ELSEVIER

Clinical Neurophysiology 117 (2006) 637–642

www.elsevier.com/locate/clinph

Alterations in cerebral perfusion in posttraumatic stress disorder patients without re-exposure to accident-related stimuli

Yong An Chung [a], Sung Hoon Kim [a], Soo Kyo Chung [a], Jeong-Ho Chae [b], Dong Won Yang [c], Hyung Sun Sohn [a], Jaeseung Jeong [d,e,*]

[a] *Department of Radiology, The Catholic University of Korea, Seoul, South Korea*
[b] *Department of Psychiatry, The Catholic University of Korea, Seoul, South Korea*
[c] *Department of Neurology College of Medicine, The Catholic University of Korea, Seoul, South Korea*
[d] *Department of BioSystems, Korea Advanced Institute of Science and Technology (KAIST), Yuseong-gu, Kuseong-dong 373-1, Daejeon 305-701, South Korea*
[e] *Department of Psychiatry, Columbia College of Physicians and Surgeons and the New York State Psychiatric Institute, New York, NY 10032, USA*

Accepted 12 October 2005
Available online 19 January 2006

Abstract

Functional neuroimaging studies have shown abnormalities of limbic regions in patients with posttraumatic stress disorder (PTSD) during symptom provocation and cognitive activation.

Objective: The aim of this study was to determine whether PTSD patients without re-exposure to accident-related stimuli would exhibit alterations in cerebral perfusion compared with age-matched normal subjects.

Methods: Brain perfusion SPECT was measured in medication-free 23 PTSD patients and 64 age-matched healthy subjects under resting conditions and analyzed using statistical parametric mapping to compare between the patient and control groups.

Results: We found that PTSD patients exhibited increased cerebral blood perfusion in limbic regions and decreased perfusion in the superior frontal gyrus and parietal and temporal regions in comparison with those of the normal controls.

Conclusions: This result indicates that PTSD patients have alterations in cerebral perfusion of limbic regions and the frontal and temporal cortex without re-exposure to accident-related stimuli.

Significance: This finding supports the hypothesis of the involvement of limbic regions, which might be associated with the regulation of emotion and memory, in the pathophysiology of PTSD.

Keywords: PTSD; SPECT; Accident-related stimuli; Limbic regions

1. Introduction

Posttraumatic stress disorder (PTSD) is an anxiety disorder resulting from experiencing or witnessing an extreme traumatic stressor that involved potential loss of life or serious injury to the self or others. The symptoms of PTSD are characterized by persistent re-experiencing of the traumatic event, avoidance of stimuli associated with the traumatic event, psychogenic amnesia, and increased arousal. Furthermore, sleep disturbances, inappropriate irritability, difficulty in concentration, and exaggerated startle responses are often observed in PTSD patients (Yehuda, 2002).

Neuroimaging studies using magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission tomography (SPECT) have

* Corresponding author. Address: Department of BioSystems, Korea Advanced Institute of Science and Technology (KAIST), Yuseong-gu, Kuseong-dong 373-1, Daejeon 305-701, South Korea. Tel.: +82 42 869 4319; fax: +82 42 869 4310.
E-mail address: jsjeong@kaist.ac.kr (J. Jeong).

1388-2457/$30.00
doi:10.1016/j.clinph.2005.10.020

provided valuable information on the pathophysiology of PTSD (for reviews, see Bremner, 2002; Grossman et al., 2002; Hull, 2002; Pitman et al., 2001). Structural abnormalities in PTSD found with MRI include reduced hippocampal volume (Bremner et al., 1995; 1997; Gurvits et al., 1996; Stein et al., 1997) and nonspecific white matter lesions (Canive et al., 1997). These abnormalities might reflect pretrauma vulnerability to developing PTSD, or they may be a consequence of traumatic exposure, PTSD, and/or PTSD sequelae (Pitman et al., 2001). Functional neuroimaging studies on PTSD patients during symptom provocation and cognitive activation have found increased activation of the amygdala and anterior paralimbic structures, which are known to regulate negative emotions like fear (Rauch et al., 1996, 1997, 2000; Semple et al., 2000; Shin et al., 1997a,b). In addition, these studies have found failure of activation of the cingulate cortex, which might play an inhibitory role in response to trauma-related stimuli (Semple et al., 1996; Shin et al., 1997b), and reduced activation of Broca's area (motor speech) and other nonlimbic cortical regions (Rauch et al., 1996; Shin et al., 1997a,b). These previous studies suggest that limbic regions and the prefrontal and temporal cortex are involved in pathogenesis of PTSD.

While previous functional neuroimaging studies on PTSD patients have been mostly performed using symptom provocation paradigms, there are few reports for evaluation of the changes in regional cerebral blood flow (rCBF) involved in PTSD without re-exposure to accident-related stimuli. Sachinvala et al. (2000) studied 17 PTSD patients under resting conditions using Tc-99m hexamethyl propylene amine oxime SPECT to find an increase in cerebral perfusion in the cingulate regions, the temporal and parietal regions, the caudate/putamen region, and the orbital and hippocampal regions in PTSD patients compared with the control group. In addition, our group demonstrated, using nonlinear dynamical analysis of the EEG, that PTSD patients have globally reduced complexity of the electrical brain activity under resting conditions compared with those of the healthy subjects (Chae et al., 2004). These studies suggest the possibility that PTSD patients may exhibit alterations in cerebral perfusion without re-exposure to accident-related stimuli.

Thus, in the present study, we investigated whether PTSD patients would exhibit alterations in cerebral perfusion compared with normal subjects without re-exposure to accident-related stimuli. SPECT scanning of PTSD patients and age-matched healthy subjects was performed under resting conditions to examine alterations in regional cerebral perfusion without provocative stimuli. Given the significant role of limbic and paralimbic regions in the pathogenesis of PTSD, we hypothesized that PTSD patients would show an elevation of rCBF levels in these regions even without provocation stimuli.

2. Materials and methods

2.1. Subjects

Regional CBF measurements of resting state using Tc-99m ECD (ethyl cysteinate dimmer) SPECT were performed on 23 patients with PTSD (M:F = 13:10; ages, 21–63 years; mean 43 years) without re-exposure to accident-related stimuli and on 64 age-matched healthy subjects (M:F = 34:30; ages, 23–61 years; mean, 43 years). PTSD patients were recruited from the PTSD clinic at St Mary's Hospital, The Catholic University of Korea. Their traumatic events were all civil trauma including 18 motor vehicle accidents, 3 domestic violence, and two physical assaults by strangers. The mean time elapsed since the traumatic events was 4.3 ± 5.2 years. The diagnosis of PTSD was established according to DSM-IV criteria (American Psychiatric Association, 1994) using the Structured Clinical Interview for DSM-IV, administered by a trained clinician. Clinician-Administered PTSD Scale (CAPS) was administered to quantitatively characterize PTSD symptoms. Their symptoms were moderate to severe (mean and SD scores of CAPS: 87.9 ± 12.7).

Subjects with a history of psychotic disorders or dementia were excluded. The healthy controls had no self-reported personal or familial psychiatric history. The patients and controls were drug-free for at least 2 weeks before this study. Brain MRI scanning was performed in all patients and controls prior to the study in order to exclude subjects with organic lesions such as hemorrhage, infarction, or tumor. No patient showed such findings, and thus no one was excluded by this criterion. All subjects gave written, informed consent to participate in the study. The Human Subjects Committee at the Catholic Medical Center approved the study.

2.2. SPECT procedure

SPECT imaging was initiated 20 min after intravenous injection of approximately 740-925 MBq of Tc-99m ECD using a multi-detector scanner (ECAM plus; Siemens, Erlangen, Germany) equipped with a low-energy, fan-beam collimator. The head unit consists of two rings of 59 probe-type detectors. There is a rotating collimator with septa varying from 0 to 3.52 mm within the right of crystals. Both the detector ring and the collimator rotate. Data were acquired on 128×128 matrix size with a 20% symmetric window at 140 keV. Continuous transaxial tomograms of the brain were reconstructed after filtered back-projection with a Butterworth (cutoff frequency 0.4 cycles/pixel, order 5) to reduce acquisition noise. Tc-99m ECD images

were corrected for tissue attenuation using a standard Chang's attenuation correction.

2.3. Image data analysis

For the analysis of SPECT imaging data, statistical parametric mapping (SPM), a technique for making pixel-by-pixel statistical comparisons between sets of images, was used in this study. All subsequent image manipulation and data analysis were performed on a personal computer using a Windows 98 operating system (Microsoft, Redmond, Wash, USA). The software for the image manipulation included Matlab (ver. 5.3, Mathworks, Inc., Natick, MA) and SPM99 software (Institute of Neurology, University College of London, UK). The raw SPECT data was converted into the Analyze (Mayo Foundation, Baltimore, MD, USA) format, using MRIcro software. The SPECT data includes 348 bytes of header, 3.9 mm of x and y pixel sizes, and 3.9 mm of slice thickness. The SPECT images of the control group and PTSD patients were separately co-registered into MNI SPECT template using the SPM method in order to remove variations resulting from different sizes and shapes of individual brains. The parameters for co-registration were intra-modality, linear algorithm, 12 affine parameter models for controlling the number of degrees of freedom used in registration, and tri-linear interpolation. All slices of a brain image were then resampled and averaged to arrive at a mean pixel intensity, or the average pixel value of the whole brain for that specific image. The intensity threshold was set at 80% of the whole-brain mean. This level eliminated low-intensity background noise inherent in the images and effectively removed brain-edge halo caused by partial-volume error, without losing any image data specific to the brain. The global cerebral blood flow rate was normalized to an arbitrary mean of 50 ml/100 ml per minute by a group-wise analysis of covariance (ANCOVA). The data were then normalized to a better resolution SPECT template (MNI template: Montreal Neurological Institution Template) and smoothed with 16 mm full with half maximum (FWHM) prior to SPM analysis (Friston et al., 1995) The final image format was 16-bit, with a size of $79\times 95\times 68$ and a voxel size of $2\times 2\times 2$ mm. For the graphic presentation of the results, sections were displayed as transverse, sagittal, and coronal slices with a hot color map.

The normalized SPECT data from the investigation were compared to a normal database constituted from 64 subjects without morphological or neurological pathology for detection of hypo- or hyperperfusion areas. After specifying the appropriate design matrix, changes in rCBF levels produced by the different subject groups were estimated according to the general linear model at each voxel. An ANCOVA model was fitted, and a t statistic image (SPM[t]) for the contrast condition effect was constructed. The resulting set of voxel t values constitutes the statistical parametric mapping SPM[t] with a threshold value of 4.80 (or $P=0.05$, corrected) and a minimal cluster size of 50 voxels. The expected voxels per cluster were 12.128 and the expected number of cluster was 0.05. The threshold of cluster P value (corrected) was 0.026. For visualization of the t score statistics, the t score voxel clusters were projected onto the standard high-resolution MRI data set using the projection protocol, which additionally displays the Talairach coordinates, thus allowing anatomic identification. The voxels with P-values of less than 0.05 were considered to be significantly different.

3. Results

Compared with that of the control group, SPECT imaging of PTSD patients showed increased uptake of radiotracer in limbic regions, i.e. hippocampus, parahippocampal gyrus, anterior cingulate gyrus, isthmic portion of the cingulate gyrus, and a portion of rhinencephalon (Table 1). In addition, PTSD patients exhibited decreased uptake of radiotracer in the left parietal angular gyrus, left frontal precentral gyrus, left inferior temporal gyrus, and right occipital sub-gyral white matter (Table 2). Fig. 1 shows maximum intensity projection images of differences of rCBF values between the two groups, indicating that PTSD patients exhibited increased cerebral blood perfusion in limbic regions and decreased perfusion in the superior frontal gyrus, parietal and temporal regions, and occipital sub-gyral white matter compared with those of the normal

Table 1
Brain regions with increased rCBF levels in PTSD patients compared with those of normal controls

Brain regions	Number of voxels in cluster	Voxel T	x, y, z (mm)
Right cerebellum, anterior lobe, culmen	1032	7.15	18, −36, −12
Right cerebrum, limbic lobe, parahippocampal gyrus, gray matter, Brodmann area 36		5.39	26, −18, −24
Right cerebrum, frontal lobe, sub-gyral	206	6.40	44, 12, −10
Right cerebrum, limbic lobe, cingulate gyrus, white matter	64	6.08	8, −16, 32
Left cerebrum, sub-lobar, caudate, gray matter, caudate body	143	6.01	−18, −18, −20
Left cerebrum, limbic lobe, parahippocampal gyrus, gray matter, amygdala		5.50	−20, −8, −12
Left cerebrum, limbic lobe, anterior cingulated	247	5.87	0, 16, −8
Left cerebrum, sub-lobar, caudate, gray matter, caudate body		5.52	−6, 14, 6

Table 2
Brain regions with decreased rCBF levels in PTSD patients compared with normal controls

Brain regions	Number of voxels in cluster	Voxel T	*x*, *y*, *z* (mm)
Left cerebrum, parietal lobe, angular gyrus, white matter	134	6.21	−42, −62, 30
Left cerebrum, frontal lobe, precentral gyrus, gray matter, Brodmann area 6	142	6.19	−24, −12, 70
Left cerebrum, temporal lobe, inferior temporal gyrus, white matter	72	5.76	−50, −36, −18
Right cerebrum, occipital lobe, sub-gyral, white matter	50	5.58	26, −72, 28

controls. Fig. 2 shows the SPM images on the template, T1 weighed high-resolution brain MRI, which allows anatomical identification of activation regions. This figure shows more clearly that PTSD patients had increased rCBF in limbic regions compared with those of the normal controls.

4. Discussion

We determined whether PTSD patients exhibit alterations in cerebral perfusion compared with age-matched normal subjects without re-exposure to accident-related stimuli. We found, using SPM analysis, that PTSD patients showed alterations in cerebral blood perfusion under resting conditions compared with normal controls over a number of brain regions, in particular increased rCBF levels in limbic regions and decreased rCBF levels in the superior frontal gyrus and parietal and temporal regions. This result indicates that PTSD patients have abnormal cerebral perfusion levels in limbic regions and the frontal and temporal cortex under resting conditions. This finding supports the hypothesis of the involvement of limbic regions, which are thought to regulate emotion and memory, in the pathophysiology of PTSD.

Sachinvala et al. (2000) also examined the changes in rCBF involved in PTSD without re-exposure to accident-related stimuli. They recorded Tc-99m hexamethyl propylene amine oxime SPECT images from 17 PTSD patients under resting conditions and found an increase in rCBF in the cingulate regions, the temporal and parietal regions, the caudate/putamen region, and the orbital and hippocampal regions in PTSD patients compared with the control group. There are some differences between Sachinvala et al. (2000) and our study: while they used the HMPAO in SPECT analysis, we used Tc-99m ECD, which is reported to be a better reflector of metabolism. Furthermore, some of patients used in Sachinvala et al. (2000) took medications, whereas patients in our study are all medication-free. Since drugs may mask the true nature of the PTSD, it is possible that the activation sites in their results are associated with drug effects.

In addition, we used the SPM to analyze SPECT imaging data, whereas previous studies have used conventional region of interest (ROI) analysis (Sachinvala et al., 2000). The conventional PET/SPECT imaging analysis requires the application of a number of ROIs on the images, and consequently ROI definition on functional images is time-consuming. In addition, due to the subjectiveness and propensity for individual operator bias, ROI analysis can be less effective in accurately distinguishing regional variations between a set of images. We demonstrated in the current study that SPM analysis is sensitive in detecting alterations in rCBF levels and useful in investigating alterations in rCBF levels in a patient group in comparison with a control group under resting conditions.

The characteristic PTSD symptoms, such as intrusive memories, flashbacks of the traumatic event, and hyperarousal, suggest abnormalities in the regulation of emotion and memory, thus implicating the limbic system as a possible brain region associated with the disorder. The limbic system is known to play a critical role in the regulation of emotions and in the storage and retrieval of

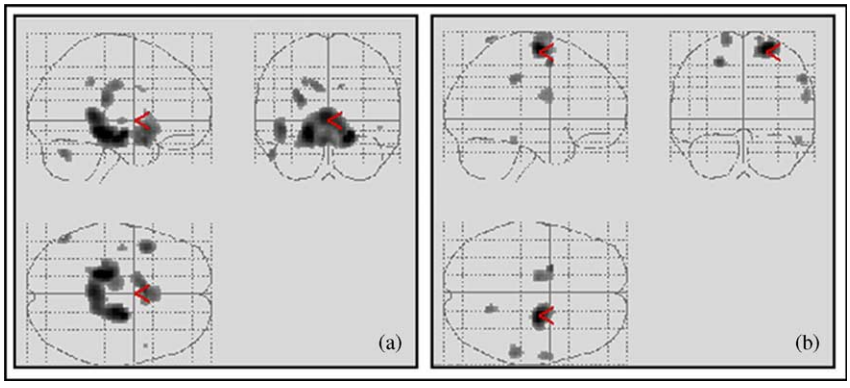

Fig. 1. Maximum intensity projection images of (a) increased rCBF levels and (b) decreased rCBF levels in PTSD patients ($n=23$) compared with normal controls ($n=64$).

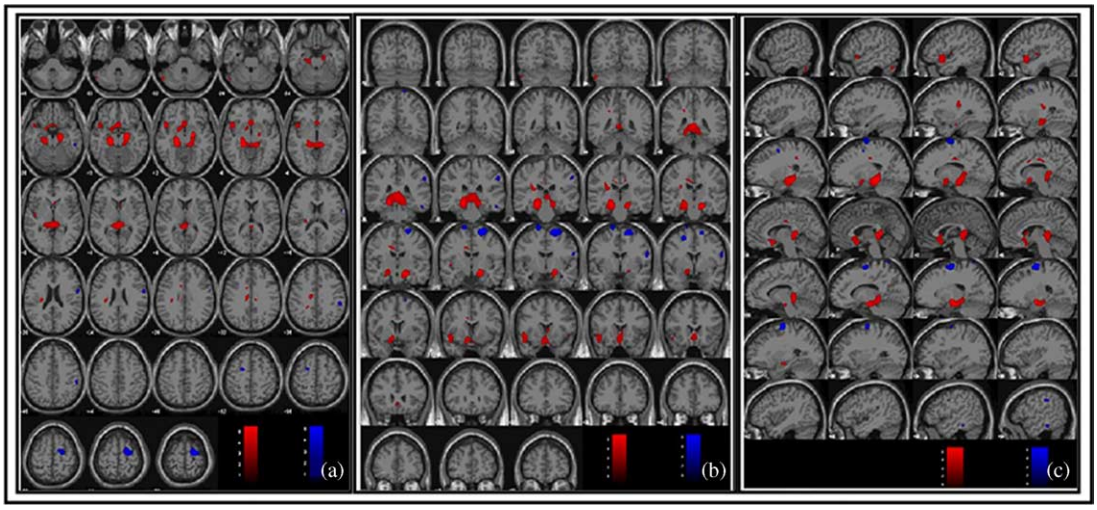

Fig. 2. (a) Axial, (b) coronal, and (c) sagittal SPM images on template T1 weighted high-resolution brain MRI. Brain regions of increased (red) and decreased (blue) rCBF levels in PTSD patients ($n=23$) compared with normal controls ($n=64$) are shown.

memories. Previous PET and SPECT studies using symptom provocation paradigms also support the hypothesis of the involvement of limbic regions in the pathogenesis of PTSD (Liberzon et al., 1999; Rauch et al., 1996; 1997; Semple et al., 2000; Shin et al., 1997a,b; Zubieta et al., 1999). For example, Liberzon et al. (1999) performed SPECT imaging on patients with combat-related PTSD to find an increased rCBF level in the amygdala and medial prefrontal cortex during provocation. Hyperperfusion of limbic and paralimbic regions may result from stress-induced long-term potentiation through the monosynaptic *N*-methyl-D-aspartate (NMDA)-mediated pathway between the amygdala and the periacqueductal grey (Hull, 2002). It is possible that NMDA receptors can be activated to produce long-term memories of events when a sufficient amount of glutamate is released as a result of the stress (Glue et al., 1993; Hull, 2002).

However, the main result of the current study is increased rCBF levels in limbic regions in PTSD patients without re-exposure to accident-related stimuli. This hyperperfusion of limbic regions in PTSD during resting conditions might be associated with the hyper-responsivity to accident-related stimuli in PTSD patients. Another possibility is that an increase in blood perfusion of limbic regions in PTSD reflects ongoing psychological and psychophysiological hyperfunction of overlearned survival response (or flash-back response) in limbic regions. Silove (1998) hypothesizes that a primitive learning center in the limbic system rehearses traumatic memories following exposure to trauma, thus inducing durable memories of the sources of novel threat. According to this hypothesis, intrusive phenomena like repetitive imagery represent an active reworking of trauma memories at the cognitive level, a process that helps the survivor to integrate the novel and threatening information into new and expanded meaning schemata which eventually provide a more accurate representation of the posttrauma world. Thus, given that hyperperfusion of limbic regions is associated with the intrusive phenomena of PTSD without re-exposure to accident-related stimuli, it possibly reflect an overlearned survival response in patients in whom the putative limbic rehearsal mechanism evades cortical control.

We also found a decrease in rCBF levels in the left parietal angular gyrus, left frontal precentral gyrus, left inferior temporal gyrus, and right occipital sub-gyral white matter in PTSD patients. These findings are partially consistent with those of previous imaging studies in patients with PTSD, implicating dysfunction of governing cortices (Hull, 2002; Shin et al., 2005). Particularly, decreasing activities of the prefrontal cortex, which has a role in the encoding and retrieval of verbal memory, appears to be consistent with patients with PTSD having difficulty in cognitively restructuring their traumatic experiences (Hull, 2002). Besides the prefrontal cortex, decreased parietal blood flow has been reported in PTSD subjects compared with healthy controls performing an attentional task (Semple et al., 1996). Our previous EEG studies using nonlinear dynamical methods also suggested that PTSD patients have globally reduced complexity in their EEG waveforms implicating their diffuse disturbed cortical information processing (Chae et al., 2004). Although not all functional imaging studies found the cortical dysfunction and comorbid psychiatric illnesses, and differences in the anxiety-provoking stimuli used in the imaging scans may contribute to the inconsistency of findings in imaging researches in those patients, the present study, which suggests the higher cortical hypofunction and limbic hyperactivation during the resting state, provides another evidence for a reciprocal interaction between these two regions in the pathophysiology of PTSD.

In summary, we showed that PTSD patients have alterations in cerebral perfusion of limbic regions and

the frontal and temporal cortex without re-exposure to accident-related stimuli compared with those of age-matched healthy controls. This finding suggests the involvement of limbic regions in the pathogenesis of PTSD.

Acknowledgements

This work was supported by the grants of the 2005 Nuclear R&D Plan Program (Study on the Radiation Brain Science) of the Ministry of Science & Technology, South Korea.

References

American Psychiatric Association, Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC; 1994.

Bremner JD. Neuroimaging studies in post-traumatic stress disorder. Curr Psychiatry Rep 2002;4:254–63.

Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry 1995;152:973–81.

Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. Biol Psychiatry 1997;41:23–32.

Canive JM, Lewine JD, Orrison WW, Edgar Jr CJ, Provencal SL, Davis JT, Paulson K, Graeber D, Roberts B, Escalona PR, Calais L. MRI reveals gross structural abnormalities in PTSD. Ann NY Acad Sci 1997;821: 512–5.

Chae JH, Jeong J, Peterson BS, Kim DJ, Bahk WM, Jun TY, Kim SY, Kim KS. Dimensional complexity of the EEG in patients with posttraumatic stress disorder. Psychiatry Res 2004;131:79–89.

Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995;2:190–210.

Glue P, Nutt DJ, Coupland NJ. Stress and psychiatric disorder: reconciling social and biological approaches.. In: Stanford SC, Salmon P, editors. Stress: an integrated approach. London: Academic Press; 1993. p. 53–73.

Grossman R, Buchsbaum MS, Yehuda R. Neuroimaging studies in post-traumatic stress disorder. Psychiatr Clin North Am 2002;25:317–40.

Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, Orr SP, Kikinis R, Jolesz FA, McCarley RW, Pitman RK. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry 1996;40:1091–9.

Hull AM. Neuroimaging findings in post-traumatic stress disorder. Systematic review. Br J Psychiatry 2002;181:102–10.

Liberzon I, Taylor SF, Amdur R, Jung TD, Chamberlain KR, Minoshima S, Koeppe RA, Fig LM. Brain activation in PTSD in response to trauma-related stimuli. Biol Psychiatry 1999;45:817–26.

Pitman RK, Shin LM, Rauch SL. Investigating the pathogenesis of posttraumatic stress disorder with neuroimaging. J Clin Psychiatry 2001;62(Suppl 17):47–54.

Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, Fischman AJ, Jenike MA, Pitman RK. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. Arch Gen Psychiatry 1996;53:380–7.

Rauch SL, Savage CR, Alpert NM, Fischman AJ, Jenike MA. The functional neuroanatomy of anxiety: a study of three disorders using positron emission tomography and symptom provocation. Biol Psychiatry 1997;42:446–52.

Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, Orr SP, Pitman RK. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biol Psychiatry 2000;47:769–76.

Sachinvala N, Kling A, Suffin S, Lake R, Cohen M. Increased regional cerebral perfusion by Tc-99m hexamethyl propylene amine oxime single photon emission computed tomography in post-traumatic stress disorder. Mil Med 2000;165:473–9.

Semple WE, Goyer PF, McCormick R, Compton-Toth B, Morris E, Donnovan B, Muswick G, Nelson D, Garnett ML, Sharkoff J, Leisure G, Miraldi F, Schulz SC. Attention and regional cerebral blood flow in posttraumatic stress disorder patients with substance abuse histories. Psychiatry Res 1996;67:17–28.

Semple WE, Goyer PF, McCormick R, Donovan B, Muzic Jr RF, Rugle L, McCutcheon K, Lewis C, Liebling D, Kowaliw S, Vapenik K, Semple MA, Flener CR, Schulz SC. 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 2000;63:65–74.

Shin LM, Kosslyn SM, McNally RJ, Alpert NM, Thompson WL, Rauch SL, Macklin ML, Pitman RK. Visual imagery and perception in posttraumatic stress disorder. A positron emission tomographic investigation. Arch Gen Psychiatry 1997a;54:233–41.

Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, Metzger LJ, Lasko NB, Orr SP, Pitman RK. A positron emission tomographic study of symptom provocation in PTSD. Ann NY Acad Sci 1997b;821:521–3.

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. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch Gen Psychiatry 2005;62:273–81.

Silove D. Is posttraumatic stress disorder an overlearned survival response? An evolutionary-learning hypothesis Psychiatry 1998;61:181–90.

Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. Psychol Med 1997;27:951–9.

Yehuda R. Post-traumatic stress disorder. N Engl J Med 2002;346: 108–14.

Zubieta JK, Chinitz JA, Lombardi U, Fig LM, Cameron OG, Liberzon I. Medial frontal cortex involvement in PTSD symptoms: a SPECT study. J Psychiatr Res 1999;33:259–64.