Common and Distinct Functional Connectivity of the Orbitofrontal Cortex in Depression and Schizophrenia

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Abstract

Background

Schizophrenia and depression are highly prevalent serious psychiatric disorders with potentially similar clinical and biological features, and disrupted connectivity have been found to play an important role in the pathophysiology of these two diseases. Here, we sought to identify common and distinct neuropathological mechanisms in schizophrenia and depression patients with resting state functional magnetic resonance imaging (fMRI).

Methods

Twenty-eight patients with depression (DEP), twenty-nine patients with schizophrenia (SCH), and thirty healthy control subjects (HC) were enrolled. A data-driven intrinsic network level analysis (Intrinsic Connectivity Contrast, ICC) was used to identify functional connectivity (FC) changes at the whole-brain level. Then the regions with group differences were used as seeds in following FC analysis.

Results

Significant ICC differences were found in bilateral orbitofrontal cortex(OFC) across three groups. Common reduced ICC in DEP and SCH were found in OFC, with more extensive abnormalities in schizophrenia than depression. Subsequent FC analysis indicated that, compared to the DEP and HC group, the FC between right OFC and the medial prefrontal cortex (MPFC) and right anterior insula(AI) were significantly lower in the SCH group. In addition, the FC between left OFC and right cerebellum and subcallosal gyrus were decreased in both patient groups compared to the HC group. Correlation analysis showed that the FC between OFC and MPFC was positively correlated with cognitive function in the SCH group.

Conclusion

These results suggest a critical role for OFC connectivity in the pathophysiology of schizophrenia and depression, which may shed new light on the potential neural mechanisms underlying these two disorders.

Introduction

Schizophrenia and depression are serious health problems worldwide with significant socio-economic impact, but the etiology and pathogenesis of the two disorders have not been well defined. Although they are two different disease entities based on all current diagnostic criteria, considerable overlap has been found in terms of genetic risk factors[1], neurobiochemical characteristics[2], immune processes[3] and clinical features[4], suggest both transdiagnostic and disease-specific neurobiological mechanism for the two disorders, which remain poor understood.

Both schizophrenia and depression are characterized by multiple brain alternations, and in the last two decades, the emergence of neuroimaging techniques has provided substantial evidence. Among these techniques, resting-state functional magnetic resonance imaging(rs-fMRI) is an effective and non-invasive neuroimaging approach that may reflect spontaneous brain neural activity and functional organization, and it has been commonly used in clinical research to help us better understand the underlying neural basis, especially for individuals with mental disorders[5, 6]. Functional connectivity (FC) is a key aspect in the analysis of rs-fMRI, which measures temporal correlations in spontaneous low frequency fluctuations between discrete brain regions[7]. Rs-fMRI studies have shown the hierarchical organization of the human brain that have been divided into large-scale networks. These networks are named as referred as resting state networks (RSNs), defined by their spatiotemporal configuration and functional roles, including

the default mode network (DMN), salience network (SN), central executive network (CEN), attentional network (AN) and so on [8, 9]. Previous evidence has pointed towards the relevance of FC aberrations in several networks in both disorders, which are increasingly regarded as dysconnectivity disorders of brain networks [10–13], however, only a few studies have directly compared FC patterns of schizophrenia and depression with rs-fMRI and the results have been inconsistent and inconclusive. For example, a research team observed that the FC between DMN and CEN was increased in schizophrenia while decreased in depression [11], and functional hyperconnectivity between DMN and SN was more profound in depression than in schizophrenia [14]. Another research demonstrated common reduction of FC between posterior DMN and bilateral superior parietal lobe in schizophrenia and depression and diagnosis-specific connectivity reductions of the parietal operculum in schizophrenia relative to depression [10].

Therefore, rs-fMRI studies that make direct comparisons of FC changes in the patients with schizophrenia and depression can yield insight into common and distinct pathophysiology underlying these two disorders. In the present work, to explore differences in the networks of resting state FC across the whole brain in schizophrenia and depression patients, we applied a voxel-based metric, termed the intrinsic connectivity contrast (ICC), which does not rely on a priori assumptions about the spatial distribution of such potential differences and can be used to unbiasedly search for FC abnormalities within the whole brain. Then, seed to whole-brain FC patterns of the region with altered ICC were further analyzed. We assumed that the patients with schizophrenia and depression would display both common and distinct FC pattern, which may contribute to the neuropathology of the two diseases.

Methods And Materials

Participants

This study enrolled thirty individuals with depression (DEP group) and thirty individuals with schizophrenia (SCH group) from the inpatients at the Department of Psychiatry, Renmin Hospital of Wuhan University (Wuhan, China), as well as thirty well-matched healthy controls subjects (HC group) from the hospital staff and local community.

The diagnose of schizophrenia or major depressive disorder was made by two experienced clinical psychiatrists independently according to the DSM-VI Disorder-Clinical Version (SCID-CV). For the patients diagnosed with schizophrenia, they were on their acute phase of psychosis and free of any current or past depressive or manic episode, major depression, bipolar disorder; while for the patients diagnosed with major depressive disorder, they had recurrent major depression with current depressive episode and free of current or past psychotic symptoms, schizophrenia, schizoaffective disorder, bipolar disorder. Most patients were medicated following established medication regimes by their psychiatrists.

Participants in the three groups were excluded if they had any neurologic disorders, organic mental disorders, other serious physical illnesses, dementia, brain injuries, substance abuse or addiction, or contraindications to MRI. Three participants were excluded from data analyses due to artefacts, leaving 30 healthy controls, 28 patients with depression and 29 patients with schizophrenia to be included in the analyses.

The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University, and all participants gave their written informed consent individually after the detailed study purpose and procedures were completely described.

Clinical and cognitive assessments

On the day of MRI scanning, symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia patients and the 17-items Hamilton Depression Rating Scale (HAM-D-17) and Hamilton Anxiety Rating Scale (HAMA) for depression patients. In addition, the self-rating Hypomania Check List (HCL-32) were

used to assess whether the patients with depression have ever experience any bipolar disorder-related symptoms. The digit symbol test (DST), digit span test (DSPT, forward and backward), and verbal fluency test (VFT) were also performed to examine the cognitive function for all participants.

Imaging data acquisition

MRI data were collected using a 3.0T General Electric (GE) Signa HDxt MR scanner by radiology professionals at the Department of Radiology, Renmin Hospital of Wuhan University. Functional images were acquired using a gradient echo planar imaging (EPI) sequence (scan parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 220 mm × 220 mm, matrix = 64 × 64, slices = 32, slice thickness = 4 mm, gap = 0.6 mm) and each run lasted 8 minutes (240 volumes to be obtained). Then high-resolution T1-weighted structural images were additionally obtained using a magnetization-prepared rapid acquisition gradient echo sequence (scan parameters: TE = 7.8 ms, TR = 3.0 ms, flip angle = 7°, inversion time = 1100 ms, FOV = 256 mm × 256 mm, matrix = 256 × 256, slices = 188, voxel size = 1 mm × 1 mm × 1 mm).

Data preprocessing

MRI data preprocessing and statistical analyses were carried out using SPM12-based (Statistical Parametric Mapping; <http://www.fil.ion.ucl.ac.uk/spm/>) CONN v.19c functional connectivity toolbox (www.nitrc.org/projects/conn) [15] running on MATLAB 2013b (MathWorks, MA, USA). The first five volumes of functional images were removed for subjects' adaptation to the scanning environment and steady-state magnetization.

Default preprocessing pipeline for volume-based analyses was applied, including functional realignment and unwrap, functional slice-timing correction, functional direct segmentation and normalization to Montreal Neurological Institute (MNI) space, structural segmentation and normalization to MNI space, and functional smoothing using a 6 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. The ART (artifact detection toolbox; http://www.nitrc.org/projects/artifact_detect) was used to identify outliers for scrubbing motion and spiking artifacts. An image was defined as an outlier if the composite motion relative to the previous timepoint was greater than 2 mm or if the global mean signal intensity was exceeding 3 standard deviations from the mean image intensity, and the identified outliers were subsequently included as nuisance regressors within the first-level general linear model.

For the denoising step, the anatomical component-based noise correction (CompCor) strategy was used to estimate and remove motion and physiological noise without regressing out the global signal [16]. CompCor regressors were defined using scrubbed data, including: the first five principal components attributable (PCA) to each individual's white matter (WM) signal; the first five PCA to individual cerebrospinal fluid (CSF) signal; six subject-specific realignment parameters (three translations and three rotations) as well as their first-order temporal derivatives; the artifacts identified by ART; and the main effect of rest scanning condition. Then Linear detrending and temporal band-pass filter of 0.008–0.09 Hz were also applied.

Intrinsic connectivity contrast analysis

Intrinsic connectivity contrast (ICC) [17] is a voxel-wise measure of network centrality at each voxel, characterized by the strength of the connectivity between each voxel and the rest of the brain. ICC is calculated as the root mean square of the correlation coefficient scores between each individual voxel and all of the voxels in the brain, with higher scores representing higher connectivity strength of a given voxel with every other voxel in the brain. When compared with other connectivity indexes, ICC has an advantage because it takes into account not only the presence of a connection but also their strength, and it can be computed without applying a correlation threshold, and therefore, it does not require any a priori information or assumptions. The ICC score was computed for each voxel in the brain as implemented in the CONN toolbox, therefore producing a whole-brain map for each subject. As the biological meaning of estimating FC of the WM voxels from BOLD data is pointless, the ICC analysis was restricted to grey matter (GM) voxels with a priori GM

mask (isotropic 2-mm voxels). Then, for statistical purposes, each subject ICC map was normalized by converting to Z scores to fit a Gaussian distribution with zero mean and unitary variance, and a higher ICC score represents greater average strength of the correlations in a given voxel. This method has been previously employed by other studies to explore FC changes without a hypothesis[18, 19].

Seed-to-voxel functional connectivity analysis

To further illustrate the associated brain regions contributing to the ICC differences, the regions revealing group differences in ICC analysis were then used as seed regions in a second-level seed-based connectivity analysis. Pearson's correlation coefficients were computed between the mean time series of the seed and the time series of each voxel in the gray matter of the whole-brain and the Fisher's r-to-z transformation was performed to improve normality. The individual functional connectivity z-maps for each seed region were obtained.

Statistical Analysis

The spatial distribution of the ICC map of each of the three groups using one-tail one-sample t-test (a voxel-wise $p < 0.005$ uncorrected and a cluster-wise threshold of $p < 0.01$, FDR-corrected). To investigate the effect of group and differences between groups, one-way analysis of covariance (ANCOVA) and post-hoc LSD tests were performed on the ICC and FC maps respectively, controlling for age, gender, years of education, and head-motion covariable (FD value). Results were considered significant at a voxel-wise $p < 0.005$ uncorrected and a cluster-wise threshold of $p < 0.01$ FDR-corrected.

To further examine the correlations between FC and clinical and cognitive variables, correlation analysis was performed separately in the two patients' groups. The altered ICC and FC scores were defined and extracted based on the results of above ICC and Seed-to-voxel FC analysis. As most variables did not meet the normality distribution assessed by Kolmogorov-Smirnov tests($p > 0.1$), spearman correlations analyses (two-sided) were performed between these variables. The correlative relationship was considered to be significant at $p < 0.05$ (two-tailed) in this exploratory analysis.

Results

Demographic, clinical and behavioral data

Demographic variables across the three groups were compared with the one-way analysis of variance (ANOVA) or independent sample t tests for continuous variables and Chi-square tests for categorical variables. Participants in the healthy control(HC), depression(DEP) and schizophrenia(SCH) groups were well matched in age, gender and years of education($p > 0.05$). The scores of cognitive function tests were also analyzed using ANOVA. Results revealed significant main effects of group for all of the cognitive function tests. Post-hoc analyses indicated, compared with the HC group, both patient groups showed reduced digit symbol test (DST), digit span test (DSPT, forward and backward), and verbal fluency test (VFT) scores, and the decrease was more apparent in the SCH group ($P < 0.05$). Detailed information can be seen in Table 1.

Table 1. Demographic and clinical characteristic of all participants

	Healthy controls	Depression	Schizophrenia	p value
	(HC,n=30)	(DEP,n=28)	(SCH,n=29)	
Gender (Male/Female)	11/19	11/17	11/18	$\chi^2=0.042$, $p=0.979$
Age (years)	28.37±5.08	27.86±6.23	27.48±4.61	$F=0.015$, $p=0.985$
Education (years)	14.27±2.16	14.42±2.28	14.21±2.74	$F=0.204$, $p=0.816$
Duration of illness(months)	-	25.0±16.1	25.6±12.7	$t=0.169$, $p=0.866$
Hamilton depression scale(HAMD)	-	22.32±2.09	-	-
Hamilton anxiety scale(HAMA)	-	11.23±4.72	-	-
Positive and negative syndrome scale (PANSS)				
Total score	-	-	83.87±8.12	-
Positive scale score	-	-	21.26±4.51	-
Negative scale score	-	-	20.07±4.01	-
General psychopathology	-	-	41.43±7.59	-
Cognitive function tests				
Digit symbol test	68.00±10.8	62.61±8.02	47.86±8.56	$F=37.265$, $p=0.000$
Digit span test(forward)	8.77±1.19	8.04±0.84	7.83±1.04	$F=6.6775$, $p=0.002$
Digit span test(backward)	5.67±1.54	5.11±0.83	4.45±1.12	$F=7.514$, $p=0.001$
Verbal fluency test	22.50±4.90	19.64±2.25	15.28±3.94	$F=25.798$, $p=0.000$

Intrinsic connectivity contrast results

The regions of high ICC scores showed a roughly bilateral distribution and were located at prefrontal cortex, posterior cingulate cortex/precuneus (PCC/Pcu), inferior parietal gyrus, anterior insula in the HC group(Figure 1A), which is similar to the cortical hubs that identified by previous ICC studies[19–21]. The spatial distributions of ICC in the DEP and SCH groups were generally consistent with the HC group (Figure 1B and 1C).

Significant group differences were found in the bilateral orbitofrontal cortex (left and right OFC), as shown in Figure 2 and Table 2. To further determine specific alterations between groups parameter estimates from the IOFC and rOFC were extracted for post-hoc LSD analyses. Results indicated that specifically rOFC connectivity was decreased in the SCH group but not the DEP group compared to the HC group and the IOFC connectivity was decreased in both SCH and DEP groups compared to the HC group.

Table 2
Regions with significant group differences with intrinsic connectivity contrast in three groups

Table 1. Demographic and clinical characteristic of all participants				
	Healthy controls	Depression	Schizophrenia	p value
	(HC,n=30)	(DEP,n=28)	(SCH,n=29)	
Gender (Male/Female)	11/19	11/17	11/18	$\chi^2=0.042$, $p=0.979$
Age (years)	28.37±5.08	27.86±6.23	27.48±4.61	F=0.015, $p=0.985$
Education (years)	14.27±2.16	14.42±2.28	14.21±2.74	F=0.204, $p=0.816$
Duration of illness(months)	-	25.0±16.1	25.6±12.7	t=0.169, $p=0.866$
Hamilton depression scale(HAMD)	-	22.32±2.09	-	-
Hamilton anxiety scale(HAMA)	-	11.23±4.72	-	-
Positive and negative syndrome scale (PANSS)				
Total score	-	-	83.87±8.12	-
Positive scale score	-	-	21.26±4.51	-
Negative scale score	-	-	20.07±4.01	-
General psychopathology	-	-	41.43±7.59	-
Cognitive function tests				
Digit symbol test	68.00±10.8	62.61±8.02	47.86±8.56	F=37.265, $p=0.000$
Digit span test(forward)	8.77±1.19	8.04±0.84	7.83±1.04	F=6.6775, $p=0.002$
Digit span test(backward)	5.67±1.54	5.11±0.83	4.45±1.12	F=7.514, $p=0.001$
Verbal fluency test	22.50±4.90	19.64±2.25	15.28±3.94	F=25.798, $p=0.000$

Seed-to-voxel functional connectivity results

One-way ANCOVA with group as between subject factor found a main effect of group in the medial prefrontal cortex (MPFC), right cerebellum, and subcallosal cortex when using the left OFC as seed, while in the MPFC and right anterior insula(AI) when using the right OFC as seed(Figure 3 and Table 3).

Table 3
Regions with significant group differences in functional connectivity of bilateral orbitofrontal cortex

Regions	MNI	The z values of FC:Mean±SD			ANCOVA		
	coordinates	HC	DEP	SCH	F value	p Value	cluster size
left orbitofrontal cortex	-20,26,-16	0.102±0.673	-0.243±0.603	-0.687±0.466	13.21	0.001	177
Right orbitofrontal cortex	16,22,-18	0.0120±0.594	-0.143±0.637	-0.743±0.384	13.91	0.001	327

Regions	MNI	The z values of FC:Mean±SD			ANCOVA		
	coordinates	HC	DEP	SCH	F value	p Value	cluster size
Seed: left orbitofrontal cortex							
Medial prefrontal cortex	6,32,12	0.287±0.089	0.241±0.082	0.115±0.099	16.06	0.001	1823
Right cerebellum	38,-56,-42	0.074±0.099	-0.079±0.070	0.030±0.071	14.80	0.001	626
Subcallosal cortex	-4,-6,-8	0.368±0.111	0.283±0.128	0.182±0.119	15.71	0.001	426
Seed:right orbitofrontal cortex							
Medial prefrontal cortex	8,32,10	0.263±0.086	0.266±0.075	0.105±0.069	19.80	0.001	4131
Right anterior insula	34,14,-14	0.259±0.108	0.268±0.120	0.106±0.123	14.30	0.001	492

For the left OFC seed, post-hoc analysis indicated that patients with SCH and DEP demonstrated reduced FC with right cerebellum and subcallosal gyrus compared to the controls, and the FC drop between the left OFC and right cerebellum was more significant in the DEP group while the FC drop between the left OFC and subcallosal gyrus was more significant in the SCH group. For the right OFC seed, post-hoc analysis showed that patients with SCH exhibited decreased FC with MPFC and rAI, compared to the DEP and HC groups (Figure 4).

Correlations between FC and clinical variables

The FC between left OFC and MPFC was positively correlated to scores of DSPT (forward) scores ($r = 0.5021$, $p = 0.0055$) while FC between right OFC and MPFC was positively correlated to scores of DSPT(backward) scores in the SCH group(Figure 5). We did not detect other significant correlations between FC values and other clinical variables in any patient group.

Discussion

The current study is the first to employ the data-driven ICC analysis to identify the alterations in whole brain intrinsic functional connectivity in schizophrenia and depression, and the following main results were obtained. First, we found regions with a decrease of the ICC scores located in the OFC in schizophrenia and depression. Specifically, IOFC connectivity was decreased in both patient groups and rOFC connectivity was decreased in the SCH group but not the DEP group. Second, functional disconnectivity between OFC and MPFC and rAI was obvious in schizophrenia but not in depression. Third, both the SCH and DEP group showed common decreased FC between left OFC and right cerebellum and subcallosal gyrus, but to a different extent. Finally, the correlation analysis showed that the FC between OFC and MPFC was associated with cognitive function in the SCH group. Taken together, these findings provide evidence for both common and different neurofunctional basis of the disorders.

The principal finding of ICC analysis is the alterations of the bilateral OFC, further analyses suggest a significant decrease of ICC scores in IOFC in both schizophrenia and depression while a significant decrease of ICC scores in rOFC in only schizophrenia but not depression. The OFC receives almost all types of sensory stimuli from other cortical regions and evaluates them based on their associations with current needs and is a main site for cortico-cortico and thalamo-cortico integration; there are multiple functions for OFC, including sensory integration and reward learning, cognitive flexibility, control of emotion, decision making, social behavior and mnemonic functions[22–24]. ICC is a data-driven whole-brain voxel-based measure of global connectivity, addresses qualitatively different question about brain connectivity than seed-based analysis and it measures the integrative capacity of a given brain region[25] and reflects each voxel's overall connectivity strength, so our results showed the OFC exhibited concurrent reductions in integrative capacity, suggesting disturbed information processing of OFC in schizophrenia and depression. Being based on FC, the ICC could not provide information regard to directionality; however, computational modeling has confirmed that nodes with high degree(high ICC scores) tend to be the target of information flow from nodes with lower degree[26]. Therefore, the reduced OFC ICC scores may suggest that OFC receive less information from the other brain regions in schizophrenia and depression, which means the informational content and diversity have been affected, and the impairment is more remarkable in schizophrenia than depression. The alterations in the OFC are consistent with previous reports in schizophrenia[27–29] and depression[22, 30]. Moreover, using functional connectivity density (FCD) analysis combined with multivariate pattern analysis (MVPA), Chen et al identified the OFC as the key region that could differentiate depression patients from schizophrenia patients[12]. Together these findings provide evidence that the OFC may be relevant to the pathogenesis of schizophrenia and depression, but perhaps in different ways.

Interestingly, the SCH patients specifically exhibited decreased connectivity between bilateral OFC with MPFC compared to both HC and DEP group, suggesting disease-specific neurofunctional impairments in schizophrenia. The MPFC shares extensive anatomic connections with the OFC, and these two regions are regarded as part of a “visceromotor network” that is thought to modulate endocrine, autonomic, behavioral, and experiential aspects of emotional behavior[22, 31]. In addition, the MPFC is believed to be the neural correlate of self-referential processing and also represents a core hub of the brain's anterior DMN, which has been consistently impaired in schizophrenia[32]. Both the OFC and MPFC are located in the PFC of the human brain[33], so the decoupling between OFC and MPFC was in line with previous studies and suggests a PFC dysconnectivity and supported the dysconnectivity hypothesis of schizophrenia[34, 35]. The PFC plays an essential role in the organization and control of goal-directed thought and behavior[36] and is involved in almost all cognitive functions, we found positive relationship between left OFC-MPFC FC and DSPT(forward) scores as well as between right OFC-MPFC FC and DSPT(backward) scores in the SCH group. The digit span test is a measure of working memory, requiring maintenance of information in memory. Our results indicated that the working memory deficits are related to the OFC-MPFC connectivity. Furthermore, we also found disconnections between OFC and rAI were specific to patients with schizophrenia. The AI is a cortical hub for SN, first

proposed by Seeley et al[37], which plays a role in recruiting relevant brain regions for the bottom-up processing of sensory information. The patients with schizophrenia have been suggested to have salience anomalies which might reflect the connectivity deficits in related SN network, and dysfunctional SN activity in schizophrenia has been reported by previous researches[38, 39]. The affected OFC-rAI connectivity in schizophrenia would lead to the disorganized salience information commutation and contribute to the psychotic symptoms. Briefly summarizing, the present findings suggest attenuated FC between OFC and MPFC and rAI in the patients with schizophrenia and relatively reversed FC in patients with depression, suggesting a disrupted balance between OFC and SN/DMN integration in schizophrenia and may serve as a disease-specific alteration for schizophrenia.

Furthermore, the findings from the present study demonstrate significant overlap in weaker FC between OFC and cerebellum and subcallosal cortex in the SCH and DEP group. The FC between OFC and cerebellum was reduced in both groups, and this reduction was more pronounced in the patients with depression, turning from positive to negative connectivity. In traditional view, the cerebellum is regarded as a primary center for controlling sensorimotor functions. However, based on clinical observations and experiments, additional roles for the cerebellum in higher-order cognitive functions have been posited, such as language, emotion, reward, social behavior, and working memory[40]. As a central node for coordinating and integrating diverse functional modalities, the cerebellum has been involved in mental disorders, which have been supported by accumulating evidence[41–43]. Shared abnormalities in cerebellum have been reported in schizophrenia and depression[44, 45]. Cerebellar dysfunction might slow the information integration, and our result further found that the loss of cerebro-cerebellar coupling between cerebellum and OFC is more significant in depression than in schizophrenia. Conversely, the FC between the left OFC and subcallosal gyrus declined more significantly in schizophrenia than in depression. The subcallosal cingulate gyrus is pivotal in mood, learning, reward, and memory and was implicated as an aberrant region in depression rather than in schizophrenia[46], and could be effectively targeted by antidepressants and deep brain stimulation. But in our study, the degree of FC reduction between OFC and subcallosal gyrus was more profound in patients with schizophrenia than depression. The methodological differences and heterogeneity of the samples between studies may account for these inconsistencies, and need further test.

Several limitations must be mentioned in this work. First, most patients recruited were medicated by different medications for psychotic or depressive symptoms, which may have different effects on functional connectivity, as previous studies showed. This source of variance may act as a major confounding factor in transdiagnostic studies. Second, we used a cross-sectional design and all patients were at their acute episode, so we are unable to address how FC may change during the clinical course and further longitudinal follow-up studies are needed to fully understand the implications of the current findings. In addition, the sample size was relatively small in each group, which may have yielded unreliable results, a larger number of participant samples are needed to increase the reliability and sensitivity. Lastly, potential confounding effect which caused by head motion might exist since previous study identified a correlation between the reduced distant functional connectivity and high head motion; however, we did not find any correlation between ICC and FC scores where between group differences were found, and we have included the head motion parameter as covariate in our analysis, indicating it is not driving the connectivity differences here.

Conclusion

In summary, the findings of current work highlighted the role of the OFC connectivity in the pathophysiology of schizophrenia and depression. We identified the OFC-MPFC/rAI disconnection as a special pattern for schizophrenia while common but varying degrees of reduced FC of OFC-cerebellum/subcallosal cortex in schizophrenia and depression, which may shed new light on the potential neural mechanisms underlying these two disorders.

Declarations

Ethics approval and consent to participate

The authors confirm that all experiments involving human participants were performed in accordance with relevant guidelines and regulations. The Ethics Committee of Renmin Hospital of Wuhan University approved the study protocol([2014] K-025). The written, informed consent of all subjects was obtained after receiving a complete description of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due that they contain patients' personal information and our hospital has strict data sharing policy, but are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

WHL and ZY designed the study. HH, RB, CC, and HJJ conducted subjects' recruitment and performed the study. HH undertook the imaging data analysis and wrote the first draft of the manuscript. WHL, LZC, CJG, WGH and ZY revised the manuscript. All authors contributed to and have approved the final manuscript.

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References

1. Cross-Disorder Group of the Psychiatric Genomics C: **Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis.** Lancet 2013, **381**(9875):1371–1379.
2. Angelucci F, Mathe AA, Aloe L: **Neurotrophic factors and CNS disorders: findings in rodent models of depression and schizophrenia.** Prog Brain Res 2004, **146**:151–165.
3. Pape K, Tamouza R, Leboyer M, Zipp F: **Immunoneuropsychiatry - novel perspectives on brain disorders.** Nat Rev Neurol 2019, **15**(6):317–328.
4. Anticevic A, Schleifer C, Youngsun TC: **Emotional and cognitive dysregulation in schizophrenia and depression: understanding common and distinct behavioral and neural mechanisms.** Dialogues Clin Neurosci 2015,

17(4):421–434.

5. Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, Beckmann CF, Adelstein JS, Buckner RL, Colcombe S *et al*: **Toward discovery science of human brain function**. Proc Natl Acad Sci U S A 2010, **107**(10):4734–4739.
6. Glasser MF, Smith SM, Marcus DS, Andersson JL, Auerbach EJ, Behrens TE, Coalson TS, Harms MP, Jenkinson M, Moeller S *et al*: **The Human Connectome Project's neuroimaging approach**. Nat Neurosci 2016, **19**(9):1175–1187.
7. Biswal B, Yetkin FZ, Haughton VM, Hyde JS: **Functional connectivity in the motor cortex of resting human brain using echo-planar MRI**. Magn Reson Med 1995, **34**(4):537–541.
8. Raichle ME, Mintun MA: **Brain work and brain imaging**. Annu Rev Neurosci 2006, **29**:449–476.
9. Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF: **Consistent resting-state networks across healthy subjects**. Proc Natl Acad Sci U S A 2006, **103**(37):13848–13853.
10. Schilbach L, Hoffstaedter F, Muller V, Cieslik EC, Goya-Maldonado R, Trost S, Sorg C, Riedl V, Jardri R, Sommer I *et al*: **Transdiagnostic commonalities and differences in resting state functional connectivity of the default mode network in schizophrenia and major depression**. Neuroimage Clin 2016, **10**:326–335.
11. Jiang Y, Duan M, Chen X, Chang X, He H, Li Y, Luo C, Yao D: **Common and distinct dysfunctional patterns contribute to triple network model in schizophrenia and depression: A preliminary study**. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2017, **79**:302–310.
12. Chen X, Liu C, He H, Chang X, Jiang Y, Li Y, Duan M, Li J, Luo C, Yao D: **Transdiagnostic differences in the resting-state functional connectivity of the prefrontal cortex in depression and schizophrenia**. J Affect Disord 2017, **217**:118–124.
13. Han W, Sorg C, Zheng C, Yang Q, Zhang X, Ternblom A, Mawuli CB, Gao L, Luo C, Yao D *et al*: **Low-rank network signatures in the triple network separate schizophrenia and major depressive disorder**. Neuroimage Clin 2019, **22**:101725.
14. Shao J, Meng C, Tahmasian M, Brandl F, Yang Q, Luo G, Luo C, Yao D, Gao L, Riedl V *et al*: **Common and distinct changes of default mode and salience network in schizophrenia and major depression**. Brain Imaging Behav 2018, **12**(6):1708–1719.
15. Whitfield-Gabrieli S, Nieto-Castanon A: **Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks**. Brain Connect 2012, **2**(3):125–141.
16. Behzadi Y, Restom K, Liao J, Liu TT: **A component based noise correction method (CompCor) for BOLD and perfusion based fMRI**. Neuroimage 2007, **37**(1):90–101.
17. Martuzzi R, Ramani R, Qiu M, Shen X, Papademetris X, Constable RT: **A whole-brain voxel based measure of intrinsic connectivity contrast reveals local changes in tissue connectivity with anesthetic without a priori assumptions on thresholds or regions of interest**. Neuroimage 2011, **58**(4):1044–1050.
18. Luppi AI, Craig MM, Pappas I, Finoia P, Williams GB, Allanson J, Pickard JD, Owen AM, Naci L, Menon DK *et al*: **Consciousness-specific dynamic interactions of brain integration and functional diversity**. Nat Commun 2019, **10**(1):4616.
19. Xu X, Dai J, Chen Y, Liu C, Xin F, Zhou X, Zhou F, Stamatakis EA, Yao S, Luo L *et al*: **Intrinsic connectivity of the prefrontal cortex and striato-limbic system respectively differentiate major depressive from generalized anxiety disorder**. Neuropsychopharmacology 2020.
20. Bagarinao E, Watanabe H, Maesawa S, Mori D, Hara K, Kawabata K, Yoneyama N, Ohdake R, Imai K, Masuda M *et al*: **Aging Impacts the Overall Connectivity Strength of Regions Critical for Information Transfer Among Brain Networks**. Front Aging Neurosci 2020, **12**:592469.

21. Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, Andrews-Hanna JR, Sperling RA, Johnson KA: **Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease.** J Neurosci 2009, **29**(6):1860–1873.
22. Drevets WC: **Orbitofrontal cortex function and structure in depression.** Ann N Y Acad Sci 2007, **1121**:499–527.
23. Rolls ET: **The functions of the orbitofrontal cortex.** Brain Cogn 2004, **55**(1):11–29.
24. Elliott R, Agnew Z, Deakin JF: **Hedonic and informational functions of the human orbitofrontal cortex.** Cereb Cortex 2010, **20**(1):198–204.
25. Wu GR, Wang X, Baeken C: **Baseline functional connectivity may predict placebo responses to accelerated rTMS treatment in major depression.** Hum Brain Mapp 2020, **41**(3):632–639.
26. Moon JY, Lee U, Blain-Moraes S, Mashour GA: **General relationship of global topology, local dynamics, and directionality in large-scale brain networks.** PLoS Comput Biol 2015, **11**(4):e1004225.
27. Kanahara N, Sekine Y, Haraguchi T, Uchida Y, Hashimoto K, Shimizu E, Iyo M: **Orbitofrontal cortex abnormality and deficit schizophrenia.** Schizophr Res 2013, **143**(2-3):246–252.
28. Kim BH, Shin YB, Kyeong S, Lee SK, Kim JJ: **Neural Basis of Ambivalence towards Ideal Self-Image in Schizophrenia.** Psychiatry Investig 2020, **17**(5):452–459.
29. Takahashi T, Nakamura M, Nishikawa Y, Komori Y, Nishiyama S, Takayanagi Y, Furuichi A, Kido M, Sasabayashi D, Higuchi Y *et al*: **Potential role of orbitofrontal surface morphology on social and cognitive functions in high-risk subjects for psychosis and schizophrenia patients.** Psychiatry Res Neuroimaging 2019, **283**:92–95.
30. Rolls ET, Cheng W, Feng J: **The orbitofrontal cortex: reward, emotion and depression.** Brain Commun 2020, **2**(2):fcaa196.
31. Drevets WC: **Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders.** Curr Opin Neurobiol 2001, **11**(2):240–249.
32. Hu ML, Zong XF, Mann JJ, Zheng JJ, Liao YH, Li ZC, He Y, Chen XG, Tang JS: **A Review of the Functional and Anatomical Default Mode Network in Schizophrenia.** Neurosci Bull 2017, **33**(1):73–84.
33. Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, Yang Z, Chu C, Xie S, Laird AR *et al*: **The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture.** Cereb Cortex 2016, **26**(8):3508–3526.
34. Zhou Y, Fan L, Qiu C, Jiang T: **Prefrontal cortex and the dysconnectivity hypothesis of schizophrenia.** Neurosci Bull 2015, **31**(2):207–219.
35. Chang X, Shen H, Wang L, Liu Z, Xin W, Hu D, Miao D: **Altered default mode and fronto-parietal network subsystems in patients with schizophrenia and their unaffected siblings.** Brain Res 2014, **1562**:87–99.
36. Szczepanski SM, Knight RT: **Insights into human behavior from lesions to the prefrontal cortex.** Neuron 2014, **83**(5):1002–1018.
37. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD: **Dissociable intrinsic connectivity networks for salience processing and executive control.** J Neurosci 2007, **27**(9):2349–2356.
38. Huang H, Botao Z, Jiang Y, Tang Y, Zhang T, Tang X, Xu L, Wang J, Li J, Qian Z *et al*: **Aberrant resting-state functional connectivity of salience network in first-episode schizophrenia.** Brain Imaging Behav 2020, **14**(5):1350–1360.
39. Tu PC, Hsieh JC, Li CT, Bai YM, Su TP: **Cortico-striatal disconnection within the cingulo-opercular network in schizophrenia revealed by intrinsic functional connectivity analysis: a resting fMRI study.** Neuroimage 2012, **59**(1):238–247.
40. Gill JS, Sillitoe RV: **Functional Outcomes of Cerebellar Malformations.** Front Cell Neurosci 2019, **13**:441.
41. Andreasen NC, Pierson R: **The role of the cerebellum in schizophrenia.** Biol Psychiatry 2008, **64**(2):81–88.

42. Yeganeh-Doost P, Gruber O, Falkai P, Schmitt A: **The role of the cerebellum in schizophrenia: from cognition to molecular pathways.** Clinics (Sao Paulo) 2011, **66 Suppl 1**:71–77.
43. Depping MS, Schmitgen MM, Kubera KM, Wolf RC: **Cerebellar Contributions to Major Depression.** Front Psychiatry 2018, **9**:634.
44. Tu PC, Chen MH, Chang WC, Kao ZK, Hsu JW, Lin WC, Li CT, Su TP, Bai YM: **Identification of common neural substrates with connectomic abnormalities in four major psychiatric disorders: A connectome-wide association study.** Eur Psychiatry 2020, **64**(1):e8.
45. Chuang JY, Murray GK, Metastasio A, Segarra N, Tait R, Spencer J, Ziauddeen H, Dudas RB, Fletcher PC, Suckling J: **Brain structural signatures of negative symptoms in depression and schizophrenia.** Front Psychiatry 2014, **5**:116.
46. Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM: **The subcallosal cingulate gyrus in the context of major depression.** Biol Psychiatry 2011, **69**(4):301–308.

Figures

Figure 1

Within-group intrinsic connectivity contrasts (ICC) maps for the control (A), depression(B), and schizophrenia(C) group. The spatial patterns represent average maps of higher (red) and lower (blue) ICC scores, with a greater score representing greater average strength of the correlations in a given voxel. Statistical maps are rendered on a surface template and are thresholded at a voxel-wise $p < 0.005$ uncorrected and a cluster-wise threshold of $p < 0.01$, FDR-corrected (One-sample t-test), the colorbar represents T values.

Figure 2

Regions (the bilateral orbitofrontal cortex) exhibiting a significant group differences of ICC in the HC, DEP and SCH groups by the ANCOVA(voxel-wise $p < 0.005$ uncorrected and a cluster-wise threshold of $p < 0.01$, FDR-corrected), and the colorbar represents F values.

Figure 3

Functional connectivity differences of the orbitofrontal cortex(OFC) in the HC, DEP, and SCH group by the ANCOVA(voxel-wise $p < 0.001$ uncorrected and a cluster-wise threshold of $p < 0.01$, FDR-corrected), and the colorbar represents F values

Figure 4

Post-hoc comparisons of functional connectivity differences of the bilateral orbitofrontal cortex(OFC) in the HC, SCH, and DEP group.

Figure 5

Correlations between abnormal functional connectivity and digit span test scores in the patients with schizophrenia.