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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