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Research paper

Essential brain structural alterations in major depressive disorder: A voxel-wise meta-analysis on first episode, medication-naive patients

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ABSTRACT

Background: Because brain morphological abnormalities in major depressive disorder (MDD) may be modulated by medication and episodes, previous meta-analyses of voxel-based morphometry (VBM) studies therefore have been biased for including medicated patients or medication-free patients who had ever received drugs, as well as patients with different episodes. We sought to identify the essential morphological features without the interference of medication and episodes in MDD.
Methods: Seed-based *d* Mapping was applied to analyze the gray matter differences between all first episode (FE), medication-naive MDD patients and healthy controls. Subgroup meta-analyses and meta-regression were used to explore the effects of methodology, demographics and clinical characteristics.
Results: We identified 10 studies comprising 329 FE, medication-naive MDD patients and 340 healthy controls. Gray matter volumes were increased in the bilateral thalamus, cuneus, left paracentral lobule and medial superior frontal gyrus, and decreased in the right dorsolateral superior frontal gyrus, left insula and middle frontal gyrus in patients. Decreased volume in the right inferior temporal gyrus was only observed in patients with short illness duration and studies with threshold corrections. Moreover, there were different results between 3.0 T MRI and 1.5 T MRI studies. Meta-regression analyses revealed that mean age and the percentage of female patients were not significantly correlated with gray matter changes.
Limitations: There are heterogeneities in demographics, clinical features and analyzing methods of selected studies.
Conclusions: The present meta-analysis revealed that structural abnormalities in the fronto-limbic networks are the essential characteristics in MDD and could contribute to the high risk of suicide in patients.

1. Introduction

As the most common psychiatric disorder, major depressive disorder (MDD) has been predicted to become the leading cause of disability in high-income countries by 2030 (Wiles et al., 2013). MDD can present complex manifestations including affected mood, psychomotor disturbances and cognitive deficits (Association, 2013). With its high prevalence and diverse symptoms, exploring the pathogenesis of MDD is critical to improve clinical diagnosis and treatment evaluation.

Over the past few decades, neuroimaging methods have been widely applied to non-invasively investigate brain abnormalities in mental disorders. One of the most common methods termed voxel-based morphometry (VBM), which can automatically segment and process structural neuroimaging data (Ashburner and Friston, 2001), has been applied in numerous magnetic resonance imaging (MRI) studies. This automated process not only allows an

Abbreviations: AES-SDM, anisotropic effect size signed differential mapping; DTI, diffusion tensor imaging; FDR, false discovery rate; FE, first episode; FSL, FMRIB software library; MDD, major depressive disorder; MFG, middle frontal gyrus; MNI, montreal neurological institute; MRI, magnetic resonance imaging; PET, positron emission tomography; PRISMA, preferred reporting items for systematic reviews and meta-analyses; ROI, regions-of-interest; SDM, seed-based d mapping; SFG, superior frontal gyrus; SPECT, single-photon emission computed tomography; SPM, statistical parametric mapping; VBM, voxel-based morphometry

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unbiased, whole brain level analysis, but it also has comparable accuracy to manual volumetry and region-of-interest approaches (Davies et al., 2009). VBM studies of MDD have reported structural abnormalities in various brain regions such as the prefrontal cortex (Salvadore et al., 2011), amygdala (Frodl et al., 2008a) and hippocampus (Zou et al., 2010). Moreover, animal models of depression (Musazzi et al., 2013) have further supported that brain structural abnormalities may be the critical pathology in MDD, such as reduced volume in the hippocampus that was induced by abnormal enhancement of glutamate release and dendritic atrophy; the latter condition is regarded as a causal factor for volumetric alterations seen in MRI. However, different VBM studies had distinct demographic characteristics, diverse imaging acquisition techniques and various methods to analyze data. Therefore, conducting the meta-analysis is quite necessary to minimize the heterogeneity and identify reliable findings.

Novel meta-analysis methods using spatial coordinates have allowed for integrating different results at the whole brain level to identify significant alterations. Several meta-analyses of VBM studies have revealed some important gray matter abnormalities in MDD, such as the anterior cingulate cortex, hippocampus and frontal gyrus (Bora et al., 2012, Du et al., 2012). However, these meta-analyses included patients who were taking drugs at the time of MRI scanning, and antidepressant medication has been demonstrated to affect brain structures in neuroimaging studies (Frodl et al., 2008b, Hamilton et al., 2008). Structural MRI study included both medicated and drug-naive MDD patients reported that depressed patients with prior antidepressant medication had larger gray matter volume in the orbitofrontal cortex compared with drug-naive patients (Lavretsky et al., 2005). Longitudinal research on depression using selective serotonin reuptake inhibitor (SSRI) for 12 weeks also revealed significantly increased gray matter volume over time in the left dorsolateral prefrontal cortex (Smith et al., 2013). In addition, animal studies also provided important evidence for antidepressant effects on brain structure, for example, tianeptine could counteract hippocampal volume loss resulting from chronic stress (Czéh et al., 2001, Liu et al., 2011) and agomelatine could help increase the total number of new granule cells in the dorsal and ventral hippocampus (Banasr et al., 2006). Furthermore, recent reviews on animal models confirmed that antidepressants could reduce the abnormally enhanced glutamate release and prevent dendritic loss to reverse the brain structural changes (D'Sa and Duman, 2002, Musazzi et al., 2013).

Another issue is that the included patients in previous meta-analyses had different episodes, which were also reported to induce different brain structural changes (Carceller-Sindreu et al., 2015; Soriano-Mas et al., 2011a). For example, the volume of hippocampus may be negatively correlated with depression episodes and volume of amygdala increased during early stages and decreased as the illness progresses (Musazzi et al., 2011). Longitudinal research also reported that the number of relapses in depression was correlated with gray matter volume reductions in the right middle occipital gyrus and the bilateral insula (Soriano-Mas et al., 2011b). Though little animal model of depression has focused on recurrence, one possible animal model for recurrent depression reported that animals with a prior depressive episode were sensitive to future stressors and exhibited more rapid decline in sucrose consumption during re-exposure compared to the initial stressor exposure (Kato et al., 2015).

Although one meta-analysis on MDD (Zhao et al., 2014) only included medication-free patients, it enrolled both medication-naive patients and medicated patients who underwent a wash-out period before MRI scanning, and its subgroup analyses revealed different results between these two patient groups. Moreover, patients in this meta-analysis also had different episodes, which can affect the accuracy of results. Therefore, we conducted this meta-analysis on first episode (FE), medication-naive MDD to exclude the influence of medication and episodes and to directly identify the most essential brain structural changes. According to prior related studies (Kong et al., 2014, Zhang et al., 2012, Zhao et al., 2014), We hypothesized that FE, medication-naive patients may present decreased gray matter volumes in the frontal lobe (e.g. middle frontal gyrus) and increased gray matter volumes in the thalamus, both of which are the critical regions for emotional regulation.

Our goals were twofold: identifying the most prominent and replicable gray matter abnormalities in FE, medication-naive MDD patients and examining the effects of demographics and clinical characteristics on gray matter volumes in MDD with a new coordinate-based meta-analytic method called Seed-based *d* Mapping (SDM) (formerly "*Signed Differential Mapping*") of version 4.31 (Radua et al., 2014). This novel method has the same advantages as the previous anisotropic effect size signed differential mapping (AES-SDM), including avoiding voxels that appear significant in opposite directions, allowing for the combination of reported peak coordinates with statistical parametric maps for both positive and negative results, applying anisotropic kernels during the recreation of effect size maps to diminish anisotropy in the spatial covariance, and providing statistical analyses such as meta-regression analysis. Moreover, it was also improved with specific Montreal Neurological Institute (MNI) coordinate transformations for FMRIB Software Library (FSL) and software other than Statistical Parametric Mapping (SPM), which makes the meta-analysis more exhaustive and accurate (Radua et al., 2014).

2. Methods

2.1. Inclusion of studies

A systematic strategy was conducted to search for relevant studies published in PubMed, Embase, Web of Science, Medline and Science Direct before November 2015, with the key words "depression" OR "depressive disorder" OR "unipolar depression" plus "voxel-based morphometry" OR "VBM" OR "voxel based" OR "morphometry". The reference lists of the identified papers were searched for additional studies that fit the inclusion criteria.

Studies were included using the following criteria: (1) the study used the whole-brain VBM method to compare the gray matter volumes between MDD patients and healthy controls; (2) the MDD patients were in the first episode and had never taken antidepressants; (3) the study reported Talairach or MNI coordinates. Studies on patients with geriatric (age >60) or adolescent (age <18) depression were excluded. Because for geriatric depression, the brain structure could be influenced by vascular conditions, such as small infarction; while for adolescent depression, it is more chronic, severe and disabled than adult depression, and the brain structure could be affected by brain maturation during developmental period, which leads to distinct neurobiology and treatment in adolescent depression (Andersen and Teicher, 2008). Studies only reporting regions-of-interest (ROI) findings or seed voxel–based analysis results were also excluded. For studies using overlapping samples, the study with the most subjects was included.

2.2. Quality analysis

We evaluated the quality of the included studies using a 10-point checklist that focused on both the clinical and demographic aspects of individual study samples and the imaging-specific method (see Supplementary Table S1). This checklist was based on previous meta-analysis (Chen et al., 2015). Though the checklist