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Intrinsic disruption of white matter microarchitecture in first-episode, drug-naive major depressive disorder: A voxel-based meta-analysis of diffusion tensor imaging

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ABSTRACT

Previous studies have demonstrated the influences of episodes and antidepressant drugs on white matter (WM) in patients with major depressive disorder (MDD). However, most diffusion tensor imaging (DTI) studies included highly heterogeneous individuals with different numbers of depressive episodes or medication status. To exclude the confounding effects of multiple episodes or medication, we conducted a quantitative voxel-based meta-analysis of fractional anisotropy (FA) in patients with first-episode, drug-naive MDD to identify the intrinsic WM alterations involved in the pathogenesis of MDD. The pooled meta-analysis revealed significant FA reductions in the body of the corpus callosum (CC), bilateral anterior limb of the internal capsule (ALIC), right inferior temporal gyrus (ITG) and right superior frontal gyrus (SFG) in MDD patients relative to healthy controls. Meta-regression analyses revealed that FA reduction in the right ALIC and right SFG was negatively correlated with symptom severity and duration of depression, respectively. Our findings provide robust evidence that the WM impairments in the interhemispheric connections and frontal-subcortical neuronal circuits may play an important role in MDD pathogenesis.

1. Introduction

Major depressive disorder (MDD) is characterized by a profound and persistent dysregulation of mood (Fitzgerald, 2013) and is the most prevalent mental illness, with an estimated lifetime prevalence of 16.2% (Kessler et al., 2003). MDD not only impairs cognitive and social functions but also leads to other morbidity, including angina, asthma, arthritis, diabetes and even mortality (Kessler and Bromet, 2013; Kupfer et al., 2012). Despite the availability of various treatments, over 30% of MDD patients still fail to achieve complete remission (Rush et al., 2006), and MDD is ranked as the second leading cause of years lived with disability in 2013 worldwide (Global Burden of Disease Study, 2015). Therefore, exploring the neurophysiological abnormalities associated with MDD pathogenesis is crucial to improving the effectiveness of both diagnostic and treatment strategies in MDD.

As a novel and noninvasive structural magnetic resonance imaging (MRI) technique, diffusion tensor imaging (DTI) has been widely used over the past few decades to discern the directionality of white matter (WM) tracts in the normal human brain (Assaf and Pasternak, 2008; Pfefferbaum et al., 2005; Stark et al., 2004) and to evaluate the integrity of white matter fibers in psychiatric illnesses, including schizophrenia (Buchsbaum et al., 1998; Hao et al., 2006; Okugawa et al., 2004), bipolar disorder (Benedetti et al., 2015; Haznedar et al., 2005; Magioncalda et al., 2016), and depression (Alexopoulos et al., 2002; Nobuhara et al., 2004, 2006; Taylor et al., 2004). A commonly used metric in DTI studies is fractional anisotropy (FA). This metric can estimate the degree to which tissue organization limits the diffusion of

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water molecules in white matter fiber tracts, with decreased FA indicating the disruption of white matter.

In recent years, substantial DTI studies have identified some important WM abnormalities in MDD patients, including the genu of the corpus callosum (CC) (Han et al., 2014; Korgaonkar et al., 2011), left anterior limb of the internal capsule (ALIC) (Jia et al., 2010; Zhu et al., 2011; Zou et al., 2008), and left superior longitudinal fasciculus (SLF) (Lai and Wu, 2014a; Versace et al., 2010; Zuo et al., 2012). However, another large sample study found no significant difference in FA between MDD patients and healthy controls (Choi et al., 2014). These inconsistent results might be attributed to various factors. The high heterogeneity of MDD individuals, such as different illness duration or episodes of depression or medication status, is considered a main cause of these inconsistencies. Previous studies have demonstrated the influences of episodes or illness duration (de Diego-Adelino et al., 2014; Lai and Wu, 2014a) and antidepressant drugs (Khalaf et al., 2015; Taylor et al., 2011; Zhang et al., 2015) on WM in MDD. Although some studies included medication-free patients who experienced a drug wash-out period, this period varied over a wide time window, ranging from 2 days to 6 months (Lyden et al., 2014; Tha et al., 2013). Varied wash-out periods may result in inconsistent medication statuses, which can affect research results. For these reasons, it is difficult to discern whether the WM abnormalities observed in these studies are the intrinsic alterations resulting from MDD or whether these alterations result from recurrent or chronic MDD or from long-term exposure to medication. Therefore, the investigation of first-episode, drug-naive MDD without the potential influences of confounding factors deriving from recurrent episodes or medication effects is of great importance for identifying the fundamental changes in the microarchitecture of WM and elucidating the essential pathophysiology of MDD.

Unfortunately, the results of recent DTI studies on first-episode, drug-naive MDD subjects have been inconclusive and controversial. Most studies have detected lower FA in various WM areas, such as the right anterior thalamic radiation (Jiang et al., 2015; Lai and Wu, 2014a), the internal and external capsule (Guo et al., 2012b; Liu et al., 2016; Xiao et al., 2015; Zhu et al., 2011), the genu and body of the CC (Guo et al., 2012b; Han et al., 2014), the middle frontal gyrus (Ma et al., 2007; Ouyang et al., 2011) and the SLF (Srivastava et al., 2016; Wu et al., 2011). One study, however, reported no significant FA differences between patients and controls (Hayashi et al., 2014). In contrast, another investigation with a relatively larger sample size observed increased FA in the WM of the left SLF (Wang et al., 2014). Moreover, Cheng et al. found that early-onset, first-episode, drug-naive MDD patients (18–29 years old) exhibited increased FA in the WM of the CC, inferior fronto-occipital fasciculus and corticospinal midbrain, whereas late-onset, first-episode, drug-naive MDD patients (30–45 years old) showed decreased FA in vast WM clusters (Cheng et al., 2014). These reported discrepancies related to the changes in FA may potentially be attributed to the factors such as the age of disease onset, illness duration and symptom severity.

In our previous meta-analysis of DTI studies using tract-based spatial statistics (TBSS) in MDD patients with different episodes and medication status (Chen et al., 2016), the subgroup analysis of first-episode, drug-naive MDD only detected FA reduction in the left ALIC, which is different from the findings of the global analysis (including recurrent, medicated or medication-free MDD patients). However, the result should be interpreted with caution and further investigation is needed to verify the finding because only 7 datasets of small sample size were analyzed. Moreover, the research only included these DTI studies using TBSS, a technique merely focusing on the central skeleton of WM tracts, which may miss the abnormalities in the near-cortical WM (Wang et al., 2013; Zalesky, 2011). Voxel-based analysis (VBA) is the other common whole-brain analysis approach that allows investigating the integrity of all WM voxels, including peripheral regions of WM and fiber crossings (Nortje et al., 2013). Thus, there is an increasing necessity to employ a meta-analysis integrating TBSS and VBA researches for identifying the robust results of intrinsic WM alterations in first-episode, drug-naive MDD to provide more insight into MDD pathogenesis.

Therefore, the first aim of this study was to conduct a pooled meta-analysis to address the most consistent and replicable WM microarchitecture abnormalities in patients with first-episode, drug-naive MDD using anisotropic effect-size signed differential mapping (AES-SDM), a voxel-based meta-analytic method that combines peak coordinates with statistical parametric maps of neuroimaging findings to recreate effect-size maps of the differences between patients and controls (Radua et al., 2012a,b). This method has several advantages over other coordinate-based meta-analytical approaches, including the reconstruction of both positive and negative coordinates on the same map, which allows for the inclusion of the studies reporting no differences and introduces a meta-regression analysis to identify potential moderators (Radua and Mataix-Cols, 2009; Radua et al., 2012b). The second aim of our study was to utilize a meta-regression analysis to investigate the potentially moderating effects of clinical characteristics on WM integrity in patients with MDD.

2. Materials and methods

2.1. Literature search strategy

A systematic and extensive retrieval strategy was used to search for relevant literature published between January 1994 and May 2016 in PubMed, EMBASE, Web of Science, Cochrane Library and Science Direct. The search keywords were (“first-episode depression”, “unipolar disorder”, “depressive disorder” or “depression”) and (“diffusion tensor”, “DTI” or “diffusion magnetic resonance imaging”). Additional articles were identified by manually checking the reference lists of both eligible articles and review articles.

2.2. Study eligibility criteria

We assessed all studies yielded by our search for potential suitability. Studies were included in the meta-analysis according to the following inclusion criteria: (i) an original article published in a peer-reviewed English language journal; (ii) patients were right-handed and had first-episode, drug-naive adult MDD to minimize the impact of drug status, depression episodes, neurodevelopment and neurodegeneration on WM integrity; (iii) the study compared the FA values of WM between first-episode, drug-naive MDD patients and healthy controls; and (iv) the study adopted a whole-brain analysis to detect FA alterations and reported either Talairach or Montreal Neurological Institute coordinates. We also contacted the corresponding authors to obtain additional information for the studies that met all criteria for meta-analysis but lacked whole-brain coordinates.

Exclusion criteria for this meta-analysis were as follows: (i) case reports or reviews; (ii) the recruitment of participants with any other combined Axis I diseases; (iii) the enrollment of adolescent or late-life MDD patients; (iv) fewer than 10 individuals in either the patient group or healthy control group; and (v) when overlapping study samples were used in separate publications, the data from the study with the largest sample were included for meta-analysis. Additionally, the guidelines of Meta-analysis of Observational Studies in Epidemiology (MOOSE) were followed in the present study (Stroup et al., 2000).

2.3. Quality assessment and data extraction

The qualities of the included studies were evaluated using a 12-point checklist (see Supplementary Table S1) that was based on both the clinical and demographic characteristics of the study population and the imaging-specific methodology (Du et al., 2014). For the included studies, demographic characteristics (sample size, age, and gender), clinical data (age at onset, illness duration, symptom severity),