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Original article

Association between flashbacks and structural brain abnormalities in posttraumatic stress disorder

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ABSTRACT

Objective: Posttraumatic stress disorder (PTSD) is reliably associated with reduced brain volume relative to healthy controls, in areas similar to those found in depression. We investigated whether in a PTSD sample brain volumes in these areas were related to reporting specific symptoms of PTSD or to overall symptom severity.
Method: Structural MRI scans were obtained from 28 participants diagnosed with PTSD according to DSM-IV-TR. Participants reported the extent of individual PTSD symptoms using the Posttraumatic Diagnostic Scale. Voxel-based morphometry applying the Dartel algorithm implemented within SPM5 was used to identify volumetric changes, related to PTSD total, symptom cluster, and individual symptom scores.
Results: Brain volume was unrelated to overall PTSD severity, but greater reexperiencing scores predicted reduced volumes in the middle temporal and inferior occipital cortices. Increased reports of flashbacks predicted reduced volume in the insula/parietal operculum and in the inferior temporal gyrus.
Conclusion: The data illustrate the value of analyses at the symptom level within a patient population to supplement group comparisons of patients and healthy controls. Areas identified were consistent with a neurobiological account of flashbacks implicating specific abnormalities in the ventral visual stream.

1. Introduction

The study of structural brain variation in posttraumatic stress disorder (PTSD) has almost exclusively been based on comparisons of overall volume levels with samples exposed to trauma but who have not developed PTSD. The abnormalities that have been found, mainly reduced volumes in frontal and limbic areas, are similar to those implicated in major depressive disorder, raising the question of whether they correspond to specific characteristics of PTSD or reflect common difficulties, for example in emotion regulation [18,40]. A complementary strategy is to investigate the relationship between brain volume and the individual symptom clusters and symptoms of PTSD. This addresses the question of whether certain brain areas are relevant to variations in clinical presentation within PTSD samples, including overall severity. Such relations may exist regardless of whether these areas are reduced in volume compared to controls. The results may help to explain the function within PTSD of areas that are already known to be reduced in volume. They may also identify new areas that could be considered as regions of interest in future investigations, or indicate how specific brain regions of normal volume contribute to symptom expression.

Meta-analyses of structural MRI studies on individuals with PTSD have consistently identified reductions in brain volume [28,41], most prominently in the hippocampus. In addition, reductions in dorsal anterior cingulate cortex (ACC) [13,30,44,46], rostral ACC [29,39], and insular cortex [13,14,29] have been implicated in PTSD. Karl et al.'s meta-analysis [28] found further evidence for a reduction in the left amygdala of adult PTSD patients, and in the frontal cortex (but not the hippocampus) of pediatric PTSD samples. The results of individual studies of brain volume in PTSD have shown wide variability, however, usually attributed to the type of trauma, prescan duration of the illness, or MRI methodology [27,32]. Studies of depressed patients have identified volume reductions in similar areas, including subgenual, pregenual, and posterior ACC, dorsal medial/lateral PFC, orbital and ventrolateral PFC, hippocampus, and amygdala [19].

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Unlike other anxiety disorders and major depression, there are as yet no "core symptoms" that are essential for a diagnosis of PTSD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), with individuals rather having to report one out of five symptoms from cluster B (reexperiencing), three out of seven symptoms from cluster C (avoidance and numbing), and two out of five symptoms from cluster D (hyperarousal). As a result individual clinical presentations may vary widely, creating diagnostic heterogeneity. Faced with this heterogeneity, as well as with the frequently noted high levels of comorbidity, PTSD researchers have suggested that some symptoms are more highly diagnostic of the condition than others. The two groups of symptoms so identified are the avoidance and numbing symptoms [36] and the reexperiencing symptoms of flashbacks and traumatic nightmares [9].

In the current study we investigated whether structural brain variation in a PTSD sample was related to overall symptom severity and to the intensity of symptoms in specific PTSD clusters such as avoidance/numbing and reexperiencing. We applied voxel-based morphometry to the structural MRI images using SPM5 and the Dartel toolbox, which has been found to optimize the sensitivity of such analyses [4,31]. We demonstrate no grey matter volume alterations related to overall PTSD severity, but do report an inverse relation between grey matter volume in the middle temporal and inferior occipital cortices and reexperiencing symptom cluster scores. Of the individual reexperiencing symptoms, reports of flashbacks were related to volume reductions, predominantly in the inferior temporal gyrus and parietal operculum/insula. Limited evidence was found for volumetric changes related to reports of nightmares and experiencing distress on trauma reminders.

2. Methods and materials

2.1. Participants

Participants were a mixed sample of individuals meeting diagnostic criteria for current PTSD. The majority of participants were outpatients recruited from a specialist traumatic stress clinic, where diagnoses were independently confirmed, and the remainder from advertisements. Exclusion criteria were a history of head injury, neurological disorders, psychosis, or other major medical conditions, as well as current substance abuse. PTSD diagnoses were confirmed with the Structured Clinical Interview for DSM-IV [21], administered by a trained postdoctoral psychologist under the supervision of a clinical psychologist expert in trauma and PTSD. Demographic and clinical characteristics of the 28 right-handed individuals who met inclusion criteria are reported in Table 1. All patients gave written informed consent, and all procedures were approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee.

2.2. Measures

The Posttraumatic Diagnostic Scale (PDS) [22] is a widely-used self-report measure with high reliability and validity. Items measuring each of the 17 PTSD symptoms are rated on a 0–3 scale and can be summed to yield subscores for the reexperiencing, avoidance/numbing, and hyperarousal symptom clusters as well as a total score. In this sample the mean PDS score (Table 1) was above the average of 33.59 scored by individuals diagnosed with DSM-IV PTSD in the original validation sample [22]. PDS scores were higher in those currently on antidepressant medication, $r(28) = 0.50$, $P < 0.01$.

Table 1
Demographic characteristics of participants.

Gender	11 men, 17 women
Age	Mean 38.25 (range 25–57 years)
Education	9 secondary education only 5 some further education 14 higher education (university)
Time since trauma	Mean 12.0 years
Type of trauma	9 disaster or terrorist attack 9 interpersonal violence 6 sexual violence 4 other
Taking antidepressant medication	$n = 13$
Posttraumatic Diagnostic Scale	Mean 35.11 (SD 9.63)
Beck Depression Inventory	Mean 31.12 (SD 11.49)

The Beck Depression Inventory 2 [3] is a widely-used 21-item self-report measure of depression severity. Items are scored on a 4-point scale (possible range 0–63). Participants were instructed to rate their mood over the past week. The average score in the sample (Table 1) indicated a mood state associated with severe depression [2].

2.3. MRI acquisition

T1-weighted images were acquired on a Siemens 1.5T Sonata whole-body scanner (Siemens Medical Systems, Erlangen, Germany), using a whole-body coil for RF transmission and a head coil for signal reception. Whole-brain structural scans were acquired using a Modified Driven Equilibrium Fourier Transform (MDEFT) sequence [42] with optimized parameters as described in the literature [17]. For each volunteer, 176 sagittal partitions were acquired with an image matrix of 256 × 224 (Read × Phase). Two-fold over-sampling was performed in read direction (head/foot direction) to prevent aliasing. The isotropic spatial resolution was 1 mm. Relevant imaging parameters were TR/TE/TI = 12.24 ms/3.56 ms/530 ms, BW = 106 Hz/Px, Î± = 23Â°. The total duration was 12 min. Spin tagging in the neck was performed to avoid flow artefacts in the vicinity of blood vessels. The flip angle of the tagging pulse was chosen to be 110Â° to account for B1 losses in the neck. Special RF excitation pulses were used to compensate for B1 inhomogeneities of the transmit coil in superior/inferior [15] and anterior/posterior [16] directions. Images were reconstructed by performing a standard 3D Fourier Transform, followed by modulus calculation. No data filtering was applied either in k-space or in the image domain.

2.4. MRI processing

T1-weighted image registration was achieved using the diffeomorphic registration algorithm implemented in the Dartel toolbox [1] for SPM5 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). First, the anatomical images were manually reoriented so that the millimetre coordinate of the AC matched the origin [0,0,0], and the orientation approximated MNI space. Next T1-weighted images were classified into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the segmentation routine implemented in SPM5 applying standard settings. The resulting parameter files were imported into the Dartel procedure to produce rigidly aligned grey and white matter tissue classes resliced to 1.5 × 1.5 × 1.5 mm voxel size. After the affine transformation, the rigidly aligned tissue class images were used to estimate the nonlinear deformations to best align all images. During this estimation stage, Dartel iterates between building a template and registering tissue class images using the template. The resulting flow-fields, which specify the parameterized deformations, were used to warp white and grey

matter images for each subject. The spatially normalized images were rescaled by the Jacobian determinants of the deformations, using 64 time points for solving the partial differential equations. Seventh degree B-spline interpolation was used when writing the normalized images. In order to obtain meaningful coordinates of activation, the final Dartel template was normalized to MNI space and the resulting deformations applied to the grey matter images of each subject using a Matlab script downloaded from the SPM email list (https://www.jiscmail.ac.uk/cgi-bin/wa.exe?A2=ind0807&L=SPM&P=R34150%20032749). Finally the images were smoothing using an $8 \times 8 \times 8$ mm Gaussian smoothing kernel. The input features for the subsequent analysis were the smoothed, modulated and normalized GM images.

2.5. Analysis

Regression was used to relate PTSD total, symptom cluster, and individual symptom scores to brain morphology. Where appropriate covariate vector scores were centred to the overall mean and no interactions were modelled. Multiple regression was used to analyze the unique effects of each symptom cluster controlling for the other two clusters. Given the relatively small variance in the symptom scores more detailed analyses at the symptom level used simple regression. We report regions that survive cluster-level corrections for multiple comparisons (family-wise error, FWE) across the whole brain at $P < 0.05$, with individual voxels thresholded at $P < 0.001$, unless otherwise specified. As non-stationarity is problematic in cluster-level inferences in VBM data [35,45] requiring adjustment of cluster sizes according to local smoothness of data [26,45], we have adjusted our cluster level results according to this method as implemented in the VBM5 toolbox developed by C. Gaser (http://dbm.neuro.uni-jena.de/vbm/download/). One subject was considered an outlier with an overall PDS score of 19, more than twice the standard deviation below the mean, but repetition of the analysis excluding this person did not affect the results.

Table 2
Brodmann area, MNI coordinates and Z value for significant volume reduction with increasing reexperiencing cluster scores (controlling for avoidance/numbing and hyperarousal cluster scores).

Foci of activation	BA	MNI Coordinates X	Y	Z	Z value	Cluster size
L Middle temporal gyrus	21	−44	−25	−11	4.08	646
R inferior occipital gyrus	18	34	−73	−8	3.94	512
R precentral gyrus[a]	4	19	−32	68	3.88	162
L operculum/Insula[a]	52	−26	−29	10	3.27	199

Threshold: $P < 0.001$ (uncorrected).
Cluster size in number of significant voxels at $P < 0.001$ (uncorrected).
Significant at $P < 0.05$ FWE whole-brain cluster-level corrected.
[a] Cluster-level significant ($P < 0.05$) but does not survive whole-brain correction.

3. Results

3.1. Overall severity of PTSD

Analysis of the total PDS score did not reveal any significant grey matter volume decreases or increases that survived cluster level correction (see above).

3.2. PTSD symptom clusters

Grey matter volume alterations were uniquely predicted by reexperiencing scores, but not by any other symptom cluster scores. Reexperiencing scores predicted reduced grey matter volume in the left middle temporal gyrus and right inferior occipital gyrus (Table 2, Fig. 1). For illustrative purposes, the adjusted data at the peak voxel (Y-axis) plotted against the reexperiencing scores (X-axis) are depicted in Fig. 1. The plot shows a strong linear effect indicating that the volume reductions are associated with overall increases in reexperiencing scores. Although two possible outliers can be detected, exclusion of these cases increased the strength of the effect.

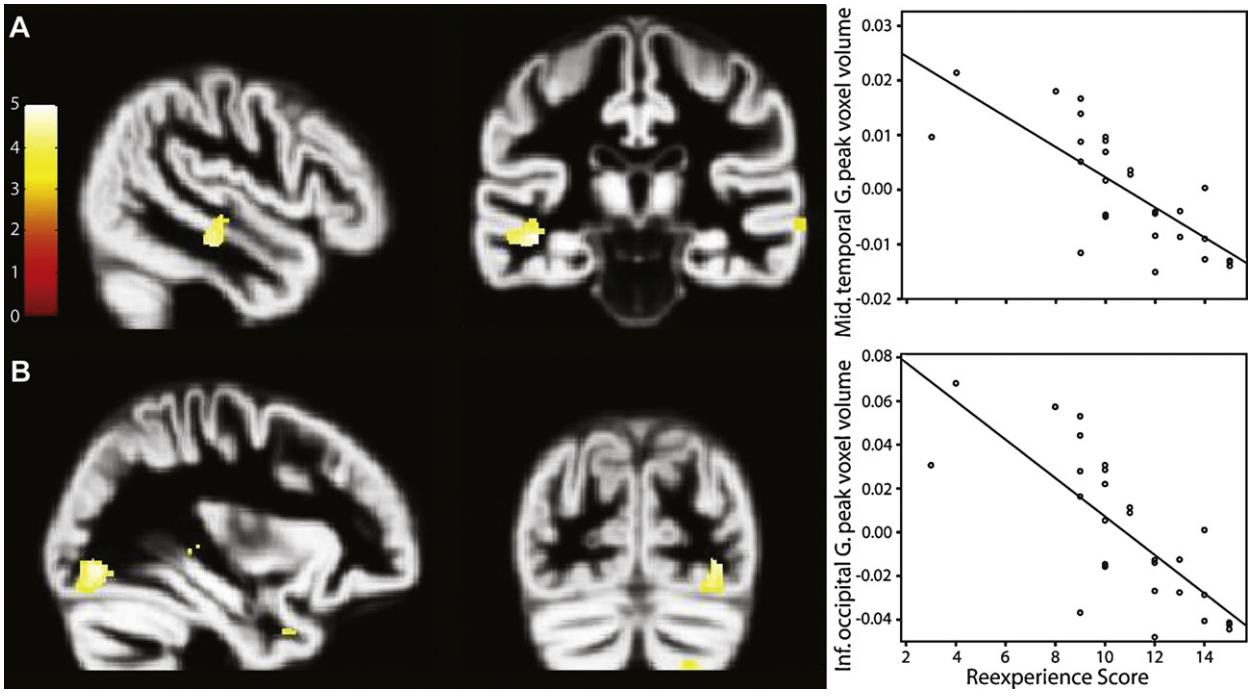

Fig. 1. Reductions in brain volume with increasing reexperiencing cluster scores.
Increased scores on the reexperiencing cluster predict decreased grey matter volume in the left middle temporal gyrus (A) and right inferior occipital gyrus (B). Results are displayed on the normalized Dartel grey matter template (image thresholded at $P < 0.001$, uncorrected). Right: the adjusted responses at the peak voxel (Y-axis) are plotted against the reexperiencing scores (X-axis) for each individual subject.

Table 3
Brodmann areas, MNI coordinates and Z values for significant volume reductions with increasing flashback scores.

		MNI Coordinates				
Foci of activation	BA	X	Y	Z	Z value	Cluster size
R inferior temporal gyrus[a]	20	53	2	−38	4.11	1517
L parietal operculum/Insula[a]	52	−32	−34	8	3.95	2653
R cerebellum[a]		19	−78	−49	3.71	431
R superior medial gyrus[b]	9	10	66	35	4.42	204
R middle temporal gyrus[b]	21	56	−40	−11	3.91	338
L inferior temporal gyrus[b]	37	−50	−57	−18	3.88	239
R inferior occipital gyrus[b]	18	35	−77	−6	3.85	286
L middle occipital gyrus[b]	19	−36	−72	11	3.57	351
L inferior frontal gyrus[b]	44	−37	8	20	3.50	265

[a] Significant at $P < 0.05$ FWE whole-brain cluster-level corrected.
[b] Cluster-level significant ($P < 0.05$) but does not survive whole-brain correction.

In additional analyses (Supplementary Tables S1–S4), we examined the effects of controlling for age, gender, education level, and BDI scores. Reductions in the middle temporal area were still observed when controlling for BDI scores, but reduction in right occipital areas were no longer detected. In all additional analyses there was strong and consistent evidence for a relationship between reexperiencing and a reduction in the size of right inferior temporal cortex (BA20).

3.3. PTSD reexperiencing symptoms

Simple regressions conducted on the five reexperiencing symptoms separately revealed marked effects only for flashback scores (symptom B3). Increasing reports of flashbacks predicted reduced grey matter volume in the right inferior temporal gyrus and left parietal operculum (Table 3, Fig. 2) as well as a cerebellar region. In addition reduced volumes within the medial extent of the superior frontal gyrus, the right middle temporal gyrus, the left inferior temporal gyrus, the right inferior occipital gyrus, the left middle occipital gyrus, and the left inferior frontal gyrus were cluster-level significant but did not survive whole-brain correction. Again for illustrative purposes plotting the adjusted data at the peak voxel against the flashback scores of any of the detected voxel-clusters reveals strong linear effects indicating that the volume reductions are associated with overall increases in flashback scores and are not driven by outliers. Flashback scores were unrelated to gender, age, or lifetime units of alcohol, largest $r(28) = 0.17$, $P > 0.10$.

In additional analyses (Supplementary Tables S5–S8), we examined the effects of controlling for age, gender, education level, and BDI scores. Reductions in the right inferior temporal gyrus (BA20) and left parietal operculum, but not the cerebellum, were still consistently observed. In contrast, increasing reports of nightmares predicted volume reductions in the right precentral gyrus and right inferior occipital gyrus that failed to reach significance after whole-brain correction (Supplementary Table S9). Increasing reports of distress on trauma reminders predicted significant volume reductions in the right cerebellum. They also predicted volume reductions in the right superior orbital gyrus but these did not survive whole-brain correction (Supplementary Table S10).

4. Discussion

Previous structural brain imaging studies of patients suffering either from PTSD or depression have identified reduced volume in similar frontal and limbic areas, including the hippocampus. Contrary to the assumption that the overall level of PTSD symptoms is linearly related to structural changes in the brain, we were unable to find any evidence that volume in these areas was related to overall symptom severity in a sample all diagnosed with PTSD. As previously noted, volumetric alterations related to symptom levels within a PTSD sample may or may not be present despite overall volume differences relative to healthy samples. PTSD is a highly heterogeneous disorder, encompassing intrusive cognition, deliberate avoidance, emotional numbing, and increased arousal. Our data indicated that smaller grey matter volumes were specifically related to reporting more symptoms from the reexperiencing cluster and, within that cluster, predominantly with flashback symptoms.

Symptom cluster analyses revealed two areas where volume was inversely related to increased rexperiencing scores, one being the left middle temporal gyrus (BA 21). This area has previously been linked to semantic processing [24] and to the retrieval of autobiographical memories [25], as well as being part of the 'default network' of brain areas that are active at rest and are thought to be involved in processing self-related information. A recent functional MRI study of individuals with PTSD related to early-life trauma found significantly reduced middle temporal activity in BA 21 compared to healthy controls [6]. Stress-induced dissociative psychopathology has also been linked to reduced middle temporal activity [33]. The other area with significantly reduced volume was the right inferior occipital gyrus (BA 18). This area is part of the ventral visual stream, involved in the selection and classification of visual information. As explained in greater detail below, it has been suggested that in PTSD processing of traumatic scenes by the ventral stream is impaired [10].

Flashbacks were the symptom within the reexperiencing cluster to be most clearly related to reductions in brain volume. Flashbacks refer to intrusive memories in which the traumatic incident, including accompanying emotions and bodily reactions, are subjectively reexperienced in the present. These features, along with the fact that retrieval is involuntary, have generally been attributed to the underlying memory representations lacking adequate contextualization [7,8,20,38]. Compared to ordinary autobiographical memories flashbacks are typified by prominent sensory and somatosensory features such as pain [12,43]. They may vary in intensity from a transient sense of reliving the past while simultaneously being aware of the present to a full-blown reliving accompanied by a complete loss of connection with the outside world. This sense of reliving in the present distinguishes the intrusive sensory memories found in PTSD from those found in other disorders such as depression [34].

We found that flashbacks were inversely related to volume in an area including the insula and the parietal operculum. The insula has previously been found to have a reduced volume in PTSD [13,14,29], and both areas are strongly implicated in somatosensory processing. A functional MRI investigation of PTSD patients using PET by Osuch et al. has reported that flashback intensity was positively related to bilateral activity in the insula, as well as being negatively related to activity in the bilateral superior frontal cortices, right medial temporal cortex, and right fusiform cortex [37].

We found flashback scores to be inversely related to the volume of lateral ventral regions of the right temporal cortex somewhat anterior to those identified by Osuch et al. The inferior temporal cortex is part of the ventral visual stream, and is thought to be involved in coding abstract features of visual scenes. Along with other temporal lobe structures such as the hippocampus, activity in this region allows events to be placed with a general temporal and spatial context. Unlike the dorsal stream, which supports egocentric representations of visual experience that retain a close link with the original perceptual input, visual processing in the ventral stream and related structures allows allocentric representations of scenes to be manipulated and combined in novel ways [11,12]. Consistent with evidence that PTSD may be

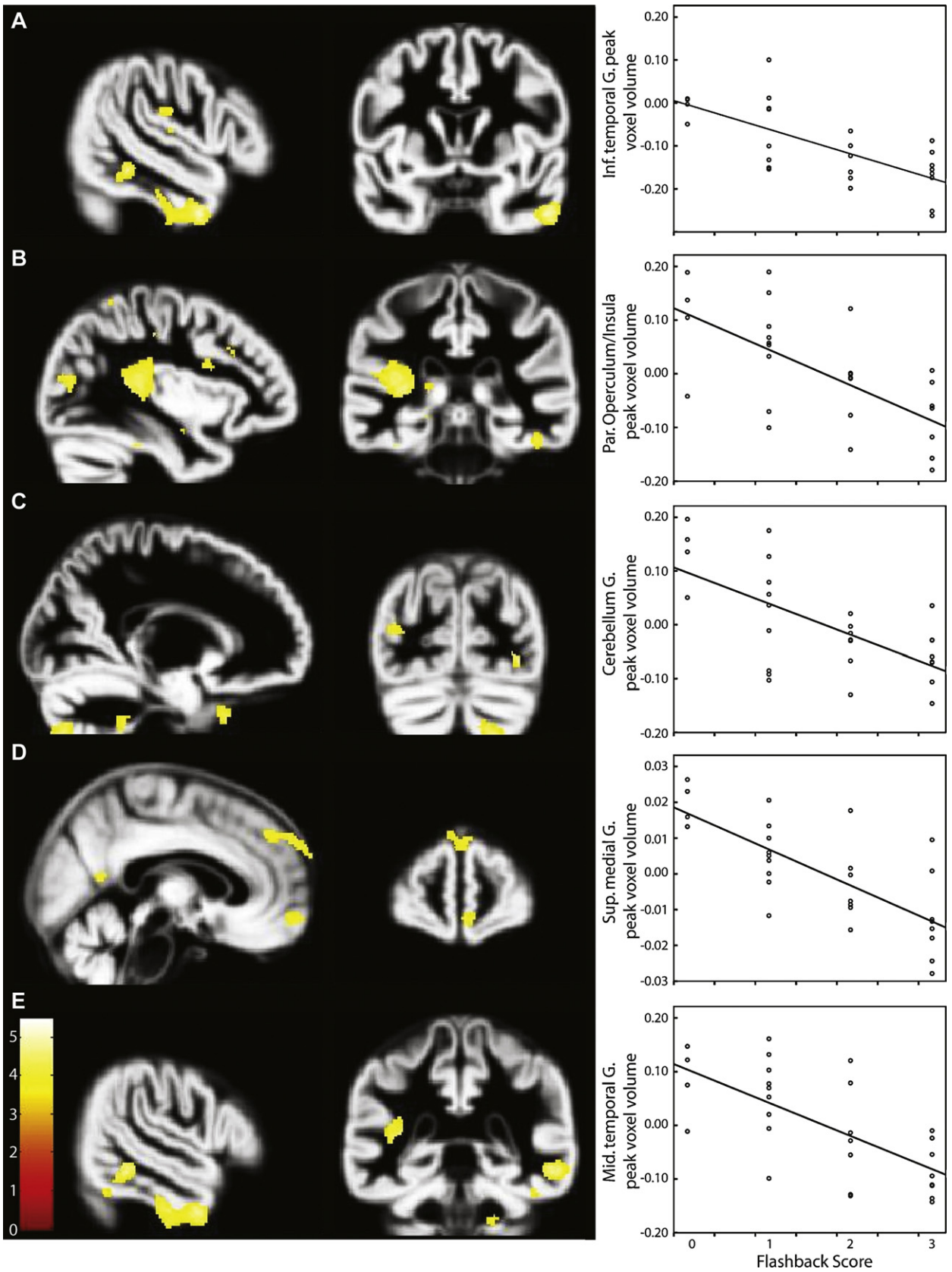

Fig. 2. Reductions in brain volume with increasing flashback scores.
Increased flashback scores predict decreased grey matter volume in the inferior temporal gyrus (A), parietal operculum (B), cerebellum (C), superior medial gyrus (D), and middle temporal gyrus (E). Results are displayed on the normalized Dartel grey matter template (image thresholded at $P < 0.001$, uncorrected). Right: the adjusted responses at the peak voxel for each region displayed (Y-axis) are plotted against the flashback scores (X-axis) for each individual subject.

associated with a preexisting deficit in allocentric processing [23], it has recently been proposed that flashbacks in PTSD arise from egocentric trauma representations within the dorsal stream that have received inadequate contextualization within the ventral visual stream [10]. An inverse association between more flashbacks and the volume of ventral temporal cortex is consistent with this theory.

Among the limitations of the present findings are the modest sample size and use of 1.5T MRI, both of which may have reduced the power to detect other significant effects. We also draw attention to the lower reliability and relatively small variance in the scores of the independent variable when analyses are conducted at the level of individual symptoms. This underscores the need for replication and could be overcome in future studies by including a more extensive assessment involving multiple items targeting the symptoms of most theoretical interest. Our sample also consisted of individuals with PTSD arising from a variety of sources and was too small to permit the analysis of subgroups. Although this suggests the results are more likely to be generalizable, it leaves open the possibility that, for example, effects may be stronger in civilian than military trauma. The data are also silent about whether there are volume differences in the identified areas compared to healthy controls, but they do identify regions of interest for future studies. A final limitation is uncertainty about the possible direction of any causal effects. Our data are consistent both with the experience of repeated reexperiencing or flashbacks causing reductions in brain volume and with preexisting volume reductions in these regions leading to increased symptoms.

In contrast to what might have been predicted from previous research, our data did not identify the hippocampus as a site in which brain volume varied with symptom intensity. There are various explanations of this. For example, hippocampal reduction has also been found in several other disorders, particularly depression, and may be a marker for more general psychopathology rather than PTSD symptoms specifically. Alternatively, the relation between hippocampal volume and symptom expression may be more variable across participants. Our data did nevertheless identify brain regions that may be involved in specific PTSD symptoms. Further, they suggest that variability in the findings of structural imaging studies in PTSD, and conceivably in other disorders as well, may be accounted for by in part by heterogeneity in the constituent symptoms.

5. Conclusion

In summary, volumetric studies at the symptom level have the ability to complement studies of participants defined by an overall syndrome. Because the analyses focus on relation to individual symptoms, they may identify areas where volumetric reductions are significant predictors of symptom expression without characterizing the disorder as a whole (and without necessarily demonstrating differences with healthy controls). We have shown that such analyses can identify new regions of interest that are consistent with a neurobiological model of flashbacks and with other recent suggestions that flashbacks are specifically related to a deficit in the brain's ability to create allocentric representations [5,23].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eurpsy.2011.03.002.

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