Exaggerated Amygdala Response to Masked Facial Stimuli in Posttraumatic Stress Disorder: A Functional MRI Study

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Background: *Converging lines of evidence have implicated the amygdala in the pathophysiology of posttraumatic stress disorder (PTSD). We previously developed a method for measuring automatic amygdala responses to general threat-related stimuli; in conjunction with functional magnetic resonance imaging, we used a passive viewing task involving masked presentations of human facial stimuli.*

Methods: *We applied this method to study veterans with PTSD and a comparison cohort of combat-exposed veterans without PTSD.*

Results: *The findings indicate that patients with PTSD exhibit exaggerated amygdala responses to masked-fearful versus masked-happy faces.*

Conclusions: *Although some previous neuroimaging studies of PTSD have demonstrated amygdala recruitment in response to reminders of traumatic events, this represents the first evidence for exaggerated amygdala responses to general negative stimuli in PTSD. Furthermore, by using a probe that emphasizes automaticity, we provide initial evidence of amygdala hyperresponsivity dissociated from the "top-down" influences of medial frontal cortex.* Biol Psychiatry 2000;47:769–776 © 2000 Society of Biological Psychiatry

Introduction

Posttraumatic stress disorder (PTSD) is characterized by a constellation of signs and symptoms that arise and persist in the aftermath of an emotionally traumatic event (American Psychiatric Association 1994). Specifically, patients with PTSD exhibit 1) re-experiencing phenomena that may occur spontaneously or in response to reminders of the traumatic event (e.g., flashbacks), 2) avoidance of reminders of the event, and 3) generalized hyperarousal (e.g., exaggerated startle response). Although the pathophysiology of PTSD remains incompletely understood, several lines of evidence converge to implicate the amygdala and related brain structures in this disorder.

Laboratory fear conditioning represents an experimental process that bears striking resemblance to PTSD in terms of both etiogenesis and phenomenology (Shalev et al 1992). In animals or humans, if a neutral stimulus is presented so as to predict a subsequent aversive stimulus, subjects come to exhibit signs of arousal in response to the previously neutral (i.e., predictive) stimulus. Moreover, subjects will exhibit a tendency to avoid the predictive stimulus or contexts in which the predictive stimulus has been delivered. In the psychophysiology laboratory, individuals with PTSD have been shown to acquire de novo conditioned responses more readily (Orr et al, in press) and extinguish them more slowly than do comparison subjects (Orr et al, in press; Peri et al, in press). Extensive literature involving fear-conditioning studies in animals indicates that the amygdala plays a central role in both the acquisition and elaboration of this type of learning (Cahill et al 1999; Davis 1997; Kapp et al 1992; LeDoux 1996). Further, lesion studies in animals suggest that medial frontal cortex may play a critical role in mediating the extinction of this learned association (Davis 1997; Morgan and LeDoux 1995). Animal research regarding the phenomenon of sensitization also suggests that the amygdala is involved in heightened unconditioned emotional responses as seen in PTSD (see Pitman et al 2000).

With the advent of contemporary functional neuroimaging methods, investigators have begun to explore models of PTSD in human subjects. Such studies have shown recruitment of the amygdala and medial frontal territories (e.g., anterior cingulate cortex ~ BA 24, 32) in response to reminders of pertinent traumatic events (Rauch et al 1996; Shin et al 1997). Moreover, in comparison with control subjects, patients with PTSD have shown exaggerated responses within the amygdala (Liberzon et al 1999; Shin

et al 1997), but attenuated responses within the medial frontal cortex (Bremner et al 1999; Shin et al 1999). Although replication across studies to date has been imperfect, taken together these data support a model of PTSD whereby the amygdala is hyperresponsive to threat-related stimuli, and interconnected areas may provide insufficient "top-down" inhibition of this amygdala response.

Previous functional neuroimaging studies of PTSD have been limited in several respects. In particular, whereas lesion experiments have elucidated the mediating anatomy of fear conditioning, human imaging studies of PTSD have not provided a means to dissociate amygdala responsivity from the top-down influences of medial frontal cortex. In addition, paradigms that have used standardized trauma-specific audiovisual stimuli do not allow for direct comparisons among cohorts with PTSD from various types of trauma nor between patients with PTSD and other neuropsychiatric disorders. Therefore, we sought to develop a probe of human amygdala responsivity that would 1) entail general threat-related stimuli, thereby ultimately enabling experiments across various study populations; and 2) emphasize automatic "bottom-up" aspects of processing, thereby minimizing the influence of modulation by medial frontal cortex.

Initial experiments in normal subjects demonstrated that the amygdala can be reliably recruited via passive viewing of emotionally expressive facial stimuli. Specifically, activity within the amygdala is increased to pictures of fearful versus neutral or happy faces (Breiter et al 1996; Morris et al 1996). Subsequently, several laboratories have shown that, using the technique of backward masking (Esteves and Öhman 1993), emotionally expressive facial stimuli presented below the level of awareness likewise activate the amygdala (Morris et al 1998; Whalen et al 1998). By using this masked-faces paradigm, the automaticity of amygdala response is highlighted, and activation of brain regions outside the amygdala is minimized. In particular, masked-faces paradigms do not yield significant medial frontal activation (Morris et al 1998; Whalen et al 1998), whereas paradigms employing overt presentation of emotional faces do (e.g., Morris et al 1996).

In the current study, we employed a previously validated functional magnetic resonance imaging (fMRI) masked-faces paradigm (Whalen et al 1998) to assess automatic amygdala responsivity to general threat-related stimuli in PTSD. Consistent with previous findings in healthy subjects (Whalen et al 1998), we hypothesized that traumatized subjects with or without PTSD would exhibit amygdala activation, but not medial frontal activation, in response to masked-fearful versus masked-happy faces. Furthermore, we predicted that patients with PTSD would exhibit exaggerated amygdala responses in comparison with a cohort of trauma-exposed subjects without PTSD. Finally, we hypothesized that fusiform cortex (an area involved in processing of facial stimuli; Kanwisher et al 1997) would be comparably activated by both groups, underscoring the regional specificity of between-group differences within the amygdala.

Methods and Materials

Subjects

Sixteen right-handed (Oldfield 1971) men, each with a history of exposure to combat-related emotional trauma as members of the U.S. armed forces in Vietnam, participated in this study as paid subjects. Informed consent was obtained before participation according to guidelines established by the Institutional Review Boards of the Massachusetts General Hospital and the Manchester (New Hampshire) VA Medical Center. Based on the DSM-IV (American Psychiatric Association 1994), eight subjects met criteria for current PTSD (PTSD group), and the other eight were free of current PTSD (non-PTSD group). Psychiatric diagnoses were established via the structured clinical interview for DSM-IV (First et al 1995). Other standardized clinical instruments, including the Clinician-Administered PTSD Scale (CAPS; Blake et al 1995), the Combat Exposure Scale (CES; Keane et al 1989), and the Beck Depression Inventory (BDI; Beck et al 1961), were administered to quantitatively characterize PTSD symptoms, severity of trauma exposure, and depression, respectively. Additional entry criteria required that all subjects be free of current substance-use disorders or psychosis, as well as any neurologic or medical condition that could confound or interfere with the current study. All subjects were free of psychotropic and cardiovascular medications for at least (the greater of) 1 month or five half lives before participation.

The two groups did not significantly differ with respect to age (see Table 1); however, the PTSD group had significantly higher scores on the CES than did the non-PTSD group. Therefore, fMRI analyses were repeated after excluding one subject from each group in a manner that yielded group-matched CES scores.

All subjects were naive to the facial stimuli used and to our hypotheses pertaining to the emotional expressions of faces. For this initial experiment, a single gender cohort and single type of traumatic experience were studied to minimize heterogeneity in an attempt to improve statistical power.

Masked-Faces Paradigm

This experimental paradigm has been described in detail previously (Whalen et al 1998). Photographic stimuli consisted of fearful, happy, and neutral facial expressions from eight individuals (Ekman and Friesen 1976). Subjects were presented with alternating 28 sec epochs of masked-fearful face targets (F), masked-happy face targets (H), or a single cross that served as a low-level fixation condition (+). During each epoch, subjects viewed either 56 masked-fearful stimuli or 56 masked-happy stimuli (each of eight fearful or happy faces masked by the neutral expression for each of the other seven individuals). Masked stimuli were presented twice per sec in a random order.

Table 1. Demographic, Clinical, and Functional Magnetic Resonance Imaging (fMRI) Data by Subject

Subjects	Age (years)	CES	CAPS	Comorbidity	fMRI response in amygdala (% change)
PTSD group					
1	48	30	94	MDD, PD, SP	3.57
2	51	34	72	MDD, Dys, GAD	1.39
3	48	34	92	PD	0.92
4	53	31	60	MDD	1.15
5	48	9	103	None	0.61
6	45	32	103	SP	1.56
7	60	31	56	SocP	1.15
8	52	40	76	Dys. OCD	0.23
Mean ± SD	50.6 ± 4.6	30.1 ± 9.1	82.0 ± 18.6		1.32 ± 1.00
Non-PTSD group					
9	54	12	3	None	0.22
10	53	21	0	None	0.67
11	54	23	0	None	0.42
12	61	27	3	None	0.26
13	52	28	10	None	0.32
14	50	8	0	None	0.79
15	55	14	9	None	0.17
16	54	28	27	None	0.80
Mean ± SD	54.1 ± 3.2	20.1 ± 7.8	6.5 ± 9.2		0.46 ± 0.26
Between-group	ns ($p = .10$)	$p = .03$	$p < .001$		$p = .02$

The fMRI response in the amygdala corresponds to the percentage change for the masked-fearful vs. masked-happy contrast; as described in Methods and Materials, this value was measured at the voxel of maximum Kolmogorov–Smirnov (KS) value within the amygdala, based on each subject's individual KS map. Excluding subjects 8 and 14 yielded $n = 7$ per group, better matched for the Combat Exposure Scale (CES; $p > .05$) with preserved significant between-group differences in fMRI amygdala response ($p = .008$). Excluding only subject 1, as a possible outlier with respect to fMRI amygdala response, likewise actually enhanced the statistical between-group difference ($p = .007$).

CAPS, Clinician-Administered Posttraumatic Stress Disorder (PTSD) Scale; MDD, major depressive disorder; PD, panic disorder; SP, specific phobia; Dys, dysthymia; GAD, generalized anxiety disorder; SocP, social phobia; OCD, obsessive–compulsive disorder.

Each 200 msec masked stimulus consisted of a 33 msec fearful or happy expression (target) immediately followed by a 167 msec neutral expression (mask). The order of the 28 sec epochs containing 56 fearful or happy masked stimuli was counterbalanced within and across subjects in an identical manner for each group: Half the subjects viewed masked-fearful followed by masked-happy targets during their first run (+, F, H, +, F, H, +, F, H, +); the other half viewed masked-happy followed by masked-fearful targets during their first run (+, H, F, +, H, F, +, H, F, +). The order of fearful and happy target epochs was then reversed for the second run for all subjects. These 10 epochs comprised a 4-min, 40-sec run. Each subject viewed two runs.

SUBJECT DEBRIEFING. Subjective report and recognition measures were used to assess subjects' explicit knowledge of presented masked facial expressions of emotion following completion of all stimulus presentations (Whalen et al 1998).

STIMULI AND APPARATUS. Facial stimuli were presented via VCR tape, and the output was projected (Sharp XG-2000U LCD) onto a screen within the imaging chamber viewable by a mirror (3.75 cm × 8.75 cm) ∼ 16 cm from the subject's face. The play speed of the VCR was 30 frames per sec, creating a 33-msec-per-frame presentation rate.

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

IMAGE ACQUISITION AND DATA ANALYSIS. Our standard image acquisition protocol was utilized as described previously (Cohen and Weisskoff 1991; Kwong 1995). An initial sagittal localizer (SPGR, 60 slices, resolution 0.898 × 0.898 × 2.8 mm) was performed to provide a reference for future slice selection and for eventual localization within Talairach space (Talairach and Tournoux 1988). Following automated shimming (Reese et al 1995) to maximize field homogeneity, an MR angiogram (SPGR, resolution 0.78125 × 0.78125 × 2.8 mm) was acquired to identify large and medium diameter vessels. Then a set of T1-weighted, high-resolution transaxial anatomic scans (resolution 3.125 × 3.125 × 8 mm) were acquired. For the fMRI series, blood oxygenation level–dependent (BOLD) signal intensity was measured, using asymmetric spin-echo (ASE) sequences to minimize macrovascular signal contributions. Functional ASE data were acquired as 15 contiguous, interleaved, horizontal, 8-mm slices that paralleled the intercommissural plane (voxel size 3.125 × 3.125 × 8 mm; 100 images per slice, TR/TE/Flip = 2800 msec/70 msec/90°).

Automated data-analytic techniques began with a quantification of subject motion and then correction using an algorithm developed by Jiang et al (1995) based on Woods et al (1992). Both functional and high-resolution structural data then were

placed into normalized Talairach space (Talairach and Tournoux 1988) and resliced into 3.125 × 3.125 × 3 mm voxels in the coronal plane. Data from each subject were then baseline normalized. Nonparametric statistical maps, using the Kolmogorov-Smirnov (KS) statistic, were constructed both for individual subject data and also from a concatenated (averaged) data set across the entire group of 16 subjects. The maps were displayed in pseudocolor, scaled according to significance, and superimposed on SPGR images that were also placed into Talairach space and resliced in the coronal plane.

All analyses were based on voxel-by-voxel statistical maps. Three search territories of interest were designated *a priori:* the amygdala, medial frontal cortex, and fusiform gyrus (face area). Boundaries of these search territories were operationally defined as follows:

1. The amygdala was defined by visual inspection of structural MRI data, guided by the atlas of Mai et al (1997). The following landmarks were used to operationally define the search volume for the amygdala: anterior = anterior commissure; posterior = prominence of the temporal horn of the lateral ventricle; inferior = entorhinal cortex; superior = base of the basal forebrain; medial = uncus; lateral = ventral claustrum. Note that at the resolution limits of the current study, the dorsal boundary of the amygdala is difficult to discern. Recent anatomical evidence suggests that neurons of the central and medial nuclei extend dorsally into the substantia innominata (SI) of the basal forebrain, comprising neurons of the bed nucleus of the stria terminalis, which is a component of the so-called "extended amygdala." Cholinergic neurons of the nucleus basalis of Meynert are also intermingled in this region (see Whalen et al 1998 and Whalen 1998 for a more detailed discussion of amygdala/SI functional contiguity).
2. Medial frontal cortex was operationally defined here as anterior cingulate cortex (i.e., all cingulate cortex anterior to the anterior commissure, including ~ BA 24 and 32); the anatomical boundaries of cingulate cortex were determined by visual inspection of structural MRI data (Vogt et al 1992) and the coronal plane through the anterior commissure was defined in Talairach space.
3. The fusiform gyrus face area was defined functionally by the range of Talairach coordinates reported by Kanwisher et al (1997).

First, the averaged map for the full cohort of 16 subjects was inspected for main effects of condition (masked fear vs. masked happy). Because we predicted amygdala activation to the present experimental manipulation, our *a priori* significance threshold ($p < 6.6 \times 10^{-4}$) represents a Bonferroni-corrected .05 probability level based on the approximately 76 voxels that make up the amygdaloid region (Filipek et al 1994). The averaged KS map was further inspected to rule out activations of comparable significance within medial frontal cortex.

Second, individual KS maps were inspected to define the location of each subject's centroid of amygdala activation for the masked-fear versus masked-happy contrast; centroids of activation were defined as the voxel with greatest KS value within the designated search territory. At that locus, percent BOLD signal intensity change was measured and entered into the between-group analysis of amygdala activation (see Table 1). For this analysis, a one-tailed *t* test, as well as a Mann–Whitney *U* test (with a significance threshold of $p < .05$) were used. An analogous procedure was employed for quantifying signal intensity changes within fusiform cortex for the combined faces versus fixation (control) contrast.

Third, a direct between-group KS map was constructed using averaged fMRI data from all subjects normalized to the masked-happy condition; BOLD signal intensity values were contrasted between groups for the masked-fear condition. This between-group map likewise was inspected for foci of significant activation within the amygdala ($p < 6.6 \times 10^{-4}$, uncorrected).

Finally, a series of secondary analyses were performed to test for significant correlations between % BOLD signal intensity changes for the masked-fear versus masked-happy contrast and clinical indices. Specifically, the fMRI data from the individual subject maps were entered into separate Pearson product–moment correlation analyses with CAPS, CES, and BDI scores. A liberal significance threshold of $p < .05$ (uncorrected for these three comparisons) was employed.

Results

Main Effects of Condition

As predicted and consistent with previous studies in healthy subjects, analysis of the fMRI data averaged across both groups (PTSD and non-PTSD) for the masked-fearful versus masked-happy contrast indicated significant activation within the left amygdala ($p = 5.2 \times 10^{-5}$; Talairach coordinates = −28, −6, −9; see Figure 1), but not within medial frontal cortex. More specifically, as in our previous study (Whalen et al 1998), the observed activation was located on the dorsal border of the amygdala, extending ventrally into the traditionally defined amygdala and dorsally into the SI. With regard to the absence of significant medial frontal activation, there were no foci anywhere in the frontal cortex anterior to the anterior commissure that met the statistical threshold used for the amygdala (i.e., $p < 6.6 \times 10^{-4}$, noting that this represents an exceedingly liberal threshold for such a large search territory). Further, for this contrast, there also was no activation within fusiform cortex that met this threshold.

BETWEEN-GROUP EFFECTS: INDIVIDUAL MAPS. Next, individual statistical maps were generated for each subject to obviate confounding influences of intersubject differences in anatomy. From these individual maps, fMRI signal intensity differences corresponding to the masked-fearful versus masked-happy contrast were measured within the amygdala for each subject. As hypothesized, in comparison with the combat-exposed subjects without PTSD, patients with PTSD exhibited significantly greater amygdala responses (Table 1 and Figure 2). Because the
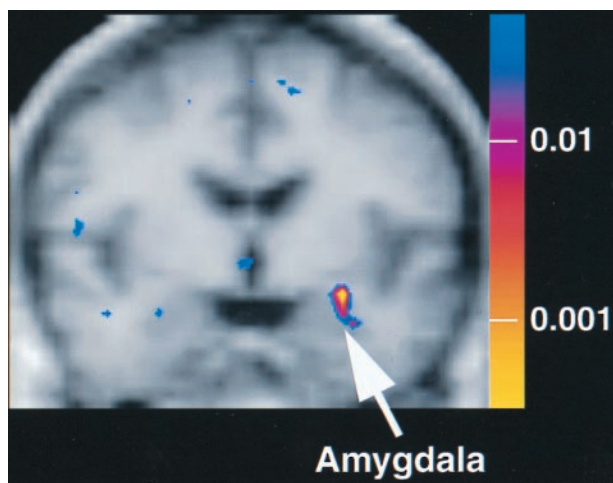
Figure 1. Statistical map of functional magnetic resonance imaging (fMRI) results: main effect of condition. A Kolmogorov–Smirnov statistical map of fMRI blood oxygenation level–dependent signal intensity differences illustrates the main effect of condition for the masked-fearful vs. masked-happy contrast, averaged over all 16 subjects. The results are displayed in Talairach space (Talairach and Tournoux 1988), superimposed over averaged structural MRI data from the cohort. The color bar shows corresponding p values. The image is presented in accordance with radiologic convention; the left side of the image corresponds to the right side of the brain. Significant activation is evident within the left amygdala.
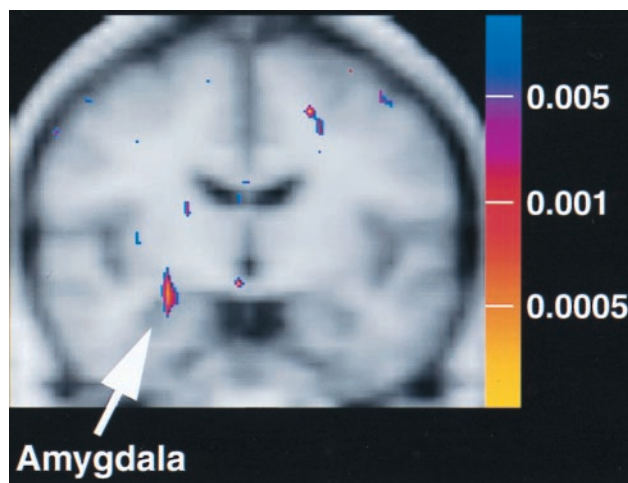

Figure 3. Statistical map of functional magnetic resonance imaging (fMRI) results: group × condition effect. A Kolmogorov–Smirnov statistical map of fMRI blood oxygenation level–dependent signal intensity differences reflecting the direct between-group comparison (masked-fear$_{PTSD}$ vs. masked-fear$_{non-PTSD}$, normalized to the masked-happy condition) is displayed in Talairach space (Talairach and Tournoux 1988), superimposed over averaged structural MRI data from the cohort. The color bar illustrates corresponding p values. The image is presented in accordance with radiologic convention; the left side of the image corresponds to the right side of the brain. A significant between-group effect is evident within the right amygdala.
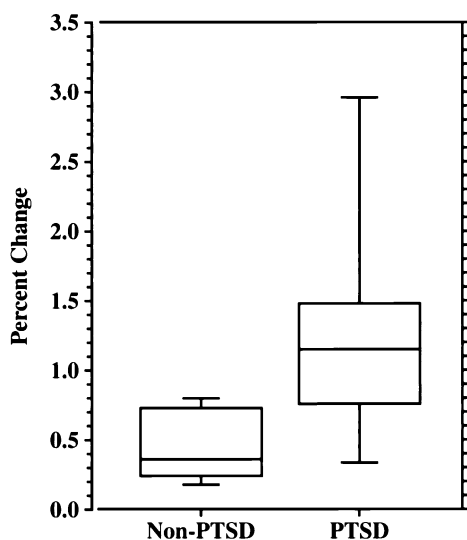

Figure 2. Box and whisker plot of functional magnetic resonance imaging (fMRI) amygdala results for the posttraumatic stress disorder (PTSD) and non-PTSD groups. The box and whisker plot depicts the percent fMRI blood oxygenation level–dependent signal intensity changes for the PTSD and the non-PTSD groups for the amygdala response corresponding to the masked-fearful vs. masked-happy contrast (see Table 1). As described in the methods, these values were measured at the voxel of maximum Kolmogorov–Smirnov (KS) value within the amygdala, based on each subject's individual KS map. Note that, as predicted, there is a significant between-group difference with regard to amygdala activation.

variance associated with the amygdala responses differed significantly between groups, a Mann–Whitney U test was also applied. This test similarly indicated a significant between-group difference in the magnitude of amygdala activation ($p = .008$).

BETWEEN-GROUP EFFECTS: GROUP-AVERAGED MAP. A direct between-group comparison was carried out via statistical mapping within Talairach space using group-averaged data. This comparison likewise indicated significantly greater activation within the amygdala for the PTSD group (Figure 3; $p = 2.9 \times 10^{-4}$; Talairach coordinates = 25, −9, −9).

Note that on the group-averaged map, this amygdala finding was located on the dorsal border of the amygdala extending ventrally into the traditionally defined amygdala and dorsally into the SI, similar to the distribution observed for the main effect of condition. Unlike the main effect of condition, however, the between-group effect was observed on the right side.

CONTROLLING FOR BETWEEN-GROUP EFFECTS. When collapsed across all 16 subjects (i.e., both groups), robust bilateral fusiform activations were present for the combined masked faces versus low-level baseline contrast

(left = −34, −54, −12, $p = 5.7 \times 10^{-36}$, uncorrected; right = 37, −54, −12, $p = 1.1 \times 10^{-33}$, uncorrected). Therefore, to control for nonspecific, between-group differences in brain activation or hemodynamic responsivity, fMRI % signal intensity differences corresponding to this contrast were measured within fusiform cortex. This was done using individual subject maps in a manner precisely analogous to the technique used to assess between-group differences in the amygdala. Note that this between-group comparison of fusiform activation yielded nonsignificant results [PTSD group = 1.35% ± 0.29%; non-PTSD group = 1.22% ± 0.25%; $t(14) = 0.95$, $p = .36$]. Thus, between-group findings in the amygdala do not appear to be attributable to nonspecific differences in brain activation or hemodynamic responsivity.

Finally, a comparison of motion correction data showed no significant difference between groups in mean displacement along the three orthogonal axes [PTSD group = 0.66 ± 0.37 mm; non-PTSD group = 0.53 ± 0.28 mm; $t(14) = 0.78$, $p = .45$]. Thus, between-group findings in the amygdala do not appear to be attributable to differences in motion or motion correction.

Correlation Analyses

Secondary analyses showed a significant correlation between fMRI signal intensity change within the amygdala and the severity of PTSD symptoms, as measured by the CAPS [$r(14) = .56$, $p = .02$]. Nonetheless, there was no significant correlation between fMRI signal intensity change within the amygdala and severity of combat exposure as measured by the CES [$r(14) = .31$, $p = .25$] nor the severity of depression as measured by the BDI [$r(14) = .41$, $p = .11$].

Discussion

The current findings indicate that patients with PTSD exhibit exaggerated automatic responses within the amygdala to general threat-related stimuli, dissociated from medial frontal activation. More specifically, a between-group difference in amygdala response was observed in the context of a paradigm where no significant activation was found in frontal cortex. This suggests that the amygdala plays a fundamental role in the pathophysiology of PTSD. Our study does not address whether such exaggerated amygdala responses reflect a vulnerability to develop PTSD that predates the traumatic event or an abnormality that evolves as part of a pathological response to it (Pitman 1997; Yehuda and Antelman 1993). Longitudinal studies, including assessments of high-risk subjects before trauma exposure, would be necessary to resolve this question.

Although DSM-IV (American Psychiatric Association 1994) represents a current gold standard, it is likely that such clinical criteria define populations of patients with pathophysiologically heterogeneous disease. Hence, optimal diagnostic criteria might be able to define a subset of patients with PTSD who are pathophysiologically homogeneous. In this regard, it is noteworthy that the magnitude of amygdala response measured via the present paradigm distinguished between subjects with PTSD versus subjects without PTSD (as defined by DSM-IV) with 100% specificity and 75% sensitivity; that is, 75% of the PTSD group exceeded the highest value in the non-PTSD group. Although preliminary, and based on a small number of subjects, this represents even better discrimination than has previously been achieved by measuring peripheral physiologic markers (Orr and Roth, in press).

Several aspects of our initial study invite follow-up experiments to elaborate on these results. First, replication is critical, as is extension to female subjects and patients with PTSD from causes other than combat exposure, to assess the generalizability of the current findings. Conversely, studies of other diagnostic entities, especially other anxiety and affective disorders, will be essential to evaluate the specificity of this phenomenon to PTSD. In this regard, the current findings should be interpreted cautiously, given the profile of psychiatric comorbidity in the study samples. Consistent with the epidemiology of combat-related PTSD (Kulka et al 1990), the PTSD group had a substantial prevalence of current comorbid disorders not present in the non-PTSD comparison group. It is noteworthy that despite the presence of such comorbidity, no single comorbid diagnosis appears to explain the observed between-group differences in amygdala responsivity (see Table 1). In particular, the results of the correlation analyses suggest that amygdala responsivity across the two groups is significantly related to severity of PTSD symptoms, rather than with severity of depressive symptoms or severity of trauma exposure. Finally, future studies should seek to determine whether this exaggerated amygdala response provides predictive information regarding the subsequent efficacy of various treatments. For instance, characterizing the amygdala response function over repeated stimulus presentations (i.e., habituation vs. sensitization) might provide predictive information regarding a patient's response to behavioral therapy.

Although we chose to emphasize the automaticity of the amygdala response by employing a standardized masked-faces paradigm, we did not seek to make any absolute distinction regarding each subject's awareness of the target stimuli. In fact, three of eight subjects in each group provided subjective reports indicating some awareness of the target stimuli at the end of the image acquisition session. Nonetheless, the relative power of this paradigm is evident in that, despite this potential source of variance,

1) significant activation corresponding to the salient contrast was confined to the amygdala, and 2) the variance in peak fMRI signal intensity changes within the amygdala was relatively small within each group (see Table 1). Still, future studies of PTSD should formally compare the benefits of this masked paradigm versus a paradigm comprising overt presentations of these same emotionally expressive face stimuli. Existing literature suggests that anxiety disorders are characterized by preconscious response biases and that such response biases can be most clearly demonstrated using probes that highlight automatic or implicit information processing (Mathews and Mac-Leod 1994; McNally 1998). Therefore, we predict that the current masked-faces paradigm will prove superior to overt presentation of facial stimuli for distinguishing patients with PTSD from healthy comparison subjects.

References

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC: American Psychiatric Association.

Beck AT, Ward CH, Mendelson M (1961): An inventory for measuring depression. *Arch Gen Psychiatry* 4:561–571.

Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, et al (1995): The development of a clinician-administered PTSD scale. *J Trauma Stress* 8:75–90.

Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, et al (1996): Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* 17:875–887.

Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS (1999): Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: A positron emission tomography study. *Biol Psychiatry* 45:806–816.

Cahill L, Weinberger NM, Roozendaal B, McGaugh JL (1999): Is the amygdala a locus of "conditioned fear"? Some questions and caveats. *Neuron* 23:227–228.

Cohen MS, Weisskoff RM (1991): Ultra-fast imaging. *Magn Reson Imaging* 9:1–37.

Davis M (1997): The neurobiology of fear responses: The role of the amygdala. *J Neuropsychiatry Clin Neurosci* 9:382–402.

Ekman P, Friesen WV (1976): *Pictures of Facial Affect.* Palo Alto, CA: Consulting Psychologists Press.

Esteves F, Öhman A (1993): Masking the face: Recognition of emotional facial expressions as a function of the parameters of backward masking. *Scand J Psychol* 34:1–18.

Filipek P, Richelme C, Kennedy D, Caviness V (1994): The young adult human brain: An MRI-based morphometric analysis. *Cereb Cortex* 4:344–360.

First MB, Spitzer RL, Gibbon M, Williams JBW (1995): *Structured Clinical Interview for DSM-IV.* New York: New York State Psychiatric Institute, Biometrics Research Department.

Jiang AJ, Kennedy DN, Baker JR, Weisskoff RM, Tootell RBH, Woods RP, et al (1995): Motion detection and correction in functional MR imaging. *Hum Brain Mapping* 3:224–235.

Kanwisher N, McDermott J, Chun MM (1997): The fusiform face area: A module in human extrastriate cortex specialized for face perception. *J Neurosci* 17:4302–4311.

Kapp BS, Whalen PJ, Supple WF, Pascoe J (1992): Amygdaloid contributions to conditioned arousal and sensory information processing. In: Aggleton JP, editor. *The Amygdala: Neurobiological Aspects of Emotion, Memory and Mental Dysfunction.* New York: Wiley, 229–254.

Keane TM, Fairbank JA, Caddell JM, Zimering RT, Taylor KL, Mora CA (1989): Clinical evaluation of a measure to assess combat exposure. *Psychol Assess J Consult Clin Psychol* 1:53–55.

Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jorda BK, Marmar CR, et al (1990): *Trauma and the Vietnam Generation: Report of Findings from the National Vietnam Veterans Readjustment Study.* New York: Brunner/Mazel.

Kwong KK (1995): Functional magnetic resonance imaging with echo planar imaging. *Magn Reson Q* 11:1–20.

LeDoux JE (1996): *The Emotional Brain.* New York: Simon & Schuster.

Liberzon I, Taylor SF, Amdur R, Jung TD, Chamberlain KR, Minoshima S, et al (1999): Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry* 45:817–826.

Mai JK, Assheuer J, Paxinos G (1997): *Atlas of the Human Brain.* San Diego: Academic Press.

Mansfield P (1977): Multi-planar image formation using NMR spin echoes. *J Physics* C10:L55–L58.

Mathews A, MacLeod C (1994): Cognitive approaches to emotion and emotional disorders. *Annu Rev Psychol* 45:25–50.

McNally RJ (1998): Information-processing abnormalities in anxiety disorders; implications for cognitive neuroscience. *Cogn Emotion* 12:479–495.

Morgan MA, LeDoux JE (1995): Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behav Neurosci* 109:681–688.

Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, et al (1996): A differential response in the human amygdala to fearful and happy facial expressions. *Nature* 383:812–815.

Morris JS, Öhman A, Dolan RJ (1998): Conscious and unconscious emotional learning in the human amygdala. *Nature* 393:467–470.

Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 9:97–113.

Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, Pitman RK (in press): De Novo conditioning in trauma-exposed individuals with and without post-traumatic stress disorder. *J Abnorm Psychol.*

Orr SP, Roth WT (in press): Psychophysiological assessment: Clinical applications for PTSD. *J Affect Disord.*

Peri T, Ben-Shakhar G, Orr SP, Ahalev AY (in press): Psychophysiologic assessment of aversive conditioning in posttraumatic stress disorder. *Biol Psychiatry.*

Pitman RK (1997): Overview of biological themes in PTSD. *Ann N Y Acad Sci* 821:1–9.

Pitman RK, Shalev AY, Orr SP (2000): Post-traumatic stress disorder: Emotion, conditioning, and memory. In: Gazzaniga MS, editor. *The Cognitive Neurosciences.* Cambridge, MA: MIT Press, 1133–1147.

Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, et al (1996): A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry* 53: 380–387.

Reese TG, Davis TL, Weisskoff RM (1995): Automated shimming at 1.5 T using echo-planar image frequency maps. *J Magn Reson Imaging* 5:739–745.

Shalev AY, Rogel Fuchs Y, Pitman RK (1992): Conditioned fear and psychological trauma. *Biol Psychiatry* 31:863–865.

Shin LM, Kosslyn SM, McNally RJ, Alpert NM, Thompson WL, Rauch SL, et al (1997): Visual imagery and perception in posttraumatic stress disorder: A positron emission tomographic investigation. *Arch Gen Psychiatry* 54:233–241.

Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, et al (1999): Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related posttraumatic stress disorder: A PET investigation. *Am J Psychiatry* 156:575–584.

Talairach J, Tournoux P (1988): *Co-Planar Stereotaxic Atlas of the Human Brain.* New York: Thieme.

Vogt BA, Finch DM, Olson CR (1992): Functional heterogeneity in cingulate cortex: The anterior executive and posterior evaluative regions. *Cereb Cortex* 2:435–443.

Whalen PJ (1998): Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala. *Curr Dir Psychol Sci* 7:177–188.

Whalen PJ, Rauch SL, Etcoff NL, McInerney S, Lee MB, Jenike MA (1998): Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci* 18:411–418.

Woods RP, Cherry SR, Mazziotta JC (1992): Automated algorithm for aligning tomographic images. II. Cross-modality MRI-PET registration. *J Comput Assist Tomogr* 16:620–633.

Yehuda R, Antelman SM (1993): Criteria for rationally evaluating animal models of posttraumatic stress disorder. *Biol Psychiatry* 33:479–486.