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Gray matter density in limbic and paralimbic cortices is associated with trauma load and EMDR outcome in PTSD patients

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ABSTRACT

There is converging evidence of gray matter (GM) structural alterations in different limbic structures in Post-Traumatic Stress Disorder (PTSD) patients. The aim of this study was to evaluate GM density in PTSD in relation to trauma load, and to assess the GM differences between responders (R) and non-responders (NR) to EMDR therapy. Magnetic Resonance Imaging (MRI) scans of 21 subjects exposed to occupational trauma, who developed PTSD (S), and of 22 who did not (NS), were compared by means of an optimized Voxel-Based Morphometry (VBM) analysis as implemented in SPM. Within S, further comparisons were made between 10 R and 5 NR. A regression analysis between GM density and the Traumatic Antecedents Questionnaire (TAQ) was also performed on all 43 subjects. Results showed a significantly lower GM density in S as compared to NS in the left posterior cingulate and the left posterior parahippocampal gyrus. Moreover, NR showed a significantly lower GM density as compared to R in bilateral posterior cingulate, as well as anterior insula, anterior parahippocampal gyrus and amygdala in the right hemisphere. Regression analysis showed that GM density negatively correlated with trauma load in bilateral posterior cingulate, left anterior insula, and right anterior parahippocampal gyrus. In conclusion, a GM lower density in limbic and paralimbic cortices were found to be associated with PTSD diagnosis, trauma load, and EMDR treatment outcome, suggesting a view of PTSD characterized by memory and dissociative disturbances.

1. Introduction

Post-Traumatic Stress Disorder (PTSD) is an anxiety disorder following an exposure to a traumatic event, and is characterized by a series of symptoms comprising intrusions (i.e. nightmares, flashbacks), hyperarousal (i.e. insomnia, exaggerated startle response), numbing (i.e. restricted affect, anhedonia), and avoidance of trauma-related stimuli (DSM-IV, American Psychiatric Association, 1994). PTSD has also been characterized as a memory disorder in which the reliving of non-integrated traumatic memories is the central dysfunction (van der Kolk et al., 1997; Högberg, 2008).

Several neural structures have been recognized to play a role in the generation of PTSD symptoms, and some models have been proposed (Rauch and Shin, 1997; Pitman et al., 2001; Liberzon and Phan, 2003), according to which PTSD may be conceptualized as a state of heightened responsivity to threatening stimuli and/or a state of insufficient inhibitory control over exaggerated threat-sensitivity (Liberzon and Sripada, 2008).

Functional neuroimaging studies have provided further information about the neural correlates of PTSD, by means of different research paradigms such as symptom provocation, cognitive activation, and functional connectivity (for recent reviews, see Francati et al., 2006; Liberzon and Sripada, 2008). These studies consistently show both amygdala hyperreactivity, and a correspondingly reduced medial prefrontal cortex (including ACC) control over amygdalae (BOLD signal in these structures was found to negatively correlate; see Shin et al., 2005), as the core functional mechanisms implicated in PTSD. However, functional changes in other neural structures have been reported in PTSD: insula (Rauch et al., 1996; Osuch et al., 2001; Liberzon et al., 2007), posterior cingulate (Bremner et al., 1999; Lanius et al., 2004), and occipital cortex (Rauch et al., 1996; Hendler et al., 2001) exhibiting an increased activity, whereas temporal regions (Shaw et al., 2002) showed reduced activity.

Structural alterations (such as gray matter reductions) may occur either as a predisposing factor for the development of PTSD, or

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as a neurotoxic consequence (higher concentration of cortisol) of the condition (Nutt and Malizia, 2004). Therefore, establishing causality in structural studies is difficult. There is evidence that cortical structural alterations in PTSD patients primarily comprise hippocampal volume loss in comparison with trauma-exposed non-PTSD subjects, or to healthy controls (Nutt and Malizia, 2004; Karl et al., 2006).

However, abnormalities in other brain structures have also been found, for instance: cavum septum pellucidum (Myslobodsky et al., 1995; May et al., 2004), anterior cingulate cortex (Rauch et al., 2003; Yamasue et al., 2003; Kitayama et al., 2006), caudate nucleus (Looi et al., 2009), and corpus callosum (Villareal et al., 2004); but negative findings have also been reported (Freeman et al., 2006; Jatzko et al., 2006). These inconsistencies may have been the result of several factors (see Karl et al., 2006), such as: type of control group, presence of co-morbid conditions, age at trauma exposure, time elapsed since trauma, trauma severity, kind of traumatization, and type of volumetric approach (i.e. manual segmentation vs. fully-automated morphometry).

In traditional manual segmentation (Bezdek et al., 1993; Zijdenbos and Dawant, 1994; Clarke et al., 1995), the volume of the whole brain (or its subparts) is measured by drawing regions of interest (ROIs) on images from brain scanning and calculating the volume enclosed. This has been used in most PTSD volumetric studies (Karl et al., 2006). However, manual segmentation has several disadvantages: the problem of inter- and intra-rater reliability, it is very time-consuming, and may be less effective in measuring smaller differences in volume. On the other hand, Voxel-Based Morphometry (VBM) is a recent and promising neuroimaging analysis technique that allows the investigation of focal differences in brain anatomy in a data-driven way, by applying Statistical Parametric Mapping to high-resolution MRI, and which avoids the above-mentioned limitations while keeping a high degree of reliability and may be suitable for larger scale studies (Ashburner and Friston, 2000).

Previous studies investigating structural brain alterations in PTSD patients using VBM have consistently found hippocampal, anterior cingulate and insular GM reductions (Yamasue et al., 2003; Chen et al., 2006; Li et al., 2006; Kasai et al., 2008). Moreover, VBM has been successfully implemented to correlate GM density with other relevant variables such as behavioral scales (Yamasue et al., 2003) and disease duration (Emdad et al., 2006).

Eye-Movement Desensitization and Reprocessing (EMDR) is a relatively new therapy method (Shapiro, 1995) of demonstrated efficacy (van Etten and Taylor, 1998; Shepherd et al. 2000; Davidson and Parker, 2001; Bradley et al. 2005), predominantly used in the treatment of PTSD. Recently, several neuroimaging studies have shown that various psychotherapeutic treatments are able to change brain functioning (see Roffman et al., 2005; Linden, 2006; Peres et al., 2007; Lindauer et al., 2008), although to date the neuroanatomical correlates of EMDR therapy have been seldom investigated (Pagani et al., 2007; Bossini et al., 2007). As a corollary, we may consider whether pre-existing structural brain abnormalities would be able to affect responsiveness to psychotherapy (in our case EMDR), and thus establish a potential biomarker for responsiveness to psychotherapy.

The aim of the present study is to investigate the differences in GM density by means of a Voxel-Based Morphometry (VBM) approach between symptomatic (S) and non-symptomatic (NS) occupational-related traumatized subjects, as well as to correlate their trauma load (as assessed by self-rating scales) to structural alterations. Such alterations are also investigated in a subset of PTSD patients who following EMDR therapy either recovered (R) or did not (NR).

In accordance with previous literature, we hypothesize that GM structural alterations related to PTSD and trauma load would be found especially in limbic and paralimbic cortices, i.e. hippocampus, insula, parahippocampal and cingulate cortex. We also hypothesize that GM structural abnormalities in these regions may be associated with responsiveness to EMDR treatment.

2. Method

2.1. Subjects

The present study was conducted on 43 workers from the public transportation system in Stockholm and Sweden (underground or long-distance trains) registered by the company as having either once or several times experienced a "person under a train" accident or having been assaulted at work. Table 1 displays relevant characteristics of all subjects employed in the present study, both on the whole and in the various subgroups.

Twenty-one patients with current PTSD (S) were compared to 22 subjects who had experienced the traumatic events but did not develop PTSD (NS). When subjects took part in the study, a period of time varying between three months and six years was elapsed since the traumatic event.

A subset of 15 PTSD patients underwent five 90 min EMDR (Eye-Movement Desensitization and Reprocessing) therapy sessions, resulting in 10 responders and 5 non-responders.

Exclusion criteria were a history of psychosis, major depressive disorder and other serious psychiatric conditions (i.e. bipolar disorder, obsessive compulsive disorder, attention-deficit/hyperactivity disorder), lifetime or current drug or alcohol abuse or dependency, significant medical condition, neurological illness, or a history of head injury. The handedness was determined by a self-administered and self-reported form.

Before entering the study, all participants were given a description of the procedures and written informed consent was obtained. The study was approved by the Local Ethics and Radiation Safety Committees.

2.2. Diagnosis

The diagnosis of PTSD was established according to DSM-IV criteria (American Psychiatric Association, 1994). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1997) formed the basis for diagnostic assessments, and was carried out by a psychiatrist not otherwise engaged in the study and blind to the experimental conditions of the participants. PTSD symptoms had to be present for at least one month and occurring at least 3 months before MRI.

In addition, the two scales of the self-rated Trauma Antecedent Questionnaire ("trauma and neglect" TAQ−, and "resilience factors" TAQ+; Herman et al., 1989), were administered to assess lifelong trauma load and resilience (Högberg et al., 2008). Each of these scales is further divided into four subscales which measure trauma load and resilience in four different life periods, i.e. age zero to six ("0–6"), seven to twelve ("7–12"), thirteen to eighteen ("13–18"), and older ("adult").

A second structured clinical interview was carried out immediately after the EMDR treatment (see below). Those who no longer fulfilled the DSM-IV criteria of PTSD were classified as remitters (R) and those who still met the diagnostic criteria of PTSD after treatment were classified as non-remitters (NR).

2.3. Therapy

The aim of the treatment in PTSD is to change the traumatic reliving to an ordinary, more neutral, episodic memory. One efficacious psychotherapeutic method is EMDR (Bradley et al., 2005). The key procedure in EMDR is the repeated simultaneous exposure

Table 1
Relevant characteristics of participants for all subjects, PTSD (S), non-PTSD (NS), remitters (R), and non-remitters (NR).

Variable	All	S	NS	R	NR	S vs. NS	R vs. NR
Woman/man	12/31	6/15	6/16	2/8	0/5	n.s.	n.s.
Swedish born/foreign born	25/18	10/11	15/7	5/5	3/2	n.s.	n.s.
Married or cohabitating/single	30/13	14/7	16/6	8/2	2/3	n.s.	n.s.
Person under train accident/assault	30/13	17/6	15/7	6/4	4/1	n.s.	n.s.
One/more work related traumata	18/25	3/18	15/7	0/10	0/5	$p < 0.01$	–
Age, mean (S.D.)	41 (9.1)	41.7 (9.4)	40.8 (8.9)	39.9 (8.8)	41.4 (11.7)	n.s.	n.s.
Years since index trauma, mean (S.D.)	2.6 (1.5)	2.5 (1.6)	2.6 (1.2)	3 (1.6)	1.2 (0.5)	n.s.	$p = 0.028$
TAQ+ mean score (S.D.)	49.2 (10.3)	47.1 (11.2)	51.1 (9.1)	45.4 (10.6)	48.2 (12)	n.s.	n.s.
TAQ− mean score (S.D.)	57.1 (34.4)	67.9 (29.4)	46.9 (36.4)	70.8 (39.1)	68.2 (16.6)	$p = 0.045$	n.s.

to an internally generated negative emotional memory with a positively valenced bilateral sensory stimulation such as following the finger of the therapist with the eyes, tapping on hands or snapping at the ears with the fingers. The therapeutic mechanism has been suggested to be counter-conditioning (Wolpe, 1958; Hedstrom, 1991; Wilson et al., 1996). The fidelity of the treatments to the EMDR protocol was evaluated by a psychologist not otherwise involved in the project.

2.4. MRI scanning protocol

MRI scanning was performed on one occasion prior to EMDR treatment on a GE Signa 1.5 T Scanner (GE, Milwaukee WI, USA) about 35 ± 21 months from index trauma. 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo) T1-weighted axial images were acquired with TR = 26 ms, TE = 7 ms, flip angle = 35°, slice thickness = 1.2 mm, matrix size = 256 × 256 × 124 slices, field of view = 220 × 220 × 149 mm, voxel size 0.86 mm^3.

2.5. Optimized VBM

Voxel-Based Morphometry (VBM) was used in an optimized version (Good et al., 2001) to process and analyze gray matter (GM) images using the VBM2 toolbox provided by C. Gaser (http://dbm.neuro.uni-jena.de/vbm/) for SPM2, running under MATLAB 6.5.1. Before running the optimized VBM protocol, each patient's dataset was manually reoriented with SPM2 by centering the origin of axes to the anterior commissure in order to improve the accuracy of both segmentation and normalization steps.

A customized GM template was then created in order to minimize potential normalization problems, to take into account the demographics of our patients, and to reduce the magnetic field inhomogeneities. This was done by segmenting and normalizing the GM volumes of each patient to a standard space with a 12-parameter affine model. In order to complete the creation of the customized template, the resulting normalized GM images of all the 43 patients were averaged and then smoothed with a Gaussian filter of 8 mm full-width at half-maximum (FWHM).

Raw segmented GM images of each patient were then normalized to the GM customized template by performing affine registration and 16 nonlinear iterations using 6 × 8 × 6 basis functions, and normalized images were resampled by trilinear interpolation to 1 × 1 × 1 mm voxel size. Finally, normalized images were smoothed with a 12-mm FWHM isotropic Gaussian filter to allow group analysis and render the data more normally distributed.

2.6. Statistical analysis

The resulting smoothed GM images underwent statistical analysis. Two design matrices were constructed: the first to test for regional differences in GM between S and NS subjects (43 images) and the second to test for regional differences between R and NR patients (15 images). In both models, age and the ratio GM/ICV (the latter calculated as the sum of GM, WM and CSF) were entered as nuisance variables to take into account their influence over brain tissue volumes (Mechelli et al., 2005). Scans were absolute thresholded for masking at 0.1 in order to exclude the influence of any remaining non-GM tissue.

Morphological differences between the groups were calculated across the whole brain on a voxel-by-voxel basis by means of *t*-tests, comparing NS > S and R > NR contrasts. A regression analysis between GM density and both the "trauma and neglect" (TAQ−), and "resilience factors" (TAQ+) scales of the Traumatic Antecedents Questionnaire was also performed on all 43 subjects irrespective of PTSD diagnosis by means of the "simple regression (correlation)" model as implemented in SPM2.

For the *t*-tests, a threshold of $p < 0.05$ corrected for multiple comparisons at cluster level was used. For regression analysis, we set a higher threshold ($p < 0.01$) corrected at cluster level, because it was performed on a considerably higher number of subjects ($n = 43$). In both analyses, an uncorrected threshold of $p < 0.001$ at voxel-level was chosen to shorten the list of the statistical peaks identified (which were very redundant and mostly located in the same areas already identified).

SPM2 coregisters the individual MR scans to the Montreal Neurological Institute (MNI) T1 template (http://www.bic.mni.mcgill.ca); since this template does not precisely correspond to the Talairach space (Talairach and Tournoux, 1988), it is necessary to correct the SPM coordinates. This was achieved using the subroutine implemented by Matthew Brett (http://www.mrccbu.cam.ac.k/Imaging/mnispace.html) that transforms the SPM coordinates into Talairach coordinates. Brodmann areas where then identified, after importing the corrected coordinates, by Talairach Daemon Database (http://ric.uthscsa.edu/projects/talairachdaemon.html).

3. Results

3.1. Clinical measures

Results for TAQ+ and TAQ− scores are summarized in Table 1. As compared to NS, S subjects showed significantly higher TAQ− scores ($t = 2.070$, $p = 0.045$), whereas NR subjects showed no significant differences in TAQ− scores as compared to R ($t = 0.140$, $p = 0.891$). TAQ+ mean scores did not show any significant difference between S and NS, nor between R and NR.

Mean scores of the four TAQ− subscales were also compared between the various groups. S and NS subjects did not significantly differ in their mean scores on the "0–6" ($t = 0.441$, $p = 0.666$), "7–12" ($t = 1.554$, $p = 0.128$), and "13–18" ($t = 1.475$, $p = 0.148$) TAQ− subscales. R and NR subjects did also not significantly differ in their mean scores on the "0–6" ($t = 0.528$, $p = 0.601$), "7–12" ($t = 0.481$, $p = 0.639$), and "13–18" ($t = 0.984$, $p = 0.343$) TAQ− subscales. S subjects showed significantly higher scores in the "adult" TAQ− subscale as compared to NS ($t = 3.165$, $p = 0.003$), whereas R and NR subjects did not significantly differ in their "adult" TAQ− subscale scores ($t = 1.191$, $p = 0.255$).

Although S and NS (as well as R and NR) as groups did not significantly differ one another in respect to the trauma load accumulated in earlier years, traumatic experiences gathered before adulthood did influence the actual trauma load within the subjects anyhow. For this reason, in the correlation analysis we used the total TAQ– score instead of the sole adult-TAQ– score, because we consider the former a more complete measure which takes into account any possible influence from earlier years.

3.2. Morphometric measures

The contrast NS > S showed a significant GM lower density in S as compared to NS in a series of structures predominantly in the left hemisphere, including posterior cingulate (Brodmann Areas 29 and 31), precuneus (BA 7), lingual gyrus (BA 18), as well as posterior parahippocampal gyrus (adjacent to BA 19) (Fig. 1A, Table 2).

The contrast R > NR exhibited a significant GM lower density in NR as compared to R in three different clusters: the first bilaterally located over posterior cingulate (BAs 23 and 31); the second centered over the left precentral (BA 4), middle and medial frontal gyri (BA 6); the third including anterior insula (BA 13), and the complex anterior parahippocampal gyrus/amygdala, over the right hemisphere (Fig. 1B, Table 3).

Regression analysis showed a significant negative correlation between GM density and TAQ– in the following areas: ACC (BA 32), PCC (BA 23), superior temporal gyrus (BA 22), and cerebellum bilaterally; anterior insula (BA 13), postcentral gyrus (BA 43), superior and medial frontal gyri (BA 6/8) over the left side; anterior parahippocampal gyrus (BA 34), subcallosal gyrus (BA 25), middle and medial frontal gyri (BA 9/10), rectal and inferior frontal gyri (BA 11), fusiform gyrus (BA 37), inferior temporal gyrus (BA 20), thalamus, and midbrain over the right hemisphere (Fig. 2, Table 4). No correlation between TAQ+ and GM density was found.

4. Discussion

In the present study, we have demonstrated that cortical GM alterations are associated with PTSD diagnosis and EMDR psychotherapy response, and that such alterations correlate with trauma load. We will first discuss the clinical implications of our findings, followed by a discussion of cortical GM concentration as a structural basis for PTSD and EMDR response.

4.1. Clinical considerations

The present study has shown that: (i) PTSD patients (S) had significantly higher trauma load total scores as compared with

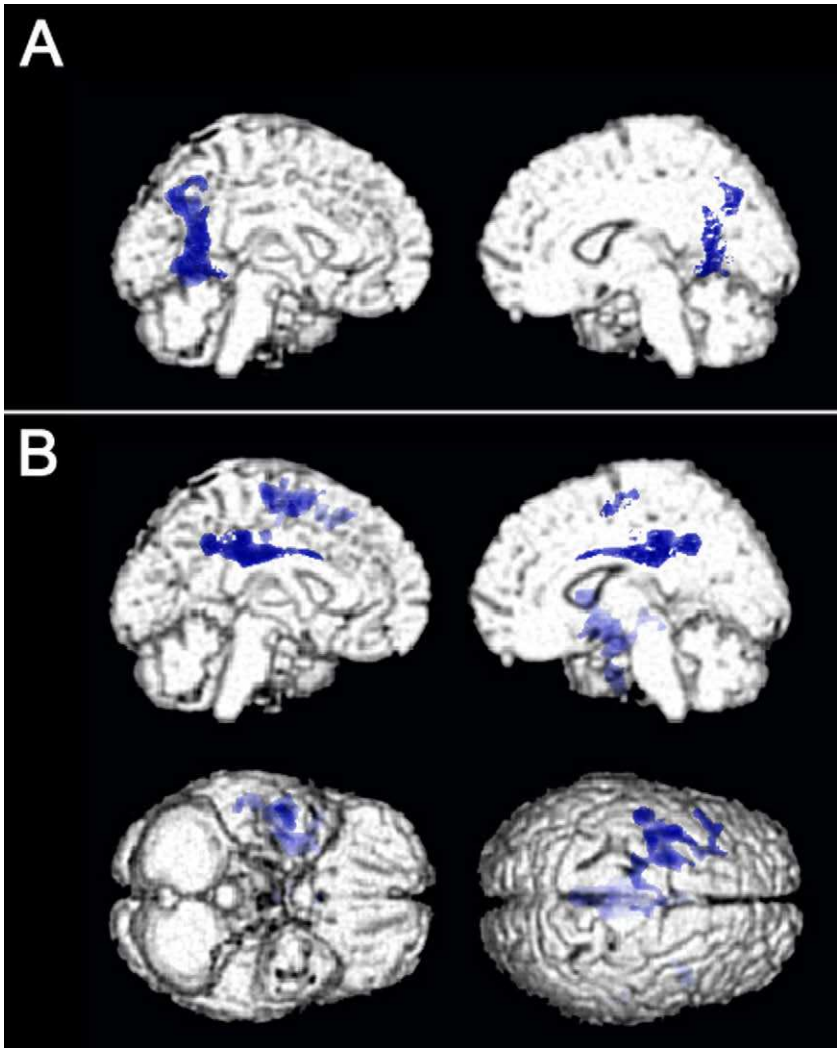

Fig. 1. (A) 3D rendering showing those regions in which GM density was significantly lower in PTSD patients (S, $n = 21$) as compared with non-symptomatic controls (NS, $n = 22$). (B) 3D rendering showing those regions in which GM density was significantly lower in non-remitting patients (NR, $n = 5$) as compared with remitters (R, $n = 10$) following EMDR therapy.

Table 2
Regions in which GM density was significantly lower in S as compared to NS (NS > S).

Cluster		Voxel		TAL			Region
p (cor.)	*K*	*Z*	*p* (unc.)⩽	*x*	*y*	*z*	
0.054	9132	3.59	0.001	−10	−60	3	L lingual gyrus BA18
		3.18	0.001	−23	−57	−2	L parahippocampal gyrus BA19
		3.05	0.001	−17	−55	32	L posterior cingulate BA31
		3.00	0.001	−3	−61	33	L precuneus BA7
		2.99	0.001	7	−50	2	R posterior cingulate BA29

p (cor.) = corrected *p*-value; *p* (unc.) = uncorrected *p*-value; *K* = cluster size; TAL = Talairach coordinates; BA = Brodmann Area.

Table 3
Regions in which GM density was significantly lower in NR as compared to R (R > NR).

Cluster		Voxel		TAL			Region
p (cor.)	*K*	*Z*	*p* (unc.)⩽	*x*	*y*	*z*	
0.036	7048	4.54	0.001	1	−27	36	R posterior cingulate BA 31
		3.78	0.001	−3	−27	33	L posterior cingulate BA 23
		3.40	0.001	−2	−32	31	L posterior cingulate BA 31
0.029	7300	4.03	0.001	−35	9	58	L middle frontal gyrus BA 6
		3.18	0.001	−46	−10	57	L precentral gyrus BA 4
		3.00	0.001	−3	0	50	L medial frontal gyrus BA 6
0.025	7471	3.16	0.001	41	12	7	R insula BA 13
		3.09	0.001	31	−5	−11	R parahippocampal gyrus/amygdala

p (cor.) = corrected *p*-value; *p* (unc.) = uncorrected *p*-value; *K* = cluster size; TAL = Talairach coordinates; BA = Brodmann Area.

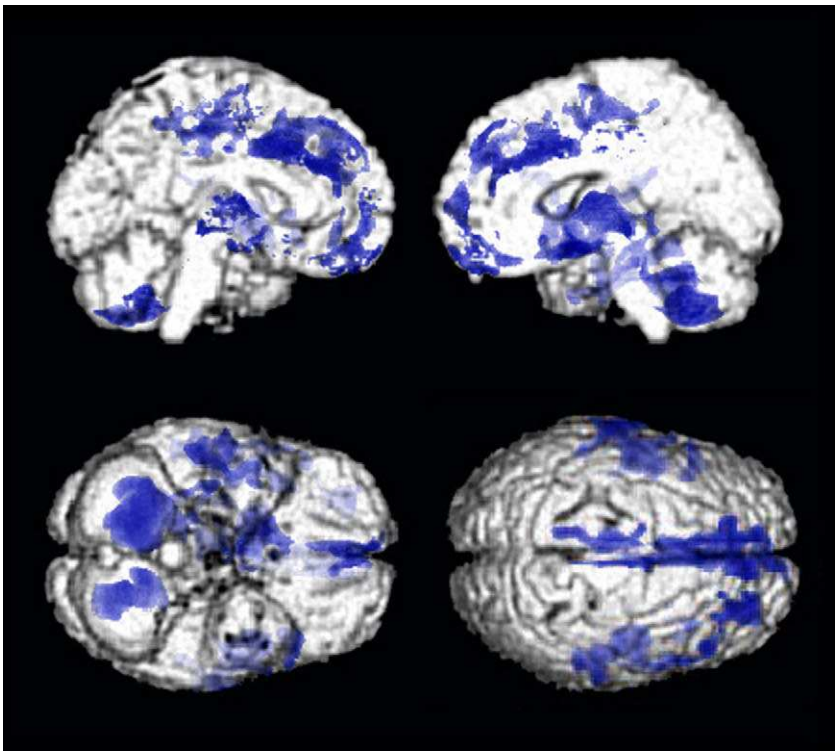

Fig. 2. 3D rendering showing those regions in which GM density negatively correlated with TAQ– in all subjects ($n = 43$) irrespective of the PTSD diagnosis.

non-symptomatic traumatized controls (NS); (ii) such higher scores were apparently not due to differences in the trauma exposure during childhood, adolescence or early youth ("0–6", "7–12" and "13–18" TAQ– subscales), but rather to a difference in the trauma load accumulated during adulthood ("adult" subscale); (iii) prior to EMDR treatment, remitting (R) and non-remitting (NR) patients did not significantly differ in their trauma load scores, neither in terms of total amount, nor in the TAQ– subscales.

An association of PTSD with a higher amount of trauma load is not surprising. Supposedly, traumatic experiences are necessary but not sufficient antecedents for PTSD. In fact, other factors such as genetic predisposition, personality, education, and gender (as well as trauma contingencies like age at exposure, and kind of traumatization) are known to play a relevant role (see van der Kolk, 1997). Thus, a given subject can experience several traumatic episodes during life, yet PTSD only occurs when the traumatic load

Table 4
Regions in which GM density negatively correlated with TAQ−.

Cluster		Voxel		TAL			Region
p (cor.)	*K*	*Z*	*p* (unc.)⩽	*x*	*y*	*z*	
0.001	8662	4.67	0.001	−44	4	−4	L insula BA 13
		4.63	0.001	−47	−9	1	L superior temporal gyrus BA 22
		4.42	0.001	−65	−13	15	L postcentral gyrus BA 43
0.001	5120	4.01	0.001	12	−3	−13	R parahippocampal gyrus BA 34
		3.55	0.001	17	7	−14	R subcallosal gyrus BA 25
		3.27	0.001	5	−9	−12	R midbrain
0.001	11536	3.92	0.001	4	23	30	R anterior cingulate BA 32
		3.86	0.001	10	50	36	R medial frontal gyrus BA 9
		3.74	0.001	−5	15	38	L anterior cingulate BA 32
0.001	10547	3.88	0.001	48	30	27	R middle frontal gyrus BA 9
		3.69	0.001	57	5	3	R superior temporal gyrus BA 22
0.032	2739	3.67	0.001	−8	−16	47	L medial frontal gyrus BA 6
		3.08	0.001	−6	−21	33	L posterior cingulate BA 23
		3.04	0.001	−9	−34	53	L superior frontal gyrus BA 6/8
0.003	4073	3.65	0.001	7	59	9	R medial frontal gyrus BA 10
		3.58	0.001	4	45	−23	R inferior frontal gyrus/rectal gyrus BA 11
0.001	5824	3.54	0.001	10	−15	3	R thalamus
0.014	3176	3.42	0.001	57	−14	−24	R fusiform gyrus BA 37
		3.32	0.001	52	−27	−22	R inferior temporal gyrus BA 20
0.001	10619	4.36	0.001	17	−60	−34	R cerebellum
0.005	3708	3.50	0.001	−11	−50	−31	L cerebellum

p (cor.) = corrected *p*-value; *p* (unc.) = uncorrected *p*-value; *K* = cluster size; TAL = Talairach coordinates; BA = Brodmann Area.

exceeds a given subjective threshold in presence of the predisposing genetic and environmental factors.

In our study, most of the trauma load was ascribed to traumatic events accumulated during adulthood. Our sample is made up of occupational-related traumatized subjects having experienced "person under the train" accidents, or having been assaulted at work. Consistent with this, S subjects reported more traumatic experiences during adulthood (i.e. their working period), whereas they do not differ from NS subjects in early life traumatic experiences. Given that age at trauma exposure is a relevant variable in PTSD, we consider that such evidence suggests certain uniformity in our sample. Moreover, the adult onset of PTSD in our subjects may account for the high response rate (66.6%) shown to the EMDR treatment (see van der Kolk et al., 2007), due to the relative recency of the trauma being more accessible to psychotherapeutic intervention.

Two thirds of our subjects no longer fulfilled PTSD diagnostic criteria following EMDR treatment. Differences in the EMDR outcome cannot be ascribed to any disparity in the trauma load between R and NR. On the basis of our protocol, we cannot address the issue of whether NR subjects would have benefited by more EMDR sessions, needed another kind of therapy, or were somehow treatment-resistant due to genetic or environmental factors. However, the structural alterations of limbic and paralimbic regions found in these subjects may account for their reduced susceptibility to the EMDR treatment (see below).

4.2. Neural substrates

Our results show that: (i) as compared to NS, S exhibited a significantly lower GM density in left posterior cingulate and posterior parahippocampal cortex; (ii) at the morphometric assessment prior to EMDR, NR showed a significantly lower GM density as compared to R in bilateral posterior cingulate, as well as right amygdala, anterior insula, and anterior parahippocampal gyrus; (iii) GM density negatively correlated with trauma load (as assessed by TAQ−) in bilateral anterior and posterior cingulate cortex, left anterior insula and in right anterior parahippocampal gyrus.

To our knowledge, this is the first study investigating GM alterations with a VBM approach in a large sample ($n = 43$) of symptomatic and non-symptomatic occupational-related traumatized subjects. As predicted, we found structural alterations mainly in limbic and paralimbic cortices, however, a lower GM density in posterior cingulate and parahippocampal cortices have not been described in previous studies on PTSD.

The parahippocampal gyrus (PHG) is very closely functionally related to the hippocampus (Witter and Wouterlood, 2002; Francati et al., 2006). Both the hippocampus and PHG are crucially involved in the encoding, consolidation and retrieval of declarative memories (Squire and Zola-Morgan, 1991; van Strien et al., 2009). The PHG receives extensive unimodal and multimodal inputs from several regions of the neocortex, which it integrates and then forwards to the hippocampus (Lavenex and Amaral, 2000; Furtak et al., 2007). Together with the amygdala, PHG is also crucially involved in fear conditioning (Majak and Pitkänen, 2003; Tanev, 2003; Knight et al., 2009), considered a central mechanism in the development of PTSD.

Within the limbic system, a functional subdivision between anterior and posterior structures have been proposed, with the former more involved in emotional processing, and the latter in memory and visuo-spatial processing (MacLean, 1955; Noback et al., 2005). Similar functional specializations have also been suggested within the parahippocampal region (Francati et al., 2006; Furtak et al., 2007), on the basis of its rostral connections with the amygdala and the insular cortex (which would underlie the processing of emotional memories), and its caudal connections with the posterior cingulate cortex (which would underlie the processing of contextual reference marks in the episodic memory).

In the present study, we found an involvement of the posterior PHG in PTSD. A failure in the functionality of this structure might well result in those memory dysfunctions such as dissociations, amnesias, and hypermnesias typically observed in PTSD (van der Kolk et al., 1997). On the other hand, our results show that subjects with a lower GM concentration in the anterior PHG (as well as amygdala and anterior insula), do not recover from PTSD following EMDR treatment, thus suggesting a lower responsiveness. This might imply an impairment in the processing of emotional stimuli and memories, i.e. a reduced ability to extinguish conditioned trauma responses (Liberzon and Sripada, 2008), as well as in modifying or integrating traumatic memories (van der Kolk et al., 1997). An involvement of the anterior PHG in the processing of emotional

and traumatic memories is further suggested by the evidence of a negative correlation between trauma load and GM density in the PHG.

The posterior cingulate cortex (PCC) subserves several evaluative functions such as monitoring sensory events and the organism's own behavior in the service of spatial orientation and memory (Vogt et al., 1992). Together with the medial prefrontal cortex, it takes part in the conscious experience of emotion, i.e. feelings (Noback et al., 2005). PCC has also been related to a series of higher cognitive functions involved in PTSD, such as episodic and autobiographical memory (Desgranges et al., 1998; Buckner et al., 2008), and self-referential processing (Vogt and Laureys, 2005; Bluhm et al., 2009). Moreover, it has been suggested that PCC could be implicated in coping with physical threats (Bremner, 2002), and play a role in the processing of distressing material (Fischer et al., 1996).

PCC is also considered part of the so-called "default mode network," i.e. the brain system preferentially active when individuals are engaged in internally focused tasks (Greicius et al., 2003; Buckner et al., 2008). Recent functional imaging studies have shown that PTSD subjects at rest exhibit altered connectivity patterns between PCC and other areas, as either part of the default network or otherwise generally implicated in PTSD (Bluhm et al., 2009), and that the resting state connectivity of the PCC with the anterior cingulate cortex and the right amygdala positively correlates with or even predicts PTSD symptoms (Lanius et al., in press).

Consistently with previous literature, we interpret our finding of a lower GM density in PCC as related to disturbances in the retrieval of autobiographical (emotional) memories and their conscious relation to the self, processes impaired in PTSD and possibly implicated in the response to EMDR treatment (Shapiro, 1999; Corrigan, 2004). Our results also indicate that GM density in PCC correlates with trauma load, further supporting the idea that PCC could be related to the processing of traumatic memories.

An involvement of the insular cortex in PTSD is not unexpected, given that both functional (Liberzon and Phan, 2003; Liberzon et al., 2003; Lanius et al., 2004; Stein et al., 2007; Simmons et al., 2008) and structural alterations (Corbo et al., 2005; Chen et al., 2006) in this structure have previously been reported. The insular cortex has extensive connections with many brain regions, among which: primary and secondary somatosensory areas, motor and premotor areas, cingulate cortex, hippocampus, amygdala, prefrontal cortex, as well as various association areas, which makes it a good candidate as the "limbic integration cortex" (Augustine, 1996; Nagai et al., 2007).

The insular cortex, especially its anterior portion, has been related to viscero-autonomic functions (Craig, 2003; Shelley and Trimble, 2004) and seems to play an important role in body representation and subjective emotional experience (Wiens, 2005). Right anterior insula has been regarded as a center for interoceptive (visceral) awareness, which integrates the processing of emotionally relevant stimuli with body arousal, resulting in the representation of subjective feeling states (Critchley et al., 2004). This region was also found to be involved in the cognitive appraisal of emotions (Taylor et al., 2003), in modulating interoceptive responses (Simmons et al., 2009), and its activity to positively correlate with the severity of re-experiencing symptoms in PTSD subjects (Hopper et al., 2007).

Our finding of a lower GM concentration in the right anterior insular cortex of NR subjects might imply impairment in their ability to cognitively reappraise emotions, as well as to integrate emotions and body sensations into a unitary feeling state, both possible processes potentially implicated in the response to EMDR treatment (Shapiro, 1999; Corrigan, 2004). Moreover, GM density in the left anterior insula was found to correlate with trauma load.

It has been suggested that traumatic experiences could be, at least initially, stored as fragments of somatic sensations and intense emotional states dissociated from, and relatively inaccessible to, semantic processing, following to a failure in the declarative memory system (van der Kolk and Fisler, 1995; van der Kolk et al., 1997). The structural alterations we observed in the anterior insula could interfere with the integration of such fragmented somatic sensations and emotional states into declarative memories, potentially leading to dissociative phenomena.

Most studies on structural alterations in PTSD consistently report GM reductions in the hippocampus (see Nutt and Malizia, 2004; Karl et al., 2006), however, reductions in this structure seem to vary according to various factors such as: time since trauma, trauma severity, kind of traumatization, presence of co-morbid conditions, substance abuse, etc. (Yamasue et al., 2003). Our negative finding of any hippocampal involvement could be due to the exclusion of subjects suffering from depression or alcoholism, but most likely to the trauma contingencies experienced by our patients. In fact, most of the studies reporting GM loss in the hippocampus were carried out on victims of sexual assault, combat veterans, or burn survivors, whose traumatic experiences were supposedly more intense and prolonged (and probably resulted in more severe PTSD) as compared to more discrete and contained occupational-exposure traumas. Alternatively, it is also possible that studies carried out with manual segmentation might have differed from each other regarding the criteria for the delimitation of the regions of interest. On the other hand, the small spatial alterations due to the normalization and smoothing processes implied in the VBM procedure we adopted may have contributed to our negative findings (see Chételat et al. 2003).

In our opinion, the strengths of the present study are: the large cohort of recruited subjects ($n = 43$), the use of self-rated clinical measures (TAQ), the employment of a fully-automated technique (VBM), and the good agreement between different kinds of analyses (t-tests, regression). It is worth noting that relatively independent analyses (i.e. differences in GM density between NS and S or R and NR, and the correlation between GM density and lifelong accumulated traumatic experience) converge on three key regions, i.e. posterior cingulate, parahippocampal, and anterior insular cortices. To our knowledge, this is the first study describing a correlation between trauma load and GM distribution, a finding with important implications for research on memory deterioration. Our results also suggest an association between GM density and EMDR therapy outcome, a finding with potential applications in PTSD treatment planning.

The present study has also a number of limitations. First, we acknowledge that VBM, though robust for larger samples, is not necessarily superior to expert manual segmentation, and that the transformations required for VBM may introduce artifactual volumetric differences (such as partial volume errors). Second, we recognize that there are other effective psychotherapeutic and pharmacological treatments of PTSD, and that we investigated just one method (EMDR). Third, our inferences on the relationship between brain structural alterations and EMDR outcome are drawn from smaller sub-samples ($n = 10$ and $n = 5$), which might have increased the likelihood of Type I error (false positive). Therefore, these should be considered preliminary findings which need further research with larger cohorts and longitudinal follow-ups to be confirmed.

It should also be mentioned the possibility that the lower GM density found in the various structures could have predated the traumatic event. In this case, the lower neuronal concentration would probably be the cause of the higher susceptibility to both traumatic experiences (along the continuum shown by the correlation analysis) and PTSD. However, similarly to what happens in many other studies, we could not address this issue, given that we could not perform any MRI scanning before the trauma occurred or PTSD was diagnosed.

5. Conclusions

In the present study, posterior cingulate, parahippocampal and insular lower GM concentrations have been related to PTSD and responsiveness to EMDR therapy. Furthermore, irrespective of the PTSD diagnosis, trauma load was found to correlate with GM density in the same regions, suggesting a high vulnerability of these structures to the effects of stress and trauma, analogous to the previously known vulnerability in hippocampus, amygdala and prefrontal cortex (McEwan, 2006). These regions are well known to be implicated in processes such as: integration, encoding and retrieval of autobiographical and episodic memories, emotional processing (i.e. classical conditioning, cognitive appraisal, experience of feeling states), interoceptive awareness and self-referential conscious experience. Thus, our study supports lower GM densities in limbic and paralimbic cortices as a potential structural basis for memory and dissociative dysfunction in PTSD. In addition, responsiveness to EMDR psychotherapy, which in part aims to ameliorate such symptomatology, has been preliminarily correlated with the same structural substrates. We advocate for more research on trauma exposure and PTSD on similar populations, with similar methods, larger numbers, and longitudinal follow-ups; to assess whether our findings hold true, and to discern the direction of structural changes prior to and following treatment. Using such approaches, we can better understand the neurostructural basis of traumatic responses and their treatment.

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Conflicts of interest

None declared.

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