An fMRI Study of Anterior Cingulate Function in Posttraumatic Stress Disorder

Lisa M. Shin, Paul J. Whalen, Roger K. Pitman, George Bush, Michael L. Macklin, Natasha B. Lasko, Scott P. Orr, Sean C. McInerney, and Scott L. Rauch

Background: *Several recent neuroimaging studies have provided data consistent with functional abnormalities in anterior cingulate cortex in posttraumatic stress disorder (PTSD). In our study, we implemented a cognitive activation paradigm to test the functional integrity of anterior cingulate cortex in PTSD.*

Methods: *Eight Vietnam combat veterans with PTSD (PTSD Group) and eight Vietnam combat veterans without PTSD (non-PTSD Group) underwent functional magnetic resonance imaging (fMRI) while performing the Emotional Counting Stroop. In separate conditions, subjects counted the number of combat-related (Combat), generally negative (General Negative), and neutral (Neutral) words presented on a screen and pressed a button indicating their response.*

Results: *In the Combat versus General Negative comparison, the non-PTSD group exhibited significant fMRI blood oxygenation level–dependent signal increases in rostral anterior cingulate cortex, but the PTSD group did not.*

Conclusions: *These findings suggest a diminished response in rostral anterior cingulate cortex in the presence of emotionally relevant stimuli in PTSD. We speculate that diminished recruitment of this region in PTSD may, in part, mediate symptoms such as distress and arousal upon exposure to reminders of trauma.* Biol Psychiatry 2001; 50:932–942

Key Words: Medial prefrontal cortex, modified Stroop, insula, emotion, neuroimaging, anxiety disorder

Introduction

Posttraumatic stress disorder (PTSD) is marked by nightmares, flashbacks, and intrusive recollections of traumatic events (American Psychiatric Association 1994). In individuals with PTSD, exposure to reminders of the trauma is associated with self-reported distress, peripheral psychophysiologic arousal (Orr et al 1998; Pitman et al 1987 1990), and regional cerebral blood flow (rCBF) increases in amygdala, orbitofrontal cortex, anterior temporal poles, insular cortex, and posterior cingulate cortex (Bremner et al 1999a, 1999b; Liberzon et al 1999; Rauch et al 1996; Semple et al 2000; Shin et al 1997, 1999).

Several neuroimaging studies have reported no significant activation or decreased activation in anterior cingulate cortex (ACC) in PTSD (Bremner et al 1999a, 1999b; Semple et al 2000; Shin et al 1999). For example, Shin et al (1999) found that the trauma-exposed control group, but not the PTSD group, exhibited significant rCBF increases in rostral ACC during the recollection and imagery of personal traumatic events. Bremner and colleagues (1999a) reported no significant activation in rostral ACC, as well as decreased activation in ventral portions of ACC (subcallosal gyrus; Brodmann area 25) in PTSD. Semple et al (2000) found that patients with PTSD exhibited lower rCBF in rostral ACC during both rest and an auditory continuous performance task than did healthy comparison subjects. Missing from the current literature are neuroimaging studies that implement cognitive tasks specifically designed to further examine the functional integrity of ACC in PTSD.

One type of paradigm that appears to reliably activate ACC in healthy individuals is the Stroop task in which subjects are shown a series of words and are asked to name the color in which each word is printed (e.g., Bench et al 1993; Bush et al 1998; Carter et al 1995; Derbyshire et al 1998; George et al 1994 1997; Leung et al 2000; Pardo et al 1990; Peterson et al 1999; for a review, see Bush et al 2000). Researchers interested in studying the processing of emotional information in psychiatric patients have used disorder-relevant words as stimuli and have measured response times of subjects performing the color-naming task. This research has demonstrated that individuals with PTSD exhibit longer response times while naming the color of trauma-related words (e.g., "bodybags" and "firefight" for combat-related PTSD) than neutral, positive, or generally negative words (e.g., Bryant and Harvey 1995; Cassiday et al 1992; Dubner and Motta 1999; Foa et al

From the Department of Psychology, Tufts University, Medford, Massachusetts (LMS); Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (LMS, RKP, GB, SPO, SCM, SLR); Departments of Psychiatry and Psychology, University of Wisconsin, Madison, Wisconsin (PJW); VA Research Service, Manchester, New Hampshire (RKP, MLM, NBL, SPO); Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (SLR).
Address reprint requests to Lisa M. Shin, Ph.D., Department of Psychology, Tufts University, Medford MA 02155.
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1991; Kaspi et al 1995; Litz et al 1996; McNally et al 1990 1993 1996; Moradi et al 1999; Thrasher et al 1994; Vrana et al 1995).

Initial studies of brain activation during the performance of emotional variants of the Stroop task in healthy individuals have yielded some consistent findings. In a positron emission tomography (PET) study, George et al (1994) reported activation in ACC during the performance of an emotional Stroop task involving sadness-related words. Activation in ACC was also reported by Whalen et al (1998) in a functional magnetic resonance imaging (fMRI) study using the Emotional Counting Stroop. During each trial, subjects saw emotionally negative or neutral words on a screen, counted the number of words, and pressed a button indicating their response. Although response times did not differ between conditions, the Negative versus Neutral comparison revealed fMRI blood oxygenation level–dependent (BOLD) signal increases in a rostral portion of ACC.

Anatomic studies suggest that rostral ACC has extensive connectivity with other limbic regions (Amaral et al 1992; Pandya et al 1981;Vogt et al 1992), and it may be useful to consider rostral ACC as an affective subdivision of anterior cingulate cortex (see Bush et al 1998; Devinsky et al 1995; Vogt et al 1992 1995; Whalen et al 1998; see also Bush et al 2000 for a review). Consistent with this notion, activation in the vicinity of rostral ACC has been associated with emotional state induction in healthy individuals (Dougherty et al 1999; George et al 1995 1996; Kimbrell et al 1999; Lane et al 1998; Rauch et al 1999; Shin et al 2000), aversive gustatory stimulation (Zald et al 1998), procaine-induced fear (Ketter et al 1996; Servan-Schreiber et al 1998), and the prediction of treatment response in depression (Mayberg et al 1997). Whalen et al (1998) reported that in healthy individuals, rostral ACC activation can occur in the absence of behavioral interference (i.e., response time increases) in an emotional Stroop task and thus proposed that activation in rostral ACC might reflect a regulatory response; that is, the successful processing of emotional stimuli in the service of facilitating task performance. Because rostral ACC may be considered a regulatory area that is activated during normal processing of emotional stimuli (Mayberg 1997), one might predict that patients with anxiety disorders would fail to show significant activation in this region during the presentation of disorder-relevant words in an emotional Stroop task.

In our study, we implemented the Emotional Counting Stroop (ecStroop; Whalen et al 1998) and fMRI to study the functional integrity of rostral ACC in eight Vietnam combat veterans with PTSD (PTSD group) and eight Vietnam combat veterans without PTSD (non-PTSD group). We selected the ecStroop because it has been shown to reliably recruit rostral ACC in healthy individuals and because previous offline behavioral studies of PTSD have used similar modified Stroop tasks containing emotional words (e.g., Bryant and Harvey 1995; Cassiday et al 1992; Dubner and Motta 1999; Foa et al 1991; Kaspi et al 1995; Litz et al 1996; McNally et al 1990 1993 1996; Moradi et al 1999; Thrasher et al 1994; Vrana et al 1995). In the current experiment, subjects received blocked presentations of combat-related (Combat), generally negative (General Negative), and neutral (Neutral) words. During each trial, subjects were required to count the number of words on the screen and to press a button corresponding to the correct number. We compared fMRI BOLD signal in the Combat versus control (General Negative or Neutral) conditions. We were particularly interested in the Combat versus General Negative comparison because its results might best isolate the processing of trauma-related information per se.

Given the results of Whalen et al (1998), we predicted that the non-PTSD group would exhibit significant fMRI BOLD signal increases in rostral ACC in the Combat versus General Negative comparison; however, given the results of recent symptom provocation neuroimaging studies of PTSD and the theoretical view of rostral ACC as performing a regulatory role in the processing of emotional stimuli, we predicted that the PTSD group would not show significant BOLD signal increases in rostral ACC and would have longer response times in the Combat versus General Negative condition than the non-PTSD group. In addition, we expected that a direct between-group comparison would confirm these predicted findings by showing greater BOLD signal (in the Combat condition) in rostral ACC in the non-PTSD group than in the PTSD group. Finally, in the Combat versus General Negative comparison, we predicted that the PTSD group would exhibit significant fMRI BOLD signal increases in amygdala and insular cortex, two regions that have been activated in recent symptom provocation neuroimaging studies of PTSD.

Methods and Materials

Subjects

Subjects were 16 right-handed (Oldfield 1971) male Vietnam combat veterans; eight met diagnostic criteria for PTSD (PTSD group), and eight were free of current PTSD (non-PTSD group). (One non-PTSD subject had met criteria for PTSD in the past.) We established PTSD diagnoses using the Clinician-Administered PTSD Scale (CAPS; Blake et al 1995). The PTSD and non-PTSD subjects were enrolled into the study in parallel. The groups did not significantly differ in age (50.6 years ± 4.6 [PTSD] and 54.1 years ± 3.2 [non-PTSD]; $t[14] = 1.8$, $p = .10$).

The PTSD group had higher scores on the Combat Exposure Scale (CES; Keane et al 1989) than did the non-PTSD group (30.1 ± 9.1 [PTSD] and 20.1 ± 7.8 [non-PTSD]; $t[14] = 2.4$, $p = .03$). Not surprisingly, the PTSD group also had higher CAPS scores than the non-PTSD group (82.0 ± 18.6 [PTSD] and 6.5 ± 9.2 [non-PTSD]; $t[14] = 10.3$, $p < .001$). The presence of other psychiatric disorders was assessed with the Structured Clinical Interview for DSM-IV (First et al 1995). Subjects in the PTSD group met criteria for the following current comorbid diagnoses: major depression ($n = 3$), dysthymia ($n = 2$), specific phobia ($n = 2$), social phobia ($n = 1$), panic disorder ($n = 2$), generalized anxiety disorder ($n = 1$), and obsessive-compulsive disorder ($n = 1$). None of the subjects in the non-PTSD group had current diagnoses.

All subjects were free of metallic implants, neurologic and major medical conditions, and psychotropic and cardiovascular medications (for at least 1 month or 5 half-lives, whichever was greater). The study was approved by the Subcommittees on Human Studies of the Massachusetts General Hospital, Boston, and the Veterans Affairs Medical Center, Manchester, New Hampshire. Written informed consent was obtained from each participant before participation.

Emotional Counting Stroop

TASK. Subjects performed the ecStroop (Whalen et al 1998) during fMRI data acquisition. During each trial, subjects viewed a set of identical words (1–4 words per trial) displayed simultaneously on a screen, counted the number of words, and pressed a button corresponding to that number. Each trial was 1.5 sec in duration and consisted of the following events: blank screen (50 msec) followed by stimulus (1.45 sec). Subjects responded using a keypad consisting of four horizontally arranged buttons that represented the numbers 1, 2, 3, and 4 from left to right. Subjects used the middle and index fingers of their left hand to press the 1 and 2 buttons, respectively; subjects used the index and middle fingers of their right hands to press the 3 and 4 buttons, respectively. Behavioral data (i.e., response times and error rates) were collected by the computer during task performance.

STIMULI. In separate conditions, subjects viewed three different types of words: 1) neutral words that named household items (Neutral; e.g., *mirror*); 2) generally negative words unrelated to combat (General Negative; e.g., *danger*); and 3) combat-related words (Combat; e.g., *firefight*) that previously were rated by combat veterans as stressful (Chemtob et al 1997; McNally et al 1987). Words from the three categories were matched for length, part of speech, and frequency of usage (Francis and Kucera 1982).

PARADIGM. Subjects completed two 5-min functional imaging runs of the ecStroop; each run consisted of ten 30-sec blocks (20 trials per block). Within each run, subjects participated in four blocks of Neutral words, alternating with two blocks of General Negative words and two blocks of Combat words. The first and last blocks per run always consisted of a low-level fixation baseline. The order of blocks was counterbalanced both within subjects (across runs) and across subjects. Immediately before the ecStroop task within the same functional imaging session, all subjects participated in a paradigm involving the passive viewing of faces (Rauch et al 2000).

DATA ANALYSIS. Response times (corresponding to trials on which subjects responded correctly) were averaged within each Word Type condition for each subject. Error rates were expressed as a percentage of the total number of responses within each Word Type condition for each subject. Behavioral data from one PTSD and one non-PTSD subject were lost because of technical difficulties.

Apparatus

The stimulus presentation software (MacStim) was run on a personal computer (Macintosh 100-MHz Power PC) with a Radius interface (model 0355, Videovision). Stimuli were projected onto a hemicircular tangent screen in the magnet bore via a color LCD projector (Sharp XG-2000V) and a collimating lens. Stimuli on the screen were visible to the subject via a mirror (1.5 in × 3 in) positioned approximately 15 cm above the subject's eyes.

Functional MRI data were collected with a General Electric Signa 1.5 Tesla high-speed imaging device (modified by Advanced NMR Systems, Wilmington, MA) using a quadrature head coil. Our Instascan software is a variant of the echoplanar technique first described by Mansfield (1977).

Functional MRI Procedures

DATA ACQUISITION. The fMRI procedures have been described previously (Cohen and Weisskoff 1991; Kwong 1995; Rauch et al 2000; Whalen et al 1998). Briefly, an initial sagittal localizer [spoiled gradient recall acquisition in steady state (SPGR), 60 slices, resolution .898 × .898 × 2.8 mm] provided a reference for slice selection and localization within Talairach space (Talairach and Tournoux 1988). Automated shimming (Reese et al 1995) was then performed to maximize field homogeneity. To identify large- and medium-diameter vessels, a magnetic resonance angiogram (SPGR, resolution .78125 × .78125 × 2.8 mm) was acquired. Then a set of T1-weighted high-resolution transaxial anatomic scans (resolution 1.56 × 1.56 × 8 mm) were obtained. For the fMRI series, BOLD signal intensity was measured using asymmetric spin-echo sequences to minimize macrovascular signal contributions. Functional data were acquired as 15 contiguous, interleaved, horizontal, 8-mm thick slices that paralleled the intercommissural plane (voxel size 3.125 × 3.125 × 8 mm; 120 images per slice, repetition time/echo time/flip angle = 2500 m/sec/70 m/sec/90°).

DATA ANALYSIS. Automated data analytic techniques began with quantification and correction of subject motion (Jiang et al 1995; Woods et al 1992). Both functional and structural data were then placed into normalized Talairach space and resliced coronally (3.125 × 3.125 × 3 mm voxels). Data from each subject were then baseline normalized. Nonparametric statistical maps, using the Kolmogorov-Smirnov (KS) statistic, were constructed from a concatenated data set across eight subjects per

Table 1. Response Times and Error Rates

	Response times		Error rates	
Condition	PTSD	Non-PTSD	PTSD	Non-PTSD
Neutral	995 (106)	753 (69)	15% (12)	3% (2)
General negative	1032 (114)	771 (74)	14% (12)	3% (2)
Combat	1059 (171)	774 (83)	21% (16)	3% (3)

Response times are given in milliseconds. Standard deviations are in parentheses. PTSD, posttraumatic stress disorder.

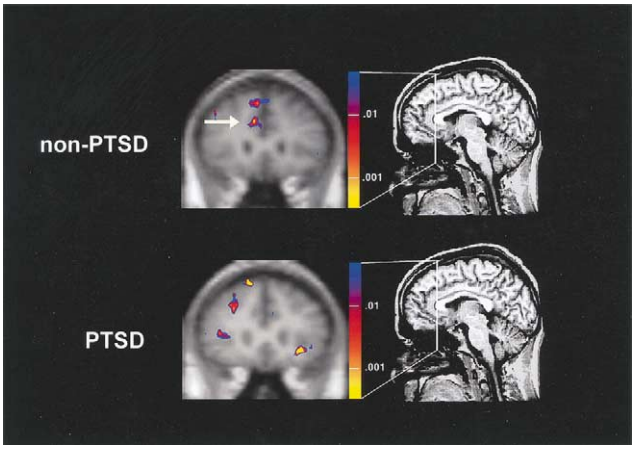

Figure 1. Functional magnetic resonance imaging blood oxygenation level–dependent signal results of the Combat versus General Negative comparison. The coronal images on the left represent colorized Kolmogorov-Smirnov (KS) statistical maps superimposed on the averaged, spatially normalized, T1 structural data for all subjects. The KS maps depict significant activation within rostral anterior cingulate cortex (ACC) in the non-PTSD group (top) only. The sagittal structural image on the right depicts the approximate location of the coronal slice presented on the left. PTSD, posttramatic stress disorder.

group (number of images per subject = 240). Images were smoothed using a Hanning 1:2:1 kernel filter. The maps were displayed in pseduocolor, scaled according to significance, and superimposed on SPGR images that had been placed into Talairach space and resliced in the coronal plane.

Although analyses were based on voxel-by-voxel statistical maps, we designated rostral ACC as our main a priori search territory. Other regions of interest were amygdala and insular cortex. Rostral ACC is a portion of the anterior cingulate that lies anterior and superior to the genu of the corpus callosum. We defined rostral ACC based on neuroanatomic tracing studies in primates demonstrating connectivity with other limbic regions (e.g., the amygdala; see Amaral et al 1992, Pandya et al 1981). The superior, anterior, and lateral boundaries of rostral ACC were determined by anatomy visualized on structural images in Talairach space. The inferior boundary was the intercommissural plane; subgenual portions of ACC (operationally defined here as ACC below z = 0) were excluded from this region of interest because our earlier studies demonstrated signal dropout in this region due to susceptibility (Bush et al 1998; Whalen et al 1998). Based on previous neuroimaging findings (Bush et al 1998; Whalen et al 1998), as well as data in the primate demonstrating that the posterior extent of limbic projections to ACC are located immediately superior to the genu of the corpus callosum (see Figure 9A in Amaral et al 1992; see also Pandya et al 1981), the posterior boundary was defined as the coronal slice 24 mm anterior to the anterior commissure. This posterior boundary of rostral ACC is approximately 15 mm anterior to the dorsal portion of ACC that is activated in cognitive interference paradigms such as the standard Counting Stroop (Bush et al 1998, 2000). (Dorsal ACC previously has been referred to as the cognitive division of anterior cingulate or ACcd; Bush et al 1998.) The statistical significance threshold for activation in rostral ACC was $p < 5.5 \times 10^{-4}$, which represents a p value of .05, corrected for the total number of voxels in this region (~90 3 × 3 × 8 mm voxels). For the sake of completeness and to obviate bias, we also report other (nonpredicted) regions that exhibited BOLD signal intensity increases with $p < 5.5 \times 10^{-4}$, although we advise the reader to use caution in interpreting them given their post hoc nature. Because we made no specific predictions regarding BOLD signal decreases, we report them only when they occur in a priori regions of interest.

We first examined KS maps representing the main contrasts of interest (Combat vs. General Negative, and Combat vs. Neutral) within each group separately. Then, for each individual subject (within each group), BOLD data in the Combat condition were proportionately scaled to data in a baseline (General Negative or Neutral) condition. All baseline means were adjusted to an arbitrary value (1000). We then constructed between-group KS maps that identified regions in which BOLD signal during the Combat condition relative to the normalized General Negative (or Neutral) condition was significantly different between the PTSD and non-PTSD groups. Methods for the between-group

Table 2. Combat versus General Negative: Non-PTSD Group

Region	p value	Coordinates
A priori regions of interest		
R rostral anterior cingulate	3.1×10^{-4}	+9, +24, +31
Other regions		
B medial frontal gyrus	6.5×10^{-5}	−9, +42, +31
	4.2×10^{-4}	+6, +27, +50
R middle frontal gyrus	2.3×10^{-4}	+34, +48, +18
	9.0×10^{-5}	+43, +21, +34
R middle temporal gyrus	1.2×10^{-4}	+53, −54, +3
R superior temporal gyrus	4.2×10^{-4}	+46, −15, +9
B inferior parietal lobule	8.3×10^{-6}	+53, −51, +31
	9.0×10^{-5}	−31, −60, +43
R lenticular nucleus	2.3×10^{-4}	+21, +12, +6
L fusiform gyrus	3.1×10^{-4}	−34, −63, −9
L precuneus	4.2×10^{-4}	−3, −69, +43

For each focus of activation, p values and Talairach coordinates are given. Coordinates are expressed in millimeters: x > 0 is right of the midsagittal plane, y > 0 is anterior to the anterior commissure, and z > 0 is superior to the anterior commissure-posterior commissure plane. R, right; L, left; B, bilateral; PTSD, posttraumatic stress disorder.

Table 3. Combat versus General Negative: PTSD Group

Region	*p* value	Coordinates
A priori regions of interest		
B insular cortex	4.7×10^{-5}	+34, +9, +6
	4.2×10^{-4}	−37, +9, +3
Other regions		
B medial frontal gyrus	3.3×10^{-5}	−3, +54, +34
	5.0×10^{-8}	+12, +51, +6
R middle frontal gyrus	2.3×10^{-4}	+34, +33, +31
B inferior frontal gyrus	4.2×10^{-4}	−40, +36, +12
	1.9×10^{-6}	−37, +27, 0
	6.5×10^{-5}	+46, +21, +6
	4.7×10^{-5}	+40, +18, −12
R dorsal anterior cingulate	4.2×10^{-4}	+12, +12, +37
B superior temporal gyrus	2.6×10^{-7}	−50, +3, +3
	1.7×10^{-4}	+53, −30, +21
L middle temporal gyrus	2.3×10^{-4}	−46, −60, +3
R lenticular nucleus	4.2×10^{-4}	+28, −3, −6
R precentral gyrus	1.7×10^{-4}	+46, 0, +34
R claustrum	6.5×10^{-5}	+34, −6, −6
R thalamus	6.5×10^{-5}	+21, −27, +6
B hippocampus	1.2×10^{-4}	−31, −27, −12
	4.0×10^{-6}	+31, −33, −9
posterior cingulate	1.3×10^{-6}	0, −57, +18
	1.3×10^{-6}	+3, −36, +28
L precuneus	9.0×10^{-5}	−6, −66, +21
B inferior parietal lobule	1.8×10^{-7}	+53, −45, +31
	1.6×10^{-7}	−40, −63, +28
B parahippocampal gyrus	1.7×10^{-4}	−9, −51, +3
	3.1×10^{-4}	+21, −51, 0
R fusiform gyrus	2.2×10^{-9}	+40, −60, −12
cuneus	1.7×10^{-4}	0, −78, +18

For each focus of activation, *p* values and Talairach coordinates are given. Coordinates are expressed in millimeters: x > 0 is right of the midsagittal plane, y > 0 is anterior to the anterior commissure, and z > 0 is superior to the anterior commissure-posterior commissure plane. R, right; L, left; B, bilateral; PTSD, posttraumatic stress disorder.

analyses have been described previously (Bush et al 1999; Rauch et al 2000).

Results

Behavioral Data

Response time and error rate data (see Table 1) were submitted to separate 2 (Group) × 3 (Word Type) analyses of variance (ANOVAs). A main effect of Group revealed that the PTSD group had longer response times than the non-PTSD group across all conditions [$F(1,12) = 26.4$; $p = .0002$]. The main effect of Word Type and the Word Type × Group interaction were not significant ($ps > .22$).

In the ANOVA for error rates, a main effect of Group showed that the PTSD group had higher error rates than the non-PTSD group across all conditions [$F(1,12) = 7.9$; $p = .02$]. The main effect of Word Type and the Word Type × Group interaction were not significant ($ps > .11$).

Table 4. Combat versus Neutral: Non-PTSD Group

Region	*p* value	Coordinates
A priori regions of interest		
L insular cortex	4.8×10^{-4}	−43, +12, −6
L rostral anterior cingulate	5.7×10^{-4} (*ns*)	−3, +24, +25
Other regions		
R middle frontal gyrus	1.4×10^{-4}	+40, +24, +37
R inferior frontal gyrus	4.8×10^{-4}	+50, +18, +18
R lenticular nucleus	4.0×10^{-4}	+21, 0, −3
L middle temporal gyrus	3.4×10^{-7}	−53, −12, −6
Posterior cingulate	3.2×10^{-6}	0, −45, +15
L inferior parietal lobule	2.1×10^{-7}	−31, −60, +40
L superior parietal lobule	3.4×10^{-4}	−25, −69, +43
R cuneus/precuneus	6.6×10^{-5}	+9, −66, +18
R lingual gyrus	4.8×10^{-4}	+9, −75, 0

For each focus of activation, *p* values and Talairach coordinates are given. Coordinates are expressed in millimeters: x > 0 is right of the midsagittal plane, y > 0 is anterior to the anterior commissure, and z > 0 is superior to the anterior commissure-posterior commissure plane. R, right; L, left; B, bilateral; PTSD, posttraumatic stress disorder. Because the *p* value for the activation in rostral anterior cingulate fell slightly above our significance threshold of 5.5×10^{-4}, this activation is considered a nonsignificant (*ns*) trend.

Functional MRI BOLD Signal Data

COMBAT VERSUS GENERAL NEGATIVE. Within the non-PTSD group, significant BOLD signal increases occurred in right rostral ACC. (See Table 2 and Figure 1.) Signal decreases occurred in left insular cortex ($p = 3.3 \times 10^{-5}$; x, y, z = −31, −12, +18).

Within the PTSD group, there were no significant BOLD signal increases in rostral ACC. (See Table 3 and Figure 1.) Significant BOLD signal increases occurred in bilateral anterior insular cortex and in dorsal ACC, a region that has been consistently activated in cognitive interference paradigms such as the standard color Stroop (see Bush et al 2000).

COMBAT VERSUS NEUTRAL. Within the non-PTSD group, BOLD signal increases in left rostral ACC ($p = 5.7 \times 10^{-4}$) just missed the *p* value significance threshold ($p = 5.5 \times 10^{-4}$) (see Table 4). Significant BOLD signal increases also occurred in left anterior insular cortex in the non-PTSD group.

The PTSD group exhibited no significant BOLD signal increases in rostral ACC (see Table 5). Significant BOLD signal increases occurred in right anterior insular cortex.

GENERAL NEGATIVE VERSUS NEUTRAL. The non-PTSD group exhibited nonsignificant BOLD signal increases in left rostral ACC ($p = 5.1 \times 10^{-3}$; x, y, z = −15, +39, +15), as well as significant increases in medial frontal cortex ($p = 4.0 \times 10^{-4}$; x, y, z = 0, +42, +43 and $p = 2.0 \times 10^{-4}$; x, y, z = −9, +51, +21), right midcingulate cortex ($p = 3.4 \times 10^{-4}$; x, y, z = +9, −21, +37), left hippocampus ($p = 9.7 \times 10^{-5}$; x, y, z = −31,

Table 5. Combat versus Neutral: PTSD Group

Region	*p* value	Coordinates
A priori regions of interest		
R insular cortex	2.0×10^{-4}	+28, +21, +6
Other regions		
B medial frontal gyrus	1.3×10^{-6}	+12, +51, +6
	9.7×10^{-5}	−6, +3, +56
B middle frontal gyrus	2.0×10^{-4}	+37, +6, +37
	4.5×10^{-5}	−37, +6, +37
B inferior frontal gyrus	9.7×10^{-5}	−37, +27, 0
	4.0×10^{-4}	+46, +21, −3
R superior temporal gyrus	3.4×10^{-4}	+46, −24, +3
Mid-cingulate	9.7×10^{-5}	0, −27, +40
L posterior cingulate	4.0×10^{-6}	−3, −42, +37
L inferior parietal lobule	4.5×10^{-5}	−40, −51, +25
	4.0×10^{-6}	−34, −69, +25
L precuneus	9.2×10^{-6}	−12, −54, +50
L fusiform gyrus	2.4×10^{-4}	−28, −57, 0
R visual association cortex	1.2×10^{-4}	+37, −75, +3

For each focus of activation, *p* values and Talairach coordinates are given. Coordinates are expressed in millimeters: x > 0 is right of the midsagittal plane, y > 0 is anterior to the anterior commissure, and z > 0 is superior to the anterior commissure-posterior commissure plane. R, right; L, left; B, bilateral; PTSD, posttraumatic stress disorder.

−30, −3), and left parahippocampal gyrus ($p = 8.0 \times 10^{-5}$; x, y, z = −18, −33, 0).

The PTSD group exhibited no significant signal increases in any region in this contrast.

BETWEEN-GROUP COMPARISONS. The BOLD signal during the Combat condition, relative to the General Negative condition, was significantly greater in the non-PTSD group than in the PTSD group in the following regions: right anterior insular cortex and a region of ACC just posterior to the posterior boundary of rostral ACC. (See Table 6.) BOLD signal during the Combat condition, relative to the General Negative condition, was significantly greater in the PTSD group than in the non-PTSD group in the following regions: left anterior and bilateral posterior insular cortex, and dorsal ACC. Similar results were obtained when BOLD signal in the Combat condition was normalized to the Neutral condition, except that BOLD signal in ACC ($p = 5.0 \times 10^{-3}$; x, y, z = −6, +21, +25) was nonsignificantly greater in the non-PTSD group than in the PTSD group.

Table 6. Between Group Comparison: Combat Condition (Normalized to General Negative)

Region	*p* value	Coordinates
BOLD Signal Greater in non-PTSD Group		
A priori regions of interest		
R insular cortex	1.3×10^{-13}	+34, +9, −6
Other regions		
R anterior cingulate	1.7×10^{-4}	+3, +18, +31
L medial frontal gyrus	3.9×10^{-7}	−9, +42, +34
	2.4×10^{-5}	−6, +27, +46
B middle frontal gyrus	3.2×10^{-8}	−25, +54, +9
	8.6×10^{-10}	+40, +48, +9
L inferior frontal gyrus	1.8×10^{-7}	−46, +24, +15
B lenticular nucleus	5.9×10^{-7}	+18, +15, 0
	1.2×10^{-10}	−18, +15, −9
R mid-cingulate gyrus	1.2×10^{-4}	+9, 0, +34
L fusiform gyrus	4.0×10^{-6}	−37, −60, −12
R lingual gyrus	1.6×10^{-11}	+18, −81, −9
BOLD Signal Greater in PTSD Group		
A priori regions of interest		
B insular cortex	5.9×10^{-7}	−34, +9, −6
	1.4×10^{-8}	−34, −21, +15
	9.0×10^{-5}	+37, −21, +12
R insular cortex/inferior frontal gyrus	5.0×10^{-8}	+34, +18, −9
Other regions		
B medial frontal gyrus	3.9×10^{-7}	−9, +51, +15
	1.8×10^{-7}	+15, +48, +12
R middle frontal gyrus	1.4×10^{-8}	+31, +42, +25
L dorsal anterior cingulate	2.4×10^{-5}	−9, +9, +40
L superior temporal gyrus	2.8×10^{-11}	−50, +3, 0
L lenticular nucleus	1.3×10^{-6}	−21, −3, −3
L postcentral gyrus	4.7×10^{-5}	−50, −9, +15
R thalamus	4.7×10^{-5}	+6, −9, +3
L hippocampus	1.8×10^{-7}	−28, −24, −12
L paracentral lobule	5.7×10^{-6}	−9, −27, +46
R posterior cingulate	4.0×10^{-6}	+3, −39, +34
	5.9×10^{-7}	+6, −51, +28
B precuneus	8.6×10^{-9}	+9, −48, +46
	8.3×10^{-6}	−6, −66, +15
L inferior parietal lobule	1.2×10^{-7}	−43, −51, +28
L parahippocampal gyrus	1.4×10^{-8}	−9, −51, 0
L cuneus	5.9×10^{-7}	−3, −78, +18

For each focus of activation, *p* values and Talairach coordinates are given. Coordinates are expressed in millimeters: x > 0 is right of the midsagittal plane, y > 0 is anterior to the anterior commissure, and z > 0 is superior to the anterior commissure-posterior commissure plane. R, right; L, left; B, bilateral; PTSD, posttraumatic stress disorder; BOLD, blood oxygenation level–dependent.

Discussion

In the comparison of Combat versus General Negative word conditions, the non-PTSD group exhibited significant activation in rostral ACC, but the PTSD group did not. These findings are interesting in light of previously reported abnormalities in ACC in PTSD (Bremner et al 1999a, 1999b; De Bellis et al 2000; Semple et al 2000; Shin et al 1999).

The results of both the present and previous studies are consistent with a neuroanatomic model of PTSD that posits a failure of medial prefrontal cortex to inhibit a hyperresponsive amygdala (e.g., Bremner et al 1999b; Rauch et al 1998, 2000). Normally functioning medial prefrontal structures are thought to play an inhibitory role with respect to brain regions involved in learned fear

responses, such as the amygdala, and appear to be involved in the extinction of fear responses after fear conditioning. For example, in animal subjects, lesions to medial prefrontal cortex appear to retard extinction (Morgan et al 1993; Morgan and LeDoux 1995). In addition, increased activity of medial prefrontal cortical neurons is associated with decreased fear responding (Garcia et al 1999). Our study and previous research have provided evidence consistent with a failure to activate part of medial prefrontal cortex (rostral ACC) in PTSD. Interestingly, subjects with PTSD exhibit slowed extinction after fear conditioning compared with control subjects without PTSD (Orr et al 2000). It should be noted, however, that animal studies of the role of medial prefrontal cortex in extinction continue to provide new insights (e.g., Gewirtz et al 1997; Quirk et al 2000); furthermore, the degree to which the true homologue of medial prefrontal cortex in humans includes rostral ACC is not known (see Pandya et al 1981 for an anatomic argument in favor of this possibility).

The absence of statistically significant rostral ACC activation in PTSD is consistent with previous results; however, two earlier studies using SPECT and the presentation of combat sounds found no group differences in ACC activation (Liberzon et al 1999; Zubieta et al 1999), and one PET study involving perception and imagery of combat stimuli reported rCBF increases in subcallosal gyrus, in addition to rCBF decreases in rostral ACC in PTSD (Shin et al 1997). Furthermore, one script-driven imagery PET study of PTSD reported rCBF increases in rostral ACC (Rauch et al 1996); however, because the latter study did not include a control group, it is unclear whether the PTSD group's rCBF changes in rostral ACC were of normal magnitude.

Although subjects in the PTSD group did not exhibit significant activation in rostral ACC, they did show significant BOLD signal increases in a dorsal region of ACC, which has been shown to be consistently activated in interference paradigms such as the standard color Stroop (Bench et al 1993; Carter et al 1995; Derbyshire et al 1998; George et al 1994, 1997; Leung et al 2000; Pardo et al 1990; Peterson et al 1999; see also Bush et al 1998, 2000). This effect was not observed in the non-PTSD group. One account for no significant activation of rostral ACC, accompanied by activation of dorsal ACC, might lie in the view of rostral ACC as serving a regulatory function (Mayberg 1997). The normal function of rostral ACC in the ecStroop might be to allocate resources during a task involving interference between the meaning of the emotionally laden words and the task of word counting (Whalen et al 1998). We speculate that failure to activate rostral ACC in PTSD might reflect an emotional load that exceeds the functional capacity of this region. A failure to activate rostral ACC might increase the cognitive processing load, increase behavioral interference, and activate more dorsal regions of ACC (Bush et al 1998, 2000). This scenario might be predicted by a functionally subdivided model of ACC whereby the rostral and dorsal ACC subserve affective and cognitive processing, respectively (Bush et al 1998, 2000; Whalen et al 1998). Further neuroimaging studies using cognitive interference tasks are needed to examine the functional integrity of dorsal ACC in PTSD.

Bush et al (1998) have demonstrated that significant activation in dorsal ACC occurs in the presence of response time increases across conditions, yet in our study, activation of this region in the PTSD group was unaccompanied by significant response time increases; however, our mean response times per condition (for both groups) were similar to those reported in previous behavioral Stroop studies in which PTSD subjects showed significant response time increases to trauma-related words (e.g., Cassiday et al 1992; Kaspi et al 1995; Litz et al 1996; McNally et al 1996). Given that previous studies have included 13 or more PTSD subjects, low statistical power in the current study may explain the lack of statistically significant response time differences between conditions.

An alternative explanation for the failure to observe significant BOLD signal responses in rostral ACC in the PTSD group might be the presence of greater variability in the structural or functional data in the PTSD group. Greater variability in patient groups is commonly observed and can result in smaller effect sizes and nonsignificant results. It is also possible that BOLD signal in rostral ACC in the baseline conditions was abnormally elevated in the PTSD group, resulting in smaller differences between conditions. Finally, the PTSD group may have been more familiar with the combat stimuli than the control group; PET studies have reported that familiarity can be associated with diminished activation in some brain regions (e.g., Vandenberghe et al 1995).

The PTSD group did not exhibit significant BOLD signal increases in amygdala in the Combat versus control comparisons. The absence of significant activation in amygdala might be due to habituation of amygdala responses to repeated word stimuli over the course of the experiment. Alternatively, the amygdala may not be particularly responsive to word stimuli (e.g., Whalen 1998; but see also Isenberg et al 1999), even when those words may be reminders of trauma for individuals with PTSD.

As predicted, activation occurred in insular cortex in the PTSD group; however, such activation also occurred in the non-PTSD group. The direct between-group contrast revealed greater BOLD signal in left anterior insular cortex in the PTSD group and greater signal in right anterior

insular cortex in the non-PTSD group. This between-group difference in the laterality of anterior insular cortex activation was not predicted, and its significance is unclear.

Activation in posterior cingulate was observed in between-condition comparisons within each group (in PTSD: Combat vs. General Negative, Combat vs. Neutral; in non-PTSD: Combat vs. Neutral). Between-group comparisons revealed that the PTSD group had greater BOLD signal in the Combat (normalized to General Negative) condition than did the non-PTSD group in two separate loci of the posterior cingulate. Although activation in posterior cingulate was not predicted, it may be consistent with reports of activation of posterior cingulate during symptom provocation in PTSD (Bremner et al 1999a), during exposure to videotaped traumatic events (Fischer et al 1996), and in the processing of emotional words in healthy individuals and in patients with panic disorder (Maddock et al 1996; Maddock and Buonocore 1997; see also Maddock 1999). Alternatively, increased activation in posterior cingulate could be due to increased recall (Vogt et al 2000).

Several regions listed in Table 6 (between-group comparison) do not also appear in Tables 2 and 3 (within-group comparisons). For example, in the between-group comparison, BOLD signal in insular cortex in the Combat condition (normalized to General Negative) was greater in the non-PTSD group than in the PTSD group; however, in the Combat versus General Negative comparison within the non-PTSD group, no significant BOLD signal increases were observed in insular cortex. This apparent discrepancy might be explained by the presence of *subthreshold* activations in insular cortex in the Combat versus General Negative comparison in the non-PTSD group. A subthreshold activation in the non-PTSD group, combined with even a slight deactivation in the PTSD group, could result in a significant between-group difference. Although not listed in the Tables, such subthreshold activations occurred in several regions within both groups.

It is important to note that the centroid of rostral ACC activation in the non-PTSD group in the Combat versus General Negative comparison was posterior to the centroid of rostral ACC activation in the General Negative versus Neutral comparison reported by Whalen et al (1998) (x, y, z = –3, +39, +15). Our designation of the present finding as being located within rostral ACC is based on 1) neuroimaging studies of emotional manipulations that reveal activations that encompass the site activated in the present study (see Bush et al 2000) and 2) the results of anatomic tracing studies in primates suggesting that connectivity of ACC with other limbic structures extends immediately superior to the genu of the corpus callosum (Amaral et al 1992; Pandya et al 1981).

Although rostral ACC activation in the non-PTSD group was located within our a priori search volume, the ACC activation in the between-group analysis (indicating greater relative BOLD signal in non-PTSD vs. PTSD) fell just posterior to our search volume. This latter activation may still reflect function of rostral ACC due to imperfect spatial resolution. Furthermore, although our definition of rostral ACC was informed by the results of anatomic and functional neuroimaging studies, the actual posterior boundary of rostral ACC has not been definitively identified.

Limitations of this study include a relatively small number of subjects and current comorbidity in the PTSD group. Comorbidity is extremely common among individuals with PTSD (e.g., Kulka et al 1990), and whether the results of this study were influenced by the presence of comorbid disorders is unclear. For example, one might argue that comorbid depression in the PTSD group may have contributed to the absence of significant activation in rostral ACC; however, whether patients with depression also lack significant activation of rostral ACC during emotional variants of the Stroop is not known. George et al (1997) reported that neither patients with mood disorders nor healthy control subjects significantly activated rostral ACC during a "sad" color Stroop task. Future studies might use the ecStroop to test rostral ACC function in trauma-exposed individuals with depression but without PTSD. Another potential concern might be that higher error rates in the PTSD group could account for group differences in rostral ACC activation; however, although overall error rates were higher in the PTSD group, the groups did not significantly differ in the error rate differences between conditions (i.e., the interaction between Word Type and Group was not significant). Furthermore, making errors is not associated with the absence of significant activation in ACC (e.g., Bush et al 2000; Carter et al 1998; Gehring et al 1993; Kiehl et al 2000). A further limitation is the lack of data regarding subjects' emotional responses to and familiarity with the word stimuli. Finally, comparisons of the Combat and control conditions yielded activation in many regions about which we had no a priori hypotheses, and those findings should be interpreted with caution.

In conclusion, the results reported here are broadly consistent with previous findings of functional abnormalities in ACC in PTSD and suggest a diminished response of rostral ACC during the performance of an interference task involving trauma-related information in PTSD. We speculate that diminished recruitment of rostral ACC in PTSD may mediate symptoms such as distress and arousal upon exposure to reminders of trauma. Future studies should employ other cognitive activation paradigms in the

context of functional neuroimaging to further examine the functional integrity of ACC in PTSD.

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