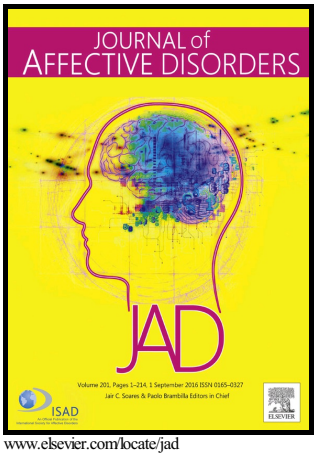

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Whole-brain resting-state functional connectivity identified major depressive disorder: a multivariate pattern analysis in two independent samples

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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.

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.

Key words: major depressive disorder, multivariate pattern analysis, resting-state fMRI, whole-brain functional connectivity, classification.

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 (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 (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., 2012; 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. indicated that MVPA of whole-brain resting-state FC data could distinguish MDD patients from HCs with 94.3% classification accuracy (Zeng et al., 2012). Meanwhile, Ma et al. found that MDD patients could be distinguished reliably from HCs with 90.6% accuracy using altered cerebellar-cerebral FC as a classification feature (Ma et al., 2013). 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; Zeng et al., 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 HS, 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 a standard head coil (16-channel SENSE head coil). Participants were positioned comfortably on the scanner bed and fitted with soft ear plugs; foam pads were used to minimize head movement. For the first sample set, a total of 240 volumes of echo planar images were obtained axially (repetition time/echo time = 2000/40 ms, thickness/gap = 5/0 mm, field of view = 240 × 240 mm, flip angle = 90°, matrix = 64 × 64, and slices = 26). For the second sample set, a total of 216 volumes of echo planar images were obtained axially (repetition time/echo time = 2000/30 ms, thickness/gap = 4/1 mm, field of view = 256 × 256 mm, flip angle = 80 degree, matrix = 64 × 64, and slices = 32).

2.3 Data preprocessing

We preprocessed the fMRI images using the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm). For each subject, the first 10 volumes of scanned data were discarded for magnetic saturation. The remaining volumes were corrected by registering and re-slicing for head motion; translation was < 1.5 mm for all subjects. Image preprocesses included realignment for head motion and spatial normalization to standard Montreal Neurological Institute (MNI) space. Previous studies indicated that data smoothing filters out the high spatial-frequency component of the effect patterns and, thus, reduces the overall effect energy. (Nikolaus Kriegeskorte, 2006; Zeng et al., 2014). To avoid the possible degradation of

classification ability, we did not perform spatial smoothing. Linear detrending and temporal bandpass (0.01–0.08 Hz) filtering were performed to remove low-frequency drifts and physiological high-frequency noise. The registered fMRI volumes in MNI space were divided into 116 regions according to an automated anatomical labeling atlas(Tzourio-Mazoyer et al., 2002) that divides the cerebrum into 90 regions (45 in each hemisphere) and divides the cerebellum into 26 regions (9 in each cerebellar hemisphere and 8 in the vermis).

We evaluated FC between pairs of regions by calculating Pearson correlation coefficients. For each subject, we obtained a resting-state functional network captured by a 116 × 116 symmetric matrix. Removing 116 diagonal elements, we extracted the upper triangle elements of the FC matrix as classification features.

2.4 MVPA

2.4.1 Feature selection

Not every whole-brain FCs will take important roles in classification. So we need to select the high discriminative features to classify. As described by Zeng et al., we selected features with high FC discrimination based on Kendall tau rank correlation coefficients, this method provides a distribution-free assessment of independence between two variables to measure the relevance of each feature to classification (Zeng et al., 2012). Briefly, for *m* samples in the patient group and *n* samples in the HC group, $X_{i,j}$ denotes the FC feature *i* of the *j*th sample, and Y_j denotes the class label of this sample (-1 for MDD patients and +1 for HCs). The Kendall tau correlation coefficient of the FC feature *i* is defined as:

$$\tau_i = \frac{n_c - n_d}{m \times n}$$

Where n_c and n_d are the number of concordant and discordant pairs respectively. A positive or negative correlation coefficient τ_i indicates that the *i*th FC coefficient decreases or increases, respectively, in the patient group relative to control group. Discriminative power was defined as the absolute value of the Kendall tau correlation coefficient. Then, we subsequently ranked features according to their discriminative powers and selected the most discriminate power's FCs as the final feature set for classification.

2.4.2 Classification and performance evaluation

Support vector machines with linear kernel function were applied to the classification problem. The results were generated with the optimal parameter settings. With the first sample we trained a classifier based on the Kendall tau rank and then ranked the features. This model was used to test on a second independent sample. A leave-one-out cross-validation method was applied to evaluate the classification performance. Classification performance was quantified in terms of accuracy, sensitivity and specificity based on our cross-validation results. Sensitivity represented the proportion of patients correctly predicted, whereas specificity represented the proportion of controls correctly predicted. The FC feature appearing in the final feature set was defined as the consensus FC (Dosenbach et al., 2010; Liu et al., 2015a). Region weight was denoted by its occurrence number in the consensus FCs in this study, which represent the region's relative contribution to the identification of MDD patients. The features that have the great weights are regarded

as the most discriminative in the classification.

3. Results

In first sample set, the linear support vector machine classifier achieved an accuracy of 91.9% (MDD patients, 89.6%; HCs, 93.9%). Approximately half (50.4 ± 1.2%) of the selected FCs were diminished in MDD patients relative to HCs and 272 consensus FCs were identified in the cross-validation. The brain regions related to consensus FC were found to be located primarily in the DMN (especially the precuneus/post cingulate cortex, inferior parietal gyrus, angular, and thalamus), the cerebellum, visual cortical areas (i.e., lingual gyrus, fusiform, cuneus and occipital lobe), and the affective network (i.e., amygdala, pallidum, and superior temporal gyrus). Several brain regions exhibited notably great weights, such as the bilateral orbital middle frontal gyrus, cerebellum, right cuneus, bilateral lingual gyrus, left fusiform, and right superior occipital gyrus (Fig. 1).

In the second sample set, the linear support vector machine classifier achieved an accuracy of 86.4% (MDD patients, 84.8%; HCs, 87.7%). Among, 51.8 ± 0.01% of the selected FCs were diminished in MDD patients relative to HCs and 108 consensus FCs were identified in the cross-validation. Consistent with the first sample set results, brain regions that emerged as being related to the consensus FC included the SN (i.e., superior temporal gyrus, pallidum, and amygdala), the DMN (especially the angular gyrus, medial prefrontal cortex, precuneus/posterior cingulate gyrus, thalamus, hippocampus, and inferior parietal cortex), the cerebellum, visual cortical areas (i.e., lingual gyrus, superior occipital gyrus, cuneus, and fusiform and the CEN

(dorsolateral prefrontal cortex and frontal eye fields). The most heavily weighted regions were the bilateral angular gyrus, bilateral lingual gyrus, dorsolateral superior frontal gyrus, and left middle frontal (Fig. 2).

The figure showed that in the two samples, the similar consensus connections are between prefrontal cortex and cerebellum, prefrontal cortex and visual area, parietal lobe and temporal gyrus, anterior cingulate cortex and parietal lobe, angular and cerebellum. There also different consensus connections in the two samples. In the first sample, there are consensus connection between prefrontal cortex and amygdala, but in the second sample, there is no amygdala reported.

4. Discussion

To the best of our knowledge, this is the first study used independent sample sets to confirm the ability of MVPA to discriminate first-episode, drug-naïve MDD patients from HCs. The MVPA showed the inspiring and consistent results across the different type of machines (1.5T and 3.0T scanners) and different samples. The classifiers that we trained captured connectivity differences between the MDD patient and HC groups successfully. For both samples, we found that the majority of altered FCs with high discriminative power were located within the SN, DMN, the cerebellum, visual cortical areas and CEN. These findings imply that the classifier detected reliable population differences between depressed patients and HCs and suggest that altered FC represents a potential neurological marker with which to identify MDD patients.

Firstly, our imaging data reflected abnormal FCs in the SN. These regions

include the temporal poles, pallidum, amygdala, and superior temporal gyrus. Among them, the pallidum and amygdala are thought to be involved in the regulation of mood, cognition, and behavior. In the limbic-cortical dysregulation model of depression, abnormal functional activities in these areas contribute to the pathophysiology of MDD(Drevets et al., 2008; Mayberg, 1997, 2003; Price and Drevets, 2010; Seminowicz et al., 2004). The superior temporal gyrus mediates essential functions in auditory processing, language development (Anand et al., 2005; Bigler et al., 2007), and mood-related cognitive processing, which is important in social cognition and emotional processing (Goulden et al., 2012; Schaefer et al., 2006). Hence, abnormal functional activity of the superior temporal gyrus may underlie, at least in part, the impaired processing of negative mood and cognition in patients with MDD (Wang et al., 2012).

Secondly, given our findings of altered FCs involving the DMN (i.e., medial prefrontal cortex, precuneus/posterior cingulate, angular, thalamus, and hippocampus) (Broyd et al., 2009; Raichle et al., 2001), it is of interest to note that anterior regions of the DMN, such as the medial prefrontal cortex, have been shown to play a role in self-referential activities (Gusnard et al., 2001), whereas posterior regions of the DMN, particularly the posterior cingulate/precuneus, have been associated with episode memory retrieval(Chen et al., 2012; Raichle, 2015). Altered FC among these regions has also been associated with rumination and autobiographical memory deficits (Hamilton et al., 2015; Sheline et al., 2010; Sumner et al., 2010; Zhu et al., 2012), which are the prominent clinical features of MDD. The precuneus has been

suggested to be a critical structure for the integration of mental processing through its role in cognitive control processes such as visual imagery, episodic memory, and self-directed operations (Cavanna and Trimble, 2006). In addition, the hippocampal gyrus is a key structure in the limbic-cortical dysregulation model of MDD and the altered FCs of the hippocampus may be related to deficits in emotion-mediated memory formation (Mayberg, 2003). Taken together, these findings suggest that altered DMN connectivity may represent a promising biomarker of MDD.

Interestingly, cerebellar connections were common across the classifiers. The cerebellum is typically recognized for its role in the coordination of motor behavior, though an increasing number of empirical studies have demonstrated its involvement in cognitive and emotional regulation, which play an important role in the pathology of MDD (Ma et al., 2013; Turner et al., 2007; Wang et al., 2012). In our study, we observed highly discriminating cerebellum FCs with the angular cortex, orbital middle frontal gyrus, fusiform gyrus, and inferior temporal gyrus, and suspect that these changes may contribute to the emotional and cognitive impairments characteristic of MDD. Cerebellar damage has been shown to affect emotion regulation (Parvizi et al., 2001; Schmahmann and Sherman, 1998) and several prior studies have implicated the cerebellum in MDD (Buckner et al., 2011; Konarski et al., 2005; Liu et al., 2010). To some extent, cerebellar involvement in MDD fits with previous findings indicating that the cerebellum has anatomical connections with limbic regions involved in mood regulation (Turner et al., 2007). Hence, the cerebellum should be explored as a possible node in the distributed disease-related

brain network of MDD. Altered cerebellum FCs may provide new insights into the pathology of MDD.

Our results showed visual cortical areas, including the lingual gyrus, fusiform gyrus, and occipital lobe, have high accuracy in discriminating patients with MDD from HCs. The lingual gyrus and fusiform gyrus—a portion of which is purported to be the processing center for (viewing of) face stimuli— are thought to be involved in the perception and processing of emotions during face stimulus presentation (Haxby et al., 2000; Wang et al., 2005; Zhang et al., 2016), and abnormal activity in these regions has been associated with symptoms of depression (Guo et al., 2013; Wang et al., 2012). The occipital lobe, well known for multiple levels of visual stimulus processing, has also been implicated in the processing of emotional facial expressions (Guo et al., 2015; Tao et al., 2013). Structurally, occipital bending (i.e., one hemisphere crossing the interhemispheric fissure with sulcus warping) is more common among patients with MDD than in HCs (Maller et al., 2014). Indeed, abnormal reactivity to viewing images of emotional faces has been adopted as an early biomarker of depression (Hahn et al., 2011). These prior findings affirm that visual system dysfunction might be a characteristic of depression (Zhong et al., 2016).

In addition, several regions also demonstrated abnormal FCs in CEN. These regions include dorsolateral prefrontal cortex and frontal eye fields. CEN is related to cognitive function including attention and working memory (Mulders et al., 2015). The interaction in CEN may change in major depressive disorder (Hamilton et al., 2011). But the region weights of these regions are relative small in our study. The

reason may be the central executive network is most active during cognitive tasks, while our study was based on resting-state fMRI.

Several recent brain imaging studies were conducted with the aim of distinguishing depressed patients from HCs (Fu et al., 2008; Ma et al., 2013; Zeng et al., 2012). However, to the best of our knowledge, no previous study has incorporated independent samples to test and confirm the findings. The present results with the two independent samples show that our classifier detected population differences reliably between patients with MDD and HCs (Golland and Fischl, 2003; Zeng et al., 2012).This study has several limitations. First, although the classification results are promising, we did not analyze potential structural differences between the groups. Data demonstrating structural abnormalities and cortical thickness differences are needed to develop a more reliable clinical diagnosis of depression. Second, we did not assess the relationship between consensus FC alterations and clinical variables, which should be explored in future studies. Thirdly, first episode, medication-naïve patients in current study were relatively unique and less representative of community depressed samples. This restriction in type of patients limits the ability to generalize to major depression in across the spectrum. Therefore, these findings needed to be replicated in the more general community depressed samples. Another limitation of the current study was the possible influence of between-group differences in physiological effects on the results. Applying a high-pass temporal filter will not remove all variance caused by these signals. It remains unclear if any difference between the two groups has influenced the results. The relatively small sample size for

machine learning study also is the limitation of this study.

5. Conclusion

In summary, the present study confirmed in two independent sample sets that connectome-based MVPA can be used to distinguish patients diagnosed with MDD from HCs with encouraging classification accuracy and sensitivity. The MVPA method captured resting-state FC patterns reliably. Most of the altered FCs with high discriminative power were located in the SN, the DMN, the cerebellum and visual cortical areas indicating that functional alterations of these networks and brain regions may be associated with the emotional and cognitive impairments characteristic of MDD. These results support the potential of connectome-based MVPA as a complementary tool in the clinical diagnosis of MDD.

Conflict of interest

The authors declare no conflict of interest.

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Author Contributions

Yao S.Q. supervised the study. Zhong X. performed the analysis and wrote paper. Shi H.Q. contributed to the analysis. Zeng L.L. helped to the Matlab analysis. Other co-authors helped to collect data and carry out the research. All co-authors revised and approved the version to be published.

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Figure 1. Regions weights and distribution of 272 consensus functional connections in the first sample. A and B are the left and top view of the first sample, C represents the consensus functions in a circle graph. Region weight representing the relative contribution to identification of depressed patients was denoted by its occurrence number in the consensus functional connections. Sizes of nodes represent region weights in A and B. The bigger size means the larger region weights. The magenta lines represent the consensus functional connections. Different colors represent nodes belong to different networks. Red means salience network, blue means the default mode network, magenta means the central executive network, yellow means cerebellum, green means visual cortical area and cyan represents other regions.

Figure 2 Regions weights and distribution of 108 consensus functional connections in the second sample. The legends are same as the figure 1.

Table 1. Sample set characteristics.

Note:

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]

[a] Pearson Chi-square test.

[b]Two-sample t-test.

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

Highlights:

- First study used MVPA identified MDD in two samples.
- Altered FCs represent potential neurological markers of MDD.
- Altered FCs mainly located in SN, DMN, cerebellum and visual cortical areas.