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ORIGINAL PAPER

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Regional cerebral blood flow during auditory recall in 47 subjects exposed to assaultive and non-assaultive trauma and developing or not posttraumatic stress disorder

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Abstract *Objective* Psychological trauma leads to posttraumatic stress disorder (PTSD) in susceptible subjects. The aim of this study was to investigate the differences in regional cerebral blood flow (rCBF) between two groups of subjects exposed to different types of traumatic stressor either developing or not developing PTSD. *Method* Twenty subjects developing (S) and 27 not developing (NS) PTSD after being exposed to either earlier person-under-the-train accident (NA) or being assaulted in the underground environment (A) were included in the study. ^{99m}Tc-HMPAO SPECT was performed and the uptake in 29 regions of the brain (VOIs), bilaterally, was assessed. rCBF distribution was compared, using analysis of variance (ANOVA), between groups (S/NS) and type (A/NA) during a situation involving an auditory evoked re-experiencing of the traumatic event. Discriminant analysis was applied to test the concordance between clinical diagnosis and SPECT findings. *Results* In the general analyses significant differences were found between groups and types and there was a significant hemisphere × type interaction. S showed higher CBF than NS and so did A as compared to NA, particularly in the right hemisphere. Discriminant analysis correctly classified 66 % of cases ($p < 0001$) in testing S/NS and 72 % ($p < 0001$) in testing NA/A. *Conclusions* Under recall of their traumatic experience we found higher relative CBF distribution values in S as compared to NS. CBF was higher in the right hemisphere and particularly in assaulted subjects. These findings underscore the role upon trauma recall of both the right hemisphere and the nature of the stressing event.

Key words PTSD · assaultive trauma · SPECT · rCBF

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Introduction

Posttraumatic stress disorder (PTSD) is a clinical condition that may occur in victims of major psychological trauma. PTSD was defined in DSM-III in 1980 and it is a dysfunctional learning leading to a conditioned fear response elicited by internal or external cues associated with the traumatic situation. The recurring symptoms of re-experiencing the trauma can be seen as new trauma-experiences leading to a sensitisation of a brain circuitry engaged in fear response and to emotional bodily reactions of autonomic arousal. It is often lifelong and is associated with intrusive distressing recollections (flashbacks and/or nightmares), avoidance to stimuli related to trauma, autonomic hyper-reactivity and emotional numbing. It is estimated that 4–8 % [6, 10, 17] of the general population have had PTSD at some time during their lifetime making PTSD the fourth most common psychiatric disorder [6].

Subjects reporting assaultive events were more likely to develop PTSD as compared to those reporting non-assaultive traumas [5, 21, 32]. Train drivers exposed to person-under-the-train accidents (NA), comparable to witnesses to accidents, are expected to develop PTSD in about 7 % of cases [16]. Persons undergoing assaultive

traumas have been described to develop PTSD in up to 20% of cases [5, 7]. Furthermore, preceding traumatic experiences [22] and the intensity of the stressor [20] lead to a higher risk of PTSD development.

Trauma-script exposure has proven to be a valid approach to elicit rCBF changes in PTSD. Recently, the improvement in both technical capabilities and methodology has rendered neuroimaging studies particularly suitable in investigating *in vivo* the neurobiology of emotions. Previous studies performed with both Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET) have reported regional cerebral blood flow changes during provocation procedures. Both increases [2, 19, 24, 27, 30, 31, 36] and decreases [2–4, 19, 24, 28, 30, 31] in rCBF were described. Raised rCBF was mostly found in the amygdala, limbic cortex and frontal cortex. Decreased rCBF was reported in the middle prefrontal, sub-callosal and temporal cortex, Broca's area and thalamus.

A working hypothesis based on the published literature of a possible differential response to the trauma-script exposure of assaulted vs non-assaulted subject is not possible due to the novelty of the present methodology, as compared to previous investigations all examining similar traumatic experiences and giving divergent results. The statistical approach utilising multifactor analysis was meant to verify whether single regions, hemispheres or the whole brain were involved in such responses and should fit well to one of the primary issues of interest in PTSD investigation, e. g. the assumption that the response to trauma recall is mediated by a network of limbic and cortical structures.

The aim of the study was to investigate by means of SPECT the difference in rCBF distribution between two groups of subjects exposed to person-under-train accident (NA) or assaultive experience (A) either developing (S) or not developing (NS) PTSD.

Method

Participants

Recruitment

The subjects were recruited (years 1999–2001) for a treatment trial in cooperation with the public transportation authorities and their occupational health agencies in Stockholm. Public transportation workers in the underground and in long-distance trains who reported having being exposed at work to either a person-under-train accident (NA) or a personal experience of assault (A) were asked to participate in the trial. Those accepting to participate in the study were further divided in symptomatic (S) and not symptomatic (NS) according to their clinical status. The subjects were given an oral and written description of the study and written informed consent was obtained. The study was approved by the Local Ethics and Radiation Safety Committees.

Inclusion criteria

Men and women developing or not developing PTSD after experiencing either NA or A at work between three months and six years before SPECT and being below the age of 65 years were included in the study. Subjects with major depressive disorder and other serious psychiatric conditions were excluded.

Diagnosis

PTSD diagnosis was made by an independent psychiatrist, based on DSM-IV and an interview according to SCID. Symptoms had to be present for at least a month and occurring more than 3 months earlier. Only a full PTSD diagnosis was accepted.

Characteristics

The demographic and physiological characteristics of the 47 subjects included in the study at the time of the first interview are summarised in Table 1. The handedness was determined by a self-administered and self-reported form. The time passed between the reported trauma and the experimental situation was calculated. No differences were found between groups in frequency distribution for gender, smoking habits and handedness (Chi-square test).

Experimental set-up

Trauma-script

An individualised script portraying the traumatic event was constructed according to the method described by Lang et al. [18] for each participant. The script was read by a research assistant and recorded on tape.

Table 1 Characteristics of the participants at base line assessment

	NS-NA	S-NA	sub-tot/mean NA	NS-A	S-A	sub-tot/mean A	Total NA + A
Subjects	20	13	33	7	7	14	47
Males	17	10	27	4	5	9	36
Age s.d.	44.8±9.4	39.5±9.3	42.7±9.6	34.9±8.2	43.4±10.5	39.1±10.1	41.6±9.8
Smoking (Yes)	10	6	16	1	2	3	19/47
Right handed	15	11	26	7	6	13	39/47
Mean Blood Pressure s.d.	92.0±10.0	93.0±11.0	92.0±19.0	91.0±35.0	92.0±10.0	91.0±8.0	92.0±21.0
Heart Rate SD	69.0±8.0	68.0±9.0	69.0±8.0	67.0±7.0	68.0±9.0	68.0±8.0	68.0±8.0
Time from trauma (months) s.d.	38.0±20.0	38.0±24.0	38.0±21.0	25.0±5.0	32.0±26.0	29.0±19.0	35.0±21.0

NS Non-symptomatic; *S* symptomatic; *NA* non-assaulted; *A* assaulted

Symptom provocation

The subjects were admitted in a quiet neutral room at 8:00 a. m. They fasted from midnight and were positioned on a couch being monitored for blood pressure (BP) and heart rate (HR) and an i. v. line was inserted into the right cubital vein. They were kept in resting conditions for 30 minutes. The previously recorded script was then presented to the subjects using ear-phones; after the tape had run for 15 seconds the radiopharmaceutical was injected in bolus into the i. v. line. The script duration was $1^1/_2$ min and the subjects were then asked to recall the event in their own mind for one more minute. Twenty minutes later subjects were brought to the SPECT camera.

Scanning protocol

The radiopharmaceutical was prepared according to the manufacturer's instructions. 1000 MBq (27.0 mCi) of ^{99m}Tc-d,l-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO, Ceretec®, Amersham International plc, Little Chalfont, UK) was injected i. v. within 20 min from reconstitution. SPECT brain imaging was performed using a three-headed gamma camera (TRIAD XLT 20, Trionix Research Laboratory Inc., Twinsburg, OH, USA) equipped with low-energy ultra-high resolution collimators. The projection data were acquired for 15 s per projection at 90 equal angles of a complete revolution (0–360°).

Before reconstruction, the projection data were pre-processed using a 2D Hamming filter with a cut-off frequency of 2.25 cycles/cm. Sectional images were reconstructed by filtered back projection using a Ramp filter with a cut-off frequency of 0.6 cycles/cm. During preprocessing, correction for attenuation was made. No scatter correction was applied. Both acquisition and reconstruction were performed in 128 × 128 matrices with a pixel size of 2.22 × 2.22 mm^2.

Image analysis

CBA (Applied Medical Imaging©, Uppsala, Sweden) is a software tool for the analysis of neuroimaging data. It is based on a detailed 3D atlas derived from a cryosectioned brain. All image sets were spatially normalised into the stereotactic space of the atlas by using the global polynomial transformation implemented in the CBA software. It consists of translations, rotations and linear scaling along and around each of the three image axes. It also contains 18 non-linear shape-deforming parameters which makes it possible to individualise the shape of the brain. In order to obtain an optimal fitting of the atlas to the SPECT data pool 8 of the possible 18 polynomial transformation parameters acting on the three axes were used. This choice was originally based on the visual evaluation of the best fully automatic fitting obtained. In this study the fully automatic fitting method was systematically implemented. The methodology and the CBF data extraction are described in detail elsewhere [13, 33].

For evaluation and statistical analysis of the reformatted data sets, 58 volumes of interest (VOIs) corresponding to Brodmann areas and anatomically defined grey matter regions were selected. These regions were bilateral, covering almost the whole temporal, prefrontal, frontal, parietal, cingulate and occipital cortex as well as amygdala, thalamus, putamen, nc. caudatus and hippocampus.

In order to obtain a set of normalised relative flow data, a scaling factor was computed by averaging the brain voxel data and setting the global brain average to a pre-defined value. Before averaging the voxel data, a fixed count/voxel threshold was selected in order to include the 30 % of all brain voxels with the highest counts in the normalisation process. The normalised values were set to 50 "uptake-units" and all relative rCBF distribution values of this work were related to this value.

Statistical analysis

After adaptation and definitions of VOI using the CBA software, the VOI data of all subjects were exported to a statistical package for subsequent statistical analysis of ^{99m}Tc-HMPAO uptake in all the 58 predefined brain regions. Moreover, the mean of the rCBF intensities in all considered VOIs under study (general mean value) was calculated.

Analysis of variance (ANOVA) was used to test statistical significance of rCBF data considering groups (PTSD: S/NS) and type of stressor (type: A/NA) as independent variables at the between-subject level and VOIs and hemispheres at the within-subject level. In both analyses the small number of females and males per cell precluded taking into account gender as a third between-subject factor. The significance level was set at $p < 0.05$.

A linear discriminant analysis at the group and type level using the general mean value was performed. It estimated the relationship between groupings performed according to either SPECT/CBF data or to the previous clinical diagnosis and to the nature of the traumatic stressor. The Jackknifed classification matrix was used along with the normal classification table. In the Jackknifed table computations are made from all data except the case being classified. Wilks' lambda for the discriminant function was assessed to test the statistical significance.

Results

Using ANOVA, no significant differences between groups were found in age, in time elapsed since the traumatic experience, in smoking habits and in handedness.

At the between-subject level there were group (S/NS, $F[1,43] = 4.17$; $p < 0.05$) and type (A/NA, $F[1,43] = 15.60$; $p < 0.001$) differences, while at the within-subject level CBF differed between VOIs ($F[28,1204] = 137.56$; $p < 0.001$) and hemispheres ($F[1,43] = 50.60$; $p < 0.001$). Interactions between VOIs*hemispheres ($F[28,1204] = 25.85$; $p < 0.001$) and hemispheres*types ($F[1,43] = 6.60$; $p < 0.025$) were also significant. General mean (all considered VOIs) and hemispheric CBF values for all four groups are summarised in Table 2. S had a relatively higher CBF distribution than NS in the analysed VOIs.

Overall the right hemisphere had a higher relative CBF distribution than the left hemisphere (see Table 2). As compared to NA, A had a higher relative CBF distribution in both hemispheres and the highest CBF was found in the right hemisphere of A subjects (Fig. 1).

Discriminant analysis performed to explore the ability of SPECT data (all analysed VOI means) to differentiate between S/NS was consistent with clinical diagno-

Table 2 Mean normalised CBF values for the general mean values and both hemispheres

	NS-NA	S-NA	Mean NA	NS-A	S-A	Mean A	Mean NA + A
General mean	44.1±0.7	44.5±0.6	44.3±0.7	44.9±0.7	45.3±0.3	45.1±0.5	44.5±0.7
Right hemisphere CBF	44.4±0.8	44.6±0.6	44.5±0.7	45.4±0.8	45.7±0.5	45.6±0.6	44.8±0.8
Left Hemisphere CBF	43.8±0.7	44.4±0.7	44.0±0.8	44.4±0.6	44.9±0.6	44.7±0.6	44.2±0.8

NS Non-symptomatic; *S* symptomatic; *NA* non-assaulted; *A* assaulted

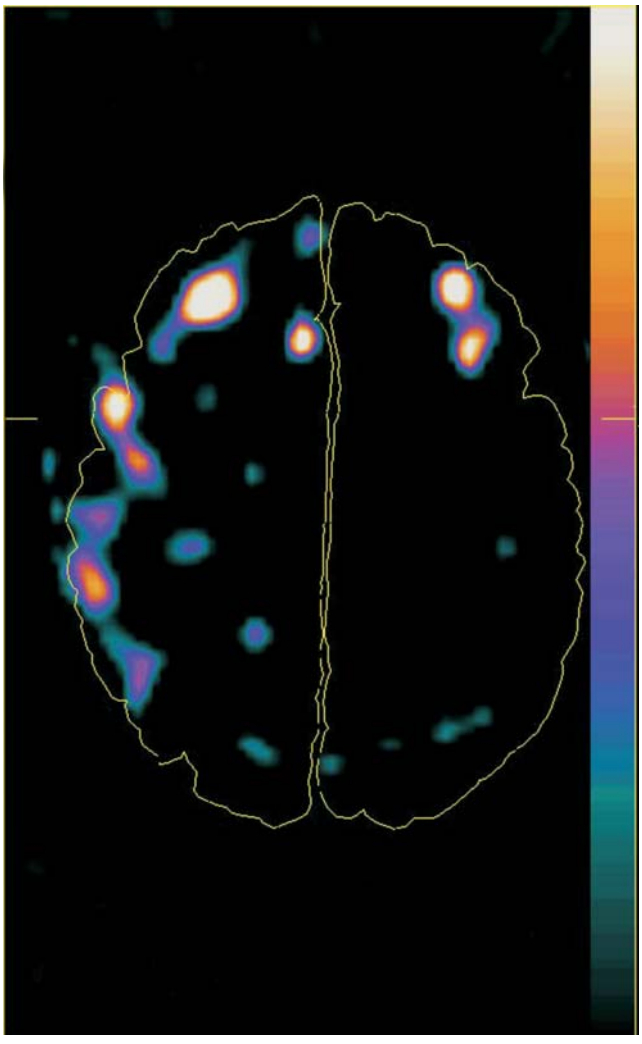

Fig. 1 Image highlighting the regions in which A CBF distribution is higher than NA CBF distribution. The image is obtained by subtracting the average SPECT CBF data pool of NA (n = 33), from A (n = 14)

sis in 66 % of cases with a sensitivity of 75 % and a specificity of 59 % (Wilks' lambda = 0.893; $p < 0.025$).

When the type of traumatic stressor was taken into account (NA/A) the discriminant analysis correctly classified 72 % of cases identifying 86 % of A and 67 % of NA (Wilks' lambda = 0.731; $p < 0.001$).

Discussion

Methodological aspects

As compared to previous PTSD studies published in the field of functional imaging, the present investigation includes a larger number of subjects and deals with a common problem in occupational health. This widens the spectrum of reported traumas, until now mostly represented by combat experience and sexual abuse [15]. Furthermore, our population included both men and women.

The CBA standardizes each subject's brain in the 3D space by steps similar to those of Statistical Parametrical Mapping [11], the software mostly used worldwide in brain imaging for group and individual comparison. The present methodology includes entire 3D regions in the statistical analysis instead of single voxels, thus increasing the size of the sample. This, as compared to SPM, could hide significant differences at the voxel level but could also highlight significant differences in larger regions.

In a recent study SPM was compared to region of interest analysis demonstrating a considerable overlap in findings [1]. SPM produces statistical maps of significant changes in distribution based on the analyses of clusters of voxels. Comparisons between groups are performed generating a SPM *t*-statistics map. We assessed the rCBF differences basing the analyses on rather large VOIs or on the entire hemisphere investigating some form of regional connectivity. In this respect, CBA has the advantage of including regions already sharing some form of "anatomo-functional" similarity (the VOIs correspond to Brodmann regions and were originally classified according to the brain citoarchitectonics) in the analysis and producing data containing a lower number of independent variables as compared to SPM. The anatomical similarity of the voxels included in each VOI might amplify changes at both the threshold and subthreshold level of significance occurring in the entire functional region.

Since brain functions are complex and multivariate in nature instances when a single variable completely explains a phenomenon are rare. Trying to explore the effect of PTSD on brain activity considering clusters of voxels might give incomplete information on changes occurring in the brain. In the present analysis we have taken into account all "possible" factors (even if an unequal number of subjects across cells ruled out the analysis of "all" factors, i. e. gender). This was a more efficient way to analyse the data than the paired t-test or one-way ANOVA, since performing fewer analyses also resulted in more information being gained. ANOVA is used to uncover the main and interaction effects. A "main effect" is the direct effect of an independent variable on the dependent variable. An "interaction effect" is the joint effect of two or more independent variables on the dependent variable. This will not be possible with one-way analysis, i. e. t-test implemented in SPM, and this could partially explain the differences in the results as compared to some of the previously published papers. Another possible reason of discrepancy between our results and other studies showing only regional differences in PTSD studies could be due to the lack of a structured global analysis including the whole brain and the hemispheres or part of them. The fact that the region by group and region by type interactions were not found ruled out any possibility of performing single ANOVA for each VOI. As previously stated, this result cannot be considered as a limitation, but as an important contribution to the understanding of PTSD pathophysiology.

Furthermore we recently investigated the issue of possible differences in results when using CBA/VOI-based statistics as compared to SPM and we concluded that multivariate analysis is more sensitive to changes in CBF as compared to univariate analysis and better reflects the possible functional interactions between brain regions [23].

The female to male ratio was similar across groups but for reasons linked to the sample under investigation; females were about one third of the men. The same held true for A/NA ratio since the recruited A sample was less than half than NA. However, in both cases the frequency distribution was not significantly different.

Discriminant analysis helped to verify the efficacy of the considered variable in allocating subjects to clinical groups. Since the VOIs did not interact with groups, discriminant analysis was performed considering the average value of all considered variables and was "fair" in correctly separating groups and classifying each subject.

Interpretation of the findings

Under recall of their traumatic experience there was a higher CBF detected in symptomatic subjects as compared to not symptomatic subjects. Such change was not limited to specific regions but was a general response. This was in accordance with previous functional studies [2, 27, 30, 31] in which PTSD subjects were exposed to individualized trauma scripts. However, both higher and lower blood flow in PTSD patients as compared to exposed subjects not developing PTSD were found when exposing the subjects to impersonal combat-related sounds [3, 19, 24, 36]. This latter stimuli could elicit in some PTSD patients an impersonal avoidance of the traumatic stimuli resulting in low rCBF in some regions. On the other hand, it was previously suggested that psychophysiologic responses are more effective when personalized scripts instead of standardized scripts are implemented [25].

There was a significantly higher relative CBF distribution in subjects experiencing assaultive trauma (A) as compared to those exposed to person-under-the-train accidents (NA). To our knowledge this is the first study systematically matching CBF of individuals exposed to traumas of different types. The finding of a higher accuracy of SPECT/CBF in discriminating A/NA as compared to S/NS underscores that the type of stressor influences the CBF more than clinical status does.

Epidemiological studies found that assaultive trauma was related to a higher risk of developing PTSD than non-assaultive trauma [5, 7, 32] and it was reported as the most distressing among traumatic experiences [21]. Following trauma-script exposure, we found in assaulted victims as compared to those not-assaulted a higher CBF in the right hemisphere, which is involved in emotions and in the processing and integration of the trauma recall. This could partially explain the epidemiologic findings of more pronounced PTSD formation in victims experiencing personal threat.

We also found higher relative blood flow distribution in all groups in the right hemisphere, and the significant interaction between hemispheres and the type of traumatic stressor was related to a pattern of particularly high CBF in the right hemisphere of the assaulted subjects. This is in accordance with a previous study of Rauch et al. [28] showing in PTSD patients a diffuse increase of rCBF in the right hemisphere and is consistent with the pivotal role of the right hemisphere in processing emotions and integrating sensory modalities [35]. Furthermore, our findings could also be related to the hypothesis of an hemispheric asymmetry for emotional perception and expression, with the right hemisphere being dominant for withdrawal emotions [12, 14, 26]. The specialization of the right hemisphere for visual and spatial attention, vigilance and autonomic arousal is consistent with the fear-reaction that is characterized by vigilance, alertness and sustained attention [14]. However, a previous study reported diffuse left hemisphere rCBF distribution decrease in PTSD patients [3] and anxiety *per se* has been reported to impair left hemisphere functioning [34]. Since SPECT methodology only allows semi-quantitative analysis, we cannot completely rule out the possibility of a relative CBF reduction on the left side instead of an increased CBF on the right side or to a combination of the two.

CBF differences were not influenced by the time elapsed from the traumatic event. This is consistent in all subjects with the presence of chronic PTSD and confirms the epidemiologic findings of Shalev [29] describing a plateau of stable symptoms starting about one year after the trauma.

No interaction between clinical status or type of stressor or single regions under study was found. This is consistent with a higher CBF in S and A involving the whole brain (specifically the right hemisphere) and speaks, in this case, against a more localized rCBF activation related to trauma response. All right regions seem to be included in the biological reaction to the trauma script and our results indicate the presence of an extended functional network mediating PTSD symptoms.

The majority of right-handed individuals are expected to have left hemisphere speech and approximately two-thirds of non-right-handed subjects have language represented in the left hemisphere. Of the remaining one-third of the left-handed subjects with right hemisphere dominance for language, about half have a bilateral representation and so the percent of left-handed subjects with a right hemisphere dominance is very small [8]. Projecting these figures to our study, only 2–3 out of 47 subjects should have such a dominance rendering the sample fairly homogenous. However, it is doubtful if handedness has any relevance for the localization of emotional processing since very little is known about any laterality shift in side dominance for emotional reactions.

The discrepancy between our finding and the re-

gional changes described in previous studies with similar protocols could be, along with the nature of the auditory stimuli, due to the statistical methodology. Most of these studies did not analyse the brain or the hemispheres as a whole. They mainly utilized the z-score to highlight the differences between corresponding voxels in the 3D space and this might have hidden differences at a higher anatomic level. Furthermore some studies limited the statistical analyses to regions known *a priori* to be involved in emotional reactions. Rauch et al. [28] noted a rCBF decrease in Broca's area (left BA 44) rCBF concomitant with a widespread increase in the right hemisphere during a script driven imagery experiment with PTSD subjects. A decreased rCBF in Broca's areas was also reported by Shin et al. [31] following individually tailored scripts.

In our study the relative rCBF in the amygdala was not statistically different from other VOIs. Damasio et al. [9] suggested that the amygdala is activated during recognition and induction of emotions by visual stimuli rather than during the reaction to recalled stimuli.

These findings also confirm the validity of neurofunctional studies in identifying different CBF distribution patterns between various groups of subjects exposed to auditory trauma recall and encourage the use of SPECT and standardization software for group comparison in psychiatry.

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References

1. Bonne O, Louzoun Y, Aharon I, Krausz Y, Karger H, Lerer B, Bocher M, Freedman N, Chisin R (2003) Cerebral blood flow in depressed patients: a methodological comparison of statistical parametric mapping and region of interest analyses. Psychiatry Res 122:49–57
2. Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS (1999) Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. Am J Psychiatry 156:1787–1795
3. Bremner JD, Staib LH, Kaloupek D (1999) Neural correlates of exposure to traumatic pictures and sound in vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. Biol Psychiatry 45:806–816
4. Bremner JD (2002) Neuroimaging studies in post-traumatic stress disorder. Curr Psychiatry Rep 4:254–263
5. Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P (1998) Trauma and posttraumatic stress disorder in the community. Arch Gen Psychiatry 55:626–632
6. Breslau N (2001) The epidemiology of posttraumatic stress disorder: what is the extent of the problem? J Clin Psychiatry 62(Suppl 17):16–22
7. Brewin CR, Andrews B, Rose S, Kirk M (1999) Acute stress disorder and posttraumatic stress disorder in victims of violent crime. Am J Psychiatry 156:360–366
8. Corballis M (2003) From mouth to hand: Gestures, speech and the evolution of right-handedness. Behav Brain Sci 26:199–260
9. Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, Hichwa RD (2000) Subcortical and cortical brain activity during the feeling of self-generated emotions. Nature Neurosci 3:1049–1056
10. Davidson JRT, Tharwani HM, Connor KM (2002) Davidson Trauma Scale (DTS): normative scores in the general population and effect sizes in placebo-controlled SSRI trials. Depress Anxiety 15:75–78
11. Friston KJ, Frith CD, Liddle PF, Frackowiak RS (1991) Comparing functional (PET) images: The assessment of significant changes. J Cereb Blood Flow Metab 11:690–699
12. Gainotti G (2001) Disorders of emotional behaviour. J Neurol 248:743–749
13. Greitz T, Bohm C, Holte S, Eriksson L (1991) A computerized brain atlas: construction, anatomical content, and some applications. J Comput Assist Tomogr 53:26–38
14. Heller W, Koven NS, Miller GA (2003) Regional brain activity in anxiety and depression, cognition/emotion interaction, and emotional regulation. In: Hugdahl K, Davidsson RJ (eds) The asymmetrical brain. Bradford, London, pp 533–564
15. Hull AM (2002) Neuroimaging findings in post-traumatic stress disorder. Br J Psychiatry 181:102–110
16. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB (1995) Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 52:1048–1060
17. Kessler RC (2000) Posttraumatic stress disorder: the burden to the individual and to society. J Clin Psychiatry 61(Suppl 5):4–12
18. Lang PJ, Levin DN, Miller GA, Kozak MJ (1983) Fear behaviour, fear imagery, and the psychophysiology of emotion: the problem of affective response integration. J Abn Psychol 92:276–306
19. 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. Biol Psychiatry 45: 817–826
20. March JS (1993) What constitutes a stressor? The "Criterion A" issue. In: Davidsson JRT, Foa EB (eds) Post-Traumatic Stress Disorder: DSM-IV and Beyond. American Press, Washington DC, pp 37–54
21. Mcquaid JR, Pedrelli P, McCahill ME, Stein MB (2001) Reported trauma, post-traumatic stress disorder and major depression among primary care patients. Psychol Med 31:1249–1257
22. Mollica RF, McInnes K, Poole C, Tor S (1998) Dose-effect relationships of trauma to symptoms of depression and post-traumatic stress disorder among Cambodian survivors of mass violence. Br J Psychiatry 173:482–488
23. Pagani M, Salmaso D, Nardo D, Jonsson C, Danielsson AM, Jacobsson H, Larsson SA (2004) Accuracy of possible and probable Alzheimer disease diagnosis: a methodological comparison using SPM and principal component analysis. Eur J Nuc Med 31(8): S218
24. Pissiota A, Frans O, Fernandez M, von Knorring L, Fischer H, Fredrikson M (2002) Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. Eur Arch Psychiatry Clin Neurosci 252:68–75
25. Pitman RK, Orr SP, Forgue DF, de Jong JB, Claiborn JM (1987) Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. Arch Gen Psychiatry 44: 970–975
26. Pizzagalli D, Shackman AJ, Davidsson RJ (2003) The functional neuroimaging of human emotion: asymmetrical contributions of cortical and subcortical circuitry. In: Hugdahl K, Davidsson RJ (eds) The asymmetrical brain. Bradford, London, pp 511–532
27. 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. Biol Psychiatry 42:446–452
28. Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, Fischman AJ, Jenike MA, Pitman RK (1996) A symptom provocation study using Positron emission tomography and Script Driven Imagery. Arch Gen Psychiatry 53:380–387

29. Shalev AY (2001) What is post traumatic stress disorder? J Clin Psychiatry 62(Suppl):4–10
30. 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. A positron emission tomographic investigation. Arch Gen Psychiatry 54:233–241
31. 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. Am J Psychiatry 156:575–584
32. Stein MB, Walker JR, Forde DR (2000) Gender differences in susceptibility to posttraumatic stress disorder. Behav Res Ther 38: 619–628
33. Thurfjell L, Bohm C, Bengtsson E (1995) CBA – an atlas based software tool used to facilitate the interpretation of neuroimaging data. Comput Meth Programs Biomed 4:51–71
34. Tucker DM (1987) Hemispheric specialization: a mechanism for unifying anterior and posterior brain regions. In: Ottoson D (ed) Duality and unity of the Brain. MacMillan Press, London, pp 180–193
35. Van der Kolk B (1997) The psychobiology of posttraumatic stress disorder. J Clin Psychiatry 58(Supp 9):16–24
36. Zubieta JK, Chinitz JA, Lombardi U, Fig LM, Cameron OG, Liberzon I (1999) Medial frontal cortex involvement in PTSD symptoms: A SPECT study. J Psychiatr Res 33:259–264