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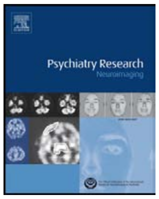

Alterations in the neural circuitry for emotion and attention associated with posttraumatic stress symptomatology

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A B S T R A C T

Information processing models of posttraumatic stress disorder (PTSD) suggest that PTSD is characterized by preferential allocation of attentional resources to potentially threatening stimuli. However, few studies have examined the neural pattern underlying attention and emotion in association with PTSD symptomatology. In the present study, combat veterans with PTSD symptomatology engaged in an emotional oddball task while undergoing functional magnetic resonance imaging (fMRI). Veterans were classified into a high or low symptomatology group based on their scores on the Davidson Trauma Scale (DTS). Participants discriminated infrequent target stimuli (circles) from frequent standards (squares) while emotional and neutral distractors were presented infrequently and irregularly. Results revealed that participants with greater PTSD symptomatology showed enhanced neural activity in ventral-limbic and dorsal regions for emotional stimuli and attenuated activity in dorsolateral prefrontal and parietal regions for attention targets. In the anterior cingulate gyrus, participants with fewer PTSD symptoms showed equivalent responses to attentional and emotional stimuli while the high symptom group showed greater activation for negative emotional stimuli. Taken together, the results suggest that hyperresponsive ventral-limbic activity coupled with altered dorsal-attention and anterior cingulate function may be a neural marker of attention bias in PTSD.

1. Introduction

Rates of posttraumatic stress disorder (PTSD) in returning veterans from Iraq and Afghanistan are high, with some estimates showing that close to 20% of Army and Marine troops meet criteria for PTSD 3 to 4 months post-deployment (Hoge et al., 2006). PTSD in these veterans is associated with cognitive deficits and functional impairment in everyday life (Hoge et al., 2006; Vasterling et al., 2006). Neuropsychological studies suggest that the nature of these cognitive deficits is more closely related to inattention and interference during the encoding process than retention loss due to amnesia (Vasterling and Brailey, 2005). One such source of interference in PTSD may be attentional bias to threatening information, which disrupts ongoing cognitive activities by redirecting attentional resources away from the cognitive task at hand. For instance, combat veterans show longer response latencies while naming the color of the ink used to print trauma-related words during an emotional Stroop task (McNally et al., 1990; Kaspi et al., 1995; Constans et al., 2004). It is therefore hypothesized that delayed naming of emotional words represents a diversion of attention away from neutral stimuli toward traumatic stimuli in individuals with PTSD. Further evidence for attentional bias in PTSD comes from ERP studies that show enhanced P3 amplitude responses to threat or novel distracting stimuli (Attias et al., 1996; Kimble et al., 2000; Stanford et al., 2001). These studies employed modified oddball paradigms in which infrequent salient target stimuli were interspersed with frequent standard stimuli. Alterations in P3 amplitudes and latencies for emotional versus neutral stimuli provide evidence for heightened responsivity to potentially threatening stimuli in PTSD.

While there is evidence for attentional bias for threat from behavioral and ERP studies, evidence from neuroimaging studies for threat bias is scarce. The majority of previous neuroimaging studies in PTSD have focused on investigating provocation of trauma symptoms (Rauch et al., 1996; Bremner et al., 1999; Liberzon et al., 1999; Shin et al., 1999; Lanius et al., 2001; Lanius et al., 2002; Pissiota et al., 2002; Lanius et al., 2003a; Gilboa et al., 2004; Shin et al., 2004; Yang et al., 2004; Britton et al., 2005; Sakamoto et al., 2005), while others have examined cognition in PTSD such as working memory impairment

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Table 1
Demographic and clinical characteristics of subject sample

Characteristic	High DTS	Low DTS	*T/chi square*	*P*
	n=14	*n*=12		
Age (years), [S.D.]	35.5 [3.6]	37.2 [11.6]	0.35	>0.73
Gender, No. (%) of females	4 (29)	1 (8.3)	1.70	>0.19
Handedness, No. (%) right-handed	12 (86)	12 (100)	1.86	>0.17
Ethnicity, No. (%) of Caucasian subjects	7 (50)	8 (66.7)	0.74	>0.39
Education (years), [S.D.]	14.5 [1.6]	15.8 [3.2]	1.28	>0.21
Davidson Trauma Scale [S.D.]	71 [23]	14 [14]	7.30	<0.001
Combat Exposure Scale [S.D.]	17.1 [8.8]	8.7 [9.1]	2.41	<0.03
Beck Depression Inventory [S.D.]	22.9 [9.5]	9.6 [8.3]	2.29	<0.04
AUDIT [S.D.]	4.0 [3.6]	5.7 [5.8]	0.87	>0.39
Drug Abuse Screening Test [S.D.]	1.21 [2.0]	0.33 [1.15]	1.32	>0.20

AUDIT = Alcohol Use Disorders Identification Test; DTS = Davidson Trauma Scale.

without inclusion of emotional stimuli (Clark et al., 2003). However, in order to understand the neural circuitry underlying concentration and attention difficulties in relation to PTSD symptomatology, examination of both emotion and executive processing is necessary. Few neuroimaging studies have examined both emotion and attention within the same paradigm to simulate emotional distraction that occurs during cognitive task performance in real life. Neuroimaging studies that have employed emotional Stroop tasks in patients with PTSD (Shin et al., 2001; Bremner et al., 2004) combine the focus of both emotion and attention systems on the same stimulus, rendering it difficult to separate these two processes.

The goal of the present study was to examine the neural circuitry underlying alterations in attention by emotional distraction in veterans with symptoms of PTSD. We employed a modified emotional oddball paradigm based on our previous work in healthy adults, in which we demonstrated that emotion and attention function segregate into two large-scale neural networks (Yamasaki et al., 2002), with emotional content engaging fronto-limbic regions including the amygdala and inferior prefrontal cortex (IFG) and attentional targets engaging dorsolateral prefrontal cortex and posterior parietal regions. Additionally, emotional distractors and attentional targets both engage the rostral anterior cingulate cortex (ACC) suggesting that this region is important for integrating executive and emotion processing streams (Yamasaki et al., 2002; Fichtenholtz et al., 2004). The present study tested several hypotheses. First, PTSD symptom severity should be related to greater activation in ventral-limbic regions during the emotional condition, including the ventromedial prefrontal cortex (vmPFC) and amygdala. Second, symptom severity should be related to attenuated activity in dorsal frontal and parietal regions during the attention task, such as the middle frontal gyrus (MFG) and supramarginal gyrus (SMG) reflecting the disruption of executive pathways in PTSD. Finally, based on our previous work, we hypothesized that PTSD symptomatology would be related to an altered pattern of ACC activity for emotional and target stimuli.

2. Methods

2.1. Participants

Twenty-six recently returned (mean±S.D.; 23±14 months) veterans from deployments to post-9/11 military conflicts completed the fMRI procedures. Veterans were recruited from a large recruitment database for the study of post-deployment mental health. Veterans entering the registry completed a neuropsychiatric self-assessment battery which included the Davidson Trauma Scale (DTS; Davidson et al., 1997), Beck Depression Inventory-II (BDI-II; Beck et al., 1996), Combat Exposure Scale (CES; Keane et al., 1989), Trauma Life Events Questionnaire (TLEQ; Kubany et al., 2000), Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), and Drug Abuse Screening Test (DAST; Skinner, 1982). Veterans with prior history of combat trauma as assessed by the TLEQ were contacted by phone and screened to exclude those with a history of psychotic symptoms, serious medical illness, head injury resulting in a loss of consciousness, or shrapnel or other metal in their bodies. Twenty-one participants served in either Iraq or Afghanistan, while the remaining subjects served in other regions including Kuwait and Saudi Arabia. Participants provided written informed consent for procedures approved by the Institutional Review Boards at Duke University and the Durham VA Medical Center.

The DTS is a 17-item self report measure that assesses trauma symptoms and has high test–retest reliability, internal consistency, convergent and divergent validity, and predictive validity (Davidson et al., 1997). This measure was administered to participants prior to scanning to obtain a current measure of PTSD symptomatology. A cutoff score of 40, which has previously shown to have good diagnostic accuracy against a clinician-administered interview (Davidson et al., 1997), was used to partition participants into a low DTS group (*n*=12; *M* DTS=14; S.D.=14) and a high DTS group (*n*=14; *M* DTS=71; S.D.=23).

Subject demographics are summarized in Table 1. The groups did not differ on age, education, gender, ethnicity, handedness, alcohol use as assessed by the AUDIT, or drug abuse as assessed by the DAST. The high DTS group reported greater exposure to combat situations than the low DTS group as assessed by the CES. The high DTS group also had significantly higher scores on the BDI than the low DTS group. Three participants (2 high DTS and 1 low DTS) were taking antidepressant medication that included selective serotonin reuptake inhibitors and/or norepinephrine dopamine modulators.

Table 2
IAPS valence and arousal

Picture ID	Picture description	Valence	Arousal
2053	Baby	2.47	5.25
2800	Sad child	1.78	5.49
2810	Boy	4.31	4.47
2900	Crying boy	2.45	5.09
3000	Mutilation	1.45	7.26
3030	Mutilation	1.91	6.76
3053	Burn victim	1.31	6.91
3060	Mutilation	1.79	7.12
3063	Mutilation	1.49	6.35
3071	Mutilation	1.88	6.86
3080	Mutilation	1.48	7.22
3100	Burn victim	1.60	6.49
3110	Burn victim	1.79	6.70
3120	Dead body	1.56	6.84
3150	Mutilation	2.26	6.55
3160	Eye disease	2.63	5.35
3220	Hospital	2.49	5.52
3230	Dying man	2.02	5.41
3280	Dental exam	3.72	5.39
3350	Infant	1.88	5.72
3400	Severed hand	2.35	6.91
3530	Attack	1.80	6.82
3550	Injury	2.54	5.92
6190	Aimed gun	3.57	5.64
6212	Soldier	2.19	6.01
6243	Aimed gun	2.33	5.99
6244	Aimed gun	3.09	5.68
6250	Aimed gun	2.83	6.54
6510	Attack	2.46	6.96
6550	Attack	2.73	7.09
6570	Suicide	2.19	6.24
9007	Needles	2.49	5.03
9040	Starving child	1.67	5.82
9041	Scared child	2.98	4.64
9253	Mutilation	2.00	5.53
9400	Soldier	2.50	5.99
9404	Soldiers	3.71	4.67
9405	Sliced hand	1.83	6.08
9420	Soldier	2.31	5.69

IAPS = International Affective Picture System.

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2.2. Stimulus presentation

Four categories of stimuli were displayed: (i) emotional distractor pictures from the International Affective Picture System (IAPS; Lang et al., 2005) (ii) neutral distractor pictures matched with negative pictures for luminance, presence of human figures, and chromatic features (iii) baseline standards consisting of squares of varying colors and sizes (iv) attentional targets consisting of circles of varying colors and sizes.

Negative IAPS pictures were utilized in this study in lieu of Iraq War combat-specific pictures for their known psychometric properties. Pictures included depictions of mutilations, burn victims, attacks and aimed guns, sick or crying children, and medical illnesses. Arousal and valence ratings of each negative picture included in the study are shown in Table 2.

Stimuli were presented for 1.5 s with a 2.0 s stimulus onset asynchrony in an event-related design. Target circles and emotional and neutral distractors were pseudorandomly distributed throughout each run. The interval between successive rare stimuli (i.e., targets, distractors, or both) was randomized. Eight runs lasted 4 min and 52 s each. Stimuli consisted of 891 standards (84.4% of all trials), 87 attentional targets (8.2%), and 39 each of emotional and neutral pictures (3.7%). Participants were instructed to press the same button for all standard, emotional and neutral stimuli, but a different button press for target stimuli.

2.3. MRI acquisition and analysis

Functional images were acquired on a 3-Tesla GE scanner. fMRI data were collected with a gradient-echo inverse spiral pulse sequence (Guo and Song, 2003) with the following imaging parameters: repetition time (TR) = 2000 ms; echo time (TE) = 30 ms, field of view (FOV) = 24; 34 axial slices parallel to the AC–PC plane, 3.75 × 3.75 × 3.8 mm. High-resolution 3D SPGR images (TR = 12 ms; TE = 5.4 ms; FOV = 24) covering the entire brain were acquired to aid in normalization and coregistration. Functional data sets were preprocessed using FSL version 3.3.5 (Smith et al., 2004). Preprocessing was applied to individual participants' data in the following steps: (i) brain extraction for non-brain removal (Smith, 2002), (ii) motion correction using MCFLIRT (Jenkinson et al., 2002), (iii) spatial smoothing using a Gaussian kernel of FWHM 5 mm, (iv) mean-based intensity normalization of all volumes by the same factor, and (v) high-pass filtering (Jenkinson et al., 2002; Smith et al., 2004). Functional images of each participant were co-registered to structural images in native space, and structural images were normalized into a standard stereotaxic space (Montreal Neurological Institute) for intersubject comparison. The same transformation matrices used for structural-to-standard transformations were then used for functional-to-standard space transformations of co-registered functional images.

Statistical analyses consisting of both voxel-based and region of interest (ROI) analyses were performed using custom software. For each individual, the fMRI signal was selectively averaged as a function of trial type (i.e., emotional, neutral, and target) and two pre-stimulus and eight post-stimulus time points (i.e., image volumes). Epoch averages were correlated at each voxel with a canonical hemodynamic response function. *T*-statistics from each participant were then submitted to a random effects group analysis to evaluate whether the mean effect from the population differs from zero. For group difference analyses, time points around the peak signal change for each condition were averaged within each individual and then contrasted between the two groups.

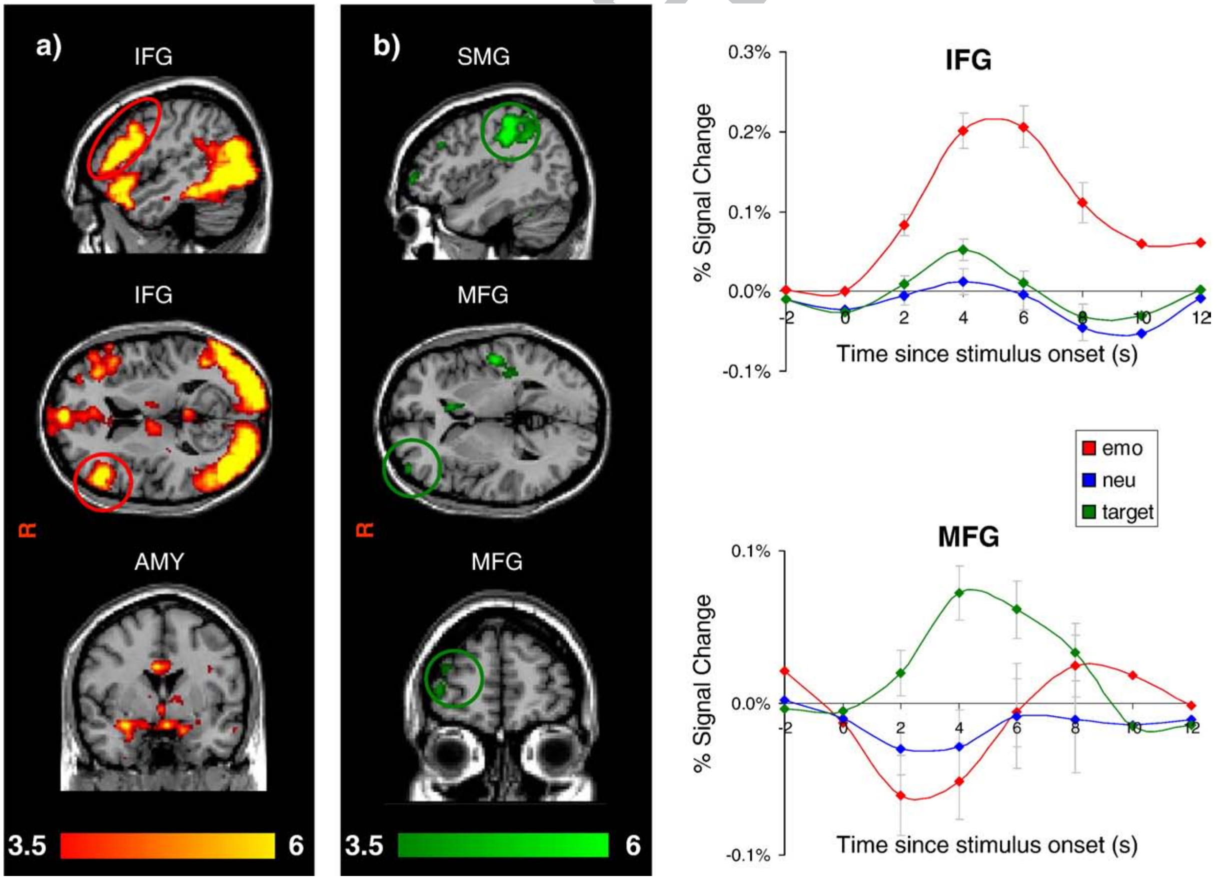

Fig. 1. Dissociable systems for ventral and dorsal regions in all 26 subjects. (a) Emotional distracters elicited activation in ventral regions including inferior frontal gyrus (IFG) and amygdala (AMY). (b) Target circles elicited activation in dorsal-attention regions including middle frontal gyrus (MFG), and supramarginal gyrus (SMG).

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Functional ROIs were selected from voxels showing maximum effects in the contrasts of interest as identified by voxel-based analyses. For both voxel- and ROI-based analyses, an intensity threshold of $P<0.002$ (two-tailed) and extent threshold of 10 contiguous voxels was used for *a priori* areas of interest, and $P<0.001$ and extent threshold of 10 voxels for all other areas. Selection of *a priori* areas of interest was guided by hypotheses derived from our previous emotional oddball studies (Yamasaki et al., 2002; Fichtenholtz et al., 2004; Morey et al., 2008) and included IFG, amygdala, vmPFC, orbitofrontal cortex (OFG), MFG, SMG, and the cingulate cortex. Percent signal change at time points 2, 4, 6, and 8 s post-stimulus for each ROI was analyzed by repeated measures MANOVA. An alpha level of 0.05 was used to determine significant activity in all MANOVA contrasts.

Finally, to investigate individual differences regarding symptom severity and executive and emotion processing, multiple regression analyses between fMRI data and DTS and BDI were performed within ROIs identified by voxel-based analyses of contrasts of interest (i.e., emotion>target and target>emotion).

3. Results

3.1. Behavioral performance

Behavioral analysis is based on 11 high DTS participants and 11 low DTS participants. Three participants were excluded from the behavioral analysis because they did not make a button press to distractor pictures, and one participant was excluded from the behavioral analysis for making the same button press to both targets and distractors. MANOVA for reaction time with condition (emotion, neutral, target, standard) as a within subjects factor and group (low or high DTS) as a between subjects factor yielded a main effect of condition (Wilks' Lambda=0.12; $F_{3,18}=44.99$, $P<0.0001$). Post hoc analyses revealed that participants had longer reaction time latencies for the emotional condition than for the other conditions ($Ps<0.001$ for all). There was no condition by group interaction (Wilks' Lambda=0.84; $F_{3,18}=1.15$, $P>0.3$).

For response accuracy, MANOVA revealed a main effect of condition (Wilks' Lambda=0.35; $F_{3,18}=11.2$, $P<0.001$). Participants were less accurate in making a button response to target stimuli in comparison to emotional, neutral and standard conditions ($P<0.0001$ for all) and also less accurate for emotion stimuli than neutral stimuli ($P=0.05$). There was a marginal condition by group interaction (Wilks' Lambda=0.66; $F_{3,18}=3.04$, $P=0.056$) suggesting that high DTS participants were less accurate in detecting targets versus the other picture types relative to low DTS participants.

3.2. fMRI results

3.2.1. Regions of activation for group

As expected, random effects group analysis for the emotional condition revealed activation in ventral brain regions including IFG, OFG, vmPFC, and amygdala (see Fig. 1). Percent signal change extracted

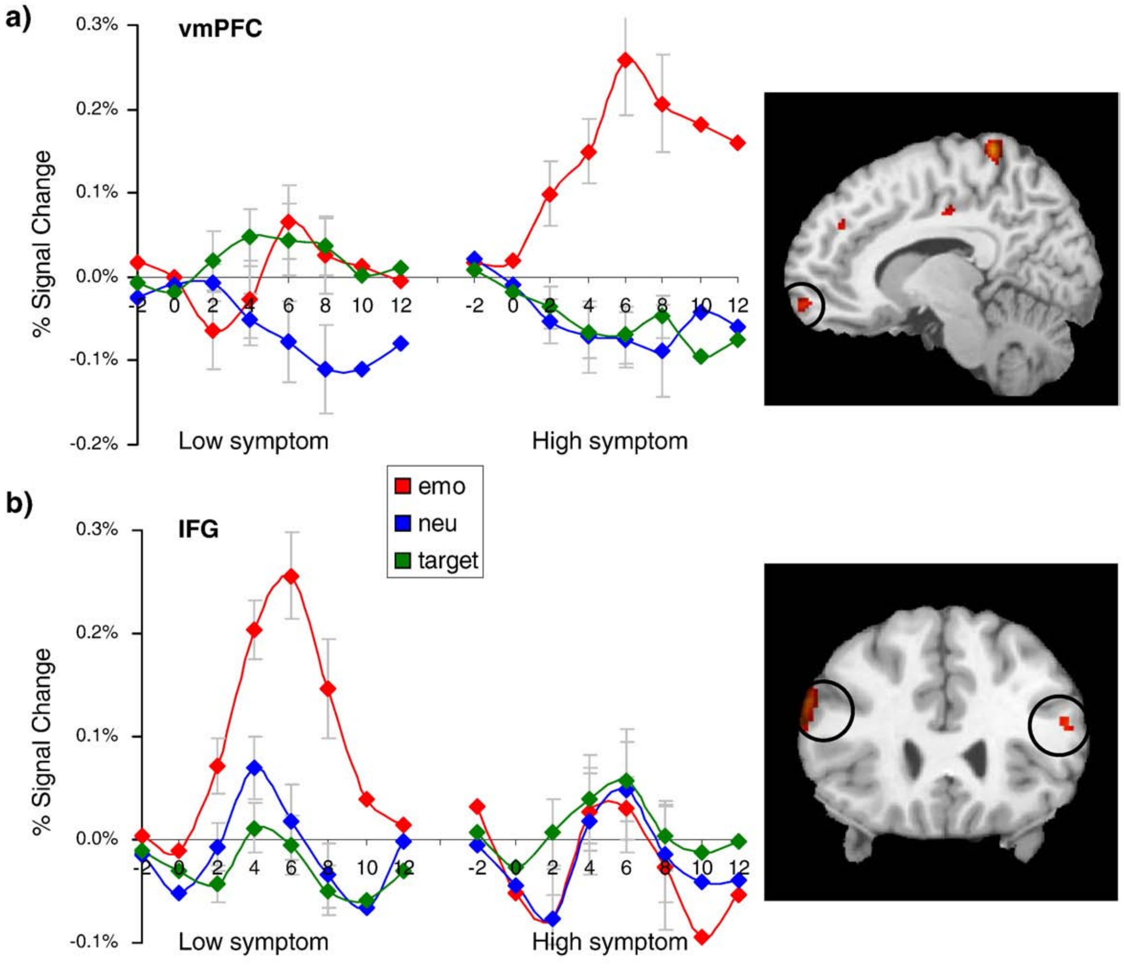

Fig. 2. Comparison of mean percent signal change in ventral emotional regions corresponding to emotional, neutral, and target stimuli in the low and high PTSD symptom groups. (a) Activation in the ventromedial prefrontal cortex (vmPFC) was greater for emotional distracters in the high symptom group but not in the low symptom group. (b) Activation in the inferior frontal gyrus (IFG) was greater for emotional distracters in the low symptom group but not the high symptom group.

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from an IFG ROI shows that this region was activated for emotional stimuli, but not for neutral or target stimuli. MANOVA was highly significant for a main effect of condition (Wilks' Lambda = 0.24; $F_{2,24}=37.19$, $P<0.00001$), time point (Wilks' Lambda = 0.28; $F_{3,23}=19.43$, $P<0.0001$) and a condition by time interaction (Wilks' Lambda = 0.39; $F_{6,20}=5.15$, $P<0.003$). Activation was greater for emotion than neutral and target at all time points examined ($P<0.002$ for all).

Conversely, the target identification task evoked activity in dorsal regions, including the right middle frontal gyrus (MFG) and other frontoparietal regions. In MFG there was a main effect for condition (Wilks' Lambda = 0.75; $F_{2,24}=4.05$, $P<0.04$) and a condition by time interaction (Wilks' Lambda = 0.39; $F_{6,20}=5.20$, $P<0.003$). Planned comparisons revealed that at 4 s, percent signal change was higher for targets than emotional ($P<0.0003$) and neutral ($P<0.04$) distractors.

3.2.2. Between groups: ventral regions

The between-group contrast of emotion > target revealed greater activation in bilateral IFG (414 voxels) in low DTS participants relative to high DTS participants (see Fig. 2). MANOVA yielded a significant condition by group interaction (Wilks' Lambda = 0.56; $F_{2,23}=9$, $P<0.002$). Planned comparisons revealed that emotional distractors elicited greater signal in the low DTS group than the high DTS group at 2 and 6 s (Ps <0.05). A left anterior temporal lobe and left cerebellar region was also activated although we did not hypothesize a role for these regions prior to the study.

Conversely, the high DTS group showed greater activation in right vmPFC, right peri-amygdala regions, and right OFG. In the vmPFC (132 voxels), MANOVA indicated a significant condition by group interaction (Wilks' Lambda = 0.7; $F_{2,23}=5$, $P<0.02$). Emotional distractors elicited greater signal in the high DTS than low DTS group at all time points (Ps <0.03). In peri-amygdala regions (110 voxels), MANOVA revealed a significant condition by group interaction (Wilks' Lambda = 0.57; $F_{2,23}=8.63$, $P<0.003$) and a condition by time by group interaction (Wilks' Lambda = 0.54; $F_{6,19}=2.71$, $P<0.05$). Follow up tests showed greater activity for emotional pictures in the high DTS group in comparison to the low DTS group at 6 and 8 s ($P<0.02$). In OFG (447 voxels), repeated measures MANOVA revealed a significant condition by group interaction (Wilks' Lambda = 0.66; $F_{2,23}=5.84$, $P<0.01$). Follow up tests showed that the high DTS group had greater activation for emotional stimuli than the low DTS group at 4, 6, and 8 s ($P<0.03$ for all).

3.2.3. Between groups: dorsal regions

For attentional targets, we hypothesized that high DTS symptoms would be associated with reduced activity in putative dorsal-attention regions. As expected, the high DTS group showed reduced activity in right MFG and right SMG for the target > emotion contrast. In MFG (731 voxels), repeated measures MANOVA indicated a significant condition by group interaction (Wilks' Lambda = 0.66; $F_{2,23}=5.83$, $P<0.01$). Planned comparisons revealed decreased activation in the high DTS group than the low DTS group in MFG for targets at 4 s

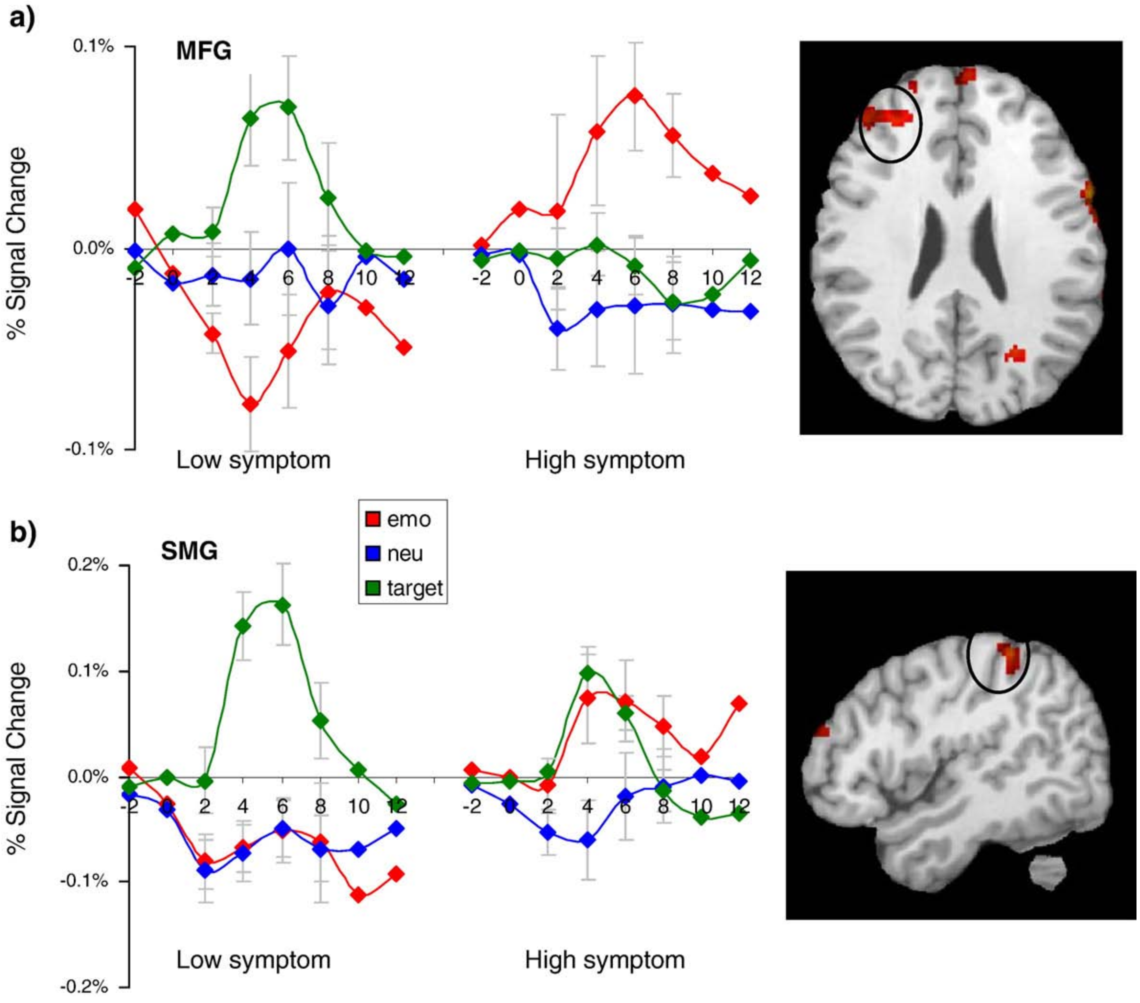

Fig. 3. Comparison of mean percent signal change in dorsal executive-attention regions corresponding to emotional, neutral, and target stimuli in the low and high PTSD symptom groups. (a) Activation in the middle frontal gyrus (MFG) prefrontal cortex was greater for circle targets in the low symptom group than the high symptom group. (b) Activation in the supramarginal gyrus (SMG) was also greater for circle targets in the low symptom group than the high symptom group.

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($P<0.03$) and 6 s ($P<0.02$). The high DTS group, however, had greater activation in this region for emotional stimuli at 4 s ($P<0.007$), 6 s ($P<.004$), and 8 s ($P<0.04$).

In right SMG (296 voxels), MANOVA revealed a significant condition by group interaction (Wilks' Lambda=0.55; $F_{2,23}=9.32$, $P<0.002$), condition by time by group interaction (Wilks' Lambda=0.49; $F_{6,19}=3.33$, $P<0.03$) and condition by time interaction (Wilks' Lambda=0.42; $F_{6,19}=4.45$, $P<0.007$) (Fig. 3). Follow up tests showed that the high DTS group had reduced activation for target stimuli in comparison to the low DTS group at 6 s ($P<0.02$), but greater activation for emotional stimuli at 4 s ($P<0.02$) and 6 s ($P<0.03$). There were no regions for which the high DTS group had greater activation than the low DTS group for target stimuli.

3.2.4. Regression by symptom severity

Multiple regression analysis by DTS and BDI scores was performed to examine the relationship between regions of interest and PTSD and depression symptomatology. Based on the between groups IFG ROI contrast, results indicate that the variables entered significantly explained the variation in IFG ($F_{2,23}=7.52$, $P<0.004$). However, only the DTS was a significant predictor in the model ($t_{23}=3.75$, $P<0.002$). The results suggest that activity in the IFG decreased as PTSD symptom severity increased. Similarly, PTSD symptom severity inversely predicted BOLD signal activity in the MFG ($t_{23}=3.79$, $P<0.002$), but again depression symptom severity was not a significant predictor in the model ($t_{23}=0.79$, $P>0.44$). This finding is consistent with our hypothesis that greater PTSD symptom severity is related to attenuation of the dorsal-attention network.

In the vmPFC ROI, DTS again was a significant predictor in the model ($t_{23}=2.75$, $P<0.02$), whereas BDI was not ($t_{23}=0.47$, $P>0.64$). This result indicates a significant positive relationship between vmPFC and PTSD symptom severity but not depression symptom severity.

3.2.5. Anterior cingulate

To investigate the putative role of the anterior cingulate in emotion and attention integration, we examined regions of overlap where both emotion and target stimuli evoked greater activation than neutral stimuli in the entire group of participants. Three cingulate regions were activated as shown in Fig. 4, including a rostral ACC region (region 1; 70 voxels), a dorsal ACC region (region 2; 41 voxels), and a posterior ventral region (region 3; 116 voxels). These regions were submitted to ROI analysis and compared across and within the two groups.

A 3-way MANOVA using condition (emotion, target, and neutral) and region (1, 2, and 3) as repeated variables and group (high, low DTS) as the between subjects factor at peak time points yielded a significant condition by region by group interaction (Wilks' Lambda=0.65; $F_{4,21}=2.87$, $P<0.05$). Follow up tests revealed that in region 2, the high DTS group showed greater activation to emotion distractors than the low DTS group.

The low DTS group showed two patterns of responses across the cingulate regions. In region 1, MANOVA revealed a significant condition

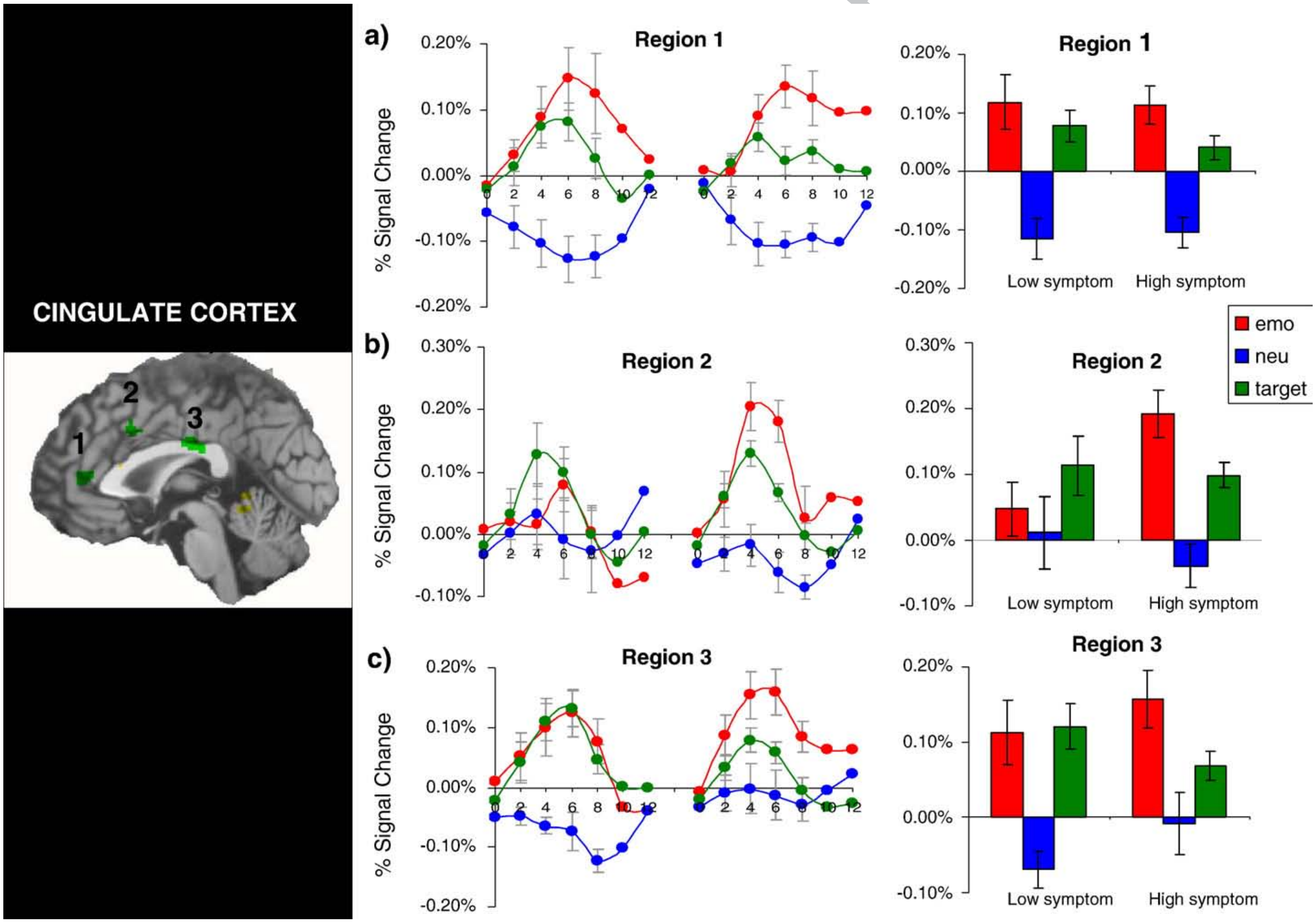

Fig. 4. Regions of overlap where both emotion and target stimuli evoked greater activation than neutral stimuli in the entire group of subjects. (a) In region 1, the low symptom group showed equivalent activity for emotion and target whereas the high symptom group showed the greatest activation for emotion. (b) In region 2, the low symptom group did not differentiate between target, emotion, and neutral stimuli. The high symptom group had greater activity to emotional stimuli than the low symptom group. (c) In region 3, the low symptom group again showed equivalent activity for emotion and target stimuli. In the high symptom group, there was a trend for greater activity for emotion than target stimuli.

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by time interaction ($F_{6,66}=3.6$, $P<0.004$). Follow up tests showed that emotion and target stimuli evoked greater activation than neutral stimuli at 6 and 8 s, but emotion and target signals were not different from each other. In region 2, differential activation for picture type was not observed. In region 3 MANOVA revealed a significant condition by time interaction ($F_{6,66}=2.3$, $P<0.05$). Both target and emotion stimuli evoked greater activation than neutral stimuli at 4, 6, and 8 s, but target and emotion did not differ from each other at any time point.

The high DTS group showed three patterns of activation. In region 1, there was a significant condition by time interaction ($F_{6,78}=2.96$, $P<0.02$). A graded activation pattern emerged such that target stimuli evoked greater activation than neutral distractors at 4 and 6 s, and in turn emotion distractors evoked greater activation than target stimuli at 6 s ($P<0.05$). In region 2, the high DTS group again showed a graded activation pattern. MANOVA revealed a significant condition by time interaction ($F_{6,78}=4.72$, $P<0.001$). Follow up tests showed that target stimuli evoked greater activation than neutral stimuli at 4, 6, and 8 s, and emotion stimuli evoked greater activation than both target and neutral stimuli at 6 s ($P<0.05$). In region 3, the high DTS group showed a main effect for condition ($F_{2,26}=6.07$, $P<0.008$). Across all time points, emotion stimuli evoked greater activation than neutral stimuli ($P<0.002$).

In summary, these results demonstrated that the high DTS group showed greater activation for the emotion distractors in the dorsal ACC, whereas the low DTS group generally showed equivalent activation for emotion and target stimuli.

4. Discussion

Examination of emotion and attention in a group of recently returned combat veterans revealed alterations in the neural circuitry associated with posttraumatic stress symptomatology indicating an attentional bias to emotional stimuli in PTSD. Integration of the findings within the broader emotion and PTSD literature is discussed below.

4.1. Ventral processing stream

Differential activation was observed in the ventral regions for the low and high DTS groups during the emotion condition in accordance with previous neuroimaging findings of PTSD symptomatology (Morey et al., 2008). High DTS symptoms were associated with activation in the vmPFC, peri-amygdala regions, and OFG. This result is largely consistent with a number of studies examining the neural pathways of trauma processing in PTSD (Liberzon and Martis, 2006).

The low DTS group showed greater bilateral IFG activity than the high DTS group. Although IFG activity in response to emotional stimuli in healthy samples has been reported in several studies (Shin et al., 1999; Yamasaki et al., 2002; Fichtenholtz et al., 2004), the function of this region in emotion remains unclear. In prior studies, the IFG – particularly in the right hemisphere – has been implicated in inhibitory functions, which allow one to carry out thoughts and actions with minimal interruption from external, distracting stimuli (Aron et al., 2004). Impaired inhibition in PTSD may be contributory towards attentional bias to emotionally relevant information (Amir et al., 2002). The present results are consistent with the IFG's role in inhibition of distracting stimuli and the growing literature suggesting that a failure to engage this putatively inhibitory IFG activity is decreased in participants with posttraumatic symptomatology.

4.2. Dorsal processing stream

There is now abundant evidence that in healthy individuals, attentional targets elicit activity in dorsal regions including the MFG and parietal cortex (Kirino et al., 2000; Yamasaki et al., 2002; Fichtenholtz et al., 2004; Morey et al., 2008). In the present study, attentional targets were associated with attenuated signal in the dorsal network in combat veterans with greater PTSD symptomatology relative to combat veterans with fewer symptoms. This neural finding coincided with lowered behavioral performance of the high symptom group for target stimuli as compared to other picture types. However, while neutral targets elicited attenuated signal in MFG in the high DTS group, emotional distractors elicited the greatest activity in MFG. There is some evidence that the MFG plays an active role in attention to salient target stimuli regardless of the emotional content (Fichtenholtz et al., 2004). Therefore, it is possible that while the low DTS group applied greatest attention to circle (target) stimuli, the high DTS group applied greater attention to the emotional distractors. These results yield findings complementary to ERP studies in which P3 signal is attenuated for neutral targets and enhanced for threat stimuli (Stanford et al., 2001). The differential MFG signal observed between groups could be a corresponding neural marker for threat bias in PTSD.

Interestingly, Bryant et al. (2005) demonstrated that PTSD was related to increased activity in dorsal-attention systems including parietal cortex during an oddball task that did not employ emotional distractors. The authors suggested that attentional systems may be enhanced in PTSD patients in the absence of emotional stimuli, reflecting generalized hypervigilance. In light of these findings, it is possible that dorsal-attention regions may be enhanced in PTSD during processing of salient neutral stimuli whereas within the context of threat, these regions are attenuated for neutral stimuli in favor of processing emotional stimuli. This finding parallels the ERP literature, in which studies that included emotional probes found increased responsivity for emotional stimuli (Stanford et al., 2001), while those that did not find increased responsivity for salient target stimuli (Kimble et al., 2000).

4.3. Role of the ACC

The ACC has reciprocal connections with both dorsal-attention regions and ventral-affective regions and therefore this region may be ideally suited to regulate interactions between dorsal-ventral pathways. However, there is some conflicting evidence in the neuroimaging literature regarding the ACC's role in PTSD. The majority of studies have shown that this region either deactivated in patients with PTSD or failed to activate in comparison to control participants (Bremner, 1999; Bremner et al., 1999; Shin et al., 1999; Lanius et al., 2001; Shin et al., 2001; Lanius et al., 2003b; Shin et al., 2004, 2005; Etkin and Wager, 2007). However, some studies have also demonstrated the opposite, that the ACC is in fact activated or correlated with PTSD symptomatology. For instance, activation in this region is associated with PTSD symptomatology during a script-driven symptom provocation study (Rauch et al., 1996), and while viewing trauma scenes (Morey et al., 2008), negative pictures, (Shin et al., 1997), and listening to combat sounds (Zubieta et al., 1999). Activity in this region is also heightened for salient non-threatening targets in an oddball paradigm (Bryant et al., 2005). The conflicting evidence therefore raises the concern that other factors likely account for the discrepancy of results including task differences, differences in dissociative states (see Lanius et al., 2002), and depression comorbidity, among others.

The present study supports the hypothesis that the ACC serves as an intermediary between attention and emotion processing. Compared to low symptom individuals, participants with high levels of PTSD symptomatology showed greater activity for emotional distractors than attentional targets in a rostral ACC region, and greater activity in a dorsal ACC region for emotional distractors. Thus, the greater activity may reflect a twofold effort to integrate emotion and attention streams, although with limited success, as observed by attenuated activity for target stimuli and poorer behavioral performance. These results are also consistent with our previous work in healthy adults which demonstrated that activity in the ACC increased when subjects are instructed to apply greater attention to emotional stimuli versus nonemotional stimuli (Fichtenholtz et al., 2004).

4.4. Limitations and strengths

A limitation of the present study is that a clinician administered measure was not used to classify groups. Although the DTS has good diagnostic accuracy against a clinician-administered interview (Davidson et al., 1997), use of the Clinician Administered PTSD Scale or another clinician-administered measure may help to more accurately diagnose whether the symptoms participants report meet DSM-IV PTSD criteria.

Another limitation of the present study is that several of the high DTS participants had significant depression scores on the BDI, leaving open the possibility that our results could be influenced by depressive symptomatology. Comorbidity rates between PTSD and other mood disorders are strikingly high. By one estimate, lifetime comorbidity with another DSM disorder was over 80% in men with PTSD (Kessler et al., 1995). This issue raises the concern that the current nosology of the DSM-IV does not adequately acknowledge depressive symptoms as a characteristic of PTSD (Simms et al., 2002). Nonetheless, the present results suggest that activation in ventral-limbic regions increased as a function of PTSD symptoms, but not depressive symptoms, suggesting that these two aspects of the disorder may have distinct neural effects. Additionally, we observed heightened activation in the dorsal ACC whereas this region is hypothesized to be attenuated in depression (Mayberg, 1997; Wang et al., in press). At least two other studies have examined neural differences in PTSD patients with and without depression (Kemp et al., 2007; Lanius et al., 2007). The findings appear to be mixed; Lanius et al. (2007) reported increases in ACC activity in PTSD patients with comorbid depression, while Kemp et al. (2007) reported increases in ACC in PTSD patients without depression. These differences may be due to additional factors including the nature of the task employed and differences in dissociative states (see Lanius et al., 2002). Additional studies directly investigating the role of depression in PTSD are warranted.

A major strength of the present study is that participants comprised a relatively homogeneous group of post-9/11 combat veterans who were exposed to similar war zone experiences. Additionally, we were able to assess acute PTSD symptomatology on average less than 2 years had elapsed between development of PTSD symptoms and date enrolled in the study. By contrast, other studies in the literature are often hampered by chronicity of symptoms.

5. Conclusions

Understanding the challenges post-9/11 soldiers face as they attempt to re-integrate into civilian life is an important public health concern, as cognitive deficits can have negative implications on work and school related productivity. In the present study, participants with high levels of PTSD symptomatology showed attenuated activity in dorsolateral prefrontal cortex and parietal regions for neutral targets but enhanced activity for emotional distractors, which coincided with lowered capacity to detect attentional targets. Furthermore, PTSD symptom severity was related to greater ventral-limbic activation during the emotional task. Taken together, the results suggest that hyperresponsive ventral-limbic activity coupled with altered function of dorsal-attention systems and increased activation for emotional stimuli in the dorsal ACC may be a neural marker of inattention and threat bias in PTSD. Additionally, this study provides testable hypotheses about the role of the IFG in inhibiting and managing distracting emotions in PTSD, and the role of the ACC in integrating attention and emotion processes. Future studies should include the contribution of these regions towards a comprehensive understanding of the neural circuitry of PTSD.

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