Psychological Medicine (2011), **41**, 2563–2572. © Cambridge University Press 2011
doi:10.1017/S0033291711000730

ORIGINAL ARTICLE

Decreased regional cerebral blood flow in medial prefrontal cortex during trauma-unrelated stressful imagery in Vietnam veterans with post-traumatic stress disorder

A. L. Gold[1]*, L. M. Shin[1,2], S. P. Orr[1,3], M. A. Carson[4], S. L. Rauch[5], M. L. Macklin[3], N. B. Lasko[1,3], L. J. Metzger[1,3], D. D. Dougherty[1], N. M. Alpert[6], A. J. Fischman[6] and R. K. Pitman[1]

[1] *Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*
[2] *Department of Psychology, Tufts University, Medford, MA, USA*
[3] *Veterans Affairs Research Service, Manchester, NH, USA*
[4] *Department of Nursing, St. Anselm College, Manchester, NH, USA*
[5] *Department of Psychiatry, McLean Hospital, Belmont, MA and Harvard Medical School, Boston MA, USA*
[6] *Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*

Background. Neuroimaging research has demonstrated medial prefrontal cortex (mPFC) hyporesponsivity and amygdala hyperresponsivity to trauma-related or emotional stimuli in post-traumatic stress disorder (PTSD). Relatively few studies have examined brain responses to the recollection of stressful, but trauma-unrelated, personal events in PTSD. In the current study, we sought to determine whether regional cerebral blood flow (rCBF) abnormalities in mPFC and amygdala in PTSD could be observed during the recollection of trauma-unrelated stressful personal events.

Method. Participants were 35 right-handed male combat veterans (MCVs) and female nurse veterans (FNVs) who served in Vietnam: 17 (seven male, 10 female) with current military-related PTSD and 18 (nine male, nine female) with no current or lifetime PTSD. We used positron emission tomography (PET) and script-driven imagery to study rCBF during the recollection of trauma-unrelated stressful *versus* neutral and traumatic events.

Results. Voxelwise tests revealed significant between-group differences for the trauma-unrelated stressful *versus* neutral comparison in mPFC, specifically in the anterior cingulate cortex (ACC). Functional region of interest (ROI) analyses demonstrated that this interaction in mPFC represented greater rCBF decreases in the PTSD group during trauma-unrelated stressful imagery relative to neutral imagery compared to the non-PTSD group. No differential amygdala activation was observed between groups or in either group separately.

Conclusions. Veterans with PTSD, compared to those without PTSD, exhibited decreased rCBF in mPFC during mental imagery of trauma-unrelated stressful personal experiences. Functional neuroanatomical models of PTSD must account for diminished mPFC responses that extend to emotional stimuli, including stressful personal experiences that are not directly related to PTSD.

Received 23 April 2010; Revised 25 January 2011; Accepted 11 April 2011; First published online 13 May 2011

Key words: Anterior cingulate cortex, anxiety, emotion, neuroimaging, positron emission tomography, post-traumatic stress disorder, script-driven imagery.

Introduction

Functional neuroanatomical models of post-traumatic stress disorder (PTSD) have been shaped by findings of decreased activation of the medial prefrontal cortex (mPFC) and increased activation of the amygdala in response to trauma- or fear-related stimuli (for reviews see Shin *et al*. 2004, 2006; Liberzon & Martis, 2006; Etkin & Wager, 2007; Francati *et al*. 2007; Liberzon & Sripada, 2008). Medial prefrontal hyporesponsivity in PTSD has been demonstrated in various types of functional neuroimaging studies (Liberzon & Sripada, 2008), including those that involve script-driven imagery, which is a technique that uses brief autobiographical narratives of personal life events (i.e. 'scripts') as stimuli. During script-driven imagery, participants recall and visualize these events

* Address for correspondence: A. L. Gold, M.S., Department of Psychology, Yale University, PO Box 208205, New Haven, CT 06520, USA.
(Email: andrea.gold@yale.edu)

while psychophysiologic (Pitman *et al*. 1987, 1990; Orr *et al*. 1998) and/or brain responses are measured. Studies of brain responses during traumatic *versus* neutral imagery in PTSD groups, relative to trauma-exposed, non-PTSD groups, have revealed diminished activation in the mPFC, including the anterior cingulate cortex (ACC), medial frontal gyrus (MFG) and subcallosal gyrus (Bremner *et al*. 1999*a*; Shin *et al*. 1999; Lanius *et al*. 2001, 2007; Liberzon *et al*. 2003; Lindauer *et al*. 2004; Britton *et al*. 2005).

Neuroimaging studies of PTSD have also found similar patterns of brain activation in response to generic (non-personalized), trauma-related stimuli. Diminished mPFC activation has been shown in response to such stimuli as trauma-related sounds and pictures (Bremner *et al*. 1999*b*; Yang *et al*. 2004; Hou *et al*. 2007), combat-related words (Shin *et al*. 2001), and abuse-related words (Bremner *et al*. 2004). Similarly, mPFC hyporesponsivity in PTSD has been associated with trauma-unrelated emotional stimuli, such as aversive photographs (Phan *et al*. 2006) and task-irrelevant, threat-related pictures (Kim *et al*. 2008), in addition to fearful facial expressions, which have also been associated with amygdala hyperresponsivity in PTSD (Rauch *et al*. 2000; Shin *et al*. 2005; Williams *et al*. 2006). Decreased activation in ventromedial PFC during extinction recall, another trauma-unrelated condition in which extinguished conditioned stimuli were presented in the absence of the fear stimulus, has also been demonstrated in PTSD (Milad *et al*. 2009).

A question that has received relatively little attention is whether patterns of mPFC hyporesponsivity and amygdala hyperresponsivity in PTSD extend to trauma-unrelated, yet stressful, personal stimuli. An initial neuroimaging study that addressed this question used script-driven imagery and functional magnetic resonance imaging (fMRI) to examine neural responses to the recollection and imagery of both trauma-related and other emotional (i.e. sad and anxious) personal life events in a cohort of trauma-exposed civilians with *versus* without PTSD (Lanius *et al*. 2003). Those with PTSD exhibited significantly less ACC activation during both trauma-related and trauma-unrelated emotional recollections.

In the current study, we used positron emission tomography (PET) and script-driven imagery in a cohort of male and female veterans with PTSD to determine whether mPFC hyporesponsivity and amygdala hyperresponsivity could be observed during the recollection and imagery of trauma-unrelated stressful personal life events compared to neutral personal life events. The current study was part of a larger script-driven imagery PET study in which we also examined regional cerebral blood flow (rCBF) responses to trauma-related *versus* neutral scripts (Shin *et al*. 2004). In this previous study of 36 Vietnam veterans, including both male combat veterans (MCVs) and female nurse veterans (FNVs), we found decreased rCBF in MFG in the PTSD group for the traumatic *versus* neutral imagery comparison. In addition, rCBF changes in MFG were inversely correlated with rCBF changes in the amygdala. For the traumatic condition, PTSD symptom severity was inversely correlated with rCBF in MFG and positively correlated with rCBF in the right amygdala.

The present research consisted of a further analysis of the data obtained from 35 of the 36 participants in the previous study. Participants recalled and imagined trauma-unrelated stressful, neutral and traumatic personal life events in separate conditions. We compared rCBF during the trauma-unrelated stressful *versus* neutral imagery conditions, and also the trauma-unrelated stressful *versus* traumatic conditions. Participants' psychophysiologic data acquired during script-driven imagery were also analyzed to quantify arousal during the trauma-unrelated stressful imagery scans. Based on previous findings (Lanius *et al*. 2003; Shin *et al*. 2004), we predicted that the Vietnam veterans with current PTSD, compared to those without a history of PTSD, would exhibit diminished activation in medial prefrontal regions (i.e. MFG and ACC) during the trauma-unrelated stressful condition compared to the neutral condition. Given that Lanius *et al*. (2003), using fMRI, reported similar patterns of decreased anterior cingulate activation during traumatic and non-traumatic emotional recollections and imagery in PTSD, we did not necessarily expect to find significant differences between the trauma-unrelated stressful and traumatic imagery conditions.

Regarding the amygdala, heightened responsivity has been more consistently linked to the processing of external (e.g. pictures) as opposed to internal (e.g. mental imagery) stimuli in healthy populations (Lane *et al*. 1997; Damasio *et al*. 2000; Phan *et al*. 2002), whereas mPFC activation does not seem to depend on the external *versus* internal nature of affective stimuli (Reiman *et al*. 1997). Based on our focus on the neural processing of script-driven imagery and previous results in PTSD (Lanius *et al*. 2003; Shin *et al*. 2004), we did not necessarily expect to find significant between-group differences in amygdala activation in the trauma-unrelated stressful *versus* neutral imagery comparison.

Method

Participants

Presented here are previously unanalyzed data from our earlier study (Shin *et al*. 2004). One of the

https://doi.org/10.1017/S0033291711000730 Published online by Cambridge University Press

non-PTSD participants included in the original report was not included in the statistical analyses described here because she did not complete the PET scans for the trauma-unrelated stressful imagery condition.

Participants were 35 right-handed Vietnam veterans who had served in combat (MCVs) or as nurses in the combat theater (FNVs) and met DSM-IV criterion A for PTSD, as assessed with the Clinician-Administered PTSD Scale (CAPS; Weathers *et al*. 2001). Presence or absence of the categorical PTSD diagnosis was determined according to DSM-IV diagnostic criteria (APA, 1994). Seventeen participants (seven MCV and 10 FNV; age 51.71 ± 3.46 years) had current PTSD at the time of study (PTSD group), and 18 participants (nine MCV and nine FNV; age 53.22 ± 2.78 years) had never had PTSD (non-PTSD group). Level of education was not significantly different between the PTSD group and the non-PTSD group [16.67 ± 2.42 *v.* 16.91 ± 1.65 years; $t(33) = 0.35$, $p = 0.73$]. Consistent with their diagnoses, the PTSD group exhibited significantly higher CAPS total scores than the non-PTSD group [73.9 ± 20.5 *v.* 4.4 ± 5.7; $t(33) = 13.8$, $p < 0.001$]. On the depression subscale of the Symptom Checklist-90-Revised (SCL-90-R; Derogatis, 1983), the PTSD group exhibited higher scores than the non-PTSD group [1.68 ± 0.96 *v.* 0.42 ± 0.80; $t(33) = 4.2$, $p < 0.001$].

Axis I co-morbidity was assessed using the Structured Clinical Interview for DSM-IV (SCID; First *et al*. 1995). Participants showed the following current co-morbidity: in the PTSD group, major depressive disorder (MDD; $n = 8$), panic disorder ($n = 3$), social phobia ($n = 2$), specific phobia ($n = 2$), binge eating disorder ($n = 1$), and somatoform disorder ($n = 1$); in the non-PTSD group, dysthymia ($n = 2$), specific phobia ($n = 1$), and somatoform disorder ($n = 1$). All participants were without a history of head injury, neurological disorders, or other major medical conditions. No participant was taking psychotropic or cardiovascular medication at the time of study, and all urine drug screens were negative.

Each participant provided written informed consent. The Institutional Review Boards of the Massachusetts General Hospital (MGH) and the Veterans Affairs Medical Center, Manchester, NH approved this study.

Procedures

These were as described previously (Rauch *et al*. 1996; Shin *et al*. 1999, 2004).

Script-driven imagery

Prior to PET scanning, participants provided written descriptions of two neutral, two Vietnam-related traumatic, and two trauma-unrelated stressful personal events (Pitman *et al*. 1987). For the trauma-unrelated stressful condition, personal events were not related to the index traumatic event and the participants' PTSD symptoms. Examples include going through a divorce; work-related stress, such as being removed from an occupational position; and getting caught driving a family member's car with no permission and no driver's license. Unlike the traumatic events, which were assessed on the basis of whether they met criterion A for PTSD, the trauma-unrelated stressful events were not formally assessed for this criterion. Scripts describing each event in the second-person, present tense were prepared by study staff and tape-recorded in a neutral voice for playback in the PET scanner. Each participant was studied in two scans per condition. Before each scan, participants were instructed to close their eyes and imagine the described event as vividly as possible, as if they were actually participating in it. After the script was played, oxygen-15-labeled carbon dioxide ($[^{15}O]CO_2$), administered via inhalation, began. PET data acquisition occurred for 60 s, during which participants continued to recall and imagine the event while inhaling the $[^{15}O]CO_2$. The order of script conditions was counterbalanced across participants, and PET scans were separated by at least 10 min to allow for radiation decay.

Psychophysiologic responses

Heart rate (HR), skin conductance (SC) and left lateral frontalis electromyographic (EMG) data were recorded with a modular instrument system (Coulbourn Instruments, USA) in the MGH PET laboratory according to established procedures (Pitman *et al*. 1987, 1990; Orr *et al*. 1998; Shin *et al*. 2004). Psychophysiologic measurements were recorded for 30 s before (baseline), 60 s during (imagery), and 30 s after (recovery) each PET scan. The mean value during the baseline period was subtracted from the mean value during the imagery period for each scan, yielding 'response' (i.e. change) scores. HR, SC and EMG responses during both scans within a condition were averaged.

$[^{15}O]CO_2$ PET data acquisition

In brief, PET data were gathered by a 15-slice, whole-body tomograph (Scanditronix PC4096; General Electric Medical Systems, USA). The camera produced contiguous slices 6.5 mm apart, with axial resolution at 6.0-mm full-width at half-maximum (FWHM; axial field 97.5 mm). Each participant was fitted with a thermoplastic custom-molded head holder, an overlying face mask attached to a vacuum, and nasal cannulae, which delivered the $[^{15}O]CO_2$ at a

https://doi.org/10.1017/S0033291711000730 Published online by Cambridge University Press

concentration of 80 mCi/l (2960 MBq/l); the flow rate was 2 l/min. Because of the design of the mask and vacuum system, only a small fraction of the [^{15}O]CO_2 delivered was inhaled. Each participant's head was aligned in the scanner relative to the canthomeatal line, and transmission measurements were made using an orbiting pin source.

Statistical analysis

Psychophysiologic analysis

Two-factor multivariate analysis of variance (MANOVA) was performed for the three simultaneous psychophysiologic responses (HR, SC and EMG), with diagnosis (current PTSD *versus* no lifetime PTSD) as a between-subjects factor and condition (trauma-unrelated stressful *versus* neutral imagery) as a within-subjects repeated measure. Univariate ANOVAs were also conducted for the HR, SC and EMG responses separately for (1) the trauma-unrelated stressful *versus* neutral imagery comparison and (2) the trauma-unrelated stressful *versus* traumatic imagery comparison. The criterion for statistical significance was $p<0.05$, two-tailed (unless indicated otherwise).

PET analysis

To maintain methodological consistency with the original report (Shin *et al*. 2004), statistical parametric mapping analysis of the PET data was conducted with the SPM99 computer software package (Wellcome Department of Cognitive Neurology, UK; Friston *et al*. 1991). Images were motion-corrected, normalized, and smoothed using a two-dimensional (2D) Gaussian filter of 10-mm width (FWHM). At each voxel, the PET data were normalized using the global mean and fit to a linear statistical model using the method of least squares. Hypotheses were tested as contrasts in which linear compounds of the model parameters were evaluated using *t* statistics, which were then transformed into *z* scores.

We conducted separate voxelwise tests of script condition for (1) the trauma-unrelated stressful *versus* neutral imagery comparison and (2) the trauma-unrelated stressful *versus* traumatic imagery comparison within each diagnostic group. We also conducted separate voxelwise tests of the differences between diagnostic groups on the trauma-unrelated stressful *versus* neutral contrast (i.e. diagnosis × condition interaction) and the trauma-unrelated stressful *versus* traumatic comparison. Significance thresholds were set in accordance with the original report: $p<0.001$, uncorrected ($z>3.09$) for *a priori* regions of interest (ROIs; i.e. mPFC and amygdala); and a more conservative significance threshold of $p<0.00001$, uncorrected ($z>4.27$) for regions for which we had no *a priori* prediction. A random-effects model was used for PET data analysis. To replicate the methods in the Shin *et al*. (2004) report, the results from a fixed-effects model are described briefly.

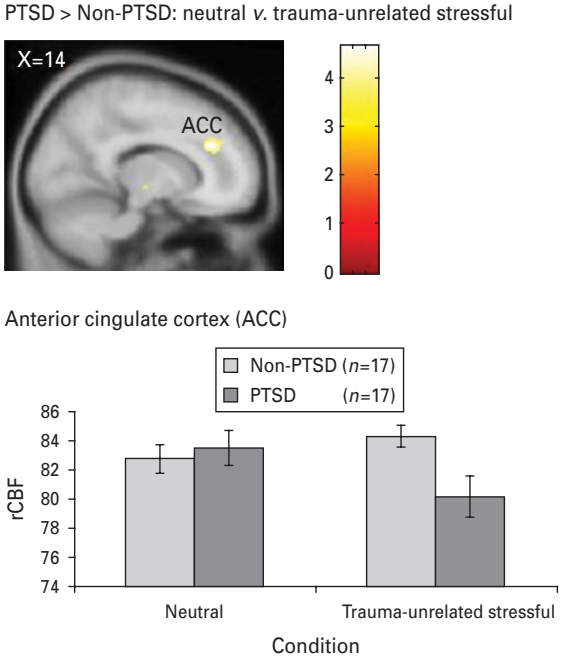

Fig. 1. (*a*) Regional cerebral blood flow (rCBF) decreases during the trauma-unrelated stressful *versus* neutral comparison in participants with post-traumatic stress disorder (PTSD; $n=17$) compared to non-PTSD participants ($n=18$). rCBF data are thresholded at $p<0.001$, shown in sagittal perspective [Montreal Neurological Institute (MNI) × coordinate = 14], and superimposed on a standard T1 template (SPM99; Wellcome Department of Cognitive Neurology, UK). (*b*) Normalized rCBF data extracted from anterior cingulate cortex (ACC; $z=4.33$; MNI coordinates +14, +34, +28) for the PTSD ($n=17$) and non-PTSD ($n=17$) groups. Error bars represent standard error of the mean (S.E.M.).

Functional ROIs were also defined around loci of greater rCBF changes in the PTSD group relative to the non-PTSD group for the trauma-unrelated stressful *versus* neutral comparison that were identified in predicted regions by the random-effects voxelwise analyses, namely the ACC, Montreal Neurological Institute (MNI) coordinates +14, +34, +28. Functional ROIs were defined as activation clusters around these peak coordinates with a significance threshold of $p<0.001$ using the MarsBaR SPM-based toolbox (http://marsbar.sourceforge.net/; Brett *et al*. 2002). From the ROI, we extracted rCBF values per condition per participant and displayed the condition means for each group in Fig. 1. Because of technical difficulties,

https://doi.org/10.1017/S0033291711000730 Published online by Cambridge University Press

Table 1. *Psychophysiologic responses to neutral and trauma-unrelated stressful imagery scripts*

Variable	PTSD group ($n=17$)	Non-PTSD group ($n=18$)
Neutral condition		
Heart rate response (beats/min)	0.32 (2.17)	0.09 (3.19)
Skin conductance response (μs)	−0.11 (0.17)	−0.17 (0.43)
Electromyograpic response (μV)	−0.13 (0.66)	0.09 (0.30)
Trauma-unrelated stressful condition		
Heart rate response (beats/min)	4.37 (6.55)	3.01 (3.72)
Skin conductance response[a] (μs)	0.27 (0.47)	−0.15 (0.43)
Electromyographic response[a] (μV)	2.32 (2.33)	0.56 (0.84)

PTSD, Post-traumatic stress disorder.
Data are given as mean (standard deviation).
[a] $p<0.05$.

we were unable to extract ROI data from one non-PTSD participant.

We examined whether the inverse functional relationship between the mPFC and amygdala previously found in the traumatic *versus* neutral imagery comparison in the PTSD group (Shin *et al*. 2004) would also be found in the trauma-unrelated stressful imagery *versus* neutral comparison. Voxelwise correlational analyses were conducted using (1) the rCBF difference scores extracted from the mPFC functional ROI and (2) the whole-brain voxelwise trauma-unrelated stressful *versus* neutral contrast maps for each participant. We also completed a voxelwise 'covariates only' analysis in the PTSD group only, to determine whether the significant correlations between PTSD symptom severity and rCBF in the amygdala and mPFC found for trauma-related stimuli in Shin *et al*. (2004) would extend to the trauma-unrelated stressful stimuli. For these replication analyses, we focused specifically on the amygdala and mPFC.

Results

Psychophysiologic responses

Trauma-unrelated stressful versus *neutral comparison*

A significant diagnosis × condition interaction was observed for the multivariate ANOVA for HR, SC and EMG responses. Overall, PTSD participants showed higher physiological responses during trauma-unrelated stressful *versus* neutral imagery, compared to non-PTSD participants [$F(1, 53)=3.0$, $p<0.05$, half-sided].

In the univariate analyses, there were significant main effects of diagnosis for SC [$F(1, 33)=7.26$, $p=0.01$] and EMG responses [$F(1, 33)=7.57$, $p=0.01$], with the PTSD group showing greater overall responses than the non-PTSD group. There were also significant main effects of condition, with greater responses during trauma-unrelated stressful *versus* neutral imagery across groups, for HR [$F(1, 33)=17.50$, $p<0.001$], SC [$F(1, 33)=4.02$, $p=0.05$] and EMG responses [$F(1, 33)=19.77$, $p<0.001$]. More importantly, there was a significant diagnosis × condition interaction for EMG response [$F(1, 33)=9.04$, $p=0.005$] and also a trend towards significance for SC response [$F(1, 33)=3.29$, $p=0.08$]. Inspection of the means indicated that EMG and SC response differences between the trauma-unrelated stressful and neutral conditions were greater in the PTSD group than in the non-PTSD group (Table 1).

Trauma-unrelated stressful versus *traumatic comparison*

There were significant main effects of diagnosis for SC [$F(1, 33)=11.88$, $p=0.002$] and EMG responses [$F(1, 33)=13.33$, $p=0.001$], with the PTSD group showing greater overall responses than the non-PTSD group. There were no significant main effects of condition or diagnosis × condition interactions for HR, SC or EMG responses.

PET results

Trauma-unrelated stressful versus *neutral comparison: within-diagnostic group results*

PTSD participants demonstrated significant decreases in frontopolar gyrus (+12, +68, 0, $z=3.74$, $k=123$ voxels) and ACC (0, +40, +24, $z=3.31$, $k=21$ voxels). The fixed-effects analysis revealed significant decreases in the PTSD group in ACC (+10, +46, +8,

https://doi.org/10.1017/S0033291711000730 Published online by Cambridge University Press

Table 2. *Voxelwise random-effects analyses: regional cerebral blood flow (rCBF) findings for trauma-unrelated stressful* versus *neutral imagery: diagnosis × condition interactions*[a]

Region	*z* score	*k*	MNI coordinates (x, y, z)
Greater decreases in the PTSD group or greater increases in the non-PTSD group			
Anterior cingulate cortex	**4.03**	**128**	**+14, +34, +28**
Frontopolar gyrus	**3.65**	**17**	**+8, +72, +14**
Left inferior frontal gyrus[b]	3.63	37	−40, +48, –4
Left orbitofrontal gyrus[b]	3.58	46	−24, +36, –14

MNI, Montreal Neurological Institute; PTSD, post-traumatic stress disorder; *k*, number of voxels reported by SPM.

[a] *A priori* regions of interest (ROIs) are shown in bold.

[b] *z* score below statistical significance threshold for unpredicted regions, but listed for completeness.

$z = 4.07$; and +12, +36, +28, $z = 4.58$). The PTSD group demonstrated no significant rCBF increases. The non-PTSD group showed no significant rCBF decreases or increases.

Trauma-unrelated stressful versus *neutral comparison: diagnosis × condition interactions*

The voxelwise tests for diagnosis × condition interaction identified a significant locus in the ACC (Table 2, Fig. 1). Data extracted from the functional ROI showed a greater rCBF decrease (i.e. deactivation, or lower rCBF in the trauma-unrelated stressful imagery condition than in the neutral imagery condition) in the PTSD group relative to the non-PTSD group [$F(1, 32) = 23.40$, $p < 0.001$; Fig. 1]. The voxelwise tests revealed no regions with greater rCBF increases (i.e. higher rCBF in the trauma-unrelated stressful imagery condition than in the neutral imagery condition) in the PTSD group, or greater rCBF increases or decreases in the non-PTSD group. Fixed-effects analyses for the diagnosis × condition interaction revealed a similar significant deactivation in ACC (+12, +36, +28, $z = 4.33$, $k = 122$ voxels), and also a significant deactivation in MFG (+8, +60, 0, $z = 3.63$, $k = 110$ voxels). To evaluate whether depressive co-morbidity contributed to these findings, we provisionally removed participants with current MDD ($n = 8$ in the PTSD group) and dysthymia ($n = 2$ in the non-PTSD group) and repeated the diagnosis × condition interaction analyses. For the random-effects analysis, the ACC deactivation remained significant (+12, +36, +28, $z = 4.16$, $k = 186$ voxels); for the fixed-effects analysis, the ACC (+10, +38, +28, $z = 4.63$, $k = 210$ voxels) and MFG (+12, +62, –2, $z = 3.34$, $k = 46$ voxels) deactivations also remained significant.

Trauma-unrelated stressful versus *traumatic comparison*

The voxelwise tests of the trauma-unrelated stressful *versus* traumatic imagery comparison yielded no statistically significant within-group rCBF changes or diagnosis × condition interactions in *a priori* ROIs.

Medial frontal/amygdala correlations

rCBF change scores derived from the statistically significant ACC deactivation in the trauma-unrelated stressful *versus* neutral contrast were not found to be correlated with rCBF changes in the amygdala within the PTSD group.

Symptom severity correlations

No significant correlations were detected between rCBF during trauma-unrelated stressful imagery and symptom severity (i.e. CAPS scores) within the PTSD group.

Discussion

The results of the present study extend previous findings of diminished recruitment of mPFC during mental imagery of traumatic events in persons with PTSD (Bremner *et al*. 1999*a*; Shin *et al*. 1999, 2004; Lanius *et al*. 2001; Liberzon *et al*. 2003; Lindauer *et al*. 2004; Britton *et al*. 2005) to include imagery of personal events that were not trauma-related but were nevertheless experienced as stressful. The PFC, which has extensive connections with other cortical and subcortical regions, plays a crucial role in cognitive processing and emotion regulation and is highly sensitive to stress exposure (Arnsten, 2009). Mild acute stress is linked to deficits in prefrontal cognitive abilities, and chronic, prolonged stress has been found to cause architectural changes such as decreased dendritic

https://doi.org/10.1017/S0033291711000730 Published online by Cambridge University Press

branching in the mPFC (Arnsten & Goldman-Rakic, 1998; Radley *et al*. 2004). Veterans with current PTSD, compared to veterans with no lifetime PTSD, exhibited rCBF decreases in the mPFC during the recollection of trauma-unrelated stressful (compared to neutral) personal life events. These findings of mPFC hyporesponsivity to emotional, non-trauma-specific symptom provocation in PTSD are in line with Lanius *et al*.'s (2003) findings using emotional, autobiographical probes in fMRI. Medial prefrontal cortical deficiency, amygdala hyperresponsivity, and hippocampal deficiency have been proposed as components of a neurocircuitry model of PTSD (Shin *et al*. 2006; Shin & Liberzon, 2010). mPFC is also implicated in fear-conditioning models of PTSD (Rauch *et al*. 2006; Milad *et al*. 2009). Within such models, mPFC abnormalities observed in PTSD may be linked to failure to extinguish responses to emotionally salient stimuli, and this failure may underlie the re-experiencing and hyperarousal symptoms of PTSD.

The results are consistent with the findings of Shin *et al*. (2004) in the same participants by showing that veterans with PTSD compared to veterans without PTSD exhibited greater relative rCBF decreases during trauma-unrelated stressful *versus* neutral recollections. This finding is consistent with a recent study showing heightened physiologic reactivity to threat in PTSD for both idiographic traumatic imagery and standard anger, panic and physical danger imagery conditions (McTeague *et al*. 2010).

The mPFC rCBF changes during trauma-unrelated stressful imagery for the PTSD group were not inversely correlated with rCBF changes in the amygdala/peri-amygdaloid cortex. It may be the case that, because the trauma-unrelated stressful life events were less severe than the traumatic events that elicited the PTSD, they elicited less variability in amygdala. We also found that mPFC changes in response to trauma-unrelated stressful imagery were not correlated with symptom severity in the PTSD group. Phan *et al*. (2006) similarly did not detect significant correlations between neural responses to aversive generic pictures in PTSD and clinical symptoms. Differential amygdala activity was not associated with PTSD in either the current study or the previous study of imagery of trauma-unrelated, emotional personal events by Lanius *et al*. (2003), and has not been consistently demonstrated during traumatic imagery (for review, see Liberzon & Sripada, 2008).

The present results are potentially confounded by Axis-I co-morbidity in the PTSD group. However, the key results remained significant even after temporarily excluding participants with co-morbid depression. In an fMRI script-driven imagery study by Lanius *et al*. (2007), a group with co-morbid PTSD and MDD showed greater activation than a PTSD-only group in ACC regions. However, in another study, reduced mPFC activity in response to fearful *versus* neutral faces was exhibited in a co-morbid PTSD-depression group compared to a PTSD-only group (Kemp *et al*. 2007). Despite their conflicting findings, these studies demonstrate the importance of controlling for depression when studying brain function in PTSD samples.

It may be tempting to conclude that because the PTSD participants showed an rCBF and psychophysiologic response pattern during recollection of trauma-unrelated stressful life events similar to the pattern they showed during imagery of the traumatic events that caused their PTSD, this pattern of responding to emotionally negative life events represents a constitutional risk factor, rather than a result of the traumatic event that caused the PTSD. Such a conclusion, however, may not be warranted. A limitation of this study is that we do not have reliable data regarding the number of trauma-unrelated stressful events that were experienced before *versus* after the index trauma. However, even in persons who experienced their most stressful, non-traumatic event before their traumatic event, brain changes caused by the latter may have altered the manner in which they recalled or responded to subsequent mental imagery of the former. Therefore, the current research design leaves unanswered whether the presently observe deficient function of medial prefrontal structures is a pre-existing risk factor for the development of PTSD after trauma exposure or an acquired sign of the disorder. Resolving this dilemma calls for prospective longitudinal research designs or twin studies (Pitman *et al*. 2006; Shin *et al*. 2006). In studies of twin pairs discordant for trauma exposure, traumatic personal stimuli are unavailable in half of the sample. However, the present results suggest that future neuroimaging studies of PTSD in trauma-discordant twin pairs may usefully include trauma-unrelated probes, such as script-driven imagery of non-traumatic but emotionally stressful life events, as reported here and by Lanius *et al*. (2003).

In conclusion, veterans with PTSD exhibited rCBF decreases in mPFC during the recollection of stressful personal events that were unrelated to their index traumatic experience. Functional neuroanatomical models of PTSD must account for dysfunctional brain responses to stress-related, personal emotional stimuli that are not trauma specific.

Acknowledgments

This study was supported by Merit Review grants from the Veterans Affairs Medical Research Service

(Drs Pitman, Carson and Orr); an Award from the National Alliance for Research on Schizophrenia and Depression, Great Neck, NY (Dr Shin); and grant MH60219 from the National Institute of Mental Health, Bethesda, MD (Dr Rauch). We are grateful to the participants. We also thank S. Barrow, A. Loring and S. Weise for technical assistance, and J. C. Britton for comments on a previous version of this manuscript.

Declaration of Interest

Dr Rauch received funded research through MGH for Brain Stimulation Therapy from Medtronics, Inc.; funded research through MGH for VNS from Cyberonics; and funded research through MGH on anxiolytic action from Cephalon. He also received honoraria from Novartis for consultation on emerging treatments; Neurogen for his participation as a consultant on emerging trends in anxiety associated with insomnia; Sepracor for his consultation on fear/conditioning/extinction; Primedia for his participation in developing a CE activity; and Medtronics, Inc for his attendance of the Advisory Board meeting on the Anatomy and Neuroscience of anxiety and depression. The financial disclosures for Dr Dougherty are as follows: *Current*: Medtronic (Research and Consulting/Honoraria – significant); Eli Lilly (Research and Consulting/Honoraria – significant); Brand Ideas (Consulting/Honoraria – modest); McNeil (Research and Consulting/Honoraria – significant); Reed Elsevier (Consulting/Honoraria – modest); Cyberonics (Research – significant); *More than 1 year ago*: Jazz Pharmaceuticals (Consulting/Honoraria – modest); Wyeth (Consulting/Honoraria –modest); Bristol–Myers Squibb (Consulting/Honoraria – modest); Northstar Neuroscience (Research and Consulting/Honoraria – significant); Forest (previous Research – significant); Trancept Pharmaceuticals (Consulting/Honoraria – modest); Cephalon (previous Research – modest); Cyberonics (Consulting/Honoraria – significant); Trancept Pharmaceuticals (Consulting/Honoraria – modest); JK Associates, Inc. (Consulting/Honoraria – modest); American Psychiatric Publishing, Inc. (Consulting/Honoraria – modest); Advocate Health and Hospitals Corporation (Consulting/Honoraria – modest); DHHS/NIH (Consulting/Honoraria – modest); Leerink Swann LLC (Consulting/Honoraria – modest); Oxford University Press (Consulting/Honoraria – modest); Professional Practice Group/Psychiatry Syracuse (Consulting/Honoraria – modest); Y&R Inc. DBA Sudler & Henessy (Consulting/Honoraria – modest).

References

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

Arnsten AFT (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience* **10**, 410–422.

Arnsten AFT, Goldman-Rakic PS (1998). Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. *Archives of General Psychiatry* **55**, 362–369.

Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS (1999*a*). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *American Journal of Psychiatry* **156**, 1787–1795.

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

Bremner JD, Vermetten E, Vythilingam M, Afzal N, Schmahl C, Elzinga B, Charney DS (2004). Neural correlates of the classic color and emotional Stroop in women with abuse-related posttraumatic stress disorder. *Biological Psychiatry* **55**, 612–620.

Brett M, Anton J-L, Valabreque R, Poline J-B (2002). Region of interest analysis using an SPM toolbox [Abstract]. *NeuroImage* **16**. (Available on CDROM.)

Britton JC, Phan KL, Taylor SF, Fig LM, Liberzon I (2005). Corticolimbic blood flow in posttraumatic stress disorder during script-driven imagery. *Biological Psychiatry* **57**, 832–840.

Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LLB, Parvizi J, Hichwa RD (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience* **3**, 1049–1056.

Derogatis LR (1983). *SCL-90-R: Administration, Scoring, and Procedures Manual – II for the Revised Version*. Clinical Psychometric Research: Townson, MD.

Etkin A, Wager TD (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry* **164**, 1476–1488.

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

Francati V, Vermetten E, Bremner JD (2007). Functional neuroimaging studies in posttraumatic stress disorder: review of current methods and findings. *Depression and Anxiety* **24**, 202–218.

Friston KJ, Frith CD, Liddle PF, Frackowiak RS (1991). Comparing functional (PET) images: the assessment of significant change. *Journal of Cerebral Blood Flow and Metabolism* **11**, 690–699.

Hou C, Liu J, Wang K, Li L, Liang M, He Z, Liu Y, Zhang Y, Li W, Jiang T (2007). Brain responses to symptom

provocation and trauma-related short-term memory recall in coal mining accident survivors with acute severe PTSD. *Brain Research* **1144**, 165–174.

Kemp AH, Felmingham K, Das P, Hughes G, Peduto AS, Bryant RA, Williams LM (2007). Influence of comorbid depression on fear in posttraumatic stress disorder: an fMRI study. *Psychiatry Research* **155**, 265–269.

Kim MJ, Chey J, Chung A, Bae S, Khang H, Ham B, Yoon SJ, Jeong DU, Lyoo IK (2008). Diminished rostral anterior cingulate activity in response to threat-related events in posttraumatic stress disorder. *Journal of Psychiatric Research* **42**, 268–277.

Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ (1997). Neuroanatomical correlates of happiness, sadness, and disgust. *American Journal of Psychiatry* **154**, 926–933.

Lanius RA, Frewen PA, Girotti M, Neufeld RW, Stevens TK, Densmore M (2007). Neural correlates of trauma script-imagery in posttraumatic stress disorder with and without comorbid major depression: a functional MRI investigation. *Psychiatry Research* **155**, 45–56.

Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld RW, Gati JS, Menon RS (2001). Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. *American Journal of Psychiatry* **158**, 1920–1922.

Lanius RA, Williamson PC, Hopper J, Densmore M, Boksman K, Gupta MA, Neufeld RWJ, Gati JS, Menon RS (2003). Recall of emotional states in posttraumatic stress disorder: an fMRI investigation. *Biological Psychiatry* **53**, 204–210.

Liberzon I, Britton JC, Phan KL (2003). Neural correlates of traumatic recall in posttraumatic stress disorder. *Stress* (*Amsterdam, Netherlands*) **6**, 151–156.

Liberzon I, Martis B (2006). Neuroimaging studies of emotional responses in PTSD. *Annals of the New York Academy of Sciences* **1071**, 87–109.

Liberzon I, Sripada CS (2008). The functional neuroanatomy of PTSD: a critical review. *Progress in Brain Research* **167**, 151–169.

Lindauer RJ, Booij J, Habraken JB, Uylings HB, Olff M, Carlier IV, den Heeten GJ, van Eck-Smit BL, Gersons BP (2004). Cerebral blood flow changes during script-driven imagery in police officers with posttraumatic stress disorder. *Biological Psychiatry* **56**, 853–861.

McTeague LM, Lang PJ, Laplante MC, Cuthbert BN, Shumen JR, Bradley MM (2010). Aversive imagery in posttraumatic stress disorder: trauma recurrence, comorbidity, and physiological reactivity. *Biological Psychiatry* **67**, 346–356.

Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, Zeidan MA, Handwerger K, Orr SP, Rauch SL (2009). Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biological Psychiatry* **66**, 1075–1082.

Orr SP, Lasko NB, Metzger LJ, Berry NJ, Ahern CE, Pitman RK (1998). Psychophysiologic assessment of women with posttraumatic stress disorder resulting from childhood sexual abuse. *Journal of Consulting and Clinical Psychology* **66**, 906–913.

Phan KL, Britton JC, Taylor SF, Fig LM, Liberzon I (2006). Corticolimbic blood flow during nontraumatic emotional processing in posttraumatic stress disorder. *Archives of General Psychiatry* **63**, 184–192.

Phan KL, Wager T, Taylor SF, Liberzon I (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage* **16**, 331–348.

Pitman RK, Gilbertson MW, Gurvits TV, May FS, Lasko NB, Metzger LJ, Shenton ME, Yehuda R, Orr SP; Harvard/VA PTSD Twin Study Investigators (2006). Clarifying the origin of biological abnormalities in PTSD through the study of identical twins discordant for combat exposure. *Annals of the New York Academy of Sciences* **1071**, 242–254.

Pitman RK, Orr SP, Forgue DF, Altman B, de Jong JB, Herz LR (1990). Psychophysiologic responses to combat imagery of Vietnam veterans with posttraumatic stress disorder versus other anxiety disorders. *Journal of Abnormal Psychology* **99**, 49–54.

Pitman RK, Orr SP, Forgue DF, de Jong JB, Claiborn JM (1987). Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. *Archives of General Psychiatry* **44**, 970–975.

Radley JJ, Sisti HM, Hao J, Rocher AB, McCall T, Hof PR, McEwen BS, Morrison JH (2004). Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience* **125**, 1–6.

Rauch SL, Shin LM, Phelps EA (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research – past, present, and future. *Biological Psychiatry* **60**, 376–382.

Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, Fischman AJ, Jenike MA, Pitman RK (1996). A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Archives of General Psychiatry* **53**, 380–387.

Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, Orr SP, Pitman RK (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biological Psychiatry* **47**, 769–776.

Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ, Friston KJ, Yun LS, Chen K (1997). Neuroanatomical correlates of externally and internally generated human emotion. *American Journal of Psychiatry* **154**, 918–925.

Shin LM, Liberzon I (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology* **35**, 169–191.

Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, Metzger LJ, Lasko NB, Orr SP, Pitman RK (1999). Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. *American Journal of Psychiatry* **156**, 575–584.

Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, Lasko NB, Peters PM, Metzger LJ, Dougherty DD, Cannistraro PA, Alpert NM, Fischman AJ, Pitman RK

(2004). Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Archives of General Psychiatry* **61**, 168–176.

Shin LM, Rauch SL, Pitman RK (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences* **1071**, 67–79.

Shin LM, Whalen PJ, Pitman RK, Bush G, Macklin ML, Lasko NB, Orr SP, McInerney SC, Rauch SL (2001). An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biological Psychiatry* **50**, 932–942.

Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B, Macklin ML, Lasko NB, Cavanagh SR, Krangel TS, Orr SP, Pitman RK, Whalen PJ, Rauch SL (2005). A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Archives of General Psychiatry* **62**, 273–281.

Weathers FW, Keane TM, Davidson JR (2001). Clinician-administered PTSD scale: a review of the first ten years of research. *Depression and Anxiety* **13**, 132–156.

Williams LM, Kemp AH, Felmingham K, Barton M, Olivieri G, Peduto A, Gordon E, Bryant RA (2006). Trauma modulates amygdala and medial prefrontal responses to consciously attended fear. *NeuroImage* **29**, 347–357.

Yang P, Wu MT, Hsu CC, Ker JH (2004). Evidence of early neurobiological alternations in adolescents with posttraumatic stress disorder: a functional MRI study. *Neuroscience Letters* **370**, 13–18.