Trauma modulates amygdala and medial prefrontal responses to consciously attended fear

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Introduction

Evidence from lesion and neuroimaging studies suggests that key components of the neural system for fear processing include the amygdala and medial prefrontal cortex (MPFC). The role of the amygdala in the appraisal, generation and maintenance of fear has been demonstrated in a wealth of human and non-human animal studies (e.g., Adolphs et al., 1994; LeDoux, 1998, Morris et al., 1996; for a review, see Adolphs, 2002; Phan et al., 2002; Zald, 2000). Amygdala modulation of MPFC activity by the amygdala. Animal fear conditioning studies have shown that the MPFC may be involved in reducing fear responses, whereas the amygdala is required for fear expression and has the effect of reducing MPFC activity.
Similarly, evidence from neuroimaging studies suggests a reciprocal relationship between the amygdala and MPFC, such that emotion-related activity in the amygdala is reduced during higher cognitive processing which engages the MPFC, as well as the reverse (Taylor et al., 1999).

From such findings, it has been suggested that pathological fear and anxiety may be the manifestation of abnormal modulations in amygdala and MPFC activity and their interaction. PTSD is defined by symptoms of reexperiencing the trauma, avoidance of associated stimuli and hyperarousal symptoms, suggesting a heightened fear response (APA, 1994). Drawing on evidence from animal fear-conditioning studies (Davis et al., 1997; Morgan and LeDoux, 1995), it has been proposed that PTSD symptoms reflect amygdala hyperresponsivity to fear-related stimuli, with a concomitant lack of ‘top–down’ prefrontal inhibition.

Consistent with this proposal, neuroimaging studies of PTSD have to date observed abnormal reductions in MPFC activity (Bremner et al., 1999; Shin et al., 1999, 2004), as well as enhanced and distinctive amygdala engagement (Liberonz et al., 1999; Rauch et al., 2000), particularly for combat veterans (Shin et al., 2004). Yet, a PET study of civilian trauma subjects with and without PTSD has reported a positive amygdala and MPFC association in PTSD and a lack of association in the non-PTSD group (Gilboa et al., 2004). We used a higher temporal resolution technique, functional MRI, to further elucidate the changes in amygdala and MPFC activity following trauma.

In this study, we examined responses to fearful face stimuli, as a standardized probe for amygdala–MPFC activity, which allows generalization to other studies and populations. To date, most PTSD neuroimaging studies have been undertaken using script-driven imagery, which may recruit state-based responses specific to the task, rather than more trait-like systems for fear processing. In the one previous study to use fearful face stimuli to study PTSD, stimuli were presented briefly and masked, to maximize automatic ‘bottom up’ aspects of processing involving the amygdala and to minimize ‘top–down’ MPFC regulation (Rauch et al., 2000). The study revealed exaggerated amygdala responses to masked (nonconscious) fear in combat PTSD compared to control subjects, while MPFC activity was absent in both groups. Changes in MPFC activity, associated with ‘top–down’ processing, have not been examined in the context of trauma using consciously attended facial signals of fear. In this study, we examined whether post-trauma reactions are characterized by reduced MPFC activity, with concomitant amygdala enhancement, in response to overtly presented signals of fear.

**Method**

**Subjects**

Thirteen patients with PTSD (mean age = 36.5 years, SD = 9.7; 7 males, 6 females) were recruited from the Westmead PTSD Unit, and 13 matched non-traumatized comparison subjects (mean age = 34.8 years, SD = 8.5; 7 males, 6 females) were recruited from equivalent geographical regions, in collaboration with the Brain Resource International Database (http://www.brainresource.com; Gordon, 2003).

Diagnoses of PTSD were made by clinicians independent of the study using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1990). Seven PTSD participants were survivors of non-sexual assault, and six had survived motor vehicle accidents, and the majority were within 1 to 2 years post-trauma (time post-trauma mean = 6 years, median = 1 year). Severity of PTSD symptoms was measured using the CAPS (mean = 82.5, SD = 21.4) as well as the Impact of Events Scale (IES; Horowitz et al., 1979; mean = 51.8, SD = 9.6). In terms of comorbid depression, PTSD patients also scored significantly higher than healthy control subjects on this component of the Depression and Anxiety Stress Scale [DASS; Lovibond and Lovibond, 1995; control mean = 3.09, SD = 5.94; PTSD mean = 12.31, SD = 5.42; \( t_{(26)} = 3.97, P = 0.001 \)]. Each of these clinical indicators was also included in correlation analyses to examine their relationship to altered brain function in PTSD.

Exclusion criteria for both groups were head injury, history of loss of consciousness, stroke or neurological disorder, serious medical conditions related to the thyroid or heart, cancer, a blood borne illness such as HIV and hepatitis, genetic disorder, sensory-motor impairments and recent history of substance abuse. Healthy comparison subjects were also screened for history of Axis I disorder (themselves or first-degree relative).

All participants provided written informed consent to participate, in accordance with the National Health and Medical Research Council guidelines.

**Behavioral task**

Participants viewed gray-scale face stimuli which had been selected from a standardized picture set (Gur et al., 2002) and consisted of four female and four male individuals depicting fear and neutral facial expressions. All faces were matched for overall luminosity and size and were equally aligned on a black background template.

Face stimuli were presented in a pseudorandom sequence of 30 blocks (15 blocks of 8 fear stimuli and 15 blocks of 8 neutral stimuli). Each stimulus was presented for 500 ms (unmasked) and was followed by a 767.5 ms blank screen inter-stimulus interval (ISI). The total block duration \( (8 \times \text{stimulus duration and ISI}) \) was therefore 10.14 s, designed to capture the maximal BOLD saturation (Penny et al., 2001). The ISI was jittered by \( \pm 500 \) ms in order to ensure that stimulus onset did not coincide with a constant slice position in image acquisition.

Face stimuli were presented via a projector (Sanyo ProX, Multiverse Projector) and mirror system. Participants received standardized and synchronized visual and audio (through headphones) instructions and were asked to consciously attend to the face stimuli, in preparation for a post-scanning briefing about these stimuli.

**Imaging protocols**

Imaging was performed on a 1.5 T Siemens Vision Plus scanner using an echo planar protocol. A total of 90 functional T2*-weighted volumes (3 per stimulus block) were acquired, comprising 15 non-contiguous slices parallel to the intercommissural (AC–PC) line, with 6.6 mm thickness and TR = 3.3 s, TE = 40 ms, flip angle = 90°; with FOV 24 x 24 cm², matrix size 128 x 128. Three initial ‘dummy’ volumes were acquired to ensure blood oxygen level dependent (BOLD) saturation. High resolution structural MRI data were also acquired, using a T1 (MPRAGE) sequence, with 180 slices (sagittal plane), 1 mm cubic voxels, 256 x 256 matrix, TR = 9.7, TE = 4, TI = 200 and flip angle = 12°.

The ability of the functional imaging protocol to elicit robust signal change in the amygdala was demonstrated by a calculation of...
signal to noise ratio (SNR). Based on Parrish et al. (2000), the minimum SNR value (for an alpha level of 0.01, beta value of 0.95, expected signal change of 1% and at least 80 images) is 96. The observed SNR values in this study were calculated for each subject on a voxel-by-voxel basis by taking the mean signal of the entire smoothed, realigned time series for the left amygdala and dividing this mean value by the standard deviation (LaBar et al., 2001).

Pre-processing and statistical analysis of fMRI data were conducted using Statistical Parametric Mapping (SPM2, Wellcome Department of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/spm2.html). Functional scans were realigned, spatially normalized and smoothed in order to remove movement artefact and to place data from different subjects into a common anatomical frame (Penny et al., 2001). In addition to realigning, we used the SPM2 procedure for unwarping, which models the residual movement-related variance. Images were then normalized into standardized MNI space and smoothed using a Gaussian kernel (FWHM: 8 mm). An HRF-convolved boxcar model with temporal derivative was created to correspond to experimental model, and a high pass filter was applied to remove low-frequency fluctuations in the BOLD signal. BOLD signal change was based on the contrast of fear versus neutral. This contrast was used for the within- and between-group random effects analyses of PTSD and comparison groups. These analyses were undertaken using a search region of interest (ROI) approach to test a priori hypothesis, as well as a whole-brain analysis to examine the context of ROI findings. Time series analyses were undertaken to further explore the ROI data.

**ROI analyses**

The search regions were the amygdala and medial prefrontal cortex (bilaterally) as defined by the Automated Anatomical Labeling (AAL) masks (Tzourio-Mazoyer et al., 2002) and selected using the WFU Pickatlas (Version 1.02). We defined the MPFC as including the anterior cingulate (BA 24/32) and medial orbital to superior frontal structures (extending to BA9/10), consistent with previous PTSD neuroimaging studies (Rauch et al., 2000; Shin et al., 1999, 2004; Zubieta et al., 1999).

Within each ROI, we constructed functional maps based on the activated voxels due to the contrast of fear versus neutral. Given the a priori hypotheses for the study, significant clusters of activity were determined according to the statistical threshold of $P < 0.05$ (small volume corrected; SVC) and the extent threshold of $\geq 3$ voxels per cluster. We used $t$ tests to compare within and between groups, for the contrast of fear versus neutral.

**Whole-brain analyses**

Whole-brain analyses were then conducted to examine whether the ROI findings for amygdala and MPFC were also displayed at the ‘whole-brain’ level. A statistical threshold of $P < 0.001$ and an extent threshold of $\geq 3$ voxels per cluster were used to determine significant activations in the whole-brain analysis. Within- and between-group comparisons were also undertaken using $t$ test analyses.

**Time series analyses**

We extracted the percentage BOLD signal change from the amygdala and anterior cingulate cortex for each individual subject. The time series were extracted from the left and right amygdala and left and right anterior cingulate, using MarsBar (http://marsbar.sourceforge.net/) and the procedure of Hariri et al. (2000). For each ROI, data were extracted from supra-threshold voxels which showed a significant ($r = 0.2, P < 0.05$) correlation with the experimental model. Effect sizes were computed, using the difference between means (for fear and neutral conditions), divided by the error variance across subjects (see Desmond and Glover, 2002).

In each ROI, the effect size of activity was examined in terms of responses averaged across the total experiment and for the Early versus Late halves of the experiment. The Early versus Late division was considered in view of evidence for attenuation of amygdala activity over the experimental time course for both fearful and neutral face stimuli (Fischer et al., 2003; Wright et al., 2001) and for differential autonomic habituation in PTSD (Rothbaum et al., 2001). Since our behavioral task comprised 30 blocks of fear and neutral stimuli, pseudorandomly, we allocated the first 15 blocks (150 s) to the ‘Early’ phase and the second 15 blocks (150 s) to the ‘Late’ phase. This procedure drew on the separation of experimental runs into Early versus Late halves in the initial studies of amygdala attenuation (Fischer et al., 2003; Wright et al., 2001). Moreover, the duration of repeated face stimuli across phases was equivalent to that used in conventional psychophysiological studies of habituation (Clark et al., 1992).

We undertook a series of mixed-model analyses of variance (ANOVs) with within-subject factors phase (Early versus Late) and Laterality (Left versus Right) and between subjects factor Group, for the effect size values for amygdala and anterior cingulate cortex, followed by planned contrasts. To add to the interpretation of ROI analyses, ANOVAs were also conducted with the Laterality factor for the Total effect size values.

**Correlational analyses**

To examine correlations between (a) amygdala and MPFC activity and (b) clinical variables and activity in the amygdala and MPFC, we used the BOLD time series data, extracted from each of these ROIs using the procedure described above. Pearson correlations (two-tailed) were used to examine the relationships between amygdala and MPFC activity in terms of effect size. A priori correlations of focus were within-hemisphere amygdala–medial prefrontal relationships for the total experimental time course and for Early and Late phases. We used Spearman rank correlations to examine the associations between these regions and clinical measures due to the significant skewness of several clinical scores (e.g., CAPS, time post-trauma and IES, skewness >2.0).

**Results**

**ROI analysis**

For non-traumatized control subjects, significant responses ($P < 0.05_{SVC}$) to fear (versus neutral) were observed in the left amygdala and bilateral MPFC, encompassing the anterior cingulate cortex (ACC) and dorso-medial prefrontal gyrus (Table 1; Fig. 1). PTSD
patients showed activity in the right amygdala and MPFC/ACC, extending more ventrally (Table 1; Fig. 1).

Between-group analyses showed that PTSD subjects had significantly less activity than comparison subjects in the bilateral MPFC (BA9/10) and AC (BA24). By contrast, PTSD subjects showed comparatively greater activity in a small (3 voxel) ventral region of the left amygdala and in a dorsal portion of the MPFC (Table 1; Fig. 1).

Given that amygdala activations for PTSD were small and at the extreme ventral boundary of the amygdala region of interest (Figs. 1b, d), we repeated these contrasts at a lower threshold ($P < 0.1$) to explore their neuroanatomical validity (Fig. 2). For the left amygdala, the region of relatively enhanced activity in PTSD compared to control subjects was slightly larger at $P < 0.1$ but still located at the edge of the neuroanatomical boundary used to define the amygdala (Fig. 2f). The presence of sub-critical threshold right amygdala activity in controls, although more dorsal, might explain why PTSD subjects did not show significantly enhanced right amygdala responses compared to controls.

**Whole-brain analysis**

Consistent with ROI findings, control subjects showed significant bilateral MPFC engagement for the contrast of fear versus neutral, spanning the ACC ($P < 0.0001$) and extending laterally to the bilateral middle frontal gyrus (Table 2). Control subjects also showed left amygdala activity at the less stringent threshold of $P < 0.01$. Whole-brain analyses revealed significant ($P < 0.0001$) activity in additional regions which were not foci of a priori interest, including visual areas associated with face processing (Table 2): the left fusiform gyrus and bilateral parietal lobule.

In whole-brain analyses, PTSD subjects exhibited significant dorsomedial prefrontal activity ($P < 0.0001$) as well as right amygdala activity at the borderline threshold of $P = 0.009$. Additional regions of distributed activity were observed within the visual and premotor cortices (Table 2).

The between-group analysis showed that activity in the occipital, frontal prefrontal and superior temporal cortices was significantly greater in PTSD than non-traumatized control subjects (Table 2). By contrast, activity in the parietal lobule was reduced for PTSD relative to controls (Table 2).

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**Table 1**

Activity in regions of interest (corrected threshold, $P < 0.05$) in response to fear (versus neutral) for within- and between-group analyses of control and PTSD groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Side</th>
<th>MNI coordinates</th>
<th>Cluster size$^a$</th>
<th>Z score</th>
</tr>
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<tr>
<td></td>
<td>$x$</td>
<td>$y$</td>
<td>$z$</td>
<td></td>
</tr>
<tr>
<td><strong>Control subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>L</td>
<td>−24</td>
<td>−2</td>
<td>37</td>
</tr>
<tr>
<td>Dorsal medial prefrontal (BA8/9)</td>
<td>L</td>
<td>−8</td>
<td>44</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−10</td>
<td>42</td>
<td>46</td>
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<tr>
<td></td>
<td>R</td>
<td>8</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>Ventral medial prefrontal (BA10)</td>
<td>L</td>
<td>−16</td>
<td>48</td>
<td>−2</td>
</tr>
<tr>
<td>Anterior cingulate (BA24)</td>
<td>L</td>
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<td>14</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>6</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td><strong>PTSD subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>R</td>
<td>30</td>
<td>−2</td>
<td>−26</td>
</tr>
<tr>
<td>Dorsal medial prefrontal (BA8)</td>
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<td>−4</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>10</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Ventral medial prefrontal (BA10/11)</td>
<td>L</td>
<td>−4</td>
<td>52</td>
<td>−8</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>12</td>
<td>48</td>
<td>−12</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>L</td>
<td>−10</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>14</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td><strong>PTSD &lt; control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial prefrontal (BA9/10)</td>
<td>L</td>
<td>−12</td>
<td>48</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>14</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>Anterior cingulate (BA24)</td>
<td>L</td>
<td>−6</td>
<td>16</td>
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</tr>
<tr>
<td></td>
<td>R</td>
<td>6</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td><strong>PTSD &gt; control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>L</td>
<td>−30</td>
<td>−2</td>
<td>−28</td>
</tr>
<tr>
<td>Dorsal medial prefrontal (BA8)</td>
<td>L</td>
<td>−8</td>
<td>54</td>
<td>42</td>
</tr>
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</table>

$^a$ The cluster with the largest number of voxels in each region is reported. MNI coordinates ($x$, $y$, $z$, in millimeters) were confirmed with Talairach conversion and refer to the maximal signal change in each cluster. BA refers to Brodmann area.
Fig. 1. Statistical parameter maps for the contrast of fear versus neutral for the regions of interest (at $P < 0.05_{\text{SVC}}$), overlaid on the canonical T1 images (derived from the Montreal Neurological Institute). Images are in neurological orientation (left hemisphere = left of image). Amygdala activations are presented in the top row and medial prefrontal cortex (MPFC) activations in the bottom row. Non-traumatized control subjects showed significant activity in the left amygdala (a), while PTSD patients showed significant activity at the ventral boundary of the right amygdala (b). PTSD subjects did not show any regions of reduced activity in the amygdala compared to controls (c; PTSD < Controls). By contrast, PTSD patients showed a small region of significantly greater activity than controls in a small region at the ventral boundary of the left amygdala (d; PTSD > Controls). Non-traumatized controls showed significant activity in the bilateral anterior cingulate, extending into contiguous regions of the MPFC, dorsally (dMPFC) and ventrally (vMPFC) (e). PTSD patients also showed significant responses in the bilateral anterior cingulate, extending into regions of both the dMPFC and vMPFC (f). While both groups showed bilateral anterior cingulate and MPFC activity, PTSD subjects were significantly reduced relative to controls in these regions (g; PTSD < Control). By contrast, PTSD patients showed significantly greater activity than controls in a small region of the right dMPFC (h; PTSD > Control).

Fig. 2. To provide an interpretive frame of reference, the statistical parameter amygdala activations are reproduced (in red) and superimposed on the neuroanatomical mask of Tzourio-Mazoyer et al. (2002; shown in green) used to define this region. Activations (for the contrast of fear versus neutral) are overlaid on the canonical T1 images (derived from the Montreal Neurological Institute). Images are in neurological orientation (left hemisphere = left of image). In the top row, images are presented for the threshold used to test a priori hypotheses ($P < 0.05_{\text{SVC}}$), and, in the bottom row, these images are presented for a lower threshold of $P < 0.1$ to assist in evaluating the robustness and extent of amygdala activations. For non-traumatized control subjects, activity in the left amygdala was more prominent at the lower threshold (a vs. e), and encompassed contiguous voxels within the region used to define the amygdala. Controls also showed a small region of right amygdala activity at the lower threshold (c). Right amygdala activity was present to a slightly greater extent in PTSD subjects at the lower threshold (b vs. f) but was similarly located towards the ventral boundary of the search region of interest. PTSD subjects showed reduced left amygdala activity relative to controls at $P < 0.1$ (g), which was not present at $P < 0.05$ (c). By contrast, the enhancement of right amygdala in PTSD subjects compared to controls was present at both $P < 0.05$ (d) and at $P < 0.1$ (h). While the left amygdala reduction in PTSD was towards the dorsal portion of the amygdala region (g), the right amygdala enhancement was apparent at the ventral boundary (h).
For Total amygdala effect size, there was a Group by Laterality interaction of borderline significance $[F(26) = 4.12, P = 0.05]$ due to the pattern of greater left than right amygdala activity in PTSD but not control subjects.

Analysis of phase showed that laterality effects varied significantly with both Group and Phase, reflected in a three-way interaction $[F(26) = 4.56, P = 0.042]$ and associated two-way interactions for Group by Phase $[F(26) = 4.8, P = 0.037]$ and Group by Laterality $[F(26) = 18.9, P < 0.001]$. Planned contrasts showed that this effect was due to significantly enhanced Late left amygdala activity in PTSD relative to control subjects $[F(26) = 8.84, P = 0.006]$, but significantly reduced Early right amygdala activity $[F(26) = 12.60, P = 0.001]$.

For the anterior cingulate, there was no Group by Laterality interaction for the Total time series $[F(26) = 2.46 P = 0.13]$, but there were significant effects involving phase. There was a significant two-way interaction between Group and Phase $[F(26) = 5.51, P = 0.02]$ due to the divergent pattern of anterior cingulate responses in each group: an increase in Early to Late left anterior cingulate activity with a decrease in Early to Late right anterior cingulate for controls and the reverse pattern for PTSD (Fig. 3b).

Correlation analyses

Correlations between effect size of percentage BOLD signal change in the amygdala and anterior cingulate revealed a different pattern of association in control and PTSD groups. For controls, there was a positive relationship between left amygdala and left anterior cingulate activity in the Early phase of the experiment (Table 3) but a negative relationship between the right amygdala and right anterior cingulate during the Early phase (Table 3). These associations were reduced in the Late phase of the experiment for both left- and right-sided activity.

By contrast, PTSD subjects showed a positive relationship between right amygdala and right anterior cingulate for the total experiment (Table 3), but no association between amygdala and anterior cingulate responses for Early or Late phases.

The measures of trauma impact in the PTSD group revealed negative associations with anterior cingulate responses across the Late phase of the experiment. While Late phase left anterior cingulate activity was negatively associated with impact of events...
and time post-trauma (Table 4), Late phase right anterior cingulate activity showed negative correlations with total PTSD symptom severity, assessed by CAPS (Table 4). In terms of CAPS subscales (not reported in Table 4), correlations with Late anterior cingulate activity were prominent for both the frequency $r_{12} = -0.71, P = 0.007$ and severity of ‘reexperiencing and intrusions’ $r_{12} = -0.65, P = 0.016$. There were no significant correlations between these trauma measures and amygdala response.

For comorbid depression (DASS scores), Total left anterior cingulate activity was correlated positively with depression (Table 4), and the relationship between these measures was again observed during the Late phase of the experiment (Table 4). These associations are the reverse of what would be expected should depression account for reduced anterior cingulate responses in this group. By contrast, there were no significant correlations between depression and amygdala activity in the PTSD group.

Given the generally low or absent (five subjects had a DASS score of 0) level of depression in controls, it was not appropriate to undertake correlations between depression and amygdala/anterior cingulate responses for this group.

Discussion

The present results provide evidence that traumatic emotional reactions have a primary impact on the medial prefrontal systems engaged by the conscious processing of fear signals. Moreover, the findings indicate that there is a breakdown in laterality of anterior cingulate responses over the experimental time course, with a greater impact of trauma during the later phase of processing. There was a corresponding disturbance in the lateralized time course of amygdala activity, with right amygdala activity comparatively reduced during the first half of time course but left amygdala activity enhanced over the later half. However, the change in amygdala response was generally small and unrelated to trauma symptomatology. While non-traumatized subjects showed a coupling of anterior cingulate and amygdala responses which varied from left to right hemispheres over the experimental time course, trauma was associated with a lack of such coupling, which may account for the disruption to the normal pattern of spatio-temporal activity.
Table 3
Correlation coefficients (and probability levels) for the associations between amygdala and anterior cingulate activity across the total experiment and for Early and Late phases

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PTSD</th>
<th>Control</th>
<th>PTSD</th>
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<tbody>
<tr>
<td></td>
<td>Right amygdala</td>
<td>Left amygdala</td>
<td>Right amygdala</td>
<td>Left amygdala</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0.22 (0.48)</td>
<td>0.47 (0.10)</td>
<td>0.10 (0.74)</td>
<td>0.47 (0.10)</td>
</tr>
<tr>
<td><strong>Early phase</strong></td>
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</tr>
<tr>
<td>Right anterior cingulate</td>
<td>-0.53 (0.05)</td>
<td>0.08 (0.78)</td>
<td>0.11 (0.71)</td>
<td>-0.15 (0.63)</td>
</tr>
<tr>
<td>Left anterior cingulate</td>
<td>-0.08 (0.79)</td>
<td>0.30 (0.32)</td>
<td>0.83 (0.001)</td>
<td>0.11 (0.71)</td>
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<tr>
<td><strong>Late phase</strong></td>
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</tr>
<tr>
<td>Right anterior cingulate</td>
<td>0.16 (0.60)</td>
<td>0.14 (0.65)</td>
<td>0.38 (0.20)</td>
<td>-0.27 (0.37)</td>
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<tr>
<td>Left anterior cingulate</td>
<td>0.13 (0.65)</td>
<td>0.21 (0.49)</td>
<td>0.47 (0.11)</td>
<td>-0.26 (0.39)</td>
</tr>
</tbody>
</table>

Significant correlations are highlighted in bold typeface.

Table 4
Correlation coefficients (and probability levels) for the associations between amygdala and anterior cingulate activity and impact of trauma measures in the PTSD group, across the total experiment, and for Early and Late phases

<table>
<thead>
<tr>
<th></th>
<th>DASS</th>
<th>Time post-trauma</th>
<th>IES</th>
<th>CAPS</th>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Right amygdala</td>
<td>0.37 (0.22)</td>
<td>0.25 (0.40)</td>
<td>-0.31 (0.30)</td>
<td>-0.50 (0.08)</td>
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<tr>
<td>Left amygdala</td>
<td>0.31 (0.31)</td>
<td>0.19 (0.58)</td>
<td>0.29 (0.34)</td>
<td>-0.10 (0.75)</td>
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<tr>
<td>Right anterior cingulate</td>
<td>0.56 (0.045)</td>
<td>0.12 (0.69)</td>
<td>-0.10 (0.75)</td>
<td>-0.39 (0.18)</td>
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<tr>
<td>Left anterior cingulate</td>
<td>-0.006 (0.99)</td>
<td>-0.48 (0.10)</td>
<td></td>
<td>0.27 (0.33)</td>
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<tr>
<td><strong>Early phase</strong></td>
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</tr>
<tr>
<td>Right amygdala</td>
<td>0.08 (0.79)</td>
<td>0.14 (0.64)</td>
<td>-0.36 (0.23)</td>
<td>-0.10 (0.75)</td>
</tr>
<tr>
<td>Left amygdala</td>
<td>0.17 (0.58)</td>
<td>-0.11 (0.72)</td>
<td>0.00 (0.99)</td>
<td>-0.29 (0.35)</td>
</tr>
<tr>
<td>Right anterior cingulate</td>
<td>-0.10 (0.74)</td>
<td>-0.20 (0.52)</td>
<td>-0.39 (0.18)</td>
<td>0.36 (0.23)</td>
</tr>
<tr>
<td>Left anterior cingulate</td>
<td>-0.26 (0.39)</td>
<td>0.24 (0.42)</td>
<td>0.21 (0.49)</td>
<td>0.36 (0.19)</td>
</tr>
<tr>
<td><strong>Late phase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right amygdala</td>
<td>0.27 (0.37)</td>
<td>0.35 (0.24)</td>
<td>0.36 (0.23)</td>
<td>-0.36 (0.23)</td>
</tr>
<tr>
<td>Left amygdala</td>
<td>0.22 (0.48)</td>
<td>-0.16 (0.60)</td>
<td>-0.53 (0.06)</td>
<td>-0.06 (0.85)</td>
</tr>
<tr>
<td>Right anterior cingulate</td>
<td>0.61 (0.03)</td>
<td>-0.37 (0.21)</td>
<td>0.19 (0.53)</td>
<td>-0.69 (0.009)</td>
</tr>
<tr>
<td>Left anterior cingulate</td>
<td>0.17 (0.58)</td>
<td>-0.62 (0.025)</td>
<td>-0.59 (0.035)</td>
<td>0.18 (0.52)</td>
</tr>
</tbody>
</table>

DASS = Depression and Anxiety Scale; IES = Impact of Events Scale; CAPS = Clinician Administered PTSD Scale.

Significant correlations are highlighted in bold typeface.
examining how the heightened experience of fear impacts the processing of sensory input. Our findings regarding trauma in relation to the time course of processing were consistent with the proposal that a dysregulation rather than enhancement of amygdala activity may characterize conscious fear processing following trauma. When responses were averaged across the total time course, the anterior cingulate and amygdala were positively associated in PTSD, particularly for the right hemisphere, but independent in non-traumatized subjects. This pattern is consistent with a previous study using guided imagery (Gilboa et al., 2004) and suggests that a simple model of failed top–down inhibition of amygdala activity is unlikely to account for post-trauma reactions.

When anterior cingulate and amygdala responses were examined separately for the first (Early) versus second (Late) halves of the experiment, a further breakdown in the normal pattern of functional lateralization was revealed in trauma subjects. In non-traumatized subjects, left anterior cingulate activity increased from Early to Late phases, but right anterior cingulate activity attenuated, suggesting that sustained conscious attention to fear signals may rely preferentially on left-sided responses in the medial prefrontal cortex. By contrast, traumatized subjects showed a reversal of this pattern, with attenuation of left-sided anterior cingulate responses but increasing right-sided activity over Early to Late phases. This reversal, observed within the context of generally reduced medial prefrontal function, may contribute to the inability to effectively extinguish fear signals seen in PTSD (Rothbaum and Davis, 2003).

Non-traumatized subjects showed the expected pattern of lateralized amygdala activity over the time course, with the left amygdala showing a more sustained response, while the right amygdala showed marked attenuation (Brieter et al., 1996; Wright et al., 2001; Fig. 2A). In trauma subjects, the disruption to this pattern was reflected in the prominence of exaggerated left amygdala responses during the Late phase but reduced right amygdala responses during the early phase. This pattern is consistent with the notion that trauma produces an amygdala dysregulation which varies according to the phase of conscious fear processing.

In non-traumatized subjects, there was a further lateralization in the associations between anterior cingulate and amygdala activity: a right-sided negative association for the Early half of the experiment and a left-sided positive association for the Late half. This pattern suggests that there may be a lateralized effect in the interactions between medial prefrontal and amygdala activity, consistent with animal lesion evidence that the left MPFC facilitates emotional arousal responses during restraint stress or exposure to fear-conditioned stimuli, while the right MPFC attenuates emotional arousal (Diorio et al., 1993; Frystak and Neafsey, 1994; Sullivan and Gratton, 1999). By contrast, PTSD subjects showed a dissociation of anterior cingulate and amygdala activity across Early and Late phases of the experimental time course, pointing to a concomitant breakdown in the normal pattern of medial prefrontal and amygdala modulation. This proposal accords with the extremely ventral location of amygdala-related activity in PTSD. The ventral amygdala receives the strongest feedback projections from prefrontal cortices (Amoarapanth et al., 2000), and a breakdown in these projections would disrupt the processing of sensory input.

Post-trauma reactions provide a compelling model for examining how the heightened experience of fear impacts the amygdala and medial prefrontal systems for fear processing. Our correlational findings suggested that a loss of prefrontal regulation in PTSD may be exacerbated with increasing time since trauma, greater stress symptomatology and a greater impact from traumatic life events. Amygdala function, on the other hand, was not associated with clinical profile. The association of greater trauma symptoms and impact with reduced anterior cingulate function in particular raises the possibility that overt processing of potential fear places a greater demand on an impaired prefrontal cortex. By contrast, Rauch et al. (6) reported a positive correlation between amygdala function (rather than the medial prefrontal cortex) and severity of symptoms, consistent with the view that covert processing places greater demands on impaired amygdala function.

Our observation that anterior cingulate function declined with time since trauma suggests that this prefrontal regions may be increasingly unable to cope with the demands of overt processing as the illness progresses. The negative relationships between anterior cingulate activity and trauma impact and symptomatology were apparent in the Late phase of the experiment, suggesting the demands of overt processing have their greatest impact when sustained attention is required. Alternatively, one might expect an improvement in function in at least some PTSD individuals over time, and a negative correlation could reflect more persistent medial prefrontal disturbances in sicker individuals.

Many previous neuroimaging studies, which have revealed impaired amygdala and MPFC function in PTSD across both active and implicit emotion tasks, have used chronic veteran samples. In the present study, PTSD patients were victims of assault and severe motor vehicle accidents, and the majority were within a few years of illness onset. The robustness of amygdala–prefrontal disturbances across studies, spanning a wide course of illness and response to different forms of trauma, highlights their potential to provide a trait-based functional brain marker of this disorder.

The observations from this study have significant implications for neurobiological models of the development of trauma reactions, which propose that amygdala hyperresponse coupled with lack of top–down cortical inhibition underlies these reactions. The presence of amygdala–prefrontal disturbances in response to consciously attended fear signals suggests that these models are applicable to understanding the impact of trauma on controlled states of emotion processing (when there may be a conscious attempt to minimize stress-related responses) as well as the relatively automatic and reflexive state of ‘fight or flight’. Future studies are warranted to explore the more explicit relationship between amygdala and medial prefrontal activity using methods of functional connectivity analysis, and a range of fear processing tasks. Given that the amygdala effect was small and located at the extreme ventral boundary of this region, replication of whether amygdala activity is reliably enhanced to nonconscious fear stimuli is also warranted. In addition, there is a need to further examine the role of comorbid depression and other co-existing diagnoses, as well as the effects of individual differences such as gender. Considering the robust evidence of increased psychophysiological reactivity following trauma (Pitman et al., 1987, 1990), there is also a need to delineate the relationship between elevated arousal and neural networks in these subjects, using concurrent recording of fMRI and measures of autonomic responsivity (Williams et al., 2001, 2004a,b).
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References


