, including letters and numbers, have been documented in individuals with PTSD, using tasks such as the Continuous Performance Test (CPT; Conners, 1992; Vasterling, Brailey, Constans, & Sutker, 1998; Vasterling et al., 2002) and the Wechsler Memory Scale digit span test (WMS; Wechsler, 1987; Brandes, Ben-Schachar, Gilboa, & Bonne, 2002), emotion processing models of PTSD (Foa and Kozak, 1986) suggest that attentional disruptions may be most robustly evident in the presence of trauma-relevant stimuli. To test this hypothesis, researchers have inserted trauma-related stimuli into attentional paradigms such as the Stroop (Stroop, 1935) and dot probe (Mogg & Bradley, 1998). Both paradigms require individuals to filter out interfering emotional cues in order to perform non-emotional attention tasks.

Stroop paradigms involve rapidly naming the colors in which words are printed. PTSD researchers have modified this task to include words related to the traumas their participants have experienced, based on the idea that response latency to naming colors of trauma-related vs. non-trauma-related words provides a measure of processing bias (Thrasher, 1993). Studies using such measures to examine attentional bias in individuals with PTSD have found evidence of extended response latencies to threat-related words in veteran populations (McNally et al., 1990; McNally, English & Lipke, 1993; Kaspi, McNally & Amir, 1995; Vrana, Roodman & Beckham, 1995), rape survivors (Cassiday, McNally, & Zeitlin, 1992; Foa, Feske, Murdock, Kozac, & McCarthy, 1991) and ferry disaster survivors (Dagleish & Yule, 1993).

The dot probe or visual probe task (Mogg & Bradley, 1999) is another experimental paradigm that allows measurement of attentional bias and has several advantages over Stroop tasks. In each trial of a typical dot probe task, a pair of stimuli, one neutral and one emotionally salient (e.g., threatening), appears briefly (500-1500 milliseconds) on a computer screen. Upon

the offset of these images, a probe (an asterisk or set of dots) replaces one of the two images. The viewer must quickly press a button that corresponds to the position of the probe on the screen (left versus right). Faster responses to probes that replace emotionally salient stimuli are thought to reflect biases in visual attention toward emotional cues; faster responses to probes that follow neutral stimuli reflect biases away from emotionally-valenced cues (R.A. Bryant & Harvey, 1997).

Unlike the Stroop, dot probe tasks do not rely on interference to measure bias in attention allocation, and thus provide a more direct measure of visual attention (Mogg & Bradley, 1998). The dot probe also allows for examination of the direction of attention biases: either toward or away from threat. Pictures can be used as stimuli in the dot probe paradigm, eliminating the effortful semantic processing that the Stroop task typically requires. The use of pictorial stimuli, such as human facial expressions, also has the advantage of providing a potentially more ecologically valid method of measuring attention bias in individuals who have suffered interpersonal trauma. The dot probe may thus provide a more precise, directional measure of bias in visual attention than the Stroop, with the further advantage that it can be modified to include stimuli that are both ecologically salient for specific populations.

The few existing studies using variants of the dot probe task to examine attentional biases in individuals with PTSD have yielded mixed findings. Two such studies used words as stimuli. Bryant and Harvey (1997) presented word pairs (neutral/threat-related, neutral/positive, or neutral/neutral) to three groups of adult survivors of motor vehicle accidents: one with PTSD diagnoses, one with subclinical PTSD symptoms, and one that consisted of low-anxious controls. They found that only the PTSD group responded more quickly to probes that replaced words related to driving threat than to probes replacing positive or neutral words, a pattern consistent

with an attentional bias toward threat (Bryant & Harvey, 1997). Dalgleish and colleagues (2003) presented another version of the dot probe, in which they displayed general threat-related or depression-related (e.g., “sad”) words that were paired with neutral words, and found that children and adolescents with PTSD demonstrated a significant bias *away* from depression-related words; however, these participants did not demonstrate a significant bias toward general threat-related words (Dalgleish et al., 2003).

Two other dot probe studies used (unspecified) trauma-related, generally aversive, pleasant, and neutral pictures in a sample of traumatized individuals and healthy controls; the authors found little evidence of any attentional bias associated with PTSD (Elsesser, Sartory, and Tackenberg 2004, 2005). In the first study (Elsesser et al., 2004), mean attention bias scores did not differ significantly among trauma survivors with Acute Stress Disorder (ASD), survivors with chronic PTSD, and healthy controls. However, there were non-significant trends for the ASD group members to direct their attention away from trauma-related pictures more than healthy controls and for participants with chronic PTSD to direct their attention toward trauma-related pictures more than controls (Elsesser, Sartory & Tackenberg, 2004). In the second study (Elsesser et al., 2005), the authors administered a dot probe task to healthy controls and individuals who had recently experienced a variety of traumas to determine whether attention bias scores (among other measures) predicted development of PTSD symptoms 3 months following initial testing. They used unspecified trauma-related pictures as well as generally aversive pictures as dot probe stimuli. The authors found that attention bias was not a significant predictor of PTSD symptoms at time two. However, they also found that traumatized participants demonstrated slower response times to probes that replaced trauma-related pictures, as compared to healthy controls, although attention bias scores did not differ significantly between groups.

Lastly, two recent dot probe studies used photographs of facial expressions to examine attention biases in individuals who had experienced interpersonal trauma; these studies revealed unexpected patterns of attention bias in two distinct populations with PTSD. Pine and colleagues (2005) found that maltreated children (most of whom were diagnosed with PTSD), unlike non-maltreated controls, demonstrated a bias *away* from threatening faces, although small group size prevented comparisons among the three groups (Pine et al., 2005). Fani, Bradley, Ressler and McClure-Tone (in press) also used photographs of facial expressions (posed predominantly by White actors) as dot probe stimuli, and found that attention bias *toward* happy faces was positively associated with PTSD symptoms in a sample of economically-disadvantaged, mostly African-American individuals who had experienced frequent interpersonal trauma.

In sum, the six existing studies that used variants of the dot probe task to examine attentional biases in individuals with PTSD (from different traumatic events) have yielded mixed findings. Studies have indicated biases toward threat (Bryant & Harvey, 1997), biases away from threat (Pine et al., 2005), biases toward happy facial expressions (Fani et al., in press), and three studies demonstrated inconsistent or non-significant patterns of bias (Dalgleish et al., 2003; Elssesser, Sartory, & Tackenberg, 2004, 2005) in different populations with PTSD. One possible explanation for the discrepancies among these findings is variability in the ecological salience of the dot probe stimuli. The two studies that found significant biases for threatening, trauma-related cues (Bryant & Harvey, 1997; Pine et al., 2005) used stimuli that were directly relevant to their respective populations. Notably, however, their findings were in opposite directions; this raises questions about developmental differences in the emergence of biases. The four other existing studies that found inconsistent or non-significant patterns of bias toward threat used stimuli that may have been differentially relevant to their traumatized groups (Dalgleish et al.,

2003; Elsesser et al., 2004, 2005; (Fani, Bradley, Ressler, & McClure-Tone, in press). Stimuli are likely to differ in the responses they elicit from viewers, depending on how emotionally salient and arousing they are to each individual. Consequently, individuals may allocate attentional resources to different stimuli in different ways; for traumatized individuals in particular, stimuli that are too general or are dissimilar from their own trauma experiences may be less effective than more trauma-relevant, and thus presumably more arousing, stimuli in evoking attentional biases. Thus, behavioral research needs to employ dot probe measures that are carefully tailored to the population under study to properly detect any existing biases.

Behavioral methods, however, represent only one way to measure attention bias. More objective methods, including recordings of neural responses associated with attentional changes, provide an additional way to characterize attention bias in individuals with PTSD, and can be used to detect abnormalities in attention to emotional cues that may not be detected behaviorally. This has been demonstrated in studies of other anxious populations; for example, McClure and colleagues (2007) found that adolescents with generalized anxiety disorder did not differ from healthy peers in their subjective ratings of fear while viewing briefly presented expressions of facial emotion. However, using functional magnetic resonance imaging (fMRI) the authors found differences between anxious and non-anxious participants in patterns of neural activation, particularly to fearful faces (McClure et al., 2007). Thus, psychophysiological measures represent alternate methods for obtaining useful information about attentional responses to salient stimuli, and may prove useful in identifying and describing biases. In combination, behavioral and psychophysiological methods may offer a more sensitive and comprehensive means to study attention bias as it is manifest in PTSD than either approach provides in isolation.

Currently, there is a lack of psychophysiological-based attention bias research in PTSD that could inform hypotheses about neural response patterns during attention bias tasks. However, a variety of neuroimaging studies using presentations of facial emotion, aversive imagery, and Stroop tasks during imaging provide a foundation for preliminary predictions about alterations in neural response to threat and other emotional cues in PTSD. One line of research has used functional neuroimaging to measure alterations in hemodynamic response in the brain during the viewing of emotional faces. Other research studies have administered attentional tasks such as the oddball paradigm and modified versions of the Stroop task during imaging to measure changes in BOLD response during presentation of trauma-related cues.

Neural Correlates of Attention to Expressions of Facial Emotion in PTSD

In one line of PTSD research, researchers have used pictures of emotional human facial expressions, which are particularly salient signals in human communication (Ohman, 2002), to elicit neural responses. Specifically, during functional neuroimaging, participants attended to threat-related, neutral, or positive facial expressions, and neural responses to the different expressions were compared (Armony, Corbo, Clement, & Brunet, 2005; Bryant, Felmingham et al., 2008; Bryant, Kemp et al., 2008; Rauch et al., 2000; Shin, Wright, Cannistraro, & al, 2005; Williams, Kemp, & Felmingham, 2006). These expressions have typically been presented for relatively short (up to 500 millisecond) durations, permitting measurement of neural response during early stages of attentional processing. Although these studies have been important in identifying neural alterations during attention to generally-threatening cues in PTSD, the absence of correlating behavioral data has prohibited investigation of attentional strategies that were engaged during scanning. Additionally, these studies largely focused on activation changes within a limited number of brain regions, namely, the amygdala and aspects of the medial

prefrontal cortex (mPFC). The mPFC is a brain region that has been loosely and variably defined in the existing PTSD literature, and the following discussion of these studies highlights the heterogeneity of mPFC regions that have shown altered function in PTSD.

Six studies to date have used fMRI to examine patterns of neural activation to different emotional facial expression types in individuals with PTSD. These studies employed two different presentation strategies: faces were either presented overtly or were displayed via masking techniques. Masking involves brief presentation of an emotional face (often less than 100 ms) immediately before the presentation of a neutral face, a technique that is thought to access more automatic aspects of information processing.

Rauch and colleagues (Rauch, et al., 2000) presented masked happy and fearful faces (emotional faces were presented for 33 ms, neutral face masks for 167 ms) to a group of traumatized participants with and without PTSD. They hypothesized that participants with PTSD, as compared to traumatized controls, would demonstrate significant elevations in activity [as indexed by blood oxygen level dependent (BOLD) response] to masked fearful faces in the amygdala, an area of the brain that has been implicated in the processing of threat-related cues (Phelps & LeDoux, 2005). The authors found that although the group as a whole demonstrated significantly greater left amygdala activation to masked fearful versus happy faces, subjects with PTSD showed stronger amygdala responses to masked fearful faces than subjects without PTSD.

Bryant and colleagues (2008) used a similar masked-face paradigm and found increased responses in both the amygdala and dorsal regions of the mPFC in individuals with PTSD relative to non-traumatized controls; by their definition, the mPFC included both dorsal ACC and medial aspects of the superior frontal gyrus (Bryant, Kemp, et al., 2008). In a PTSD treatment outcome study, patients with PTSD and non-psychiatric controls completed this masked-face

task twice—for patients, at pre- and post-treatment and for controls, before and after an interval of the same length as patients' treatment (Bryant, Felmingham, et al., 2008). Within-group contrasts for the patient group indicated that participants who were not responsive to treatment demonstrated significantly greater pre-treatment amygdala and ventral ACC activation to fearful versus neutral faces than did treatment-responsive participants. At post-treatment, increased ventral ACC and amygdala activity were positively correlated with residual PTSD symptoms. Compared to controls, PTSD participants demonstrated greater amygdala and rostral ACC activity overall to masked fearful versus masked neutral. The authors concluded that greater pre-treatment amygdala reactivity can predict poorer treatment response. They attributed the observed heightened mPFC (specifically, ACC) response (a seemingly unanticipated result that conflicted with findings from earlier PTSD studies) to the masked presentation of the faces, speculating that an unmasked presentation may elicit an opposite pattern of response in the mPFC.

Armony and colleagues (2005) studied a sample of participants with acute PTSD with a similar masked-face task, but also added an unmasked (overt) face display condition (Armony et al., 2005). They found that during the masked condition, PTSD symptoms significantly and positively correlated with right lateral amygdala activity to fearful versus happy faces. They also found that, for this fearful-versus-happy contrast, PTSD scores and amygdala activation were negatively correlated during the unmasked condition. Overall, findings from these studies suggest that threat-relevant faces produce increased amygdala activity in traumatized individuals with PTSD as compared to traumatized controls, and that increases in amygdala activity may correspond with elevations in current PTSD symptoms and poor treatment response.

Two other studies that used overtly presented emotional facial expressions as stimuli yielded evidence of alterations in activity within brain regions associated with affect regulation and cognitive control in participants with PTSD. These regions include the anterior cingulate cortex (ACC), and ventral and lateral aspects of the mPFC. Shin and colleagues (2005) presented pictures of happy, fearful, and neutral faces (for 200ms each) to men with and without PTSD, all of whom had been exposed to combat or firefight trauma (Shin et al., 2005). When comparing patterns of neural activation to fearful versus happy faces, the authors found that traumatized controls demonstrated greater activity in the rostral ACC and ventral and dorsal medial frontal gyri, whereas participants with PTSD demonstrated greater activity in the amygdala, cerebellum and posterior cingulate gyrus. Significant negative associations were also found between right amygdala and dorsal medial frontal gyrus activation in PTSD+, but not trauma control, participants. PTSD symptom severity was negatively correlated with rostral ACC activity.

Williams and colleagues (2006) presented fearful and neutral face stimuli for 500 ms each to participants with PTSD (from either non-sexual assault or motor vehicle accidents) and non-traumatized controls (Williams et al., 2006). When contrasting activation to fearful versus neutral faces, they found less activity in bilateral regions of the medial prefrontal gyrus (Brodmann's area 9/10) and the ventral ACC and greater activity in both the left amygdala and dorsal medial prefrontal gyrus (Brodmann's area 8) in participants with PTSD, as compared to non-traumatized controls. These studies suggest that individuals with PTSD may demonstrate functional alterations within brain regions associated with emotion regulation and inhibitory processes.

Other Studies of Attention and Emotion in PTSD

Three additional functional neuroimaging studies have found alterations in neural responses in participants with PTSD during tasks that combine attention and emotion. Although the mPFC is implicated in all of these studies, the findings from these lines of research further illustrate the heterogeneity of mPFC response (increased versus decreased activation in different aspects of the mPFC) in PTSD versus control groups.

The emotional Stroop task was employed in two PTSD neuroimaging studies (Bremner et al., 2004; Shin et al., 2001). Shin and colleagues (2001) found decreased activation in the rostral ACC, but increased activation in the dorsal ACC, in PTSD relative to control participants in their version of the emotional Stroop. Bremner and colleagues (2004) administered emotional as well as neutral Stroop tasks to a sample of women who had experienced childhood sexual abuse. The authors found that women with PTSD demonstrated decreased activation in regions of the ACC (Brodmann's area 32) in the emotional Stroop condition. However, these changes were only found in a within-group analysis, making it difficult to determine if these changes were more related to the effects of trauma versus post-traumatic psychopathology; interestingly, both groups happened to demonstrate increased activation in regions of the ACC while engaging in a neutral Stroop task.

An fMRI study of veterans with either high or low numbers of PTSD symptoms employed another attentional paradigm, the oddball task, which included shapes as targets and emotionally-salient images as distractors (Pannu Hayes, LaBar, Petty, McCarthy, & Morey, 2009). The oddball task has a simple structure: participants are asked to attend to a target stimulus while ignoring frequently-presented distractors. Like the dot probe, the oddball task may be modified to include emotionally-salient stimuli (as distractors). The authors found that PTSD symptoms were positively associated with vmPFC activity during presentation of

emotional distractors, and that PTSD symptoms were negatively associated with activity in dlPFC regions as participants responded to targets (Pannu Hayes et al., 2009). This study was distinctive in that it included emotionally-salient stimuli in an attentional task; however, because the oddball task is not designed to measure attentional *biases*, per se, it does not provide any information about whether participants with PTSD were vigilant toward or avoidant of threatening or trauma-related stimuli.

Neural Circuits Involved with Attention and Emotion in PTSD

In sum, neuroimaging studies have used various stimuli to examine neural responses during attentional tasks in PTSD, including photographs of facial expressions, presented briefly in masked and unmasked conditions (Armony et al., 2005; Rauch et al., 2000; Shin et al., 2005; Williams et al., 2006), aversive images in an oddball task (Pannu Hayes et al., 2009), and trauma-related words in Stroop tasks (Bremner, et al., 2004); Shin et al., 2001). Research using these paradigms collectively implicates functional alterations in a network of brain regions, including the amygdala and regions of the mPFC, that are associated with attention and emotion processing, in the development and maintenance of PTSD. A brief review of these regions, their known functions and their potential involvement in PTSD, is provided below.

Amygdala. Studies that have examined neural responses to facial expressions in PTSD have largely focused on the role of the amygdala, with particular attention to atypical processing of threat-related cues. The amygdala is a brain structure that plays crucial roles in the acquisition of learned fear responses, a process that is often described as “fear conditioning.” During fear conditioning, a previously neutral stimulus comes to elicit a defensive physiological response (e.g., arousal, hypervigilance) in an individual after being repeatedly paired with a threat-related or aversive stimulus (Phelps & LeDoux, 2005). Some theorists have proposed that individuals

with PTSD demonstrate exaggerated physiological and behavioral responses (e.g., hyperarousal) in response to trauma-related or neutral stimuli as a result of abnormal fear conditioning processes, which are likely to be mediated, at least in part, by the amygdala (Davis, 1992). In support of this hypothesis, Bremner and colleagues (Bremner et al., 2005) found that traumatized women with PTSD demonstrated greater amygdala activation than a non-traumatized control group during a fear acquisition condition (pairings of electrical shock with visual presentation of a shape) versus a control condition (shock was randomly administered, unpaired with shape).

The amygdala is also implicated in the rapid detection and processing of emotionally-salient material; in keeping with this hypothesis, some neuroimaging studies of healthy adult samples have shown that different types of facial emotion elicit increased activation in the amygdala, regardless of the valence of the emotion, when compared to an object-presentation condition (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006). However, findings from many other healthy adult studies suggest that the amygdala may respond more specifically to threat-related (usually fearful) facial expressions (Morris et al., 1996; Whalen et al., 1998).

Some studies of clinical populations suggest that pathologically anxious individuals demonstrate greater amygdala response when attending to pictures of faces conveying threat than do non-anxious controls (McClure et al., 2007). Consistent with this, imaging studies of PTSD show evidence of amygdala hyper-reactivity to threat-related facial expressions (Armony et al., 2005; Rauch et al., 2000; Shin et al., 2005; Williams et al., 2006); when comparing PTSD+ and control groups, these authors found heightened amygdala responses to fearful (versus neutral or happy) facial expressions in PTSD. To summarize, the amygdala has been implicated in fear conditioning and attention to emotion-related cues, particularly for facial expressions, in non-clinical samples. Further, although less consistently, individuals with broadly defined anxiety

disorders have shown amplified amygdala responses to facial threat cues relative to controls. Findings for PTSD appear more robust--individuals with PTSD consistently have shown atypical amygdala function when presented with fear conditioning paradigms and briefly-presented facial expressions that convey threat.

Medial prefrontal cortex (mPFC). The amygdala has received a great deal of attention in the PTSD literature, given its role in fear conditioning and emotion-processing; however, this structure has numerous connections to other brain regions that may serve to modulate amygdala response, including medial prefrontal regions. The medial prefrontal cortex (mPFC) is a functionally heterogenous brain region whose constituent structures include the ACC, medial frontal gyrus, and vmPFC. Regarding the vmPFC, a clear definition of what constitutes this sub-region of the mPFC and its anatomical boundaries is lacking in the existing literature, with some PTSD studies including the anterior PFC (Brodmann area 10; Morey, Petty, Cooper, LaBar, & McCarthy, 2008), inferior frontal gyrus (Pannu Hayes, LaBar, Petty, McCarthy, & Morey, 2009), and ventral aspects of the ACC (vACC; Felmingham, et al., 2009) in their definitions of this region.

These mPFC regions, and particularly ventral mPFC structures, have extensive connections with the amygdala, have been implicated in extinction of the conditioned fear response in both animals (Morgan & Le Doux, 1995) and humans (Phelps, Delgado, Nearing, & LeDoux, 2004). Given evidence that PTSD may be characterized in part by deficits in the extinction of conditioned fear (Rauch, Shin, & Phelps, 2006), mPFC regions merit examination in affected individuals.

Extinction is a type of learning that results when a neutral cue that had been paired with an aversive stimulus during conditioning appears repeatedly in the absence of an aversive

stimulus. This process promotes attenuation of the defensive physiological response observed in fear conditioning (Phelps & LeDoux, 2005). The only published neuroimaging study of fear acquisition and extinction in the context of PTSD demonstrated that individuals with PTSD had less mPFC activation (particularly in the ACC and subcallosal gyrus) during extinction than controls (Bremner et al., 2005).

The mPFC has been highlighted in numerous other functional neuroimaging studies of PTSD (see Rauch et al., 2006 for a review). Findings from these studies, which have used varied tasks to elicit neural activation, suggest that different regions within the mPFC can be differentially activated, depending on the task or type of stimulus used in a task. For example, Pannu Hayes and colleagues (2009) presented an oddball paradigm to patients with high and low levels of PTSD symptoms during MRI scanning. They found that participants with more PTSD symptoms had greater activation in dorsal regions of the ACC to oddball targets and in the vmPFC to emotional distractor images than did participants with fewer PTSD symptoms. Additionally, the high PTSD symptom group showed reduced activity in the middle frontal gyrus to target shapes when compared to the low PTSD symptom group. This study exemplifies how varied task stimuli may differentially activate mPFC structures in individuals with PTSD. However, given the relatively small number of studies that have examined atypical neural responses to attention and emotion in PTSD, there are limits to the generalizations that can be made from these findings regarding how various mPFC regions may be differentially associated with cognitive processes in PTSD.

Summary and Hypotheses

In sum, functional neuroimaging studies have provided important information about atypical neural responses to tasks that involve attention and emotion in individuals with PTSD.

Neuroimaging studies using emotional face stimuli have revealed altered patterns of activation in brain regions that are involved in threat processing and emotion regulation in populations with PTSD. However, there are significant gaps in this literature. First, few neuroimaging studies have measured behavioral responses while participants attend to emotional face stimuli, and they thus offer no way to evaluate attentional strategies that are engaged. Although one study included an attentional task, the oddball paradigm (Pannu Hayes et al., 2009), and two other neuroimaging studies included modified versions of the Stroop task, these studies were limited in that neither task is designed to measure *bias* in attention. Altogether, particularly given evidence of biased attention for threat cues in individuals with PTSD, there is a surprising lack of neuroimaging research in this population that has employed measures of attentional biases for emotionally-salient information.

Therefore, the proposed study was designed to examine performance on a precise and ecologically valid measure of attentional bias, the diverse dot probe (DDP) paradigm, while examining concurrent neural responses in adults with and without PTSD. I administered the DDP, a version of the dot probe modified to increase trauma relevance, during fMRI scanning to a sample of African American adults who had experienced psychological trauma. I used stimuli that were both salient (photographs of emotional facial expressions—threatening, happy, or neutral) and relevant (half of the dot probe stimuli are photographs of African-American faces) to the population under study. Functional MRI was used to obtain information about neural correlates of attentional anomalies predicted to emerge in adults with PTSD during completion of the DDP task.

Specifically, I examined associations among patterns of attention bias, patterns of neural response, and PTSD symptoms in a sample of highly traumatized adults with varying levels of

PTSD symptoms. I hypothesized that: 1) current PTSD symptoms would be positively associated with a significant attentional bias toward threat; 2) participants with current PTSD symptoms would show significantly greater attentional biases (higher mean bias scores) for threat in more relevant (same-race, versus other-race) faces; 3) participants with current PTSD, as compared to traumatized individuals without PTSD, would demonstrate significantly different patterns of neural activation in brain regions associated with attention and emotion processing, including the mPFC (here, I define the mPFC to include the medial frontal gyrus and ACC), vmPFC (I define the vmPFC region to include ventral aspects of the ACC), dlPFC, and amygdala, to threatening versus neutral or happy facial expressions; 4) participants with current PTSD, as compared to traumatized controls, would show significantly different patterns of neural activation in these specified brain regions in response to threat incongruent versus threat congruent trials (a contrast associated with attentional bias to threat); and 5) current PTSD symptoms would be significantly correlated with altered patterns of activity in specified regions of interest in response to threat versus neutral or happy facial expressions.

Method

Study procedures were approved by the institutional review boards of Emory University School of Medicine and Georgia State University, Atlanta, Georgia.

Participants

A total of 26 adult females aged 20-60 years were enrolled in this study; given that all face pairs in the dot-probe task are of female faces, only female participants were recruited to provide an implicit control for gender effects on attentional biases. Participants were recruited through an ongoing collaboration with researchers at Emory University who are conducting

research on risk factors for PTSD in a highly traumatized, low socioeconomic status, urban population. Participants were recruited from the general medical clinics of Grady Memorial Hospital, a publicly funded, not-for-profit healthcare system that serves economically disadvantaged individuals in downtown Atlanta. Patients attending these clinics have been found to exhibit high rates of interpersonal trauma and post-traumatic symptoms that vary considerably in severity (Ressler, Bradley, Cubells, & Binder, 2007).

Patients were deemed eligible for participation if they were able to give informed consent and understand English, as determined by a study researcher. As a part of the parent project, participants were administered the Traumatic Events Inventory (TEI; described below) to detail frequency and type of trauma(s) experienced and the PTSD Symptom Scale (PSS; Falsetti, Resnick, Resick, & Kilpatrick, 1993; described below), to measure frequency of current PTSD symptoms. Based on their responses to the TEI and PSS, potential candidates for the present study were identified and contacted by phone to determine their potential interest in participating in the present study. For the purposes of this study, the PSS was administered again one to two days before scanning procedures to confirm PTSD status; participants were either classified as having current PTSD (PTSD) or no PTSD (Trauma Control--TC) based on DSM-IV criteria (detailed below). Only PSS scores from this specific administration session were included in statistical analyses.

Participants were also screened with a short questionnaire to assess for the presence of these exclusion criteria: current psychotropic medication use, medical or physical conditions that preclude MRI scanning (e.g., metal implants), a history of schizophrenia or other psychotic disorder, a previous diagnosis of a mood or anxiety disorder (for trauma controls), medical conditions that contribute significantly to psychiatric symptoms (such as dementia), history of

head injury or loss of consciousness for longer than 5 minutes, or a history of neurological illness.

Consistent with earlier findings in samples drawn from the same population (Powers, Ressler, & Bradley, 2009), trauma rates were high in the overall sample. All participants had witnessed, experienced, or been confronted with at least two types of trauma (e.g., witnessing violence perpetrated by a stranger; being sexually assaulted by a family member). Traumatized controls experienced a range of 2-7 trauma types, with a mode of 2; PTSD participants experienced a range of 4-10 trauma types, with a mode of 5. Examples of types of traumatic experiences endorsed for both TC and PTSD participants are detailed in Appendix A. Not surprisingly, participants with PTSD experienced significantly more trauma than TCs (Cramer's $V = .64$; $p < .05$). However, no significant differences were found in demographic characteristics between PTSD and TC groups, including age, household monthly income and educational level; demographic and clinical characteristics of this sample are detailed in Table 1.

Total PSS scores for TCs ranged from 0 to 6, with a mean of 2.56 ($SD = 2.51$); total PSS scores for PTSD participants ranged from 14 to 41, with a mean of 24.6 ($SD=9.25$). There were significant differences between PSS scores between PTSD and TC groups, as was expected. However, given the variability in PTSD symptoms both between and within the two diagnostic groups (PTSD+ and TC), continuous measures of current PTSD symptoms (total PSS scores) were also included in regression models to examine how variability in current PTSD symptomatology relates to overall BOLD response for threat versus happy or neutral faces or threat incongruent versus threat congruent face pairs.

Measures

PSS. The PTSD Symptom Scale (PSS; Falsetti, Resnick, Resick, & Kilpatrick, 1993) is a brief self-report questionnaire that provides a measure of re-experiencing, avoidance, and arousal symptoms that have occurred in the 2 weeks prior to test administration. To evaluate for presence and severity of PTSD symptomatology, the PSS was administered orally by trained clinicians. This administration approach is intended to decrease potential confounds introduced by literacy problems common to the population under study.

The PSS includes items such as: “Have you had recurrent or intrusive distressing thoughts or recollections about the event(s)?” and “Have you persistently been making efforts to avoid activities, situations, or places that remind you of the event(s)?” Participants will be asked to rate frequency and severity of 18 such symptoms using a Likert-type scale. Frequency ratings range from 0 (not at all) to 3 (5 or more times per week/very much/almost always); severity ratings range from 0 (not at all distressing) to 4 (extremely distressing). A final question assesses how long symptoms have been present (<1 month to \geq 1 year). Separate severity and frequency scores can be obtained from this measure (only frequency will be used in this study), and scores can be classified as either dichotomous or continuous variables. Falsetti and colleagues (1993) report that on this measure, typical total scores for individuals with PTSD fall between 46 and 71 points. The PSS has good concurrent validity with the PTSD module of the structured clinical interview for DSM-III-R (Falsetti et al., 1993). The PSS also has adequate reliability; Foa and colleagues (1993) reported a Cronbach’s α of .91 for the total scale and a 1-month retest reliability of .74 (Foa, Riggs, Dancu, & Rothbaum, 1993).

The PSS was administered by a study researcher one day prior to the participant’s scan. For the purposes of this study, participants were classified as PTSD+ if they endorsed the presence of one or more symptom in the re-experiencing cluster (items 1-4); three or more

symptoms in the avoidance and numbing symptom cluster (items 5-11) two or more symptoms in the hyperarousal cluster (items 12-17); and symptom duration of 3 months or longer (as measured by question 18), in keeping with DSM-IV criterion for PTSD.

TEI. The Traumatic Events Interview (TEI) is a clinician-administered questionnaire developed for the purposes of the parent project to assess number and type of traumatic events the participant has experienced in their lifetime. This measure includes 19 questions about a range of potential traumatic events, including “Have you experienced a sudden life-threatening illness?” and “Have you witnessed a family member or friend being attacked without a weapon?” For each question, the TEI queries frequency of occurrence and age at onset of the “worst” incident. Collection of reliability and validity data for the TEI is underway (Ressler, Bradley, Cubells, & Binder, 2007). For the purposes of this study, only frequency of trauma type(s) experienced was reported.

Dot Probe Task (Mogg & Bradley, 1999). The dot probe is a computerized behavioral task that requires participants to respond rapidly to a behavioral cue in the context of information that is emotional or neutral in nature. The task was presented during neuroimaging using E-prime software, version 1.1 (Psychology Software Tools, Inc.). Each trial began with the presentation of a central fixation cross for 500 ms. Subsequently, a pair of face photographs (both of the same actor) were presented for 500 ms. In each face pair, one face displays an emotional expression (either threatening or happy) and the other a neutral expression. After the offset of the face pair, an asterisk was presented in place of one of the faces. Participants indicated as quickly as possible with a forced-choice button press response whether the asterisk appeared on the left- or right-hand side of the screen. To facilitate investigation of between-group differences in neural response to threatening, happy, and neutral faces (posed by either an African American or a

Caucasian model), forty blank trials were also presented as implicit baseline trials. This task consisted of 200 randomly ordered trials (64 positive-neutral face pairs, 64 threat-neutral face pairs, 32 neutral-neutral face pairs, and 40 blank trials). The faces used in this task were selected from three separate sets of stimuli; Black faces were selected from the Center for Productive Aging (Minear & Park, 2004) and NimStim (Tottenham, et al., 2009) databases and White faces were selected from a commonly-used version of the dot probe (Bradley, Mogg, & Lee, 1997). A total of 50% Black and 50% White face pairs were used in this version of the dot probe.

The probe replaced emotionally-valenced stimuli during half of the trials and replaced neutral stimuli during the other half of the trials. During neutral-neutral trials, the probe appeared on the left or right side of the screen an equal number of times. Emotion bias scores were calculated by subtracting response time to emotion-incongruent stimuli (probes that replace neutral pictures) from response time to emotion-congruent stimuli (probes that replace happy or threatening pictures). These bias scores were further decomposed into threat and happy bias scores, both for all stimuli of each emotion type combined and separately for African American and Caucasian face pairs. Although various versions of dot probe tasks have been used in experimental settings, no published data regarding reliability are available. However, findings from prior research suggest that this class of measures validly discriminates between anxious and non-anxious adults and youth (Bradley, Mogg, White, Groom, & de Bono, 1999; Mogg, Philippot, & Bradley, 2004; Pine et al., 2005; Wilson & MacLeod, 2003).

Ecological validity of the modified dot-probe task. As described by Bordens and Abbott (1991), measures with adequate ecological validity reflect “what people must do in real-life situations” (Bordens & Abbott, 1991). To enhance ecological salience of the dot probe with this population, we modified the task from its original version (Bradley, et al., 1997) to include 50%

African-American face pairs and 50% Caucasian face pairs. Because a large proportion of individuals within this population live in racially homogeneous neighborhoods, they are likely to interact more frequently with same-race (African-American) individuals than individuals of other racial backgrounds. Consequently, the likelihood that they will experience interpersonal trauma involving same-race individuals is elevated; the inclusion of both same-race and different-race images is intended to heighten the trauma-relevance of the DDP task. Further, photographs of facial expressions, rather than printed words, were included as task stimuli because of concerns about low literacy rates and limited educational attainment in this population (Gillespie et al., 2009).

Behavioral data analyses. Bivariate correlations were computed between attention bias scores and PSS total and subscale scores (re-experiencing, avoidance/numbing, and hyperarousal). To examine between-group (PTSD+ versus traumatized control) differences in mean attentional bias score for same-race (African-American) and other-race (Caucasian) faces, a repeated measures analyses of variance (ANOVA) was conducted, with diagnostic group as the independent variable and bias scores (for threatening and happy facial expressions; African-American and Caucasian faces) as the dependent variables. A threshold of $p < .05$ was used to determine statistical significance for all behavioral data analyses.

fMRI procedures. On the day prior to scanning, each participant was familiarized with the dot probe task and the MRI response box and completed an MRI screening checklist (see Appendix A) to ensure safety. Scanning took place on a research-dedicated Siemens 3-Tesla scanner at Emory University Hospital. On the scan day, study personnel reviewed the MRI and dot probe task procedures with each participant; participants were then asked to remove all metallic objects from their person and enter the scanner room. Participants were asked to recline

in a supine position on the scanner bed, their heads were placed in a radiofrequency coil, and foam padding was placed around participants' heads to minimize movement during the scan. Magnet noise was suppressed by a headphone-like hearing protection device placed over participants' ears. Participants were able to view task stimuli via an adjustable mirror affixed to the radiofrequency coil; the mirror reflected a computer screen located at the end of the MRI aperture.

At the start of the scanning process, a shimming procedure was conducted in order to generate a constant, homogenous magnetic field. This was followed by a short calibration scan. Next, a high-resolution T1-weighted structural scan was acquired using a magnetization-prepared rapid acquisition with gradient echoes (MPRAGE) sequence (176 slices, field of view= 256 mm cubic voxels; 1 x 1 x 1 mm slice; TR = 2600ms; TE = 3.02 ms; TI = 900ms; flip angle = 8 degrees).

Following structural scan acquisition, participants were given time to review instructions for the dot probe task. After participants indicated comprehension of the instructions, functional scan acquisition began, as the dot probe task was triggered by the start of image acquisition. Participants viewed a screen that displayed the words "Get Ready" for 4 seconds, which was followed by task trials; the data acquired during this "Get Ready" screen served as a control for saturation effects and were discarded during image processing. A total of 26 contiguous echo-planar, T2 weighted images parallel to the anterior-posterior commissure line were acquired with a Siemens 3T scanner (TR = 2530 msec; TE = 30 msec; field of view = 240 mm; 64 x 64 matrix; 3.75 x 3.75 x 4.0 mm voxel).

fMRI data processing and analyses

Before images were pre-processed, all DICOM formatted files were converted to Analyze format using the Utilities function in Statistical Parametric Mapping, version 5 (SPM5, Wellcome Department of Neurology, London, UK: <http://www.fil.ion.ucl.ac.uk/spm/>). Next, functional images were slice-time corrected with a high-pass filter applied. Functional images were then realigned to the first image in the session to correct for motion. The mean of the realigned undistorted images was then coregistered with the structural T1 volume, spatially normalized to standardized Montreal Neurological Institute (MNI) space based on the position of the anterior and posterior commissure and, finally, smoothed with an 8mm FWHM Gaussian kernel.

To examine BOLD signal change to task stimuli, a first-level, fixed-effects analysis was conducted by creating vectors for onset time of each condition, including threat/neutral probe congruent, threat/neutral probe incongruent, happy neutral probe congruent, happy/neutral probe incongruent, and neutral/neutral. Given my hypothesis that PTSD+ participants, relative to TCs, would demonstrate atypical neural responses in the amygdala, mPFC, and dlPFC while demonstrating attentional biases for threat, threat incongruent conditions (probe appeared on the opposite side of the threatening face) versus threat congruent conditions (probe appeared in the location of the threatening face) and threat/neutral conditions minus both happy/neutral and neutral/neutral face pair conditions (combined) were the primary t-contrasts for examining BOLD signal change to each trial, which included face pair presentation and probe; the threat incongruent minus threat congruent contrast was modeled after a previous dot probe study investigating attention biases in anxious children and adolescents (Telzer, et al., 2008). In order to create models for these comparisons, box-car functions using 1, -1 contrast conventions were used to indicate voxels that had a higher activation level for a contrast condition (e.g., threat-

incongruent minus threat-congruent). Regression analyses were also conducted, in which PSS total score served as a predictor of hemodynamic response for threat incongruent minus threat congruent conditions and threat/neutral minus happy/neutral and neutral/neutral conditions (combined). Specifically, hemodynamic response for each comparison condition served as a dependent variable in each general linear model.

Contrasts based on the race of face stimuli were also established to address my hypothesis that participants with current PTSD symptoms would show atypical patterns of neural response in the mPFC, dlPFC, and amygdala that may be indirectly associated with attentional biases for threat in same-race versus other-race faces. To examine potential alterations in neural activity when viewing same-race or other-race faces, a contrast for Black faces (all expressions) minus White faces (all expressions) was first established. Next, to examine potential differences in neural response associated with attention for threat in Black faces versus White faces, within participants in the entire sample and between PTSD and TC groups, a contrast of Black threat/neutral versus White threat/neutral face pairs was established. Finally, two other contrasts were constructed to examine neural responses that may be indirectly associated with attentional biases for threatening Black faces and threatening White faces: Black threat incongruent versus Black threat incongruent face pairs; and White threat incongruent minus White threat congruent faces pairs.

Random-effects, between-groups analyses were conducted to compare brain-wide responses between groups using paired-sample t-tests. Standard whole-brain analyses were used to examine patterns of activation between PTSD and TC groups for each contrast using paired t-tests. A statistical threshold of $p < .005$ (uncorrected) and an extent threshold of ≥ 5 voxels per cluster were used to determine significant activations in the whole-brain analysis. A non-linear

transformation (<http://www.bioimagesuite.org/Mni2Tal/index.html>) was used to transform coordinates from MNI to Talairach (Rajeevan & Papademetris), and a Talairach daemon (Lancaster, et al., 2000) was used to localize anatomical coordinates of voxels associated with statistically significant patterns of BOLD activation.

Power Analysis

Behavioral data. A power analysis was conducted to determine sample size for this study using effect size for attention bias scores. Samples sizes were determined based on power analyses conducted using a computerized power calculator (<http://www.dssresearch.com/toolkit/spcalc/power.asp>).

Prior neuroimaging research examining associations between attention bias and anxious psychopathology in a sample of patients with generalized anxiety disorder and healthy controls yielded an effect size of $d = -0.64$ for behavioral effects (Monk et al., 2006). In order to achieve an 80% probability of detecting effects of this size when alpha is set at .05, 26 participants are needed.

fMRI. A power calculator for fMRI research is available online <http://www.fmripower.org/>. However, power calculations conducted with this application require data from earlier image analyses (conducted with FSL software) in addition to an ROI-based approach to produce results. Given the lack of data from prior studies on which to base effect size calculations, as well as the whole-brain statistical approach of this study, sample size estimates for fMRI were made based on earlier imaging studies of attention to emotional faces in PTSD that found significant differences in BOLD activation in different brain regions between PTSD and control groups (Armony et al., 2005; S.L. Rauch et al., 2000; Shin et al., 2005; Williams et al., 2006; Bryant, Felmingham et al., 2008; Bryant, Kemp et al., 2008). The sample

sizes in these studies ranged from 13 (Armony et al., 2005) to 30 (Bryant, Kemp et al., 2008). Given these sample sizes and financial limitations of this study, a minimum sample size of 24 participants was proposed for this study, comprising 12 PTSD+ participants and 12 traumatized controls.

Results

Behavioral Results

Dot probe behavioral data from one participant were not included in statistical analyses due to a high number of missed trials (38%). A univariate ANOVA of the remaining sample revealed no significant differences in age between PTSD+ and TC groups ($F_{1,16}=.01$, $p = .94$). Age did not significantly correlate with error rate on trials ($r = -.34$, $p = .18$) or mean response time ($r = .37$, $p = .12$). Distributions of attention bias scores were inspected and assumptions of normality were met for both threat and happy bias scores.

Correlational analyses yielded no evidence to support the hypothesis that current PTSD symptoms would be positively associated with a significant attentional bias toward threat to either Black or White faces. Bivariate correlations revealed no statistically significant associations between PSS total and subscale scores and attention bias scores (overall or for Black or White faces); there were also no significant associations between depressive symptoms and attentional biases for threat (see Table 2). Means and standard deviations for attention bias scores are detailed in Table 3.

Similarly, between-group analyses revealed no significant differences in mean attentional bias for threat between PTSD and TC groups. Univariate ANOVAs were used to

compare mean attention bias scores (threat bias and happy bias) between PTSD+ and TC groups; no significant between-group differences were found for attentional bias for threatening or happy faces ($p > .05$). A 2 x 4 repeated measures analysis of variance (ANOVA) was used to compare mean attention bias scores for Black and White threatening or happy faces between diagnostic groups (PTSD+, TC). Attention bias scores did not significantly vary between PTSD+ and TC groups: Wilks = .91, $F(3, 14) = .46$, $p > .05$.

Chi Square analyses comparing PTSD+ and TCs with positive versus negative bias scores revealed no significant differences for overall threat bias ($\chi^2 = 1.27$, $p > .05$), happy bias ($\chi^2 = .46$, $p > .05$), or threat bias for White ($\chi^2 = .038$, $p > .05$) faces. A trend toward significance was found between groups for threat bias for Black faces ($\chi^2 = 2.77$, $p = .1$)

fMRI Results

Functional MRI data from 7 subjects were not available or were excluded from analyses due to: excessive motion artifact ($n=1$), gross abnormalities in brain parenchyma ($n=3$), and inability to tolerate scan procedures ($n=3$); a total of 19 participants (10 PTSD+, 9 TC) were included in final statistical analyses of fMRI data. No significant differences were found between bias scores obtained from behavioral data within the overall sample ($N = 23$) and the final sample included in fMRI data analyses ($N = 19$, $p > .05$).

Patterns of neural activation associated with threat cue context: Threat incongruent versus threat congruent trials. To test the hypothesis that individuals with PTSD, relative to TCs, would demonstrate atypical patterns of neural activation in the mPFC, amygdala, dlPFC in association with attention to threatening faces (Black and White, combined), a whole-brain analysis was conducted using a contrast of threat incongruent (probe appeared in the location of the neutral

face) versus threat congruent (probe appeared in the location of the threatening face) versus trials. Contrary to expectations, there were no statistically significant differences in activation between PTSD and TC groups in these *a priori* specified regions. However, participants with PTSD, relative to traumatized controls, demonstrated increased bilateral activation in the superior parietal lobe in this contrast condition (see Figures 1 and 2 and Table 4). For the same contrast condition, traumatized controls, relative to PTSD participants, demonstrated increased activation in the right insula and bilateral caudate (see Figures 3 and 4, and Table 4).

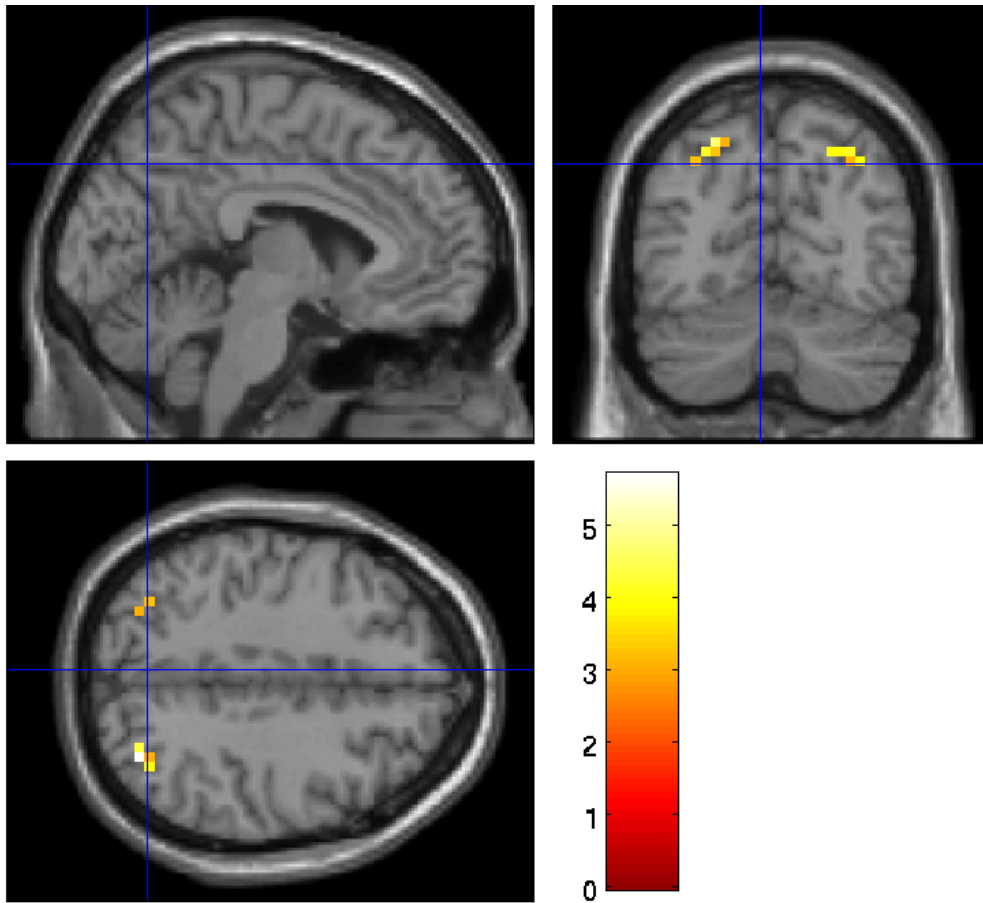


Figure 1. Threat incongruent versus threat congruent, PTSD > TC. Statistical parametric map of brain activation during the processing of Threat incongruent face pairs relative to Threat congruent face pairs in PTSD relative to TC participants. Activations are shown overlaid onto an averaged structural MRI. Color bar represents t scores for activations. Maximally activated voxel in right parietal lobe: $x = 33$, $y = -68$, $z = 40$, $t = 5.69$, 10 voxels, $p < 0.005$ (uncorrected). All neuroimaging data are reported using the coordinate system of Talairach and Tournoux.

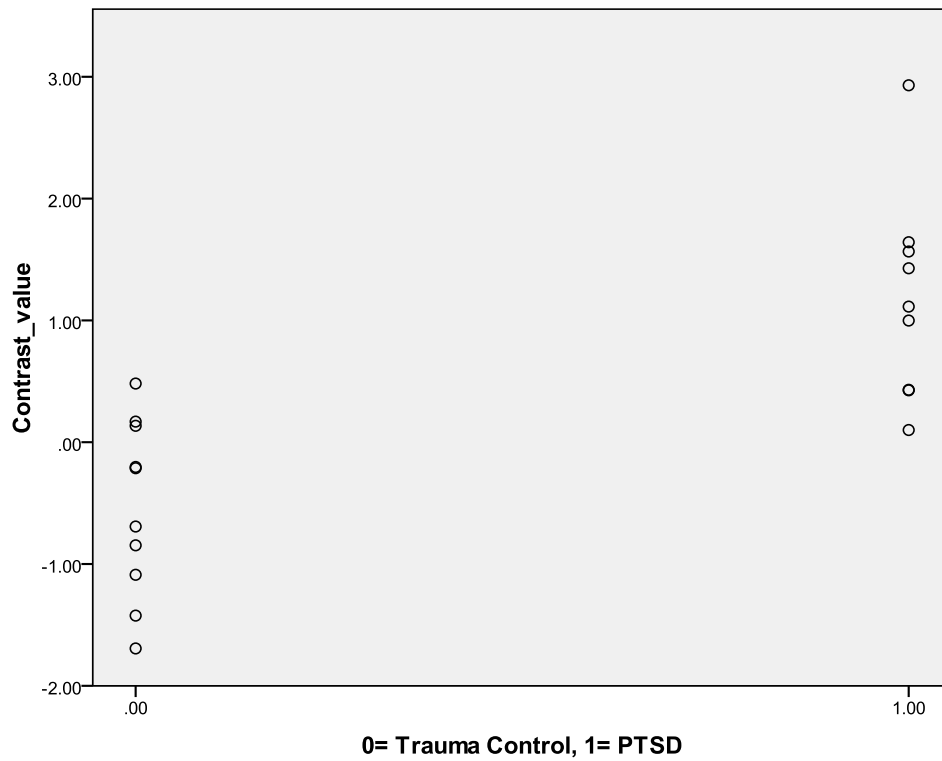


Figure 2. Contrast values indicating peak voxel activation (Talairach coordinates: 33, -68, 40, right parietal lobe) in PTSD versus trauma control participants for the threat incongruent > threat congruent contrast condition.

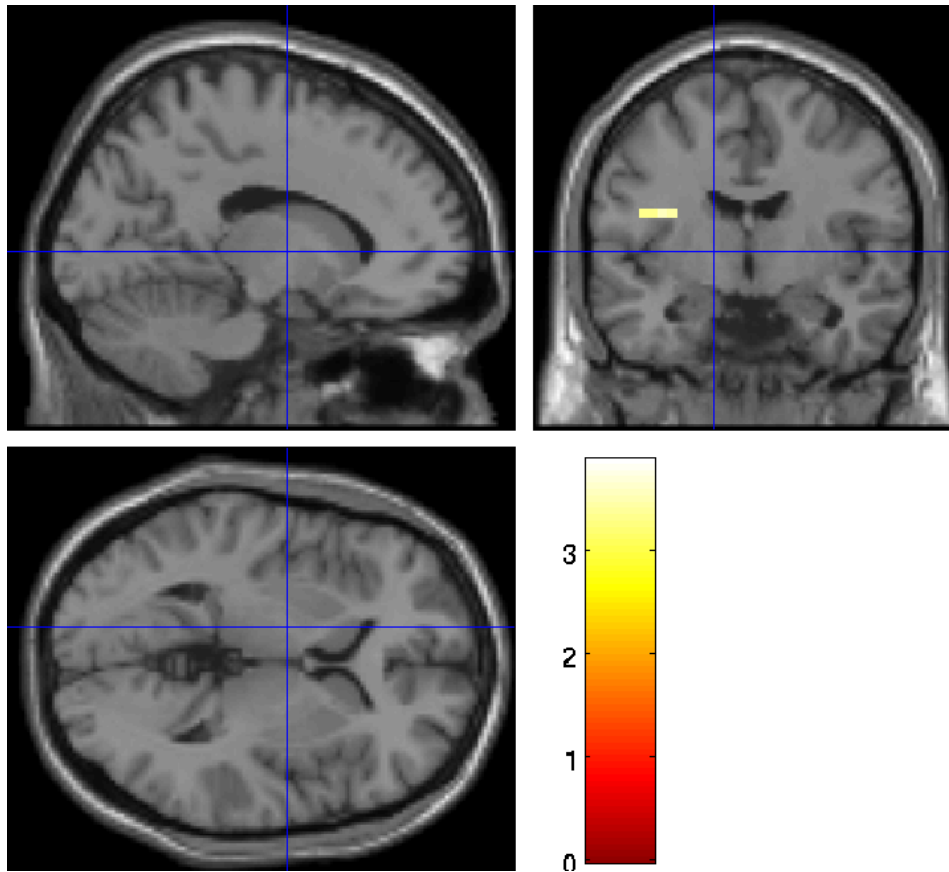


Figure 3. Threat incongruent versus threat congruent, TC > PTSD. Statistical parametric map of brain activation during the processing of Threat incongruent face pairs relative to Threat congruent face pairs in TC > PTSD participants. Activations are shown overlaid onto an averaged structural MRI. The colored bar represents t scores for activations. Maximally activated voxel in left insula: $x = -34$, $y = -12$, $z = 20$, $t = 3.87$ voxels, $p < 0.005$ (uncorrected). All neuroimaging data are reported using the coordinate system of Talairach and Tournoux.

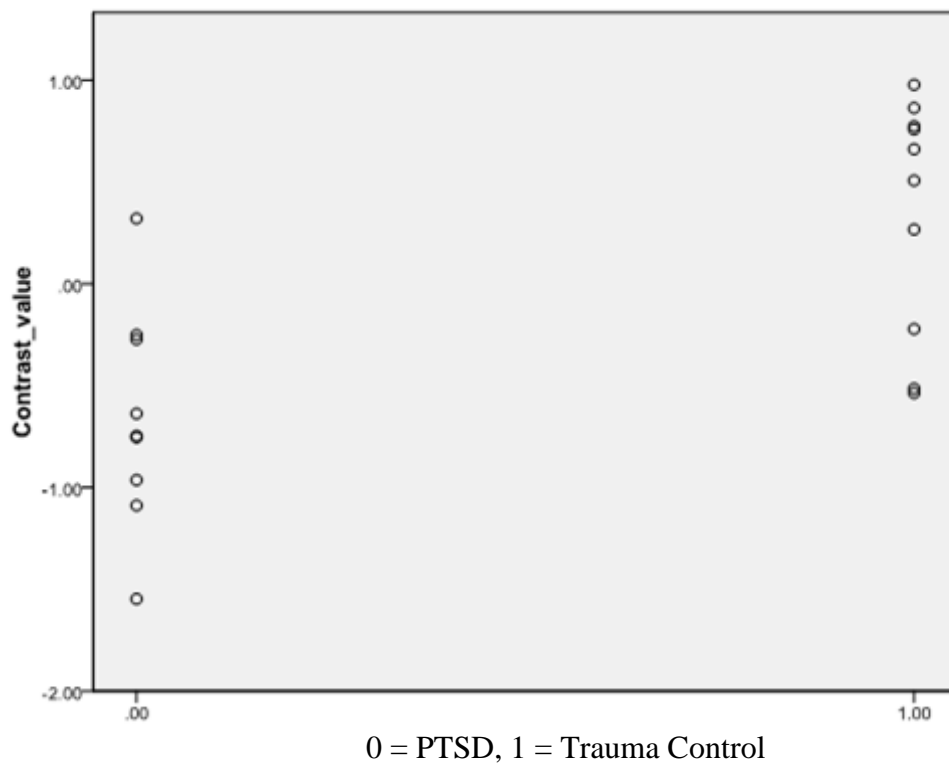


Figure 4. Contrast values indicating peak voxel activation (Talairach coordinates: -34, -12, 20, left insula) in TC versus PTSD participants for the threat incongruent versus threat congruent contrast condition.

Patterns of neural activation associated with threat presentation: A contrast of threat/neutral versus happy/neutral and neutral/neutral face pairs, combined. To test the hypothesis that individuals with PTSD, relative to TCs, would demonstrate atypical patterns of neural activation in the mPFC, amygdala, and dlPFC during the presentation of threatening faces, a whole-brain analysis was conducted using a contrast of threat/neutral versus happy/neutral and neutral/neutral trials, combined. As expected, participants with PTSD, relative to traumatized controls, demonstrated significantly greater activation to threat in some *a priori* specified regions, including dorsal aspects of the middle cingulate gyrus and right medial frontal gyrus. Additionally, significant increases in activation were found in other brain regions, including the left superior temporal gyrus, left cerebellum, right inferior parietal lobe, left middle temporal gyrus, left substantia nigra, and left inferior temporal gyrus in participants with PTSD relative to TCs; see Figures 5 and 6, Table 4. For the same contrast condition, traumatized controls, relative to PTSD participants, demonstrated increased activation in the anterior lobe of the left cerebellum; see Figure 7, Table 4.

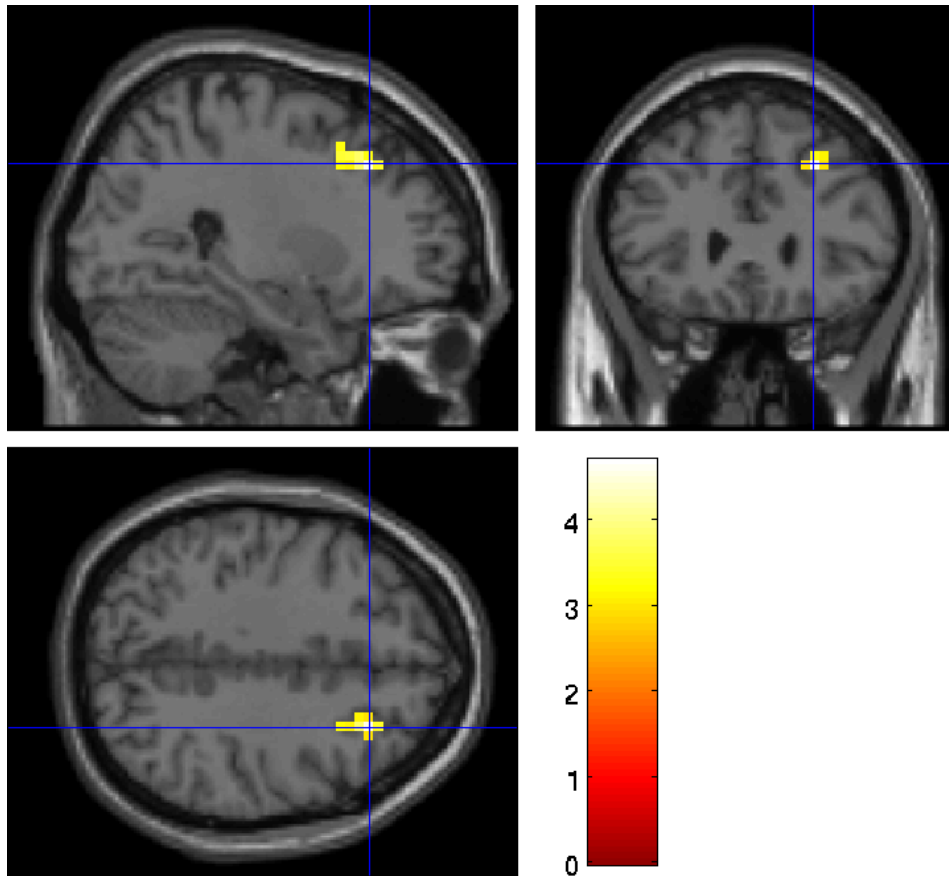


Figure 5. Threat/neutral versus happy/neutral and neutral/neutral face pairs, combined, PTSD > TC. Statistical parametric map of brain activation during the processing of Threat/neutral face pairs relative to happy/neutral and neutral/neutral face pairs in PTSD > TC participants. Activations are shown overlaid onto an averaged structural MRI. The colored bar represents t scores for activations. Figure illustrates a peak voxel cluster in the right middle frontal gyrus: $x = 28$, $y = 29$, $z = 38$, $t = 4.47$, 18 voxels, $p < 0.005$ (uncorrected). All neuroimaging data are reported using the coordinate system of Talairach and Tournoux.

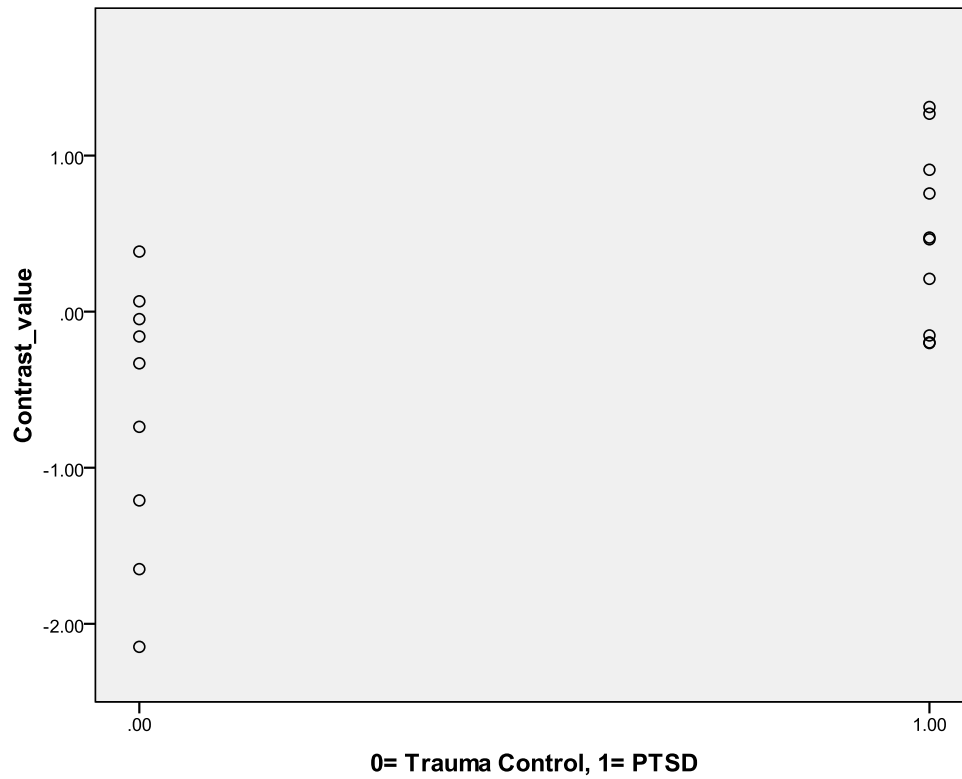


Figure 6. Contrast values indicating peak voxel activation (Talairach coordinates: 8, -5, 47, right cingulate gyrus) in PTSD versus TC participants for the threat/neutral versus happy/neutral and neutral/neutral contrast condition.

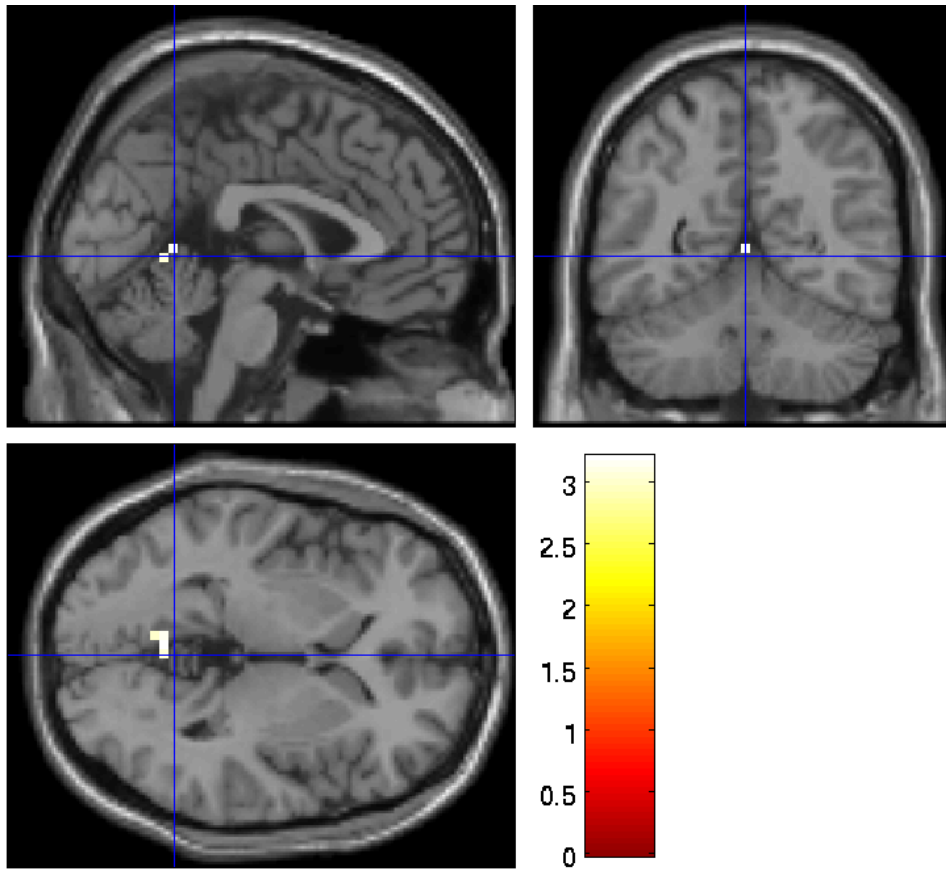


Figure 7. Threat/neutral versus happy/neutral and neutral/neutral face pairs, TC > PTSD. Statistical parametric map of brain activation during the processing of threat/neutral face pairs versus happy/neutral and neutral/neutral face pairs for TC > PTSD participants. Activations are shown overlaid onto an averaged structural magnetic resonance image. The colored bar represents t scores for activations. Maximally activated voxel: $x = -3$, $y = -59$, $z = 4$, $t = 3.2$, 5 voxels, $p < 0.005$ (uncorrected). All neuroimaging data are reported using the coordinate system of Talairach and Tournoux.

Patterns of neural activation associated with threat cue context: PSS as a predictor of activation to threat incongruent versus threat congruent face pairs. A simple linear regression was conducted to examine how variability in current PTSD symptomatology related to alterations in neural activation in specified brain regions for threat incongruent versus threat congruent faces, with total PSS score as a predictor of neural activation to threat incongruent versus threat congruent face pairs. As predicted, total PSS score was positively associated with increased activation to threatening faces in some *a priori* specified regions of interest, including the left medial frontal gyrus; significant increases in activation were also found in the left superior frontal gyrus see Figures 8 and 9, Table 4. R square (for left medial frontal gyrus cluster) = .433, $p = .002$. No significant correlation was found between attention bias score (any type) and peak voxel activation for this contrast condition.

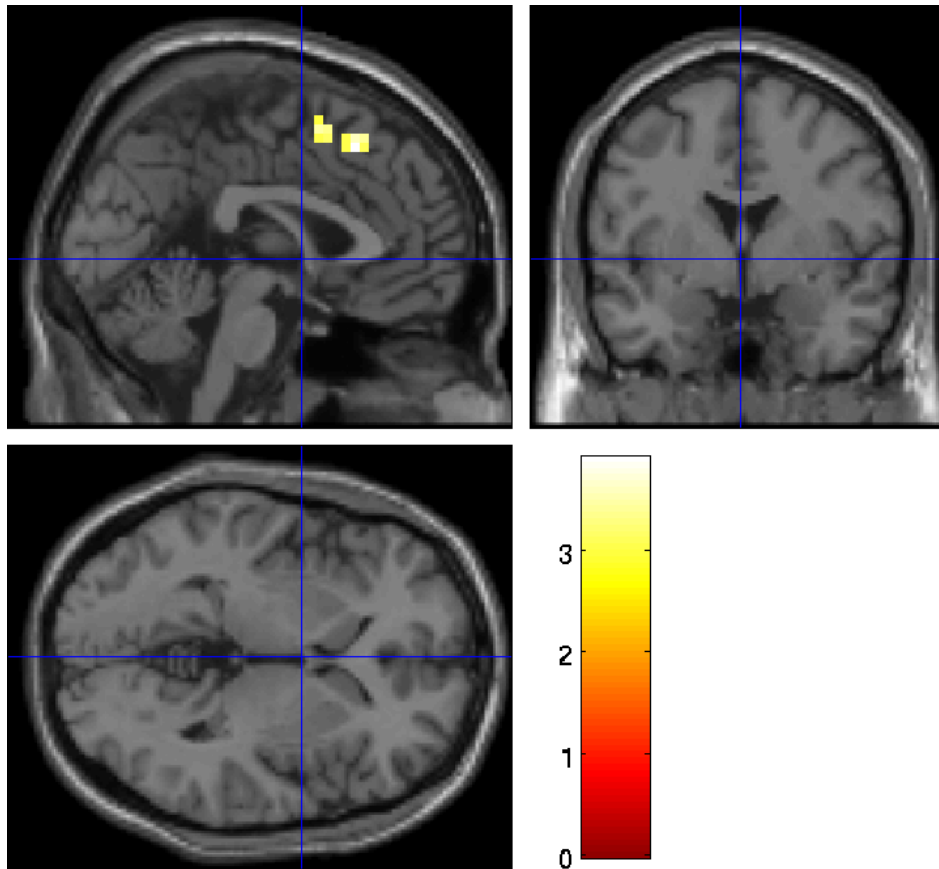


Figure 8. PSS total score predicts neural activation to threat incongruent versus threat congruent trials. Statistical parametric map of increases in neural activation corresponding with increases in total PSS score during the processing of threat incongruent versus threat congruent trials. Activations are shown overlaid onto an averaged structural MRI. The colored bar represents t scores for activations. Figure illustrates maximally activated voxel cluster at left medial frontal cortex: $x = 0$, $y = 26$, $z = 44$, $t = 3.9$, 9 voxels, $p < 0.005$ (uncorrected). All neuroimaging data are reported using the coordinate system of Talairach and Tournoux.

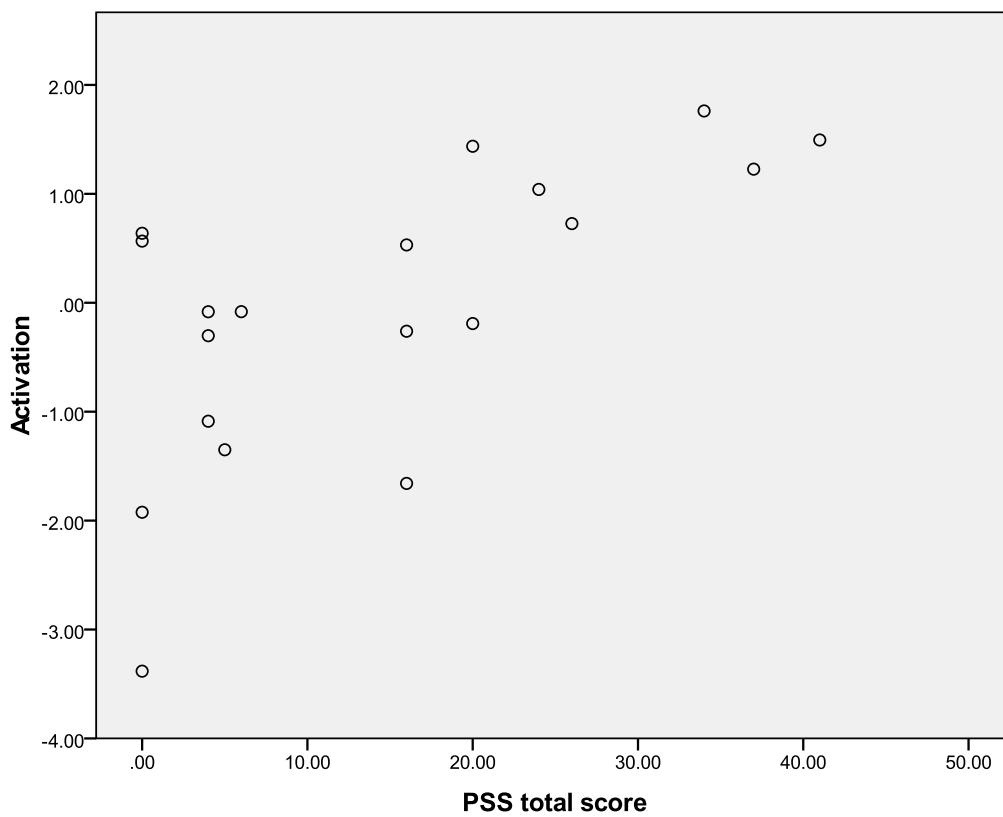


Figure 9. Contrast values indicating peak voxel activation (Talairach coordinates: 0, 26, 44, medial frontal gyrus) that corresponds with increases in PTSD symptoms for the threat incongruent versus threat congruent contrast condition.

Patterns of neural activation associated with threat presentation: PSS as a predictor of activation to threat/neutral versus happy/neutral and neutral/neutral face pairs, combined.

Another regression analysis was conducted to test the hypothesis that current PTSD symptoms would be associated with atypical BOLD response in specified brain regions during trials that presented threatening versus happy or neutral emotional expressions. In a simple linear regression with total PSS score as a predictor of neural activation to threat/neutral versus happy/neutral and neutral/neutral face pairs combined, total PSS score was positively associated with increased activation in some *a priori* specified regions of interest, including the right medial frontal gyrus (dorsolateral prefrontal cortex) and the right middle frontal gyrus (see Figures 10 and 11, Table 4). Increased activation was also found in other brain regions, including the left superior temporal gyrus, left middle temporal gyrus, and bilateral cerebellum. R square (for dorsolateral PFC cluster) = .48, $p = .001$. No significant correlation was found between attention bias score (any type) and peak voxel activation for this contrast condition.

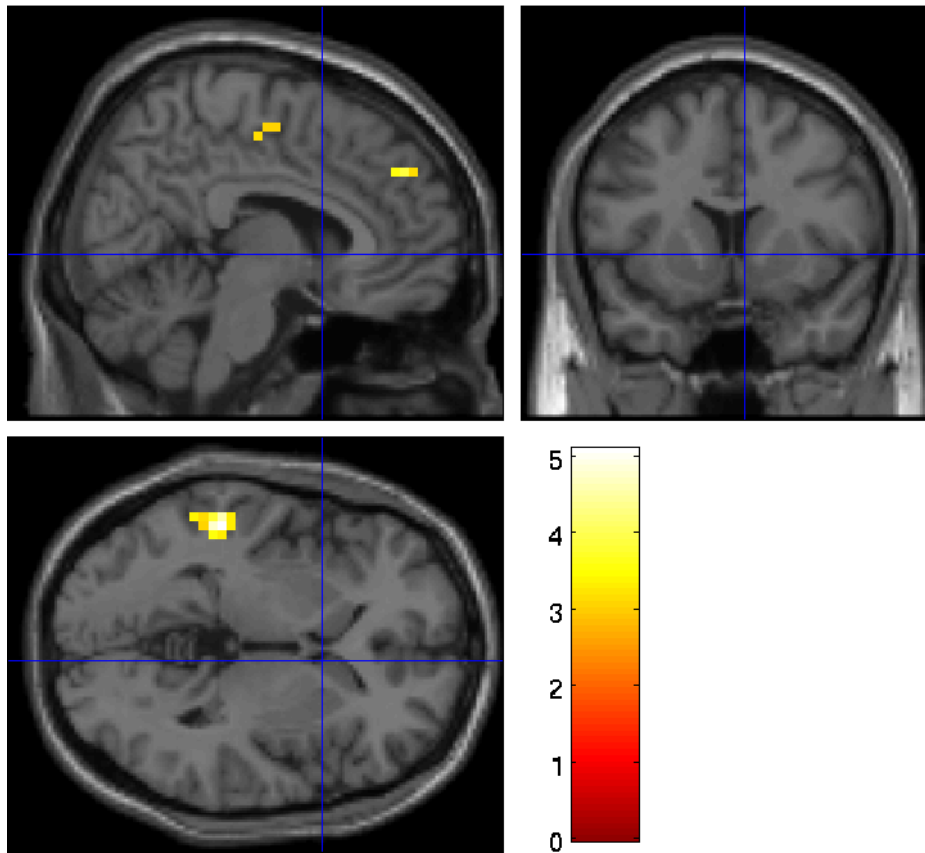


Figure 10. PSS total score predicts neural activation to threat versus happy and neutral faces (combined). Statistical parametric map of increases in neural activation corresponding with increases in total PSS score during the processing of threat/neutral faces versus happy/neutral or neutral/neutral face pairs. Activations are shown overlaid onto an averaged structural MRI. The colored bar represents t scores for activations. Maximally activated voxel at the superior temporal gyrus: $x = -49$, $y = -32$, $z = 4$, $t = 5.08$, 18 voxels, figure presented at $p < 0.005$ threshold. All neuroimaging data are reported using the coordinate system of Talairach and Tournoux.

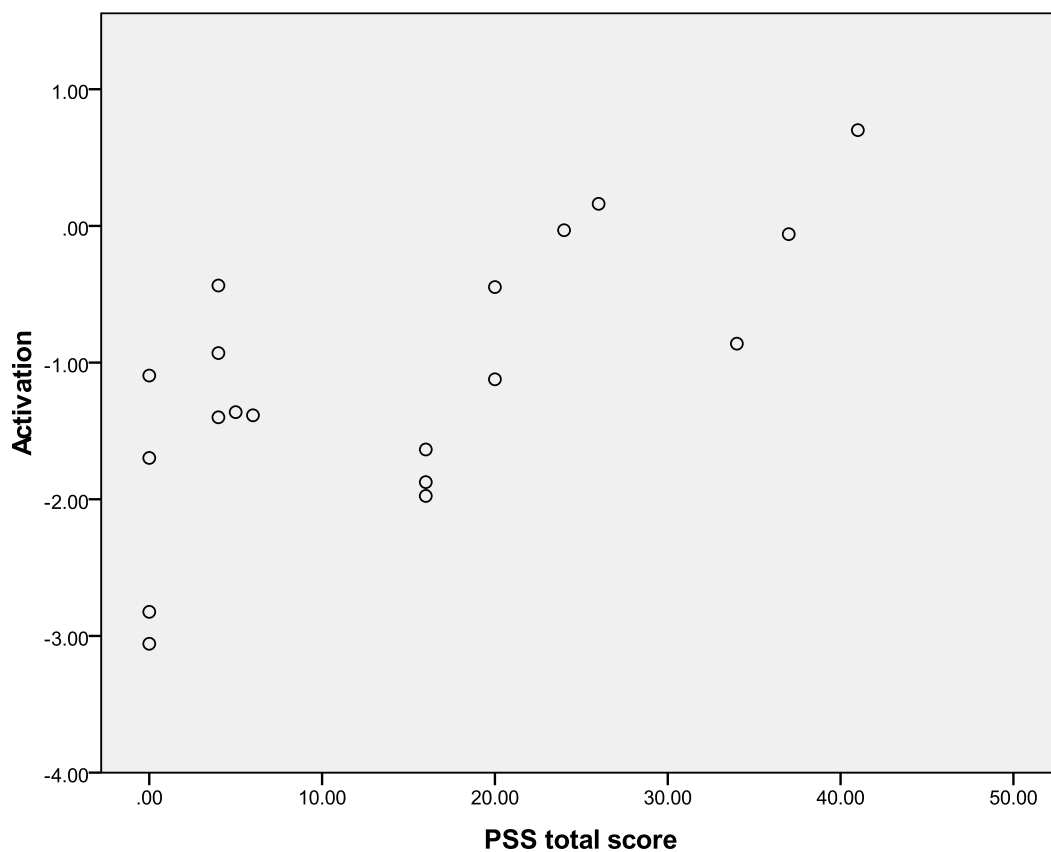


Figure 11. Contrast values indicating peak voxel activation (Talairach coordinates: 3, 47, 32, right dorsolateral prefrontal cortex) corresponding with increases in PTSD symptoms for threat/neutral versus happy/neutral and neutral/neutral face pairs (combined).

Stimulus race fMRI analyses: Neural response to presentations of Black versus White faces (all expressions). To examine potential differences in neural activation in response to viewing same-versus different-race faces within *a priori* specified regions, neural responses to presentations of Black versus White faces (threatening, happy, and neutral expressions, combined) were compared between PTSD and TC groups. No significant differences in neural activation were found between PTSD and TC groups to Black versus White faces within these specified regions. Participants with PTSD, relative to traumatized controls, demonstrated increased activation in two other brain regions to this contrast condition: the right parahippocampal gyrus and right lingual gyrus; see Figures 12 and 13, Table 4.

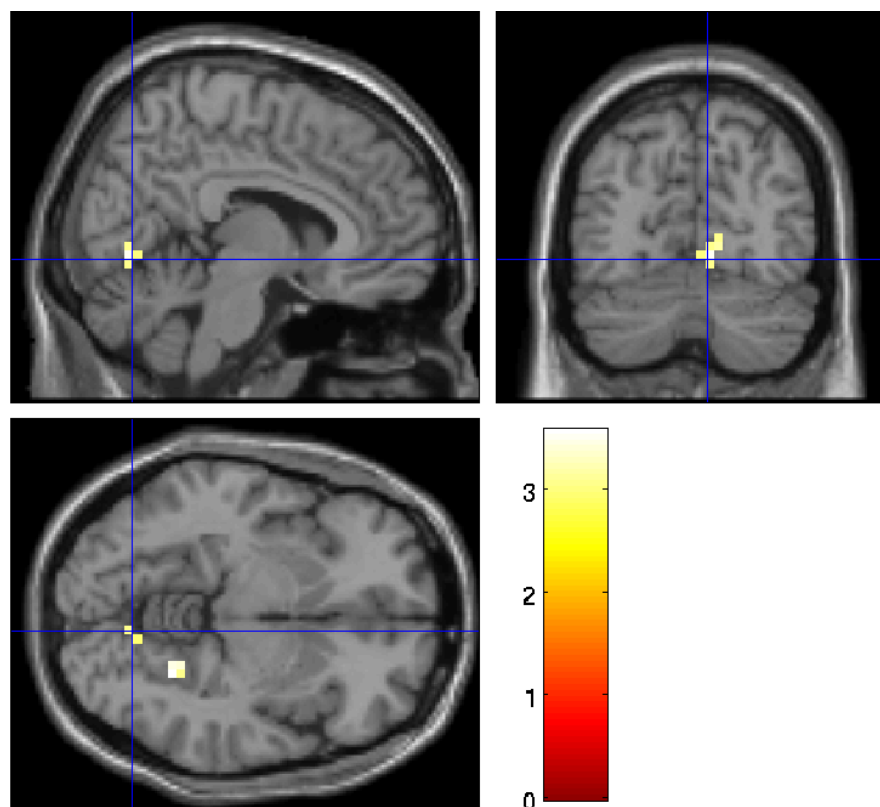


Figure 12. Black versus White faces (all expressions), PTSD > TC. Statistical parametric map of brain activation during the processing of Black faces relative to White faces (all expressions) in PTSD relative to TC participants. Activations are shown overlaid onto an averaged structural MRI. The colored bar represents t scores for activations. Maximally activated voxel in the right parahippocampal gyrus: $x = 27$, $y = -52$, $z = -2$, $t = 3.57$, 5 voxels, $p < 0.005$ (uncorrected). All neuroimaging data are reported using the coordinate system of Talairach and Tournoux.

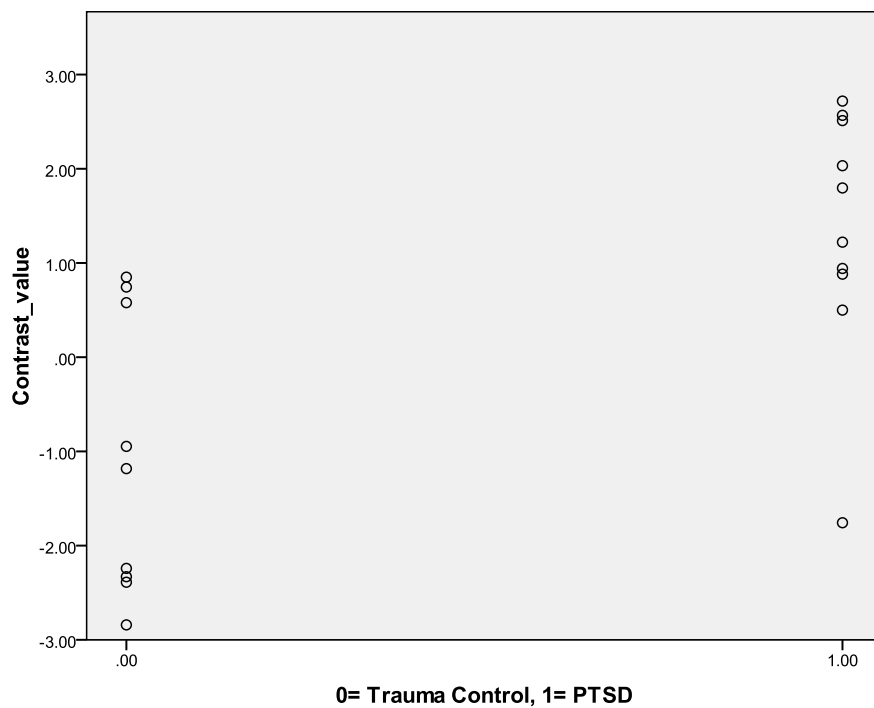


Figure 13. Contrast values indicating peak voxel activation (Talairach coordinates: 27, -52, -2, right parahippocampal gyrus) in PTSD versus trauma control participants for the Black versus White face contrast condition

Patterns of neural activation associated with threat cue presentation in Black faces: A contrast of Black threat incongruent versus Black threat congruent trials. To test the hypothesis that individuals with PTSD, relative to TCs, would demonstrate atypical patterns of neural activation in specified *a priori* brain regions that may be indirectly associated with attention biases to threat in same-race faces, a whole-brain analysis was conducted using a contrast of Black threat incongruent versus Black threat congruent trials. As predicted, participants with PTSD, relative to traumatized controls, demonstrated significantly increased neural activation to threatening Black faces in an *a priori* specified region, the right anterior cingulate, to Black threat incongruent face pairs versus Black threat congruent face pairs (see Figures 14 and 15, Table 4). No other significant differences in activation between PTSD and TC groups were found for this contrast condition.

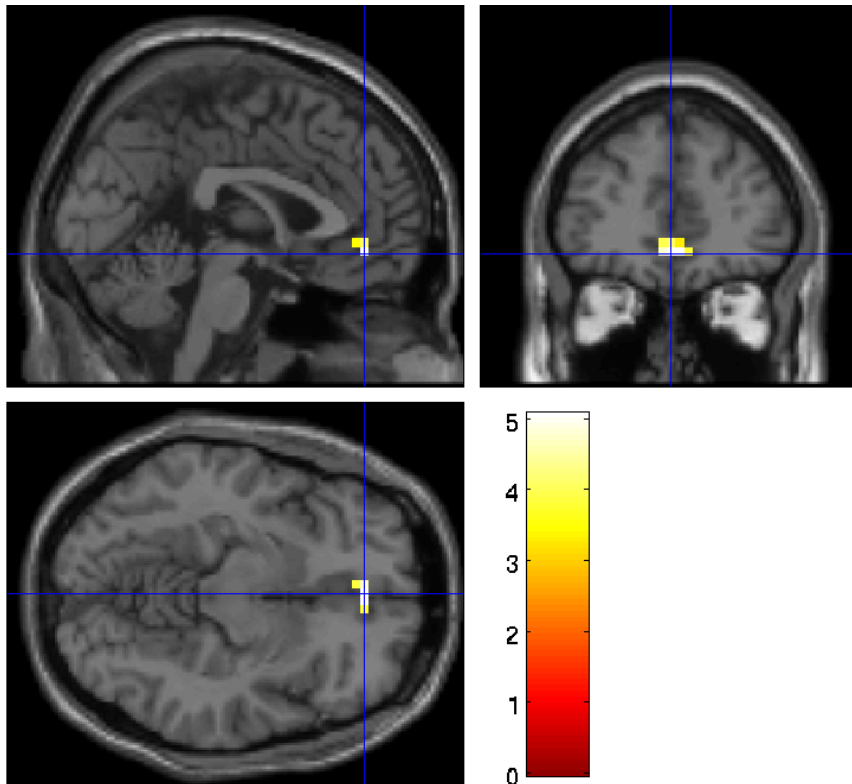


Figure 14. Black threat incongruent versus Black threat congruent face pairs, PTSD > TC. Statistical parametric map of brain activation during the processing of Black threat incongruent face pairs relative to Black threat congruent face pairs in PTSD > TC participants. Activations are shown overlaid onto an averaged structural magnetic resonance image. The colored bar represents t scores for activations. Figure illustrates maximally activated voxel in the anterior cingulate: $x = 3$, $y = 39$, $z = -8$, $t = 5.06$, 11 voxels, $p < 0.005$ (uncorrected). All neuroimaging data are reported using the coordinate system of Talairach and Tournoux.

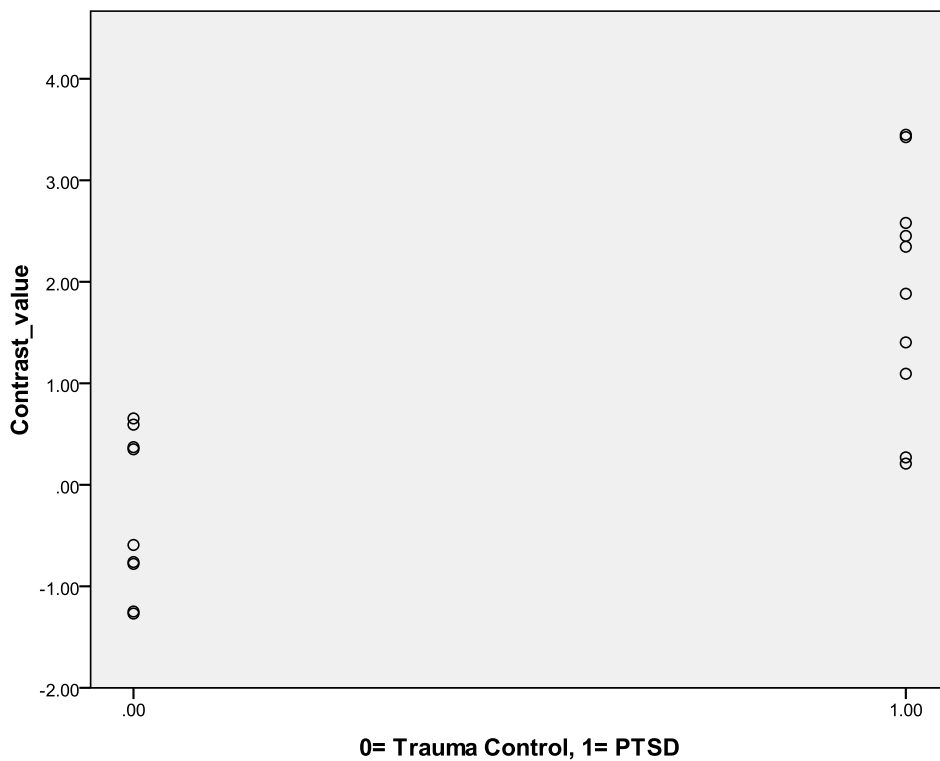


Figure 15. Contrast values indicating peak voxel activation (Talairach coordinates: 3, 39, -8, right anterior cingulate) in PTSD versus trauma control participants for the Black threat incongruent versus Black threat congruent contrast condition.

Patterns of neural activation associated with threat cue presentation in White faces: A contrast of White threat incongruent versus White threat congruent trials. Participants with PTSD, relative to traumatized controls, did not demonstrate differences in activation indirectly associated with biases to threat in other-race faces in *a priori* specified brain regions. However, participants with PTSD demonstrated activation in two other brain regions, the precuneus and middle temporal gyrus, to this contrast condition (see Figures 16 and 17, Table 4).

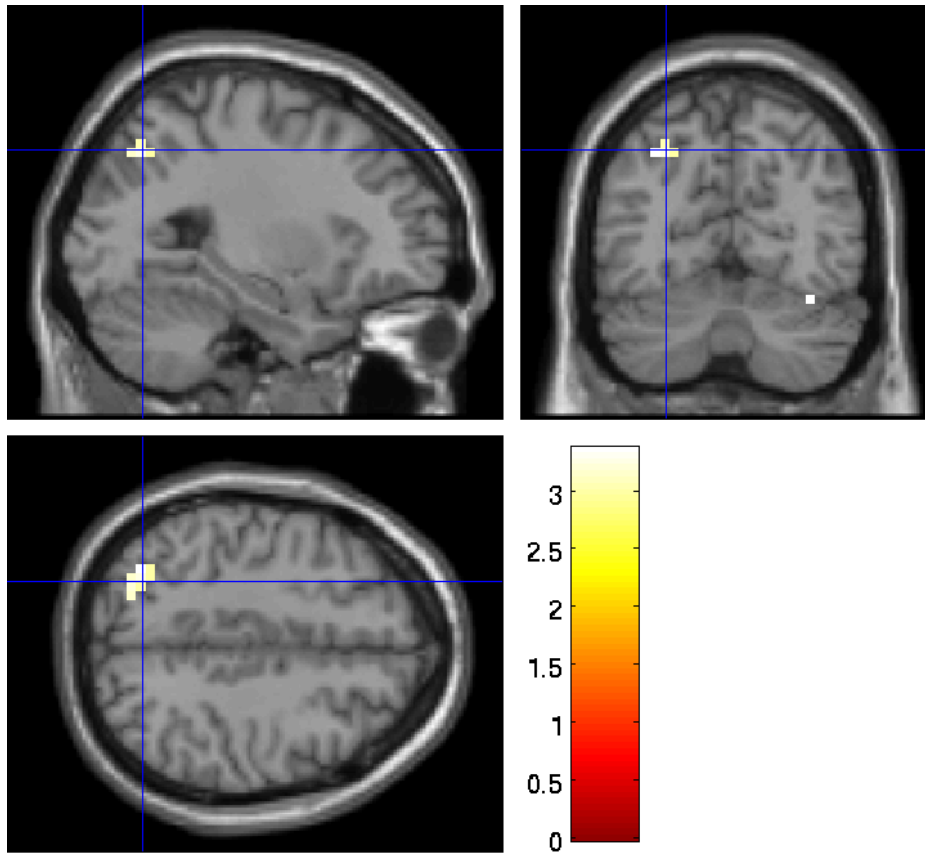


Figure 16. White threat incongruent versus White threat congruent face pairs, PTSD > TC. Statistical parametric map of brain activation during the processing of White threat incongruent face pairs relative to White threat congruent faces in PTSD > TC participants. Activations are shown overlaid onto an averaged structural magnetic resonance image. The colored bar represents t scores for activations. Maximally activated voxel in the left precuneus: $x = -32$, $y = -64$, $z = 41$, $t = 3.36$, 10 voxels, $p < 0.005$ (uncorrected). All neuroimaging data are reported using the coordinate system of Talairach and Tournoux.

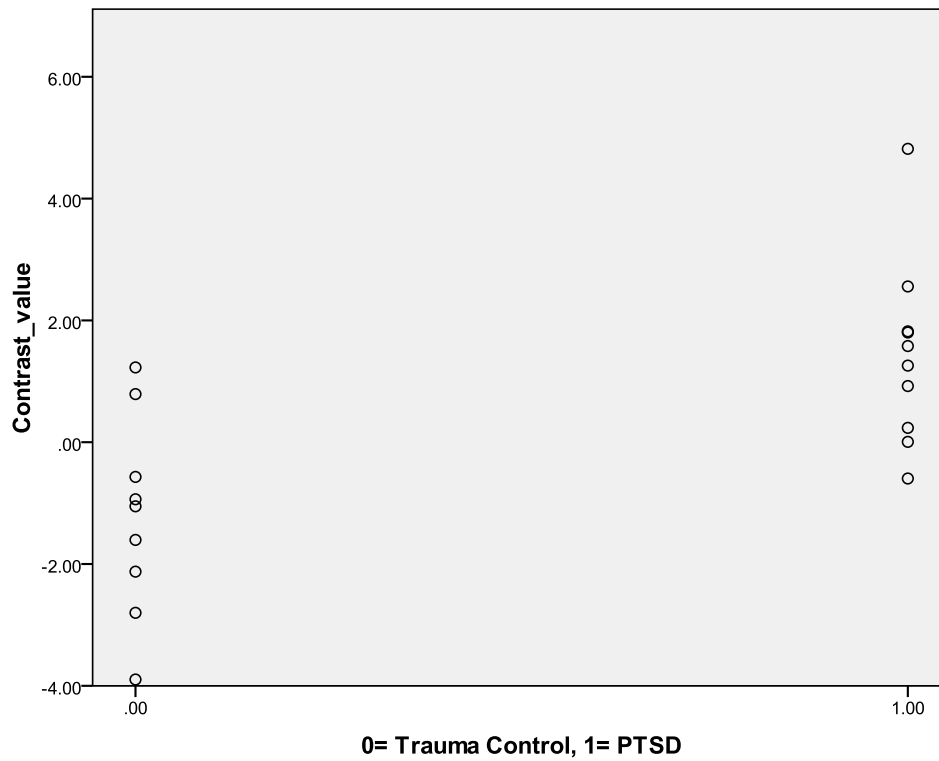


Figure 17. Contrast values indicating peak voxel activation (Talairach coordinates: -32, -64, 41, left precuneus) in PTSD versus trauma control participants for the White threat incongruent versus White threat congruent contrast condition.

Table 1. Demographic and Clinical Characteristics

	Trauma Control (n=9)	PTSD (n=10)	
	<u>Mean (SD)</u>	<u>Mean (SD)</u>	<u>t</u>
Age	34 (11.8)	34.7 (13.5)	-.12
Age range	20-53	20-60	
PSS re-experiencing	.89 (1.17)	4.8 (2.35)	-4.51**
PSS avoidance and numbing	.56 (.73)	11.6 (5.42)	-6.05**
PSS hyperarousal	1.11 (1.23)	8.2 (3.29)	-6.05**
PSS total	2.56 (2.51)	24.6 (9.25)	-6.91**
	<u>N(%)</u>	<u>N(%)</u>	<u>χ^2/Cramer's V</u>
Total types of trauma experienced			.64*
2 – 3	5 (55.6%)	0	
4 – 6	3 (33.3%)	6 (60%)	
7 – 10	1 (11.1%)	4 (40%)	
Education			.39
< 12 th grade	3 (33.3%)	3 (30%)	

12 th grade/high school graduate	3 (33.3%)	2 (20%)	
Some college/technical school	2 (22.2%)	4 (40%)	
College/tech school graduate	1 (11.1%)	1 (10%)	
Monthly Income			0.27
\$0 – 249	1 (11.1%)	2 (20%)	
\$250 – 499	2 (22.2%)	3 (30%)	
\$500 – 999	2 (22.2%)	1 (10%)	
\$1000-1999	2 (22.2%)	3 (30%)	
\$2000+	2 (22.2%)	1 (10%)	

*p < .05

**p < .01

Table 2. Bivariate correlations among attention bias scores, PTSD and depressive symptoms

N=19

	2	3	4	5	6	7	8	9	10	11
1. PSS_ re-experiencing	.82**	.84**	.91**	.68**	-.16	-.42	-.08	-.37	-.19	-.34
2. PSS_ avoidance/numbing		.85**	.97**	.73**	-.26	-.14	-.12	-.03	-.32	-.20
3. PSS_ hyperarousal			.94**	.78**	-.24	-.31	-.11	-.12	-.29	-.38
4. PSS total score				.78**	-.23	-.27	-.11	-.13	-.30	-.30
5. BDI					.01	-.22	.00	-.09	.02	-.26
6. Threat bias						.19	.84**	.27	.86**	.06
7. Happy bias							.15	.80**	.16	.86**
8. Threat bias Black								.37	.44	-.08
9. Happy bias Black									.10	.38
10. Threat bias White										.17
11. Happy bias White										--

** p <.01

Table 3. Means and standard deviations of attention bias scores, within subjects and between groups

	All subjects (N = 18)	PTSD+ (N = 9)	Trauma Control (N = 9)
1. Threat bias	-14.20 (43.33)	-21.70 (42.12)	-6.70 (45.71)
2. Happy bias	1.65 (44.50)	2.81 (55.59)	.48 (33.38)
3. Threat bias, Black faces	-13.23 (49.71)	-22.39 (44.03)	-4.08 (55.90)
4. Happy bias, Black faces	-2.92 (48.72)	-2.49 (39.27)	-3.34 (59.18)
5. Threat bias, White faces	-15.17 (52.35)	-21.02 (63.43)	-9.32 (41.53)
6. Happy bias, White faces	6.2 (58.18)	8.12 (80.47)	4.30 (26.62)

Table 4. Anatomical locations of activity ($p < .005$, uncorrected) in response to specified contrasts for within- and between-group analyses of PTSD and TC groups

Contrast Condition	Anatomical location	Brodmann Area	Voxel extent	Talairach coordinates					
				t	Z	p	x	y	z
Threat incongruent versus threat congruent, PTSD > TC									
	R. Parietal lobe	7	10	5.69	4.2	0.000	33	-68	40
	L. Superior parietal lobe	7	12	4.6	3.66	0.000	-24	-64	47
	L. Superior parietal lobe	7		3.46	2.97	0.001	-32	-60	47
Threat incongruent versus threat congruent, TC > PTSD									
	L. Insula	13	11	3.87	3.23	0.001	-34	-12	20
	L. Insula	13		3.15	2.76	0.003	-31	-20	20
	L. Caudate		11	3.24	2.82	0.002	-2	2	20
	R. Caudate			3	2.65	0.004	7	6	20
Threat versus happy and neutral face pairs, PTSD > TC									
	L. Superior temporal gyrus	22	9	4.68	3.7	0.000	-49	-32	4
	R. Middle frontal gyrus	8	18	4.47	3.59	0.000	28	29	38
	L. Cerebellum		6	4.1	3.37	0.000	-3	-75	-16
	R. Inferior parietal lobe	40	7	3.75	3.16	0.001	37	-40	48
	L. Middle temporal gyrus	39	6	3.75	3.16	0.001	-48	-67	15
	R. Dorsal mid-cingulate gyrus	24	12	3.5	2.99	0.001	8	-5	47
	R. Medial frontal gyrus	6		3.15	2.76	0.003	12	-17	48
	L. Cerebellum		6	3.32	2.87	0.002	-7	-37	-13

	L. Substantia nigra			3.15	2.76	0.003	-7	-25	-9
	L. Inferior temporal gyrus	19	6	3.23	2.82	0.002	-45	-53	-5
Threat versus happy and neutral face pairs, TC > PTSD									
	L. Cerebellum		5	3.2	2.79	0.003	-3	-59	4
PSS as a predictor of activation to threat incongruent versus threat congruent face pairs									
	L. Medial frontal gyrus	8	9	3.9	3.25	0.001	0	26	44
	L. Superior frontal gyrus	6	5	3.39	2.92	0.002	0	11	51
PSS as a predictor of activation to threat versus happy and neutral face pairs									
	L. Superior temporal gyrus	22	18	5.08	3.91	0.000	-49	-32	4
	L. Middle temporal gyrus	22		3.35	2.89	0.002	-53	-44	4
	R. Dorsolateral prefrontal cortex	9	5	3.84	3.22	0.001	3	47	32
	R. Middle frontal gyrus	8	18	3.63	3.08	0.001	36	23	45
	R. Middle frontal gyrus	8		3.52	3.01	0.001	28	29	38
	L. Cerebellum		7	3.55	3.03	0.001	-7	-37	-13
	R. Cerebellum			3.11	2.73	0.003	4	-33	-13
	L. Cerebellum		5	3.47	2.97	0.001	-3	-75	-16
	R. Medial frontal gyrus	6	7	3.26	2.83	0.002	12	-13	48
Black faces versus White faces (all expressions), PTSD > TC									

	R. Parahippocampal gyrus	19	5	3.57	3.04	0.001	27	-52	-2
	R. Lingual gyrus	18	10	3.43	2.95	0.002	8	-70	1
Black threat incongruent versus Black threat congruent face pairs, PTSD > TC	R. Ventral anterior cingulate gyrus	32	11	5.06	3.9	0.000	3	39	-8
White threat incongruent versus White threat congruent face pairs, PTSD > TC	L. Parietal lobe	19	10	3.36	2.9	0.002	-32	-64	41
	R. Middle temporal gyrus	39	5	3.34	2.89	0.002	37	-69	21

Discussion

The goals of the present study were to examine attentional responses to threat cues, both behaviorally and physiologically, in a sample of traumatized African-Americans with and without PTSD by administering an ecologically-salient attention bias task while examining patterns of neural activation via fMRI. Specifically, the *a priori* hypotheses of this study were twofold: current PTSD symptoms would be positively associated with a significant attentional bias toward threat, particularly when expressed by same-race faces; and individuals with PTSD, relative to traumatized controls, would demonstrate significantly different neural responses associated with attentional biases for threat in the mPFC (including vmPFC, medial frontal gyrus, and ACC), dlPFC, and amygdala.

Behavioral findings

Behavioral findings were inconsistent with *a priori* hypotheses; attentional biases for either happy or threatening facial expressions (for White or Black faces) were not significantly associated with current PTSD or depressive symptoms. Given that only 18 participants were included in behavioral analyses and *a priori* power analyses projected the need for a sample of at least 26 participants, it is possible that inadequate power precluded detection of statistically significant between-group differences in these behavioral data. Although this pattern was not statistically significant, a close examination of these findings indicates a trend for PTSD participants to demonstrate an attentional bias away from threat; this may suggest that, in this population of highly-traumatized individuals, PTSD is associated with a tendency for attentional *avoidance* of threat cues.

However, the presence of atypical neural response patterns to threatening faces (measured through fMRI) in the absence of positive behavioral findings, has been documented

previously in some samples of anxious individuals (McClure et al., 2007), and an earlier dot probe study that sampled individuals from the present population also failed to find positive associations between PTSD symptoms and attentional biases for threatening faces (Fani, Bradley, Ressler, & McClure-Tone, manuscript in press); together, this suggests that more objective physiological measures, such as fMRI, may be more sensitive than behavioral measures in detecting responses to threat cues presented in the context of attention bias tasks, particularly in the present population.

fMRI findings

Some of the fMRI results from this study support core hypotheses; of particular note, individuals with PTSD, when compared to traumatized controls, demonstrated differences in BOLD signal to threatening versus neutral or happy faces within regions of the mPFC (including a region of the vmPFC) and the dlPFC. However, predicted statistically significant differences in amygdala response to threatening faces were not found between PTSD and TC groups.

Increased mPFC activation associated with attention to threatening faces in PTSD

Some of the most consistent findings to emerge from the present study, in keeping with earlier research findings, involve differential activation between participants with PTSD and traumatized controls in regions of the prefrontal cortex, including the dlPFC and mPFC. Findings were particularly striking for the mPFC. When compared to traumatized controls, participants with PTSD demonstrated increased activation in regions of the mPFC under four separate contrast conditions that examined responses to threat versus other emotional expressions: 1) threat/neutral versus combined happy/neutral and neutral/neutral face pairs; 2) PSS total score as a predictor of response to threat/neutral versus combined happy/neutral and neutral/neutral face

pairs; 3) PSS total score as a predictor of activation to threat incongruent versus threat congruent face pairs; and 4) Black threat incongruent versus Black threat congruent conditions.

A variety of studies have found PTSD-specific alterations in mPFC activity to generally aversive or trauma-related cues, such as fearful faces and trauma-specific words in Stroop tasks (e.g., Bremner et al., 2004; Bryant, Felmingham et al., 2008; Shin et al., 2001; Shin et al., 2005; Williams et al., 2006); notably, most of these studies have found *decreased* mPFC activation to such cues. This has often been interpreted as indicating PFC failure to generate an appropriate regulatory response to exaggerated subcortical, and specifically amygdalar, activity during presentation of these trauma-related cues (Koenigs & Grafman, 2009). However, a close examination of existing research yields some evidence of *increased* mPFC activation in PTSD relative to controls in studies using presentations of fearful faces (Bryant, Kemp, et al., 2008), oddball paradigms (Bryant, et al., 2005; Felmingham, et al., 2009), Stroop (Shin et al., 2001) and other response inhibition tasks, including versions of the go-nogo paradigm (Carrion, Garrett, Menon, Weems, & Reiss, 2008).

One possible factor underlying inconsistencies in mPFC activation across these lines of PTSD research is differential task demands across studies. It is likely that the various tasks employed probed a broad array of cognitive processes in whose implementation the mPFC participates. For example, the elevated mPFC function observed in PTSD patients in studies requiring attention to briefly-presented neutral targets in the face of distractor stimuli (Bryant, et al., 2005; Felmingham, et al., 2009) or inhibition of response in the face of distracting stimuli (Carrion, et al., 2008) (Shin et al., 2001) could reflect hyper-engagement of attention/cognitive control networks in PTSD.

Further, these disorder-linked increases versus decreases in activation may be specific to particular regions of the mPFC, which comprises a complex set of structures with multiple putative functions. There is some evidence that individuals with PTSD demonstrate increased activation in dorsal aspects of the mPFC when attempting to identify target stimuli in the face of distractor stimuli; given that dorsal aspects of the mPFC have been implicated in cognitive control processes (Bush, Luu, & Posner, 2000), the evidence from these studies may indicate overwhelmed cognitive control networks in PTSD. For example, two studies used an auditory variation of the oddball task, measuring BOLD response while participants attended to target tones presented at 50 ms durations (Bryant, et al., 2005; Felmingham, et al., 2009). Felmingham and colleagues (2009) found that participants with PTSD demonstrated increased activation in dorsal aspects of the mPFC to oddball targets whereas controls demonstrated increased activation in ventral mPFC regions. Specifically, in response to target auditory tones that elevated skin conductance (a measure of autonomic arousal), participants with PTSD demonstrated significant increases in activity in the dorsal ACC and bilateral dlPFC, whereas controls showed increased activity in the ventral ACC and inferior lateral frontal cortex. Bryant and colleagues (2005), who used a similar oddball task, likewise found that participants with PTSD demonstrated increases in the dorsal ACC and dlPFC to target tones, whereas controls showed increased ventral ACC activation to these cues. Felmingham and colleagues (2009) postulated that this phenomenon may reflect overall *enhancement* in attentional processing in PTSD, and that systems involved with attention to novel or arousing cues become over-engaged in this disorder: “once arousal networks are engaged to novel, or potentially threatening stimuli, they may overwhelm affective vACC networks.”

Thus, consideration of the design of the dot probe task used in the present study and cognitive processes that it is meant to elicit could inform insights about why *increases* in mPFC and dlPFC activation emerged in individuals with PTSD, relative to traumatized controls. During this task, participants are instructed to attend to the location of neutral probes; as in the oddball task, participants are confronted with distractor images that have the potential to interfere with their attention to probes. The act of responding quickly to neutral target images while being confronted with briefly-presented distracting images (particularly, images with emotional value or trauma-related salience) is likely to engage attention and cognitive control networks. Therefore, individuals with PTSD, who experience cognitive and emotional dysfunction in the presence of trauma-related stimuli, may show different neural responses to emotional faces presented briefly as distractors in an attention bias task (such as the dot probe) than they do to facial emotion displays that are the primary focus of attention (as in Armony et al., 2005; S.L. Rauch et al., 2000; Shin et al., 2005; Williams et al., 2006), or aversive trauma-related distractors presented for longer durations in oddball tasks (1.5 to 2 seconds; Pannu Hayes et al., 2009), which may probe different cognitive processes altogether. Indeed, the briefly-presented emotional distractors in a dot probe task could lead to hyper-engagement of attentional resources to “control” the emotional disruption that these cues cause and that interferes with completion of the target task (locate the neutral probe).

Therefore, the increases in dlPFC and mPFC (including medial frontal gyrus and ACC) activation to threatening faces observed in this study could reflect a higher engagement of cognitive control, attention, and conflict monitoring resources in individuals with post-traumatic psychopathology, relative to individuals who are not currently experiencing post-traumatic symptoms. Increases in ACC and dlPFC function have been observed previously in healthy

individuals who were confronted with similar attention bias tasks; these increases in ACC and dlPFC activation can be heightened further in conditions that require increased attentional control (reviewed in Banich, et al., 2009). In individuals experiencing mood disruptions, attentional networks may become over-engaged and a disproportionate amount of neural resources may be spent in the context of experimental tasks that require attention and/or working memory. For example, Matsuo and colleagues (2007) found that although depressed individuals performed as well as non-depressed controls on a N-back task, depressed participants demonstrated significantly greater dlPFC activation during task performance (Matsuo, et al., 2007). It is possible that the distracting threatening faces presented in this dot probe task led to a greater expenditure of attentional and conflict monitoring resources in participants with clinical levels of post-traumatic psychopathology as compared to their psychopathology-free peers.

Increased superior parietal cortex activation associated with attention to threatening faces in PTSD

Additionally, the present study found activation to threat in other brain regions that have been implicated in attentional processing, namely, the superior parietal cortex. This finding provides further evidence that participants with PTSD over-engaged attention and cognitive control networks when presented with these threatening distractors. Findings of PTSD-specific increases in activity in parietal regions to threatening faces is consistent with earlier studies that found increases in posterior parietal activation to targets in oddball tasks (Bryant, et al., 2005) trauma-related images in executive function tasks (Morey, et al., 2008) and trauma-related words in Stroop tasks (Shin, et al., 2001). Specifically, bilateral activation in the *superior* parietal lobe was found in response to the threat incongruent minus threat congruent contrast, and at least one other study has yielded similar findings. Recently, Catani and colleagues (2009) found increased

superior parietal activation to briefly-presented aversive (and largely, trauma-relevant) images in war torture survivors with PTSD, relative to traumatized controls. Given the role that the superior parietal cortex appears to play in attention to spatial stimuli, including complex attentional processes such as selection of visual targets from distractors (Corbetta, Shulman, Miezin, & Petersen, 1995), these findings lend support to the idea that attentional processing of visual stimuli may be enhanced in individuals with PTSD.

Absence of between-group differences in amygdala activation during attention to threatening faces

There was no evidence for PTSD-related increases in amygdala function to threatening facial expressions in this study. A number of other studies have also failed to find any PTSD-specific alterations in amygdala activity to trauma-related cues (Bremner, Narayan, et al., 1999; Bremner, Staib, et al., 1999; Lanius, et al., 2002; Lanius, et al., 2001; Sakamoto, et al., 2005; Shin, et al., 2001). Increased activation in medial prefrontal regions, particularly the ACC, to attentional targets has been shown to predict attenuated activity in the amygdala in healthy individuals (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006), which is not surprising given evidence of reciprocal connections between the amygdala and mPFC (Ghashghaei, Hilgetag, & Barbas, 2007). Researchers generally agree that top-down suppression of amygdala activity by the mPFC represents an adaptive response; however, the increased mPFC and dlPFC response and absence of amygdala response observed in this sample of PTSD participants may reflect unsuccessful efforts to control cognitive or emotional disruptions caused by threatening facial expressions. In this study, the increased mPFC response in concert with a lack of observed differential amygdala response may indicate efforts to overcompensate for emotional disruption caused by threatening facial expressions and disturbing trauma memories that these images

might evoke. This assumption fits well with emotion-processing theories of PTSD, which posit that PTSD is characterized by unsuccessful attempts to suppress or avoid trauma-relevant cues, a process that serves to perpetuate PTSD symptoms. Until traumatic memories (and the emotions associated with these memories) are fully elaborated, they cannot be effectively “controlled” (Foa, Huppert, & Cahill, 2006).

Increased insula activation associated with threat congruence/incongruence in traumatized controls

Ventromedial prefrontal cortex activation and neural response to threat in same-race faces in PTSD

Ventral aspects of the ACC were defined for the purposes of this study to be the vmPFC region of interest. Cognitive researchers have implicated the ACC in a number of attentional processes, including conflict monitoring and cognitive control of incoming information (Banich, et al., 2009). An emerging line of research suggests that dorsal and ventral aspects of the ACC may be differentially engaged by neutral versus emotional information (respectively) presented in complex attentional paradigms (reviewed in Banich, et al., 2009). The idea that ventral aspects of the ACC are most associated with attentional regulation of emotional information makes sense, given the physical proximity of the vACC to the amygdala (arguably the most critical brain structure in the detection of emotionally-salient cues). In fact, the vACC has been shown to have direct projections to this region (Devinsky, Morrell, & Vogt, 1995). A number of elegant studies have found that dorsal and ventral aspects of the ACC have dissociable functions (Bush, et al., 2000; Mohanty, et al., 2007; Whalen, et al., 1998), with ventral aspects more closely associated with attentional regulation of emotional information. For example, in a study of healthy adults, Mohanty and colleagues (2007) found that dorsal regions of the ACC were more

active during standard color-word Stroop task performance (which involves only neutral stimuli), and more ventral aspects of the ACC were engaged during emotional Stroop task performance (Mohanty, et al., 2007).

The present study found PTSD-specific activation in a ventral region of the ACC for one contrast condition: Black threat incongruent versus Black threat congruent trials. The threat incongruent versus threat congruent contrast represents a condition that may indirectly reflect a correlate of attentional bias for threat, and, interestingly, ventral ACC activation was selectively found for *Black*, but not *White*, threatening faces in PTSD versus TC participants for this contrast. In fact, ACC activation was not observed in other contrast conditions that combined White and Black threatening faces [threat/neutral versus happy/neutral and neutral/neutral face pairs (combined); PSS total score as a predictor of response to threat/neutral versus happy/neutral and neutral/neutral face pairs (combined); PSS total score as a predictor of activation to threat incongruent versus threat congruent face pairs].

The PTSD-specific increase in ventral ACC activation to threatening Black, but not White, faces may have occurred because threatening Black faces were more emotionally salient and arousing to these participants than were threatening White faces. Some studies of healthy individuals have shown evidence for greater sensitivity to emotion (Messick & Mackie, 1989) and greater feelings of arousal (Brown, Bradley, & Lang, 2006) evoked by pictures of same-race, versus other-race, faces. This phenomenon may be exaggerated in individuals with PTSD, a disorder that is characterized by hypervigilance for trauma-related cues and subsequent increases in physiological arousal.

Viewing threatening Black faces might have reminded emotionally vulnerable participants of the perpetrators of their traumatic experiences, which, in turn, triggered

disruptions in vACC function. If threatening Black faces were more likely to reflect the race of the trauma perpetrator in this sample of viewers, then threatening Black (versus White) faces would be more likely to elicit the exaggerated physiological responses associated with this disorder. Therefore, these data can be interpreted as supporting the hypothesis that same-race, versus other-race faces, are more likely to engage viewers with PTSD and to elicit increased activity in brain regions, such as the ACC, involved with attention to emotion. However, this explanation is purely speculative, given that no data about the race of trauma perpetrators was available.

Further, no significant within- or between-group differences were found in specified *a priori* brain regions to Black faces versus White faces (all expressions combined), which suggests that the observed ACC effects were not attributable to simply viewing different-race faces, overall. The fact that participants with PTSD exhibited increased ventral ACC activation while attending to threatening Black, but not White, faces may suggest that threatening Black faces more successfully enlisted attentional resources and were more effective probes for attention to threat in this sample of individuals with PTSD. This does not suggest that threatening White faces were ineffective at engaging networks involved with attention/cognitive control in PTSD (the increase in dlPFC and mPFC activation to threatening faces overall provides evidence for this) but rather that threatening Black faces may have been more emotionally relevant, and thus emotionally arousing, stimuli for this sample of African-American individuals with PTSD, engaging brain regions involved in cognitive control of emotional information (i.e., the vACC).

Altogether, the finding of PTSD-specific increases in vACC function to probe-congruent threatening Black, but not White, faces, illustrates the value of using more ecologically-salient stimuli in PTSD information-processing research, and introduces the possibility that variations in

features of experimental stimuli, including stimulus race, can elicit differential neural activation from attention/cognitive control network components in individuals with PTSD.

Increased activation in other brain regions

In addition to *a priori* regions of interest and associated areas, participants with PTSD demonstrated increased activation to threatening faces in other brain regions, including the cerebellum and superior, middle and inferior aspects of the temporal gyrus. Findings of increased activation in the cerebellum (Osuch, et al., 2001; Shin, Wright, Cannistraro, & al, 2005; Williams, Kemp, & Felmingham, 2006; Yang, Wu, Hsu, & Ker, 2004) and temporal cortex (Hopper, Frewen, van der Kolk, & Lanius, 2007; Lanius, et al., 2002; Osuch, et al., 2001) during presentation of trauma-related reminders are not uncommon in individuals with PTSD. These findings commonly emerge in studies that analyze whole-brain data which, even after correction for multiple comparison testing, can yield unexpected findings. Although these unexpected increases in activation have largely been ignored in previous studies of attention and emotion in PTSD, their emergence in the present study serves as a reminder that brain structures implicated in the disorder, such as the ACC and amygdala, do not operate as isolated units, but in the context of functional systems. Therefore, it is possible that cerebellar and temporal regions play an integral role in neural processes associated with post-traumatic psychopathology; medial temporal regions (particularly the hippocampus and peri-hippocampal gyrus) have been frequently implicated in dysfunctional encoding and memory retrieval in PTSD (Shin & Handwerker, 2009), and some studies of attention and response inhibition in healthy individuals have implicated involvement of medial temporal and cerebellar regions in these processes (Egner & Hirsch, 2005). Thus, these brain regions may be worthwhile targets for investigation in future studies.

Limitations

This study has numerous strengths; in particular, it helps to extend the rather limited literature on neural correlates of attention to emotion in PTSD to include a high risk population that has historically been understudied. However, a number of study limitations are also worth noting. Although participants in this study represent an understudied population in the PTSD literature, the circumscribed demographic profile of the population sampled in this study may limit the generalizability of these findings to other traumatized populations. In particular, this study included only female participants; given that only female face stimuli were used in this version of the dot probe, it was impossible to investigate potential interactive effects of gender and attentional biases. Similarly, a lack of White participants in this study precluded examination of stimulus- by participant-race interactions and their effects on attentional biases. Additionally, most participants had experienced chronic adversity of multiple types throughout their lifetimes, including economic disadvantage and repeated trauma exposure. Given what is known about the deleterious cognitive and biological effects of chronic and/or prolonged trauma exposure (Vermetten & Bremner, 2002), it is possible that the observed findings are more relevant to the effects of trauma exposure or age at trauma onset than to PTSD sequelae. The inclusion of a non-traumatized control group would have been helpful in examining unique associations of attentional biases with trauma versus post-traumatic psychopathology. Unfortunately, I was not able to recruit an adequate number of participants from our target population who were free of trauma histories. Finally, as noted previously, the relatively small sample size might have limited power to detect attentional biases in behavioral responses, or the detection of atypical responses in neural structures outside of hypothesized regions.

Theoretical and clinical implications

The rich findings that emerged from this study have important implications for current information-processing models of PTSD, which can subsequently inform treatment methods. The alterations in dlPFC and mPFC function found in the present study complement findings from earlier PTSD studies that also revealed atypical function in these brain regions. However, the present data also suggest that PTSD is not simply a disorder of cognitive failures or deficiencies (i.e., the mPFC is simply “failing” to inhibit the amygdala), but also one of improper cognitive resource allocation and imbalanced attentional systems. The ecologically-salient attention bias task employed in this study elicited increased activation during relevant contrasts in brain regions involved with attention, cognitive control, and emotion regulation, but only in participants with current PTSD. Hyper-engagement of attention and cognitive control resources to emotional or trauma-relevant information perpetuates PTSD symptomatology by preventing adequate processing of other relevant environmental information and contemplative appraisal of the various thoughts and feelings associated with the trauma(s). This rigid attentional style can, in turn, lead to poor mental efficiency and impairment in cognitive processes such as working memory, since fewer cognitive resources will be available at any given time.

In light of these findings, acceptance-based therapeutic techniques, such as ACT (Hayes, Strosahl, & Wilson, 1999), may be useful in addressing the emotional disruption associated with implementation of this ineffective cognitive style. ACT promotes the acknowledgment and acceptance of the entire range of one’s internal and external experiences; according to ACT theorists, efforts to control or suppress negative thoughts or feelings serve to exacerbate or perpetuate psychological distress and hinder therapeutic growth (Hayes, et al., 1999). Given that ACT emphasizes tolerance of negative thoughts and emotions and promotes cognitive flexibility,

it may constitute a useful treatment option for traumatized individuals who are attempting, albeit unsuccessfully, to control their reactions to trauma-related cues and consequently worsening their own distress.

Future directions

The investigation of attentional biases and associated dysregulation in neurobiological processes in PTSD is a worthwhile endeavor, given the surprising lack of research in this area. The data presented here provide some insights into these processes that may guide or inform further research aimed at characterizing attentional biases in PTSD. Particularly, the present findings underscore the need for research utilizing a combination of techniques to measure responses to emotionally evocative stimuli. For example, the use of eye-tracking measures during dot probe administration would provide information about the direction of an individual's visual attention to task stimuli; these techniques, combined with fMRI recording, have the potential to provide an even richer set of information about the variables of interest in this study. The findings presented here also illustrate the need for cognitive paradigms that are not only tailored for use with their respective study populations, but are also precise and effective at measuring the construct they are intended to measure. Finally, there is an unfortunate lack of research on economically underprivileged individuals, who experience a disproportionately high amount of trauma throughout their lives (Gillespie, et al., 2009; Schwartz, Bradley, Sexton, Sherry, & Ressler, 2005) but are typically not the focus of PTSD neuroimaging research. The inclusion of these groups in studies of information-processing biases in PTSD would be invaluable for informing appropriate treatments for this often neglected population.

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Appendix

Examples of Traumatic Experiences Endorsed by Trauma Control and PTSD Participants (each participant is represented by a number)

Trauma Controls

1. Witnessed a man being attacked with a weapon; experienced motor vehicle accident
2. Witnessed cousin's boyfriend pull a gun on her; jaw broken when breaking up a fight between others; confronted with mother's sudden death from heart failure
3. Confronted with mother's sudden death from cardiac arrest
4. Witnessed man chasing another man with a gun; witnessed fighting between strangers on the street
5. Experienced rape in childhood; experienced mugging in adulthood
6. Witnessed sudden death of father as a child; experienced attempted rape; experienced emotional abuse in childhood
7. Robbed in her home at gunpoint, her family was present
8. Witnessed assault of family member; witnessed grandson lose his leg when caught in a cord and dragged by a moving vehicle
9. Witnessed a classmate's death in a motor vehicle accident

PTSD

1. Experienced childhood physical abuse; robbed at gunpoint in home; saw body of daughter who was hit and killed by a vehicle; witnessed daughter's physical assault by partner
2. Chronic childhood sexual abuse; clothing caught on fire in a home accident and suffered severe burns in childhood
3. Sexually assaulted by co-worker
4. Confronted with son's murder; witnessed domestic violence between parents as well as extended family
5. Experienced childhood sexual and physical abuse; experienced physical assault as adult
6. Experienced physical assault in adulthood

7. Found body of family member after they had been strangled; witnessed stranger being assaulted; witnessed domestic violence between parents
8. Experienced childhood sexual abuse; experienced physical assault in adulthood
9. Witnessed friend's death in a motor vehicle accident; gun was pulled on her and others by a group of men during a social event; experienced sexual abuse in childhood by mother's partner
10. Experienced emotional and physical abuse from father in childhood