Original article

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Effects of EMDR psychotherapy on ^{99m}Tc-HMPAO distribution in occupation-related post-traumatic stress disorder

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Background **Post-traumatic stress disorder (PTSD) is a derangement of mood control with involuntary, emotionally fraught recollections that may follow deep psychological trauma in susceptible individuals. This condition is treated with pharmacological and/or cognitive therapies as well as psychotherapy with eye movement desensitization and reprocessing (EMDR). However, only a very limited number of studies have been published dealing with work-related PTSD, and investigations on the effect of treatment on cerebral blood flow represent an even smaller number.**

Aim **To investigate the short-term outcome of occupation-related PTSD after EMDR therapy by ^{99m}Tc-HMPAO SPECT.**

Method **Fifteen patients, either train drivers suffering from PTSD after having been unintentionally responsible for a person-under-train accident or employees assaulted in the course of duty, were recruited for the study. ^{99m}Tc-HMPAO SPECT was performed on these patients both before and after EMDR therapy while they listened to a script portraying the traumatic event. Tracer distribution analysis was then carried out at volume of interest (VOI) level using a three-dimensional standardized brain atlas, and at voxel level by SPM. The CBF data of the 15 patients were compared before and after treatment as well as with those of a group of 27 controls who had been exposed to the same psychological traumas without developing PTSD.**

Results **At VOI analysis significant CBF distribution differences were found between controls and patients before and after treatment ($P=0.023$ and $P=0.0039$, respectively). Eleven of the 15 patients responded to treatment, i.e., following EMDR they no longer fulfilled the DSM-IV criteria for PTSD. When comparing only the eleven responders with the controls, the significant group difference found before EMDR ($P=0.019$) disappeared after treatment. Responders and non-responders showed after therapy significant regional differences in frontal, parieto-occipital and visual cortex and in hippocampus. SPM analysis showed significant uptake differences between patients and controls in the orbitofrontal cortex (Brodmann 11) and the temporal pole (Brodmann 38) both before and after treatment. A significant tracer distribution difference present before treatment in the uncus (Brodmann 36) disappeared after treatment, while a significant difference appeared in the lateral temporal lobe (Brodmann 21).**

Conclusion **Significant ^{99m}Tc-HMPAO uptake regional differences were found, mainly in the peri-limbic cortex, between PTSD patients and controls exposed to trauma but not developing PTSD. Tracer uptake differences between responders and patients not responding to EMDR were found after treatment suggesting a trend towards normalization of tracer distribution after successful therapy. These findings in occupational related PTSD are consistent with previously described effects of psychotherapy on anxiety disorders.** ***Nucl Med Commun*** **28:757–765 © 2007 Lippincott Williams & Wilkins.**

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Keywords: post-traumatic stress disorder, eye movement desensitization and reprocessing, follow-up, ^{99m}Tc-HMPAO SPECT, VOI analysis, SPM

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Introduction

Post-traumatic stress disorder (PTSD) may follow upon a psychological trauma involving the experience of extreme physical danger and/or of acute fear. The major symptom is the evocation of traumatic memory with concomitant autonomic reactions to trauma associated triggers. This troublesome mental repetition of the trauma leads to avoidance of triggers and a general numbing of feelings as well as disturbed impulse control with hyper-vigilance, reactions that cause impairment in the capacity to lead a normal life [1]. Previous studies have described PTSD as the fourth most common psychiatric disorder [2] with 4–8% prevalence among the general population [2–4].

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Important factors for the development of PTSD are aggregated trauma exposure and the nature of the trauma. Earlier traumatic experiences increase the risk [5], and exposure to direct physical threats increases the likelihood of PTSD than purely witnessing a traumatic event. In this respect, events involving assault are more likely to provoke PTSD than other traumatic experiences [6–8].

Train drivers having been unintentionally responsible for person-under-train accidents are expected to develop PTSD in about 7% of cases [9], whereas persons suffering assault have been reported to develop PTSD in up to 20% of cases [6,10].

PTSD is treated with pharmacological as well as psychological therapies most successfully with behavioural therapy and eye movement desensitization and reprocessing (EMDR) [11]. EMDR is a manualized method utilizing, among other things, relaxation exercises, cognitive restructuring, imagery combined with sensory stimulation, safe place exercises and future projections [12].

Follow-up studies on cases of major depression [13–17] and PTSD [18] have described the effect of various drugs on regional cerebral blood flow (rCBF, in the following CBF). Previous CBF studies on PTSD utilizing both positron emission tomography (PET) and single photon emission computed tomography (SPECT) have mainly focused on victims of sexual and combat assault [19]. Only one study on a limited number of subjects reported an improvement in blood flow impairment to cingulated and frontal cortex with psychotherapy [20].

The purpose of the present study was to investigate the short-term effect of EMDR therapy on occupation-related PTSD, where CBF differences in patients before and after EMDR were assessed by perfusion SPECT analysed at volume of interest (VOI) and voxel (statistical parametric mapping, SPM) levels. Also assessed were the tracer distribution differences between patients and a group of controls exposed to the same type of trauma without developing PTSD.

Methods

Subjects

Fifteen subjects suffering from PTSD were recruited in the years 1999–2002 among Stockholm Public Transport employees working as train drivers, ticket collectors or service staff on subways, commuter trains and national long-distance trains. Train drivers registered by the company as having been unintentionally responsible for a person-under-train accident ($n = 10$) or employees having been assaulted ($n = 5$) on the job were invited to participate in the study. All subjects had been exposed to one or more accidents and were drug naive at the time of examination. As for the assault sub-group, subjects were victims of robberies or random harassment violence. There were no head injuries and no injuries to internal organs but there were muscle–skeletal pain and bruises. There was one bone fracture.

It was a homogenous group in terms of psychological negative load and physical damage. All subjects had previously taken part in an earlier investigation [21] and were included in this study after agreement to undergo a post-EMDR treatment SPECT.

Subjects were investigated both before and 2–4 weeks after the completion of treatment. The ^{99m}Tc-D,L-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO, Ceretec, Amersham International plc, Little Chalfont, UK) uptake on these occasions was compared with the uptake distribution in a group of 27 controls who had been exposed to the same type of trauma but had not developed any long-lasting PTSD symptoms. This study was carried out in close cooperation with the occupational health services. Subjects with a trauma exposure occurring over three months but less than 6 years before the investigation were included. At the start of treatment, the time from the trauma was over 1 year for all participants. The only exclusion criterion was major psychiatric disorder.

Participants were given written and oral information and gave written and oral consent. The study was approved by the local Ethics and Radiation Safety Committees.

Diagnostic interviews

Psychiatric diagnoses, including PTSD, were established according to the *Diagnostic and Statistical Manual of Mental Disorder*, edn 4 (DSM-IV) criteria [1]. Clinical assessment was performed according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1) [22] by a psychiatrist blind to the experimental condition of the participants and not otherwise engaged in the study. An individualized script portraying the traumatic event was constructed according to the method described by Lang [23] for each participant. The scripts were recorded on tape by a research assistant.

Procedure

The subjects, fasting from midnight, were admitted to a quiet neutral room at 8:00 a.m. and positioned on a couch where an i.v. line was inserted into the right cubital vein. They were then kept in resting conditions for 30 min, during which time blood pressure and heart rate were monitored. The previously recorded script was then presented to each subject through ear phones for a duration of 1.5 min. When the tape had been running for 15 s the radiopharmaceutical was injected in bolus into the i.v. line. Thereafter subjects were asked to recall the

event in their own minds for one more minute. Twenty minutes later, subjects were brought to the SPECT camera.

Treatment

EMDR is a novel eclectic therapy method developed by Shapiro [12] and utilizing, among other techniques, relaxation exercises, safe-place exercises, cognitive restructuring, future projections and imaging of the trauma combined with positive sensory stimulation. New trauma memories that arise during exposure to the recalled trauma are dealt with in a similar way. The bilateral sensory stimulation includes either (1) eye movements while following the finger of the therapist; (2) alternating sound produced by the therapist snapping fingers; or (3) tapping the hands of the client.

The therapy was given in five 90-min sessions with an interval of 1–2 weeks over a maximum period of 8 weeks. Fidelity of the treatments to the EMDR protocol was evaluated by an external psychologists not otherwise involved in the project.

Scanning protocol

The radiopharmaceutical was prepared according to the manufacturer's instructions. One thousand megabecquerels (27.0 mCi) of ^{99m}Tc-HMPAO were 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, Ohio, 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 two-dimensional Hamming filter with a cut-off frequency of 2.25 cycles·cm^{-1}. Sectional images were reconstructed by filtered back projection using a ramp filter with a cut-off frequency of 0.6 cycle·cm^{-1}. During pre-processing, 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

Volume of interest analysis

Computerized Brain Atlas (CBA; Applied Medical Imaging, Uppsala, Sweden) is a software tool for analysis of neuroimaging data based on a detailed three-dimensional atlas derived from a cryosectioned brain. All image sets were spatially normalized into the stereotactic space of the atlas by using the global polynomial transformation implemented in the CBA software, consisting of translations, rotations and linear scaling along and around each of the three image axes. The CBA also contains 18 non-linear shape-deforming parameters that make it possible to individualize the shape of the brain. In this study, the fully automatic fitting method was systematically implemented. The methodology and CBF data extraction are described in detail elsewhere [24,25].

For evaluation and statistical analysis of the reformatted data sets, 58 volumes of interest (VOIs) corresponding to Brodmann areas (BA) and anatomically defined grey matter regions were selected. These regions, bilaterally, covered almost the whole temporal, prefrontal, frontal, parietal, cingulated and occipital cortex as well as the amygdala, thalamus, putamen, nc. caudatus and hippocampus. Global CBF was considered to be the average value of all 58 analysed VOIs.

In order to obtain a set of normalized relative flow data, a scaling factor was computed by averaging the brain voxels data and setting the global brain average to a pre-defined value. The normalized values were set to 50 'uptake units' and all relative CBF distribution values in this work were related to this value. After adaptation and definitions of VOIs using the CBA software, the VOI data on all subjects were exported to a statistical package [26] for subsequent statistical analysis.

Analysis of variance (ANOVA) was used to test the statistical significance of CBF data, considering the groups (patients and controls; responders and controls; responders and non-responders) as independent between-subject variables, and VOIs and hemispheres as within-subject variables. In both analyses, the small number of females and males per cell precluded gender as a third between-subject variable. The significance level was set at $P < 0.05$. After significant VOI* groups interaction, single ANOVA were performed.

Voxel-based analysis

SPECT raw images were transformed into the analyse format by XMedCon package. Data were analysed with SPM2 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 6.5.1. All images smoothed with a Gaussian kernel filter of 12 mm (FWHM) to account for the inter-subject normal variations and to increase the signal-to-noise ratio. The grey matter threshold was set at 0.8 and normalization of global CBF to 50 was performed with proportional scaling.

The SPM{t} maps were then transformed to the unit of normal distribution (SPM{z}, z-scores). Because of the lack of any topographic a priori hypothesis, the significance of identified regions was assessed using P-values corrected for multiple comparisons and implemented in SPM2. The first statistical significance to be accepted at the cluster level was $P < 0.001$ corrected. Only those clusters containing more than 100 voxels were accepted

as significant. This was based on the calculation of the partial volume effect resulting from the spatial resolution.

The voxel-based analyses were performed using SPM2 and implementing the 'compare populations, 1 scan/subject (two-sample *T* test)' design model. When within-subjects analyses were carried out 'population main effect, 2conds, 1 scan/cond (paired *T*)' was implemented. Significances were analysed for the following four tracer uptake distribution comparisons: (1) patients before EMDR minus patients after EMDR; (2) patients before EMDR minus controls; (3) patients after EMDR minus controls; (4) responders minus controls; and vice versa.

SPM2 co-registers the individual SPECT to the 152 brains average of the Montreal Neurological Institute (http://www.bic.mni.mcgill.ca). Because this template does not completely match the Talairach brain [27], it is necessary to correct the SPM{*t*} coordinates. This was achieved by using the subroutine implemented by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) that gives the correspondence between SPM coordinates and Talairach coordinates. Brodmann areas were then identified, after importing the corrected coordinates, by the Talairach Deamon Database (http://ric.uthscsa.edu/projects/talairachdaemon.html).

Results

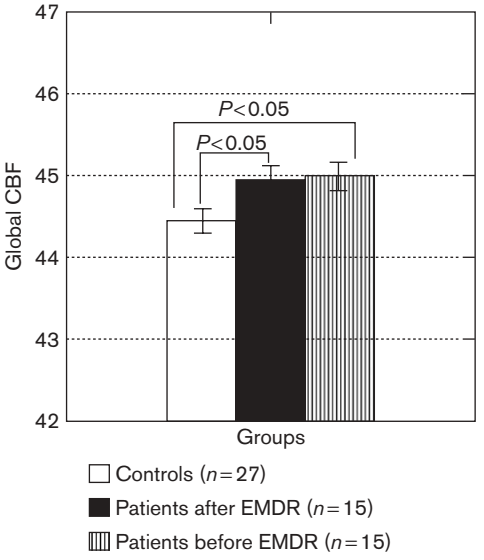
EMDR therapy was effective in 11 of 15 patients as assessed by DSM-IV criteria for PTSD. Frequencies of patients in the person-under-the-train and assault subgroups did not statistically differ. Moreover, when ANOVA was performed on VOIs data the type of trauma, considered as between-subjects factor, did not have any statistically significant effect, neither before nor after therapy.

CBA analysis

Comparing the CBF data between all patients before treatment and controls resulted in a significant global increased ^{99m}Tc-HMPAO distribution in the former group (Fig. 1; $F(1,40) = 5.612$; $P = 0.023$). Significant differences were also found by ANOVA in VOIs ($F(26, 1040) = 151.613$; $P < 0.001$), hemispheres ($F(1,40) = 54.237$; $P < 0.001$) and VOI*hemisphere interaction ($F(26,1040) = 26.076$; $P < 0.001$). Significant global increase in tracer uptake between all patients and controls was also found after treatment (Fig. 1; $F(1,40) = 4.573$, $P = 0.039$).

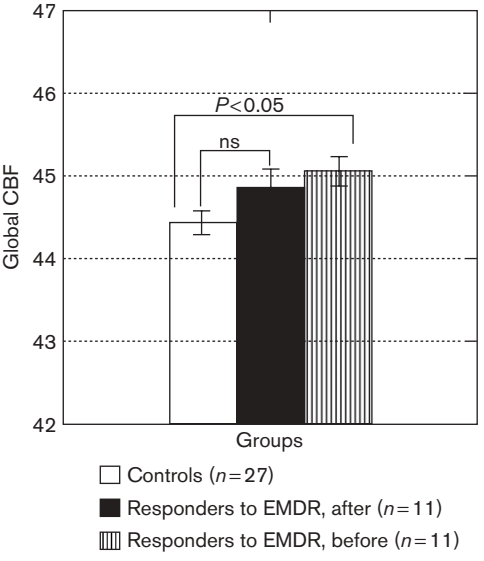
Following EMDR a further analysis was performed on the eleven patients that responded to treatment. Before treatment a significant global tracer distribution difference between responders and controls ($F(1,36) = 6.081$; $P = 0.019$) was found. Such difference disappeared after treatment (Fig. 2).

Fig. 1



Graph depicting normalized tracer uptake distribution global values and statistical differences between PTSD patients ($n=15$), before and after EMDR treatment, and controls ($n=27$).

Fig. 2



Graph depicting normalized tracer uptake distribution global values and statistical differences between responders ($n=11$), before and after EMDR treatment, and controls ($n=27$).

The CBF of the 11 responders was then compared to that of the four non-responders. Before treatment VOI analysis did not show any difference between the two groups, while a significant VOI*group interaction was found after treatment ($F(26,338) = 1.737$, $P < 0.025$).

Table 1 Means and SD for significant volumes of interest in the comparison of responders versus non-responders to eye movement desensitization and reprocessing

Brain area	Responders ($n=11$)		Non responders ($n=4$)		$F(1,13)$	P-value
	Mean	SD	Mean	SD		
BA17	46.4	1.9	49.2	1.9	6.414	0.025
BA37	41.6	1.5	44.0	1.8	6.397	0.025
BA46	43.0	0.6	41.9	1.2	6.220	0.027
Hippocampus	41.8	1.4	44.3	1.1	10.078	0.007

BA, Brodmann's area.

Single ANOVA revealed that this effect was due to significant differences in BA17 ($F(1,13) = 6.414$, $P = 0.025$), BA37 ($F(1,13)=6.397$, $P=0.025$), BA46 ($F(1,13)= 6.220$, $P=0.027$) and hippocampus ($F(1,13)=10.078$, $P=0.007$; Table 1).

Voxel-based analysis

SPM did not show in patients any significant regional difference in ^{99m}Tc-HMPAO distribution as assessed before and after EMDR treatment.

Comparing the CBF distribution in patients before treatment with that of controls resulted in a significantly increased tracer uptake in the temporal pole, medial temporal cortex and orbito-frontal cortex (Table 2, Fig. 3).

In the comparison between patients after treatment and controls, tracer distribution differences were found in the same regions as in the previous comparison, but extended to the lateral temporal cortex and to the hypothalamus and were not present in the medial temporal cortex (Table 3, Fig. 4).

Both VOI and SPM analyses in patients did not show significant differences when comparing ^{99m}Tc-HMPAO distribution before and after EMDR. This held true even when the analysis was restricted to the 11 responders.

Discussion

There was a significantly increased ^{99m}Tc-HMPAO uptake in PTSD patients compared with controls both before and after therapy with EMDR (Figs 1, 3 and 4; Tables 2 and 3). Eleven of 15 patients improved after EMDR and treatment at between-subject level had a substantial global effect on ^{99m}Tc-HMPAO uptake as inferred by the disappearance of the group effect in VOI analysis after treatment (Fig. 2). This indicates a trend towards normalization of PTSD related CBF changes following psychotherapy.

Regional CBF differences between the 15 PTSD patients before treatment as compared with controls were found in orbito-frontal (BA 11) as well as in temporal cortex. Orbito-frontal cortex is a multifaceted cortical territory that links to widespread brain structures, has a pivotal role in encoding and retrieval of verbal memories and is involved in mediating anxiety symptoms. The CBF uptake increase found in our PTSD patients in BA11 is consistent with previous studies suggesting the involvement of this structure in anxiety disorders [28–30] and PTSD [31–34].

The relatively increased PTSD-related CBF distribution in the temporal pole (BA38), belonging to the paralimbic belt, confirms the emotional dysregulation and hyper-reactivity disturbances previously reported for this group [33,34].

The medial temporal lobe (BA36, uncus, belonging to the para-hippocampal gyrus) involved in the repetition of emotionally salient stimuli [35] as well as in processing defence reactions to threat [36], showed before treatment a significant tracer uptake increase, but this difference disappeared after treatment. This possible effect of EMDR on medial temporal lobe was also supported by the finding that responders as compared to non-responders showed post-treatment a significantly lower hippocampal, occipito-temporal (BA37) and visual (BA17) cortex CBF (Table 1). This trend of a tracer distribution normalization is consistent with previous investigations, where a significant deactivation of the hippocampus following pharmacological and/or psychotherapy has been found in both functional [29,37,38] and neuroanatomic [39] studies. In particular, a PET study showed that cognitive–behavioural therapy was found to decrease CBF in the rhinal and para-hippocampal cortices of phobic patients [37] and to increase right posterior cingulated cortex in depressed patients [40].

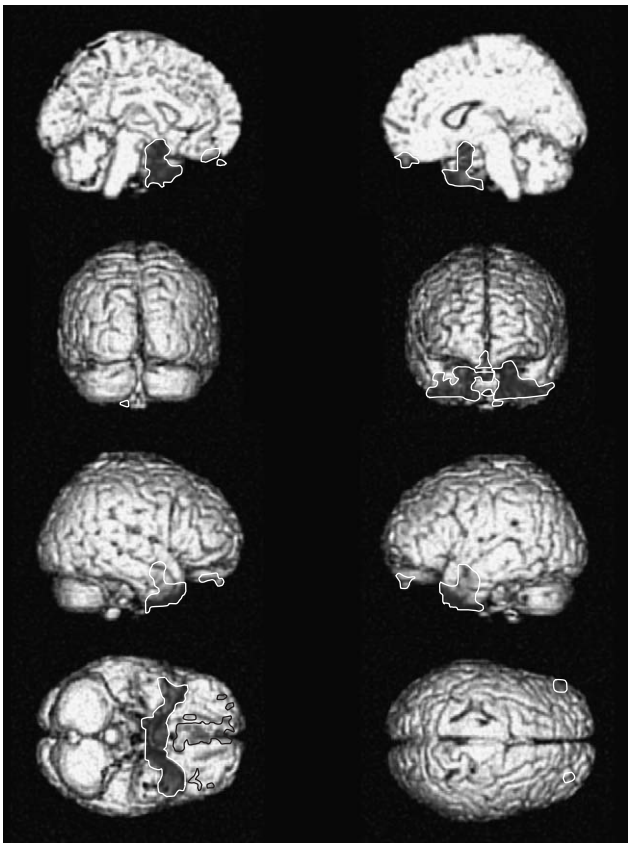
The finding of increased tracer uptake in PTSD patients before therapy extending to the lateral aspect of the temporal lobe (BA21) at the SPECT performed after EMDR is in agreement with a previous investigation into major depressive disorder showing an inter-personal therapy-dependent increase in regional metabolism in the temporal lobe [15]. This could be interpreted

Table 2 SPM statistics relative to the image resulting from the subtraction of rCBF data of non-symptomatic subjects from those of PTSD patients before EMDR treatment

Cluster level		Voxel level				Talairach coordinates			Anatomical and functional locations
p(cor)	equivk	p(FDR-cor)	T	equivZ	p(unc)	*x*	*y*	*z*	
0.001	2698	0.007	5.21	4.52	0.000	−24	15	−39	L: Superior temporal gyrus BA 38
		0.007	4.63	4.12	0.000	3	36	−35	R: Orbital gyrus BA 11
		0.012	4.16	3.77	0.000	−21	−1	−25	L: Uncus BA 36
		0.018	3.91	3.58	0.000	15	51	−30	R: Orbital gyrus BA 11
		0.026	3.70	3.41	0.000	24	51	−25	R: Superior frontal gyrus BA 11
		0.064	3.25	3.04	0.001	30	51	−23	R: Superior frontal gyrus BA 11
		0.077	3.15	2.96	0.002	3	−1	−15	Hypothalamus
		0.089	3.07	2.89	0.002	39	22	−31	R: Superior temporal gyrus BA 38
		0.070	3.01	2.84	0.002	42	25	−26	R: Superior temporal gyrus BA 38
		0.085	2.89	2.74	0.003	27	42	−27	R: Superior frontal gyrus BA 11
		0.091	2.85	2.70	0.003	21	−1	−25	R: Uncus BA 36

SPM, statistical parametric mapping; rCBF, regional cerebral blood flow; PTSD, post-traumatic stress disorder; EMDR, eye movement desensitization and reprocessing.

Fig. 3



Three-dimensional rendering of voxels reflecting higher tracer distribution in patients before EMDR ($n=15$) as compared to controls ($n=27$). The significant statistical differences are highlighted. The first row represents the medial aspect of left (on the left) and right (on the right) hemispheres; the second row represents the posterior (on the left) and anterior (on the right) aspect on the brain; the third row represents the lateral aspect of the right (on the left) and of the left (on the right) hemispheres; the fourth row represents the inferior (on the left) and the superior (on the right) aspects of the brain.

as a change in the inner trauma experience from conditioned repetitions towards a normalized autobiographical memory.

The tendency of global tracer uptake to normalize found at between-subjects level by VOI analysis in responders (Fig. 2) is consistent with previous reports of regional CBF changes in anxiety disorders following therapy [15,18,29,37,38,40]. However, at within-subjects analysis level no significant global difference was found comparing CBF before and after treatment. A possible explanation for the discrepancy between the improvement of symptoms and the lack of global CBF changes might be, along with the relatively small sample size, the short duration of the psychotherapy, as well as the short interval between treatment completion and the second SPECT, preventing the detection of individual CBF changes that might have occurred during the following months. In this respect, a recent MRI investigation of PTSD patients found no difference in hippocampal volume as assessed a few weeks after psychotherapy [41].

The only SPECT follow-up study in PTSD after psychotherapy that we are aware of also used a script-driven imagery provocation procedure, showing an anterior cingulated and left frontal lobe CBF increase following EMDR therapy [20]. The smaller group size and the different subtype of PTSD subjects might have accounted for the discrepancies with our results.

Patient selection in the present study was based on occupational hazard PTSD and as such is one of the very few investigations dealing with work-related traumas.

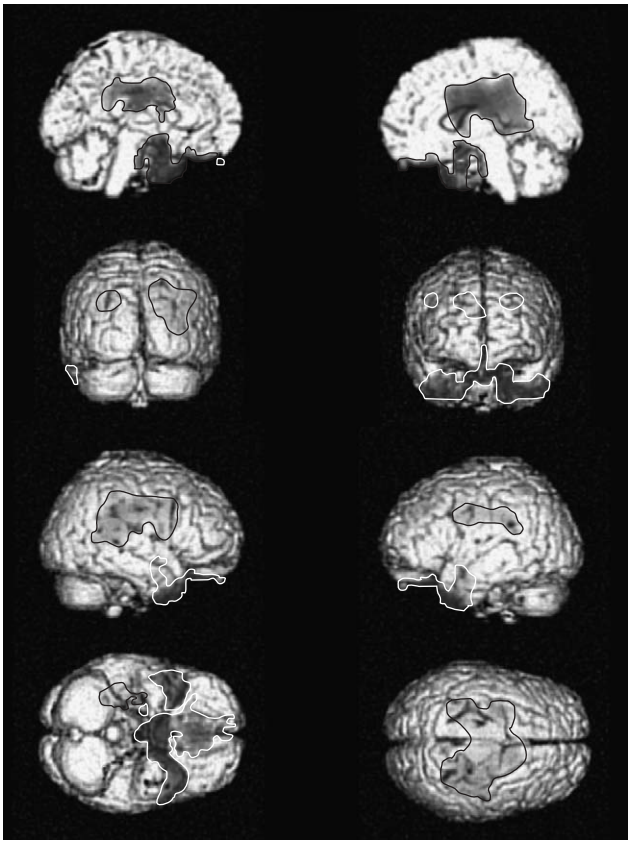
In the present investigation, the neurobiological changes at global level were highlighted by the multivariate approach of ANOVA implemented in VOI analysis, enabling the identification of more general effects as compared with the univariate statistics implemented by SPM. Using SPM, diffuse changes at subliminal statistical level or not clustering in a number of voxels exceeding the determined threshold (100 voxels in

Table 3 SPM statistics relative to the image resulting from the subtraction of rCBF data of non-symptomatic subjects from those of PTSD patients after EMDR treatment

Cluster level		Voxel level				Talairach coordinates			Anatomical and functional locations
p(cor)	equivk	p(FDR-cor)	T	equivZ	p(unc)	*x*	*y*	*z*	
0.000	2828	0.000	7.04	5.65	0.000	−18	16	−36	L: Superior temporal gyrus BA 38
		0.000	6.24	5.19	0.000	9	39	−35	R: Orbital gyrus BA 11
		0.016	3.80	3.49	0.000	0	−4	−15	Hypothalamus
		0.018	3.75	3.45	0.000	27	42	−27	R: Superior frontal gyrus BA 11
		0.019	3.71	3.42	0.000	24	51	−25	R: Superior frontal gyrus BA 11
		0.019	3.71	3.42	0.000	−50	7	−36	L: Middle temporal gyrus BA 21
		0.020	3.70	3.41	0.000	48	4	−38	R: Middle temporal gyrus BA 21
		0.066	3.06	2.88	0.002	30	51	−23	R: Superior frontal gyrus BA 11
		0.085	2.61	2.49	0.006	50	13	−31	R: Superior temporal gyrus BA 38

Abbreviations as in the footnote to Table 2.

Fig. 4



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our study) are not recognized preventing the identification of possible global and local differences, respectively. On the other hand, SPM highlighted finer regional changes than VOI analysis since the size of SPM-derived cluster was considerably smaller than the VOIs templates predetermined by CBA. Other sources of discrepancies of findings between the two methods may derive from the different spatial normalization processes and from the lack of topographic coincidence between significant clusters at SPM and VOIs. In the present study these methodological differences might have accounted for the lack in VOI analysis of significant differences in orbitofrontal and temporal lobe cortices in which the size of the significant cluster at SPM was considerably smaller and/or not topographically corresponding to the homologous VOI.

In this respect, Bonne *et al.* [42] reported some overlap of the significant differences between two groups of depressed patients in a conjunct ROI/SPM analysis. The choice of a double-data analysis has underscored the specific capability and complementarity of different methodologies in identifying local and global changes in functional neuroimaging.

In conclusion, we found significant CBF distribution differences, mainly in the peri-limbic cortex, between PTSD subjects and trauma exposed controls who did not develop PTSD symptoms. When restricting the analysis to the 11 responders to treatment, CBF differences found before treatment disappeared, indicating that the effect of EMDR on the clinical status paralleled a trend towards normalization of tracer uptake. These findings are consistent with the previously described influence on CBF of pharmacological and psychotherapeutical interventions in anxiety disorders and encourage the use of SPECT to explore the neurobiological changes in a variety of psychiatric syndromes in which defined patterns of tracer distribution have not been extensively investigated yet.

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