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Review

Grey matter reduction associated with posttraumatic stress disorder and traumatic stress

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ABSTRACT

In recent decades, many imaging studies have reported brain structural alterations in posttraumatic stress disorder (PTSD). However, due to differences in the selection of control subjects, it is difficult to conclude whether the observed alterations were related to disease or traumatic stress. The present study was to provide a quantitative voxelwise meta-analysis of grey matter (GM) changes in PTSD relative to either trauma-exposed controls without PTSD (TEC) or non-traumatised healthy controls (HC) separately and to conduct a systematic review of voxel-based morphometry (VBM) studies that compared trauma-exposed individuals with HC to explore the effect of traumatic stress. GM reduction was identified in the medial prefrontal cortex in PTSD compared to both TEC and HC. Additional GM reduction was also observed in PTSD in the left hippocampus, left middle temporal gyrus and right superior frontal gyrus compared with TEC. Additionally, GM decreased in the left occipital cortex in PTSD compared with HC. The present study delimited the significant differences among VBM results in PTSD research when different control groups were chosen.

Contents

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1. Introduction

Posttraumatic stress disorder (PTSD) is newly defined as a trauma- and stressor-related disorder in the most recent edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-V). PTSD is characterised by four symptom clusters, i.e., re-experience, avoidance, negative cognitions and mood, and arousal (Association, 2013). With a lifetime prevalence rate of up to 6.8% in a survey of the American general population and a significant impairment of daily function (Kessler et al., 2005), there is a substantial need for a better understanding of the neurobiological dysfunctions underlying PTSD. Neuroimaging techniques, such as high-resolution structural magnetic resonance imaging (MRI) combined with either voxel-based whole brain analysis or region of interest analysis of particular structures, provide opportunities to investigate brain structural abnormities that are unrecognisable by the naked eye. Recent structural MRI studies have used these advanced techniques to suggest that PTSD is associated with numerous cerebral morphological abnormalities (Kuhn and Gallinat, 2013; Woon and Hedges, 2008; Woon et al., 2010).

However, inconsistent regions of grey matter (GM) reduction have been reported due to differences in the selection of control groups. For example, Sui et al. (2010) observed GM reduction in the right uncus in PTSD compared with trauma-exposed controls without PTSD (TEC), while GM reduction was observed in the bilateral medial frontal cortex compared with non-traumatised healthy controls (HC). These different results may reflect different neural mechanisms in the pathophysiology of PTSD. For example, some structural alterations may be disease-related (either predispositions to develop PTSD or a by-product of suffering from PTSD), while others may be induced by traumatic stress. This hypothesis is consistent with previous studies. On the one hand, it was proposed that some brain structural reductions in PTSD could be disease-related. For example, in a longitudinal study (Cardenas et al., 2011), PTSD patients with increasing symptoms showed accelerated atrophy in the anterior cingulate cortex (ACC), suggesting that the disease induced the modification of this area. Moreover, Gilbertson et al. (2002, 2007) observed smaller hippocampal volumes in both PTSD patients and their non-exposed monozygotic twins, which supports the assumption that lower hippocampal volume may be disease-related and may lead to a predisposition to develop PTSD. On the other hand, several studies have demonstrated that traumatic stress could have a substantial impact on brain function and structure, regardless of whether the subjects met the criteria for PTSD (Ito et al., 1993; Teicher et al., 2004). Arnsten (2009) proved that stress exposure, independent of psychiatric disorder, can cause architectural changes in the prefrontal cortex by damaging intracellular signalling pathways. Woon et al. (2010) suggested in their meta-analysis that trauma exposure itself could be associated with hippocampal volume deficits in the absence of PTSD. Therefore, it is difficult to determine from a given PTSD study whether the reported brain changes are disease- or traumatic stress-related, which underscores the need to integrate the current findings from different control groups to elucidate the core neural mechanism of PTSD.

Imaging meta-analysis can integrate multiple original studies of one type and explain quantitative research that has examined a certain problem. Activation likelihood estimation (ALE), a quantitative meta-analytic technique, can summarise statistical relationships between study characteristics and findings, which goes beyond qualitatively pooling results from diverse neuroimaging studies. In this study, ALE was used to conduct a meta-analysis of all voxel-based morphometry (VBM) studies in PTSD; this method compared PTSD with either TEC or HC. In addition, a systematic review of VBM studies on trauma-exposed individuals compared to HC was also conducted to analyse the morphologic effect of traumatic stress. The major aim of these studies focused on the brain structural reductions induced by traumatic stress. The trauma-exposed individuals were primarily TEC, though a few PTSD individuals were not completely excluded; this design made the samples more representative. A qualitative review was chosen over a meta-analysis to compare the trauma-exposed individuals to the HC due to the heterogeneity of the reviewed studies. Additionally, VBM studies were sought over region of interest studies to avoid a bias towards specific regions.

To our knowledge, Kuhn and Gallinat (2013) have published a voxelwise meta-analysis of GM reduction in PTSD via ALE. However, there exist two major deficits in their study. First, their study only included TEC as a control group and ignored HC, which may ignore some disease-related brain structural alterations in PTSD. Therefore, in this study, we analyse the structural alternations associated with PTSD by conducting a meta-analysis comparing PTSD with TEC and HC separately. Second, the Kuhn and Gallinat study did not rule out any possible effects of psychotropic drugs on GM alterations in PTSD patients. We thus perform a subgroup meta-analysis to compare medication-free PTSD patients with TEC to avoid the potential confounding effects of medication. Furthermore, the current study includes five recently published VBM articles on PTSD, which makes this study the most updated and comprehensive meta-analysis to date.

2. Materials and methods

2.1. Study selection

A comprehensive literature search of studies published in English through May 2013 was conducted using the PubMed, Cochrane Library, EBSCO, Web of Knowledge, ScienceDirect databases and the National Technical Information Service and System for Information on Grey Literature. The search keywords were (1) "posttraumatic stress disorder" or "PTSD" or "stress" or "trauma" or "adversity" or "child*abuse" or "maltreatment" or "rape" or "crime" or "violence" or "assault" or "war" or "combat" or "accident" or "disaster"; these keywords were crossed with (2) "voxel-based morphometry" or "VBM" or "morphometry" or "volumetry" or "grey matter". The reference lists of the identified papers and review articles were also examined to find additional studies that met our inclusion criteria.

Studies were selected for the meta-analysis using the following inclusion criteria: (1) a formal diagnosis of PTSD based on DSM-IV or ICD-10 diagnostic criteria; (2) use of the whole-brain VBM method to analyse GM reduction; (3) comparisons of PTSD patients with either TEC or HC; and (4) clearly reported Talairach or Montreal Neurological Institute (MNI) coordinates of the activation areas.

For the systematic review of studies that investigated cerebral morphological alteration related to traumatic stress, the inclusion criteria were (1) a focus on the morphologic effect of traumatic stress; (2) use of the whole brain VBM method to analyse GM