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Gender differences in brain activity and the relationship between brain activity and differences in prevalence rates between male and female major depressive disorder patients: A resting-state fMRI study

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HIGHLIGHTS

- Gender differences produce widely distributed abnormal resting-state brain activity between male and female patients with major depressive disorder (MDD).
- The abnormal brain activity is associated with different somatic symptoms between male and female MDD patients.
- We provide another means for understanding the underlying pathomechanism of the higher prevalence of MDD in females.

ABSTRACT

Objective: We examined the gender-difference effect on abnormal spontaneous neuronal activity of male and female major depressive disorder (MDD) patients using the amplitude of low-frequency fluctuation (ALFF) and the further clarified the relationship between the abnormal ALFF and differences in MDD prevalence rates between male and female patients.
Methods: Fourteen male MDD patients, 13 female MDD patients and 15 male and 15 female well matched healthy controls (HCs) completed this study. The ALFF approach was used, and Pearson correlation was conducted to observe a possible clinical relevance.
Results: There were widespread differences in ALFF values between female and male MDD patients, including some important parts of the frontoparietal network, auditory network, attention network and cerebellum network. In female MDD patients, there was a positive correlation between average ALFF values of the left postcentral gyrus and the severity of weight loss symptom.
Conclusions: The gender-difference effect leading to abnormal brain activity is an important underlying pathomechanism for different somatic symptoms in MDD patients of different genders and is likely suggestive of higher MDD prevalence rates in females.
Significance: The abnormal ALFF resulting from the gender-difference effect might improve our understanding of the differences in prevalence rates between male and female MDD patients from another perspective.

1. Introduction

Major depressive disorder (MDD) is a common mental disorders and is clinically characterised by persistent and pervasive depressed mood, anxiety and dysphoria, psychomotor changes, guilt, worthlessness and sleep abnormalities (Gmitrowicz and

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Kucharska, 1994). Female MDD patients show higher prevalence rates than male MDD patients, and some studies note such significant resistance up to two to three times (Kessler et al., 2003; Holsen et al., 2011; Black et al., 2012).

Existing studies have tried to explain the phenomenon of differences in the prevalence rates between depressed male and female patients. One consistent view from a psychology study demonstrated that the intrapsychic and psychosocial gender role related to risk factors might contribute to the higher depression risk in women, although these factors could not be easily identified and measured (Kuehner, 2003). From an alternative perspective, the gender differences in depression might arise from different depressive symptoms including fatigue, appetite and sleep disturbance (Silverstein, 1999). Patients with those symptoms were defined by Silverstein as having somatic depression. Compared to male depression, a series of studies found that there was a higher incidence of somatic symptoms in female depression (Middeldorp et al., 2006; Wenzel et al., 2005; Silverstein et al., 2013). There are not many studies showing that the differences in the somatic symptoms were not significant enough to explain gender differences (Delisle et al., 2012). It is interesting that similar somatic symptoms lead to different incidences; this is suggestive of the underlying abnormal mechanisms likely to occur at the neural level for patients with clusters of similar somatic symptoms. The differences in the somatic symptoms, in our study, are depression with or without somatic symptoms and the types of somatic symptoms that exist: disordered eating, poor body image, insomnia, fatigue, headaches, and unexplained breathing difficulty (Silverstein et al., 2013). It would be interesting and meaningful to explore the underlying associations between the abnormal brain activity and the differences in MDD prevalence rates between male and female patients.

Many neuroimaging studies have found that the gender effect affects structural brain imaging and functional brain imaging. In morphometric MRI studies, Karakas et al. reported the averages of some dimensions of the corpus callosum in healthy adult females and males (Karakas et al., 2011). Fan et al. found sexual dimorphism in young Chinese adult cerebellums (Fan et al., 2010). It was reported that gender affects pathological brains, including brains from subjects with subclinical depression (Spalletta et al., 2013) and MDD. Structural abnormalities of the hippocampus were found by comparing depressed men and women with healthy controls (HCs) (Frodl et al., 2002; Kronmuller et al., 2009). Over the last decade, blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) has been considered a powerful approach for measuring human brain activity (Weisskoff and Rosen, 1995). Previous fMRI studies in healthy people showed that the gender effect influence extended to tasks involving cognitive function, working and episodic memory (Haut and Barch, 2006), language processing (Hirnstein et al., 2013; Soleman et al., 2013), and emotional control (Bremner et al., 2001; McRae et al., 2008; Blanton et al., 2010). Less attention has been paid to the gender effects in MDD patients in an fMRI study. In task-related fMRI studies, gender differences in task-related brain function are likely determined by multiple biological and environmental factors, such as differences in cultural environment and education (Speck et al., 2000). With the change of tasks in fMRI studies, the results are different (Bremner et al., 2001; McRae et al., 2008; Blanton et al., 2010). Resting-state fMRI has become an increasingly popular technique of fMRI since the study of Biswal et al. (1995). It has been used extensively to study ongoing spontaneous neuronal activity (Weisskoff and Rosen, 1995; Ogawa, 2012; Lv et al., 2014). Resting-state fMRI, which does not require people to perform any task and avoids any paradigm design, might be a good method to explore the gender-difference effect in MDD patients.

Preliminary evidence from functional imaging studies has suggested that males and females show different patterns of activation during recognition tasks, emotional control and working memory (Haut and Barch, 2006; Blanton et al., 2010; Soleman et al., 2013). Earlier studies using electroencephalography (EEG) found different frequency band activations during attention (Razumnikova and Vol'F, 2006) and cognitive recognition behavioural patterns (Lee et al., 2012). The studies of resting EEG reported that males and females were different in the excitability dynamics of their cortical networks (Jausovec and Jausovec, 2010), and found that gender differences exist in the EEG activity in stimulus and nonstimulus conditions (Wada et al., 1994). To the best of our knowledge, despite a lack of clear evidence of specific resting-state network (RSN) related brain area differences between male and female MDD patients, there could be sex differences in the RSNs, including the frontoparietal networks and attention network.

The amplitude of low-frequency fluctuations (ALFFs) can be measured from resting fMRI data (Zang et al., 2007). Spontaneous low frequency (0.01–0.08 Hz) fluctuations (LFFs) are considered related to spontaneous neural activity within a region and contribute strongly to the correlations between the BOLD signal time courses across regions (Cordes et al., 2001; Yang et al., 2007). This new metric has been well applied to evaluate ALFF in subjects with pathological brains, such as those with attention deficit hyperactivity disorder (ADHD) (Zang et al., 2007), schizophrenia (Hoptman et al., 2010) and MDD (Guo et al., 2012, 2013; Wang et al., 2012a). Some reports have directly investigated the correlation between the brain activity of MDD patients and the depressive symptoms using resting-state fMRI (Yao et al., 2009; Guo et al., 2012, 2013). This method was used to examine the clinical correlates of ALFF measurements (Guo et al., 2012, 2013).

In the present study, which was supported by the reported statements that some specific depressive symptoms are associated with differences in MDD prevalence rates between male and female patients, we hypothesised that the gender-difference effect led to abnormal ALFF in brain regions that were important parts of the frontoparietal networks and the attention network. We hypothesised that the abnormal ALFF in the brain regions might be related to specific depressive symptoms. We first investigated alterations in the regional spontaneous neuronal activity during resting state in MDD patients of different genders using the ALFF approach (Zang et al., 2007). We attempted to explore the underlying associations among the abnormal brain activity in MDD patients of different genders, the somatic symptoms and the differences in the MDD prevalence rates between male and female patients.

2. Methods

2.1. Subjects

Of the patients with first-episode MDD, 30 (15 male and 15 female) were recruited from in-patient facilities at the Department of Psychiatry, Nanjing Brain Hospital of Nanjing Medical University, between May 2011 and November 2012: (1) all of the patients met the following inclusion criteria: (1) all of the patients were diagnosed with the Structured Clinical Interview of DSM-IV-TR (SCID) criteria (First et al., 2002; American Psychiatric Association, 2000); (2) all of the patients were suffering from a major depressive episode, and the patients were required to meet a minimum 2-week medication washout period prior to the MRI scans; (3) the Hamilton Rating Scale for Depression (HRSD) 17-item (Hamilton, 1967) scores were higher than 17 on the day of scanning; (4) all of the patients reported at least three of the following symptoms: frequent severe headaches, frequent trouble in breathing for no reason, frequent trouble falling asleep at night or staying asleep without waking up, frequent unexplained fatigue, disordered eating and poor body image/preference for thinness