A Functional Magnetic Resonance Imaging Study of Amygdala and Medial Prefrontal Cortex Responses to Overtly Presented Fearful Faces in Posttraumatic Stress Disorder

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Background: Previous functional neuroimaging studies have demonstrated exaggerated amygdala responses and diminished medial prefrontal cortex responses during the symptomatic state in posttraumatic stress disorder (PTSD).

Objectives: To determine whether these abnormalities also occur in response to overtly presented affective stimuli unrelated to trauma; to examine the functional relationship between the amygdala and medial prefrontal cortex and their relationship to PTSD symptom severity in response to these stimuli; and to determine whether responsivity of these regions habituates normally across repeated stimulus presentations in PTSD.

Design: Case-control study.

Setting: Academic medical center.

Participants: Volunteer sample of 13 men with PTSD (PTSD group) and 13 trauma-exposed men without PTSD (control group).

Main Outcome Measures: We used functional magnetic resonance imaging (fMRI) to study blood oxygenation level-dependent signal during the presentation of emotional facial expressions.

Results: The PTSD group exhibited exaggerated amygdala responses and diminished medial prefrontal cortex responses to fearful vs happy facial expressions. In addition, in the PTSD group, blood oxygenation level–dependent signal changes in the amygdala were negatively correlated with signal changes in the medial prefrontal cortex, and symptom severity was negatively related to blood oxygenation level–dependent signal changes in the medial prefrontal cortex. Finally, relative to the control group, the PTSD group tended to exhibit diminished habituation of fearful vs happy responses in the right amygdala across functional runs, although this effect did not exceed our a priori statistical threshold.

Conclusions: These results provide evidence for exaggerated amygdala responsivity, diminished medial prefrontal cortex responsivity, and a reciprocal relationship between these 2 regions during passive viewing of overtly presented affective stimuli unrelated to trauma in PTSD.

Arch Gen Psychiatry. 2005;62:273-281

Several recent functional neuroimaging studies have provided evidence consistent with amygdala hyperresponsivity during exposure to traumatic reminders in posttraumatic stress disorder (PTSD). In addition, PTSD symptom severity is positively correlated with blood flow in the amygdala during such exposure.

To characterize the scope of amygdala hyperresponsivity in PTSD, it is important to determine whether amygdala responses to stimuli unrelated to trauma are also exaggerated in this disorder. Previous research has established that the normal human amygdala is responsive to facial expressions of fear and that individuals with PTSD exhibit exaggerated amygdala responses to these facial expressions. Using functional magnetic resonance imaging (fMRI), Rauch and colleagues measured blood oxygenation level–dependent (BOLD) signal responses to backwardly masked fearful and happy facial expressions in combat veterans with and without PTSD. In that study, the fearful and happy facial expressions were presented very briefly (33 milliseconds) and were followed immediately by neutral facial expressions. Relative to the control group, the PTSD group exhibited greater BOLD signal increases in the right amygdala in response to masked fearful vs
happy facial expressions. In addition, PTSD symptom severity was positively correlated with BOLD signal changes in the amygdala. Whether amygdala hyperresponsivity in PTSD can be demonstrated when participants are explicitly aware of the presence of emotional facial expressions is not known. In addition, whether this amygdala hyperresponsivity declines normally across repeated-stimulus presentations has never been assessed in PTSD.

Medial prefrontal structures also have been implicated in the pathophysiology of PTSD. Several functional neuroimaging studies have demonstrated relatively diminished activation in the subcallosal, anterior cingulate, and medial frontal gyri, and medial prefrontal regions in this disorder. These findings highlight the potential importance of interactions between the amygdala and medial prefrontal structures in this disorder. However, whether such interactions can be observed during the presentation of more general, affective stimuli unrelated to trauma is unknown.

The goals of the present study were to determine whether (1) individuals with PTSD exhibit exaggerated amygdala responses and diminished medial prefrontal responses to nonmasked (ie, overtly presented) fearful vs happy facial expressions; (2) there is a reciprocal relationship between BOLD signal changes in the amygdala and medial prefrontal regions in this contrast; (3) symptom severity is related to signal changes in the amygdala and medial prefrontal regions; and (4) the amygdala and medial prefrontal responses to fearful vs happy faces habituate normally in patients with PTSD.

We studied fMRI BOLD signal in trauma-exposed men and women with and without PTSD while they viewed blocks of emotional facial expressions. In the fearful vs happy comparison, we predicted that participants with PTSD would exhibit greater activation in the amygdala and diminished activation in medial prefrontal regions (including medial frontal, anterior cingulate, and subcallosal gyri), compared with participants without PTSD. In addition, we predicted that fMRI BOLD signal changes in the amygdala would be negatively correlated with signal changes in medial prefrontal regions in the fearful vs happy contrast. We also predicted that symptom severity would be positively correlated with responses in the amygdala and negatively correlated with those in medial prefrontal regions. Finally, we predicted that, relative to the control group, the PTSD group would show diminished habituation of amygdala responses over repeated presentations of fearful vs happy expressions.

STIMULUS PRESENTATION

Stimuli were gray scale images of 6 fearful, 6 happy, and 6 neutral facial expressions selected from a well-validated set. Facial expressions were posed by 3 men and 3 women. Each face was presented for 200 milliseconds, with a 300-millisecond interstimulus interval, in a pseudorandom order such that facial expressions of a single identity were never presented in succession. Across each run, each fearful and happy face was presented an equal number of times. Subjects viewed 4 runs of these facial expressions, with each run consisting of ten 28-second alternating blocks. Each run began and ended with a 28-second block of low-level fixation (eg, +NHFHFFHFN+).

METHODS

PARTICIPANTS

Participants included 26 trauma-exposed men without a history of head injury, neurological disorders, or other major medical conditions. Thirteen participants met DSM-IV diagnostic criteria for current PTSD (PTSD group), and 13 never had PTSD (control group) according to a structured clinical interview (the Clinician-Administered PTSD Scale [CAPS]). Twenty-four participants were right-handed, and 2 (1 in the PTSD and 1 in the control group) were left-handed. Participants had served in combat in Vietnam (10 in the PTSD and 8 in the control group) or were firefighters (3 in the PTSD and 5 in the control group). Examples of Vietnam experiences included being wounded or in mortal danger in combat, witnessing the injury or death of friends, and handling body parts. Examples of firefighter experiences included being trapped and injured in a collapsed burning building, witnessing the death and/or disfigurement of others including children and coworkers, and witnessing an accident scene of a family member. All cases of PTSD were chronic. Duration of illness ranged from 10 to 35 years. No participant was taking psychotropic or cardiovascular medication at the time of the study. Seven participants (5 in the PTSD and 2 in the control group) had been taking such medications before the study but had discontinued them for 2 to 6 weeks, depending on the type of medication.

The groups did not differ with regard to age (mean ± SD, 52.8 ± 7.3 [PTSD group] vs 49.7 ± 8.9 years [control group]; F1,22 = 6.5; P = .02), but a greater proportion of participants in the PTSD group were unemployed (38% [PTSD group] vs 0% [control group]; χ² = 6.2; P = .02). Relative to the control group, the PTSD group had significantly higher mean ± SD scores (indicating greater symptom severity) on the following clinical measures: CAPS (62.0 ± 23.2 [PTSD group] vs 3.3 ± 6.0 [control group]; F1,22 = 61.9; P < .001); the Beck Depression Inventory II (BDI) (20.7 ± 17.0 [PTSD group] vs 4.2 ± 4.3 [control group]; F1,22 = 11.5; P = .003); and Beck Anxiety Inventory (18.8 ± 14.5 [PTSD group] vs 5.0 ± 6.2 [control group]; F1,22 = 10.1; P = .004). All symptoms of PTSD were represented among the various cases of PTSD, although not every symptom in each case. Flashbacks were less frequent, and amnesia was rare. The PTSD group’s mean CAPS score represents moderately severe PTSD symptoms, and the control group’s mean CAPS score represents minimal PTSD symptoms.

The presence of other Axis I mental disorders was assessed with the Structured Clinical Interview for DSM-IV. Participants in the PTSD group met criteria for the following current comorbid diagnoses: major depression (n = 4), dysthymia (n = 2), bipolar disorder II (n = 1), panic disorder (n = 3), social phobia (n = 2), and specific phobia (n = 1). None of the participants in the control group met criteria for a current Axis I diagnosis.

This study was approved by the institutional review boards of the Massachusetts General Hospital and the Veterans Affairs Medical Center. Written informed consent was obtained from each participant.
order of conditions and runs was counterbalanced across subjects and groups. The paradigm was modeled after those used in previous studies. Although it does not permit the acquisition of online behavioral data, we chose to use a passive viewing paradigm because it has been found to be associated with relatively robust amygdala responses. The facial stimuli were displayed using standardized software (MacStim 2.5.9; WhiteAnt Occasional Publishing, West Melbourne, Australia) and an XG-2000V color liquid crystal display projector (Sharp, Osaka, Japan). Immediately after each scanning session, outside the scanner, participants rated the facial expressions on scales of valence (negative to positive, −3 to +3) and arousal (low to high, 0 to 6).

IMRI PROCEDURES

Scans were obtained from a Symphony/Sonata 1.5-T whole-body high-speed imaging device equipped for echo planar imaging (Siemens Medical Systems, Iselin, NJ) with a 3-axis gradient head coil. Head movement was restricted using expandable foam cushions. After an automated scout image was acquired and shimming procedures were performed to optimize field homogeneity, high-resolution 3-dimensional magnetization-prepared rapid acquisition gradient echo sequences (repetition time/echo time/flip angle, 7.25 milliseconds/3 milliseconds/7°) with an in-plane resolution of 1.3 mm and 1-mm-slice thickness were collected for spatial normalization and for positioning the slice prescription of the subsequent sequences. Then T1- (repetition time/echo time/flip angle, 8 seconds/39 milliseconds/90°) and T2-weighted sequences (repetition time/echo time/flip angle, 10 seconds/48 milliseconds/120°) were gathered. Functional MRI images were acquired using a gradient echo T2-weighted sequence (repetition time/echo time/flip angle, 2.8 seconds/40 milliseconds/90°). Before each scan, 4 images were acquired and discarded to allow longitudinal magnetization to reach equilibrium. The T1- and T2-weighted and functional images were collected in the same plane (24 coronal slices angled perpendicular to the anterior commissure–posterior commissure line) with the same slice thickness (7 mm, skip 1 mm; voxel size, 3.125×3.125×8 mm), excitation order (interleaved), and phase encoding (foot-to-head).

DATA ANALYSIS

We performed preprocessing and statistical analysis of the IMRI data using a statistical parametric mapping method (SPM99 software package; Wellcome Department of Cognitive Neurology, London, England). Within SPM99, images were motion corrected (sinc interpolation) and transformed into a standard (Montreal Neurological Institute [MNI] coordinate system; McGill University, Montreal, Quebec) stereotactic space (bilinear interpolation). Images were then smoothed with a 4-mm gaussian kernel. At each voxel, the data were fit to a linear statistical response function. Hypotheses were tested as contrasts in which linear components of the model parameters were evaluated using t statistics, which were then transformed to z scores.

We chose to focus on the fearful vs happy contrast to facilitate comparison of our present results with those of Rauch et al. The fearful vs neutral contrasts yielded results similar to those of the fearful vs happy contrasts but will not be discussed further herein for the sake of brevity.

We first computed the voxelwise fearful vs happy contrast within each group, and then assessed our prediction of exaggerated amygdala responses and diminished medial prefrontal responses to fearful vs happy facial expressions in PTSD with a voxelwise test of the condition×diagnosis interaction. These analyses were conducted within the first functional run to avoid any habituation or sensitization effects. We chose to conduct the fearful vs happy 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 presented in the “Results” section are similar to those of a previous fMRI study. Furthermore, random-effects analyses (not shown) revealed similar (although less robust) findings in the amygdala and medial prefrontal regions.

To determine whether IMRI BOLD signal changes in the amygdala were significantly related to signal changes in the medial prefrontal cortex in PTSD, we (1) defined a functional region of interest (diameter, 6 mm) around the amygdala activations in run 1 in the PTSD group (MNI coordinates, +22, +4, −14; +18, −6, −20; and −20, −8, −18), (2) extracted signal values per condition per subject from that region of interest, (3) calculated the fearful vs happy signal change value per subject, and (4) determined whether those change values were associated with signal changes in other brain areas in the fearful vs happy comparison (using individual subject contrast images via a voxelwise correlation analysis). To determine the relationship between PTSD symptom severity (CAPS scores) and fearful vs happy signal change in the amygdala and medial prefrontal regions in the PTSD group, we conducted voxelwise correlational analyses within SPM99. We chose to focus specifically on the amygdala and medial prefrontal regions in these correlational analyses. Finally, to examine habituation differences between groups, we compared fearful vs happy responses in early (run 1) vs late (run 4) functional runs.

STATISTICS

The statistical parametric maps resulting from these analyses 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 score, ≥3.09) for activations in these regions. Because the procedure of correcting P values based on the region size is biased toward finding significance in small structures, we chose to use a 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 score, ≥4.27). Ratings data are expressed as means±SD.

RESULTS

FACIAL EXPRESSION RATINGS

Ratings of valence and arousal were submitted to separate 2×3 (diagnosis [PTSD and control] × expression [fearful, happy, and neutral]) analyses of variance. With regard to valence, only the main effects of group (F1,24 = 9.3, P = .006) and expression (F2,48 = 64.5; P < .001) were significant. The PTSD group gave more negative ratings across all facial expressions than the control group. Post hoc testing showed significant valence ratings differences among all 3 types of facial expressions: fearful (−1.8±1.4) vs happy (1.7±1.1) (t24 = 9.2, P < .001); fearful vs neutral (0.0±0.6) (t24 = 6.0, P < .001); and neutral vs happy (t24 = 7.7, P < .001). Analysis of the arousal ratings revealed only a significant main effect of expression (F2,48 = 17.9; P < .001). Post
hoc testing revealed lower arousal ratings for the neutral faces (1.6±1.3) than for the fearful (3.5±2.0) (t25=5.8; \(P < .001\)) and happy faces (3.1±1.6) (t24=4.8; \(P < .001\)); arousal ratings of the latter 2 expression types did not differ significantly from each other (t24=1.1; \(P = .27\)).

**fMRI RESULTS**

**Fearful vs Happy Comparison: First Run**

In the PTSD group, BOLD signal increases occurred in bilateral amygdala and rostral anterior cingulate gyrus (Table 1). BOLD signal decreases occurred in the ventral medial frontal and rostral anterior cingulate gyrus.

In the control group, BOLD signal increases occurred in bilateral amygdala, rostral and dorsal anterior cingulate gyrus, and dorsal medial frontal gyrus, as well as other regions about which we had no specific a priori hypotheses (Table 1).

The voxelwise condition \(\times\) diagnosis interaction revealed greater BOLD signal increases in the PTSD group (or greater decreases in the control group) in the right amygdala (Figure 1 and Table 2) among other regions. Greater BOLD signal increases in the control group (or greater decreases in the PTSD group) occurred in the

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<th>Table 1. Fearful vs Happy Comparison in PTSD and Control Groups</th>
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Abbreviations: BOLD, blood oxygenation level-dependent; MNI, Montreal Neurological Institute; PTSD, posttraumatic stress disorder.
rostral anterior cingulate (Figure 2 and Table 2), ventral medial frontal, and dorsal medial frontal gyri. This pattern of results remained when BDI scores were controlled via analysis of covariance and when 4 subjects with PTSD and comorbid major depressive disorder were removed from the analyses.

**Amygdala/Medial Prefrontal Correlations**

Within all PTSD participants in the first run, BOLD signal changes in the right amygdala (MNI coordinates, +22, +44, −14) were negatively correlated with BOLD signal changes in the dorsal medial frontal gyrus (z = 3.09; MNI coordinates, +14, +50, +16) (Figure 3). BOLD signal changes in the more posterior right amygdala activation (MNI coordinates, +18, −6, −20) were negatively correlated with BOLD signal changes in the dorsal medial frontal gyrus (z = 3.50; MNI coordinates, −10, +50, +14). Signal changes in the right and left amygdala were also significantly negatively correlated with ventral medial prefrontal regions; however, the removal of 1 extreme score in each of these latter correlations resulted in subthreshold (<3.09) z scores. This pattern of results persisted when subjects with PTSD and comorbid depression were removed from the analyses. No such significant correlations were observed in the control group.

**Symptom Severity Correlations**

In the PTSD group, PTSD symptom severity (as measured by the CAPS) was negatively correlated with BOLD signal changes in the rostral anterior cingulate gyrus (z = 3.62; MNI coordinates, −4, +44, +8) (Figure 4) but was not significantly correlated with signal changes in the amygdala. Depression symptom severity in the PTSD group (as measured by the BDI) was positively correlated with BOLD signal changes in the ventral medial frontal/orbitofrontal gyrus (z = 3.60; MNI coordinates, +14, +44, −16) and negatively correlated with signal changes in the right amygdala (z = 3.25; MNI coordinates, +28, −4, −16). Thus, the CAPS and BDI appeared to be related very differently to BOLD signal changes in our regions of interest.

**Habituation Analyses**

In the control group, fearful vs happy responses decreased from run 1 to run 4 in the right amygdala (z = 4.33; MNI coordinates, +18, −6, −18), rostral anterior cingulate gyrus (z = 3.18; MNI coordinates, 0, +36, −8), and medial frontal gyrus (z = 3.22; MNI coordinates, −12, +56, +4). In the PTSD group, fearful vs happy responses decreased from runs 1 to 4 in the amygdala/periamygdaloid cortex (z = 3.00; MNI coordinates, +22, +6, −14) and ventral medial frontal gyrus (z = 3.56; MNI coordinates, −6, +48, −16; z = 3.25; MNI coordinates, 0, +46, −10).

The decline in fearful vs happy responses in the right amygdala tended to be greater in the control vs PTSD group, but did not exceed a priori statistical thresholds (z = 2.08; MNI coordinates, +18, −4, −18; z = 2.04; MNI coordinates, +26, 0, −16). The decline in fearful vs happy responses in rostral anterior cingulate gyrus was greater in the control vs PTSD group (z = 3.18; MNI coordinates, −2, +32, −10).

**COMMENT**

In the present study, the PTSD group exhibited exaggerated amygdala responses and diminished medial prefrontal cortex responses to overtly presented fearful vs happy facial expressions. In addition, only in the PTSD group were BOLD signal changes in the amygdala negatively correlated with signal changes in the medial prefrontal cortex. Furthermore, in the PTSD group, symptom severity was negatively related to BOLD signal changes in the medial prefrontal cortex. Finally, relative to the control group, the PTSD group tended to exhibit diminished habituation of fearful vs happy responses in the right amygdala over functional runs, although this effect did not exceed our a priori statistical threshold.

Our finding of relatively greater amygdala responses in PTSD is consistent with previous research using traumatic reminders1-5 and masked facial expressions.12 Taken together, the present results and those of Rauch et al12 show that amygdala hyperresponsivity in PTSD can be demonstrated using facial expression stimuli that are above or below the threshold of conscious recognition.6

In general, studies using overt facial expressions8,10,24,25,32 have reported BOLD signal changes in a greater number of brain regions, compared with studies using masked facial expressions.11,33 Thus, using stimuli that are above the threshold of conscious recognition might afford the ability to examine BOLD signal changes in brain regions other than the amygdala. In the present study, we report relatively diminished BOLD signal changes in medial prefrontal regions in PTSD and a negative correlation between symptom severity and BOLD signal changes in the medial prefrontal cortex. These findings are consistent with those of previous functional
neuroimaging studies of PTSD using other types of stimuli and, along with recent reports of structural abnormalities in these regions, further implicate medial prefrontal cortex in the pathophysiology of this disorder.

In the PTSD group, we found that BOLD signal changes in the amygdala were negatively correlated with signal changes in the medial frontal gyrus. This finding, which is similar to one recently reported in the context of a symptom provocation paradigm, supports the presence of a reciprocal relationship between these regions, but cannot offer information regarding the direction of causality. Medial prefrontal regions send projections to the amygdala in primates, modulate amygdala output, and play an important role in the process of extinction of fear conditioning. Conversely, the amygdala may modulate prefrontal neuronal activity. Although the current finding of a reciprocal relationship between the amygdala and medial prefrontal cortex is consistent with that of a previous report, it also differs from the results of a recent positron emission tomographic symptom provocation study in which multivariate structural equation modeling suggested the possibility of a positive relationship between the amygdala and cingulate/subcallosal cortex blood flow in PTSD. Additional research is needed to further clarify this issue.

The present and previous studies suggest functional abnormalities in medial prefrontal regions in PTSD. However, across studies, these functional abnormalities have differed in location within the medial prefrontal cortex, including the medial frontal gyrus and anterior cingulate gyrus. However, it is unlikely that all medial prefrontal regions perform a unitary function. Insights regarding the functional differences between various medial prefrontal regions in humans with PTSD will likely arise from the findings of future basic science studies of conditioning and extinction.

Analyses of BOLD signal changes from runs 1 to 4 suggested that fearful vs happy responses in the right amygdala decreased in the control group, consistent with the findings of previous studies of habituation in healthy individuals. There was a nonsignificant trend for the PTSD group to show diminished habituation in the right amygdala, compared with the control group. However, we must emphasize that this pattern occurred in only 2 small loci in the right amygdala and that future studies involving larger numbers of subjects are needed to confirm this finding. If replicated, diminished habituation of amygdala responses may be seen as broadly consistent with previous findings of slower habituation of psychophysioologic responses to loud tones in PTSD. Habituation of medial prefrontal cortex responses occurred in both groups, although it was significantly greater in the control vs PTSD group in the rostral anterior cingulate gyrus. We attribute this group difference in re-
sponse changes over time to a floor effect: the PTSD group started out (in run 1) with lower rostral anterior cingulate responses compared with the control group, and further decreases were necessarily smaller in magnitude.

Although amygdala responses to fearful vs happy faces were bilateral within each group, the condition × diagnosis interaction occurred in the right amygdala. Indeed, most but not all findings of amygdala hyperresponsivity in PTSD have been right-sided. In addition, correlations between PTSD symptom severity and amygdala activity also have been right-sided. Functional abnormalities in the right amygdala may be associated with a failure of habituation or of sensitization to emotional stimuli.

Exaggerated amygdala responses to fearful facial expressions have been observed in PTSD, but not in specific (small-animal) phobia or in social phobia. Further research on panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder would be needed to determine the specificity of these findings to PTSD vs other anxiety disorders. However, individuals with social phobia appear to exhibit exaggerated amygdala responses to neutral faces alone, as well as to contemptuous and angry faces vs happy faces. Thus, whether exaggerated amygdala activation is demonstrated in a particular disorder may depend on the facial expressions used and their relevance to the disorder in question. Fearful faces may be particularly relevant to patients with PTSD, whereas contemptuous, angry, or even ambiguous neutral faces might be particularly relevant to patients with social phobia.

Definitive conclusions from the present study are limited by the presence of comorbidity in the PTSD group, although the key results remained significant even after controlling for BDI scores and excluding participants with current major depression. In addition, responsivity of our regions of interest was related to BDI and CAPS scores in very different ways, suggesting that depression symptoms cannot explain the main findings. The relatively small sample size precluded comparisons between firefighters and combat veterans with PTSD. In addition, the participants in this study were all men; whether the findings can be generalized to women with PTSD remains to be determined. Finally, as with any passive viewing paradigm, behavioral data could not be collected or compared between groups.

The present results are consistent with exaggerated amygdala responsivity, diminished medial prefrontal cortex responsivity, and a reciprocal relationship between these 2 regions in PTSD. Additional studies are needed to confirm the finding of diminished habituation of amygdala responses over repeated fearful vs happy facial expressions in PTSD, and to determine whether such habituation abnormalities occur in response to other types of stimuli.

Submitted for Publication: December 15, 2003; final revision received July 27, 2004; accepted August 20, 2004.

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Funding/Support: This study was supported by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression, Great Neck, NY (Dr Shin); the Robert Wood Johnson Foundation, Princeton, NJ (Dr Wright); grants MH-64806 (Dr Wright) and MH-60219 (Dr Rauch) from the National Institute of Mental Health, Bethesda, Md; and a Medical Research Service Merit Review grant from the Department of Veterans Affairs, Washington, DC (Dr Orr).

Acknowledgment: We thank Mohammed R. Milad for his comments on this manuscript; the individuals who served as research participants; and Mary Foley, Jennifer Holmes, and Lawrence White for their technical assistance.

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