

Research Article

POSTTRAUMATIC STRESS SYMPTOMS AND BRAIN FUNCTION DURING A RESPONSE-INHIBITION TASK: AN fMRI STUDY IN YOUTH

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Youth who experience interpersonal trauma and have posttraumatic stress symptoms (PTSS) can exhibit difficulties in executive function and physiological hyperarousal. Response inhibition has been identified as a core component of executive function. In this study, we investigate the functional neuroanatomical correlates of response inhibition in youth with PTSS. Thirty right-handed medication-naïve youth between the ages of 10 and 16 years underwent a 3-Tesla Functional Magnetic Resonance Imaging scan during a response-inhibition (Go/No-Go) task. Youth with PTSS (n = 16) were age and gender matched to a control group of healthy youth (n = 14). Between-groups analyses were conducted to identify brain regions of greater activation in the No/Go-Go contrasts. PTSS and control youth performed the task with similar accuracy and response times. Control subjects had greater middle frontal cortex activation when compared with PTSS subjects. PTSS subjects had greater medial frontal activation when compared with control subjects. A sub-group of youth with PTSS and a history of self-injurious behaviors demonstrated increased insula and orbitofrontal activation when compared with those PTSS youth with no self-injurious behaviors. Insula activation correlated positively with PTSS severity. Diminished middle frontal activity and enhanced medial frontal activity during response-inhibition tasks may represent underlying neurofunctional markers of PTSS. Depression and Anxiety 0:1–13, 2007. Published 2007 Wiley-Liss, Inc.[†]

Key words: PTSS; functional imaging; anxiety; early life stress; response-inhibition; child maltreatment

INTRODUCTION

Children who experience maltreatment and develop posttraumatic stress symptoms (PTSS) may manifest cognitive and behavioral symptoms, including poor executive function and physiological hyperarousal [Perry et al., 1995]. These symptoms may interfere with their ability to process information, especially

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when related to traumatic events. In addition, they suffer from developmental delays that adversely affect their interpersonal and academic functioning [Carrion et al., 2002; Saigh et al., 1997]. Some of these children develop full DSM-IV criteria for posttraumatic stress disorder (PTSD), however many youth develop symptoms that do not meet full criteria. Research shows that this partial response can significantly impact children's emotional, academic and social functioning [Aaron et al., 1999; Carrion et al., 2002; Terr et al., 1999].

Significant cognitive deficits in attention and response inhibition often accompany the behavioral symptoms of PTSD. For example, attentional bias toward trauma-related words have been reported in adults with PTSD [Buckley et al., 2000], and Persian Gulf War Veterans demonstrate deficiencies in response inhibition during tasks of sustained attention [Vasterling et al., 1998]. Response inhibition and executive function have also been shown to be impaired in adult women who experience interpersonal violence, regardless of PTSD status, when compared with non-victimized controls [Stein et al., 2002]. Youth with PTSD secondary to maltreatment also perform worse than a comparison group on measures of attention, such as the Stroop color and Word Test and the Digit Vigilance test [Beers and De Bellis, 2002]. Cognitive impairment in PTSD can be enhanced by the presence of comorbidity. For example, adult Vietnam combat veterans with PTSD and comorbid diagnoses demonstrate more cognitive deficits in standard neuropsychological tests than adults with PTSD and no comorbidity [Barrett et al., 1996]. This has also been demonstrated in children, where children with anxiety and comorbid attention-deficit hyperactivity disorder (ADHD) demonstrate greater cognitive and academic vulnerability than children with anxiety alone [Manassis et al., 2007]. In PTSS, comorbidity is the rule rather than the exception with rates as high as 80% [Pfefferbaum, 1997].

Little is known about the relationship between the cognitive deficits and physiological arousal. Kolb [1987] has theorized that attention problems may arise from globally heightened arousal, which renders an individual less capable of discriminating relevant from irrelevant stimuli. Other studies concur that attention and vigilance appear to be disrupted by arousal dysregulation [Mirsky et al., 1991].

Studies of children with ADHD could shed light into the relationship between cognitive deficits and physiological arousal. The state regulation hypothesis of ADHD states that these children have deficits in regulating their arousal state to counteract a performance decrement [Wiersema et al., 2005]. Furthermore, other conditions seem to aggravate this process. For example, when exposed to a standardized provocation protocol, children with ADHD and comorbidity responded with higher levels of behavioral aggression, greater heart rate acceleration and more anger than

children with only ADHD or no diagnosis [Waschbusch et al., 2002], suggesting a synergistic role for psychiatric symptoms on limiting an individual's capacity to control behavior and arousal. Physiological studies in patients with PTSD demonstrate heightened heart rate reactivity to both neutral and trauma-related stimuli [Litz et al., 2000], greater skin conductance, heart rate, and electromyogram (EMG) responses to conditioned stimuli [Orr et al., 2000], and decreased ability to suppress electroencephalogram (EEG) responses to sensory stimuli [Neylan et al., 1999]. Children with PTSS also demonstrate altered physiologic reactivity when compared with non-symptomatic traumatized children [Kassam-Adams et al., 2005; McPherson et al., 1997] and increased diurnal cortisol levels when compared with healthy controls [Carrion et al., 2002b].

Converging evidence from functional imaging studies identify the insular cortex as a critical structure involved in the subjective evaluation of one's physiological state [Craig, 2002]. Activation of the insula has been linked to awareness of internal states and to awareness of arousal more specifically [Critchley et al., 2002; Pollatos et al., 2007; Stein et al., 2007]. Interestingly, *in situ* hybridization studies labeling mRNA have identified corticotrophin-releasing factor receptors in the insula, suggesting the role of this structure in processing homeostatic regulation of stress [Sanchez et al., 1999]. If cognitive difficulties with attention and response inhibition are related to symptoms of arousal in youth with PTSS, these children may show altered functioning of brain regions associated with physiological arousal, attention and response inhibition.

Functional magnetic resonance imaging (fMRI) provides an opportunity to examine these neural correlates. The Go/No-Go task taps the ability to sustain attention and inhibit a prepotent response, and has been successfully utilized in several fMRI studies in control subjects [Garavan et al., 1999; Kiehl et al., 2000; Konishi et al., 1998; Liddle et al., 2001; Menon et al., 2001; Rubia et al., 1998]. These studies support the involvement of the frontal lobes in suppression of inappropriate behavioral responses. Specifically, tasks of response inhibition usually activate inferior, middle and medial frontal gyri and orbitofrontal cortex (OFC) [Aron et al., 2003; Garavan et al., 1999; Menon et al., 2001]. The Go/No-Go task has been utilized in typically developing children, children with fragile X and children with ADHD to assess response inhibition and cognitive control [Menon et al., 2004; Tamm et al., 2002; Vaidya et al., 1998]. The presentation of this task in an event-related design has been used to isolate cognitive processes associated with response inhibition in adolescents with ADHD [Schulz et al., 2004]. Compared with healthy controls, youth with ADHD demonstrated enhanced activation during inhibition in ventrolateral prefrontal cortical areas. There was also increased activation in the

anterior cingulate gyrus and left medial frontal gyrus. In another study, children with ADHD had less activation than controls in ventral prefrontal regions and the inferior parietal cortex during the inhibitory trials [Durstun et al., 2006]. Booth et al. [2005] reported hypoactivation in frontal areas, specifically inferior, middle, superior and medial frontal gyri, when compared with controls during the inhibitory trials of the Go/No-Go. When studying ADHD children who were medication naïve, results showed decreased activation in the left rostral mesial frontal cortex during the inhibitory trials of the Go/No-Go [Smith et al., 2006]. Taken together, these studies indicate functional abnormalities in regions typically involved in response inhibition in youth with ADHD.

To date there are no functional imaging studies of children with PTSS or PTSD. Given the similarities and symptom overlap between this condition and ADHD in terms of cognitive difficulties and physiological arousal and the gap in the literature regarding functional studies in pediatric PTSD, we decided to examine response inhibition in a traumatized population with PTSS. Using structural MRI in another sample, our group reported previously that youth with PTSS demonstrate an attenuation of normal frontal lobe asymmetry [Carrion et al., 2001], pointing to the possibility of functional abnormalities involving the frontal lobes. Accordingly, we used an fMRI-based Go/No-Go task in youth with PTSS to determine if associated functional abnormalities of the frontal cortex also would be detectable in this population. If present, such abnormalities could represent the neural substrate of attention and response-inhibition difficulties in children with PTSS, and provide important clues linking cognitive deficits and regulation of physiological arousal. Alternatively, identification of abnormalities in the neural substrates of response inhibition may cut across clinical populations helping clarify symptom overlap in behaviorally defined diagnoses.

In this investigation, we hypothesized that youth with PTSS would demonstrate reduced activation in frontal areas associated with response inhibition and a related increased activation in areas associated with physiological arousal, such as the insular cortex, when compared with normal controls.

It has been hypothesized that physiological arousal facilitates self-injurious behaviors (SIB) in children with history of interpersonal trauma [Weaver et al., 2004]. In fact, compared with psychiatric controls, youth with PTSS are significantly more likely to have attempted suicide and have suicidal ideation [Famularo et al., 1996; Lipschitz et al., 1999] and adults with PTSS show an association between impulsivity and suicide risk [Kotler et al., 2001]. Therefore, we explored SIB in this sample of children with PTSS. History of trauma and posttraumatic symptoms have been associated with self-cutting, the most common form of SIB [Brown et al., 2005].

Expecting to identify brain activity in areas that may be associated with SIB, we divided our clinical group into those that have a clinical history consistent with SIB and those that do not (Non-SIB). We hypothesized that the subjects with a history of SIB would show increased activation in the insula (reflecting a focus on internal sensations related to anxiety and arousal) and ventral frontal lobes compared with Non-SIB subjects. This prediction is based on the neuroimaging literature suggesting that insula activation is associated with interoceptive awareness, as described above [Pollatos et al., 2007; Stein et al., 2007] and that regions of the ventral frontal lobes are activated during tasks that require inhibition of emotion-related processes [Blair et al., 2007; Dolcos et al., 2006].

MATERIALS AND METHODS

PARTICIPANTS

Thirty medication-naïve right-handed youth were recruited. Sixteen youth with history of early life trauma and PTSS (nine girls and seven boys; mean age 13.7 years) and 14 age and gender healthy matched controls (eight girls and six boys; mean age 13.3) were enrolled. All procedures were approved by Stanford University's Institutional Review Board (IRB) and parent consent and child assent were obtained in all subjects.

The clinical sample was recruited from local social service departments and mental health clinics. We recruited youth who (1) had at least one episode of exposure to interpersonal trauma, as defined by DSM-IV criterion A; (2) endorsed PTSS on the Clinician Administered PTSD Scale for Children and Adolescents (CAPS-CA) and scored 18 or higher (see below); (3) lived in a current environment with no exposure to trauma; and (4) had no known history of alcohol or drug abuse/dependence, neurological disorder or other major medical conditions, as assessed at intake with a medical history form. Types of trauma included sexual abuse ($N = 8$), physical abuse ($N = 11$) and witnessing violence ($N = 6$). Nine youth experienced multiple traumas. The mean time since the trauma was 5 years and the SD was 3 years. The Schedule for Affective Disorders and Schizophrenia for School-Age Youth (K-SADS; see below) was used to identify comorbidity and history of SIB. Those experimental subjects that endorsed self-harm were categorized as SIB ($N = 7$; five girls and two boys) and those subjects that did not have this history were categorized as non-SIB ($N = 9$; four girls and five boys). Ethnic composition was Euro-American ($N = 8$), African-American ($N = 2$), Asian ($N = 2$), Hispanic ($N = 2$), American Indian ($N = 1$) and more than one ethnicity ($N = 1$). Regarding family income, 23.81% reported incomes between 0 and \$31,000, 33.33% reported incomes between 31,000 and \$76,000 and 23.81% of the families reported incomes over \$76,000. A portion of the sample (19.05%) did not report

income data. This was due to children being in foster care, residential treatment or other non-traditional rearing environments. With respect to caregiver education level, caregivers reported junior high education (2.94%), a high school education (20.59%), partial college (20.59%), college (23.53%) or graduate school education (5.88%). For a portion of the sample (26.47%) caregiver education level was not available. This was also due to the children being in foster care, residential treatment or other non-traditional rearing environments.

Fourteen healthy control subjects with no history of psychiatric illness or trauma were chosen to match the age and sex of the clinical group. Control subjects were screened for a history of trauma and their caretakers completed the Child Behavior Checklist (CBCL; see below) and none scored in the clinical range. Controls had been recruited for this study or for other studies conducted in our lab. Ethnic composition was Euro-American ($N=11$), Asian ($N=2$) and more than one ethnicity ($N=1$). Fourteen healthy control subjects with no history of psychiatric illness were chosen to match the age and sex of the clinical group. Caretakers for control subjects completed the CBCL (see below) and none scored in the clinical range. Ethnic composition was Euro-American ($N=11$), Asian ($N=2$) and more than one ethnicity ($N=1$). Regarding family income, 13.79% reported incomes between 31,000 and 76,000, and 26.32% of the families reported income over 76,000. A portion of the sample (57.89%) did not report income data. With respect to caregiver education level, caregivers reported high school (2.63%), partial college (7.89%), college (13.15%) or graduate school education (15.79%). For a portion of the sample (60.53%) caregiver education level was not available.

BEHAVIORAL INSTRUMENTS

The CAPS-CA [Nader et al., 1996] is a structured clinical interview that is a developmentally sensitive counterpart to the Clinician Administered PTSD Scale (CAPS) for adults [Blake et al., 1995]. It facilitates assessment of exposure to criterion A1 events, including current exposure to trauma and the individuals' experience of these events (A2), frequency and intensity for each of the 17 symptoms for PTSD clustered in DSM-IV (i.e., criteria B, C, and D) and the 1-month duration requirement (criterion E). Additional features to increase the utility of this instrument with youth include: iconic representations of the behaviorally anchored 5-point frequency and intensity rating scales. A certified child psychiatrist (VGC) or child psychologist (CFW), who was trained to administer the instrument, conducted the CAPS-CA interview. Training involved observing live interviews and matching diagnoses with one of the originators of the CAPS-CA (Dr. Elana Newman) or with another trained coder using videotaped recordings of the interviews. Our

previous research [Carrion et al., 2002] has established interrater agreement for the CAPS-CA by comparing the agreement between two raters, one who observed 10 videotaped interviews given by the primary interviewer and was blind to the rating of the primary interviewer. The intra-class correlation coefficient was .97. A symptom is considered present if it receives scores of at least 1 in frequency and 2 in intensity for a total of 3 in severity. We set an inclusion threshold for a CAPS total score of 18 based on our previous research indicating functional impairment in children with PTSS [Carrion et al., 2002] and research by others underscoring the importance of studying children that fell short of the diagnostic criteria, but still experience severe stress reactions [Deblinger et al., 1996; King et al., 2000].

The K-SADS-Present and Lifetime Version, a semi-structured clinical interview designed to identify Axis I DSM-IV disorders [Kaufman et al., 1997], was administered by a certified child psychiatrist (VGC) or child psychologist (CFW) to assess comorbid Axis I psychiatric disorders and SIB. The K-SADS facilitates clinical assessment of suicidal ideation, suicidal acts and non-suicidal physical self-damaging acts and includes a rating scale to assess frequency. The CBCL [Achenbach, 1991] was used to rule out the presence of internalizing or externalizing disorders in the control sample and the Childhood Trauma Questionnaire [Bernstein and Fink, 1998] to rule out trauma in this group. The Weschler Abbreviated Scales of Intelligence was used to assess IQ [The Psychological Corporation, 1999]. The Edinburgh Handedness Inventory was used to determine participants' handedness [Oldfield, 1971]. All experimental and control subjects scored in the right-handed dominance range.

fMRI PROCEDURES

Go/No-Go task design. The experiment consisted of a beginning and ending 30-sec rest period and 12 alternating experimental and control blocks of 26 sec each. Although event-related designs are useful in isolating cognitive processes associated with a particular task, a block design may maximize the capability of capturing any processes involved in that task. In particular, the block design task used in this study requires attention, target recognition and response selection skills. Other studies have presented the Go/No-Go task using a block design [Menon et al., 2004; Tamm et al., 2002]. For all trials, a single letter was presented every 2 sec. Subjects were instructed to press a button in response to every letter except "X". During the control (GO) blocks, the letter "X" was not presented. During the experimental (NoGo) blocks, the letter "X" was presented on 50% of the trials (see Fig. 1). Written instructions (2-sec duration) signaled the beginning of each block. All responses were made using the index finger of the right hand. The computer

recorded reaction times and responses. Initiation of scan and task was synchronized using a TTL pulse delivered to the scanner timing microprocessor board. Stimuli were presented visually at the center of a projection screen, and viewed using a mirror attached to the head coil.

Image acquisition. Images were acquired on a 3T GE Signa scanner using a standard GE whole head coil. A custom-built head stabilization system prevented head movement. The entire brain was imaged in 28 axial slices (4 mm thick, 0.5 mm skip) parallel to the anterior commissure-posterior commissure line. Functional images were acquired using a T2* weighted gradient echo spiral pulse sequence (TR = 2,000 msec, TE = 30 msec, flip angle = 89° and 1 interleave; FOV = 200 × 200 mm²; matrix = 64 × 64; in-plane resolution = 3.125 mm) [Glover and Lai, 1998]. A high resolution T1-weighted Spoiled Grass Gradient Recalled (SPGR) three-dimensional anatomical image was acquired during the same session (TR = 35 msec; TE = 6 msec; flip angle = 45°; 24 cm field of view; 124 slices in the sagittal plane; 256 × 192 matrix; acquired resolution = 1.5 × 0.9 × 1.2 mm).

Acquisition of fMRI data used a spiral sequence developed by Dr. Gary Glover of Stanford University. Spiral fMRI optimizes signal to noise and minimizes susceptibility effects, therefore improving BOLD signal in regions such as the ventral prefrontal cortex and the medial temporal lobe [Glover and Law, 2001].

Data analysis. fMRI data analysis has been described in detail previously [Crottaz-Herbette et al., 2004]. Briefly, images were reconstructed by inverse Fourier transform into 64 × 64 × 18 image matrices (voxel size: 3.75 × 3.75 × 7 mm). Using SPM99 (<http://www.fil.ion.ucl.ac.uk/spm>) images were movement corrected, normalized and spatially smoothed. Data were high-pass filtered and temporally smoothed. For each subject, low-frequency noise was removed from the time series using a high-pass filter set to 0.5 cycles per minute and applied to the fMRI time series at each voxel. Voxel-wise *t* statistics were normalized to *Z* scores for the contrast between NoGo and Go trial blocks.

Between-group analyses used a random-effects model [Holmes and Friston, 1998]. Significant clusters of activation were determined using the joint expected probability distribution of height ($Z > 1.76$; $P < 0.05$) and extent ($P < 0.05$) of *Z* scores and corrected for multiple comparisons. Activation foci were localized with reference to the stereotaxic atlas of Talairach and Tournoux [1988].

Between-groups analyses were conducted to identify brain regions that showed greater activation in the control group compared with the PTSS group in the No/Go-Go contrast, whereas statistically controlling for group differences in IQ. Because this is a double subtraction of statistical maps, significant clusters of voxels can potentially arise from two sources: (1) increased activity in the control group in the No/Go-Go comparison (activation) or (2) increased activity in the PTSS group in the Go-No/Go comparison (deactivation from the comparison group). We restricted our analysis to group differences in activation and removed group differences in deactivation by using the following method. First, we identified activation associated with the No/Go-Go contrast for all subjects combined, regardless of diagnostic group. The resulting activation map was then used as an inclusion mask during the comparison of control and PTSS groups. Thus, we only considered group differences in activation if they were also present in the combined activation map. This method increases the likelihood that group differences are attributable to No/Go-Go activation.

As a post hoc analysis, we attempted to determine whether group differences in brain activation were related to PTSS severity, as measured by the total score on the CAPS-CA. Clusters of activation that were significantly different between groups were chosen as regions of interest (ROIs). These included a middle frontal gyrus (MFG) cluster (from the contrast of control > PTSS), a medial frontal cluster (from the contrast of PTSS > control) and the insular region (from the contrast of SIB > Non-SIB). The average activation (*T* score) in each of these regions was determined for each subject in the PTSS group, and subjected to Spearman correlation analyses to determine relationships between ROI activation and total CAPS-CA and hyperarousal scores.

RESULTS

CLINICAL CHARACTERISTICS

The CAPS-CA scores ranged from 18 to 72 with a mean score of 41 and a standard deviation of 16. Four participants in the clinical group met the diagnostic criteria for PTSD as assessed by the CAPS-CA. The other 12 demonstrated significant PTSD symptoms on the CAPS-CA, but were sub-threshold for the diagnosis of PTSD. This range reflects the natural continuum of posttraumatic reactions in children.

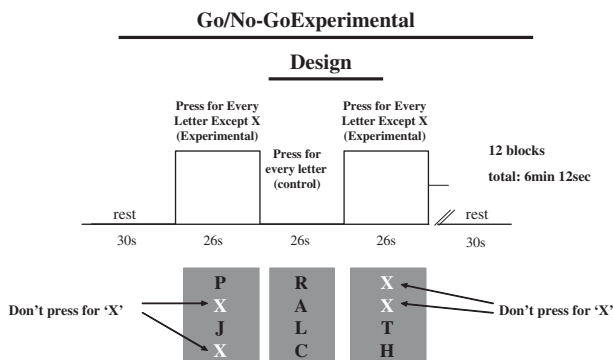


Figure 1. Design of the Go/No-Go task.

Hence, we refer to the complete group as children with a history of trauma and PTSS. The limited understanding and use of empirically derived developmental information regarding the classification of PTSD in youth make the use of PTSS a developmentally viable stance [see Carrion et al., 2001; Scheeringa et al., 2001].

Comorbid psychiatric disorders included mood disorders: major depressive disorder in three subjects; anxiety disorders: panic disorder in one subject and obsessive compulsive disorder in one subject; and behavioral disorders: ADHD-combined type in one subject and enuresis in one subject. This comorbidity is representative of clinical populations with PTSS where comorbidity for mood, anxiety and behavioral disorders can be as high as 80% [Pfefferbaum, 1997]. The PTSS group did not differ in age ($t[28] = .56, P = .58$, two-tailed) but had significantly lower full scale IQ compared with the control group ($t[27] = 4.96, P = .0001$, two-tailed). The PTSS and control groups did not differ on gender, ethnicity, or family income. None of the 14 healthy controls scored in the clinical range (64 or more) for either internalizing or externalizing symptoms on any CBCL factor.

The mean full scale IQ of the group of children with SIB was 95.0 ($SD = 5.5$) and for the Non-SIB group was 96.3 ($SD = 11.3$). The SIB group did not differ from the Non-SIB group in terms of full scale IQ ($P = .80$). However, the subjects in the control group had a mean IQ of 107.33 ($SD = 4.8$), which was significantly higher than the SIB group ($t[19] = 5.8, P = .001$) and the Non-SIB group ($t[20] = 3.7, P = .002$).

The mean CAPS-CA PTSS score of the group of children with SIB was 29.1 ($SD = 10.1$) and the Non-SIB group was 25.5 ($SD = 19.8$). The SIB group did not differ significantly from the Non-SIB group in terms of PTSS scores ($P = .64$).

TASK PERFORMANCE

All subjects performed the Go/No-Go task accurately, and there were no group differences in percent correct or reaction time for the Go trials, NoGo trials

or all trials combined. Mean and standard deviation of task performance variables for the PTSS and control groups are given in Table 1. Mean and standard deviation of task performance variables for the SIB and Non-SIB groups are given in Table 2.

The PTSS and control groups had a similar degree of movement during the fMRI scan. Mean translational movement for the PTSS group over the course of the scan was 1.52 mm ($SD = 0.73$) and for the control group was 1.26 mm ($SD = 0.76$), which were not significantly different ($P = .36$). Mean rotational movement for the PTSS group was 1.63° ($SD = 0.83$) and for the control group was 1.18° ($SD = -0.63$), which were not significantly different ($P = .11$).

fMRI RESULTS

Table 3 presents the location and Z scores of clusters of significant activation within each group (PTSS and controls). Significant differences between groups are described below.

Controls versus PTSS. One cluster centered in the left middle frontal cortex was significantly more activated in the control than the PTSS group for the No/Go-Go comparison. This region is described in Table 4. Figure 2 (top) illustrates greater activation in the left middle frontal cortex of the control group.

PTSS versus controls. The PTSS group had significantly greater activation than controls in three clusters. These clusters are listed in Table 4 and included the left cuneus in one cluster, the left inferior occipital and left inferior temporal gyri in another and the right and left medial frontal and right and left anterior cingulate gyri in a third cluster. Figure 2 (center) illustrates greater activation in the medial frontal gyri of the PTSS group.

SIB versus Non-SIB. Differences in brain activation for SIB subjects compared with Non-SIB subjects were present in two clusters. They included the right orbitofrontal, right inferior frontal/operculum and the right insula and putamen. These clusters are listed in Table 5. Figure 2 (bottom) illustrates greater insula activation in the SIB subgroup.

TABLE 1. Go-No/Go task performance summary for the PTSS and control groups

Variable	PTSS group	Control group	P
Total percent correct	92.0 (5.2)	94.1 (4.2)	.08
Go trials percent correct	95.6 (4.7)	97.5 (3.2)	.18
Percent errors of omission	4.5 (4.7)	2.5 (3.2)	.18
No Go percent correct	78.8 (2.0)	87.3 (8.6)	.15
Percent errors of commission	21.2 (19.8)	12.7 (8.6)	.15
Total reaction time (ms)	394.0 (95.2)	387.9 (53.4)	.83
Go trials reaction time (ms)	395.0 (98.6)	386.4 (54.2)	.78
No Go errors of commission reaction time (ms)	377.1 (66.9)	407.6 (61.2)	.22

Data expressed as mean plus or minus standard deviation. *P* was determined from a two-tailed independent groups *t* test; ms = milliseconds. PTSS, posttraumatic stress symptoms.

TABLE 2. Go–No Go task performance summary for the SIB and Non-SIB groups

Variable	SIB	Non-SIB	Control	<i>P</i> (SIB versus Non-SIB)	<i>P</i> (SIB versus control)
Total percent correct	87.0 (10.2)	92.2 (3.5)	93.1 (4.6)	.18	.13
Go trials percent correct	94.4 (5.4)	96.3 (4.1)	96.9 (3.9)	.45	.31
Percent errors of omission	5.6 (5.4)	3.7 (4.1)	3.1 (3.9)	.45	.31
No Go percent correct	72.2 (29.0)	84.0 (6.2)	85.5 (8.5)	.25	.21
Percent errors of commission	27.8 (29.0)	16.0 (6.2)	14.5 (8.5)	.25	.21
Total reaction time (ms)	374.1 (98.3)	409.5 (95.5)	372.6 (42.1)	.48	.97
Go trials reaction time (ms)	374.9 (103.78)	410.5 (97.5)	371.7 (43.1)	.49	.93
No Go errors of commission reaction time (ms)	337.1 (24.17)	408.2 (73.9)*	392.7 (45.2)*	*.03	*.01

Data expressed as mean plus or minus standard deviation. *P* was determined from a two-tailed independent groups *t* test. ms, milliseconds; SIB, self-injurious behaviors.

**P* < .05.

Brain activation and posttraumatic stress symptoms. CAPS-CA total score (PTSS severity) correlated positively with right insula activation (Spearman's $\rho = .80$, $P < .001$). Correlations with the MFG and the medial frontal gyrus were not significant ($P = .76$ and $.94$, respectively). Figure 3 illustrates the significant correlation between right insula and PTSS severity. Because ROIs were identified from SIB > Non-SIB contrasts, we also performed correlations for the SIB and Non-SIB groups separately. There was a significant correlation between PTSS severity and insula activation within the SIB group ($\rho = .82$, $P = .02$) and a trend toward significance within the Non-SIB group ($\rho = .64$, $P = .06$).

To determine if the association between insula activation and CAPS-CA score was specifically related to symptoms of hyperarousal, we also performed correlations with the total score from Clusters B, C and D subscales (reexperience, avoidance/numbing and hyperarousal symptoms, respectively) from the CAPS-CA. Activation in the right insula was significantly correlated with Cluster C score (Spearman's $\rho = .70$, $P = .002$) and Cluster D score (Spearman's $\rho = .60$, $P = .01$) as shown in Figure 4. There were no correlations with Cluster B score (Spearman's $\rho = .33$, $P = .22$).

Task performance was not associated with activation in any of the ROIs, including the following: Pearson's correlation showed that total percent correct was not associated with activation in the insula ($P = .21$), medial frontal ($P = .30$) or MFG ($P = .14$). Total reaction time was not associated with activation in the insula ($P = .70$), medial frontal ($P = .27$) or MFG ($P = .96$).

DISCUSSION

The average CAPS-CA score of 41 indicated that the PTSS group had a significant amount of PTSS.

Nevertheless, the PTSS and control subjects performed similarly on the Go/No-Go task, demonstrating a comparable ability to sustain attention and inhibit responses. From the standpoint of neural function, however, these two groups demonstrated significant differences in brain activation during the performance of the NoGo task. The fact that these groups performed the task with similar accuracy and response times, underscores that these brain activation differences may be associated with neurofunctional processes and not reflect different behavioral responses. During response inhibition trials, the control group showed significantly increased activation in the MFG, an area that has been implicated in cognitive operations involving response inhibition [Aron et al., 2003; Garavan et al., 1999; Menon et al., 2001]. This suggests that children with PTSS are not utilizing key areas of the frontal cortex to the same extent as a healthy age and gender-matched control group. This result may be associated with our previous finding indicating attenuation of normal frontal lobe asymmetry in children with PTSS secondary to larger left frontal gray matter when compared with controls. For example, aberrant pruning of the left frontal lobe may result in functional deficits in this area. Results are also consistent with findings from studies of adults with PTSD indicating decreased activation in the left MFG and superior frontal gyri during a continuous performance task [Semple et al., 2000]. Thus, abnormalities in the structure and function of prefrontal cortical regions may represent neurofunctional markers of PTSS. Deficits in activation of the MFG during this task have also been identified in children with ADHD [Booth et al., 2005]. In that study, however, Booth et al. also identified decreased activation of the medial frontal gyrus.

Compared with controls, youth with PTSS demonstrated increased activation in the medial frontal and anterior cingulate gyri during the Go-No/Go task.

TABLE 3. Significant differences within groups: No Go versus Go blocks

Brain region (Brodmann's area)	Corrected <i>P</i> of cluster	No. voxels in cluster	Peak Z (corrected) in region	Peak location in region <i>x, y, z</i>
PTSS				
R inferior frontal gyrus (45/47)	.001	624	3.78	36, 39, 4
L inferior frontal gyrus (47)			3.51	-28, 21, -11
R superior frontal gyrus (9/10)	.012	383	2.41	20, 61, 19
R middle frontal gyrus (9/46)			3.37	40, 45, 16
R medial frontal gyrus (9)			2.88	6, 45, 14
R orbital frontal gyrus (11)			3.26	22, 28, -13
L orbital frontal gyrus (11)			3.27	-32, 23, -11
R insula	.010	392	2.91	48, 16, 1
L insula			3.37	-32, 19, -3
R putamen			2.86	30, -2, 2
L caudate			2.27	-18, 10, 12
R inferior temporal gyrus (20)	.017	362	3.63	46, -29, -7
R middle temporal gyrus (21)			2.78	61, -32, -9
R fusiform gyrus (37)			3.50	42, -49, -8
L fusiform gyrus (19/37)	.001	528	3.37	-40, -60, -5
L inferior occipital gyrus (18)			3.22	-34, -87, 6
Control				
R inferior frontal gyrus (45/47)	.001	1609	3.91	36, 29, 4
L inferior frontal gyrus (45/47)			3.24	-30, 25, -8
R orbital frontal gyrus (11)			2.35	26, 30, -12
L orbital frontal gyrus (11)			3.50	-26, 27, -10
R medial frontal gyrus (8)			3.13	8, 33, 33
R superior frontal gyrus (8)			4.02	8, 43, 46
R middle frontal gyrus (8/9)	.019	427	3.41	30, 34, 20
R posterior medial frontal gyrus (6)			3.56	8, 10, 46
R insula			3.67	44, 19, -1
L insula			2.69	-40, 21, -8
R caudate	.001	2874	2.86	12, 18, 1
L caudate			2.31	-16, 14, 0
L ventral striatum			4.15	-6, 10, 0
R putamen			2.88	22, 13, -11
L putamen			2.58	-26, 8, 7
R thalamus			2.73	6, -25, 3
R hypothalamus			2.23	6, -8, 2
R precentral gyrus (6)	.017	434	3.98	30, 7, 53
R inferior temporal gyrus (37)			2.67	50, -52, -4
R middle temporal gyrus (21)			3.94	46, -24, -14
R superior temporal gyrus (22)	.001	688	2.32	55, -4, -8
R fusiform gyrus (19)			3.04	42, -61, -10
L fusiform (19)			3.26	-44, -71, -12
L parahippocampal gyrus (35)			2.99	-20, -45, -4
R superior parietal sulcus (7)	.001	1015	3.61	-20, -42, 48
R inferior parietal sulcus (40)			3.11	46, -39, 42
R precuneus brainstem	.006	505	3.07	8, -60, 38
			2.88	-6, -30, -10
L lingual gyrus (19)	.001	677	3.04	-22, -49, 1
R inferior occipital gyrus (18)			2.67	44, -66, -5
L inferior occipital gyrus (18)			2.96	-42, -74, -10

Location and Z scores of clusters of significant activation within each group. Cluster-wise probability, cluster size, peak Z-score in region and Talairach coordinates of peak per region are given. L, left; R, right.

In another study of children with ADHD, these regions have also shown increased activation during this task [Schulz et al., 2004]. These studies suggest that inappropriate levels of medial frontal activation may be part of a functional correlate of deficits in response

inhibition. Furthermore, poor medial frontal activation may be related to poor control over limbic responses since the medial frontal lobe is strongly connected with the amygdala [Price, 1999]. One recent symptom provocation, positron emission tomography study,

TABLE 4. Significant differences between groups after covarying for IQ: No Go versus Go blocks

Brain region (Brodmann's area)	Corrected <i>P</i> of cluster	No. voxels in cluster	Peak <i>Z</i> (corrected) in region	Peak location in region <i>x, y, z</i>
Control > PTSS				
L middle frontal (9/46)	.041	119	3.31	-34, 38, 17
PTSS > Control				
L cuneus (17/18)	.017	138	3.97	-12, -77, 15
L inferior occipital (18/19)	.001	220	3.14	-46, -66, -7
L inferior temporal (37)			2.96	-44, -72, 0
R medial frontal gyrus (8/9)	.016	140	3.02	6, 26, 19
L medial frontal gyrus (8/9)			2.74	-10, 34, 15
R anterior cingulate (32/24)			2.64	4, 28, 17
L anterior cingulate (32/24)			2.69	-6, 30, 17

Location and *Z* scores of clusters of activation significantly different between subject groups. Cluster-wise probability, cluster size, peak *Z*-score in region and Talairach coordinates of peak per region are given. L, left; R, right.

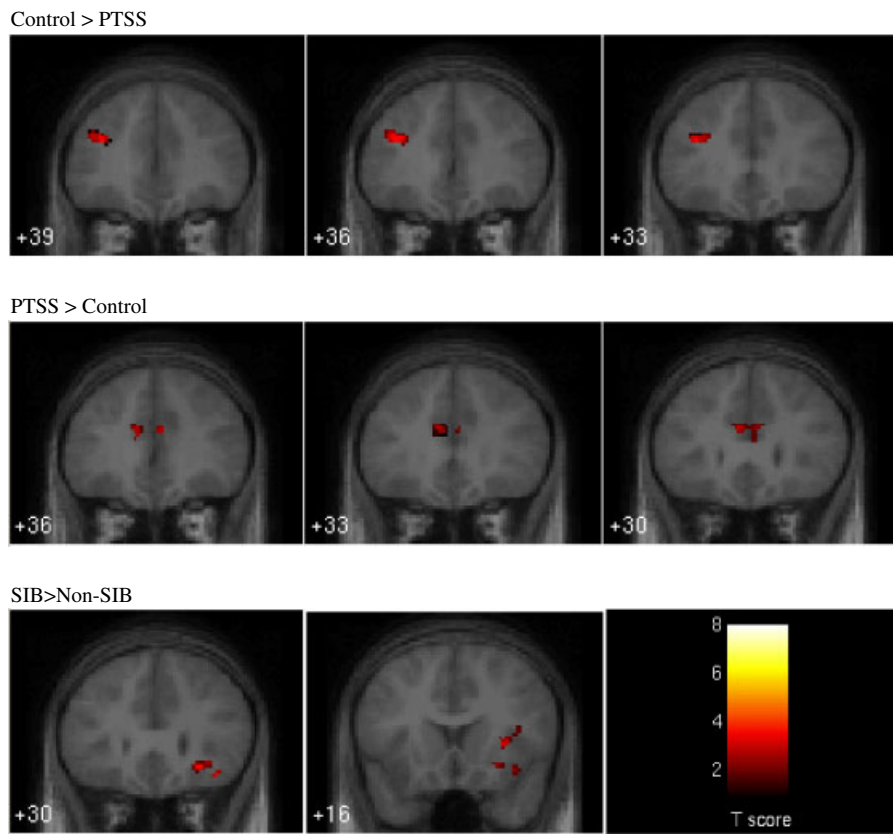


Figure 2. Clusters of activation that are different between groups. On the top, activation significantly greater in the Control compared with posttraumatic stress symptoms (PTSS) group. The center picture shows activation significantly greater in the PTSS compared with Control group. The bottom picture shows activation significantly greater in the PTSS/SIB group compared with the PTSS/Non-SIB group. Cluster-wise significance = 0.05, corrected for multiple comparisons. The thermometer shows the *T* score values displayed on panels. SIB, self-injurious behaviors.

however, did not find a direct interaction between amygdala activation and failure of inhibition by medial frontal regions in adults with PTSD [Gilboa et al., 2004]. In fact, through functional connectivity analyses, they identify positive influences of the amygdala on

medial regions. Accordingly, the authors conclude that rather than an extinction of amygdala-mediated fear conditioning, medial frontal regions may be involved in a nonspecific regulation of autonomic responses to stressful situations.

TABLE 5. Significant activation related to self-injurious behavior No Go versus Go blocks

Brain region (Brodmann's area)	Corrected <i>P</i> of cluster	No. voxels in cluster	Peak Z (corrected) in region	Peak location in region <i>x, y, z</i>
SIB > Non-SIB				
R orbital frontal (11)	.001	158	2.30	28, 30, -10
R inferior frontal/operculum (45/47)				30, 23, -1
R insula	.003	133	2.76	32, 14, 3
R putamen			2.59	32, 9, -7

Location and Z scores of clusters of activation significantly different between SIB and Non-SIB subject groups. Cluster-wise probability, cluster size, peak Z-score in region, and Talairach coordinates of peak per region are given. L, left; R, right; SIB, self-injurious behavior.

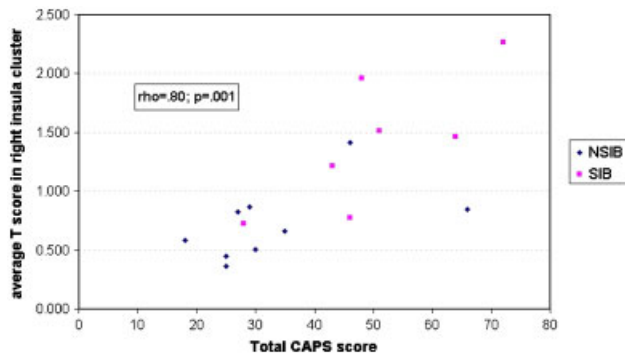


Figure 3. Total posttraumatic stress symptoms (PTSS) score and right insula Cluster Activation Correlation in the PTSS group. CAPS, Clinician Administered PTSD Scale; SIB, self-injurious behaviors, NSIB, non-SIB.

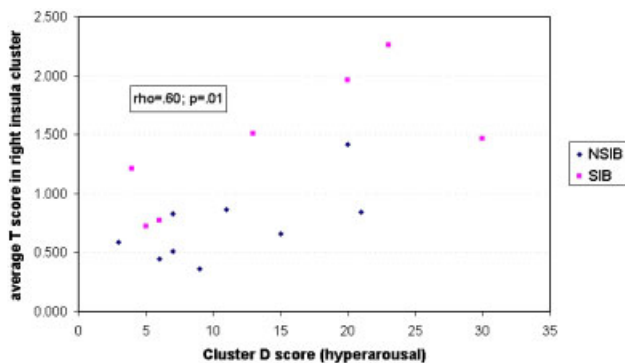


Figure 4. Cluster D hyperarousal score and right insula Cluster Activation Correlation in the posttraumatic stress symptoms group.

To explore the role of the impact of depressive symptoms, we reanalyzed the data excluding the subjects with major depressive disorder. After removing the subjects with major depressive disorder (MDD), and comparing PTSS minus control subjects, the medial frontal cluster activation failed to replicate. Hence, medial frontal activation may, in fact, be related to depressive symptoms. In contrast, in the analysis

of Control minus PTSS subjects the left middle frontal activation remained. The cluster is larger, in fact, and there is a small cluster in the opposite hemisphere.

The SIB subgroup showed increased activity in right orbitofrontal gyrus when compared with youths with PTSS and Non-SIB. Activation of the OFC by individuals who injure themselves is interesting in view of anatomical data suggesting that the OFC integrates visceral and sensory information to produce an affective state [Price, 1999] and lesion data suggesting that the OFC is needed to associate stimuli with their reinforcement value in conditioning paradigms [Pears et al., 2003]. OFC findings should be interpreted with caution because even with spiral imaging there may be signal loss in this region due to susceptibility artifacts. We would expect, however, this signal loss to be equivalent in both experimental and control subjects.

Increased insula activation suggests that the SIB group is experiencing increased physiological arousal during a simple cognitive task. This interpretation is based on previous neuroimaging studies of healthy adults that showed insula activation associated with both physical and mental stress tasks [Critchley et al., 2000] and while anxiously anticipating a shock [Chua et al., 1999]. In adults with PTSD, increased insula activation has been demonstrated during presentation of trauma-related words [Shin et al., 2001] and was found to correlate with flashback intensity [Osuch et al., 2001]. In contrast, in our cognitive task, our findings demonstrate that insula activation correlates with hyperarousal and avoidance/numbing symptoms. Although the association between hyperarousal symptoms and insula activation was expected in view of the insula's role in physiological arousal, the association with emotional numbing symptoms may represent developmental trends in the progression of symptoms and the link between clusters. In fact, our laboratory has demonstrated that hyperarousal symptoms at baseline can predict the development of emotional numbing symptoms at follow-up in traumatized youth [Weems et al., 2003].

It is important to remember that the NoGo minus Go subtraction used in this study elucidates brain activation associated with several cognitive processes,

including response inhibition, attention, decision making and decision monitoring. We used a block design task to examine these processes over a sustained period. Therefore, our study does not attempt to conclude exactly which cognitive process is sub-served by each activated brain region, but rather, to investigate brain regions employed when subjects perform a response-inhibition task over a block of time. As this design incorporates a combination of neural processes, our findings should be interpreted within the context of this complexity.

A shortcoming of the study is that we did not use a parametric task design. A parametric task would include trials of a range of difficulty such that the PTSS subjects showed decreased accuracy on trials with greater difficulty, whereas control subjects were able to accurately perform all trials. This would be helpful in showing deficits in response inhibition in PTSS. For example, Rubia et al. [2001] found that impaired response inhibition in youth with ADHD was observed only during the more demanding components of a Go/No-Go task. A more challenging Go/No-Go task might highlight attentional and inhibitory deficits in PTSS subjects. In this study, lack of group differences in task performance indicate that either the task was not difficult enough to challenge the PTSS subjects, that there are no behavioral deficits in response inhibition in our sample of youth with PTSS, or that the sample is too small to detect differences. As previous studies have shown that PTSD is associated with deficits in attention and response inhibition [Beers and De Bellis, 2002; Vasterling et al., 1998], we propose that the PTSS group did not show task-performance deficits because our task was comparatively easy. However, the interpretation of our fMRI data is aided by the fact that there were no behavioral differences in task performance, as group differences in brain activation cannot be accounted for group differences in task accuracy.

CONCLUSIONS

Replication of this pilot study using larger subject groups may help determine more specific cognitive processes affected by PTSS. A larger sample size may allow for further analyses of relevant sub-groups, such as a group with history of trauma, but no posttraumatic symptoms. Interpretation of nonsignificant findings (e.g., lack of behavioral performance difference during the Go/NoGo task) should be interpreted with caution as this result may be due to limited power. Comorbid psychiatric illness and reduced IQ and socio-economic status, although representative of the PTSS population, need to be addressed with comparable clinical groups in future studies. The role of birth and prenatal history needs evaluation as children exposed to interpersonal violence may experience socio-emotional deprivation and this may manifest on brain function. Finally, future control groups should be assessed with structured

clinical interviews, such as the K-SADS, to rule out psychopathology even if the group is free from clinical symptoms as assessed by a questionnaire.

Our results suggest that youth with PTSS have decreased activation in the middle frontal cortex while inhibiting a pre-potent response. Because other conditions, such as ADHD, have shown similar findings, these results may represent deficits of response inhibition that cut across different clinical groups. This decreased activation in the middle frontal cortex may affect inhibition of regions that mediate arousal, as demonstrated by increased insula activation in the SIB group. The physiological mechanisms by which activation in the frontal cortex is compromised during response inhibition in children with PTSS remain to be elucidated, but autonomic and endocrine processes are promising areas of study.

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