Journal of Affective Disorders 201 (2016) 153–161

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Altered neuronal spontaneous activity correlates with glutamate concentration in medial prefrontal cortex of major depressed females: An fMRI-MRS study

Xiaoliu Zhang [a,b,1], Yingying Tang [c,d,1], Mirjana Maletic-Savatic [e], Jianhua Sheng [c], Xuanhong Zhang [c], Yajing Zhu [a,b], Tianhong Zhang [c,d], Junjie Wang [d], Shanbao Tong [a,b], Jijun Wang [c,d,*], Yao Li [a,b,**]

[a] School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China
[b] Med-X Research Institute, Shanghai Jiao Tong University, Shanghai 200030, China
[c] Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Wanping Nan Road, Shanghai 200030, China
[d] Department of EEG and Imaging, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Wanping Nan Road, Shanghai 200030, China
[e] Departments of Pediatrics, Neuroscience, Baylor College of Medicine, Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, Houston TX 77030, USA

ARTICLE INFO

Article history:
Received 31 December 2015
Received in revised form
18 April 2016
Accepted 11 May 2016
Available online 12 May 2016

Keywords:
Major depressive disorder
Female
Functional magnetic resonance imaging
Magnetic resonance spectroscopy
Medial prefrontal cortex

ABSTRACT

Background: Major depressive disorder (MDD) is twice more prevalent in females than in males. Yet, there have only been a few studies on the functional brain activity in female MDD patients and the detailed mechanisms underlying their neurobiology merit further investigations. In the present work, we used combined fMRI-MRS methods to investigate the altered intrinsic neuronal activity and its association with neurotransmitter concentration in female MDD patients.

Methods: The whole brain amplitude of low frequency fluctuation (ALFF) analysis using resting state functional magnetic resonance imaging (fMRI) was performed to explore the alteration of intrinsic neuronal signals in MDD females (n=11) compared with female healthy controls (n=11). With a specific interest in the medial prefrontal cortex (mPFC) area, we quantified the concentration of amino acid neurotransmitters including GABA ((*r*-aminobutyric acid)), Glu (Glutamate), and Glx (Glutamate + Glutamine) using ^{1}H-MRS technology. Moreover, we conducted Pearson correlation analysis between the ALFF value and neurotransmitter concentration to find out the functional-biochemical relation in mPFC area. The relationship between the metabolites concentration and MDD symptomatology was also examined through Spearman correlation analysis.

Results: We found that the female MDD patients showed increased neuronal spontaneous activity in left medial prefrontal cortex (mPFC) and left middle frontal cortex, with decreased ALFF level in right putamen and right middle temporal cortex ($p < 0.01$, Alphasim corrected). The ALFF in mPFC was shown positively correlated with Glu concentration in female MDD patients (r=0.67, p=0.023). The Glu concentration in mPFC was positively correlated with patients HAMA scores (r=0.641, p=0.033).

Limitations: The relatively small sample size, metabolite information acquired only in mPFC and not all patients were unmedicated are the major limitations of our study.

Conclusions: Using combined fMRI-MRS methods, we found increased spontaneous neuronal activity was correlated with Glu concentration in mPFC of female MDD patients. Other regions including left middle frontal gyrus, right putamen and middle temporal gyrus also showed altered spontaneous neuronal activities. The abnormal intrinsic neuronal activities in fronto-cortical regions shed light on the pathogenesis underlying MDD females. The multimodal resting-state neuroimaging technique served as a useful tool for functional-biochemical investigation of MDD pathophysiology.

* Corresponding author at: Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, 600 Wanping Nan Road, Shanghai 200030, China.
** Corresponding author at: School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China.
E-mail addresses: jijunwang27@163.com (J. Wang), yaoli118@gmail.com (Y. Li).
[1] These authors contributed equally to this study.

http://dx.doi.org/10.1016/j.jad.2016.05.014
0165-0327/

1. Introduction

Major depressive disorder (MDD), clinically characterized by persistent and pervasive feelings of sadness, guilt and worthlessness, has been reported as the second cause of disability worldwide (Ferrari et al., 2013; Kessler et al., 2003). Women are twice as likely to develop MDD compared to men (Holsen et al., 2011). In addition, female MDD patients have a higher incidence of somatic symptoms including fatigue, appetite and sleep disturbance compared to men (Middeldorp et al., 2006; Silverstein, 1999; Wenzel et al., 2005). Despite the high incidence of depression in women and the increasing burden of MDD on society, the detailed mechanisms underlying the neurobiology are not well understood, most likely because there are no good animal models of depression. To gain insight into the human brain function, a variety of MRI-based functional neuroimaging methods have been developed over the past decade. Interestingly, several reports have demonstrated that gender affects both structural and functional brain features, such as the excitability dynamics of the cortical network at resting state (Fan et al., 2010; Frodl et al., 2002; Jaušovec and Jaušovec, 2010; Kronmüller et al., 2009; Spalletta et al., 2014). Yet, there have been few studies on the functional brain activity in female MDD patients.

Resting state functional magnetic resonance imaging (rs-fMRI) offers insights into the brain spontaneous neuronal activity (Liu et al., 2014; Northoff et al., 2011). Current findings in MDD using rs-fMRI suggest the abnormal inter-regional neuronal activity within the default mode network (DMN) and its functional connectivity with the salience network and central executive network (Mulders et al., 2015). As a central part of anterior DMN, the medial prefrontal cortex (mPFC) is closely associated with human spontaneous self-generated mental activity (Gusnard et al., 2001). Altered mPFC functional activity has been explored in MDD (Greicius et al., 2007; Lui et al., 2011) and was linked to low self-reflection in female MDD patients, since they were more inclined to form negative thoughts when facing social rejection challenges (Stroud et al., 2002). Different ALFF value in the frontal brain regions was found between the female and male MDD patients (Yao et al., 2014). The difference in prevalence and somatic symptoms between female and male MDD has also been testified (Schuch et al., 2014; Silverstein, 1999). A recent study investigated the female MDD patients with negative bias and showed significantly higher neuronal activation in the frontal lobe (Gollan et al., 2015). This converging evidence has demonstrated mPFC as an important brain region for female MDD (Johnson et al., 2009; Macrae et al., 2004; Northoff et al., 2006).

While most rs-fMRI MDD studies focus on the inter-regional features, the regional functional fluctuations could improve our understanding about the local physiological status of the brain. The low frequency (0.01 – 0.08 Hz) fluctuation (LFF) in resting state blood oxygenation level dependent (BOLD) signal provided a physiologically important biomarker and the amplitude of LFF (ALFF) has been used as an effective indicator of regional spontaneous neuronal oscillations (Yang et al., 2007). The ALFF analysis has been utilized in depression studies and showed cortico-limbic-thalamic-striatal impairments underlying affective and cognitive dysfunctions in the patients (Guo et al., 2012; Tadayonnejad et al., 2015). Moreover, it was recently suggested that the pathophysiology of MDD includes multiple biological systems that influence each other and that functional alterations are accompanied by neurochemical changes (Jentsch et al., 2015). One combinational study on female MDD patients showed an association between brain activity deficits and hormonal disruption contributing to the sex-related difference (Holsen et al., 2013). As a unique non-invasive and nonradioactive approach, proton magnetic resonance spectroscopy (^{1}H-MRS) has been increasingly used to examine the altered neurochemical metabolite concentration in MDD patients (Hasler et al., 2007; Sanacora et al., 1999). Both preclinical and clinical evidence has showed altered neuronal metabolites in fronto-subcortical structures, already demonstrated to be part of the pathophysiology of MDD (Brambilla et al., 2005; Rosenberg et al., 2005; Soares et al., 1996). In particular, the regional dysfunctional glutamatergic sytem has been identified as an important contributor to the etiology of MDD (Popoli et al., 2011; Sanacora et al., 2004). Evidence for glutamatergic system alteration in MDD has been long reported but findings varied. Increased Glutamete (Glu) levels were observed in plasma samples and postmortem tissue from MDD patients (Altamura et al., 1993; Hashimoto et al., 2007; Kim et al., 1982). While a recent meta-analysis of MRS imaging studies found that MDD was associated with a substantial decrease in Glu levels within the mPFC (Järnum et al., 2011; Luykx et al., 2012; Merkl et al., 2011; Portella et al., 2011). In the contrary, higher Glu level within mPFC was found in postpartum depression women compared with healthy controls (McEwen et al., 2012). No significant Glu difference was found in the dorsolateral prefrontal cortex between the MDD and healthy control groups (Frey et al., 2007; Merkl et al., 2011). The discrepancy may be due various patients subtypes and different brain areas involved in glutamatergic signaling changes (Yksel and Öngür, 2010).

In the present work, we investigate the intrinsic neuronal activity through whole brain ALFF analysis in female MDD patients. Further, focusing on the mPFC area, we explore the concentration of amino acid neurotransmitters including GABA (gamma-aminobutyric acid), Glu, and Glx (Glutamate + Glutamine) using ^{1}H-MRS methodology. We then integrate the functional oscillation and biochemical data within mPFC to test whether they are implicated in female MDD patients.

2. Materials and methods

2.1. Participants

Eleven female MDD patients and eleven healthy female controls matched in age, handedness and education years, were included in this study. The patients were recruited from the Shanghai Mental Health Center and healthy controls were recruited through local advertising. All patients fullfilled ICD-10 (the tenth revision of International Classification of Diseases) diagnostic criteria of major depressive disorder (current episode of depression and no history of manic episode)(Müssigbrodt et al., 2000). Diagnosis verification was made by a senior psychiatrist at the rank of professor. In the MDD group, six females were taking anti-depressant medication (2 duloxetine, 2 citalopram, 1 paroxetine, 1 mianserin) and five were unmedicated. The demographic and clinical information for the 22 participants are illustrated in Table 1. In our cohort, no significant difference existed in demographic variables between the two groups. The whole study was approved by Shanghai Mental Health Center Ethics Committee and each subject signed the written informed consent before participation. The 24-item Hamilton Rating Scale for Depression (HAMD) and 14 item-Anxiety (HAMA) were used to rate the participant depression and anxiety level (Williams, 2001). We also report the self-rating anxiety scale (SAS) and depression scale (SDS) for participants (Knight et al., 1983).

2.2. fMRI data acquisition and processing

All MRI, MRS and rs-fMRI data were acquired on a 3.0-T Siemens Verio MR Scanner (Siemens AG, Erlangen, Germany) with a 32-channel head coil at the Shanghai Mental Health Center. During