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Frontal and subcortical grey matter reductions in PTSD

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ABSTRACT

Post-traumatic stress disorder (PTSD) is characterised by a range of debilitating psychological, physical and cognitive symptoms. PTSD has been associated with grey matter atrophy in limbic and frontal cortical brain regions. However, previous studies have reported heterogeneous findings, with grey matter changes observed beyond limbic/frontal areas. Seventy-five adults were recruited from the community, 25 diagnosed with PTSD along with 25 healthy and 25 trauma exposed age and gender matched controls. Participants underwent clinical assessment and magnetic resonance imaging. The data-analyses method Voxel Based Morphometry (VBM) was used to estimate cortical grey matter volumes. When compared to both healthy and trauma exposed controls, PTSD subjects demonstrated decreased grey matter volumes within subcortical brain regions—including the hippocampus and amygdala—along with reductions in the anterior cingulate cortex, frontal medial cortex, middle frontal gyrus, superior frontal gyrus, paracingulate gyrus, and precuneus cortex. Significant negative correlations were found between total CAPS lifetime clinical scores/sub-scores and GM volume of both the PTSD and TC groups. GM volumes of the left rACC and right amygdala showed a significant negative correlation within PTSD diagnosed subjects.

1. Introduction

Post-traumatic stress disorder (PTSD) is a debilitating condition that can develop in some individuals following the experience of traumatic events. Symptoms include intrusive recollections, avoidance, withdrawal and hyperarousal (American Psychiatric Association, 2013) with sufferers exhibiting a reduced capacity to inhibit fear and negative emotional responses. The common hyper-aroused type of PTSD is characterised by heightened responses to stimuli perceived by certain individuals as threatening, followed the inability to extinguish fear (Garfinkel and Liberzon, 2009). On the other hand, the dissociative subtype of PTSD may experience disconnection from their self of environment, depersonalisation, derealisation and neurological symptoms affecting memory and movement (Wolf et al., 2012). PTSD can have long-term, debilitating psychological, physical and cognitive effects, greatly affecting sufferers' quality of life (Bremner et al., 1993; Yehuda et al., 1995). Initially associated with war veterans, for whom the lifetime prevalence rate is between 19–22% (Dohrenwend et al., 2006; Seal et al., 2009), the majority of PTSD sufferers are civilians who have experienced or witnessed trauma arising from domestic, personal and sexual violence, accidents, crime, and of more recent focus, terrorism. In the general population, the lifetime prevalence of PTSD across the Western world is between 1.9 – 6.8% (Australian Bureau of Statistics, 2007; Kessler et al., 2005). The current study applies Voxel Based Morphometry (VBM) techniques to identify grey matter (GM) volume abnormalities in subjects diagnosed with PTSD, as compared to subjects exposed to trauma as well as healthy controls.

Previous studies investigating structural brain changes in PTSD sufferers have hypothesised an association between PTSD and GM volume differences within limbic and prefrontal cortices (Chalavi et al., 2015a, 2015b; Chen et al., 2012; Kasai et al., 2008; Nardo et al., 2013; Vogt et al., 2003; Yamasue et al., 2003). However, evidence of GM alterations have been observed across the brain on a global scale, and are hypothesised to reflect the heterogeneous nature of trauma types and the subsequent spectrum of PTSD manifestations (Daniels et al., 2015; Rocha-Rego et al., 2012).

Extant structural studies and meta-analyses using MRI (Fennema-Notestine et al., 2002; Karl et al., 2006; Shin et al., 2006) have identified diminished volume across widespread regions in the brain, such as in the hippocampus (Kitayama et al., 2005; Li et al., 2014; O'Doherty et al., 2015; Rodrigues et al., 2011; Smith, 2005; Woon and Hedges, 2011; Woon et al., 2010), the anterior cingulate cortex (ACC), and the amygdala (Baldaçara et al., 2014; Karl et al., 2006; Schuff et al.,

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2001; Woon and Hedges, 2009). Findings such as these support the assertion that further analysis of PTSD subjects at the whole-brain level is needed, rather than focus being confined to the medial prefrontal cortex and limbic system. In previous VBM studies at the whole brain level, PTSD subjects showed significant GM reduction, especially in the frontal and the occipital regions in comparison to HC (Meng et al., 2014; Nemeroff et al., 2006). In comparison to TC, PTSD subjects also showed significant GM reduction in the left ACC, left insula, caudate and right parahippocampal gyrus (Meng et al., 2014; Sussman et al., 2016). GM deficits have also been reported in children with PTSD, with global cerebral GM volume reduction, reduction in the superior temporal gyrus (De Bellis et al., 2002) and structural abnormalities in the corpus collosum, anterior cingulate and frontal lobe (Carrion et al., 2001; De Bellis et al., 1999; Jackowski et al., 2009).

This study seeks to identify GM changes in PTSD diagnosed subjects exposed to civilian trauma, compared to healthy controls and subjects exposed to trauma who have not developed PTSD. We hypothesise that reductions in GM will be found primarily in frontal regions known to be involved in hypothalamic-pituitary-adrenal (HPA) modulation and fear conditioning. i.e. medial fontal gyrus, orbital frontal cortex, and ACC. Further to this, we expect to find PTSD symptoms, as measured by clinical severity scores, should correlate with observed ROI GM changes.

2. Methods

2.1. Participant recruitment and clinical assessment

Seventy-five participants (25 PTSD diagnosed (PTSD), 25 healthy control subjects (HC) and 25 trauma exposed controls subjects (TC)) aged 18–50 years were recruited from community settings via print and electronic media.

PTSD participants and trauma exposed controls were assessed by a psychologically trained health professional using the following instruments: (i) Clinician Administered PTSD scale [CAPS: 30 questions]; (ii) Structured Clinical Interview for DSM-IV for comorbid disorders [SCID]; (iii) Depression, Anxiety and Stress Scales [DASS: 42 questions] self-report; and (iv) Impact of Event Scale - Revised [IES-R] self-report. Healthy controls completed the DASS: 42 self-report only.

Study inclusion criteria: (i) PTSD participants met the DSM-IV criteria for primary diagnosis of PTSD after a Criterion-A traumatic event/stressor not less than 3 months or longer than 10 years previously; (ii) TC participants required exposure to Criterion A trauma (not less than 3 months, and no longer than 10 years previously), but no psychiatric diagnosis or history of psychiatric disorder including PTSD; (iii) HC participants had no exposure to criterion-A trauma and no psychiatric diagnosis or history of psychiatric disorder including PTSD; (iv) all participants were 18–50 years of age; (v) all participants were fluent in English language so as to maximize accuracy and validity of clinical diagnosis; and (vi) all participants provided written informed consent.

Participants were excluded if they met any of the following criteria: (i) a significant psychiatric diagnosis other than PTSD e.g. bipolar disorder, schizophrenia; (ii) pregnant or breastfeeding; (iii) any significant medical or neurological condition including, but not limited to, congestive heart failure, hypertension, stroke, chronic liver disease, autoimmune or connective tissue disease, blood clotting disorder; (iv) a history of brain injury or concussion which resulted in loss of consciousness greater than 10 min; (v) a history of/or current substance dependence; and (vi) any contraindication to having an MRI scan e.g. metallic implants, claustrophobia.

2.2. MRI protocol

Imaging was conducted on the same day as clinical assessment at the Brain and Mind Centre imaging facility using a 3 T GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI, US) equipped with an 8-channel phased array head coil (InVivo, Fl, US). For each subject, two structural images were acquired in the same session using a T1-weighted-magnetization prepared rapid gradient-echo (MP-RAGE) sequence producing 196 sagittal slices (TR = 7.2 ms; TE = 2.8 ms; flip angle = 12°; matrix 256 × 256; 0.9 mm isotropic voxels).

2.3. VBM analysis

For each subject, two individual T1-weighted MRI scans were combined and averaged using the FMRIB Software Library (FSL) software tool (Smith et al., 2004), to increase signal-to-noise ratio (SNR). An unbiased optimised VBM protocol using FSL-VBM (v1.1) was then carried out using the following procedure. Firstly, FSL Brain Extraction Tool (BET) (Jenkinson et al., 2005) was applied to remove non-brain material, before all T1-weighted images were transformed into standard space using a limited degrees-of-freedom non-linear model to ensure spatial alignment and images were corrected for non-uniformity/intensity inhomogeneities (Andersson et al., 2007). The FAST4 tool (Zhang et al., 2001) was then applied to carry out tissue-type segmentation. The segmented grey matter partial volume images were aligned into MNI standard space by applying the affine registration tool FLIRT (Greve and Fischl, 2009) and nonlinear registration FNIRT methods (Woolrich et al., 2009). A study-specific averaged template was created, to which grey matter partial volume images were re-registered, and these images were then modulated to correct for Jacobian warping. Visual inspection was used to ensure the quality of brain image extraction, segmentation and registration for each structural image. Segmented images were smoothed using sigma = 3; Gaussian Full width at half maximum (FWHM) kernel of 7.06 mm. A customised randomiser and study-blinding program allowed for unbiased assessment and the clean-up of MRI data during VBM pipeline.

2.4. Statistical analysis

Whole-brain permutation-based non-parametric testing was carried out via a voxel-wise GLM (Nichols and Holmes, 2002) using a 5000 permutation set contrasting differences between the PTSD vs HC, PTSD vs TC, and TC vs HC groups. Total intracranial volume, calculated using the Freesurfer software package (http://surfer.nmr.mgh.harvard.edu) was entered as a covariate into all study design matrices to ensure against confounding. Family-wise error (FWE) correction (Nichols and Hayasaka, 2003) was used to correct the threshold for multiple comparisons across space and threshold-free cluster enhancement (TFCE) was employed to assess cluster significance (Smith and Nichols, 2009). A FWE corrected threshold significant p-value of $p < 0.01$ and cluster size minimum of 10 voxels was selected for each paired group analysis i.e. PTSD vs HC, PTSD vs TC, and TC vs HC. Masks used for region of interest (ROI) results reporting were generated via the Harvard-Oxford Cortical and Subcortical Structural atlases (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006), with a 60% threshold applied. SPSS version 20.0 for Windows (SPSS, 2011) was used to perform comparisons between group demographic and clinical variables were tested using one-way ANOVA, Chi-square and independent *t*-test. A two-tailed Pearson correlations analysis was performed to identify correlations between ACC and amygdala ROI GM volumes, as well as between symptom severity (as measured by CAPS clinical scores) and ROI GM volume in the PTSD and TC groups.

3. Results

3.1. Sample characteristics

PTSD, TC and HC groups did not differ in terms of age $F(2, 72) = 2.44$, $p = 0.095$, or years of education $F(2, 72) = 2.76$ [0.07]. DASS

Table 1
Demographic and clinical variables.

	PTSD Subjects ($n=25$)	Trauma Exposed Controls ($n=25$)	Healthy Controls ($n=25$)	Significance Test (df) [p value]
Gender (F/M)	13/12	13/12	13/12	χ^2 (2) = 0.00 [1]
Age (years)	34.0 ± 8.4	36.4 ± 8.1	31.7 ± 6.0	F (2, 72) = 2.44 [0.095]
Time since trauma (years)	4.61 ± 2.57	4.26 ± 2.45	–	t (48) = −0.493 [0.805]
Years of education	16.16 ± 1.3	15.04 ± 1.5	15.44 ± 2.24	F (2, 72) = 2.76 [0.07]
DASS	57.2 ± 32.6	16.2 ± 25.1	9.5 ± 10.3[a]	F (2, 66) = 24.22 [< 0.001]
CAPS				
Lifetime	95.6 ± 25.9	13.0 ± 21.8	–	t (48) = −12.20 [< 0.001]
Month	57.0 ± 26.8	6.7 ± 13.5	–	t (35.4) = −8.38 [< 0.001]
Week	53.6 ± 27.6	5.8 ± 12.1	–	t (32.9) = −7.93 [< 0.001]
IES-R	45.1 ± 18.5	15.0 ± 21.6	–	t (48) = −5.30 [< 0.001]

Mean scores (± standard deviation) for age and DASS clinical score across groups.
CAPS/IES-R group differences were tested using two-tailed continuous data significant at $p < 0.05$.
[a] DASS scores available for only 19 healthy control participants.

Table 2
PTSD < HC: Whole Brain VBM grey matter results.

Cortical Area	Hemisphere	Brodmann Area	MNI Coordinates	Cluster size (mm^3)	Grey matter signal intensity (SD)		FWE Corrected p-value (max)
					PTSD	HC	
Amygdala	Left	–	−22, −2, −28	2352	0.496 (0.06)	0.592 (0.06)	< 0.001
Amygdala	Right	–	28, −2, −28	2768	0.504 (0.06)	0.594 (0.05)	< 0.001
rACC	Left	24	0, 34, −8	2056	0.559 (0.11)	0.646 (0.09)	< 0.001
rACC	Right	24	2, 32, −8	1368	0.578 (0.10)	0.658 (0.10)	< 0.001
PCC	Left	23	−4, −26, 38	864	0.560 (0.07)	0.638 (0.08)	< 0.001
PCC	Right	23	2, −28, 40	560	0.575 (0.07)	0.654 (0.08)	< 0.001
Frontal Medial Cortex	Midline	11, 12	8, 44, −22	1544	0.596 (0.07)	0.677 (0.10)	0.005
OFC	Left	10, 11	−36, 28, −22	2936	0.462 (0.04)	0.536 (0.05)	0.004
OFC	Right	10, 11	36, 28, −22	2304	0.419 (0.05)	0.503 (0.06)	< 0.001
Frontal Pole	Left	9, 10	−2, 58, 4	10,288	0.389 (0.05)	0.458 (0.03)	0.005
Frontal Pole	Right	9, 10	16, 70, 2	12,920	0.393 (0.04)	0.465 (0.04)	0.001
Hippocampus	Left	28	−22, −8, −28	720	0.526 (0.07)	0.609 (0.07)	< 0.001
Hippocampus	Right	28	28, −10, −28	2024	0.518 (0.04)	0.586 (0.05)	< 0.001
Insular Cortex	Left	13, 14	−40, −4, 0	608	0.610 (0.08)	0.687 (0.08)	< 0.001
Insular Cortex	Right	13, 14	38, −6, −6	1624	0.611 (0.06)	0.695 (0.08)	< 0.001
Middle Frontal Gyrus	Left	46	−42, 6, 48	4928	0.384 (0.06)	0.471 (0.08)	< 0.001
Middle Frontal Gyrus	Right	46	48, 30, 22	2328	0.395 (0.06)	0.465 (0.07)	< 0.001
Paracingulate Gyrus	Left	32	0, 34, −12	4368	0.617 (0.09)	0.718 (0.07)	< 0.001
Paracingulate Gyrus	Right	32	2, 48, 6	3624	0.549 (0.07)	0.652 (0.07)	< 0.001
Precuneus Cortex	Left	7	−6, −76, 30	2408	0.468 (0.04)	0.548 (0.05)	0.007
Precuneus Cortex	Right	7	8, −72, 34	4704	0.485 (0.05)	0.568 (0.05)	< 0.001
Putamen	Left	–	−16, 6, −12	3472	0.466 (0.10)	0.560 (0.08)	< 0.001
Putamen	Right	–	20, 8, −12	5152	0.462 (0.08)	0.542 (0.07)	< 0.001
Superior Frontal Gyrus	Left	8, 9	−4, 56, 22	5608	0.449 (0.06)	0.541 (0.06)	< 0.001
Superior Frontal Gyrus	Right	8, 9	4, 54, 24	5888	0.436 (0.05)	0.528 (0.05)	< 0.001
Thalamus	Right	23	−2, −4, −2	88	0.177 (0.04)	0.210 (0.03)	< 0.001

rACC = rostral anterior cingulate cortex; OFC = orbital frontal cortex; PCC = posterior cingulate cortex.

scores differed across all subject groups $F(2, 66) = 24.22$, $p < 0.001$. The PTSD and TC groups differed in IES-R scores $t(48) = -5.30$, $p < 0.001$, and CAPS scores; [week $t(48) = -12.20$, $p < 0.001$], [month $t(35.4) = -8.38$, $p < 0.001$], [lifetime $t(32.9) = -7.93$, $p < 0.001$] (see Table 1). PTSD and TC groups did not differ in time since trauma (years) $t(48) = -0.493$ $p = 0.805$. None of the PTSD diagnosed subjects scored above the threshold on the depersonalisation and derealisation CAPS items (cut-off > 4) to warrant classification as dissociative PTSD subtype. Trauma types experienced by PTSD and TC groups are listed in Supplementary Materials 1. The PTSD group had a larger number of sexual assault experiences compared to the TC (PTSD = 12, TC = 2), while the TC group experienced a larger number of witnessing to scenes of death or severe injury (PTSD = 12, TC = 18). Subjects in the PTSD group had a greater use of psychotropic medications than TC subjects (see Supplementary Materials 2).

3.2. Imaging data

3.2.1. PTSD vs HC analysis

The PTSD vs HC whole brain VBM analysis revealed significant differences in GM volume in the following subcortical regions: bilateral amygdala, hippocampus, putamen, parahippocampal gyrus anterior division, right parahippocampal gyrus posterior division, and left thalamus – with the largest differences observed in the amygdala, hippocampus and putamen. Across all of these ROIs, the PTSD group showed reduced GM compared to controls. Similarly, the PTSD group showed significant GM reductions across frontal ROIs including: bilateral cingulate gyrus anterior division, frontal medial cortex, frontal orbital cortex, frontal pole, middle frontal gyrus, and paracingulate gyrus. Within frontal regions the largest differences were found in the cingulate gyrus and frontal pole. GM decreases were also observed bilaterally in the insula, and precuneus cortex. (See Table 2 and visualisation of GM reductions in Fig. 1).

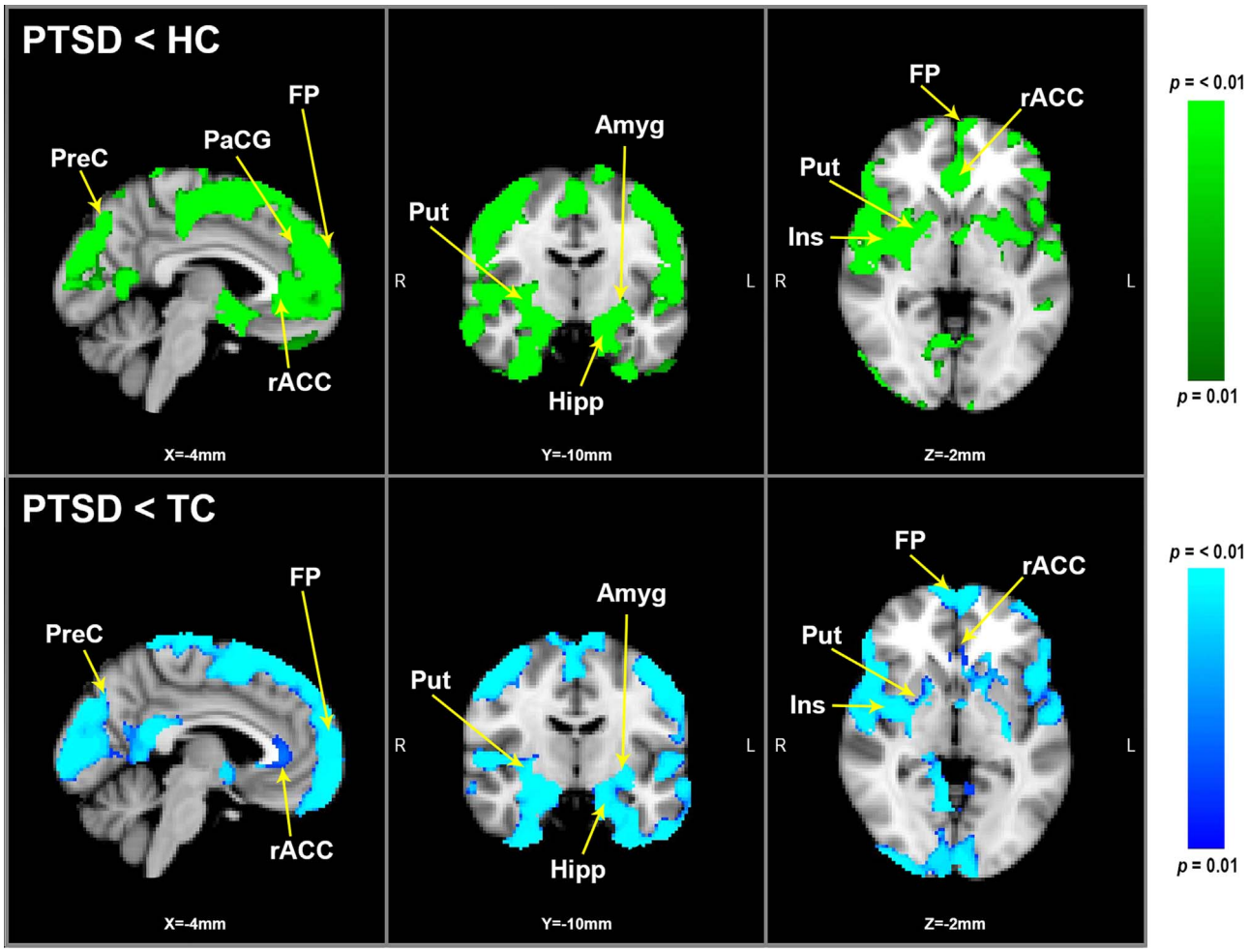

Fig. 1. VBM grey matter results: group difference depicting GM reductions. Statistically significant clusters of GM changes calculated using 25 (13F/12M) PTSD subjects, 25 (13F/12M) HC and 25 (13F/12M) TC. Top panel depicts PTSD vs HC whole brain analysis; green indicates significant clusters of voxels (FWE corrected for multiple comparisons at $p < 0.01$, $k > 10$ voxels) with reduced GM volume in PTSD compared to HC. Bottom panel depicts PTSD vs TC whole brain analysis; blue indicates significant clusters of voxels (FWE corrected, $p < 0.01$, $k > 10$ voxels) with reduced GM volume in PTSD compared to TC. GM volume maps rendered on standard MNI152 structural template. Images are radiologically oriented. Abbreviations are as follows: HC = healthy controls; TC = trauma controls; GM = grey matter; Amyg = amygdala; rACC = rostral anterior cingulate cortex; FP = frontal pole; Hipp = hippocampus; Ins = insula; PaCG = paracingulate gyrus; PreC = precuneus cortex; Put = putamen; L = Left; R = Right.

3.2.2. PTSD vs TC analysis

Significant grey matter reductions in the PTSD group when compared with TC were present, to a lesser degree, across cortical and subcortical regions observed in the PTSD vs HC analysis, with some notable exceptions. Bilaterally, the cingulate gyrus (posterior division), hippocampus, and frontal medial cortex all showed greater volume loss in PTSD vs TC. The left frontal pole, and right thalamus also presented larger volumes of reduction (see Fig. 1, Table 3).

3.3. Correlational analysis

3.3.1. Anterior cingulate cortex and amygdala correlation

A correlational analysis between GM volumes in the left rACC and right amygdala within PTSD diagnosed subjects showed a significant negative correlation ($r = -0.449$, $p = 0.024$, $r^2 = 0.202$). See Table 4, Figs. 2 and 3. No significant correlations were found within the TC and HC groups.

3.3.2. CAPS clinical scores and ROI GM volume

Significant negative correlations were found between total CAPS lifetime clinical scores/sub-scores and GM volume of both the PTSD and TC groups. Within frontal regions including the left rACC ($r = -0.473$, $p = 0.001$, $r^2 = 0.224$), frontal medial cortex ($r = -0.441$, $p = 0.001$, $r^2 = 0.194$), left OFC ($r = -0.497$, $p = 0.001$, $r^2 = 0.247$), and left middle frontal gyrus ($r = -0.623$, $p = 0.001$, $r^2 = 0.388$), the strongest association was observed with the CAPS hyperarousal lifetime sub-score. While the superior frontal gyrus showed a slightly stronger association bilaterally with CAPS re-experiencing lifetime sub-score. Hippocampal GM volumes showed a stronger association with CAPS re-experiencing lifetime sub-scores (left; $r = -0.498$, $p = 0.001$, $r^2 = 0.248$, right; $r = -0.421$, $p = 0.002$, $r^2 = 0.177$), while the strongest association with the amygdala was observed with the CAPS avoidance lifetime sub-score (left; $r = -0.426$, $p = 0.003$, $r^2 = 0.181$, right; $r = -0.476$, $p = 0.001$, $r^2 = 0.227$). See Table 5.

4. Discussion

This study sought to investigate GM changes in PTSD diagnosed subjects compared to both trauma exposed (TC) and healthy controls (HC), using a whole brain technique (VBM). It found significant reductions in GM volumes of PTSD subjects across multiple frontal and subcortical regions compared to both TC and HC groups. Significant negative correlations were observed between CAPS lifetime clinical scores/sub-scores and GM ROI volumes in the PTSD and TC groups. Additionally, a significant negative correlation between the left rACC and right amygdala GM volumes was found within PTSD diagnosed subjects. No significant difference in GM volumes was found between the TC and HC groups.

Table 3
PTSD < TC: Whole Brain VBM grey matter results.

Cortical Area	Hemisphere	Brodmann Area	MNI Coordinates	Cluster size (mm^3)	Grey matter signal intensity (SD)		FWE Corrected p-value (max)
					PTSD	TC	
Amygdala	Left	–	−18, −2, −24	2408	0.495 (0.07)	0.566 (0.05)	< 0.001
Amygdala	Right	–	26, −2, −28	2632	0.502 (0.06)	0.578 (0.05)	< 0.001
rACC	Left	24	−4, 34, 2	304	0.392 (0.08)	0.465 (0.08)	0.005
PCC	Left	23	−4, −48, 18	1632	0.452 (0.06)	0.539 (0.10)	< 0.001
PCC	Right	23	6, −50, 12	1392	0.471 (0.07)	0.570 (0.11)	< 0.001
Frontal Medial Cortex	Midline	11, 12	6, 48, −26	2168	0.594 (0.09)	0.684 (0.11)	< 0.001
OFC	Left	10, 11	−44, 26, −16	2256	0.440 (0.05)	0.515 (0.08)	0.002
OFC	Right	10, 11	46, 22, −8	1352	0.426 (0.06)	0.497 (0.06)	< 0.001
Frontal Pole	Left	9, 10	−2, 60, −20	16,304	0.380 (0.04)	0.447 (0.06)	< 0.001
Frontal Pole	Right	9, 10	8, 56, −26	10,496	0.402 (0.04)	0.471 (0.05)	< 0.001
Hippocampus	Left	28	−24, −12, −28	944	0.504 (0.05)	0.572 (0.05)	< 0.001
Hippocampus	Right	28	28, −10, −28	3352	0.495 (0.04)	0.556 (0.04)	< 0.001
Insular Cortex	Left	13, 14	−42, 14, −10	488	0.566 (0.09)	0.636 (0.07)	< 0.001
Insular Cortex	Right	13, 14	38, −4, −2	1808	0.611 (0.07)	0.691 (0.07)	< 0.001
Middle Frontal Gyrus	Left	46	−44, 6, 52	3320	0.386 (0.06)	0.470 (0.06)	< 0.001
Middle Frontal Gyrus	Right	46	36, 0, 56	1760	0.421 (0.06)	0.489 (0.07)	< 0.001
Paracingulate Gyrus	Left	32	−4, 56, 6	736	0.555 (0.09)	0.641 (0.09)	< 0.001
Paracingulate Gyrus	Right	32	6, 10, 48	728	0.537 (0.10)	0.632 (0.10)	< 0.001
Precuneus Cortex	Left	7	0, −76, 32	2088	0.511 (0.06)	0.591 (0.09)	< 0.001
Precuneus Cortex	Right	7	4, −56, 8	3000	0.535 (0.09)	0.636 (0.11)	< 0.001
Putamen	Left	–	−16, 6, −12	2952	0.401 (0.07)	0.462 (0.06)	< 0.001
Putamen	Right	–	16, 8, −12	2944	0.456 (0.07)	0.524 (0.05)	< 0.001
Superior Frontal Gyrus	Left	8, 9	−4, 48, 42	5344	0.444 (0.06)	0.528 (0.07)	< 0.001
Superior Frontal Gyrus	Right	8, 9	4, 54, 38	3696	0.427 (0.06)	0.512 (0.07)	< 0.001
Thalamus	Right	23	18, −30, −4	168	0.173 (0.04)	0.201 (0.04)	0.001

rACC = rostral anterior cingulate cortex; OFC = orbital frontal cortex; PCC = posterior cingulate cortex.

Table 4
Correlational analysis between rACC (left) and amygdala (right) GM volumes in PTSD subjects ($n = 25$).

	Amygdala (right) (cog 26, −2, −28)		
Cortical area	*r*	*p*	r^2
rACC (left) (cog −4, 34, 2)	−0.449	0.024	0.202

rACC = rostral anterior cingulate cortex cog = centre of gravity.

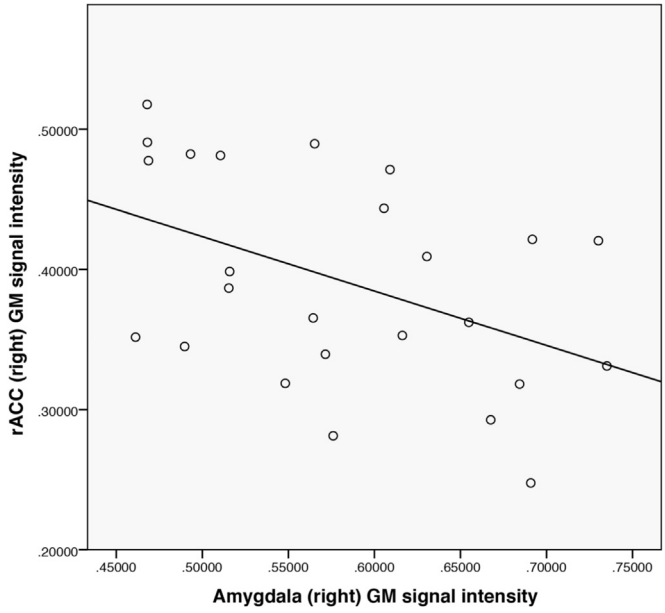

Fig. 2. Correlational analysis of left rACC and right amygdala in PTSD subjects ($n = 25$) found a moderate negative correlation of $r = -0.449$, $p = 0.024$, $r^2 = 0.202$. rACC = rostral anterior cingulate cortex.

Identified reductions in limbic structures including the hippocampus and amygdala, are consistent with research linking dysfunction in emotional regulation and memory formation to GM volume loss in these regions (Britton et al., 2005; McLaughlin et al., 2009; Nardo et al., 2010). Previous studies have observed a link between the intrusive memories symptoms common in PTSD—as measured by re-experiencing clinical scores—and reductions in hippocampal volume (Lindauer et al., 2004; Villarreal et al., 2002). This link is supported by the correlational analysis results from the current study, with the strongest association observed with hippocampal GM volumes and CAPS re-experiencing lifetime sub-scores.

While PTSD related hippocampal reductions have been reported in recent meta-analyses, consensus on amygdala GM volume changes is less clear (Karl et al., 2006; Kuhn and Gallinat, 2013; Li et al., 2014; O'Doherty et al., 2015; Woon and Hedges, 2009). This could in part be due to the anatomical proximity of the amygdala and hippocampus, resulting in differentiation difficulties. The current study found reduced amygdala GM volumes in PTSD subjects compared to both TC and HC groups. A significant negative correlation was found between the amygdala and CAPS scores, the strongest association being with the CAPS avoidance lifetime sub-score. This association has previously been reported (Rogers et al., 2009), however only in the left amygdala—rather than the bilateral association currently observed.

Decreases in frontal GM ROI found, namely the rACC, frontal medial cortex, OFC, middle frontal gyrus, and superior frontal gyrus, are thought to contribute to a state of constant vigilance and alertness associated with PTSD (Akirav and Maroun, 2007; Bremner, 2006; Garfinkel and Liberzon, 2009). Reductions in the rACC and prefrontal cortex have been shown to impair inhibitory modulation of the hypothalamic-pituitary-adrenal (HPA) axis (Herman et al., 2005). This inhibitory impairment reduces HPA regulation, disrupting extinction of fear conditioning (Bremner and Vermetten, 2001). The GM reductions observed throughout the prefrontal cortex and rACC suggest greater inhibitory control dysfunction of the HPA in subjects diagnosed with PTSD. This is further supported by the significant negative correlation found between the left rACC and right amygdala GM volumes in PTSD

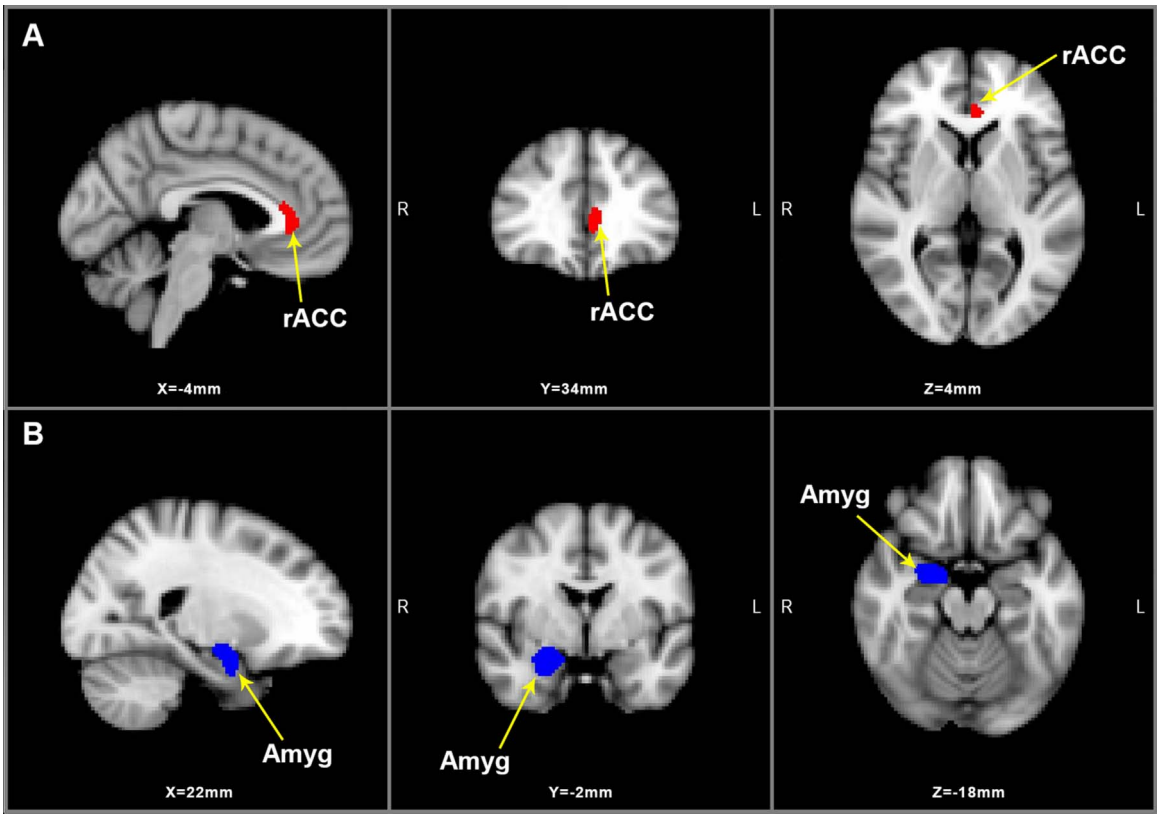

Fig. 3. Correlational analysis of ROI GM volumes in PTSD subjects: (A) Depicts left rACC size of statistically significant cluster negatively correlated to (B) right amygdala. GM volume maps rendered on standard MNI152 structural template. Images are radiologically oriented. GM = grey matter; Amyg = amygdala; rACC = rostral anterior cingulate cortex; L = Left; R = Right.

Table 5
Correlational analysis between CAPS clinical scores and GM volumes in PTSD and TC subjects ($n = 50$).

	CAPS Lifetime			Re-experiencing lifetime sub-score			Avoidance lifetime sub-score			Hyperarousal lifetime sub-score		
Cortical area	*r*	*p*	r^2	*r*	*p*	r^2	*r*	*p*	r^2	*r*	*p*	r^2
Amygdala (left)	−0.425	0.002	0.181	−0.416	0.003	0.173	−0.426	0.002	0.181	−0.407	0.003	0.166
Amygdala (right)	−0.474	0.001	0.225	−0.472	0.001	0.223	−0.476	0.001	0.227	−0.453	0.001	0.205
rACC (left)	−0.444	0.001	0.197	−0.416	0.003	0.173	−0.437	0.002	0.191	−0.473	0.001	0.224
Frontal medial cortex	−0.412	0.003	0.169	−0.376	0.007	0.141	−0.347	0.013	0.121	−0.441	0.001	0.194
OFC (left)	−0.434	0.002	0.189	−0.383	0.006	0.147	−0.393	0.005	0.154	−0.497	0.001	0.247
OFC (right)	−0.384	0.006	0.148	−0.355	0.011	0.126	−0.352	0.012	0.124	−0.423	0.002	0.179
Frontal pole (left)	−0.507	0.001	0.257	−0.476	0.001	0.226	−0.454	0.001	0.206	−0.522	0.001	0.273
Frontal pole (right)	−0.479	0.001	0.229	−0.466	0.001	0.217	−0.426	0.002	0.181	−0.533	0.001	0.284
Hippocampus (left)	−0.470	0.001	0.221	−0.498	0.001	0.248	−0.460	0.001	0.211	−0.431	0.002	0.186
Hippocampus (right)	−0.410	0.003	0.168	−0.421	0.002	0.177	−0.395	0.005	0.156	−0.406	0.003	0.165
Insular (left)	−0.303	0.032	0.092	−0.289	0.042	0.084	−0.261	0.067	0.068	−0.351	0.012	0.123
Insular (right)	−0.447	0.001	0.200	−0.489	0.001	0.239	−0.341	0.015	0.116	−0.475	0.001	0.226
Middle frontal gyrus (left)	−0.567	0.001	0.322	−0.542	0.001	0.294	−0.497	0.001	0.247	−0.623	0.001	0.388
Middle frontal gyrus (right)	−0.441	0.001	0.194	−0.421	0.002	0.177	−0.405	0.004	0.164	−0.474	0.001	0.224
Paracingulate Gyrus (left)	−0.322	0.023	0.103	−0.330	0.019	0.109	−0.303	0.032	0.092	−0.349	0.013	0.122
Paracingulate Gyrus (right)	−0.345	0.014	0.119	−0.333	0.018	0.111	−0.317	0.025	0.101	−0.351	0.012	0.123
PCC (left)	−0.338	0.016	0.115	−0.314	0.026	0.099	−0.327	0.021	0.107	−0.432	0.002	0.187
PCC (right)	−0.339	0.016	0.115	−0.313	0.027	0.098	−0.330	0.019	0.109	−0.436	0.002	0.190
Precuneus (left)	−0.421	0.002	0.177	−0.418	0.003	0.175	−0.347	0.014	0.120	−0.520	0.001	0.271
Precuneus (right)	−0.385	0.006	0.148	−0.392	0.005	0.153	−0.328	0.020	0.108	−0.453	0.001	0.205
Putamen (left)	−0.345	0.014	0.119	−0.372	0.008	0.138	−0.320	0.024	0.102	−0.292	0.039	0.085
Putamen (right)	−0.370	0.008	0.137	−0.428	0.002	0.183	−0.373	0.008	0.139	−0.309	0.029	0.095
Superior Frontal Gyrus (left)	−0.502	0.001	0.252	−0.514	0.001	0.264	−0.447	0.001	0.200	−0.502	0.001	0.252
Superior Frontal Gyrus (right)	−0.483	0.001	0.233	−0.513	0.001	0.264	−0.417	0.003	0.174	−0.480	0.001	0.231

rACC = rostral anterior cingulate cortex; OFC = orbital frontal cortex; PCC = posterior cingulate cortex.

subjects, and negative correlation of the left rACC with CAPS severity scores — the strongest association being with the hyperarousal lifetime sub-score.

While evidence points towards the global nature of neuroanatomical changes in PTSD subjects (with particularly significant findings in the frontal and occipital lobes), there is yet no explanation as to the underlying mechanisms for these findings. Possible factors contributing to significant whole-brain findings include altered HPA modulation resulting in stress-induced glucocorticoid neurotoxicity effects on brain structure and functioning (Atmaca et al., 2017; Hendler et al., 2003; McEwen, 2000), genetic and or environmental factors causing predisposition and impaired resilience (Ho et al., 2007; Rubin et al., 2016; Zhang et al., 2006) and the confluence of different trauma types included in studies (Kelley et al., 2009; Meng et al., 2014).

In addition to reductions in the rACC and amygdala, the current study observed bilateral insula GM loss. A recent study found decreased connection between the insula and amygdala, resulting in the disruption of insula function and processing of sensory information in PTSD (Yoon et al., 2016). The insula is reported to contribute to memory processes, emotional self-awareness and dissociative states (Chalavi et al., 2015b; Chen et al., 2006; Craig, 2009; Critchley, 2005; Lanius et al., 2010). The insula has also been shown to function with the rACC during threat perception and anticipation (Fiddick, 2011). Reduced neuronal activity of the insula caused by GM loss may contribute to GM reductions in the multiple PTSD symptom affiliated regions connected to it. The performed correlational analysis revealed a significant negative association between insula GM volume and CAPS clinical scores—the strongest being the re-experiencing lifetime sub-score.

Reduced GM volumes in the insula and precuneus cortex have also been linked to the intrusive memories of trauma, or 'flashbacks' commonly reported by PTSD sufferers (Brewin et al., 2010; Kroes et al., 2011a). In the current study, reductions in GM of the precuneus in both PTSD vs HC, and PTSD vs TC analyses, were found to be clustered significantly in the posterior and central subdivisions. The posterior and central precuneus cortex have been linked to visual processing, environment perception/planning, episodic memory retrieval and reflective self-awareness (Freton et al., 2014; Margulies et al., 2009). Emotional response to visual stimulus in PTSD subjects have been coupled to bilateral GM reductions of the visual cortex (Morris et al., 1998). Divergent visual processing during face reading tasks have been linked to reduced occipital lobe activation (Lanius et al., 2006). The current findings of significant negative correlations between the bilateral posterior precuneus cortex and CAPS severity scores further implicate the role of the precuneus in PTSD related memory intrusions.

4.1. Limitations

There are several limitations which need to be taken into consideration when interpreting results from the current study. Firstly, sample sizes for each subject cohort are relatively small and may have contributed to a lack of significant findings in a whole brain analysis between the TC and HC groups. Additionally, while the subjects within each group were age and gender matched, the age range was large. Some PTSD diagnosed subjects were currently being treated, or had previously received treatment in the form of psychosocial (e.g. cognitive behavioural therapy) and/or pharmaceutical interventions (e.g. selective serotonin reuptake inhibitors). These treatment therapies have been shown, over time, to slow or reverse grey matter atrophy caused by glutamate neurotoxicity, in addition to promoting neurogenesis through increasing BDNF (Levy-Gigi et al., 2013; Martinowich and Lu, 2008). As this is a cross-sectional study, it is not possible to identify if regional GM reductions are the result of PTSD progression, or if such structural abnormalities were already present in the study participants *prior* to exposure to trauma. Pre-existing structural abnormalities in certain individuals may predispose them to developing PTSD after exposure to trauma, and additionally exacerbate PTSD severity due to further GM reductions. While subjects were screened to exclude anyone who had experienced concussion which resulted in loss of consciousness greater than 10 min, recent research has suggested that sub-concussive impacts acquired during sports or accidents can result in measureable brain changes (Davenport et al., 2016). Trauma experienced in early life has also been reported to increase risks of developing PTSD (Yehuda et al., 2001), and the current study does not use a measure such as the childhood trauma questionnaire (CTQ) to screen for early life trauma. Finally, GM reductions in regions such as the rACC, insula, and hippocampus have been reported in other psychiatric disorders often found to be co-morbid with PTSD (e.g. depression/anxiety disorder) (Kroes et al., 2011b). As such, results from the present study must be considered with caution given the possibility that these psychiatric disorders may also contribute to GM reductions.

4.2. Conclusion

Previous VBM studies exploring GM differences between PTSD and HC subjects have reported heterogeneous results (Corbo, 2005; Eckart et al., 2011; Jatzko et al., 2006; Sui et al., 2010; Tavanti et al., 2012). A recent systematic review of PTSD VBM investigations identified a paucity of studies including three groups (i.e. PTSD diagnosed, TC and HC)(Li et al., 2014). Whilst the current study did not find significant GM differences between the TC and HC groups, the reported findings of PTSD vs TC and PTSD vs HC provide additional evidence that assists in clarifying some of the existing VBM finding inconsistencies. The literature has identified global GM reduction throughout the brain of PTSD subject groups, with a tendency for findings to be localised in limbic and frontal structures (Corbo, 2005; Jatzko et al., 2006; Tavanti et al., 2012). Results from the current study suggest that GM reductions in the prefrontal, precuneus, and limbic structures may participate in the neural network mechanism dysfunction associated with PTSD. This pattern of progressive GM loss in PTSD subjects compared to TC and HC groups adds further weight to evidence revealing disruptions of rACC regulation over the HPA axis after trauma exposure. These findings also underscore documented issues of comorbidities and symptom admixture associated with PTSD investigations, which are suspected to underpin inconsistent VBM findings (Brady et al., 2000; Dorrington et al., 2014). Future studies examining mechanisms of PTSD acquisition and maintenance of these symptoms will need to be confirmed using additional MRI modalities.

Conflict of interest

The authors report no conflict of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2017.05.008.

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