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Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study

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Summary Patients with combat-related posttraumatic stress disorder (PTSD) show altered cognitive and affective processing and symptomatic responding following exposure to trauma reminders. Previous symptom provocation studies using brain imaging have involved Vietnam veterans. In this study neural correlates were investigated in patients with PTSD resulting from trauma in more recent war zones. ^{15}Oxygen water and positron emission tomography were used to measure regional cerebral blood flow (rCBF) in patients with war- and combat-related chronic PTSD during exposure to combat and neutral sounds. Self-reports and heart rate confirmed symptomatic responding during traumatic stimulation. The war-related condition, as compared to the neutral, increased rCBF in the right sensorimotor areas (Brodmann areas 4/6), extending into the primary sensory cortex (areas 1/2/3), and the cerebellar vermis. RCBF also increased in the right amygdala and in the periaqueductal gray matter adjacent to the pons. During provocation rCBF was lowered in the right retrosplenial cortex (areas 26/29/30 extending into area 23). Symptom provocation in PTSD promote sensorimotor, amygdaloid and midbrain activation. We conclude that perceptually induced symptom activation in PTSD is associated with an emotionally determined motor preparation and propose that subcortically initiated rather than cortically controlled memory mechanisms determine this pattern.

Key words combat · anxiety · positron emission tomography · neuroimaging · regional cerebral blood flow

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Introduction

Posttraumatic stress disorder (PTSD) is a debilitating anxiety disorder resulting from exposure to extreme trauma, characterized by intense psychological distress as well as increased physiological arousal at the presence of trauma reminders (American Psychiatric Association 1994). For example, patients with PTSD generally react with increased startle responses particularly during trauma recollection as compared to nontraumatized controls (see Pitman et al. 1999 for a review). This suggests an increased sensitivity of the fear network in the brain known to modulate the startle reaction. The amygdala is central in this network (cf. Angrilli et al. 1996; Davis et al. 1982) but neuroimaging studies of regional cerebral blood flow (rCBF) in PTSD have not invariably demonstrated an increased rCBF in the amygdala during symptom provocation. For example, Bremner and co-workers (1999a) and Shin et al. (1999) used script-driven symptom provocation but did not report amygdala activation in response to sexual abuse reminders. In contrast, Rauch et al. (1996), using combat-related imagery reported a right-sided amygdala activation. Similarly, Shin and co-workers (1997), when comparing script-driven trauma imagery with visual trauma re-

minders, observed right-sided amygdala activation in patients with PTSD resulting from war and combat experiences. Liberzon et al. (1999), who compared combat sounds to white noise in PTSD patients, also reported activation in the left amygdaloid region. But when comparing combat slides combined with combat sounds to neutral slides paired with music Bremner et al. (1999b) did not observe increased activity in the amygdala. In addition, Rauch et al. (2000) reported exaggerated amygdala blood oxygen level-dependent (BOLD) responses to masked fearful human faces in PTSD subjects and Semple et al. (2000) observed increased right amygdala rCBF in PTSD patients with comorbid cocaine and alcohol abuse during an auditory continuous performance task, suggesting a generally heightened sensitivity to aversive stimuli and demanding tasks in PTSD.

During symptom provocation trauma-related alterations have been also observed in the motor (Bremner et al. 1999b; Rauch et al. 1996) and parietal cortices particularly the retrosplenial area (Bremner et al. 1999b; Fischer et al. 1996). Increased rCBF has been demonstrated in other limbic and paralimbic regions and both decreased and increased blood flow has been observed in the temporal and prefrontal cortices after symptom provocation. Thus, affected brain territories and the direction of change are not always consistent across studies. For example, in the anterior cingulate cortex, rCBF has been reported both to increase (Liberzon et al. 1999; Rauch et al. 1996; Shin et al. 1997) and decrease as a function of trauma exposure (Bremner et al. 1999b; Shin et al. 1997, 1999). Thus, while trauma reminders seem to alter activity in regions involved in sensory and visuospatial processing, memory and emotion, the direction and consistency of alterations across studies seem modulated by factors not yet fully characterized.

Some of the inconsistencies in neurofunctional correlates of PTSD symptomatology might be attributed to study designs (i. e. script-driven vs. perceptually induced symptoms), study populations (i. e., Vietnam veterans vs. rape victims or men vs. women) and imaging techniques (i. e., PET vs. SPECT – Single Photon Emission Computed Tomography). To the best of our knowledge all brain imaging studies published with combat-related stimulation have been performed with U. S. soldiers who served in Vietnam as participants (Bremner et al. 1997, 1999b, 2000; Liberzon et al. 1999; Rauch et al. 1996; Semple et al. 1996, 2000; Shin et al. 1997; Zubieta et al. 1999). The Vietnam War ended almost three decades ago and the veterans have a high comorbidity of substance abuse and psychiatric disorders (cf. Semple et al. 2000). Thus, it might be informative to study other traumatized populations with more recent war and combat experiences. In the Western Hemisphere several wars have been fought during the past decades. These victims have more recent war and combat experiences than Vietnam veterans.

The purpose of the present study was to examine neurocorrelates of symptom provocation in patients having war- and combat-related PTSD from more recent war zones than Vietnam using ^{15}oxygen water to measure rCBF during symptom provocation with auditory trauma reminders and baseline control stimuli. In addition to a directed region of interest search for amygdala activation we also performed a pixel by pixel evaluation of the entire brain volume using traditional subtractive methodology corrected for multiple comparisons. We predicted increased activity in the amygdala (Liberzon et al. 1999; Rauch et al. 1996, 2000; Shin et al. 1997) and in the motor cortex (Bremner et al. 1999a; Liberzon et al. 1999; Rauch et al. 1996). We also hypothesized the involvement of the anterior cingulate but since both trauma-related increases (Liberzon et al. 1999; Rauch et al. 1996; Shin et al. 1997) and decreases (Bremner et al. 1999b; Shin et al. 1997, 1999) in rCBF have been reported we did not predict the direction of change. Neural activity in the posterior cingulate cortex, particularly the retrosplenial area, has been reported to increase during retrieval of emotional autobiographical memories (Maddock 1999). However, in patients with PTSD this brain area has been reported to decrease its activity during symptom provocation (Liberzon et al. 1999) and hence we predicted altered activity in the retrosplenial cortex. Both the prefrontal and orbitofrontal cortex have been observed to be dysfunctional in PTSD, and it has been argued that this could be a correlate to aberrant emotional and social behavior (cf. Bremner 1999b) possibly mediated by a decreased benzodiazepine receptor binding (Bremner et al. 2000). However, because both increased and decreased (cf. Rauch et al. 1996; Shin et al. 1999; Zubieta et al. 1999) rCBF has been observed during symptom provocation we predicted participation of, but not direction of change in, those prefrontal brain regions.

In summary, we performed a directed search for the amygdala and used a traditional subtractive approach to search for limbic, paralimbic and cortical regions associated with symptom provocation in patients with combat-related posttraumatic stress disorder of relatively recent origin.

Methods and materials

Participants

Seven male subjects (mean age 37.7 years, range 28–52) fulfilling the DSM-IV criteria for chronic severe PTSD were studied. The most recent traumatic experience for study participants occurred in 1995. All subjects participated as unpaid volunteers and were outpatients at the University Hospital's Unit of Transcultural Psychiatry in Uppsala with a history of heavy combat and some times also intense torture experiences including beating, binding, attempted drawing and sham executions. Screening included the Structured Clinical Interview (SCID) (First et al. 1995), the Clinician-Administrated PTSD Scale (CAPS) (Blake et al. 1990) and the PTSD checklist (PCL) (Blanchard et al. 1996; Weathers et al. 1993) as well as a psychophysiological assessment of heart rate and electrodermal responsivity to auditory trauma reminders (e. g., machine gun fire, explosions, helicopter sounds). This was done to identify PTSD patients who could tolerate the types of traumatic stimuli used in this study for at least two minutes. Out of 17 PTSD patients screened eight met criteria and were

asked to participate. At screening those eight displayed a mean heart rate increase of 5 beats per minutes and a 44 point increase in subjective units of distress (SUDs 0–100) when responses to combat stimulation was compared to reactions to the neutral sounds. Seven chose to participate in the positron emission tomography study. Patients could not meet criteria for previous or present alcohol or other drug abuse and were free of psychoactive medication at least two weeks prior to participation in this study. Two patients met diagnostic criteria for mild depression, one of those had chronic pain disorder and another two also met criteria for chronic pain. Three had no comorbidity. It is important to note that none of the patients had panic disorder. All patients gave informed consent and the study was approved by the Uppsala University Medical Faculty Ethical Review Board and the Uppsala University Isotope Committee. Table 1 describes subject characteristics.

Symptom provocation procedures

Subjects were scanned while listening to loudness-matched (≈90 dBA) audiotapes of neutral and trauma-related sounds, not individually tailored and binaurally presented through headphones. The traumatic war stimulation included combat related sounds (e. g., machine gun fire, explosions, helicopter sounds) and the neutral stimulation consisted of simple 1000 Hz tones. Each condition was presented twice, in a fixed ABBA order; A being neutral and B trauma related. This controls for within session order effects of neutral and traumatic sounds, since both conditions were administered in one session. The subjects had their eyes closed during scanning. After the session patients were debriefed by an experienced psychiatrist (MFe). The results presented here were obtained by contrasting the first traumatic to the first neutral condition only [traumatic – neutral]. This was done because anxiety elicited by the traumatic stimulation persisted into the second neutral condition producing an asymmetric bias. Limiting analyses to two scans only is also compatible with a random effect model, thereby increasing generalizability of results.

Subjective and somatic anxiety measures

Heart rate [HR, calculated from the Inter Beat Interval and expressed in beats per min (bpm)] and electrodermal activity expressed as nonspecific fluctuations per minute (NSF/min) were recorded during all scans in a standard form using the PSYLAB6 integrated system for psychophysiology (http://www.psylab.com). Time epochs for autonomic nervous system recordings correspond to the length of the PET summation images (i. e., 70 seconds).

Subjective ratings of anxiety were obtained immediately after each scan using the state part of the Spielberger State Trait Anxiety Inventory (STAI-S 20–80) (Spielberger et al. 1983) and Subjective Units of Distress (SUDs 0–100). In addition, subjects were given the Panic Anxiety Scale (PAS) (Wik et al. 1993), which is a visual analogue scale (VAS; 0–100) that contains all items from the DSM-IV definition of a panic attack. This was done in order to evaluate how many of the patients actually had a full-blown panic attack in the scanner. To be diagnosed with panic subjects had to rate four or more items as 51 (above the median) or higher. Because we had a priori hypothesis of increased responsivity of subjective and somatic anxiety symptoms as a function of trauma reminders the behavioral data were analyzed using directional t-tests of significance, with the StatView5 for Windows (SAS Institute, Inc).

PET procedures

PET scanning

PET scans were obtained using a GEMS PC2048–15B eight-ring brain PET scanner with a 6 mm axial and transaxial resolution, a 100 mm axial field of view and a 6.5 mm slice spacing. First, subjects were positioned in the scanner and gently fixated in a commercial headholder using fast hardening foam. Then a venous catheter was inserted and a transmission scan of 10 min duration was obtained with a rotating 68GE pin source. Thereafter, a venous catheter was inserted and a sham injection was given in the resting state before the initial scan in order to attenuate novelty effects. In each of the following emission scans subjects received an injection of 700–1300 MBq of ^{15}Oxygen (approximately 15 MBq/kg body weight) dissolved in 3–4 ml of water. CBF data were collected in fifteen 10-s frames following tracer injection. The auditory stimulation was timed to start simultaneously with the injection and to end with the termination of each scan. Finally, a scan with full axial coverage of the subject's brain was obtained, which aids in the stereotactical normalization of PET images.

Image reconstruction and anatomical standardization

Data from the first seven frames after bolus arrival to the brain in each scan were summed, thus producing a 70-s rCBF image for each scan. Images were then reconstructed from the summation data to a 128 x 128 matrix with a pixel size of 2 mm after correction for attenuation (using the transmission scan), dead time and scatter (Bergström et al. 1983), using a 15 mm Hanning filter. The scan with full axial coverage was first reconstructed to a 30-slice image set with a 20 cm coverage in axial direction using contour finding for attenuation correction (Bergström et al. 1983) and then automatically adapted to the Greitz computerized brain atlas (CBA) template (Greitz et al. 1991). Each emission scan was automatically aligned to the 20 cm scan (Andersson 1995), to bring them into the stereotactic space and to correct for head movements between scans. The CBA software allows for identification of anatomical structures and cortical cytoarchitectonic areas (Brodmann areas) as well as Talairach co-ordinates (Talairach and Tournoux 1988).

PET-data analysis

The rCBF was corrected for within and between subjects variations in global flow through linear scaling and analyzed as a one way blocked analysis of variance (ANOVA) using multiple linear regression (Friston et al. 1995). The analytic software used in the present study is an inhouse program based on the general linear model approach used in spm (Friston et al. 1994, 1995).

A *t*-map was created for the contrast and subsequently converted to a z-score map. The significance of the z-score maps was assessed locally using the spatial extent of connected clusters of voxels with a z-score above 2.6 ($p < 0.01$) corrected for multiple comparisons (Fris-

Table 1 Clinical and demographic data as well as data on the presence of DSM-IV defined panic attacks during base and provocation

Ethnicity/age	Trauma/Year	PCL-score	Panic during base/ # panic criteria fulfilled	Panic during provocation/ # panic criteria fulfilled
Turkish (Kurd) /28	Combat + torture /93	52	No/2	Yes/10
Iranian (Kurd) /52	Combat /89	55	Yes/9	Yes/8
Jordanian (Palestinian) /48	Combat + torture /72	56	No/1	Yes/8
Bosnian (Muslim) /30	Combat + prison /95	50	No/0	No/0
Eritrean /42	Combat /78	58	No/0	Yes/13
Bosnian (Muslim) /35	Combat /93	55	Yes/4	Yes/9
Bosnian (Croatian) /29	Combat /93	52	No/0	Yes/9

ton et al. 1994). The effective degrees of freedom of the PET data in the present study was 903. A directed region of interest (ROI) *a priori* search was performed using directional *t*-tests of significance and the value of the central voxel in the right and left amygdala (using the CBA-defined amygdala ROI) for each scan and subject respectively (Talairach co-ordinates x 23, y –4, z –17, and x –22, y –6, z –17 respectively). Finally, amygdala activity at these co-ordinates and subjective ratings of anxiety during the traumatic condition were correlated.

Results

Behavioral data

Heart rate (t [6]= 2.10, $p < 0.05$) and ratings of anxiety (STAI-S: t [6]= 4.09, $p < 0.01$ and SUDs: t [6]= 2.03, $p < 0.05$) but not electrodermal activity (t [6]= 1.36, n. s) were higher during exposure to auditive trauma reminders as compared to neutral stimulation (see Fig. 1).

Data from the Panic Anxiety Scale revealed that 6 of the 7 patients had a full-blown panic attack in the scanner during traumatic stimulation. However, also during the initial neutral stimulation two subjects panicked as defined by the DSM-IV criteria (1994) and assessed using the PAS (Wik et al. 1993) (Table 1).

PET data

Clusters of voxels with significant alterations in rCBF as a function of combat vs. neutral sound exposure are presented in Table 2 and Fig. 2. Regional CBF increased in the right sensorimotor cortex (Brodmann areas 4/6), extending into the primary sensory cortex (BA 1/2/3), the cerebellar vermis and the periaqueductal gray matter (PAG) adjacent to the pons. In addition, rCBF decreased in the right retrosplenial cortex (BA 26/29/30 extending into area 23) as a function of combat sound provocation.

RCBF was significantly higher in the right (t [6]= 2.05, $p < 0.05$) (see Fig. 3), but not the left amygdala ROI (t [6] < 1, n. s) during traumatic as compared to neutral sound stimulation.

RCBF in the right amygdala correlated significantly with self-reported anxiety (SUDs: $r_{xy} = 0.79$, $p < 0.05$ and

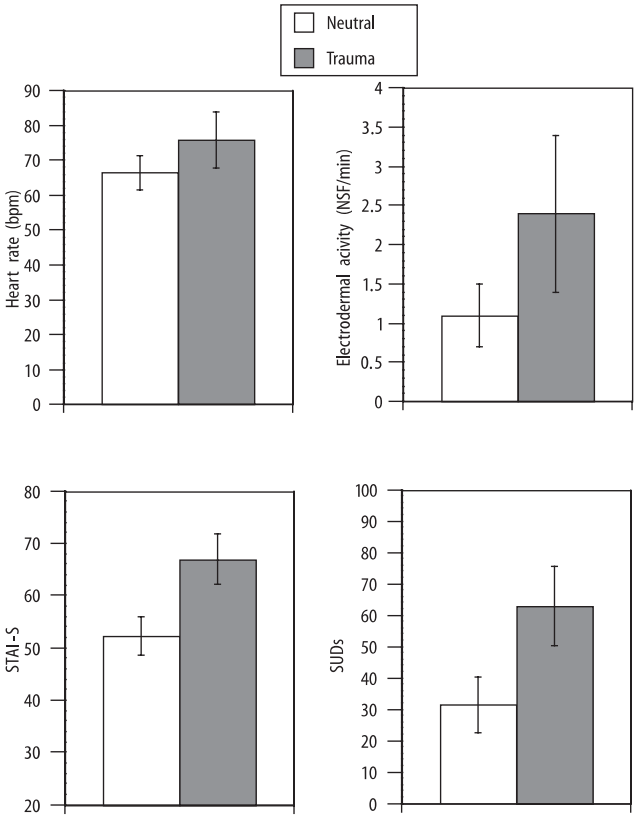

Fig. 1 Mean (± S. D) subjective and somatic anxiety measures during exposure to auditory war and combat reminders in patients with posttraumatic stress disorder. Heart rate in beats per minute (bpm), electrodermal activity (nonspecific fluctuations per minute; NSF/min) and scores from the state part of Spielberger's Trait-State Anxiety Inventory (STAI-S 20–80) as well as subjective units of distress (SUDs 0–100) during traumatic and neutral stimulation in a group of patients with posttraumatic stress disorder.

Table 2 Regional CBF differences between symptom provocation and neutral base, brain and Brodmann areas included in each cluster, Talairach coordinates for maximum pixel z-value within each cluster, and cluster p-values for significant increases and decreases in rCBF

Brain areas	Brodmann areas	x	y	z	Maximum pixel z-value	Cluster *p*-value
Regions with increased rCBF						
Cluster 1						
Premotor cortex (R)	6	28	–7	33	3.70	0.02
Primary motor cortex (R)	4	36	–21	37	3.50	
Primary sensory cortex (R)	1, 2, 3	35	–25	37	3.46	
Cluster 2						
Cerebellar vermis		–2	–45	–10	4.05	0.009
Periaqueductal gray matter		0	–40	–14	2.85	
Regions with decreased rCBF						
Cluster 1						
Retrosplenial cortex (R)	26, 29, 30	8	–39	22	4.35	0.004
Posterior cingulate cortex (R)	23	9	–52	21	3.32	

R right hemisphere; *L* left hemisphere. The coordinates in millimeters correspond to the stereotactic atlas of Talairach & Tournoux. The x and z coordinates indicate the distance from a line between the anterior and posterior commissures, while the y coordinate indicates the position relative to the anterior commisure. Significance of clusters has been evaluated based on the spatial extent of suprathreshold clusters with z-scores at 2.58 or above

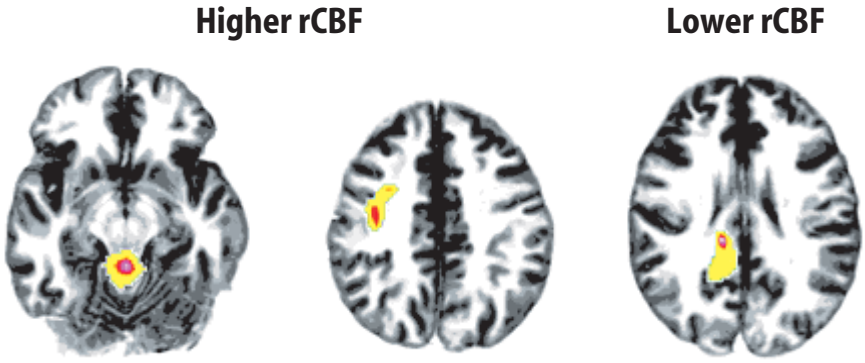

Fig. 2 Significantly higher and lower relative regional cerebral blood flow (rCBF) to auditory war and combat reminders than neutral stimulation in a group of patients with posttraumatic stress disorder displayed on transversal PET images, superimposed on magnetic reference images, adapted to a standardized brain. Activity was higher in the cerebellar vermis (left image) and in the right supplementary motor cortex (middle image) and lower in the right retrosplenial cortex (right image). The right hemisphere is to the left in the figure.

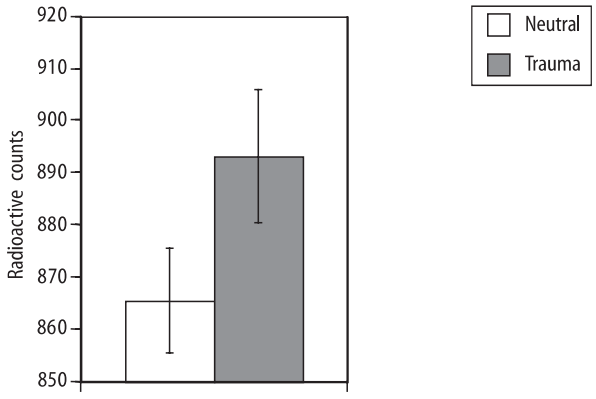

Fig. 3 Enhanced right amygdala activity (± S. D) during exposure to auditory war and combat reminders in a group of patients with posttraumatic stress disorder. Relative regional cerebral blood flow (rCBF) was higher in the right amygdala (Talairach co-ordinates 23, –4, –17) during exposure to traumatic than neutral stimulation in a group of patients with posttraumatic stress disorder.

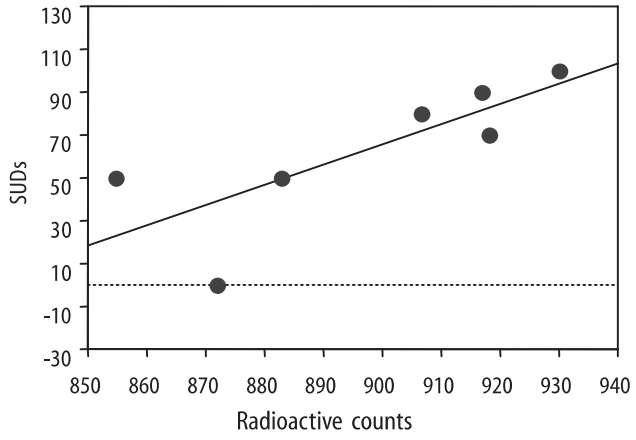

Fig. 4 Correlations between subjective units of distress (SUDs) and relative regional cerebral blood flow (rCBF) expressed in radioactive counts in the right amygdala during exposure to auditory war and combat reminders in a group of patients with posttraumatic stress disorder.

STAI-S: $r_{xy} = 0.78$, $p < 0.05$) (see Fig. 4). RCBF in the left amygdala was not correlated with SUDs ($r_{xy} = -0.19$, n. s) or STAI-S scores ($r_{xy} = -0.38$, n. s).

Discussion

Patients with war- and combat-related PTSD showed a significant difference in rCBF responses to auditory trauma reminders as compared to neutral sounds. The pattern was characterized by increased neural activity in sensorimotor areas, the cerebellar vermis as well as in the right amygdala and the periaqueductal gray matter. Thus, our data support that the increased startle reaction generally observed in individuals with posttraumatic stress disorder (for recent reviews cf. Newport and Nemeroff 2000; Pitman et al. 1999) could be mediated by an increased activity of the fear network involving the amygdala as well as the periacqueductal gray matter and adjacent cortical territory (Angrilli et al. 1996; Davis et al. 1982). These areas have close structural and functional interconnections, since the central nucleus of the amygdala projects to the periacqueductal gray matter (cf. Swanson and Petrovich 1998) and both structures seem involved in the fight/flight reaction (Bandler and Shipley 1994; Behbehani 1995; Gray 1987) as well as fear conditioning in animals (cf. LeDoux 1996) and humans (Büchel et al. 1998; Furmark et al. 1997; LaBar et al. 1998). Because PTSD has been conceptualized as resulting from fear conditioning, our data are consistent with such a view. It has been demonstrated (Amorapanth et al. 2000) that the lateral nucleus in the amygdala links the conditioned and unconditioned stimulus to support the acquisition of memory experiences. Thus, it is worth noticing that amygdaloid neural activity in the lateral nucleus (Mai et al. 1997) was strongly related to experience of fear supporting subcortically initiated memory recollection.

We recently observed (Pissiota et al. 2002) that the acoustic startle reflex activates a pons area close to the periacqueductal gray matter corresponding to the anatomical location of the nucleus reticularis pontis caudalis (Talairach co-ordinates x = 8, y = –36, z = –18). This nucleus is essential for startle activity and lesions in it abolish the startle reflex (Davis et al. 1982; Lee et al. 1996). The center of gravity of the activated midbrain area in the present study (Talairach co-ordinates x = 0, y = –40, z = –14) is in close proximity of the previously described human startle area (Pissiota et al. 2002) and might be associated with startle activation also in PTSD

patients. The simultaneous activation of the amygdala might mediate the trauma-determined startle potentiation previously observed in PTSD patients (cf. Pitman et al. 1999) because lesions to the right amygdala impair emotional modulation of the human startle reaction (Angrilli et al. 1996).

The areas with an increased blood flow also included the cerebellum, the primary (BA 4), and supplementary motor cortices (BA 6) as well as the primary somatosensory cortex (BA 1, 2, 3). The increased neural activity in the primary and secondary motor cortex, the cerebellum, the amygdala and the periaqueductal gray matter might represent a functional network supporting emotionally determined motor preparation. The activated midbrain area adjacent to the pons may support aspects of the acoustic startle reflex in particular (Pissiota et al. 2002), while the supplementary motor cortex may carry motor aspects of the memory necessary for the fight or flight preparation (Squire and Zola-Morgan 1991). Because recent PET studies have established a role for the cerebellum not only in locomotion but also in attention and memory (Cabeza and Nyberg 2000), it is possible that emotionally driven attentional processes associated with motor activity are represented in the cerebellum (see also Damasio et al. 2000).

Lowered rCBF in the retrosplenial area of the posterior cingulate as a function of panic induced by auditory trauma reminders is in line with observations made by Liberzon et al. (1999) using a combat sound provocation paradigm. Studies on emotional activation in healthy individuals, including traumatized bank officials without a PTSD diagnose (Fischer et al. 1996), generally result in increased activity in the retrosplenial cortex (Maddock 1999). Thus, decreased activity in this area as a function of perceptually induced symptomatic responding in traumatized subjects with a PTSD diagnose, but not in those without (Fischer et al. 1996), may suggest that normal and pathological emotions affect similar cortical territory but in an opposite manner. Contrary to this hypothesis are findings of increased rCBF in posterior cingulate cortex in subjects with PTSD as compared to controls (Bremner et al. 1999a).

Because it has been argued that traumatic memories are organized in an affective perceptually linked system with limited verbal representation (van der Kolk and Fisler 1995), it is tempting to speculate that traumatic memories may be encoded and/or retrieved differentially than memories for non-emotional events. Amygdala activity during encoding has been associated with better memory recall for emotional but not non-emotional memory in several studies (see Calder et al. 2001 for a review). Thus, it might be argued that the fear network centered around the amygdala is essential for forming emotionally relevant memories and that recollection of such traumatic memories reactivate the fear network or conversely that fear network activation facilitates memory retrieval.

The nature of symptom provocation, whether it is conceptual using scripts or perceptual using external trauma reminders, might influence the pattern of responding. While both script-driven imagery (Rauch et al. 1996; Shin et al. 1997) and perceptually elicited symptomatic responding often seem to result in amygdala activation (Liberzon et al. 1999; the present study) only perceptually induced anxiety seem to relate to lower activity in the retrosplenial cortex (Liberzon et al. 1999; the present study). From the present literature it is not clear whether different laterality of amygdala activation in PTSD represent something theoretically meaningful or reflect the use of different methods. It is not clear why we observed right amygdala activation while Liberzon et al. (1999), who also induced PTSD symptomatology through perceptual means, reported left amygdala involvement. It might reflect the higher prevalence of depression and/or prior substance abuse in the patients Liberzon and coworkers (1999) studied or simply that we studied a more recently traumatized group. However, there are some hypotheses that perceptually induced anxiety is relatively more right lateralized. For example, Rauch and co-workers (2000) recently demonstrated right amygdala activation to masked fearful faces supporting facilitation of an unconscious pre-attentive implicit processing capacity for general threat stimuli in PTSD patients. In contrast, Dolan et al. (2000) reported that conscious retrieval of episodic emotional memories activated the left amygdala. Also other data support left lateralized amygdala activation to cognitive representations of fear (Phelps et al. 2001) while perceptually induced fear and anxiety seem right lateralized (Tillfors et al. 2001).

The nature of PTSD implies the presence of fear conditioning. Data from the present study support that notion because similar brain regions are activated both by posttraumatic stress and the conditioned fear response. Thus, the pattern of amygdala activation observed in the present study may be shaped by fear conditioning. For example, experimental studies on fear conditioning in humans have supported a role for the amygdala in the retrieval of conditioned fear responses (Büchel et al. 1998; Furmark et al. 1997; LaBar et al. 1998). Also, most fear conditioning studies report modulation of neural activity in motor areas including the cerebellum (Fischer et al. 2000; Morris et al. 1999), the red nucleus (Büchel et al. 1998), the supplementary motor area (Büchel et al. 1998) and the premotor cortex (Büchel et al. 1998; Fischer et al. 2000; LaBar et al. 1998). Also, the periaqueductal gray matter is involved in human fear conditioning (Fischer et al. 2000; Fredrikson et al. 1995). Thus the pattern of brain activation is similar in studies on experimental fear-conditioning and symptom provocation in PTSD.

Our initial predictions were only partly supported by the results and activity was altered in a more restricted neural network than predicted. Also, we did not predict activation in the periaqueductal gray matter, but because it formed part of a significant cluster we have interpreted the finding. However, our failure to observe activation or deactivation in the predicted areas should

not be confused with the proof of absence of activation or deactivation because this study involved only a limited group of patients. In addition, the fact that two patients had a panic attack at rest, probably reflecting anticipation, acts to reduce rCBF differences between traumatic stimulation and resting baseline. Because none of the subjects had comorbid panic disorder, the panic attacks during symptom provocation most likely represent flashbacks. Another drawback of the study includes the lack of a control group meaning that we can not determine the specificity of the observed rCBF pattern. However, studies with control groups have indicated that, for example, motor cortex activation and amygdala activation seem to be specific and not nonspecific signs of PTSD (Bremner et al. 1999a, 1999b; Shin et al. 1997) Finally, we can not determine any order of causality and exaggerated amygdala responses may reflect vulnerability to develop PTSD (cf. Orr et al. 2000) or evolve in the aftermath of the traumatic event.

In conclusion, this study suggests that symptom provocation also in relatively recently traumatized individuals with chronic PTSD alter neural activity in brain territories involved in sensory processing, memory, emotion, attention as well as motor control. These findings increase the generalizability of results from previous neuroimaging studies of posttraumatic stress.

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