Neurosci Bull February 1, 2013, 29(1): 59–74. http://www.neurosci.cn
DOI: 10.1007/s12264-013-1300-8

·Original Article·

Ventral medial prefrontal functional connectivity and emotion regulation in chronic schizophrenia: A pilot study

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ABSTRACT

People with schizophrenia exhibit impaired social cognitive functions, particularly emotion regulation. Abnormal activations of the ventral medial prefrontal cortex (vMPFC) during emotional tasks have been demonstrated in schizophrenia, suggesting its important role in emotion processing in patients. We used the resting-state functional connectivity approach, setting a functionally relevant region, the vMPFC, as a seed region to examine the intrinsic functional interactions and communication between the vMPFC and other brain regions in schizophrenic patients. We found hypo-connectivity between the vMPFC and the medial frontal cortex, right middle temporal lobe (MTL), right hippocampus, parahippocampal cortex (PHC) and amygdala. Further, there was a decreased strength of the negative connectivity (or anticorrelation) between the vMPFC and the bilateral dorsal lateral prefrontal cortex (DLPFC) and pre-supplementary motor areas. Among these connectivity alterations, reduced vMPFC–DLPFC connectivity was positively correlated with positive symptoms on the Positive and Negative Syndrome Scale, while vMPFC–right MTL/PHC/amygdala functional connectivity was positively correlated with the performance of emotional regulation in patients. These findings imply that communication and coordination throughout the brain networks are disrupted in schizophrenia. The emotional correlates of vMPFC connectivity suggest a role of the hypo-connectivity between these regions in the neuropathology of abnormal social cognition in chronic schizophrenia.

Keywords: schizophrenia; emotion regulation; ventral medial prefrontal cortex; functional connectivity; resting state; functional MRI

INTRODUCTION

Social cognition impairments have been consistently reported in the prodromal, first episode, and chronic phases of schizophrenia[1]. As one of the important aspects of social cognition, abnormal emotion regulation (also called emotion management) is an important feature of schizophrenia in the clinic[2]. The concept of emotion regulation refers to a diverse set of processes by which "individuals influence which emotions they have, when they have them, and how they experience and express these emotions"[3].

Although emotional dysfunction has been regarded a hallmark of schizophrenia since the early days[4], a complete understanding of its underlying neuropathology is still lacking.

The medial frontal cortex (MFC) has been implicated in social cognition, especially in emotion regulation[5]. Anatomically, the ventral MFC (vMFC) is the lower part of the frontal cortices and consists of the rostral and subcallosal parts of the anterior cingulate gyrus, the medial portion of the orbitofrontal cortex, and the area in between[6]; it is intimately connected to the limbic system[7,8]. It is critical to the integration of emotion and cognition by the use of so-called "somatic markers"[9,10]. Convergent evidence has also shown that the ventral medial prefrontal cortex (vMPFC) is important for social decision-making and emotion processing[11-15]. Previous studies[16-18] have demonstrated abnormal vMPFC activations in schizophrenia, suggesting its important role in emotion processing in this clinical group. Although most neuroimaging studies of emotion processing in schizophrenia have focused on the vMPFC, some evidence suggests that other brain structures involved in emotion regulation (amygdala, insula, frontocingulate cortex) may also be affected in schizophrenia[19,20]. Typically, these patients are characterized by a lack of integration between thought, emotion, and behavior[21].

Resting-state functional connectivity (RSFC) has proven a powerful and reliable method to examine the intrinsic functional architecture of brain networks[22-27]. Preliminary findings have suggested a "disconnection syndrome" in schizophrenia[28-31]. For example, RSFC studies have demonstrated disconnection features of two intrinsic networks, the task-negative network (also called the default network) and the task-positive network (also called the task-control network) in schizophrenia[32-35]. Among these studies, the most consistent finding is that the RSFC between the posterior cingulate cortex and the MPFC, two core regions of the default network, is reduced in schizophrenia. Hoptman and colleagues showed significant reductions in the RSFC between amygdala and ventral prefrontal cortex, and a lower RSFC is associated with higher levels of aggression[36], which is one specific psychopathological form of emotion regulation[37]. More generally, emotion regulation includes the ability to experience emotion and combine it with cognitive control in order to make the best possible decisions and take the most effective actions.

Given these considerations, the current study aimed to adopt the RSFC approach using the functionally relevant region, the vMPFC, as a seed region to examine the intrinsic functional interactions and communication between the vMPFC and other brain regions in patients with schizophrenia. We further investigated whether an aberrant RSFC predicted the performance of emotion regulation in patients with schizophrenia. Specifically, we expected to see hypoconnectivity between the vMPFC and other brain regions of both the default network and the task-positive network in patients with schizophrenia compared to healthy controls, especially in the amygdala, dorsal lateral prefrontal cortex (DLPFC) and MPFC, in light of the key roles of these areas in emotion processing. We further hypothesized that social cognition, particularly emotion regulation, would be significantly associated with RSFC reduction in patients with schizophrenia.

PARTICIPANTS AND METHODS

Participants

Participants were 15 healthy controls (41.4 ± 6.3 years; 8 males) and 27 inpatients (39.7 ± 7.2 years; 16 males) who met the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) (DSM-IV-TR) criteria for schizophrenia after a Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient's Version. Participants with a lifetime history of substance dependence or meeting the criteria for a substance abuse diagnosis within the 6 months prior to assessment were excluded from the study, as were participants with a history of electroconvulsive treatment, head injury with loss of consciousness >10 min, neurological disorders, or human immunodeficiency virus seropositivity. Medication dosages (chlorpromazine equivalents) were computed according to the American Psychiatric Association guidelines[38]. Demographic data are given in Table 1. All participants gave informed consent as approved by the Ethics Committee of Beijing Huilongguan Hospital.

Neurocognitive/Psychopathology Assessment

Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS)[39,40]. Social cognition was assessed using the "Managing Emotions" section of the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT)[41], which is recommended by the US National Institute of Mental Health Measurement and Treatment Re-

Table 1. Clinical and demographic information

Variables	Control (n = 15)		Schizophrenia (n = 27)		t-value	P-value
	Mean	SD	Mean	SD		
Age (years)	41.4	6.3	39.7	7.2	−0.79	0.44
Education (years)	12.5	2.7	12.4	2.3	−0.15	0.89
Gender (male/female)	8/7		16/11			
PANSS total	-		63.0	8.3		
PANSS positive	-		11.8	3.8		
PANSS negative	-		19.9	3.9		
General psychopathology symptoms	-		27.7	3.2		
CPZ equivalents (mg)	-		443.1	221.4		
Duration (years)	-		16.5	7.4		
Executive function-Mazes test score	59.0	9.4	47.2	11.7	3.26	0.002
MSCEIT-Managing emotions branch	51.7	12.2	44.7	12.7	1.71	0.096

CPZ, chlorpromazine; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test (standard scores); PANSS, Positive and Negative Syndrome Scale.

search to Improve Cognition in Schizophrenia Committee as a key measure of social cognition in schizophrenia[41-45]. The MSCEIT is divided into four branches: perceiving, facilitating, understanding, and managing emotions. The managing emotions branch contains two subtasks: emotion management and emotional relations. In the emotion management subtask, subjects are provided with several responses and have to judge the efficacy of each response for maintaining or regulating the emotions. The emotional relations subtask contains three situations concerning interpersonal problems and presents several responses under each situation. Subjects have to judge the efficacy of each response for achieving the goals of each situation[41]. Managing emotions scores are calculated based on the sum of individual item scores and transformed to T-Scores with a mean of 50 (SD = 10), with higher scores reflecting better emotional management/regulation.

Executive function was measured by the Neuropsychological Assessment Battery (NAB) Mazes test[46]. Seven single paper-and-pencil tests of increasing difficulty are included in the test. If the respondent completes the test within the time limit, 1–5 points are awarded for that test (1–2 points for the first 3 tests and 1–5 points for tests 4–7) so performances with shorter times yield higher scores. The total raw score of the Mazes test is calculated as the sum of the seven single scores. The raw scores are transformed to T-scores with a mean of 50 (SD = 10). Higher T-scores reflect better executive function.

Magnetic Resonance Imaging

Scanning took place on a 3.0 Tesla scanner (Magnetom Trio, Siemens, Germany) in the PLA 306 Hospital, Beijing. Participants received a magnetization-prepared rapidly acquired gradient echo T1-weighted scan [repetition time (TR) = 2300 ms, echo time (TE) = 3.01 ms, inversion time (TI) = 900 ms, matrix = 512 × 256, field of view (FOV) = 220 mm × 220 mm, number of excitations (NEX) = 1, thickness/gap = 1/0.5 mm, 176 slices] and a 7-min resting-state functional magnetic resonance imaging (fMRI) scan (210 time points, TR = 2000 ms, TE = 30 ms, matrix = 64 × 64, FOV = 210 mm × 210 mm, NEX = 1, 4 mm slice thickness, 30 axial slices, no gap). For the resting-state scan, participants were instructed to close their eyes and remain awake. No participant fell sleep, which was confirmed by self-reports on feelings in the scanner.

Data Preprocessing

For each participant, image preprocessing was carried out

using the Connectome Computation System (CCS), which combines AFNI[47], FSL[48] and Freesurfer[49]. The preprocessing comprised both anatomical and functional steps. Specifically, the anatomical steps were implemented in Freesurfer and FSL: (1) removal of image noise using a spatially adaptive non-local means filter[50,51], (2) removal of non-brain tissue using a hybrid watershed/surface deformation procedure[52], (3) automated segmentation of the white matter and deep gray matter volumetric structures (hippocampus, amygdala, caudate, putamen, and ventricles)[53,54], and (4) a two-step registration of the high-resolution anatomical image to a common stereotaxic space (the Montreal Neurological Institute 152-brain template, MNI152)[55]. First, a 12-degrees-of-freedom linear affine transformation from individual brain images to the template was computed using FLIRT[56,57]. Subsequently, the registration was refined using FNIRT nonlinear registration[55].

The functional preprocessing used here is similar to the '1000 Functional Connectomes Project' scripts (http://www.nitrc.org/projects/fcon_1000)[27] implemented in AFNI and FSL: (1) discarding the first five EPI volumes from each scan to allow for signal equilibration, (2) slice timing correction, (3) 3D motion correction, (4) co-registration between individual functional and anatomical images using a 6-degrees-of-freedom linear affine transformation, (5) 4D mean-based intensity normalization, (6) removal of nine nuisance covariates (signals from white matter, cerebrospinal fluid, the full brain, and six motion parameters), (7) band-pass temporal filtering (0.01–0.1 Hz), (8) removal of linear and quadratic trends, and (9) spatial smoothing (6 mm FWHM Gaussian kernel). The resultant 4D residual time series were used for subsequent participant-level analyses. Fig. 1 illustrates these preprocessing steps and their relationship in the CCS. The inclusion criteria were a maximum absolute head motion displacement of <3 mm and rotation <3° in x/y/z; none were excluded.

Participant-level RSFC Analyses

We examined the RSFC associated with a seed region (a sphere of 8 mm radius) in the vMPFC (x = 0, y = 38, z = −18 in the MNI152 standard space) derived from a previous meta-analysis of cognitive emotion regulation[58]. The seed region was further masked with a group-level mask including all voxels showing non-zero temporal variances to produce the final seed region of interest. For each participant, we first transferred individual residual 4D data to the MNI152 2-mm space and extracted the mean time series by averaging across all voxels in the seed region of interest. Using this mean time series, we performed a whole-brain seed correlation analysis for each participant using the AFNI program 3dfim+, carried out in each individual's native space. This analysis produced participant-level correlation maps of all voxels that were positively or negatively correlated with the time series of the seed. Finally, these correlation maps were converted to z-value maps using Fisher's r-to-z transformation to improve the normality of the data.

Group-level RSFC Analyses

Group-level analyses were carried out using the FMRIB Local Analysis of Mixed Effects. First, all participant-level z-value maps were transformed to standard MNI152 3-mm space by applying the previously-computed transformation. We then performed a standard mixed-effect analysis on all individual maps. Cluster-based statistical corrections for multiple comparisons were performed using Gaussian random field theory (Z >2.3; P <0.05, corrected). This group-level analysis produced thresholded Z-statistic maps showing brain regions with significantly detectable RSFC with the vMPFC seed region for healthy controls and patients, as well as differences in the RSFC of the vMPFC (i.e., group difference maps). This procedure was also performed for a split-half analysis by dividing the patients into two groups (14 *versus* 13) to validate whether the unequal sample sizes significantly changed the findings (data not shown).

Head Motion Assessment

In considering the potential sensitivity of the RSFC to head motion[59,60], both absolute and relative movement measures were computed to give the degree of head motion in the scanner. The absolute movement was quantified by the root mean squares of individual movement curves produced by the motion correction procedure, while the relative movement was the root mean squares of temporal derivatives of the movement curves. The overall head displacement was the mean of the displacements across the x/y/z-axis, while the overall head rotation was the mean of the rotation across the roll/pitch/yaw directions. Two-sample *t*-tests were performed on each of four summary metrics of

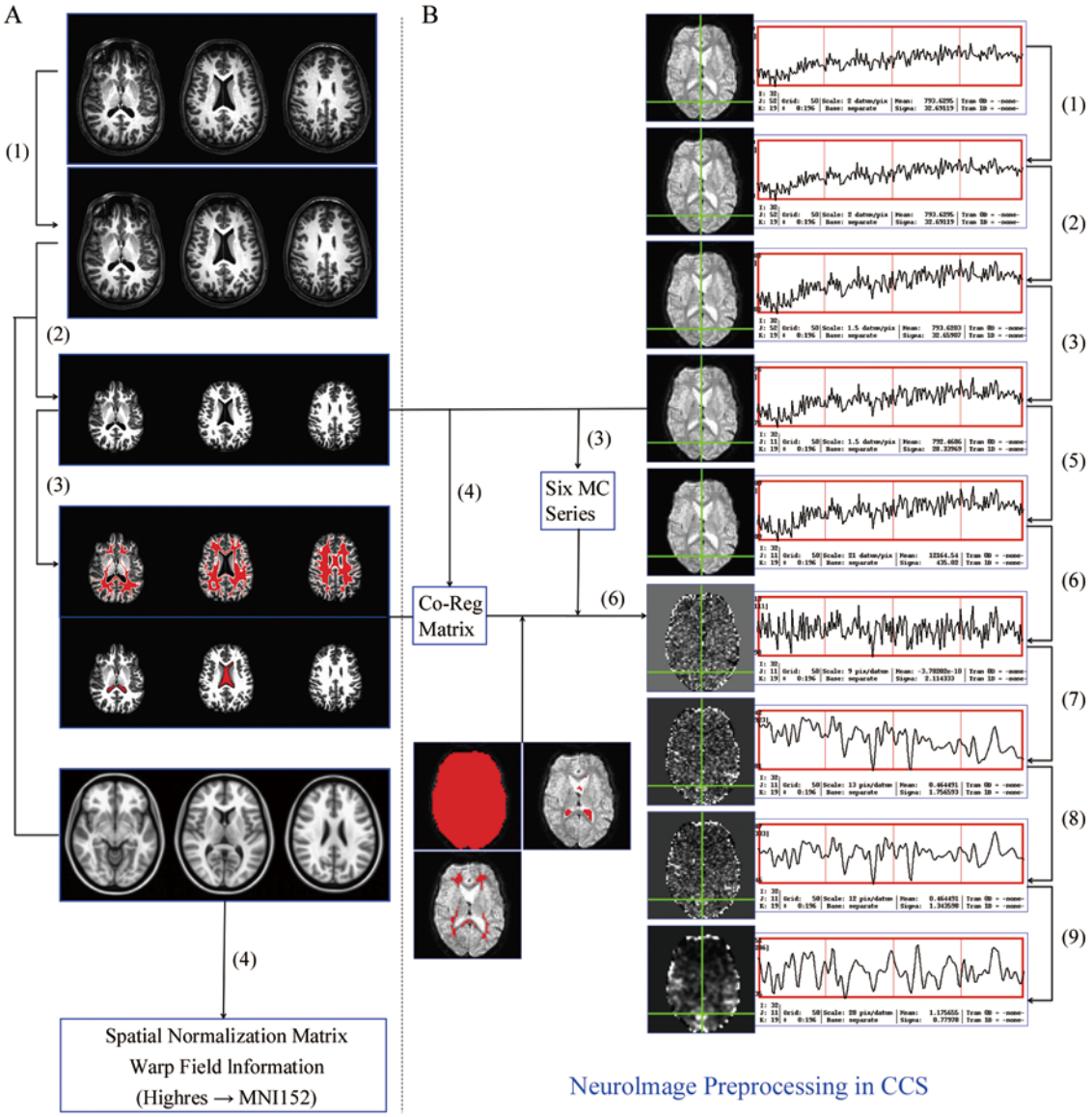

Fig. 1. Preprocessing steps in our resting-state fMRI pipeline for both anatomical and functional MRI data. These steps were implemented as a set of shell scripts calling AFNI, FSL and Freesurfer and integrated into the connectome computation system (CCS) at the Laboratory of Functional Connectome and Development (http://lfcd.psych.ac.cn).

head motion (i.e., absolute displacement, absolute rotation, relative displacement, and relative rotation) between patients and controls. Metrics exhibiting significant patient-control differences were included as covariates of no interest to adjust for head motion[61,62]. To determine whether the head motion was associated with the behavior measures, we conducted movement metrics-behavior correlational analyses. Finally, beyond controlling for head motion as covariates in the whole sample (27 patients *versus* 15 controls), we also performed equivalent group-level analyses based on subjects by excluding the data of those contaminated by movement (i.e., absolute translation >0.1 mm, relative translation >0.15 mm, and both absolute and relative rotation >0.1°) to test the reproducibility of the findings in samples with more strictly-controlled head movements.

Correlation with Neurocognitive Assessment/Psychopathology

To determine whether the vMPFC RSFC was correlated with neurocognitive function and symptom severity in the patient sample, we conducted partial correlation analysis by controlling for the effects of medication dosage, age and head motion, because previous studies on schizophrenia have demonstrated effects of dosage[63], age[64] and motion[59,60] on functional connectivity. Across participants in the patient group, the RSFC in each region in which patients and controls differed was averaged across voxels in the region to correlate with PANSS symptoms and scores on emotion management and executive function. Correlations between connectivity and neurocognitive scores (emotion regulation and executive function) were also calculated for healthy controls, controlling for the effect of age and head motion.

RESULTS

Behavioral Data

Table 1 shows the demographic and clinical information for patients with schizophrenia and healthy controls. Measurements of emotion management and executive function were compared using two-sample *t*-tests. Compared with controls, executive function was significantly lower in schizophrenic patients (t = 3.26, df = 40, P = 0.002), and emotion management showed a trend toward lower values in patients (t = 1.71, df = 40, P = 0.096).

vMPFC RSFC in Healthy Controls

Consistent with previous studies on the default network[23,65-67], healthy controls were found to have positive vMPFC RSFC with the MPFC, posterior cingulate cortex, middle temporal lobe (MTL), right hippocampus, parahippocampal cortex (PHC) and amygdala, along with negative vMPFC RSFC mainly within the bilateral middle frontal gyrus, insula and supramarginal gyrus (Fig. 2).

vMPFC RSFC in Patients with Schizophrenia

Patients with schizophrenia showed similar but markedly less spatially extensive patterns of the vMPFC-seeded functional network (Fig. 2). Specifically, the default network and its anti-correlated task-positive network had reduced spatial extents, including posterior cingulate, medial frontal, dorsolateral prefrontal, dorsal anterior cingulate and insular cortices. In contrast, patients demonstrated greater negative RSFC extension to the brainstem region (not shown on the surface in Fig. 2).

Alteration of vMPFC RSFC in Schizophrenia

Compared with healthy controls, patients exhibited hypoconnectivity of the vMPFC with default network regions including the anterior MPFC, right MTL, hippocampus, PHC and amygdala. Task-positive network areas including bilateral DLPFC and pre-supplementary motor area (SMA) showed significantly lower connectivity strength in schizophrenic patients (Fig. 2). The coordinates in MNI152 standard space, cluster size and Brodmann areas of these regions are summarized in Table 2.

Relationship between vMPFC RSFC and Behavior

There were significant correlations between vMPFC connectivity and neurocognitive assessments in schizophrenic patients (Fig. 3). As expected, patients with poorer emotion management (i.e., lower managing emotion test scores) showed decreased vMPFC–right MTL/PHC/amygdala functional connectivity (r = 0.39, df = 26, P < 0.04, Fig. 3B). In addition, schizophrenic patients with more severe PANSS positive symptoms showed increased vMPFC–right DLPFC connectivity (r = 0.51, df = 26, P < 0.007, Fig. 3A). Of note, medication dosage, age and head motion (no significant correlation without regressing medication dosage out) had been taken into account in the above correlations. We performed correlation analyses to rule out the possibility of different behavior measurements correlating with each other. No significant correlation between executive function and managing emotion scores was found (r = 0.22, P = 0.26). No significant correlation was found between RSFC and neurocognitive score in healthy controls.

Effects of Head Motion

The four metrics of absolute and relative head motion were calculated for all individuals (Table 3). Both absolute and relative head motion differed significantly between patients and controls with inverse directions of comparisons: healthy controls demonstrated higher absolute motion while patients exhibited higher relative motion. Further visual inspection of individual movement curves indicated that

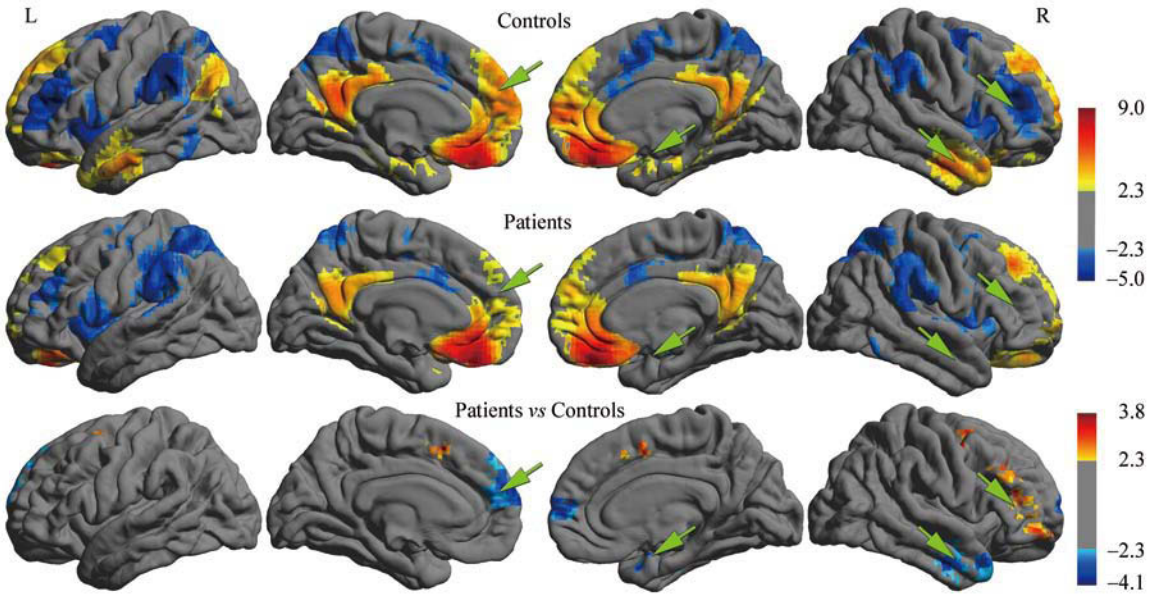

Fig. 2. Ventral medial prefrontal cortex (vMPFC) functional connectivity in schizophrenic patients and control group. One-sample tests produced the spatial patterns of brain regions functionally connecting with the vMPFC (MNI coordinates: x = 0, y = 38, z = –18) for both healthy controls (upper panels) and schizophrenic patients (middle panels). Warm colors represent positive while cool colors indicate negative functional connectivity. A two-sample *t*-test assessed the differences in vMPFC functional connectivity (patients *versus* controls) as depicted in the lower panels. Warm colors indicate higher functional connectivity while cool colors denote lower functional connectivity in patients. Green arrows indicate the regions with significant group difference. Cluster-based statistical correction for multiple comparisons was performed by applying Gaussian random field theory (Z >2.3; cluster significance: *P* <0.05, corrected). The final statistical volumes were interpolated onto the fsaverage surfaces in Freesurfer and are visualized as lateral and medial views for both left (L) and right (R) hemispheres with the color bar indicating the Z-statistics.

Table 2. Significant vMPFC RSFC differences between patient and control groups

Regions	X	Y	Z	BA	Cluster size	Z-statistic
Schizophrenia *vs* control (lower strength of positive connectivity)						
Medial frontal cortex	−6	63	21	9/10	417	−4.10
Temporal lobe, parahippocampal cortex, hippocampus, amygdala	51	−6	−30	20/21/38	265	−4.22
Schizophrenia *vs* control (lower strength of negative connectivity)						
Lateral prefrontal cortex	24	48	−6	9/10/11/46	453	3.72
Supplementary motor area (right)	36	0	57	6	218	3.91
Supplementary motor area (left)	−18	6	57	6	94	3.54

Coordinates (X, Y, Z) are based on the MNI brain; BA, Brodmann area; RSFC, resting-state functional connectivity; vMPFC, ventral prefrontal cortex. Regions showing lower strength of negative connectivity are in warm colors in Fig. 2, and regions showing lower strength of positive connectivity are in cool colors.

the movement style was more like a stable trend in healthy controls while a frame-to-frame oscillating pattern occurred in the patients. Such a systematic difference in movement style between the two groups may have clouded the patient-control differences in functional connectivity as well as the connectivity-behavior relationship we detected. Therefore, we included all four head motion measures in the final group-level comparisons. The findings were most robust

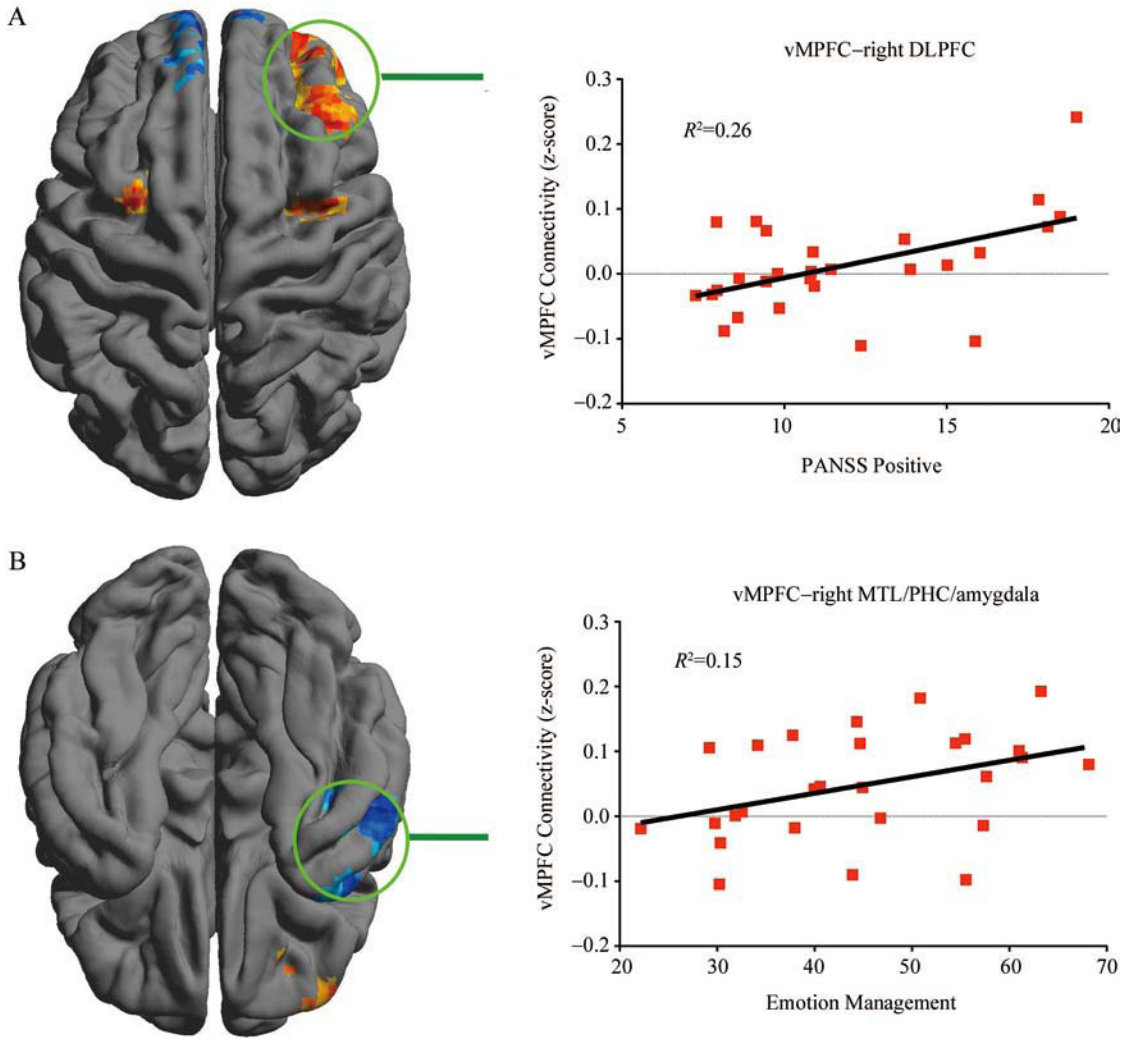

Fig. 3. Correlation between vMPFC connectivity and behavioral performance in patients. A: Schizophrenic patients with more severe PANSS positive symptoms showed increased vMPFC–right DLPFC connectivity (r = 0.51, df = 26, P <0.007)(dorsal views). B: Patients with poorer emotion management showed decreased vMPFC-right MTL/PHC/amygdala functional connectivity (r = 0.39, df = 26, P <0.04)(ventral views). DLPFC, dorsal lateral prefrontal cortex; MTL, middle temporal lobe; PHC, parahippocampal cortex; vMPFC, ventral medial prefrontal cortex.

Table 3. Summary of head motion in the patient and control groups

	SCZ (n = 27)		CON (n = 15)		SCZ *vs* CON	
	Mean	Std	Mean	Std	*T*-value	*P*-value
A-displacement (mm)	0.07	0.03	0.10	0.05	–2.69	0.0103
A-rotation (degrees)	0.05	0.02	0.10	0.07	–3.73	0.0006
R-displacement (mm)	0.14	0.05	0.09	0.03	3.62	0.0008
R-rotation (degrees)	0.07	0.03	0.04	0.01	3.59	0.0009

A, absolute; CON, control; R: relative; SCZ, schizophrenia.

and reproducible across group-level comparisons (patients *versus* controls) with and without modeling head motion as covariates of no interest. Of note, one additional region, the PCC, showed significant hypo-connectivity with the vMPFC when the model did not include the head motion measures as covariates (Fig. S1), indicating a movement contribution to the group differences in functional connectivity.

To further mitigate this recurring concern with head motion, we performed correlational analyses between the four head motion metrics and MSCEIT, NAB, and PANSS scores; no significant correlation (P >0.2) was found (Table 4). We also performed equivalent group-level analyses based on only 22 subjects (13 patients *versus* 9 controls) by excluding the data contaminated by movement. Only the right MTL showed hypo-connectivity with the vMPFC (uncorrected voxel-level P <0.01; cluster-level P < 0.05, corrected), which extended to the PHC, insula and amygdala by relaxing the voxel-level P-value to 0.05, implying potential consistency with the findings based on the full sample. However, no connectivity-behavior correlation was found in this smaller sample. Of note, the default network did not show significant group differences in vMPFC connectivity, suggesting that head motion had significant influence on the default network functional connectivity as noted in the work from Buckner's group[59].

DISCUSSION

In this study, we compared the functional organization of vMPFC connectivity networks in patients with schizophrenia with that in age- and sex-matched controls using resting fMRI. A vMPFC seed derived from meta-analysis was selected to construct vMPFC connectivity networks because it has been implicated in cognitive emotion regulation. Overall, the pattern of altered connectivity in schizophrenia showed reduced functional integration between the vMPFC and the default network (anterior MPFC, right MTL/PHC/amygdala), and reduced functional segregation between the vMPFC and the task-positive network (DLPFC and preSMA). The data showed reduced vMPFC connectivity, which is consistent with the dysconnection hypothesis of schizophrenia[68]. Interestingly, in schizophrenic patients, vMPFC–right MTL/PHC/amygdala functional connectivity showed a significant relationship with emotion regulation – poorer managing emotions scores correlated with lower vMPFC-right MTL/PHC/amygdala connectivity (i.e., reduced functional integration). We believe such a relation might suggest the underlying role of vMPFC–MTL/PHC/amygdala connectivity in abnormal emotion regulation in schizophrenia.

Alteration of vMPFC RSFC in Schizophrenia

We detected reduced functional integration between the vMPFC and the default network, which is consistent with previous findings of reduced connectivity in the default network in schizophrenia[33,68-70]. The present study supports the idea that schizophrenia may arise from disrupted functional integration of widespread brain areas[30].

To situate the present study within the context of previous research on the intrinsic networks in schizophrenia,

Table 4. Relationship between head motion and behavior in the patient group (n = 27)

	A-Disp (mm)		A-Rot (degree)		R-Disp (mm)		R-Rot (degree)	
	R-value	*P*-value	*R*-value	*P*-value	*R*-value	*P*-value	*R*-value	*P*-value
PANSS total	0.02	0.94	0.01	0.98	−0.07	0.74	−0.15	0.45
PANSS positive	0.10	0.61	0.09	0.64	0.08	0.68	−0.09	0.66
PANSS negative	0.00	1.00	0.03	0.89	−0.11	0.58	−0.07	0.71
General psychopathology symptoms	−0.04	0.85	−0.14	0.50	−0.06	0.78	−0.15	0.46
Executive function	0.10	0.63	−0.09	0.64	0.12	0.56	−0.24	0.22
MSCEIT-Managing emotion branch	0.13	0.52	0.09	0.65	0.25	0.20	−0.08	0.69

A, absolute; Disp, displacement; R: relative; Rot, rotation.

we have confirmed the concept of reduced network connectivity in patients with chronic schizophrenia. So far, it is not consistent among previous studies whether the connectivity of the intrinsic networks is increased or decreased in schizophrenia. Two recent studies support our findings by providing evidence of structural abnormalities associated with dysfunctional regions in the default network. Camchong *et al.*[68] identified abnormal functional connectivity in the anterior node of the default network, plus reduced fractional anisotropy on diffusion tensor imaging in the white matter subjacent to this area. Pomarol-Clotet *et al.*[71] found that grey matter volume reduction in a group of chronic schizophrenic patients predominated in the medial frontal cortex, where they overlapped substantially with the area where failure of deactivation was found during performance of the n-back task. Meanwhile, other studies have found either hyper-connectivity[35] or a mixed pattern of increased and decreased connections within the default network[72,73]. Such inconsistencies might be due to many factors such as methods used, medication, patient cohort, state of the patient's symptoms at the time of the scan, and strength of magnetic field. All these functional and structural alterations support the neural dysconnection hypothesis of schizophrenia[74]. The functions of the default network include monitoring internal thoughts and rendering cognitive flexibility to self-relevant mental simulations[75], and our findings may reflect deficits in the ability of the default network in schizophrenic patients to allocate resources properly between internal thoughts and external stimuli.

Aside from the anterior MPFC regions, the right MTL also showed significant hypo-connectivity with the vMPFC. Dysfunctional connectivity between fronto-temporal regions is a central feature of schizophrenia[31,76,77]. This idea is supported by reduced asymmetry of white matter integrity in the uncinate fasciculus[78], which connects frontal and temporal regions, in patients with schizophrenia. Also, reduced fractional anisotropy in frontal and temporal regions was found in a diffusion tensor imaging meta-analysis[79]. In addition, studies examining functional connections during task performance also have observed reduced connectivity in patients with schizophrenia[80,81]. Reduced fronto-temporal functional connectivity during an n-back working memory task was found in medication-naive patients with schizophrenia using positron emission tomography (PET)[80]. A possible explanation for the major patterns of aberrant connectivity reported in the above literature, together with the present study, is that they may together reflect the dysfunctional integration of functional brain networks in schizophrenia[30,33,34,77,82].

We detected reduced functional segregation between the vMPFC and the task-positive network. In the schizophrenia group, lower connectivity strength between the vMPFC and the task-positive network was found mainly in bilateral DLPFC and preSMA. The RSFC for these regions correlated negatively with the default network RSFC, and these regions are activated during attention-demanding tasks. The two networks have an intrinsic competitive relationship[83] described as "anti-correlated"[66]: engagement of one network suppresses activity in the other[84]. Several studies have also highlighted the role of functional segregation as measured by anti-correlations between distinct brain networks[66,67,83,85-87]. The strength of negative connectivity has been suggested to reflect the degree of segregation between different functional units[87,88]. We thus suggest that the reduced vMPFC–right DLPFC connectivity may reflect poor functional segregation between the two regions. Numerous studies in schizophrenia have identified abnormalities in the task-positive network regions. Dysfunction of the DLPFC was found in schizophrenia using resting fMRI and PET[34,89-93]. Consistent with our findings, Whitfield-Gabrieli *et al.*[82] demonstrated that schizophrenic patients had reduced anti-correlations during both rest and a working memory task between the default network (MPFC) and the DLPFC, a region where patients also showed hyper-activation during task performance. Anatomically, aside from its connections with the limbic system[7], the vMPFC is connected to the DLPFC[94] which is important for working memory performance and the temporal organization of behavior[90,95]. The DLPFC exerts executive control on the vMPFC, through which the limbic system is affected in turn[96], which might explain the vMPFC–MTL/PHC/amygdala dysconnectivity observed in the present study.

Given the relevance of the intrinsic network functions to schizophrenia, there has been increasing interest in the role that altered connectivity of these networks may play in the illness[32,97]. Cognitive deficits, such as impaired working memory, attention allocation, and central executive function, are not only core symptoms of schizophrenia[98] but also functions ascribed to the task-positive network[99,100].

The default network is reliably engaged during spontaneous internal mentation[65], including self-referential processes[101,102]. Imbalance between functional integration and segregation, two major organizational principles of the human brain[103], might induce dysfunction. Our findings of reduced integration and segregation in the two networks in schizophrenic patients may contribute to further understanding of the pathophysiology of schizophrenia.

Relationship between RSFC and Behavior

Consistent with increasing evidence that the ventral prefrontal regions involved in emotion processing are dysfunctional in schizophrenia[16-18], patients with poorer managing emotions scores had lower vMPFC–right MTL/PHC/amygdala connectivity. It has also been reported that these patients show reduced activation or connectivity in the amygdala and parahippocampus during emotion processing[104-106]. The nature of this association may be related to the involvement of the amygdala and parahippocampus in managing emotion. Our results are also consistent with findings that reduced functional connectivity between amygdala and ventral prefrontal cortex has been associated with aggression[36] (a product of failure of emotion regulation), supporting the idea that vMPFC–MTL/PHC/amygdala functional dysconnection is associated with emotion regulation. Although the causes and mechanisms of emotional impairment in schizophrenia are still unclear, our results suggest that it is associated with reduced integration between the vMPFC and the MTL/PHC/amygdala.

In addition, we found significantly positive correlations between vMPFC–right DLPFC connectivity and positive PANSS symptoms, which suggest that schizophrenic patients with more severe positive symptoms have reduced vMPFC–right DLPFC negative connectivity strength. Although no significant functional connectivity between the vMPFC and the DLPFC was found in the patient group (Fig. 2), the strength of functional connectivity across patient samples differed, which might have some relationship with psychopathology. The significant correlation might imply that decreases in the strength of vMPFC–right DLPFC connectivity (parts of the default network and the task-positive network) or poor functional segregation between the two regions underlie symptom severity.

Influence of Head Motion and Interpretation of Findings

The interpretation of the reduced default network connectivity and the brain-behavior correlations should be cautious. Although we considered parameters of head motion as covariates in our analyses, the recurring issue of head motion has not been fully addressed due to the complexity of the motion-connectivity nonlinear interaction, which was the case in our analyses of head motion patterns. A promising direction is to collect a large sample of patients and matched controls and ensure careful movement quality control. Although the split-half analyses did not alter the main findings, a larger sample size, particularly for controls, could potentially better delineate the population and increase the statistical power. A large-sample study is thus warranted to confirm the clinical feasibility of these findings. In the current study, controls and patients had similar rating values as indicated by inter-group comparisons of emotion regulation scores, but an intra-group brain-behavior association was observed. Although the patterns of intra-group brain-behavior relationship were not necessarily the same for patients and healthy controls, the interpretation of such a relationship should not be considered conclusive, but rather an exploratory attempt that needs to be confirmed by replications from different labs. Another factor leading to correlations of no significance could be the smaller sample size of healthy controls than the patient group, which is an avoidable factor due to the sample size of controls in the current study.

Other Limitations and Directions

The current study has several other limitations. The seed region lay in a region prone to magnetic susceptibility artifacts, which might reduce the likelihood of detecting group differences. However, we limited the seed voxels of interests within the group-level mask, which was generated according to non-zero temporal variability of the BOLD signal. In addition, the average signal intensity of the seed region was computed for each participant and used as a covariate during group analyses to mitigate this concern. Second, all the patients had chronic schizophrenia and were on antipsychotic medication. However, all the participants were inpatients and had been on a stable dose of medication for at least 2 months prior to entering the study. Our *post-hoc* analyses indicated that the RSFC between the vMPFC and regions showing significant differences between patients and controls was not correlated with

medication dosages in the patients. Third, the intelligence quotient (IQ) was not tested in this study. Though IQ is associated with the functional and structural organization of the brain in normal controls[107,108], the relevance of IQ to resting-state functional networks in schizophrenia needs further investigation. In addition, seed-based functional connectivity approaches have been demonstrated to be sensitive to the seed-selection strategy[109], which could also be reflected in the inconsistent patterns of altered default network connectivity of patients in previous studies. It is necessary and interesting to systematically investigate the default network and its functional fractionation in schizophrenia in future.

CONCLUSION

This study demonstrated both reduced functional integration between the vMPFC and areas of the default network, and reduced segregation between the vMPFC and areas of the task-positive network in chronic schizophrenic patients. Given the central and regulatory roles of the MPFC and DLPFC, the regional hypo-connectivity identified here imply that communication and coordination throughout the two intrinsic connectivity networks are disrupted in schizophrenia. The emotional correlates of vMPFC–MTL/PHC/amygdala connectivity further suggest that this hypo-connectivity underlies the neuropathology of abnormal social cognition in schizophrenia.

SUPPLEMENTAL DATA: Supplemental data include one figure and can be found online at http://www.neurosci.cn/epData.asp?id=58.

ACKNOWLEDGMENTS

We are grateful to all the volunteers and patients for their participation in the study. We thank Yu-Feng Zang for assistance in providing resting-state fMRI scanning parameters, and Matthew J. Hoptman and Raymond C.K. Chan for helpful editorial advice and comments. This work was supported by grants from the Beijing Municipal Science & Technology Commission (D0906001040191, D101107047810005, D101100050010051), the Beijing Natural Science Foundation (7102086) and the Fund for Capital Medical Development and Research (2007-3059), the National Natural Science Foundation of China (81171409) and the Startup Foundation for Distinguished Research Professors of the Institute for Psychology (Y0CX492S03) and Fund for Outstanding Talents in Beijing (2012D003034000003).

Received date: 2012-04-15; Accepted date: 2012-07-26

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