Journal of Affective Disorders 168 (2014) 21–29

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Altered brain network modules induce helplessness in major depressive disorder

Daihui Peng [a,b,1], Feng Shi [b,1], Ting Shen [a], Ziwen Peng [b], Chen Zhang [a], Xiaohua Liu [a], Meihui Qiu [a], Jun Liu [c], Kaida Jiang [d], Yiru Fang [a,*], Dinggang Shen [b,e,**]

[a] Division of Mood Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, 600 Wanping South Road, Shanghai 200030, PR China
[b] Department of Radiology and BRIC, University of North Carolina, 130 Mason Farm Road, Chapel Hill, NC 27599-7513, USA
[c] Department of Medical Imaging, the Fifth People's Hospital of Shanghai, Shanghai, PR China
[d] Huashan Hospital, Fudan University, Shanghai, PR China
[e] Department of Brain and Cognitive Engineering, Korea University, Seoul, Korea

ARTICLE INFO

Article history:
Received 17 March 2014
Received in revised form
28 May 2014
Accepted 29 May 2014
Available online 1 July 2014

Keywords:
Major depressive disorder
Helplessness
Functional connectivity
Small-worldness
Modularity

ABSTRACT

Objective: The abnormal brain functional connectivity (FC) has been assumed to be a pathophysiological aspect of major depressive disorder (MDD). However, it is poorly understood, regarding the underlying patterns of global FC network and their relationships with the clinical characteristics of MDD.
Methods: Resting-state functional magnetic resonance imaging data were acquired from 16 first episode, medication-naïve MDD patients and 16 healthy control subjects. The global FC network was constructed using 90 brain regions. The global topological patterns, *e.g.*, small-worldness and modularity, and their relationships with depressive characteristics were investigated. Furthermore, the participant coefficient and module degree of MDD patients were measured to reflect the regional roles in module network, and the impairment of FC was examined by network based statistic.
Results: Small-world property was not altered in MDD. However, MDD patients exhibited 5 atypically reorganized modules compared to the controls. A positive relationship was also found among MDD patients between the intra-module I and helplessness factor evaluated via the Hamilton Depression Scale. Specifically, eight regions exhibited the abnormal participant coefficient or module degree, *e.g.*, left superior orbital frontal cortex and right amygdala. The decreased FC was identified among the sub-network of 24 brain regions, *e.g.*, frontal cortex, supplementary motor area, amygdala, thalamus, and hippocampus.
Limitation: The limited size of MDD samples precluded meaningful study of distinct clinical characteristics in relation to aberrant FC.
Conclusions: The results revealed altered patterns of brain module network at the global level in MDD patients, which might contribute to the feelings of helplessness.

1. Introduction

Major depressive disorder (MDD) is a complex disease that can be characterized by a variety of symptoms: negative moods, cognitive deficits, and somatic symptoms (APA, 2013). The array of symptoms can make diagnoses a difficult problem, a fact exacerbated by how little is presently known about the actual neurobiological mechanisms underlying the symptoms of MDD. Functional neuroimaging studies found abnormal neurological activities in some specific brain areas of MDD patients, including prefrontal cortex (Frodl et al., 2009; Lui et al., 2009), parahippocampal (Peng et al., 2011), and thalamus (Frodl et al., 2009). Recent reports have further observed atypical functional connectivity (FC) networks among MDD patients. For instance, Veer et al. (2010) noted that a decrease of resting-state FC may be involved in the dysfunctional affects and cognition networks among MDD patients. Likewise, in other sampled MDD patients, atypical FC was found within the default mode network (DMN) involving medial prefrontal cortex, precuneus/posterior cingulate

* Corresponding author.
** Corresponding author at: Department of Radiology and BRIC, University of North Carolina, 130 Mason Farm Road, Chapel Hill, NC 27599-7513, USA. Tel.: +1 9199664397.
E-mail addresses: yirufang@gmail.com (Y. Fang), dgshen@med.unc.edu (D. Shen).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.jad.2014.05.061
0165-0327/

cortex (Guo et al., 2013; Sheline et al., 2010), subgenual cingulate cortex, thalamus (Greicius et al., 2007), and bilateral caudate (Bluhm et al., 2009).

However, most previous studies do not actually examine functional interconnections of the brain at global level in patients with MDD. Graph theoretical analysis is a novel method used to explore the integration and segregation of global brain information for both small-world model analysis and modular analysis (Bullmore and Sporns, 2009; Wang et al., 2010). Using small-world properties, Zhang et al. (2011) reported that the MDD patients at first episode showed lower path length and higher global efficiency in the whole brain networks. However, replicating these findings in recent studies using unipolar depression including both first episode and recurrent samples failed (Lord et al., 2012), as did those among samples with late-life depression (Bohr et al., 2012). Using the module organization, Tao et al. (2013) reported significant rearrangement in the first episode and recurrent MDD, but the measures of modularity showed no significant alteration among MDD patients in other studies (Bohr et al., 2012; Lord et al., 2012). Conversely, abnormal topological properties of module networks have been found in depressed patients in most previous studies. For instance, Lord et al. (2012) reported that the increased participant index of nodes was significantly distributed in the frontal and parietal temporal regions, while the decreased participant index was located in the occipital, temporal and inferior-frontal regions in first episode and recurrent episode unipolar depression subjects. The increased nodal centralities were found in the caudate nucleus and DMN regions, while the reduced nodal centralities were found in the occipital, frontal (orbital part) and temporal regions of first episode MDD patients (Zhang et al., 2011). In another study of late-life depression, hub analysis of nodes indicated that posterior medial parietal regions were more highly connected with the distant neighbors, thereby increasing the average Euclidean distance of connectivity paths as compared to the healthy controls (Bohr et al., 2012). Due to somewhat conflicting reports in both small-world and modular properties (Bohr et al., 2012; Lord et al., 2012; Tao et al., 2013; Zhang et al., 2011), further investigation into the topological alterations of the global brain regions in the relatively specific depression samples may offer some novel insights.

In the meantime, the relationship between clinical symptoms and patterns of FC networks is still remaining unclear, especially for the core symptoms of helplessness, hopelessness, and worthlessness that often accompany MDD's negative moods (Beck et al., 1979). The bias cognition model emphasizes that the negative evaluations of environment, future and selfness may specifically contribute to the symptoms of helplessness, hopelessness, and worthlessness in MDD patients (Beck et al., 1979). These clinical symptoms can be quantitatively measured using 24-item Hamilton Depression Scale (HAMD) (Hamilton, 1967; Zhang, 1998), the scoring values of which may be acquired across five points (from 0 through 4) by a semi-structured clinician-rated interview (Zhang et al., 2011; Zhang, 1998). Some studies have paid more attention to both feelings of hopelessness (Becker-Weidman et al., 2009; Young et al., 1996) and worthlessness among MDD patients (Rimes and Watkins, 2005; Spijker et al., 2010), but studies on helplessness were conducted only in animal models, and these findings indicated abnormal activities in the prefrontal cortex (Hoyle et al., 2011; Petty et al., 1994), hippocampus (Kohen et al., 2005; Lachman et al., 1992), and some subcortical areas (Shumake et al., 2003, 2010). Interestingly though, the aforementioned neuroimaging studies indicated that most of the brain areas related to the helplessness were within the abnormal FC networks. Actually, it is valuable to further explore the alterations of brain FC network underlying core symptoms such as helplessness in MDD patients. This will help extend our understanding of the symptoms in MDD from clinical cognitive psychology to neurobiology at a global brain network level.

Both small-worldness and modularity are the novel quantitative measures of topological properties in the global brain level, which offer some helpful indices for investigating the underlying neurological bases of MDD symptoms. The current study tests two hypotheses on these metrics: (1) the global brain network or functional modularity would be disrupted in MDD patients, and (2) the topological pattern alterations may be related with some core clinical factors of MDD, such as helplessness. To test these hypotheses, first, we conducted small-world analysis by constructing the global functional network of MDD and further explored its relationship with clinical factors. Next, we applied modular analysis to measure the local properties of the global functional network in MDD patients and investigated the relationship between local properties and clinical factors. Similarly, we also examined the patterns of impaired brain networks in MDD patients by using the network-based statistic (NBS) method.

2. Methods

2.1. Subjects

In total, 16 medication-naïve patients with MDD were recruited from outpatient clinics at the Huashan Hospital and Shanghai Mental Health Centre, China. Healthy subjects matched with MDD patients for age, sex, and education level were recruited via advertisement. Both 16 MDD patients and 16 healthy controls were then interviewed independently by two psychiatrists. All participants were verified as being right-handed with the right eye being dominant. Eligibility screening procedures included the Structured Clinical Interview for DSM-IV (SCID), 24-item HAMD (Hamilton, 1967; Zhang, 1998), and 14-item Hamilton anxiety scale (HAMA). Written informed consent was obtained from all subjects prior to their inclusion in the study. All protocols of this study were approved by the Investigational Review Board (IRB00002733-Shanghai Mental Health Center, China).

Inclusion criteria for depressed subjects were as follows: aged 25–50 years, satisfying DSM-IV diagnosis criteria of MDD, first episode, medication-naïve, 24-HAMD score $>$ 20 (Hamilton, 1967), 14-HAMA score $<$ 7, and outpatient treatment. Depressed patients were excluded according to the following criteria: meeting criteria of any current or past Axis I disorder of DSM-IV (*e.g.*, schizophrenia, schizoaffective disorder, bipolar disorder, or anxiety disorder as primary diagnosis), any prescription or psychotropic medications in the past 4 weeks, clinically verified feelings of being acutely suicidal, homicidal or requiring inpatient treatment, meeting criteria for substance dependence within the past year (except for caffeine or nicotine), positive urinary toxicology screening at baseline, use of alcohol in the past week, serious medical or neurological illness, current pregnancy or breastfeeding, and metallic implants or other contraindications to magnetic resonance imaging (MRI).

Healthy subjects were included if they met the following criteria: aged 25–50 years, no history of psychiatric illness or substance abuse/dependence, no family history of major psychiatric or neurological illness in the first degree relatives, not currently taking any prescription or psychotropic medications, no use of alcohol in the past week, and no serious medical or neurological illness on record. Exclusion criteria for healthy subjects included those who were pregnant or breastfeeding, or those who had metallic implants or other contraindications that would inhibit MRI.