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Gray matter volume in major depressive disorder: A meta-analysis of voxel-based morphometry studies

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ABSTRACT

We designed this study to perform a meta-analysis of gray matter (GM) findings in major depressive disorder (MDD) by using the signed differential mapping (SDM) toolbox. The Pubmed, ScienceDirect and Scopus databases were searched, and only studies published or published online before November 2010 have been included. Twenty voxel-based morphometry (VBM) studies of adult MDD patients were entered in the meta-analysis by SDM toolbox with threshold criteria set as error probability less than 0.00005 and cluster more than 50 voxels. Onset age, numbers of patients and controls, gender ratio of both groups, ratio of medicated patients, depression rating scores, illness duration, co-morbidity and existence of corrected *p* value were also meta-regressed as covariates to exclude confounding biases. Voxel-wise meta-analytic results of these 20 VBM studies in MDD patients revealed that GM deficits were observed in the right anterior cingulate cortex and left anterior cingulate cortex when patients were compared with controls. The findings remained mostly unchanged in jackknife sensitivity analyses. The potential confounding factors had little impact on the results. This meta-analysis suggested GM deficits of the anterior cingulate cortex might be important in the etiology of MDD.

1. Introduction

Major depressive disorder (MDD) is a chronic illness that influences the social and occupational functions of patients. The relationship between deficits of gray matter (GM) as determined by magnetic resonance imaging (MRI) and the pathogenesis of MDD is an intriguing issue. Among the regions of reported GM deficits, the anterior cingulate cortex (ACC) is an important area for the pathogenesis of MDD. The ACC is involved in cognitive and affective regulation, attention, problem solving, motivation, and decision making (Bush et al., 2000; Allman et al., 2001; Rushworth et al., 2007), all of which are implicated in MDD. The ACC is composed of two components, affective and cognitive subdivisions (Bush et al., 2000; Yucel et al., 2003). The affective subdivision is connected to limbic regions that are involved in the modulation of emotions, such as the amygdala and the brainstem (Devinsky et al., 1995). The cognitive subdivision is involved in cognitive processing through response selection and cognitive information (Yucel et al., 2003). The two subdivisions are thought to have important roles in the pathophysiology of MDD (Mayberg, 1997; Ressler and Mayberg, 2007). Among MRI studies of MDD, there are several reports supporting GM reduction in the ACC of MDD patients when compared with age- and sex-matched controls (Drevets et al., 1997; Botteron et al., 2002; Hastings et al., 2004). Decreased GM in the ACC has also been found in several studies using the method of manual delineation (Ballmaier et al., 2004; Caetano et al., 2006; Lavretsky et al., 2007). However, there are also several MRI reports that failed to find significant GM deficits in the ACC of patients with MDD (Brambilla et al., 2002; Bremner et al., 2002; Pizzagalli et al., 2004). More recently, voxel-based morphometry (VBM) has been applied to assess the possibility of GM deficits in MDD patients. Several VBM studies have found GM reductions in the ACC (Chen et al., 2007; Tang et al., 2007). In a volumetric MRI study, Coryell et al. (2005) reported volumetric reductions of the left ACC in patients with MDD. These studies also suggested that ACC structural deficits might be related to clinical and demographic factors, such as age (Lavretsky et al., 2007), family history of illness (Drevets et al., 1997), treatment response (Coryell et al., 2005) and current mood state (Caetano et al., 2006). The ACC is also vulnerable to glucorticoid toxicity, which may be related to depression (Ahima and Harlan, 1990; Akana et al., 2001), possibly resulting in damage to the ACC that would be consistent with the neuroimaging findings. Based on these reports, it appears that the ACC might play a vital role in the pathogenesis of MDD.

In addition to the ACC, other brain regions may also be involved in the pathophysiology of MDD. Frodl et al. suggested that structural abnormalities of the hippocampus and the prefrontal cortex might be related to physical and emotional abuse of MDD patients in their region-of-interest study (Frodl et al., 2010). Several meta-analytic

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reports of MDD showed reduced brain volume in the frontal cortex, orbitofrontal cortex, hippocampus and striatum of MDD patients (Koolschijn et al., 2009; Arnone et al., 2012). These regions, taken together with the ACC, correspond to Sheline's limbic–cortical–striatal–pallidal–thalamic theory of the pathogenesis of MDD (Sheline, 2000).

Structural MRI studies are potentially amenable to comparisons between patients with MDD and controls because they are paradigm-free, and hence without the paradigm-related problems of functional MRI studies. Initial morphometric studies mostly relied on manual tracing methods, which would be associated with potential biases. The advent of the fully automated, whole-brain VBM method (Ashburner and Friston, 2000, 2001), which shows comparable accuracy to that of manual volumetry (Uchida et al., 2008; Davies et al., 2009) and overcomes the limitations of the region-of-interest (ROI) approach, can provide a powerful and unbiased tool to study neural substrates of many kinds of illnesses, including MDD. However, these VBM studies are usually limited by relatively small sample sizes with insufficient statistical power and the accompanying risk of false-positive errors. From the statistical viewpoint, the issue of sample size probably could be resolved by combining these studies to produce a population large enough to conclusively evaluate the hypothesized GM deficits in patients with MDD.

Radua et al. recently developed a voxel-based meta-analytic toolbox, the signed differential mapping (SDM) toolbox, which would be suitable to evaluate GM in MDD. The SDM toolbox has been applied in obsessive–compulsive disorder and other anxiety disorders (Radua and Mataix-Cols, 2009; Radua et al., 2010). It has the potential to quantify the reproducibility of neuroimaging findings and thus generate insights that are difficult to obtain in individual studies (Costafreda et al., 2009).

We designed this study to systematically search published VBM studies in patients with MDD. We used the SDM toolbox to perform a meta-analysis of studies examining GM deficits among those that applied VBM in MDD. From the literature reviewed above, we further hypothesized that GM decreases of the ACC might represent a core deficit of MDD.

2. Method

2.1. Inclusion of studies

Our literature searches used the following keywords "depression" plus "voxel-based" or "morphometry" or "voxelwise" or "GM" to collect the related articles in the PubMed, ScienceDirect and Scopus databases. We did not use the terms "MRI" and "major depressive disorder" because "MRI" as a keyword would include studies that did not use the VBM method and "major depressive disorder" would miss the studies using the term "major depression" or other descriptors of "depression". The articles were limited to those published in print or online before November 2010. We only included the VBM studies with structural comparisons between MDD patients and controls. These studies were also published in English in journals included in the Science Citation Index database. For the studies without reported coordinates or coordinates not in the Montreal Neurological Institute (MNI) space [such as in the study of van Tol et al. (2010), which used DARTEL space], the authors were contacted to obtain the MNI coordinates. The studies of MDD comorbid with anxiety disorders were accepted for inclusion because MDD is very commonly comorbid with anxiety disorders (Biederman et al., 2005; Phillips et al., 2009, 2011), so that comorbidity of this type might characterize a substantial proportion of MDD patients.

2.2. Exclusion criteria for studies

This meta-analytic study was designed to focus on GM deficits in adult MDD, not geriatric depression or late-onset depression (after 60 years old), because the structural etiology of geriatric depression might differ from that of adult MDD. Accordingly, studies of geriatric depression or late-onset depression were excluded. Had patients with geriatric depression or late-onset depression been included, we would have had to consider the complicating factors of co-morbid neurological or systemic illness, such as Parkinson's disease or diabetes, which would likely have additive effects on brain structure beyond those of depression, per se. Similarly, studies of adolescents and children were excluded because the age and stage of brain development in these subjects would also be expected to influence the meta-analysis. Studies that lacked healthy controls were excluded because the VBM method requires a comparison group to assess GM differences. Studies with overlapping samples were also excluded. Finally, studies of treatment-resistant depression were excluded due to the possible bias that the underlying pathophysiology might be different from most MDD patients [treatment-resistant depression represents less than one third of MDD patients and brain structure in such cases might be influenced by exposure to multiple types of medications (Shelton et al., 2010)].

2.3. Regional differences in GM

The meta-analyses of GM differences were performed using SDM (http://www.sdmproject.com), which combines the advantages of two previous methods, activation likelihood estimate (Turkeltaub et al., 2002) and multilevel kernel density analysis (Wager et al., 2007). The reasons for the choice of SDM were as follows:

(1) SDM uses a strict criterion for selection of the reported peak coordinates to ensure that only regions with statistical significance at the whole-brain level are considered the inclusion in the meta-analysis. This step could prevent biases related to methods using liberal thresholds and ROI methods in neuroimaging studies.
(2) It permits the reconstruction of both increases and decreases of GM in the same map.

The following steps constituted the SDM processing procedures for meta-analysis:

(1) A map of GM differences [based on Talairach space (Lancaster et al., 2000), voxel size $2 \times 2 \times 2\ m^3$] was created, respectively, for each study after the coordinates were selected and converted.
(2) A 25-mm full-width at half-maximum un-normalized Gaussian kernel was used to assign indicators of proximity to reported coordinates. The parametric setting of a 25-mm kernel was used to control for false-positives (Salimi-Khorshidi et al., 2009).
(3) A modification from multilevel kernel density analysis limited the value within one study to a maximum and created both positive (e.g., increased volume) and negative (e.g., decreased volume) at the same time, which could prevent a particular voxel from being shown as both positive and negative. This step avoided biases toward studies reporting various coordinates in proximity and reconstructing both increases and decreases of GM in the same map.
(4) A modification from multilevel kernel density analysis defined the meta-analytic value of a voxel as the mean of studies reporting the coordinate around the voxel, which were weighted by the square root of the sample size of each study. The studies with larger sample sizes contribute more to the meta-analytic results.
(5) A whole-brain null distribution of the meta-analytic values was created to test which voxels made more appearances than expected by chance. The distribution was produced by Monte Carlo randomizations of the location of coordinates (within a mask of GM plus 8 mm of white matter), which can maximize statistical stability with reduced computation time (almost 40 million values are obtained with 500 randomizations) (Radua and Mataix-Cols, 2009).
(6) The results with uncorrected p value < 0.0001 and cluster size > 50 voxels (Radua et al. indicated that a p value < 0.001 was empirically equivalent to a false discovery rate corrected $p < 0.05$ in their simulations) were observed (Genovese et al., 2002; Radua and Mataix-Cols, 2009). So our statistical threshold was set more conservatively than in the study of Bora et al. (2012a), where it was set as $p < 0.001$. The statistical significance of each voxel was determined by standard tests with randomization for 5000 times.
(7) Possible confounding parameters, such as mean age and GM of patient and control groups, gender ratios of both groups, the percentage of medicated patients, scores of clinical rating scales, MRI machine type (1.5 T or 3 T), sample size of each study (patient number and control number), age at onset, duration of illness and comorbidities, are entered as covariates in the SDM analysis.

2.4. Descriptive analysis of quartiles

This step was performed to provide the actual proportion of studies reporting coordinates in the same region (regardless of p value). The calculations were weighted by sample size so that studies with large samples contributed more. The