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ORIGINAL ARTICLE

Effects of psychotherapy on regional cerebral blood flow during trauma imagery in patients with post-traumatic stress disorder: a randomized clinical trial

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Background. Functional brain-imaging studies in post-traumatic stress disorder (PTSD) have suggested functional alterations in temporal and prefrontal cortical regions. Effects of psychotherapy on these brain regions have not yet been examined.

Method. Twenty civilian PTSD out-patients and 15 traumatized control subjects were assessed at baseline using psychometric ratings. Cerebral blood flow was measured using trauma script-driven imagery during ^{99m}technetium hexamethyl-propylene-amine-oxime single-photon emission computed tomography scanning. All 20 out-patients were randomly assigned to treatment or wait-list conditions. Treatment was brief eclectic psychotherapy (BEP) in 16 weekly individual sessions.

Results. At baseline, greater activation was found in the right insula and right superior/middle frontal gyrus in the PTSD group than in the control group. PTSD patients treated with BEP significantly improved on all PTSD symptom clusters compared to those on the waiting list. After effective psychotherapy, lower activation was measured in the right middle frontal gyrus, compared to the PTSD patients on the waiting list. Treatment effects on PTSD symptoms correlated positively with activation in the left superior temporal gyrus, and superior/middle frontal gyrus.

Conclusions. BEP induced clinical recovery in PTSD patients, and appeared to modulate the functioning of specific PTSD-related sites in the prefrontal cortical regions.

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Key words: Brain imaging, post-traumatic stress disorder, psychotherapy, randomized clinical trial.

Introduction

Patients with post-traumatic stress disorder (PTSD) have intrusive memories of a traumatic event, avoid stimuli associated with the event, and live in a constant state of heightened arousal (APA, 1994). They feel as if the traumatic event keeps repeating itself.

Based on reported neuroanatomical models and functional brain-imaging studies in PTSD, both temporal and prefrontal cortical brain regions are thought to be involved in the pathophysiology of PTSD (Pitman *et al*. 2001; Bremner, 2002; Hull, 2002). First, temporal structures are presumed to play a critical role in the acquisition and extinction of conditioned fear and in the expression of associated autonomic arousal (Davis & Whalen, 2001; Pitman *et al*. 2001). Trauma-related stimuli may cause hyperactivity in

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these regions, especially in the amygdala and insula (Pitman *et al*. 2001). Second, the medial prefrontal cortex modulates responses to fear through inhibitory connections with the amygdalar, peripheral sympathetic and peripheral hormonal responses to stress (LeDoux, 2000; Devinsky *et al*. 1995). In PTSD, dysfunction of the medial prefrontal cortex has been postulated as a reason why fear responses are not sufficiently suppressed (Bremner, 2002). A reciprocal relationship has been found between medial prefrontal cortex function and amygdala function in PTSD (Shin *et al*. 2004). However, Gilboa and colleagues (2004) found only little evidence for failure of inhibition of cingulate or subcallosal cortex over the amygdala. Third, the dorsolateral prefrontal cortex may play an important role in the neural network, subserving the working memory that is responsible for the short-term storage, manipulation and utilization of mental representations (Smith & Jonides, 1999; LeDoux, 2000; Levy & Goldman-Rakic, 2000). The controlling of unwanted memories has been associated with increased dorsolateral prefrontal activation in a non-patient group (Anderson *et al*. 2004). In episodic memory studies activations in the right mid-dorsolateral prefrontal cortex were often reported, but such activations were absent in autobiographical memory studies (Gilboa, 2004). In PTSD, abnormal patterns of frontal and parietal activity were found during working-memory tasks (Shaw *et al*. 2002; Clark *et al*. 2003; Weber *et al*. 2005). Thus, dysfunction of the dorsolateral prefrontal cortex in PTSD might be hypothesized to explain at least some of the pathophysiology of PTSD.

The first hypothesis of our study concerns the pathophysiology of PTSD. Taking all the above information into consideration, we hypothesize that trauma-related stimuli in PTSD result in higher activation of the temporal structures and the dorsolateral prefrontal cortex, and lower activation of the medial prefrontal cortex.

Little is known as yet about changes in brain function after psychotherapy. Two studies have examined brain function changes in patients with major depression when treated with interpersonal psychotherapy (Brody *et al*. 2001) or cognitive–behavioural therapy (CBT; Goldapple *et al*. 2004). Similar studies were performed on patients with social phobia (Furmark *et al*. 2002) or obsessive–compulsive disorder (Baxter *et al*. 1992) treated with CBT. For PTSD, only two single-case reports (Levin *et al*. 1999; Fernandez *et al*. 2001) and one research report (Seedat *et al*. 2004) have been published, describing the effects of eye-movement desensitization and reprocessing (EMDR; Levin *et al*. 1999) and selective serotonin reuptake inhibitors (SSRIs; Fernandez *et al*. 2001; Seedat *et al*. 2004) using single-photon emission computed tomography (SPECT; Levin *et al*. 1999; Seedat *et al*. 2004) and photon emission tomography (PET; Fernandez *et al*. 2001). The effects of SSRI treatment in PTSD patients were found in the temporal lobe structures (Fernandez *et al*. 2001; Seedat *et al*. 2004) and the effects of EMDR were found in the prefrontal cortical regions (Levin *et al*. 1999). Hence, the second hypothesis of this study postulates that effective psychotherapy influences regional blood flow in the prefrontal cortical regions.

To test the first hypothesis, we obtained psychometric ratings and measured regional cerebral blood flow (rCBF) changes induced by trauma script-driven imagery in patients with PTSD, comparing these to data obtained in traumatized control subjects. To test the second hypothesis, we used a randomized controlled study design to evaluate the effects of psychotherapy, comparing the baseline psychometric ratings and rCBF values with measurements repeated 4 months after baseline. For the intervening period, patients were randomly assigned to treatment or waitlist conditions. To the best of our knowledge, this is the first randomized controlled trial that assesses the effects of psychotherapy in PTSD in terms of psychometric ratings and changes in rCBF measured by ^{99m}technetium hexamethyl-propylene-amine-oxime ([^{99m}Tc]HMPAO) SPECT.

Subjects and method

Subjects and clinical assessment

Twenty-four civilian Dutch out-patients with DSM IV-defined PTSD (APA, 1994) and 15 control subjects were included. The control subjects had experienced one or more traumatic events in their lives without ever developing PTSD. The patients with PTSD were referred by general practitioners and the academic out-patient clinic of the Department of Psychiatry. The traumatized control subjects were police officers who responded to an advertisement in police papers. The same control group was also part of another study in which rCBF changes were measured in police officers with PTSD (Lindauer *et al*. 2004). The study was approved by the Institutional Medical Ethics Committee of the Academic Medical Centre, Amsterdam. Before entering the study, all participants received study information and gave signed informed consent.

The diagnosis of PTSD was based on the DSM-IV criteria and was obtained using the Structured Interview for Posttraumatic Stress Disorder (SI-PTSD; Davidson *et al*. 1989). For the Dutch version of the SI-PTSD, we found a Cronbach's α of 0.93 and a Cohen's κ of 0.88, which can be considered acceptable (Carlier *et al*. 1998). In addition to assessing PTSD, the SI-PTSD

elicits information about the presence or absence of the three symptom clusters (re-experiencing, avoidance, and hyperarousal) and scales their severity in both a current and a lifetime perspective. The Structured Clinical Interview for DSM-IV (SCID; Spitzer *et al*. 1996) was administered to assess comorbidity, and provided an indication of the severity of major depression, expressed as the intensity of major depression (mild to severe). The List of Traumatic Events is a semi-structured interview inquiring about any traumatic experiences participants have had (Carlier *et al*. 2000). They were asked whether they had experienced such events at any time in the past. An additional question about the perceived adverse effects of each specific event was rated on a 5-point scale (1 = 'no effects'; 5 = 'very strong effects'). The described events satisfy the stressor A(1) criterion for a diagnosis of PTSD. Sixteen of the 24 PTSD subjects had developed PTSD after exposure to interpersonal violence and eight had developed PTSD after exposure to accidents or disasters. Ten of the 15 control subjects had exposure to interpersonal violence and five had exposure to accidents. The traumatic events experienced by the control subjects were events that had had the greatest impact on their lives. The traumatic events of both groups satisfy the stressor A(1) criterion with a rating score of >3 on adverse effects. The Dissociation Experiences Scale (DES) assessed the severity of any dissociative symptoms (Bernstein & Putnam, 1986). The DES was also translated into Dutch (Carlier *et al*. 1996). A background questionnaire was also performed to collect demographic information.

Exclusion criteria for both groups included major lifetime or current medical or psychiatric diagnoses: organic mental disorder, head trauma with loss of consciousness, mental retardation, seizures, neurological disorders, schizophrenia, psychotic disorders, bipolar disorder, moderate and severe major depression, panic disorder, phobia, obsessive–compulsive disorder and dissociative disorders. Persons with lifetime or current alcohol or drug abuse or dependence, use of psychiatric medication, and left-handedness were also excluded.

Procedure

After inclusion, all participants visited the Department of Psychiatry to create a standardized script lasting 30–35 seconds on the traumatic event they had personally experienced. The scripts made conformed to the literature (Pitman *et al*. 1987). For the out-patients with PTSD, the traumatic event that was thought to have triggered the PTSD was chosen as the trauma script, and for the traumatized control subjects without PTSD it was the traumatic event that had made the heaviest impact on their lives. For about one third of both the patients and the control subjects, the trauma scripts involved accidents or disasters; the other two thirds of the scripts involved interpersonal violence. The scripts were audiotaped and were played back immediately prior to the SPECT scanning. Patients with PTSD showed a significantly stronger physiological response to the trauma script than the traumatized control subjects (an increase of $\geqslant 5$ heartbeats per minute [$t(-2.91) = 22.28$, $p = 0.008$]; Lindauer *et al*. 2005). After the baseline scanning, the patients with PTSD were randomly assigned to either the psychotherapy or the wait-list condition. A colleague who had performed no assessments used a computer program to randomly assign patients to each condition in a block design. Four patients dropped out after randomization due to emigration, illness in family, work obligations or technical problems in SPECT scanning. The wait-list patients were told they would receive treatment in 4 months' time. After the 4-month treatment period, all patients (both the treated and the wait-listed groups) were assessed a second time with SI-PTSD, List of Traumatic Events and SCID. A second SPECT scan, again using script-driven imagery to measure changes in rCBF, was obtained within 1 week from this clinical assessment. The clinical raters were blind to the scan data.

Psychotherapy

Details of our psychotherapy have been published previously (Gersons *et al*. 2000) and are reviewed here only briefly. The treatment comprised brief eclectic psychotherapy (BEP) in 16 weekly individual sessions of 45–60 min each. The course of BEP was administered as prescribed by the manual (Gersons *et al*. 2004). BEP incorporates several intervention techniques also used in the effective CBT protocols, such as psychoeducation, imaginal exposure, writing tasks, and cognitive restructuring. BEP also includes a focal psychodynamic approach as well as the use of a farewell ritual at the end of the treatment. The psychotherapists were clinically experienced psychiatry residents who were supervised by two senior psychiatrists (I.V. and B.P.R.G.). One of them had developed the treatment (B.P.R.G.). All sessions were audiotaped. A special rating system covering the five elements of BEP described above was developed to analyse treatment integrity. Five audiotapes of each treatment were scored. Treatment integrity was approximately 75%, with $\kappa > 0.81$, indicating good adherence to the protocol.

SPECT method

rCBF imaging was measured by [^{99m}Tc]HMPAO SPECT. Image acquisition was performed with a

brain-dedicated SPECT camera (Strichman 810X; Strichman Medical Equipment Inc., Medfield, MA, USA).

Before the scanning, all participants were prepared in a quiet environment. For a few minutes before the script was played, they lay still and relaxed, closed their eyes, and breathed through their mouth to minimize extracranial blood flow to the temporal muscles that might arise from teeth clenching (Drevets *et al*. 1992). While listening to the script and for about 10 min thereafter, they were asked to imagine the traumatic event as vividly as possible, as though they were actually re-experiencing it. Twenty seconds after the start of the script, they received an intravenous injection of approximately 275 MBq of the radiotracer [^{99m}Tc]HMPAO. At the end of the 10 min following the script, they completed a State-Trait Anxiety Inventory-State (STAI-State) questionnaire to score their state of anxiety while imagining the event described by the script (Spielberger *et al*. 1970). The SPECT imaging then commenced, 15 min after the injection. It recorded the subjects' condition at the time the radiotracer was injected, immediately after they had heard the script. Subjects were placed in the scanner with their head held in a holder to minimize motion, and positioned with the canthomeatal line parallel to an external laser light. Each acquisition consisted of approximately 20 slices at 3 min per slice from the cerebellum up to the vertex of the skull (interslice distance 5 mm). The energy window was set at 124–158 keV. Other acquisition parameters were set and the images reconstructed as described previously (Booij *et al*. 1997).

Statistical and image analyses

Statistical analyses were performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA). Demographic characteristics and clinical variables were analysed with an independent *t* test (two-tailed) for the continuous variables and a χ^2 test for the categorical ones. Treatment effects on clinical variables were analysed by multivariate analyses of covariance (MANCOVA), using the baseline measurements of the PTSD scores as covariates. The significance level was set at 5% ($\alpha = 0.05$).

Statistical parametric mapping [SPM99 (www.fil.ion.ucl.ac.uk/spm)] was implemented in Matlab 6.1 (Mathworks, Sherborn, MA, USA) (Friston *et al*. 1995) to analyse the SPECT data. SPM located areas of significant change in mean voxel intensity between groups of scans in different brain states and/or from different groups of participants. SPM (Friston *et al*. 1995, 1996) performed automated co-registration of all brain images into standard stereotaxic space as defined by Talairach & Tournoux (1988), followed by voxelwise statistical analysis based on the theory of Gaussian fields. Montreal Neurological Institute (MNI) coordinates were used, which differ from Talairach coordinates in their origin: MNI (0, 0, 0) is Talairach (−0.8, −3.3, −0.4) (Brett *et al*. 2002; Chau & McIntosh, 2005). No smoothing filter was applied because of limited resolution. Statistical parametric maps of the *t* statistics, SPM (*t*), were then calculated and transformed to the unit normal distribution, SPM (*z*). Only clusters of connected voxels above an extent threshold of 20 voxels (voxel threshold probability of 0.01, z score = 2.33, two-tailed, uncorrected) were tested for significance using special extent statistics (Worsley *et al*. 1992; Friston *et al*. 1996). The voxel size (x, y, z) was 3.175 mm × 3.175 mm × 5 mm.

Four general steps were performed in the SPM analyses: (1) comparison of the baseline SPECT scans of the PTSD and the traumatized control groups; (2) comparison of the baseline SPECT scans of the treatment and wait-list groups; (3) interaction effects between time (pre *v*. post) and group (treatment *v*. wait-list); and (4) bivariate correlations between PTSD symptoms and rCBF. The first three steps were analysed within one linear statistical model. The last step was analysed by a regression analysis.

Results

Baseline comparisons across groups

Demographic and clinical variables for the entire PTSD group compared to traumatized controls

Demographic characteristics of patients ($n = 20$) and drop-outs ($n = 4$) showed no significant differences. In the statistical analyses, the net sample size was 20 for the PTSD group and 15 for the traumatized control group. No statistical differences were found between the PTSD and the traumatized control groups on the demographic characteristics of age, gender or education (Table 1).

The PTSD total scores, the re-experiencing, avoidance and hyperarousal scores, the STAI-State scores, and the DES scores were significantly higher in the PTSD group than in the traumatized control group. Three of the 20 patients with PTSD also had a current secondary (onset after PTSD) first-episode mild major depression, but no significant difference was found between the two groups in the occurrence of mild major depressions (Table 1).

SPECT data for the entire PTSD group compared to traumatized controls

rCBF was significantly greater in the right insula ($p = 0.001$) and the right superior/middle frontal gyrus

Table 1. *Demographic and clinical variables of the PTSD and traumatized control group*

	PTSD ($n=20$)		Controls ($n=15$)		Analysis	
Variables	Mean	S.D.	Mean	S.D.	df	p
Age (years)	39.7	8.5	37.2	9.9	−0.78	0.44
Education (years)	12.9	2.9	11.3	2.5	−1.71	0.10
PTSD total score	11.3	1.8	0.1	0.5	−26.21	<0.001
Re-experiencing score	3.7	0.9	0.0	0.0	−19.14	<0.001
Avoidance score	3.8	1.0	0.0	0.0	−17.86	<0.001
Hyperarousal score	3.8	0.9	0.1	0.5	−15.25	<0.001
STAI-State score	60.4	12.7	32.3	10.1	−7.03	<0.001
DES score	6.1	4.5	2.5	1.4	23.58	0.003
Duration of PTSD symptoms in years	4.6	7.5				
Sex, *n* (%)					0.35	0.73
Male	10 (50)		9 (60)			
Female	10 (50)		6 (40)			
MDD diagnosis, *n* (%)	3 (15)		0 (0)		2.46	0.24

PTSD, Post-traumatic stress disorder; STAI-State, State-Trait Anxiety Inventory-State; DES, Dissociation Experiences Scale; MDD, major depressive disorder.

Table 2. *Statistical parametric mapping analyses showing (1) significant rCBF differences ($p<0.01$, unadjusted) between the PTSD and traumatized control group; (2) significant effects between time (pre v. post) and group (treatment v. wait-list) interactions; (3) correlations between PTSD symptoms and rCBF*

Condition	MNI coordinates (x, y, z)	R/L	Affected lobe	Affected gyrus	*z* score
(1) PTSD *versus* controls					
Increases in PTSD	36, 25, 15	R	Sublobar	Insula	3.68
	25, 63, 11	R	Frontal lobe	Superior/middle frontal gyrus	3.50
(2) Time × group interactions					
Decreases in treatment group	40, 37, 27	R	Frontal lobe	Middle frontal gyrus	4.44
Decreases in wait-list group	25, 9, −22	R	Limbic lobe	Uncus	4.48
(3) Correlations with PTSD symptoms	−45, −24, 2	L	Temporal lobe	Superior temporal gyrus	3.1
Positive	25, 51, 7	R	Frontal lobe	Superior/middle frontal gyrus	3.36
	−24, 38, 36	L	Frontal lobe	Superior/middle frontal gyrus	3.52

rCBF, Regional cerebral blood flow; PTSD, Post-traumatic stress disorder; MNI, Montreal Neurological Institute; R, right; L, left; PTSD, post-traumatic stress disorder.

($p=0.004$) in the PTSD group compared to the traumatized control group (Table 2).

Treatment effects

Demographic and clinical variables for the PTSD treatment group compared to the PTSD wait-list group

Statistical analysis of the treatment effects was carried out on the net PTSD sample ($n=20$), comparing the treatment subgroup ($n=10$) to the wait-list subgroup ($n=10$); six male and four female patients received treatment, and four male and six female patients were on the wait-list. No significant differences existed between the treatment and wait-list groups on any of the demographic characteristics and clinical variables recorded at baseline. One patient who could not remain on the waiting list received treatment and was transferred to the treatment subgroup.

No significant baseline differences were found between the treatment and wait-list groups on any clinical variables. After treatment, the patients in the treatment group were significantly improved on all

Table 3. *Treatment effects on clinical variables*

	PTSD treatment ($n=10$)		PTSD wait-list ($n=10$)		Test of treatment effects[a]	
	Mean	S.D.	Mean	S.D.	df	p
PTSD total score					19.27	<0.001
Pre-treatment	11.7	1.6	11.1	1.7		
Post-treatment	3.7	4.9	10.1	4.0		
Re-experiencing score					14.66	0.001
Pre-treatment	3.7	0.7	3.9	0.9		
Post-treatment	1.1	1.4	3.6	1.4		
Avoidance score					9.00	0.008
Pre-treatment	4.0	1.2	3.6	0.7		
Post-treatment	1.4	2.1	3.5	1.6		
Hyperarousal score					9.48	0.007
Pre-treatment	4.0	0.8	3.6	1.0		
Post-treatment	1.2	1.8	3.0	1.3		
STAI-State score					3.57	0.076
Pre-treatment	58.0	12.6	62.8	13.0		
Post-treatment	45.7	17.1	60.5	13.5		
PTSD diagnosis, n (%)					7.20	0.023
Pre-treatment	10	100	10	100		
Post-treatment	2	20	8	80		
MDD diagnosis, n (%)					2.25	0.33
Pre-treatment	3	30	0	0		
Post-treatment	1	10	1	10		

PTSD, Post-traumatic stress disorder; STAI-State, State-Trait Anxiety Inventory-State; MDD, major depressive disorder.
[a] Interaction effects between time (pre *v.* post) and group (treatment *v.* wait-list).

PTSD clinical variables in comparison to the wait-list group. There was a trend towards improvement on the STAI-State scores, but not for the prevalence of mild major depression (Table 3).

SPECT data for the PTSD treatment group compared to the PTSD wait-list group

No significant differences in rCBF were found between the treatment and wait-list groups at baseline. Time (pre *v.* post) x group (treatment *v.* wait-list) interaction effects were found with significantly lower rCBF in the right middle frontal gyrus ($p=0.004$; Table 2 and Fig. 1) and right uncus ($p=0.009$; Table 2).

The effect of treatment on the PTSD total score correlated positively with the rCBF changes in the left superior temporal gyrus ($p=0.016$), and the middle frontal gyrus (left, $p<0.001$; right, $p=0.02$) (Table 2 and Fig. 2).

Discussion

Our study consisted of two parts, addressing two hypotheses. The first concerned the pathophysiology of PTSD. In support of our hypothesis, we found greater activation in the insula and the right dorsolateral prefrontal cortex (superior/middle frontal gyrus) in the PTSD subjects. Comparable results have been reported by others (Pitman *et al*. 2001; Anderson *et al*. 2004). However, we found no differences in activation in the medial prefrontal cortex. Some studies have reported decreased activation of the medial frontal gyrus in PTSD (Bremner *et al*. 1999; Shin *et al*. 1999, 2001; Semple *et al*. 2000), while others have found no activation (Lucey *et al*. 1997; Rauch *et al*. 1997, 2000; Mirzaei *et al*. 2001; Osuch *et al*. 2001; Pissiota *et al*. 2003) or even increased activation (Rauch *et al*. 1996; Liberzon *et al*. 1997; Shin *et al*. 1997; Zubieta *et al*. 1999). Thus, decreased activation of the medial frontal gyrus has not been a consistent finding in PTSD. For example, in our previous study we found decreased activation of the medial frontal gyrus in police officers with PTSD which was not found in the present study (Lindauer *et al*. 2004). This difference could be explained by the different patient populations and/or the different scripts that were used for provocation. Other possible sources of this inconsistency include co-morbidity study design (e.g.

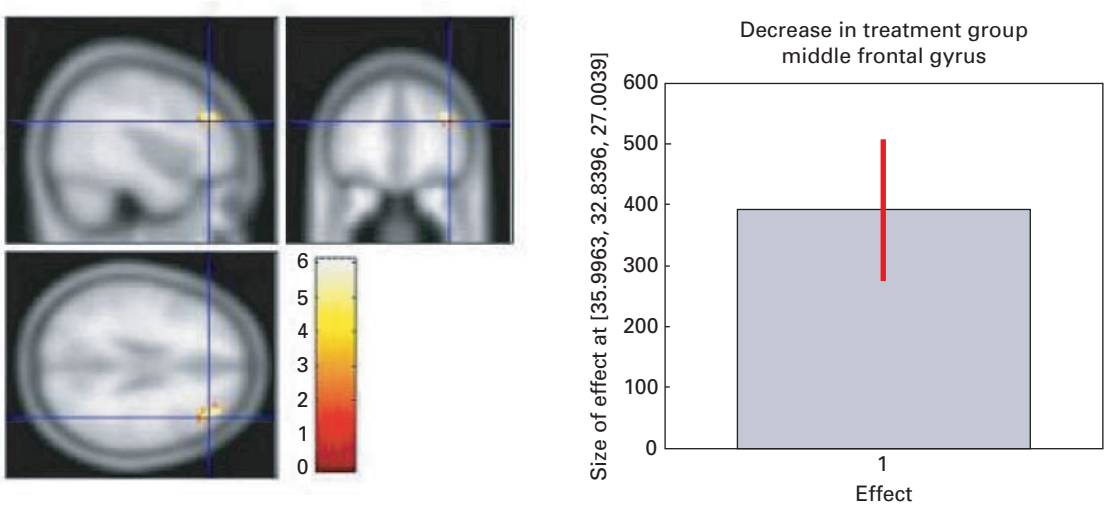

Fig. 1. Treatment effects: lower regional cerebral blood flow (rCBF) in the right middle frontal gyrus (x, y, z = 40, 37, 27).

healthy as opposed to traumatized controls), and/or imaging methods [SPECT *versus* PET or functional magnetic resonance imaging (fMRI)]. Future studies should examine the contribution of each item separately.

Up to now, functional brain-imaging studies in PTSD have recruited mostly victims of war (Semple *et al*. 1993; Bremner *et al*. 1997; Shin *et al*. 1997, 2001; Liberzon *et al*. 1999; Zubieta *et al*. 1999; Rauch *et al*. 2000; Pissiota *et al*. 2003) or sexual abuse (Bremner *et al*. 1999, 2003; Shin *et al*. 1999; Lanius *et al*. 2001, 2002, 2003; Osuch *et al*. 2001). Most subjects have had long-term PTSD and have shown relatively high rates of comorbidity (Semple *et al*. 1993, 1996, 2000; Rauch *et al*. 1996, 2000; Bremner *et al*. 1997, 1999, 2003; Liberzon *et al*. 1997; Shin *et al*. 1997, 1999, 2001; Lanius *et al*. 2001, 2003; Osuch *et al*. 2001) or use of psychiatric medication (Sachinvala *et al*. 2000; Osuch *et al*. 2001), which are potentially confounding factors. Some studies did not include a traumatized, non-PTSD control group (Rauch *et al*. 1996, 1997; Semple *et al*. 1996; Bremner *et al*. 1997, 2003; Lucey *et al*. 1997; Shin *et al*. 1997; Mirzaei *et al*. 2001; Osuch *et al*. 2001; Pissiota *et al*. 2003). The present study assessed a different PTSD patient population, which had experienced a wider spectrum of traumas and which exhibited relevant comorbidity to a minimum; and the patient data were compared to that of a traumatized control group. We would therefore argue that the present results are specific to PTSD.

The second part of the study assessed the effects of psychotherapy on rCBF during trauma imagery in PTSD, using a randomized controlled study design. In our group of patients, BEP significantly reduced all PTSD symptom clusters and led to clinical recovery. This is a finding consistent with our previous study demonstrating the effectiveness of this treatment (Gersons *et al*. 2000). In the present study, after using trauma imagery to revive traumatic memories during SPECT scanning, we similarly found greater activation in the dorsolateral prefrontal cortex in PTSD subjects *versus* controls at baseline, significantly decreased activation after psychotherapy, and positive correlations between PTSD symptoms and the activation in this brain region.

Only two case reports and one research report have similarly used functional brain imaging to describe treatment effects in PTSD. Levin and colleagues described a male patient who received EMDR therapy. They assessed rCBF changes using script-driven imagery and [^{99m}Tc]HMPAO SPECT. Blood flow in the anterior cingulate gyrus and left frontal lobe increased after successful treatment (Levin *et al*. 1999). Fernandez and colleagues described a male patient with PTSD who received a SSRI. On a post-treatment PET scan, they found that activation had returned to normal in the insula, the prefrontal and inferior frontal cortices, the cerebellum, the precuneus and the supplementary motor cortex (Fernandez *et al*. 2001). Our study confirmed the finding of decreased blood flow in the dorsolateral prefrontal cortex after treatment. But comparability with these two case studies is limited, in that each dealt with only one male subject, while our study included both genders and a larger number of cases. Seedat and colleagues, on the other hand, described 11 adult patients with PTSD who received the SSRI citalopram. They assessed rCBF changes after 8 weeks of treatment using [^{99m}Tc]HMPAO SPECT. Treatment resulted in significant deactivation in the left medial temporal cortex and a

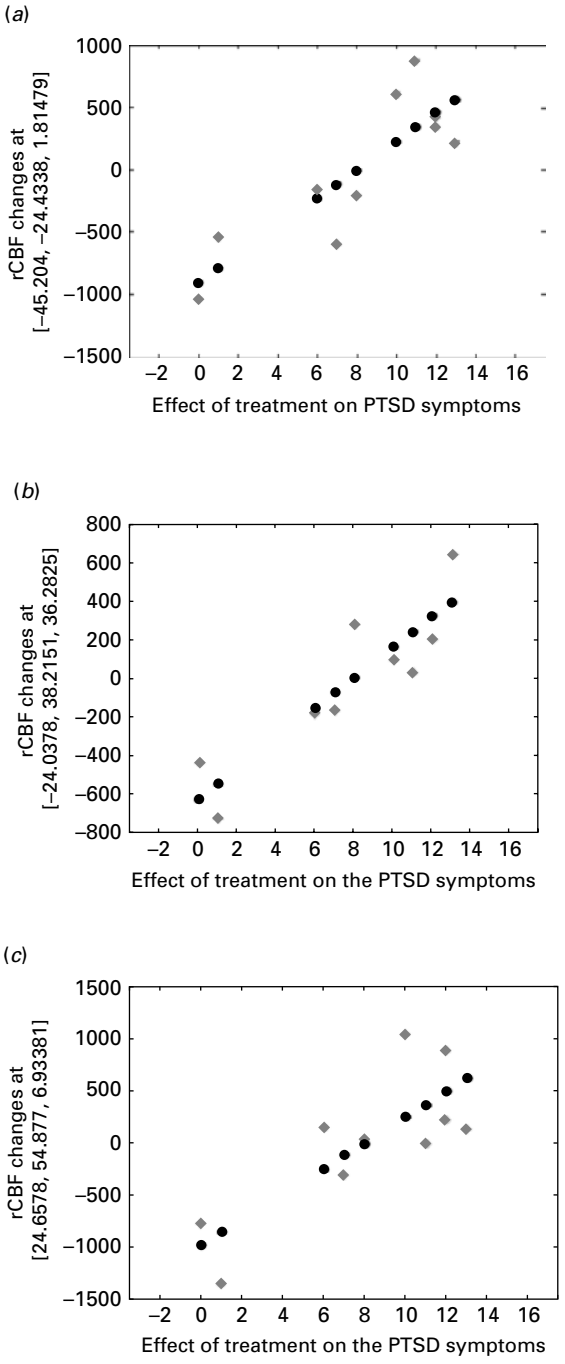

Fig. 2. The effect of treatment on the PTSD symptoms correlated positively with the regional cerebral blood flow (rCBF) changes in (*a*) the left superior temporal gyrus (x, y, z = −45, −24, 2), (*b*) left superior/middle frontal gyrus (x, y, z = −24, 38, 36), and (*c*) right superior/middle frontal gyrus (x, y, z = 25, 51, 7).

correlation between PTSD symptoms decrease and activation of the medial prefrontal cortex was found (Seedat *et al*. 2004). They did not compare the PTSD group with a non-PTSD group at baseline and also did not include a control group. Therefore, it is not possible to draw any conclusions about whether their results are due specifically to effective treatment.

How to integrate the biological findings into the theoretical model of psychotherapy for PTSD? Brewin (2001) has argued that psychotherapy for PTSD generally involves two elements: detailed and repeated exposure to traumatic information, and modification of maladaptive beliefs about events, behaviours and/or symptoms. Although traumatic memories are believed to last forever (LeDoux, 2000), psychotherapy may help to integrate them and control the symptoms they cause. Bouton (2002) has similarly argued that extinction is not based on an erasure of original information, but reflects new learning. An aim of therapy might be to connect as many shared cues as possible in order to generalize the inhibition of fear to other contexts that resemble the safe situation. BEP uses imaginal exposure to have the patient relive the traumatic event in vivid detail, with a sharp focus on the most painful moment of the event, but now in a safe context in which the patient can learn from a new experience (Gersons *et al*. 2000, 2004). LeDoux has decribed the possible effects of different kind of treatments on the brain. SSRIs can go straight to the amygdala and other brain regions, and CBT is likely to require the working-memory functions of the prefrontal cortex (LeDoux, 2002).

Key brain structures in the pathophysiology of PTSD are found in the prefrontal cortex. It has various parts (medial, orbital, dorsolateral) and functions. One critical function of the dorsolateral prefrontal cortex is in the neural network subserving working memory (Smith & Jonides, 1999; LeDoux, 2000; Levy & Goldman-Rakic, 2000; Anderson *et al*. 2004). Anderson and colleagues (2004) have found greater activation in this region to be associated with increased control of unwanted memories. A hypothesis is that the dorsolateral prefrontal cortex controls memory intrusions and mediate their influence on the temporal lobe (LeDoux, 2002). We speculate that after effective psychotherapy, the working memory is no longer occupied by traumatic memories as appears in decreased activation in the dorsolateral prefrontal cortex. Indeed, some PTSD studies found abnormal patterns of frontal and parietal activity during working-memory tasks (Shaw *et al*. 2002; Clark *et al*. 2003; Weber *et al*. 2005).

Several limitations of the present study should be noted. The sample size for the treatment and wait-list groups were relatively small. However, exclusion of severe co-morbidity in the present study resulted in findings that are specific to PTSD. BEP was compared with a wait-list condition. Therefore, we could not conclude that the effects after the treatment

period were specific for BEP. Changes in the dorsolateral prefrontal cortex in the psychotherapy-treated patients are due to a reduction of PTSD symptoms and might not be a direct effect of treatment. We could only use the trauma script in our pre-/post-treatment design and also no follow-up assessment was possible, because more than two SPECT scans in one year would have exceeded the maximum radiation burden allowed. Another limitation concerns SPM analysis, which describes the results in five stages from large to small brain areas: cerebrum, lobe, gyrus, grey and white matter and Brodmann areas. Given the limited spatial resolution of SPECT imaging and the wide variability in brain anatomy between individuals, the method is inadequate for describing our results in terms of Brodmann areas (Amunts *et al*. 1999; Uylings *et al*. 2005). A further limitation was that, since SPECT cannot perform absolute measurements of rCBF, we normalized the values to the mean global activity. This prevented us from detecting changes in global cerebral blood flow, as have been reported in the literature to accompany acute anxiety. A limitation is that rCBF measurements with SPECT cannot be linearly related to PET measurements, therefore comparison is limited. A final limitation is that SPECT studies could measure only one emotional state per scan, and the PET and fMRI studies could compare different emotional states within one scanning procedure. However, the overall trauma script-driven imagery is recognized for its relevance in PTSD research.

The strenghts of the study are that we have recruited patients with PTSD who had a very low comorbidity rate and a short duration of symptoms, which significantly reduces confounds in the assessment of the imaging results. The use of a traumatized control group without PTSD is important to control for the effects of traumatization. Furthermore, to the best of our knowledge, this study represents the first report to describe changes in rCBF after effective psychotherapy in patients with PTSD in a randomized controlled trial, going well beyond a few case reports.

In future studies, it will be important to examine the effects of treatment in different PTSD populations and to apply functional brain-imaging techniques that do not suffer from the radiation limitations of SPECT. Follow-up assessments are needed to investigate the neurobiological mechanisms that underlie long-term effects and relapse. Using functional brain imaging to assess state and trait effects in different kinds of treatment, including psychotherapy and medication, may further explain the underlying neurobiological mechanisms that influence the effectiveness of these treatments in PTSD.

We believe the study has helped to further unravel the underlying neurobiological mechanisms of psychotherapy in PTSD.

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Declaration of Interest

None.

References

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

Amunts K, Schleicher A, Burgel U, Mohlberg H, Uylings HBM, Zilles K (1999). Broca's region revisited: cytoarchitecture and intersubject variability. *Journal of Comparative Neurology* **412**, 319–341.

Anderson MC, Ochsner KN, Kuhl B, Cooper J, Robertson E, Gabrieli SW, Glover GH, Gabrieli JDE (2004). Neural systems underlying the suppression of unwanted memories. *Science* **303**, 232–235.

Baxter Jr. LR, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, Alazraki A, Selin CE, Gerng HK, Munford P (1992). Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Archives of General Psychiatry* **49**, 681–689.

Bernstein EM, Putman FW (1986). Development, reliability and validity of a dissociation scale. *Journal of Nervous and Mental Disorders* **174**, 727–735.

Booij J, Tissingh G, Boer GJ, Speelman JD, Stoof JC, Janssen AGM, Wolters ECH, Van Royen EA (1997). [^{123}I]FP-CIT SPECT shows a pronounced decline of striatal labelling in early and advanced Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* **62**, 133–140.

Bouton ME (2002). Context, ambiguity, and unlearning: sources of relapse after behavioural extinction. *Biological Psychiatry* **52**, 976–986.

Bremner JD (2002). Neuroimaging of childhood trauma. *Seminars in Clinical Neuropsychiatry* **7**, 104–112.

Bremner JD, Innis RB, Ng CK, Staib LH, Salomon RM, Bronen RA, Duncan J, Southwick SM, Krystal JH, Rich D, Zubal G, Dey H, Soufer R, Charney DS (1997). Positron emission tomography measurement of cerebral metabolic correlates of yohimbine administration in combat-related posttraumatic stress disorder. *Archives of General Psychiatry* **54**, 246–254.

Bremner JD, Narayan M, Staib L, Southwick SM, McGlashan T, Charney DS (1999). 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, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, Khan S, Vaccarino LV, Soufer R, Garg PK, Ng CK, Staib LH, Duncan JS, Charney DS (2003). MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *American Journal of Psychiatry* **160**, 924–932.

Brett M, Johnsrude IS, Owen AM (2002). The problem of functional localization in the human brain. *Nature Reviews Neuroscience* **3**, 243–249.

Brewin CR (2001). A cognitive neuroscience account of posttraumatic stress disorder and its treatment. *Behaviour Research and Therapy* **39**, 373–393.

Brody AL, Saxena S, Stoessel P, Gillies LA, Fairbanks LA, Alborzian S, Phelps ME, Huang SC, Wu HM, Ho MK, Au SC, Maidment K, Baxter Jr. LR (2001). Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. *Archives of General Psychiatry* **58**, 631–640.

Carlier IVE, Fouwels AJ, Lamberts RD, Gersons BPR (1996). Posttraumatic stress disorder and dissociation in traumatized police officers. *American Journal of Psychiatry* **153**, 1325–1328.

Carlier IVE, Lamberts RD, Van Uchelen JJ, Gersons BPR (1998). Clinical utility of a brief diagnostic test for PTSD. *Psychosomatic Medicine* **60**, 42–47.

Carlier IVE, Voerman BE, Gersons BPR (2000). Intrusive traumatic recollections and comorbid posttraumatic stress disorder in depressed patients. *Psychosomatic Medicine* **62**, 26–32.

Chau W, McIntosh AR (2005). The Talairach coordinate of a point in the MNI space: how to interpret it. *Neuroimage* **25**, 408–416.

Clark CR, McFarlane AC, Morris P, Weber DL, Sonkkilla C, Shaw M, Marcina J, Tochon-Danguy HJ, Egan GF (2003). Cerebral function in posttraumatic stress disorder during verbal working memory updating: a positron emission tomography study. *Biological Psychiatry* **53**, 474–481.

Davis M, Whalen PJ (2001). The amygdala: vigilance and emotion. *Molecular Psychiatry* **6**, 13–34.

Davidson JRT, Smith R, Kudler HS (1989). Validity and reliability of the DSM-III criteria for posttraumatic stress disorder: experience with a structured interview. *Journal of Nervous and Mental Disorders* **177**, 336–341.

Devinsky O, Morrell MJ, Vogt BA (1995). Contributions of anterior cingulate cortex to behaviour. *Brain* **118**, 279–306.

Drevets WC, Videen TQ, MacLeod AK, Haller JW, Raichle ME (1992). PET images of blood flow changes during anxiety: Correction [Letter]. *Science* **256**, 1696.

Fernandez M, Pissiota A, Frans O, Von Knorring L, Fischer H, Fredrikson M (2001). Brain function in a patient with torture related post-traumatic stress disorder before and after fluoxetine treatment: a positron emission tomography provocation study. *Neuroscience Letters* **297**, 101–104.

Friston KJ, Holmes AP, Poline JB, Price CJ, Frith CD (1996). Detecting activation in PET and fMRI: levels of inference and power. *Neuroimage* **4**, 223–235.

Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frakowiak RSJ (1995). Statistical parametric maps in functional imaging: general approach. *Human Brain Mapping* **2**, 189–210.

Furmark T, Tillfors M, Martlinsdottin I, Fischer H, Pissiota A, Langstrom B, Fredrikson M (2002). Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioural therapy. *Archives of General Psychiatry* **59**, 425–433.

Gersons BPR, Carlier IVE, Lamberts RD, Van der Kolk BA (2000). Randomized clinical trial of brief eclectic psychotherapy for police officers with posttraumatic stress disorder. *Journal of Traumatic Stress* **13**, 333–347.

Gersons BPR, Carlier IVE, Olff M (2004). *Manual Brief Eclectic Psychotherapy* (*BEP*) *for Posttraumatic Stress Disorder*. Academic Medical Centre: Amsterdam.

Gilboa A (2004). Autobiographical and episodic memory – one and the same? Evidence from prefrontal activation in neuroimaging studies. *Neuropsychologia* **42**, 1336–1349.

Gilboa A, Shalev AY, Laor L, Lester H, Louzoun Y, Chisin R, Bonne O (2004). Functional connectivity of the prefrontal cortex and the amygdala in posttraumatic stress disorder. *Biological Psychiatry* **55**, 263–272.

Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, Mayberg H (2004). Modulation of cortical-limbic pathways in major depression. *Archives of General Psychiatry* **61**, 34–41.

Hull AM (2002). Neuroimaging findings in post-traumatic stress disorder. *British Journal of Psychiatry* **181**, 102–110.

Lanius RA, Williamson PC, Boksman K, Densmore M, Gupta M, Neufeld RWJ, Gati JS, Menon RS (2002). Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. *Biological Psychiatry* **52**, 305–311.

Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld RWJ, 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.

LeDoux JE (2000). Emotion circuits in the brain. *Annual Review of Neuroscience* **23**, 155–184.

LeDoux JE (2002). *Synaptic Self*. Viking Penguin: New York.

Levin P, Lazrove S, Van der Kolk BA (1999). What psychological testing and neuroimaging tell us about the treatment of posttraumatic stress disorder by eye movement desensitization and reprocessing. *Journal of Anxiety Disorders* **13**, 159–172.

Levy R, Goldman-Rakic PC (2000). Segregation of working memory functions within the dorsolateral prefrontal cortex. *Experimental Brain Research* **133**, 23–32.

Liberzon I, Taylor SF, Amdur R, Jung TD, Chamberlain KR, Minoshima S, Koeppe RA, Fig LM (1999). Brain activation in PTSD in response to trauma-related stimuli. *Biological Psychiatry* **45**, 817–826.

Liberzon I, Taylor SF, Fig LM, Koeppe RA (1997). Alteration of corticothalamic perfusion ratios during a PTSD flashback. *Depression and Anxiety* **4**, 146–150.

Lindauer RJL, Booij J, Habraken JBA, Uylings HBM, Olff M, Carlier IVE, Den Heeten G, Van Eck-Smit BLF, Gersons BPR (2004). Cerebral blood flow changes during script-driven imagery in police officers with posttraumatic stress disorder. *Biological Psychiatry* **56**, 853–861.

Lindauer RJL, van Meijel EPM, Jalink M, Olff M, Carlier IVE, Gersons BPR (2005). Heart rate responsivity to script-driven imagery in posttraumatic stress disorder: specificity of response and effects of psychotherapy. *Psychosomatic Medicine* **68**, 33–40.

Lucey JV, Costa DC, Adshead G, Deahl M, Busatto G, Gacinovic S, Travis M, Pilowsky L, Ell PJ, Marks IM, Kerwin RW (1997). Brain blood flow in anxiety disorders: OCD, panic disorder with agoraphobia, and post-traumatic stress disorder on 99mTcHMPAO single photon emission tomography (SPET). *British Journal of Psychiatry* **171**, 346–350.

Mirzaei S, Knoll P, Keck A, Preitler B, Gurtierrez E, Umek H, Kohn H, Pechenstorfer M (2001). Regional cerebral blood flow in patients suffering from post-traumatic stress disorder. *Neuropsychobiology* **43**, 260–264.

Osuch EA, Benson B, Geraci M, Podell D, Herscovitch P, McCann UD, Post RM (2001). Regional cerebral blood flow correlated with flashback intensity in patients with posttraumatic stress disorder. *Biological Psychiatry* **50**, 246–253.

Pissiota A, Frans O, Fernandez M, Von Knorring L, Fischer H, Fredrikson M (2003). Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. *European Archives of Psychiatry and Clinical Neuroscience* **252**, 68–75.

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.

Pitman RK, Shin LM, Rauch SL (2001). Investigating the pathogenesis of posttraumatic stress disorder with neuroimaging. *Journal of Clinical Psychiatry* **62** (Suppl. 17), 47–54.

Rauch SL, Savage CR, Alpert NM, Fischman AJ, Jenike MA (1997). The functional neuroanatomy of anxiety: a study of three disorders using positron emission tomography and symptom provocation. *Biological Psychiatry* **42**, 446–452.

Rauch SL, Van der Kolk BA, Fisher 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.

Sachinvala N, Kling A, Suffin S, Lake R, Cohen M (2000). Increased regional cerebral perfusion by 99mTc hexamethyl propylene amine oxime single photon emission computed tomography in post-traumatic stress disorder. *Military Medicine* **165**, 473–479.

Seedat S, Warwick J, Van Heerden B, Hugo C, Zungu-Dirwayi N, Van Kradenbrug J, Stein DJ (2004). Single photon emission computed tomography in posttraumatic stress disorder before and after treatment with a selective serotonine reuptake inhibitor. *Journal of Affective Disorders* **80**, 45–53.

Semple WE, Goyer PF, McCormick R (2000). Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. *Psychiatry* **63**, 65–74.

Semple WE, Goyer PF, McCormick R, Compton-Toth B, Morris E, Donovan B, Muswick G, Nelson D, Garnett ML, Sharhoff J, Leisure G, Miraldi F, Schulz SC (1996). Attentional and regional cerebral blood flow in posttraumatic stress disorder patients with substance abuse histories. *Psychiatric Research: Neuroimaging* **67**, 17–28.

Semple WE, Goyer PF, McCormick R, Morris E, Compton-Toth B, Muswick G, Nelson D, Donovan B, Leisure G, Berridge M, Miraldi F, Schulz SC (1993). Preliminary report: brain blood flow using PET in patients with posttraumatic stress disorder and substance abuse histories. *Biological Psychiatry* **34**, 115–118.

Shaw ME, Strother SC, McFarlane AC, Morris P, Anderson J, Clark CR, Egan GF (2002). Abnormal functional connectivity in posttraumatic stress disorder. *Neuroimage* **15**, 661–674.

Shin LM Kosslyn SM McNally RJ, Alpert NM, Thompson WL, Rauch SL, Macklin ML, Pitman RK (1997). Visual imagery and perception in posttraumatic stress disorder. *Archives of General Psychiatry* **54**, 233–241.

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, Orr SP, 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, 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.

Smith EE, Jonides J (1999). Storage and executive processes in the frontal lobes. *Science* **283**, 1657–1661.

Spielberger CD, Gorsuch RL, Lushene RE (1970). *STAI Manual for The State-Trait Inventory*. Consulting Psychologist Press: Palo Alto.

Spitzer B, Gibbon RL, Janet M, Janet W (1996). *Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition* (*SCID-I/P, version 2.0*). American Psychiatric Press: New York.

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

Uylings HBM, Rajkowska G, Sanz-Arigita E, Amunts K, Zilles K (2005). Consequences of large interindividual variability for human brain atlases: converging macroscopical imaging and microscopical neuroanatomy. *Anatomy and Embryology* **210**, 423–431.

Weber DL, Clark CR, McFarlane AC, Moores KA, Morris P, Egan GF (2005). Abnormal frontal and parietal activity during working memory updating in posttraumatic stress disorder. *Psychiatry Research* **140**, 27–44.

Worsley KJ, Evans AC, Marrett S, Neelin P (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow Metabolism* **12**, 900–918.

Zubieta J-K, Chinitz JA, Lombardi U, Fig LM, Cameron OG, Liberzon I (1999). Medial frontal cortex involvement in PTSD symptoms: a SPECT study. *Journal of Psychiatric Research* **33**, 259–264.