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Neural systems for executive and emotional processing are modulated by symptoms of posttraumatic stress disorder in Iraq War veterans

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Abstract

The symptom-provocation paradigms generally used in neuroimaging studies of posttraumatic stress disorder (PTSD) have placed high demands on emotion processing but lacked cognitive processing, thereby limiting the ability to assess alterations in neural systems that subserve executive functions and their interactions with emotion processing. Thirty-nine veterans from Iraq and Afghanistan underwent functional magnetic resonance imaging while exposed to emotional combat-related and neutral civilian scenes interleaved with an executive processing task. Contrast activation maps were regressed against PTSD symptoms as measured by the Davidson Trauma Scale. Activation for emotional compared with neutral stimuli was highly *positively* correlated with level of PTSD symptoms in ventral frontolimbic regions, notably the ventromedial prefrontal cortex, inferior frontal gyrus, and ventral anterior cingulate gyrus. Conversely, activation for the executive task was *negatively* correlated with PTSD symptoms in the dorsal executive network, notably the middle frontal gyrus, dorsal anterior cingulate gyrus, and inferior parietal lobule. Thus, there is a strong link between the subjectively assessed behavioral phenomenology of PTSD and objective neurobiological markers. These findings extend the largely symptom provocation-based functional neuroanatomy to provide evidence that interrelated executive and emotional processing systems of the brain are differentially affected by PTSD symptomatology in recently deployed war veterans.

Keywords: fMRI; Executive processing; Emotion processing; vmPFC; dlPFC; Combat stress

1. Introduction

The mental health consequences of post-9/11 military deployments to Iraq and Afghanistan have garnered much attention (Miller, 2006). Large-scale studies have found significant deployment-associated neuropsychiatric

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morbidity, with posttraumatic stress disorder (PTSD) rates reported at 18–20% (Hoge et al., 2004), and cognitive impairment, notably for sustained attention (Vasterling et al., 2006). PTSD symptoms include the classic triad of (i) re-experiencing or re-living symptoms, (ii) emotional numbing or avoidance, and (iii) hypervigilance or hyperarousal (First et al., 1997). PTSD is also associated with several domains of cognitive impairment in executive processing, attention, verbal declarative memory, and autobiographical memory (Buckley et al., 2000; Danckwerts and Leathem, 2003).

Symptom-provocation paradigms involving script-driven imagery, or viewing trauma-related or other negatively valenced emotional scenes, have been used to characterize brain-activation patterns, particularly in frontolimbic regions often implicated in the emotion processing dysfunction of PTSD. For instance, when PTSD patients were compared with controls while viewing trauma-related and neutral pictures, patients had greater activation for combat pictures in the amygdala, cingulate cortex, occipitotemporal cortices, and inferior frontoparietal regions (Shin et al., 1997; Bremner et al., 1999b; Yang et al., 2004). In a comparison of fearful to neutral faces, PTSD patients had greater activation to fearful faces in the amygdala, dorsomedial prefrontal cortex (PFC), and posterior cingulate gyrus (Rauch et al., 2000; Shin et al., 2005; Williams et al., 2006). Studies using script-driven imagery have shown varied regional response patterns in frontolimbic regions, including increased activation in PTSD patients in the anterior temporal pole and inferior PFC but reduced activation in other regions such as the anterior cingulate, insula, and amygdala (Shin et al., 1999; Lanius et al., 2001, 2002, 2003a). Results in the orbitofrontal cortex show higher activity (Shin et al., 1999) whereas the ventromedial PFC show lower activity (Lanius et al., 2001; Shin et al., 2004, 2005).

In addition to emotional dysfunction, PTSD is also associated with reduced performance on executive and sustained attention tasks such as the Continuous Performance, Trails B, Digit Span, and Digit Symbol (Vasterling et al., 1998; Jenkins et al., 2000; Sachinvala et al., 2000). However, few neuroimaging studies have directly tested executive deficits in PTSD or the interplay of affective and cognitive processing. A study of the emotional counting Stroop task for combat versus neutral words found lower activation in the rostral anterior cingulate cortex (ACC) in the PTSD group (Shin et al., 2001). A subsequent study confirmed lower ACC activation in the PTSD group for the emotional Stroop condition, and lower activation in inferior parietal lobule, visual association cortex, and precuneus for the classic Stroop condition (Bremner et al., 2004). An auditory continuous performance task study of patients with comorbid cocaine and alcohol abuse also found lower activity in rostral ACC (Semple et al., 2000). Converging support across symptom-provocation studies combined with neuropsychological assessment posits an inability of the PFC to inhibit a hyperresponsive limbic system in PTSD (Bremner et al., 1999b; Rauch et al., 2000; Shin et al., 2001).

Of particular interest is the relationship between severity of PTSD symptoms and central neural markers of executive and emotional functions. Positive correlations were reported for a trauma script condition with amygdala and anterior hippocampus activation, and negative correlations in the medial frontal gyrus and the ACC (Shin et al., 2004). Positive correlations for fearful versus happy faces were also found in the amygdala (Rauch et al., 2000; Shin et al., 2005). Finally, a negative correlation was reported between re-experiencing symptoms and ACC activity (Williams et al., 2006).

We have previously reported on the interplay of emotion processing and executive function in studies of healthy subjects using an emotional oddball paradigm (Yamasaki et al., 2002; Fichtenholtz et al., 2004; Wang et al., 2005) in which detection of a target geometric shape is interrupted by occasional task-irrelevant emotional and neutral distracters. Our earlier work demonstrated that executive and emotional functions are dissociated into parallel dorsal and ventral streams respectively, that extend into the PFC (Yamasaki et al., 2002; Fichtenholtz et al., 2004; Wang et al., 2005). Reciprocal engagement of these streams showed relative deactivation of the ventral frontolimbic regions during attentional target detection and relative deactivation of the dorsal frontoparietal regions during emotional picture processing. This reciprocal relationship between dorsal and ventral processing of executive and emotional functions may be biased towards emotional processing in patients with anxiety disorders (Drevets and Raichle, 1998), similar to that found in depression (Mayberg, 1997). Thus, our earlier work supports a model of emotion and attention processing that is well suited for investigating PTSD.

The aim of the present study was to investigate the relationship of executive and emotion-processing regions with severity of PTSD symptoms, and to assess whether the reciprocal relationship between activity in emotion and executive processing systems found in healthy adults (Drevets and Raichle, 1998; Yamasaki et al., 2002) would be a model that extended to subjects with PTSD symptoms. In the present study, the executive function block involved making a choice response to each of a short series of geometric shapes.

The symptom provocation blocks involved presentation of combat-related pictures. Control blocks of matched civilian (neutral) pictures were also included. The sensory and motor aspects of this task were relatively simple and easy to accommodate in patients during fMRI scanning.

Broadly, we expected that based on the model of dorsal–ventral segregation observed in healthy subjects, that patients with PTSD symptoms would show an imbalance towards the ventral processing of combat scenes at the expense of reduced dorsal processing of executive attention. Furthermore, we predicted that this pattern would be modulated by PTSD symptom severity such that activation for emotional stimuli in ventral frontolimbic regions during symptom provocation would be positively correlated with PTSD symptoms, whereas activation for executive processing in dorsal regions during executive processing would be negatively correlated with PTSD symptoms. Secondarily, we predicted deactivation in dorsal regions during emotion processing, and in ventral regions during executive processing. If supported, these reciprocal interactions between processing streams and their relationship to symptomatology would advance knowledge regarding the large-scale neural systems that mediate the cognitive–affective symptoms of PTSD.

2. Methods

2.1. Participants

Forty-six participants recently returning [means± standard deviation =29±26 months] from deployments to post-9/11 military conflicts who lacked a history of neurological disorders or major medical conditions were enrolled in the study. Thirty-nine participants completed the fMRI procedures and a picture rating task immediately following the scan. Seven subjects were unable to complete the fMRI procedures secondary to discomfort in the scanner but completed the picture rating task. Subjects provided written informed consent for procedures approved by the Institutional Review Boards at Duke University and the Durham VA Medical Center. Participants were recruited from a large registry of post-9/11 military service members and veterans [Durham VA Medical Center, Durham, NC, USA]. Subjects entering the registry completed a neuropsychiatric self-assessment battery that included the Davidson Trauma Scale (DTS) (Davidson et al., 1997), Beck Depression Inventory (BDI) (Beck et al., 1961), Combat Exposure Scale (Keane et al., 1989), Traumatic Life Events Questionnaire (Kubany et al., 2000), Connor–Davidson Resilience Scale (Connor and Davidson, 2003), Drug Abuse Screening Test (Skinner, 1982), and Alcohol Use Disorders Identification Test (Saunders et al., 1993). The DTS, which re-administered immediately prior to scanning to allow for a possible change in PTSD symptoms, showed lower average DTS scores at the pre-scan assessment than at registry intake [paired $t(38)=2.5$, $P<0.02$]. Participants ranged in age from 21 to 54 (mean±S.D.; 35.9±9.4) with older participants tending towards lower DTS scores [$r=-0.32$, $F(1, 38)=4.3$, $P=0.04$]. The DTS has a short administration time (under 10 min), high test–retest reliability, internal consistency, convergent and divergent validity, predictive validity, and responsiveness evidence (Davidson et al., 1997). Eighteen participants had scores at or above a cutoff of 40, previously shown to confirm a DSM-IV diagnosis of PTSD, and 23 participants met or exceeded a cutoff of 27, suggesting posttrauma psychopathology and likelihood to meet DSM-IV criteria for PTSD (Cuthbertson et al., 2004). Ten participants (mean DTS=65.4±23.7) were taking antidepressant medication that included selective serotonin reuptake inhibitors and/or norepinephrine-dopamine modulators. Participants had mild to moderate depression as assessed by the BDI [17.5± 37.4]. Full demographic and clinical characteristics of the sample are reported in Table 1.

2.2. Stimulus presentation

Stimuli compiled from Internet searches and photo collections of returning soldiers (not participating in the present study) were subdivided into the following four categories: (i) emotional stimuli depicting combat-related scenes from Iraq and Afghanistan; (ii) neutral civilian scenes matched for overall visual complexity, luminance, presence of human figures/faces, and chromatic features; (iii) baseline images that were digitally scrambled from the emotional and neutral pictures; and (iv) executive stimuli consisting of monochromatic circles or squares. The scrambled pictures had the same average spatial frequency and luminance as the meaningful pictures. Stimuli were presented for 2 s, with six stimuli from a single category forming a 12-s block of that category that alternated in a repeating pattern of baseline–executive–baseline–neutral–baseline–combat. Each run lasted 6 min and 24 s, for a total functional scan time of 52 min. Each block type (emotional, neutral, executive) occurred five times per run for eight runs for 40 total events. Subjects provided right-handed button presses during the executive condition based on a judgment of circle versus square stimuli.

Table 1
Demographic and clinical characteristics of subject sample

Characteristic	$n=39$	Correlation with symptom severity (DTS)
Age (years), [S.D.]	35.9 [9.4]	$r=-0.32$, $F(1, 38)=4.3$, $P=0.04$
Age range [youngest:oldest]	[21:54]	–
Gender, no. (%) of females	7 (17.9)	$t(38)=1.3$, $P=0.20$
Handedness, no. (%) right-handed	37 (94.9)	–
Handedness, no. (%) ambidextrous	1 (2.6)	–
Ethnicity, no. (%) of Caucasian subjects	18 (46.2)	$t(38)=0.29$, $P=0.77$
Education (years), [S.D.]	14.2 [2.6]	$r=0.11$, $F(1, 38)=0.43$, $P=0.52$
Davidson Trauma Scale [S.D.]	39.4 [32.6]	–
Combat Exposure Scale [S.D.]	14.5 [11.2]	$r=0.30$, $F(1, 38)=3.7$, $P=0.06$
Traumatic Life Events Questionnaire (early life sub-score) [S.D.]	5.5 [7.2]	$r=0.1$, $F(1, 38)=0.34$, $P=0.56$
Connor–Davidson Resilience Scale [S.D.]	74.7 [14.6]	$r=-0.33$, $F(1, 38)=4.4$, $P=0.04$
Beck Depression Inventory [S.D.]	17.5 [37.4]	$r=0.53$, $F(1, 38)=14.8$, $P<0.0005$
Alcohol Use Disorders Identification Test [S.D.]	5.9 [6.7]	$r=0.20$, $F(1, 38)=1.5$, $P=0.23$
Drug Abuse Screening Test, [S.D.]	1.0 [2.0]	$r=0.22$, $F(1, 38)=1.9$, $P=0.17$
Antidepressant medication, no. (%) prescribed[a]	10 (25.6)	$t(38)=3.3$, $P<0.005$
DTS of subjects taking medication [S.D.]	65.4 [23.7]	–

Data values represent means except where indicated otherwise.
[a] Antidepressant medications taken were either selective serotonin reuptake inhibitors (SSRI) or norepinephrine-dopamine modulators (NDM, Bupropion).

Subjects also responded with button presses during the emotional, neutral, and baseline conditions (the baseline condition did not involve a judgment but was merely an incidental task to confirm focus of attention). Subjects were asked to provide accurate responses but were not instructed to optimize response time. Stimuli were displayed using GPF software [Duke-UNC Brain Imaging and Analysis Center] on a liquid crystal display projector system.

2.3. fMRI procedures

Scans were obtained from a General Electric 3 Tesla Signa EXCITE system equipped with high-power 40-mT/m gradients at 150 T/m/s and eight-channel head coil. Head movement was restricted using foam cushions and Velcro straps. The anterior (AC) and posterior commissures (PC) were identified in the mid-sagittal slice of a localizer series, and 34 contiguous slices were prescribed parallel to the AC–PC plane prior to obtaining 3D high-resolution anatomical images using a spoiled gradient-recalled acquisition pulse sequence (TR=500 ms; TE=31 ms; image matrix=256×256×68; slice thickness=1.9 mm, in-plane resolution=0.9375 mm^2; T1 inversion time=300 ms). Functional images were acquired using an echo-planar imaging sequence (TR=2000 ms, TE=30 ms, FA=60°, in-plane resolution=3.75 mm^2; slice thickness=3.8 mm; image matrix=64×64×34) sensitive to blood oxygen-level dependent (BOLD) contrast. Before each scan, four images were acquired and discarded to allow longitudinal magnetization to reach equilibrium.

2.4. Picture rating procedure

Following the scan, 41 participants viewed and rated visual stimuli for arousal and valence on a desktop computer. Five subjects were able to complete the fMRI portion but were markedly distressed by the combat pictures and elected not to participate in the picture rating task. Ratings were provided using the Self-Assessment Mannequin on a 9-point arousal (1=lowest; 9=highest) and valence (1=most negative; 9=most positive) scale (Lang et al., 2005). Subjects were provided 3 s to view each stimulus and were permitted up to 8 s following onset of stimulus presentation to provide responses. Subjects rated 392 pictures subdivided into seven approximately equal sets with up to a 10-min break between sets to reduce subject fatigue.

2.5. Data analysis

Functional data sets were analyzed using FSL version 3.3.5 [Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford University, U.K.] (Smith et al., 2004). Paradigm timing files were converted to FSL-compatible format, and NIFTI image data files were generated. Preprocessing (first-level analysis) was applied to individual subjects' 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 subject were co-registered to structural images in native space, and structural images were normalized to structural Talairach standard images, defined by the MNI standard brain supplied with FSL. The same transformation matrices used for structural-to-standard transformations were then used for functional-to-standard space transformations of co-registered functional images. All registrations were carried out using an intermodal registration tool based on the correlation ratio (Jenkinson and Smith, 2001). Pre-whitening or voxel-wise temporal autocorrelation was estimated and corrected using FMRIB's Improved Linear Model (FILM) (Woolrich et al., 2001). Onset times of events were used to model a signal response containing a regressor for each response type, which was convolved with a γ function to model the hemodynamic response. Model fitting generated whole brain images of parameter estimates and corresponding variance, representing average signal change above baseline (activation; positive regressor) and below baseline (deactivation; negative regressor) during each condition (emotional, neutral, executive, emotional > neutral). Contrast images were fed into a second-level statistical analysis to examine effects for the overall group as a function of symptom severity in the form of demeaned DTS scores. Given the high correlation between DTS and BDI measures, we repeated the preceding step using demeaned BDI scores. Activation and deactivation images of main effects during each condition were produced by calculating an average map based on all individual maps for each run, in a mixed effects higher level analysis using Bayesian estimation techniques, FMRIB Local Analysis of Mixed Effects (FLAME) (Beckmann et al., 2003; Woolrich et al., 2004) with a conservative cluster mean threshold of $Z > 2.3$ and a cluster-corrected significance threshold of $P < 0.05$ (Worsley et al., 1992; Friston et al., 1993; Forman et al., 1995).

We assessed BOLD signal recovery by examining raw functional images thresholded at 50% of the maximal signal. This resulted in signal dropout due to susceptibility artifact throughout most of the region of the amygdala except the most superior and lateral aspect. However, there was no evidence of appreciable signal dropout in the ventromedial PFC and orbitofrontal PFC, and minimal signal dropout in the hippocampus. The analysis was conducted post hoc on the basis of expected amygdalar activation during the emotion condition.

2.6. Statistics

Mixed effects analysis as implemented in FSL feeds variance in the data and in parameter estimates from individual fMRI runs and subjects to group-level analysis leading to results that are representative of the general population. Our analysis was based on correlations of symptom severity with activation for the contrasts of interest. Voxels were identified using FSL mixed-effects analysis to regress demeaned DTS and BDI scores with parameter estimates. Cluster-corrected mean Z-scores were used to generate regression plots for Figs. 3 and 4. This method is statistically more

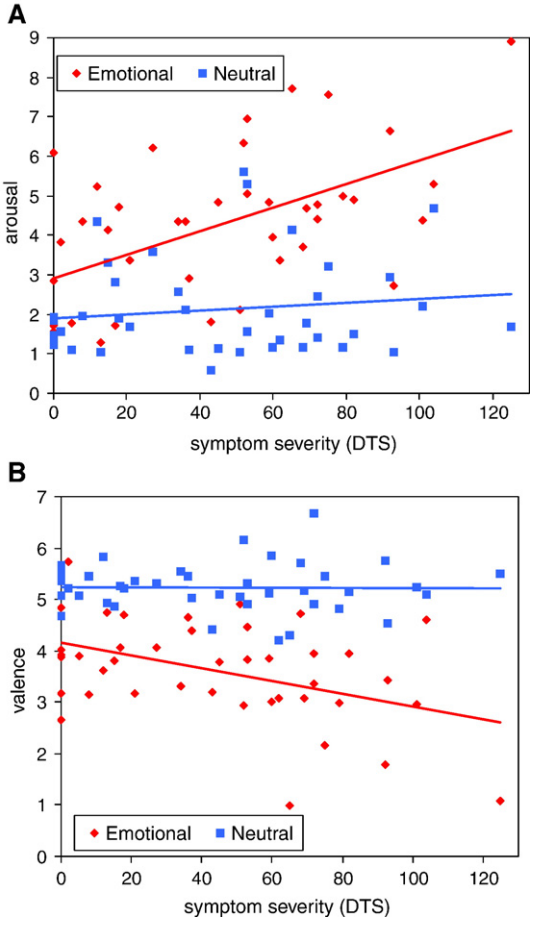

Fig. 1. A) Arousal ratings for emotional pictures were correlated with severity of PTSD symptoms measured with the Davidson Trauma Scale (DTS) [$r = 0.55$, $F(1, 40) = 16.6$, $P = 0.0002$] but not for neutral pictures [$r = 0.12$, $F(1, 40) = 0.74$, $P = 0.39$], with a significant interaction of symptom severity * picture type [$F(1, 78) = 7.3$, $P < 0.01$]. B) Valence ratings for emotional pictures were negatively correlated with DTS [$r = 0.43$, $F(1, 40) = 8.8$, $P = 0.005$] but not for neutral pictures [$r = 0.02$, $F(1, 40) = 0.02$, $P = 0.90$], with a significant interaction of symptom severity * picture type [$F(1, 78) = 6.5$, $P = 0.01$].

powerful than comparing two participant groups based on a median split or a categorical grouping such as PTSD versus non-PTSD.

3. Results

3.1. Picture rating task

Regression analysis of picture ratings (see Fig. 1) showed that symptom severity, as measured by the Davidson Trauma Scale, was predictive of arousal ratings for emotional pictures [$r=0.55$, $F(1, 40)=16.6$, $P<0.001$] but not neutral pictures [$r=0.12$, $F(1, 40)=0.74$, $P=0.39$]. Analysis of covariance (ANCOVA) showed an interaction of symptom severity * picture type for arousal ratings [$F(1, 78)=7.3$, $P<0.01$]. Likewise, valence was negatively correlated with symptom severity for emotional pictures [$r=0.43$, $F(1, 40)=8.8$, $P=0.005$] but not neutral pictures [$r=0.02$, $F(1, 40)=0.02$, $P=0.90$] and an interaction of symptom severity * picture type for valence rating [$F(1, 78)=6.5$, $P=0.01$].

3.2. Behavioral performance

Correlational analysis between the rate of correct responses in the executive condition and symptom severity scores did not reveal a significant relationship [$r=-0.26$, $F(1, 36)=2.8$, $P=0.10$]. Analysis of variance (ANOVA) of response latency revealed a main effect for condition (emotional, neutral, executive) [$F(2,72)=14.2$, $P<0.001$]. Post hoc analysis showed a longer latency for the emotional condition than for neutral [$t(74)=1.8$, $P<0.04$] and executive [$t(74)=2.6$, $P<0.005$] conditions. Regression analysis did not reveal a relationship of latency with symptom severity for executive [$r=0.12$, $F(1, 36)=0.55$, $P=0.46$], emotional [$r=0.02$, $F(1, 36)=0.02$, $P=0.89$], and neutral [$r=0.05$, $F(1, 36)=0.11$, $P=0.74$] conditions.

3.3. Analysis of functional MRI data

Main contrasts for FSL mixed effects analysis were performed for emotional>neutral pictures and the executive task (relative to pre-task baseline) (see Table 2). Corresponding analyses of BOLD deactivation were also conducted for these contrasts (see Table 3). Regression analyses yielded areas of BOLD activation (see Table 4) and deactivation (see Table 5) significantly correlated with PTSD and BDI symptoms.

3.4. Regions of activation and deactivation

As predicted, activation for the emotional>neutral condition (see Table 2) was prominent in ventral brain regions including dorsomedial PFC, inferior frontal gyrus,

Table 2
Regions of activation for experimental contrasts

Neural system	Brodmann area	Side	Talairach coordinates			Max Z values of contrasts ($P<0.05$ cluster-corrected)	
			x	y	z	Executive	Emotional>neutral
Dorsomedial prefrontal cortex	10	B	4	58	6	–	4.2
Superior/middle temporal gyrus	22/37/39	L>R	−46	−60	26	–	6.0
Precuneus	7/31	L	−2	−54	42	–	6.1
Inferior parietal lobe	–	R	34	−46	50	–	4.2
Caudate	–	L	−10	2	12	–	4.4
Inferior frontal gyrus	44	R	54	20	20	–	3.1
Precentral gyrus	6	L	−42	−4	34	–	3.6
Posterior cingulate	23/30	B	2	−44	24	–	5.0
Dorsal anterior cingulate cortex	32	B	−6	8	40	3.9	–
Inferior frontal gyrus	9	B	−50	6	26	5.4	–
Inferior parietal lobule	40	B	48	−32	54	7.9	–
Superior parietal lobule	7	B	30	−54	54	6.7	–
Precentral gyrus	6	R	34	−10	64	5.3	–
Postcentral gyrus	5	B	−40	−40	58	6.6	–
Superior frontal gyrus	6	B	6	8	48	6.4	–
Middle frontal gyrus	10/9	B	−40	40	22	5.3	–
Insula	13	B	−34	20	0	6.6	–
Cerebellum	–	L>R	−20	−52	−18	6.6	–
Putamen	–	B	−18	0	8	6.7	–
Thalamus	–	B	−16	−8	12	8.0	–

Table 3
Regions of deactivation for experimental contrasts

Neural system	Brodmann area	Side	Talairach coordinates			Max Z values of contrasts ($P<0.05$ cluster-corrected)	
			x	y	z	Executive	Emotional>neutral
Superior temporal gyrus	22	B	58	2	−6	–	4.5
Insula	13	R	38	−18	18	–	3.8
Medial frontal gyrus	6	B	4	−16	58	–	3.8
Dorsal anterior cingulate	24	R>L	4	2	40	–	3.2
Precentral gyrus	4	B	64	−10	28	–	3.9
Postcentral gyrus	43	B	−58	−8	20	–	4.4
Hippocampus	–	B	30	−12	−20	5.1	–
Orbitofrontal cortex	11	B	4	40	−22	6.5	–
Ventromedial prefrontal	10	R>L	4	62	4	5.2	–
Superior frontal gyrus	9	R	26	26	40	6.5	–
Subgenual cortex	25	B	4	8	−12	6.5	–
Inferior frontal gyrus	47	R	54	28	2	4.1	–
Precuneus	31	B	2	−48	32	6.5	–
Inferior parietal lobule	40	R	54	−50	30	5.5	–
Insula	13	L	−40	−18	16	5.1	–
Middle temporal gyrus	20	R>L	58	−18	−12	5.5	–
Parahippocampal gyrus	–	R>L	28	−30	−12	6.6	–
Caudate	–	B	4	8	0	6.6	–

Table 4
Correlations of activation with symptom severity (DTS)

Neural system	Brodmann area	Side	Talairach coordinates			Max Z values of contrasts ($P<0.05$ cluster-corrected)	
			x	y	z	Executive	Emotional>neutral
Orbitofrontal cortex	11/25	B	−10	50	0	–	4.4
Ventromedial prefrontal	10	B	−4	50	12	–	3.4
Ventral anterior cingulate	24	L	−2	36	−2	–	4.2
Inferior frontal gyrus	45	L	−50	36	2	–	3.5
Caudate	–	R	10	2	12	–	4.4
Inferior parietal lobule	40	L	−60	−36	42	–	3.4
Insula	–	L	−36	8	2	–	3.5
Superior temporal gyrus	39/22	L	−50	−60	26	–	5.4
Middle frontal gyrus	–	R	36	40	22	–	3.5

Table 5
Negative correlations of activation with symptom severity (DTS)

Neural system	Brodmann area	Side	Talairach coordinates			Max Z values of contrasts ($P<0.05$ cluster-corrected)	
			x	y	z	Executive	Emotional
Middle frontal gyrus	45/46	B	26	46	−6	4.2	–
Medial frontal gyrus	9	B	−2	36	30	3.9	–
Dorsal anterior cingulate	24	B	2	30	20	2.7	–
Ventral anterior cingulate	24	B	−2	34	16	4.0	–
Superior frontal gyrus	10	L	−24	50	0	4.2	–
Inferior frontal gyrus	44	B	−54	12	12	4.0	–
Thalamus	–	R	20	−18	6	4.2	–
Inferior occipital gyrus	19	R	30	−86	−4	4.0	–
Superior parietal lobule	7	R	30	−52	60	2.9	–
Inferior parietal lobule	40	R	46	−46	40	4.0	–
Cerebellum	–	R	6	−66	−28	3.3	–
Insula	13	B	38	16	2	3.9	–

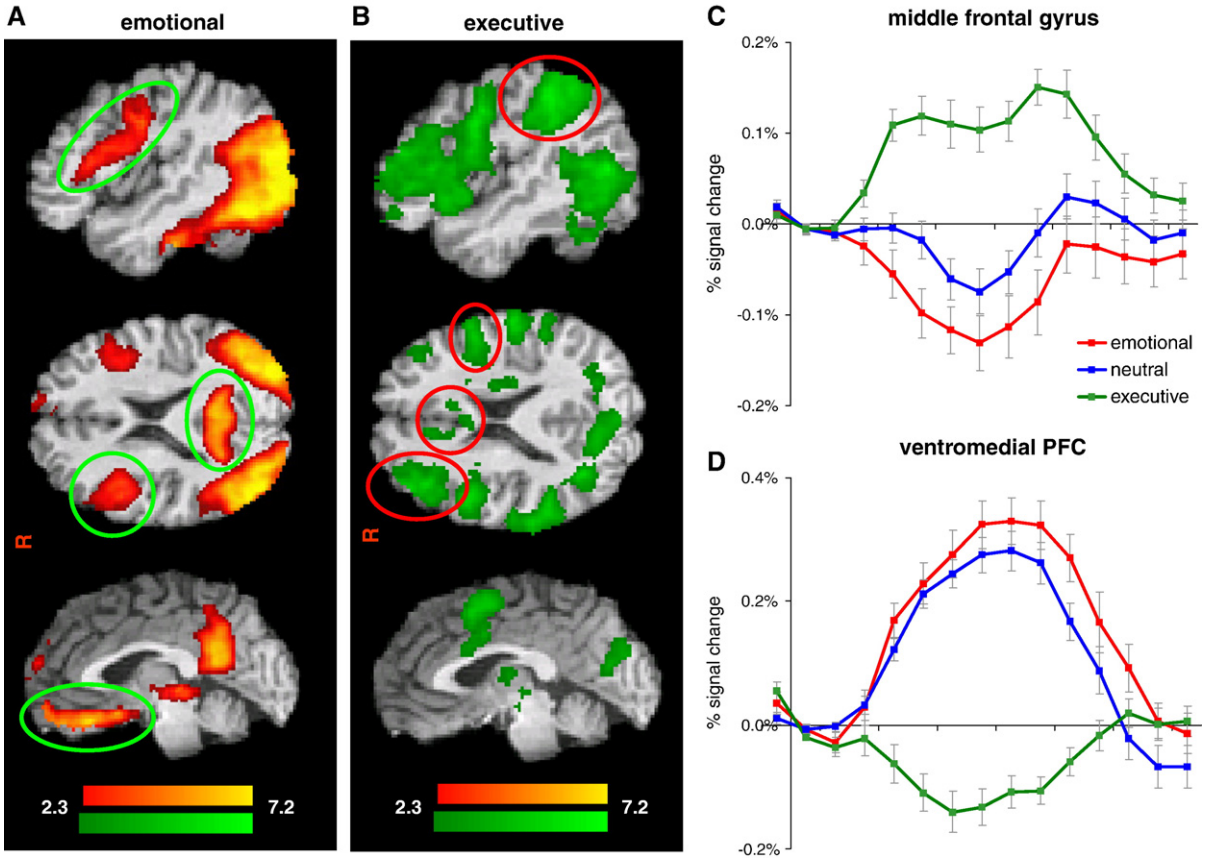

Fig. 2. Participants ($n=39$) showed A) regions of activation (red) are prominent in ventromedial prefrontal cortex, inferior frontal gyrus, and precuneus. B) regions of activation (green) for the executive task are prominent in middle frontal gyrus, superior parietal cortex, and dorsal anterior cingulate gyrus, C) time course of BOLD signal for emotional (red), neutral (blue) and executive (green) for the middle frontal gyrus and D) the ventromedial prefrontal gyrus. Each task block represented by the activation time courses was preceded by a block of scrambled images that constituted our baseline condition.

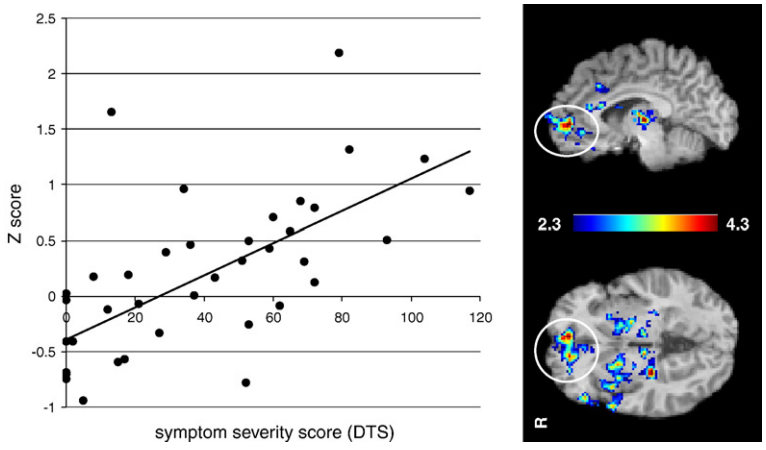

Fig. 3. Mixed effects analysis with FSL identified clusters of voxels including the ventromedial prefrontal cortex and the ventral anterior cingulate cortex that were highly correlated with PTSD symptoms as measured by the Davidson Trauma Scale (DTS). The mean Z-scores in the cluster for subjects ($n=39$) were regressed against DTS scores [$r=0.64$, $F(1, 40)=25.7$, $P=0.00001$]. Activation maps represent voxel-wise correlation of Z-score with DTS score.

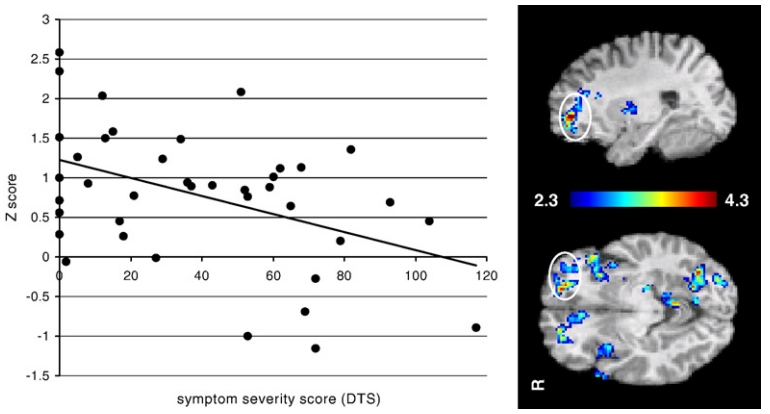

Fig. 4. Mixed effects analysis with FSL identified clusters of voxels including the dorsolateral prefrontal cortex that were negatively correlated with severity of PTSD symptoms as measured by the Davidson Trauma Scale (DTS). Mean *Z*-scores in the cluster for subjects ($n=39$) were plotted against DTS scores (DTS) [$r=-0.44$, $F(1, 40)=8.7$, $P=0.005$]. Activation maps represent voxel-wise correlation of *Z*-score with DTS score.

superior temporal gyrus (posterior portion), and precuneus. Activation for the executive task was prominent in dorsal frontoparietal regions (see Fig. 2B) including dorsal ACC, superior and middle frontal gyri, inferior and superior parietal lobules, and subcortical regions (see Table 2). Some ventral PFC activation was seen in the inferior frontal gyrus.

Regions of deactivation were identified where the BOLD signal was significantly below the baseline condition (scrambled picture). Deactivation for the emotional task overlapped significantly with positive activation for the executive task. For instance, while there was robust activation in the middle frontal gyrus during the executive condition, this region was deactivated during the neutral condition and further deactivated during the emotional condition as seen in Fig. 2C. Deactivation for the emotional condition was greater (more negative) than for the neutral condition in the superior temporal gyrus and insula (see Table 3). In a reciprocal fashion, regions of deactivation for the executive task overlapped significantly with positive activation for the emotional task. For instance, while the ventromedial PFC showed positive activation during the emotional condition, this region was deactivated during the executive condition as seen in Fig. 2D. Deactivated areas for the executive condition included the ventromedial and dorsomedial PFC, orbitofrontal cortex, inferior parietal lobule, and precuneus (see Table 3).

3.5. Correlation of activity with PTSD symptom severity

Several ventral frontolimbic regions were highly correlated with PTSD symptoms for the emotional > neutral condition (see Fig. 3), including orbitofrontal cortex, ventromedial PFC, ventral ACC and inferior frontal gyrus (see Table 4). There were no regions where activation during the emotional > neutral decreased with symptom severity. However, activation during the executive condition decreased with symptom severity (see Fig. 4) primarily in the middle and inferior frontal gyri, ACC and inferior parietal lobule (see Table 5). There were no regions where activation during the executive task increased with symptom severity.

3.6. Correlation of activity with depression symptom severity

Correlations of activation with depression symptom severity (BDI) were performed based on our observation that DTS scores were highly correlated with BDI scores [$r=0.53$, $F(1, 38)=14.8$, $P<0.001$], and consistent with earlier reports (Breslau et al., 1997; North et al., 1999). There were no regions for which the emotional > neutral condition was correlated to BDI. The executive condition was negatively correlated with BDI scores in the dorsal ACC and superior parietal lobule. Thus, regions of activation correlated with BDI scores were quite different and relatively circumscribed compared with those for DTS scores, reported previously (Shin et al., 2005).

4. Discussion

The present study examined the neural correlates of emotional and executive processing and their relationship with PTSD symptomatology in war veterans who had recently returned from deployment to Iraq and Afghanistan. We found that processing of combat-related stimuli largely activated ventral frontolimbic regions whereas executive processing generally

activated dorsal frontoparietal regions. Importantly, we found that activation for combat-related stimuli, in contrast to neutral stimuli, was positively correlated with PTSD symptom severity in a number of key regions of the ventral emotional processing stream, including ventromedial PFC, inferior frontal gyrus and ventral ACC. These results were consistent with higher arousal and lower valence ratings for combat-related pictures in subjects with higher symptom severity. Conversely, activation for the executive task was strongly correlated with lower symptom severity in several key regions of the dorsal frontoparietal network, including middle frontal gyrus, dorsal ACC, and inferior parietal lobule. We also found that PTSD severity was correlated with activation for combat-related (>neutral) stimuli outside the expected ventral system, in regions such as the middle frontal gyrus, which suggests that affective processing is usurping putative executive regions.

As predicted, we found that subjects' overall response times were slowest for the emotional condition and fastest for the executive task. We hypothesized that during the executive task, subjects' accuracy would decrease with increasing PTSD symptoms, and that subjects' response times for emotional pictures would be slower with increasing PTSD symptoms. Our data did not support either of these hypotheses. We note, however, that functional brain measures distinguished subjects on the basis of PTSD severity, but were not discernible from behavioral performance measures.

The present findings provide empirical support to a neuroanatomical model of PTSD (Bremner et al., 1999b; Rauch et al., 2000; Shin et al., 2001) that posits a hyperresponsive limbic system that in turn places greater processing demands on fronto-cingulo-parietal regulatory resources. Thus, our results suggest a cognitive–affective imbalance where a dysregulation of a ventral affective processing network is ostensibly responsible for interference of processing in the dorsal executive network.

4.1. Integration with the symptom-provocation literature

The regions consistently reported in functional neuroimaging studies of symptom provocation in PTSD include amygdala, orbitofrontal cortex, ventromedial PFC, and ACC (Liberzon and Martis, 2006). Our findings show that activation in ventral ACC for the emotional condition was correlated with greater symptom severity and activation in the dorsal ACC was negatively correlated with symptom severity in the executive condition. However, it is difficult to compare and interpret the present study relative to earlier findings given the heterogeneity of past stimulus presentation paradigms and subject samples. It has generally been reported that the ACC has lower activation associated with PTSD (Shin et al., 1997; Lanius et al., 2001; Shin et al., 2001, 2004, 2005; Gilboa et al., 2004; Yang et al., 2004; Williams et al., 2006). Higher activation was found for the combat imagery condition (but not the perception condition) in Vietnam veterans (Rauch et al., 1996; Shin et al., 1997) and with script-driven provocation in a dissociative state (Lanius et al., 2002). The conflicting findings may be explained by differential involvement across studies of the dorsal ("cognitive") versus ventral–rostral ("affective") subdivisions of the ACC (Bush et al., 2000; Shin et al., 2001). Our findings are consistent with affective versus cognitive subdivisions, with ventral ACC activation for emotional stimuli correlated with higher PTSD symptoms and dorsal ACC activity correlated with lower PTSD symptoms in the executive condition.

We found activation in the ventromedial PFC for the emotion-processing condition was highly correlated with PTSD symptoms. Correspondingly, we found deactivation for the executive task in laterally situated ventral PFC was correlated with PTSD symptoms. These findings are consistent with the findings of Northoff et al. (2000), who have proposed that negative emotional states engage ventromedial PFC whereas positive emotional states engage the ventrolateral PFC. The ventromedial PFC area has been implicated in emotion, motivation, and social behavior (Kringelbach, 2005; Heimer and Van Hoesen, 2006), as well as regulation of the peripheral glucocorticoid and sympathetic response to stress (Bremner et al., 1999a; Erickson et al., 2003) and emotion modulation through inhibitory connections to the amygdala (Bremner et al., 1999a; Shin et al., 2004). Dysfunction of this area may represent a neural correlate of the failure of extinction to fear responding, as well as a heightened state of arousal in PTSD.

The literature contains conflicting data regarding activation of ventromedial PFC, with higher activation found using script-driven imagery of childhood trauma (Shin et al., 1999), and during dissociative states induced in young adult PTSD patients (Lanius et al., 2002). On the other hand, generally older Vietnam era veterans with chronic PTSD showed lower activation using script-driven imagery (Shin et al., 2004), fearful faces (Shin et al., 2005), trauma pictures and sounds (Bremner et al., 1999b) and emotional pictures (Phan et al., 2006). The fact that our findings, and those of some earlier groups who also found increased ventromedial prefrontal activation for emotional stimuli, were obtained in subjects with recent-onset PTSD, suggests that illness chronicity may account for discrepant findings. Chronicity of PTSD has been shown to accelerate age-associated cognitive decline (Golier et al., 2006).

Furthermore, chronic PTSD patients may represent a vulnerable subset of early onset PTSD typified by our sample (Perkonigg et al., 2005).

We found that activation for the emotional (>neutral) condition was correlated with PTSD severity in subcortical regions including the caudate, while activation for the executive task was negatively correlated in the thalamus. The basolateral nucleus of the amygdala has strong connections with the striatum and thalamus, which in turn project to the PFC (Davis and Whalen, 2001). Previous studies show lower thalamic activation in PTSD patients for combat sights and sounds as well as script-driven symptom provocation (Bremner et al., 1999b; Lanius et al., 2001, 2003b). Our findings suggest that in PTSD the role of the thalamus is impaired in executive processing, and striatal regions generally are impaired in affective processing.

4.2. Deactivation

As expected, we found that during activation of dorsal frontoparietal regions (executive task), there was a concomitant deactivation of ventral frontolimbic regions. On the other hand, during activation of ventral frontolimbic regions (emotional task), there was a concomitant deactivation of dorsal frontoparietal regions (Drevets and Raichle, 1998; Yamasaki et al., 2002). Explorations of deactivation are largely missing from the PTSD literature. A study of women participants listening to scripts of childhood trauma found deactivation in the subcallosal region of the ACC, hippocampus, fusiform gyrus, supramarginal gyrus, and visual association cortex (Bremner et al., 1999a), and a study of Vietnam veterans presented with combat sights and sounds found deactivation in the medial PFC, subcallosal gyrus and middle temporal gyrus (Bremner et al., 1999b). The present study provides a preliminary model for understanding deactivation patterns in PTSD by systematically evaluating the reciprocal system of activation and deactivation in dorsal executive and ventral affective brain networks.

4.3. Interpretation of unexpected findings

Unexpectedly, we found that activation in the inferior frontal gyrus during the executive task was negatively correlated with PTSD severity. The role of the inferior frontal cortex is considered vital to inhibitory processes which are considered to be an essential component of a selection task (reviewed in Aron et al., 2004). The executive task of our study is primarily a selection task and consistent with strong IFG activation. Our findings suggest that IFG dysfunction during executive processing is associated with greater severity of PTSD symptoms. Thus, IFG dysfunction seems to play a role in both emotion and executive processing in PTSD.

4.4. Strengths and limitations

Three major strengths of the present study improve upon previous efforts to identify the functional neuroanatomy of PTSD. First, the experimental design incorporated both symptom provocation and executive decision-making tasks that were interleaved to provide separate analyses of both of these functions. Second, we used a relatively large sample compared with other neuroimaging studies, and a homogeneous sample of fairly young post-9/11 war veterans with recent trauma and a relatively low level of comorbid substance use. Third, a more powerful analytic approach was applied to the neuroimaging data, which exploited illness severity as a dimensional variable in favor of the usual binary categorical variable (i.e. PTSD or non-PTSD) and subtraction approach. Our approach enhances statistical power and permits characterization of the relationship between a continuous endophenotype measure with a continuous behavioral measure. Previous studies that performed similar correlations between activation measures and illness severity limited their analyses to subjects that met full diagnostic criteria for PTSD (Rauch et al., 2000; Shin et al., 2004, 2005), and they therefore lack the ability to characterize neural findings associated with sub-threshold PTSD symptomatology (Grubaugh et al., 2005).

We used brain-imaging data to distinguish PTSD and depression symptom severity in a way that is not possible using standard behavioral measures. Our analyses showed no correlations of activation for the emotional>neutral condition with BDI scores and relatively limited regions of correlation for the executive condition. This analysis provides evidence that the DTS correlations we observed may be uniquely associated with PTSD symptoms and not related to comorbid depressive symptoms.

Several participants in the present sample are being treated with psychotropic medication. It is alleged, but not yet substantiated, that psychotropic agents reduce the BOLD signal (Goldman et al., 1996; Rose et al., 2006). It is unlikely that the present results are fully explained by medication effects given that highly symptomatic participants had greater activity for one condition and simultaneously lower activity for another condition and vice-versa, depending on the brain region. Moreover, the regional patterns of activation and their relationship with illness severity were largely consistent with our a priori hypotheses.

It is possible that the observed negative correlation of activation for the executive task with DTS scores was a result of a persisting state produced by the preceding emotional block. It appears, however, that this observed state effect (trauma-related thought) is being modulated by a trait effect (symptom) severity. Broadly, this is consistent with the dissociative effects of PTSD on attention reported in neuropsychological studies (Kaufman, 2002; Roca et al., 2006). A correlation between behavioral performance on the executive task and DTS may have been observed by increasing the cognitive demands of the task.

Our study was hampered by poor BOLD signal recovery in the amygdala region due to differences in magnetic susceptibility. Previous findings for the amygdala are discordant. Most studies report greater amygdalar activation associated with PTSD (Shin et al., 1997, 2004, 2005; Rauch et al., 2000; Semple et al., 2000; Hendler et al., 2003; Williams et al., 2006), but there are contradictory reports of greater activation in controls (Britton et al., 2005; Phan et al., 2006), and numerous studies lack amygdalar findings entirely (Bremner et al., 1999a,b; Lanius et al., 2001, 2002, 2003b; Shin et al., 2001; Sakamoto et al., 2005). Quantitative analysis of signal-to-noise in this region showed poor signal quality using our standard echo-planar imaging sequence at 3T. For future studies, a change in fMRI sequence such as inverse spiral imaging, spiral in/out, or a shortened TE with EPI is likely to enhance our ability to discern amygdalar activity (Glover and Law, 2001).

Finally, SCID assessment of comorbid psychiatric disorders was lacking. However, we collected important information on a number of comorbid disorders that often accompany PTSD using self assessment measures for depression, substance and alcohol use disorders.

4.5. Conclusions

To our knowledge, this is the first neuroimaging study of recent-onset combat-related PTSD from post-9/11 military conflicts. We emphasize that the brain–behavior relationships are inherently correlational and are retrospective in nature, and as such they do not indicate whether the alterations in brain function were caused by deployment or were a precipitating factor. Determining the plasticity in these brain regions following treatment will be of keen interest. The present findings lend further credence to mounting evidence establishing a clear link between the subjectively assessed behavioral phenomenology of PTSD and objective neurobiological markers. Our findings extend the current symptom provocation-based functional neuroanatomy of PTSD by providing evidence that reciprocally functioning dorsal executive and ventral emotion processing systems are differentially affected by severity of PTSD symptoms. We used brain imaging data to distinguish PTSD and depression symptom severity in a way that is not possible using standard behavioral measures. Our results support a model of PTSD emphasizing a cognitive–affective dysmetria that can promote further study on the effects of dysregulation of emotion processing on cognitive brain regions.

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