ORIGINAL ARTICLE

Regional Cerebral Blood Flow in the Amygdala and Medial Prefrontal Cortex During Traumatic Imagery in Male and Female Vietnam Veterans With PTSD

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Context: Theoretical neuroanatomic models of posttraumatic stress disorder (PTSD) and the results of previous neuroimaging studies of PTSD highlight the potential importance of the amygdala and medial prefrontal regions in this disorder. However, the functional relationship between these brain regions in PTSD has not been directly examined.

Objective: To examine the relationship between the amygdala and medial prefrontal regions during symptom provocation in male combat veterans (MCVs) and female nurse veterans (FNVs) with PTSD.

Design: Case-control study.

Setting: Academic medical center.

Participants: Volunteer sample of 17 (7 men and 10 women) Vietnam veterans with PTSD (PTSD group) and 19 (9 men and 10 women) Vietnam veterans without PTSD (control group).

Main Outcome Measures: We used positron emission tomography and the script-driven imagery paradigm to study regional cerebral blood flow (rCBF) during the recollection of personal traumatic and neutral events. Psychophysiologic and emotional self-report data also were obtained to confirm the intended effects of script-driven imagery.

Results: The PTSD group exhibited rCBF decreases in medial frontal gyrus in the traumatic vs neutral comparison. When this comparison was conducted separately by subgroup, MCVs and FNVs with PTSD exhibited these medial frontal gyrus decreases. Only MCVs exhibited rCBF increases in the left amygdala. However, for both subgroups with PTSD, rCBF changes in medial frontal gyrus were inversely correlated with rCBF changes in the left amygdala and the right amygdala/periamygdaloid cortex. Furthermore, in the traumatic condition, for both subgroups with PTSD, symptom severity was positively related to rCBF in the right amygdala and negatively related to rCBF in medial frontal gyrus.

Conclusions: These results suggest a reciprocal relationship between medial prefrontal cortex and amygdala function in PTSD and opposing associations between activity in these regions and symptom severity consistent with current functional neuroanatomic models of this disorder.

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SEVERAL RECENT FUNCTIONAL neuroimaging studies have investigated brain activation during exposure to trauma-related stimuli in posttraumatic stress disorder (PTSD). For example, the presentation of combat sights and sounds to male combat veterans (MCVs) with PTSD has been associated with relatively increased activation in the amygdala[1,2] and cerebellum[3-5] and relatively decreased activation in subcallosal gyrus.[3] The recollection of personal traumatic events (via the script-driven imagery paradigm) in PTSD has been associated with activation in the amygdala,[6] orbitofrontal cortex, anterior temporopolar cortex,[6,7] and insular cortex[6] and relatively decreased activation in anterior cingulate gyrus,[7,8] medial frontal gyrus,[8] and subcallosal gyrus.[9]

Recent functional magnetic resonance imaging studies using cognitive activation paradigms have further demonstrated the importance of the amygdala and medial prefrontal regions in PTSD. Rauch et al[10] demonstrated hyperresponsivity of the amygdala to masked fearful facial expressions in MCVs with PTSD. Shin et al[11] reported diminished recruitment of anterior cingulate cortex during the emotional counting Stroop task in MCVs with PTSD. Medial prefrontal structural abnormalities also have been reported in PTSD, including decreased volumes of pregenual anterior cingulate cortex and subcallosal cortex[12] and diminished neuronal integrity in anterior cingulate cortex.[13]

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Table 1. Demographic and Clinical Data*

Variable	PTSD Group		Control Group	
	MCVs (n = 7)	FNVs (n = 10)	MCVs (n = 9)	FNVs (n = 10)
Age	51.6 (5.2)	51.8 (1.9)	54.9 (2.7)	51.6 (1.6)
Education	14.8 (2.0)	18.0 (1.8)	16.3 (1.6)	17.3 (1.7)
CAPS total score	80.3 (25.2)	69.5 (16.5)	4.8 (6.3)	4.1 (5.1)
SCL-90-R depression subscale score	1.4 (0.9)	1.9 (1.0)	0.4 (0.5)	0.4 (1.0)

Abbreviations: CAPS, Clinician-Administered PTSD Scale; FNVs, female nurse veterans; MCVs, male combat veterans; PTSD, posttraumatic stress disorder; SCL-90-R, Symptom Checklist-90–Revised.
*Data are given as mean (SD).

The results of these neuroimaging studies are broadly consistent with the hypotheses that, in PTSD, the amygdala is hyperresponsive and medial prefrontal regions are hyporesponsive, and that these regions are reciprocally related.[14,15] Although researchers have hypothesized such a reciprocal relationship between the amygdala and medial prefrontal regions in PTSD, no previous studies in the literature have provided correlational data in support of this hypothesis. The most relevant evidence to date comes from Semple et al,[16] who reported higher regional cerebral blood flow (rCBF) in the amygdala and lower rCBF in anterior cingulate/medial frontal gyrus in patients with PTSD and substance abuse. However, correlations between rCBF changes in the amygdala and medial frontal regions were not reported.

Most of the neuroimaging studies of PTSD to date have included either MCVs or women with histories of physical or sexual abuse. In contrast to male Vietnam veterans, women who served as nurses in Vietnam have received relatively little research attention.[17-20] Female nurse veterans (FNVs) were exposed to horrific war-related injuries, mutilated bodies, death, and threats to personal safety and thus were also at risk of developing many negative outcomes, including PTSD.[17,18]

In the present research, we studied rCBF in 36 male and female Vietnam veterans using positron emission tomography (PET) and a script-driven imagery paradigm.[6,7,21] In separate conditions, participants recalled and imagined personal traumatic (war-related) and neutral events. During traumatic imagery, compared with neutral imagery, we predicted that veterans with PTSD would exhibit (1) greater activation in the amygdala, orbitofrontal cortex, temporopolar cortex, and insular cortex and (2) diminished activation in medial prefrontal regions (including medial frontal gyrus, rostral anterior cingulate gyrus, and subcallosal gyrus) compared with veterans without PTSD. We also performed parallel analyses in MCVs and FNVs separately to determine whether patterns of brain activation in our regions of interest differed in these subgroups. Given the lack of neuroimaging data on FNVs, we had no a priori hypotheses regarding the direction of such subgroup differences. In addition, we conducted correlational analyses to determine (1) the functional relationship between the amygdala and medial prefrontal regions and (2) the relationship between PTSD symptom severity and rCBF in the amygdala and medial prefrontal regions during the traumatic imagery condition. To demonstrate that participants achieved an emotional state during scanning, we also analyzed their subjective ratings and psychophysiologic data.

METHODS

PARTICIPANTS

Participants were 36 right-handed[22] Vietnam veterans without a history of head injury, neurologic disorders, or other major medical conditions. Seventeen participants (7 men and 10 women) met *DSM-IV* diagnostic criteria for current PTSD (PTSD group) and 19 participants (9 men and 10 women) never had PTSD (control group) according to the Clinician-Administered PTSD Scale (CAPS),[23] a structured clinical interview. All of the male participants had served in combat, and all of the female participants had served as nurses in Vietnam. Urine drug screen results were negative for all participants. No participant was taking psychotropic or cardiovascular medications at the time of the study.

Demographic and clinical data are given in **Table 1**. Age, education, and CAPS scores were analyzed using separate 2 (diagnosis: PTSD vs control) × 2 (subgroup: MCVs vs FNVs) analyses of variance. For the sake of brevity, we list only the statistically significant effects. A main effect of subgroup was observed for education ($F_{1,32}=12.3$; $P=.002$). Female nurse veterans had a greater mean number of years of education than MCVs, reflecting FNVs' nursing training (Table 1). A significant main effect of diagnosis was observed for CAPS scores ($F_{1,32}=205.1$; $P<.001$) and for mean depression subscale scores on the Symptom Checklist-90–Revised[24] ($F_{1,32}=17.4$; $P<.001$). The PTSD group had higher scores on these measures than the control group.

The presence of other Axis I mental disorders was assessed using the *Structured Clinical Interview for* DSM-IV.[25] Participants in the PTSD group met diagnostic criteria for the following current comorbid diagnoses: major depression (3 MCVs and 5 FNVs), panic disorder (2 MCVs and 1 FNV), social phobia (1 MCV and 1 FNV), specific phobia (2 FNVs), binge eating disorder (1 FNV), and somatoform disorder (1 FNV). Participants in the control group met diagnostic criteria for dysthymia (2 MCVs), specific phobia (1 FNV), and somatoform disorder (1 MCV).

This study was approved by the institutional review boards of the Massachusetts General Hospital, Boston, and the Veterans Affairs Medical Center, Manchester. Written informed consent was obtained from each participant.

SCRIPTS

The design and procedures of the script-driven imagery task were identical to those reported elsewhere.[6,7] Before the PET

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session, participants provided written descriptions of 2 neutral and 2 Vietnam-related traumatic autobiographical events. After describing each event, participants examined a list of bodily responses (eg, "heart races" and "labored breathing") and circled those responses (if any) that they experienced during each event. Later, one of us (M.A.C. or M.L.M.) composed scripts describing each event in the second person and the present tense, including up to 5 of the bodily responses that each participant selected.[21] The scripts were tape-recorded in a neutral voice for playback in the PET scanner.

Each participant was studied in 2 conditions (neutral and traumatic) with 2 scans (ie, replicates) per condition. (Participants completed other tasks in the larger scanning session, and those data will be reported separately.) During each scan, participants recalled and imagined the contents of a neutral or a traumatic script. The order of conditions was counterbalanced across participants.

Before each scan, participants were instructed to close their eyes, listen carefully to the script, and imagine the described event as vividly as possible, as if they were actually participating in it. The PET camera was turned on when the script started playing. Thirty seconds later, the script ended and oxygen-15–labeled carbon dioxide administration began. During the next 60 seconds, participants continued to recall and imagine the event while PET data were acquired. Then, oxygen-15–labeled carbon dioxide administration and PET data acquisition were terminated, and participants were instructed to stop imagining the event. After a 30-second "recovery" period, participants gave ratings of their emotional state. The PET scans were separated by at least 10 minutes to allow for radiation decay.

PSYCHOPHYSIOLOGIC RESPONSES

Participants' heart rate, skin conductance, and left lateral frontalis electromyographic (EMG) responses were measured via a modular instrument system (Coulbourn Instruments, Allentown, Pa) in the PET laboratory (Massachusetts General Hospital, Boston) according to established procedures.[21,26,27]

Psychophysiologic measurements were recorded for 30 seconds before each PET scan (baseline), for 60 seconds during each PET scan (imagery), and for 30 seconds immediately after each PET scan (recovery). Within the baseline and imagery periods (for each scan), readings were averaged. For each scan, the mean value during the baseline period was subtracted from the mean value during the imagery period, yielding "response" (ie, change) scores.

SUBJECTIVE RATINGS

Immediately after each scan, participants rated the intensity of several emotions using separate visual analog scales (0=absent and 12=maximal).[7,21,26] The rated emotions included happiness, sadness, anger, fear, disgust, surprise, and guilt. Participants also rated their arousal level, vividness of imagery, awareness of present surroundings, and degree to which they felt that the visualized event was happening again.

POSITRON EMISSION TOMOGRAPHY

Procedures

The PET equipment and procedures have been described in previous studies.[6,7,28] Briefly, PET data were gathered using a 15-slice, whole-body tomograph (Scanditronix PC4096; General Electric Medical Systems, Milwaukee, Wis). The camera produced contiguous slices 6.5 mm apart, with axial resolution at 6.0-mm full-width half maximum (axial field, 97.5 mm). Images were reconstructed using a measured attenuation correction and a Hanning-weighted reconstruction filter set to allow for 8-mm in-plane spatial resolution (full-width half maximum).

After entering the scanner, each participant was fitted with a thermoplastic custom-molded face mask, an overlying face mask attached to a vacuum, and nasal cannulae, which delivered the oxygen-15–labeled carbon dioxide. The concentration of oxygen-15–labeled carbon dioxide was 80 mCi/L (2960 MBq/L); the flow rate was 2 L/min. Each participant's head was aligned in the scanner relative to the canthomeatal line, and transmission measurements were made using an orbiting pin source.

Data Analysis

Statistical parametric mapping analysis of the PET data was conducted using a computer software package (SPM99; Wellcome Department of Cognitive Neurology, London, England).[29] Within SPM99, all images were corrected for interscan movement using sinc interpolation and then were transformed into a standard stereotactic space using bilinear interpolation. Images were then smoothed using a 2-dimensional Gaussian filter with a width of 10-mm full-width half maximum. At each voxel, the PET data were normalized using the global mean and fit to a linear statistical model using the method of least squares. Hypotheses were tested as contrasts in which linear compounds of the model parameters were evaluated using t statistics, which were then transformed to z scores.

We assessed our predictions with (1) separate voxelwise traumatic vs neutral contrasts in each diagnostic group and (2) a voxelwise test of the condition × diagnosis interaction. Separate parallel statistical parametric mapping analyses were conducted for each subgroup. We chose to conduct the traumatic vs neutral contrasts within a fixed-effects model because this procedure minimizes type II error. Although fixed-effects analyses limit our ability to generalize from the study sample to the larger population of patients with PTSD, the present findings in the amygdala and medial prefrontal cortex (see the "Results" section) are similar to those of previous studies[3,6,7,9] using fixed-effects models. Furthermore, random-effects analyses of the present data set revealed similar findings in the amygdala and medial prefrontal cortex.

To determine whether the rCBF changes in medial prefrontal regions were related to rCBF changes in the amygdala in PTSD, we (1) defined a functional region of interest (diameter, 4 mm) around the deactivation in medial frontal gyrus in the traumatic vs neutral contrast in the PTSD group (Montreal Neurological Institute [MNI] coordinates, +10, +52, +2), (2) extracted rCBF values per condition per participant from that region of interest, (3) calculated the traumatic vs neutral rCBF change score per participant, and (4) determined whether those change scores were associated with rCBF changes in other brain areas in the traumatic vs neutral comparison (using individual participant "con" images) via a voxelwise correlational analysis. Finally, within SPM99, voxelwise "covariates only" analyses were conducted to determine the relationship between PTSD symptom severity (CAPS) scores and rCBF in the amygdala and medial prefrontal regions for the traumatic condition. All of these correlational procedures were performed on the entire PTSD group and separately for the MCV and FNV subgroups with PTSD. For the sake of brevity, we focused specifically on the amygdala and medial prefrontal regions in the correlational analyses.

STATISTICAL ANALYSIS

The statistical parametric maps resulting from the analyses described herein were inspected for activations in our a priori regions of interest. Given our strong, directional hypotheses, we used a significance threshold of $P<.001$, uncorrected ($z\geq3.09$)

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Table 2. Psychophysiologic Responses to Traumatic and Neutral Imagery Scripts*

Variable	PTSD Group		Control Group	
	MCVs (n = 7)	FNVs (n = 10)	MCVs (n = 9)	FNVs (n = 10)
Traumatic condition				
Heart rate response, beats/min	4.5 (4.9)	4.7 (4.0)	1.4 (2.5)	2.8 (1.2)
Skin conductance response, μs	0.2 (0.3)	0.5 (0.5)	0.06 (0.5)	−0.2 (0.5)
Electromyographic response, μV	1.9 (1.6)	3.4 (2.5)	0.3 (0.6)	1.1 (0.6)
Neutral condition				
Heart rate response, beats/min	1.3 (2.0)	−0.4 (2.1)	−0.1 (4.4)	0.2 (1.5)
Skin conductance response, μs	−0.1 (0.1)	−0.1 (0.2)	−0.3 (0.5)	−0.1 (0.4)
Electromyographic response, μV	0.1 (0.4)	−0.3 (0.8)	0.02 (0.4)	0.1 (0.3)

Abbreviations: FNVs, female nurse veterans; MCVs, male combat veterans; PTSD, posttraumatic stress disorder.
*Data are given as mean (SD).

for activations in these a priori regions. Most of the key activations occurring in the amygdala and medial prefrontal cortex would remain significant even if we used an extremely conservative Bonferroni volume-corrected $P=.002$ ($z\geq2.88$, 24 voxels of $6\times6\times6$ mm) for the amygdala and $P=.0007$ ($z\geq3.19$, 75 voxels) for medial prefrontal cortex. Because the procedure of correcting P values based on region size is biased toward finding statistical significance in small structures, we used the previously stated constant significance threshold. For regions about which we had no a priori prediction, we used a more conservative constant significance threshold of $P<.00001$, uncorrected ($z\geq4.27$).

The statistical analyses of the psychophysiologic and subjective rating data were conducted not to present these results as findings in their own right (which has already been done in numerous publications with essentially the same results) but rather to demonstrate that the predicted emotional activations and associated group and condition differences, on which the validity of the neuroimaging findings depends, had been achieved. For this reason, corrections for multiple comparisons were not performed for the results of these analyses.

RESULTS

PSYCHOPHYSIOLOGIC RESPONSES

Heart rate, skin conductance, and EMG responses to traumatic and neutral imagery scripts were averaged across scans in each condition and were analyzed using separate 2 (diagnosis: PTSD vs control) × 2 (subgroup: MCVs vs FNVs) × 2 (condition: neutral vs traumatic) analyses of variance (**Table 2**).

Regarding heart rate responses, the only significant effect was a main effect of condition ($F_{1,32}=22.7$; $P<.001$). Heart rate responses were greater in the traumatic condition than in the neutral condition across both groups (Table 2).

Regarding skin conductance responses, there were significant main effects of diagnosis ($F_{1,32}=4.1$; $P=.05$) and condition ($F_{1,32}=19.2$; $P<.001$). The condition × diagnosis interaction was also significant ($F_{1,32}=7.7$; $P=.01$). Increases in skin conductance responses from the neutral to the traumatic condition were greater in the PTSD group vs the control group (Table 2). Also significant was the condition × diagnosis × subgroup interaction ($F_{1,32}=10.7$; $P=.003$). Examination of the means indicated that the difference in skin conductance response changes between PTSD and control participants was greater in FNVs than in MCVs.

Finally, regarding EMG responses, significant main effects of diagnosis ($F_{1,32}=14.0$; $P<.001$), subgroup ($F_{1,32}=4.3$; $P=.05$), and condition ($F_{1,32}=30.3$; $P<.001$) were observed. The condition × diagnosis interaction was also significant ($F_{1,32}=11.5$; $P=.002$). The EMG response increases from the neutral to the traumatic condition were greater in the PTSD group than in the control group (Table 2). A significant condition × subgroup interaction was also found ($F_{1,32}=4.3$; $P=.05$). Inspection of the means demonstrated that EMG response increases from the neutral to the traumatic condition were greater in FNVs than in MCVs.

SUBJECTIVE RATINGS

Ratings were averaged across scans in each condition and were submitted to separate 2 (diagnosis: PTSD vs control) × 2 (subgroup: MCVs vs FNVs) × 2 (condition: neutral vs traumatic) analyses of variance. Significant main effects of condition were observed for happiness, sadness, anger, fear, disgust, surprise, guilt, arousal, and vividness of imagery (for all: $F_{1,32}\geq20.4$; $P<.001$). Compared with the neutral condition, the traumatic condition was associated with lower ratings of happiness and higher ratings on all the other scales. Significant main effects of condition also were observed for ratings of awareness of present surroundings and the degree to which participants felt that the visualized event was happening again (for all: $F_{1,30}\geq7.7$; $P\leq.01$). All participants reported feeling less aware of their surroundings and more like the visualized event was happening again during the traumatic condition relative to the neutral condition.

Furthermore, significant main effects of diagnosis were found for fear, arousal, disgust, and guilt (for all: $F_{1,32}\geq4.4$; $P\leq.05$). Ratings on these scales were higher in the PTSD group compared with the control group. Significant condition × diagnosis interactions were observed for fear, arousal, guilt, and surprise (for all: $F_{1,32}\geq4.6$; $P\leq.05$). The PTSD group had greater increases on these scales than the control group. A significant condition × diagnosis × subgroup interaction was observed for ratings of surprise ($F_{1,32}=4.9$; $P=.04$). The increase in surprise ratings between conditions was stron-

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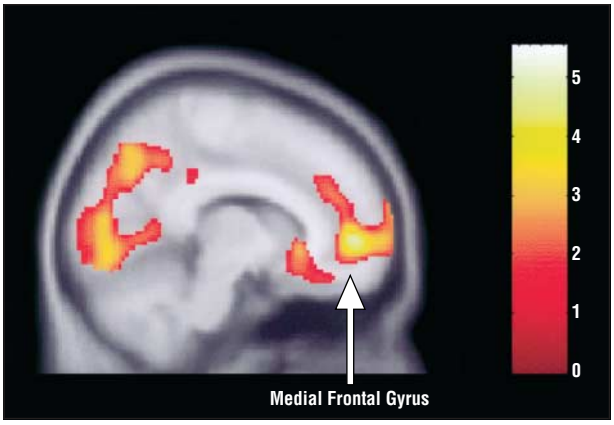

Figure 1. Regional cerebral blood flow decreases in medial frontal gyrus (z=4.70; Montreal Neurological Institute coordinates, +10, +52, +2) in the traumatic vs neutral comparison in all participants with posttraumatic stress disorder (n=17). Regional cerebral blood flow data are superimposed on a standard T1 template (SPM99; Wellcome Department of Cognitive Neurology, London, England) and displayed according to neurologic convention.

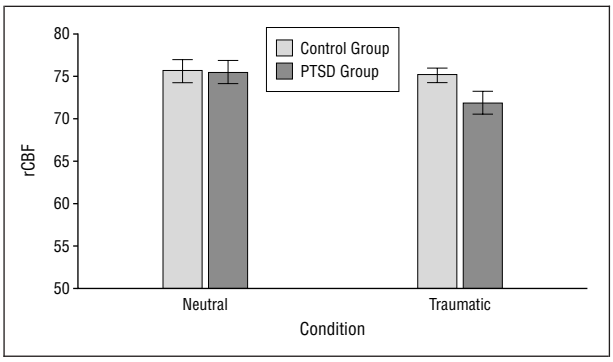

Figure 2. Normalized regional cerebral blood flow (rCBF) values in medial frontal gyrus (z=4.70; Montreal Neurological Institute coordinates, +10, +52, +2) in the traumatic and neutral conditions in the posttraumatic stress disorder (PTSD) (n=17) and control (n=19) groups. Error bars represent SEM.

ger for MCVs with PTSD than for FNVs with PTSD. Finally, a significant condition × diagnosis interaction was observed for the degree to which participants felt that the visualized event was happening again ($F_{1,30}$=5.6; P=.03); the PTSD group had greater increases on this scale compared with the control group.

PET RESULTS

Traumatic vs Neutral Comparison: PTSD and Control Groups

In the PTSD group (n=17), the traumatic vs neutral comparison yielded no statistically significant rCBF increases. Significant rCBF decreases occurred in medial frontal gyrus (z=4.70; MNI coordinates, +10, +52, +2) (**Figure 1** and **Figure 2**). Nonpredicted regions with significant rCBF decreases included superior frontal gyrus (z=4.35; MNI coordinates, −28, +62, +2), middle temporal gyrus (z=4.61; MNI coordinates, −52, −10, −16; and z=4.40; MNI coordinates, +58, −4, −26), inferior parietal cortex (z=5.00; MNI coordinates, −42, −50, +40), and occipital cortex (z=5.20; MNI coordinates, −34, −90, +2).

In the control group, the traumatic vs neutral comparison yielded no statistically significant rCBF increases or decreases. For completeness, we note that a nonsignificant rCBF increase occurred in medial frontal gyrus (z=2.60; MNI coordinates, +16, +58, +20).

The diagnosis × condition interaction revealed no regions with greater rCBF increases in the PTSD group or greater decreases in the control group. Regions with greater increases in the control group or greater decreases in the PTSD group included medial frontal gyrus (z=3.56; MNI coordinates, +6, +58, +2) and occipital cortex (z=4.79; MNI coordinates, −34, −88, +4).

Traumatic vs Neutral Comparison: Subgroup Analyses

Table 3 gives regions of rCBF increases in MCVs and FNVs with PTSD. Increases in rCBF in the amygdala were observed in MCVs with PTSD only. **Table 4** gives regions of rCBF increases in MCVs and FNVs without PTSD. Finally, diagnosis × condition interactions in the MCV and FNV subgroups demonstrated that amygdala activation in the traumatic vs neutral comparison was greater in MCVs with PTSD than in MCVs without PTSD (**Table 5**). No such differential activation in the amygdala was observed in the analogous interaction among FNVs.

Medial Frontal/Amygdala Correlations

In all of the PTSD participants, rCBF changes in medial frontal gyrus (MNI coordinates, +10, +52, +2) were negatively correlated with rCBF changes in the left amygdala (z=3.23; MNI coordinates, −26, +2, −14) and the right amygdala/periamygdaloid cortex (z=3.48; MNI coordinates, +18, +6, −22). In other words, smaller rCBF responses in medial frontal gyrus were associated with larger rCBF responses in the amygdala and periamygdaloid cortex. These correlations remained when participants with current major depression were removed from the analyses.

In addition, this relationship was observed in each PTSD subgroup separately. In MCVs with PTSD, rCBF changes in medial frontal gyrus were negatively correlated with rCBF changes in the left amygdala (z=3.51; MNI coordinates, −16, +2, −12) and right periamygdaloid cortex (z=2.88; MNI coordinates, +22, +6, −26). In FNVs with PTSD, rCBF changes in medial frontal gyrus were negatively correlated with rCBF changes in the left amygdala (z=3.54; MNI coordinates, −28, +4, −18) and the right amygdala/periamygdaloid cortex (z=3.38; MNI coordinates, +16, +4, −18).

To assess the specificity of this inverse functional relationship between medial frontal gyrus and amygdala, analogous correlational analyses were performed using rCBF change data in another prefrontal region that demonstrated rCBF decreases in the traumatic vs neutral comparison in the PTSD group; rCBF changes in superior frontal gyrus were not correlated with rCBF changes in the amygdala. In addition, no other regions were statistically significantly correlated with rCBF changes in medial frontal gyrus except in MCVs with PTSD. In that subgroup, we also observed positive correlations with the

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Table 3. Traumatic vs Neutral Comparison: PTSD Group*

Male Combat Veterans			Female Nurse Veterans		
Region	*z* Score	MNI Coordinates (x, y, z)	Region	*z* Score	MNI Coordinates (x, y, z)
Increase					
Amygdala	**3.47**	**–18, 0, –24**	None	NA	NA
	2.74†	**+14, –6, –24**			
Decrease					
Medial frontal gyrus	**3.52**	**+10, +52, +2**	**Medial frontal gyrus**	**3.25**	**+10, +50, +2**
Inferior temporal gyrus	5.07	+58, –6, –24	Occipital cortex	4.54	–32, –90, –2
Occipital cortex	4.29	–32, –86, +14			

Abbreviations: MNI, Montreal Neurological Institute; NA, not applicable; PTSD, posttraumatic stress disorder; rCBF, regional cerebral blood flow.
*A priori regions of interest are shown in bold.
†*z* Score is below the statistical significance threshold for a priori regions but is listed for completeness.

Table 4. Traumatic vs Neutral Comparison: Control Group*

Male Combat Veterans			Female Nurse Veterans		
Region	*z* Score	MNI Coordinates (x, y, z)	Region	*z* Score	MNI Coordinates (x, y, z)
rCBF Increase					
Medial frontal gyrus	**2.60†**	**–10, +50, +30**	**Medial frontal gyrus**	**4.31**	**–6, +56, +26**
rCBF Decrease					
None			Superior temporal gyrus	4.53	+56, –30, +16
			Occipital cortex	4.45	+28, –92, +24

Abbreviations: MNI, Montreal Neurological Institute; rCBF, regional cerebral blood flow.
*A priori regions of interest are shown in bold.
†*z* Score is below the statistical significance threshold for a priori regions but is listed for completeness.

Table 5. Diagnosis × Condition Interactions*

Male Combat Veterans			Female Nurse Veterans		
Region	*z* Score	MNI Coordinates (x, y, z)	Region	*z* Score	MNI Coordinates (x, y, z)
Greater Increases in the PTSD Group or Greater Decreases in Controls					
Amygdala	**3.45**	**–20, 0, –26**	None		
	2.46†	**+14, –4, –22**			
Greater Decreases in the PTSD Group or Greater Increases in Controls					
Medial frontal gyrus	**3.09**	**+6, +58, +2**	**Medial frontal gyrus**	**2.28†**	**+6, +72, +14**
				2.26†	**+2, +50, –14**
Anterior cingulate gyrus	**3.34**	**–10, 0, +42**	Lingual gyrus	4.29	+14, –76, –8
Occipital cortex	4.75	–34, –90, +4			

Abbreviations: MNI, Montreal Neurological Institute; PTSD, posttraumatic stress disorder.
*A priori regions of interest are shown in bold.
†*z* Score is below the statistical significance threshold for a priori regions but is listed for completeness.

left hippocampus (z=4.37; MNI coordinates, –28, –12, –12) and fusiform gyrus (z=4.28; MNI coordinates, +38, –46, –8) and negative correlations with the cerebellum (z=4.68; MNI coordinates, +20, –30, –16) and orbitofrontal cortex (z=4.42; MNI coordinates, +26, +42, –14).

Symptom Severity Correlations

In the PTSD group (n=17), CAPS scores were positively associated with rCBF in the traumatic condition in the right amygdala (z=3.83; MNI coordinates, +28, +4, –14) (although centered on the anterior/lateral margin of the amygdala, this activation extended posteriorly and medially to include the entire right amygdala and the anterior right hippocampus [z=4.01; MNI coordinates, +22, –10, –16]). In MCVs with PTSD, CAPS scores were positively associated with rCBF in the traumatic condition in the right amygdala (z=2.93; MNI coordinates, +24, +4, –16) extending posteriorly to the right hippocampus (z=3.07; MNI coordinates, 20, –12, –16) and were nega-

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tively associated with rCBF in medial frontal gyrus (z=3.29; MNI coordinates, −2, +52, +6) and anterior cingulate gyrus (z=3.46; MNI coordinates, −4, +20, +28). In FNVs with PTSD, CAPS scores were also positively associated with the right amygdala/hippocampus (z=2.63; MNI coordinates, +24, −6, −14) and negatively associated with medial frontal gyrus (z=4.40; MNI coordinates, +10, +70, −6). These relationships remained even after controlling for depression severity scores.

COMMENT

During the recollection and imagery of traumatic vs neutral personal events, MCVs and FNVs with PTSD exhibited rCBF decreases in medial frontal gyrus. Only MCVs showed rCBF increases in the left amygdala. However, for both subgroups with PTSD, rCBF changes in medial frontal gyrus were inversely correlated with rCBF changes in the left amygdala and the right amygdala/periamygdaloid cortex. Furthermore, in the traumatic condition, for both subgroups with PTSD, symptom severity was positively related to rCBF in the right amygdala and negatively related to rCBF in medial frontal gyrus.

Our finding of decreased activation of medial frontal gyrus during the symptomatic state in PTSD is consistent with the results of previous research[3,7-9] and with models of PTSD that hypothesize abnormal function of medial prefrontal structures. However, not all studies have reported such decreased activation of medial prefrontal regions in PTSD. For example, using single-photon emission computed tomography, Zubieta et al[30] reported relatively increased medial prefrontal cortex blood flow in a combat sounds condition relative to a white noise condition. The reason for such a disparate result is unclear but may be attributed to the different neuroimaging techniques (single-photon emission computed tomography) implemented in that study. Lanius et al[8,31] found that functional magnetic resonance imaging signal changes in medial frontal gyrus and anterior cingulate gyrus may vary depending on the dissociative state of participants; specifically, patients with PTSD who dissociated during scanning showed increased activation in these regions, whereas those who did not dissociate showed less activation in these regions. Thus, perhaps discrepant findings in the literature regarding medial prefrontal regions can be explained by variability in the dissociative state of participants across (and within) studies.

In participants with PTSD, blood flow changes in medial frontal gyrus were inversely correlated with blood flow changes in the amygdala. This finding resonates with those of a previous study[16] reporting decreased blood flow in anterior cingulate gyrus/medial frontal gyrus and increased blood flow in the amygdala in patients with PTSD. Although the direction of causality cannot be inferred from correlational analyses, the relationship between the amygdala and medial prefrontal cortex is likely to be reciprocal. Medial prefrontal regions send projections to the amygdala in primates,[32-35] and they may play an important role in the process of extinction of fear conditioning.[36-39] Conversely, in rodents, prefrontal neurons show decreases in spontaneous activity in the presence of a conditioned aversive tone as a function of amygdala activity, suggesting that the amygdala may modulate prefrontal neuronal activity.[40] Longitudinal and twin studies of PTSD may help elucidate the precise functional relationship between these structures and determine whether the more primary abnormality involves medial prefrontal regions or the amygdala.

In the PTSD group, PTSD symptom severity was positively correlated with rCBF in the right amygdala and negatively correlated with rCBF in medial frontal gyrus during traumatic imagery. Positive correlations between subjective ratings of distress and right amygdala activity have been reported previously in PTSD[2] and in social anxiety.[41] The present results supplement these previous findings.

In the present study, left amygdala activation in the traumatic vs neutral comparison was found among MCVs with PTSD but not among FNVs with PTSD. This difference between PTSD subgroups may be driven by differences in trauma type (eg, directly experiencing danger vs witnessing frightening situations) or sex or may have reflected a type II error in FNVs with PTSD. However, regarding rCBF findings in our a priori regions of interest, these 2 subgroups exhibited more commonalities than differences.

In contrast to the results of previous research, we found no evidence of rCBF increases in orbitofrontal cortex, temporopolar cortex, or insular cortex during traumatic imagery in the PTSD group. An explanation for this remains elusive, especially given that the methods implemented in this study were similar to those of previous studies.[6,7] In addition, previous studies have reported increased activation in medial frontal regions in control participants without PTSD.[3,7,9] In the present study, FNVs without PTSD exhibited significant activation in medial frontal gyrus (Table 4), but similar activations in MCVs without PTSD, and in the control group as a whole, fell below our significance threshold. The reason for subthreshold medial frontal activation in the control group is unclear.

This study cannot (and was never intended to) directly assess sex differences in neural responses to traumatic imagery because the men and women in this study experienced different types of trauma. Thus, any rCBF differences between MCVs and FNVs may be attributable to sex, trauma type, or a combination of the two. In addition, although the number of participants in our PTSD group was relatively large by functional neuroimaging standards (n=17), analyzing data in MCVs and FNVs separately resulted in a relative loss of power and an increased risk of type II error for the subgroup analyses. However, despite the small numbers per subgroup, the rCBF results in a priori regions of interest were strikingly similar in MCVs and FNVs with PTSD. The present study is limited by the presence of comorbidity in the PTSD group, and future neuroimaging studies of PTSD should use psychiatric control groups. It should be noted, however, that the key results from the present study remained even after controlling for depression. Finally, the present design did not include a low-level baseline condition as a secondary comparison condition, which could have helped determine the patterns of activation associated with the neutral and traumatic conditions sepa-

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rately and might have further clarified activation differences between groups.

In summary, veterans with PTSD exhibited rCBF decreases in medial frontal gyrus during traumatic vs neutral script-driven imagery. These rCBF changes were inversely correlated with rCBF changes in the left amygdala and the right amygdala/periamygdaloid cortex. Furthermore, in the traumatic condition, symptom severity was positively related to rCBF in the right amygdala and negatively related to rCBF in medial frontal gyrus. These results are consistent with functional neuroanatomic models of PTSD that posit a reciprocal relationship between medial prefrontal cortex and amygdala in PTSD.

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Correction

Error in Figure. In the original article titled "Efficacy of Olanzapine and Olanzapine-Fluoxetine Combination in the Treatment of Bipolar I Depression," published in the November issue of the ARCHIVES (2003;60:1079-1088), the key in **Figure 3** was incorrect. In the corrected key, the top line is for the olanzapine-fluoxetine combination group, and the middle line is for the olanzapine monotherapy group. Figure 3 is reprinted correctly here.

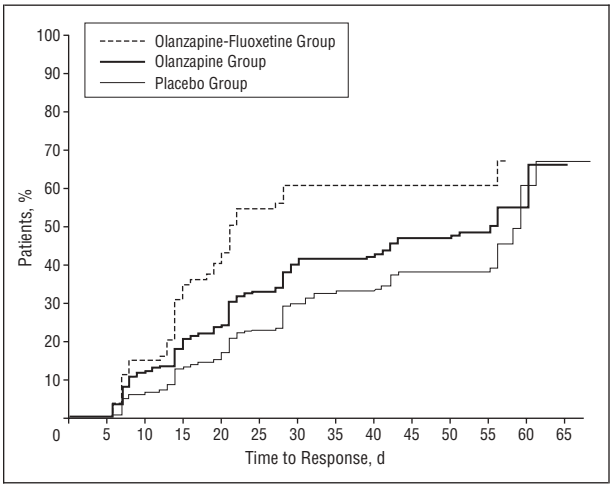

Figure 3. Kaplan-Meier estimates of time to response. Response is defined as a decrease in Montgomery-Åsberg Depression Rating Scale total score of 50% or more after at least 4 weeks of treatment. Median time to response for the olanzapine group (55 days) was significantly earlier compared with the placebo group (59 days). Median time to response for the olanzapine-fluoxetine combination group (21 days) was significantly earlier than for the olanzapine and placebo groups.

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