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Neural correlates during working memory processing in major depressive disorder

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ABSTRACT

Background: Functional magnetic resonance imaging (fMRI) studies in major depressive disorder (MDD) have revealed cortical-limbic-subcortical dysfunctions during working memory (WM) processing, but the results are inconsistent and it is unclear to what extent these findings are influenced by demographic, clinical characteristics and task performance of patients. The present study conducted a quantitative coordinate-based meta-analysis of fMRI data to investigate the hypothesized dysfunction in the neural correlates during WM processing in MDD.
Methods: A systematic research was conducted for fMRI studies during WM processing comparing MDD patients with healthy controls (HC). Meta-analysis was performed using effect size signed differential mapping (ES-SDM). Meta-regression analyses with age, sex and medication as factors were performed in MDD group.
Results: Functional MRI data of 160 MDD patients and 203 HC from 13 WM experiments across 11 studies were included in this meta-analysis. In the pooled meta-analysis of all included studies, significant increased activation during WM in the left lateral prefrontal cortex, left precentral gyrus, left insula, right superior temporal and right supramarginal areas, and significant decreased activity in the right precentral gyrus, right precuneus and right insula were observed in MDD compared with controls. In the subgroup analysis of the studies with matched task performance, MDD subgroup showed hyperactivation only in the left prefrontal cortex and hypoactivation in the regions similar to the pooled analysis. The meta-regression with age, sex and medication showed no significance in MDD group.
Conclusions: Regardless of differences in task performance between groups, patients with MDD showed consistent functional abnormalities in the cortical-limbic-subcortical circuitry during WM processing. Distinct patterns of neural engagement may reflect compensatory neural strategies to potential dysfunction in MDD.

1. Introduction

Major depressive disorder (MDD) is a mental disorder characterized by affective, cognitive and somatic symptoms. A growing literature on cognition in MDD has revealed that MDD patients frequently show cognition deficits, such as impaired working memory (WM), attention and executive functioning (Shenal et al., 2003) and WM impairments are one of the common features of depression (Ilsley et al., 1995). As a cognitive system, working memory (WM) is fundamental to the performance of many cognitive tasks and day-to-day activities (Wager and Smith, 2003). It is defined as a processing resource of limited capacity, involved in preserving information while processing the same or other information (Baddeley and Logie, 1999; Rottschy et al., 2012; Unsworth and Engle, 2007), including content manipulation and transfer between inputs and outputs (Engle et al., 1999). Over the years, researchers have employed multiple paradigms to investigate WM, including n-back, Sternberg, delayed matching to sample (DMTS), delayed simple matching, continuous performance test (CPT), mental arithmetic (MA), and Tower of London (TOL) tasks (Rottschy et al., 2012).

Neuroimaging research has been conducted with MDD patients performing WM paradigms, which documented that WM impairments were mediated by the abnormalities in related brain regions such as the prefrontal, parietal, temporal, cerebellar and subcortical regions

Abbreviations: MDD, major depressive disorder; fMRI, functional magnetic resonance imaging; WM, working memory; ES-SDM, effect size signed differential mapping; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; ACC, anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; PFC, prefrontal cortex; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; CBF, cerebral blood flow; SPECT, single photon emission computed tomography; STG, superior temporal gyrus; DMN, default-mode network.

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(Harvey et al., 2005; Vasic et al., 2009; Walter et al., 2007b). The cortical-limbic-subcortical circuit is involved in the regulation of mood, cognition and behavior (Dougherty and Rauch, 2007; Mayberg, 1997), and the pathophysiology of MDD (Soares and Mann, 1997). Functional brain imaging literature has revealed alteration in brain activation in this circuit during WM in depression. For instance, a few studies using WM-related tasks (Harvey et al., 2005; Matsuo et al., 2007; Walter et al., 2007b) reported increased activation of the dorsolateral prefrontal cortex (DLPFC) and/or ventrolateral prefrontal cortex (VLPFC) in patients relative to controls, but others observed decreased activity in these areas (Goethals et al., 2005; Kerestes et al., 2012; Pu et al., 2011). In contrast, null findings have also been reported (Barch et al., 2003; Rose et al., 2006; Sandstrom et al., 2012). Moreover, there are few studies that have demonstrated WM load-related hyperactivity in the frontal areas in MDD patients relative to healthy controls (HC) (Harvey et al., 2005; Walsh et al., 2007). A similar inconsistent pattern exist for the involvement of the anterior cingulate (ACC) during WM processing in MDD, with studies reporting both enhanced (Bertocci et al., 2012; Harvey et al., 2005; Schoning et al., 2009) and reduced (Elliott et al., 1997; Hugdahl et al., 2004; Matsuo et al., 2007) dorsal anterior cingulate cortex (dACC) activity in MDD when compared to controls. In addition, a few studies have also reported no alterations in the ACC activity in MDD patients when compared with controls (Matsuo et al., 2007; Sandstrom et al., 2012). Furthermore, compared to HC, MDD patients also show aberrant activation in the parietal cortex (Barch et al., 2003), temporal and occipital cortex (Barch et al., 2003; Fitzgerald et al., 2008; Garrett et al., 2011; Korgaonkar et al., 2013) during WM processing.

Notably, among the above-mentioned studies, task performance during the WM tasks seems to play a critical role in some of the aberrant activations that were observed in MDD. In particular, reported hyperactivity in the prefrontal cortex (PFC) (Fitzgerald et al., 2008; Harvey et al., 2005; Matsuo et al., 2007; Walsh et al., 2007; Walter et al., 2007b) and ACC (Bertocci et al., 2012; Harvey et al., 2005; Schoning et al., 2009) in MDD when compared with controls was observed with intact performance on WM tasks in MDD patients. By contrast, other studies that reported hypoactivation in the dACC (Elliott et al., 1997; Pu et al., 2011) and parietal cortex (Hugdahl et al., 2004) observed impaired performance during WM tasks in depressed participants. This possibly suggests that intact performance in MDD is associated with increased cortical activity while impaired performance is associated with reduced cortical activation. However, this is not always the case, as attenuated activity was also reported in the PFC (Goethals et al., 2005; Kerestes et al., 2012), precentral gyrus, parietal cortex and thalamus (Barch et al., 2003) during n-back tasks in depressed participants despite no observed behavioral deficit. In this regard, performance level during cognitive processing is also suggested to be a factor influencing the activation profile of the brain regions (Thomas and Elliott, 2009).

As discussed above, findings obtained from these experiments are largely inconsistent with respect to alterations of the neural activity in WM-related regions in depressed patients when compared with controls. These could potentially be due to considerable variation in terms of the demographic characteristics of patients, clinical factors, experimental paradigm and imaging protocols used in these published studies. For example, a few published MDD studies have relatively small sample sizes, which may result in spurious findings (Holmes et al., 2005; Rose et al., 2006). Additionally, only a few studies included drug-free MDD participants, indicating potential bias in reported results due to medication (Korgaonkar et al., 2013; Matsuo et al., 2007; Walsh et al., 2007).

Therefore, identifying consistent neural activity alterations of the WM-related brain regions in MDD patients across functional magnetic resonance imaging (fMRI) studies through meta-analysis is of particular significance. Thus, the present study conducted a quantitative coordinate-based meta-analysis of available fMRI data using effect size signed differential mapping (ES-SDM) to investigate the neural dysfunction of WM processing in MDD. The ES-SDM is a valid and reliable quantitative coordinate-based meta-analysis approach, which allows integration of neuroimaging results across studies. It possesses good overlap with pooled analysis, adequate sensitivity, and excellent control over false positives (Radua et al., 2012). It has been successfully applied to several neuropsychiatric disorders such as posttraumatic stress disorder (Sartory et al., 2013), Alzheimer's disease (Li et al., 2012), bipolar disorder (Nortje et al., 2013) and anxiety disorders (Shang et al., 2014). As task performance is believed to contribute to aberrant activity in MDD, a subgroup analysis was also conducted to analyze only tasks in which the MDD subgroup showed equal performance relative to the matched HC group.

2. Methods

2.1. Studies selection

PubMed, Embase and ISI Web of Science databases were searched using the following keywords: “depression” or “unipolar disorder” or “depressive disorder;” and “functional magnetic resonance Imaging” or “fMRI;” and “memory” or “working memory” or “short term memory.” Additional articles were identified through major reviews and reference lists of eligible articles.

A study was included if it (1) reported comparisons between patients with MDD and HC; (2) employed fMRI; (3) assessed brain activation during WM processing; (4) reported the whole-brain results of activity alterations in standard stereotactic coordinates (Talairach/Tournoux or Montreal Neurological Institute (MNI) space). In cases that similar studies met the aforementioned inclusion criteria but had overlapping data, the study with the largest sample size was selected. If one study reported more than one experiment, the different experiments were included in this meta-analysis.

Studies were excluded if (1) participants were in an age range of <18 or >65 years; (2) the data were unavailable (e.g., missing neuroanatomical coordinates) even after the author/s were contacted by e-mail or telephone; (3) the data overlapped with those of another included publication; (4) depression was secondary to a somatic condition such as temporal lobe epilepsy or multiple sclerosis and was investigated solely as a comorbid psychiatric condition or as postpartum depression; and (5) region-of-interest approach was used.

2.2. Voxel-based meta-analysis

The coordinates in each study were independently extracted by two authors (XiuLi Wang and MingYing Du) according to the ES-SDM method (Radua et al., 2012) and inconsistencies were resolved by a third independent assessor (QiYong Gong).

This meta-analysis was performed using ES-SDM (Bora et al., 2011; Radua and Mataix-Cols, 2012; Radua et al., 2012) (http://www.sdmproject.com/software). ES-SDM incorporates useful features from previous methods, such as ALE (Eickhoff et al., 2009) and multilevel kernel density analysis (MKDA) (Wager et al., 2007), and also embodies some improvements and new features. For example, in ES-SDM, both positive (i.e., increased activation) and negative (i.e., decreased activation) coordinates are reconstructed in the same map, to prevent a particular voxel from erroneously appearing positive and negative at the same time. Second, ES-SDM assigns each voxel a measure of the effect size, namely, the standardized mean (for one-sample designs) and the standardized mean difference (for two-sample designs), referred to as Hedge's d at the sample level. The use of effect sizes allows the combination of reported peak coordinates with statistical parametric maps, thereby allowing more exhaustive and accurate meta-analyses. Third, complementary analyses, such as jack-knife and meta-regression analyses, were used to assess the robustness and heterogeneity of the results. Recently, one meta-analysis (Rose and Donohoe, 2013) performed an empirical analysis of effect sizes in genetic studies of cognitive and