Journal of Affective Disorders 218 (2017) 346–352

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Whole-brain resting-state functional connectivity identified major depressive disorder: A multivariate pattern analysis in two independent samples

Xue Zhong[a], Huqing Shi[b], Qingsen Ming[a], Daifeng Dong[a], Xiaocui Zhang[a], Ling-Li Zeng[c], Shuqiao Yao[a,*]

[a] Medical Psychological Institute, Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, People's Republic of China
[b] Department of psychology, Shanghai Normal University, Shanghai 200234, People's Republic of China
[c] College of Mechatronics and Automation, National University of Defense Technology, Changsha, Hunan 410073, People's Republic of China

ARTICLE INFO

Keywords:
Major depressive disorder
Multivariate pattern analysis
Resting-state fMRI
Whole-brain functional connectivity
Classification

ABSTRACT

Background: there has been a recent increase in the use of connectome-based multivariate pattern analysis (MVPA) of resting-state functional magnetic resonance imaging (fMRI) data aimed at distinguishing patients with major depressive disorder (MDD) from healthy controls (HCs). However, the validity of this method needs to be confirmed in independent samples.

Method: we used resting-state fMRI to explore whole-brain functional connectivity (FC) patterns characteristic of MDD and to confirm the effectiveness of MVPA in distinguishing MDD versus HC groups in two independent samples. The first sample set included 29 MDD patients and 33 HCs and second sample set included 46 MDD patients and 57 HCs.

Results: for the first sample, we obtained a correct classification rate of 91.9% with a sensitivity of 89.6% and specificity of 93.9%. For the second sample, we observed a correct classification rate of 86.4% with a sensitivity of 84.8% and specificity of 87.7%. With both samples, we found that the majority of consensus FCs used for MDD identification were located in the salience network, default mode network, the cerebellum, visual cortical areas, and the affective network.

Limitation: we did not analyze potential structural differences between the groups.

Conclusion: results suggest that whole-brain FC patterns can be used to differentiate depressed patients from HCs and provide evidence for the potential use of connectome-based MVPA as a complementary tool in the clinical diagnosis of MDD.

1. Introduction

Major depressive disorder (MDD) is characterized by persistent and overwhelming feelings of guilt, sadness, anhedonia, worthlessness, and hopelessness (Guo et al., 2014b). It is a psychiatric illness with devastating social, personal, and medical consequences (Kessler, 2012). At present, diagnosis of MDD is based mainly on subjective evaluations of clinical signs and symptoms, whereas treatment guidelines are derived from clinical empirical evidence and expert consensus (Fu et al., 2008). The subjectivity of current MDD screening tools has seeded questions of their diagnostic reliability (Yu et al., 2016). Undoubtedly, it is important to explore valid and objective biomarkers of MDD to alleviate these concerns.

In recent years, resting-state functional magnetic resonance imaging (fMRI) has come to be widely used to demonstrate functional alterations associated with MDD (Liu et al., 2012a; Anand et al., 2009; Guo et al., 2014a; Liu et al., 2013; Song et al., 2016; Veer et al., 2010; Wang et al., 2014; Zhang et al., 2016). Numerous findings concentrated in three major networks: the default mode network (DMN), the central executive network (CEN) and the salience network (SN) (Hamilton et al., 2013; Mulders et al., 2015). The DMN regarded as areas showed deactivation during goal-directed tasks while activation during rest

Abbreviations: MDD, major depressive disorder; fMRI, functional magnetic resonance imaging; FC, functional connectivity; DMN, default mode network; SN, salience network; CEN, central executive network; HCs, healthy controls; MVPA, multivariate pattern analysis; CES-D, epidemiologic studies depression scale; HDRS, Hamilton depression rating scale; MNI, Montreal Neurological Institute

* Corresponding author.
E-mail address: shuqiaoyao@163.com (S. Yao).

http://dx.doi.org/10.1016/j.jad.2017.04.040
Received 14 January 2017; Received in revised form 19 April 2017; Accepted 20 April 2017
Available online 21 April 2017

(Raichle et al., 2001). This network consisted of precuneus/posterior cingulate cortex, medial prefrontal cortex and medial, lateral and inferior parietal cortex, which is related to self-referential processing, emotional regulation and consciousness processing (Broyd et al., 2009; Cavanna and Trimble, 2006; Zhu et al., 2012). Contrary to DMN, the CEN usually actives when the brain is engaging in a task requiring attention (Goulden et al., 2014). This network included the lateral prefrontal cortex, the posterior parietal cortex and part of the dorsomedial prefrontal cortex (Hamilton et al., 2011; Seeley et al., 2007). The SN usually involved in processing emotion or monitoring for salient events (Goulden et al., 2014). This network consists of fronto-insular cortex, amygdala and temporal poles, which plays a crucial role in biasing the processing of negative information in MDD (Hamilton et al., 2016). Researchers suggested depression has been linked to imbalanced communication among large-scale brain networks, as reflected by abnormal resting-state functional connectivity (FC) (Drevets et al., 2008; Kaiser et al., 2015; Mayberg, 1997). Resting-state FC measured with fMRI analysis, defined as correlated patterns of fluctuations between brain areas, has the potential for broad translation into clinical care (Fox and Greicius, 2010). Altered functional connectivity between networks may relate to deficits in regulating mood. In particular, it may be used in the diagnosis of individual patients with MDD and other mental illnesses (Craddock et al., 2009).

Currently, interest in exploring the brain alterations between patients with psychiatric disorders and healthy controls (HCs) using machine learning methods based on neuroimaging data has increased (Liu et al., 2015b; Oquendo et al., 2012). Multivariate pattern analysis (MVPA) is a type of supervised machine learning that, as a data-driven technique, is designed to create algorithms that can characterize complex data automatically (Orru et al., 2012). MVPA could demonstrate neurobiological patterns that differ reliably between patients and HCs; furthermore, this method tends to have greater power than traditional methods for making such differentiations (Hoeft et al., 2011). It has the potential to detect neuroimaging-based biomarkers of disease in individuals and to reveal spatially distributed information that may further elucidate the neural mechanisms of MDD (Liu et al., 2012b; Zeng et al., 2012).

Several fMRI studies have demonstrated the clinical value of employing MVPA methods to distinguish depressives from HCs based on functional neural bias (Craddock et al., 2009; Fu et al., 2008; Ma et al., 2013). For instance, Fu et al. examined whole-brain FC as a feature during the performance of an emotional task and found that the most discriminative features were some limbic-cortical connection differences (Fu et al., 2008). Zeng et al. (2012) indicated that MVPA of whole-brain resting-state FC data could distinguish MDD patients from HCs with 94.3% classification accuracy. Meanwhile, Ma et al. (2013) found that MDD patients could be distinguished reliably from HCs with 90.6% accuracy using altered cerebellar-cerebral FC as a classification feature. These studies have achieved inspiring classification results and indicate that MVPA not only could find potential neuroimaging-based biomarkers to differentiate patients from healthy controls, but also potentially detect spatially distributed information to further highlight the neural mechanisms underlying the pathophysiology of MDD. Therefore, it was necessary and crucial to explore further exploration of whole-brain FC patterns aimed at extracting the most discriminative features of MDD should be pursued.

To date, limitations of previous MVPA studies of MDD are a small sample size and the lack of a large independent sample with which to confirm their classification performance (Ma et al., 2013; Zeng et al., 2012, 2014). Hence, in this study, we planned to recruit two independent sample sets to confirm the application of MVPA , which could providing more accurate and reliable classification features for discriminating MDD patients from healthy controls. The aim of the current study was to investigate the effectiveness of applying MVPA methods to discriminate patients with MDD from HCs employing whole-brain FC as a classification feature. We hypothesized that FC could be used as a potential biomarker with which to distinguish MDD patients from HCs reliably. Specifically, based on the findings of previous studies (Ma et al., 2013; Zhu et al., 2012), we hypothesized that abnormal FC in individuals with MDD may be detected in the DMN, cerebellum regions, visual cortical regions, and the affective network.

2. Materials and methods

2.1. Participants

All patients with MDD (sample set 1, N = 29; sample set 2 = 46) were diagnosed with MDD at the outpatient clinic of the Second Xiangya Hospital of Central South University with a structured clinical interview based on the DSM-IV criteria(First, 1997). The exclusion criteria were any history of neurological disease, other medical illnesses, or other psychiatric disorders, such as schizophrenia, bipolar disorder, or substance-induced mood disorder. All patients were required to be abstinent from caffeine, nicotine, and alcohol at least one week prior to their scanning session. All of the patients with MDD in this study were first-episode, drug-naïve patients. As previous studies have already demonstrated significant brain function changes after antidepressant medication treatments (Schaefer et al., 2006) as well as after multiple depression episodes (Turner et al., 2007). We focused on first episode MDD subjects to avoid potential confounding effects from previous medication, depression history, and comorbidities. They were experiencing their first depressive episode when recruited and none had ever taken any antipsychotic or other psychoactive medications at the time of the MRI scan.

The HC participants (sample 1, N = 33; sample set 2, N = 57) were recruited by advertisement from the local community. All of them had no history of any psychiatric disorder, neurological disorder, or head injury. They were well matched with the patients in terms of age, gender, and education level (Table 1). Immediately before scanning, the depressive symptoms of the participants were rated on the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1997) in the first sample set and on the 17-items Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) in the second sample set. All participants were right-handed and native Mandarin speakers. This study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, China, and all of the participants provided written informed consent.

2.2. MRI data acquisition

Resting state fMRI images were captured by a 1.5 T (sample set 1) or 3.0 T (sample set 2) Siemens Magnetom Symphony scanner at the Magnetic Resonance Center of the Second Xiangya Hospital of Central South University in Changsha, China. All subjects placed their heads in

Table 1
Sample set characteristics.

Sample set	Variable	MDD patients	HCs	*P*
1	Sample size	29	33	
	Gender (male/female)	11/18	16/17	0.70[a]
	Age (years)	20.45 ± 1.80	20.75 ± 1.50	0.46[b]
	Education (years)	13.72 ± 1.03	13.88 ± 0.86	0.52[b]
	CES-D score	56.10 ± 5.73	37.26 ± 7.67	0.002[b]
2	Sample size	46	57	
	Gender (male/female)	22/24	26/31	0.94[a]
	Age (years)	22.63 ± 5.22	21.49 ± 2.52	0.15[b]
	Education (years)	13.85 ± 2.78	14.75 ± 1.81	0. 06[b]
	HDRS	22.92 ± 14.44	1.39 ± 1.69	0.000[b]

MDD, major depressive disorder; HC, healthy control; CES-D, Center for Epidemiologic Studies Depression Scale; HDRS, Hamilton Depression Rating Scale.

[a] Pearson Chi-square test.

[b] Two-sample *t*-test.