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Functional asymmetry of thalamocortical networks in subjects at ultra-high risk for psychosis and first-episode schizophrenia

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Abstract
Disrupted functional asymmetry has been implicated in schizophrenia. However, it remains unknown whether disrupted functional asymmetry originates from intra-hemispheric and/or inter-hemispheric functional connectivity (FC) in the patients, and whether it starts at very early stage of psychosis. Seventy-six patients with first-episode, drug-naive schizophrenia, 74 subjects at ultra-high risk for psychosis (UHR), and 71 healthy controls underwent resting-state functional magnetic resonance imaging. The 'Parameter of asymmetry' (PAS) metric was calculated and support vector machine (SVM) classification analysis was applied to analyze the data. Compared with healthy controls, patients exhibited decreased PAS in the left thalamus/pallidum, right hippocampus/parahippocampus, right inferior frontal gyrus/insula, right thalamus, and left inferior parietal lobule, and increased PAS in the left calcarine, right superior occipital gyrus/middle occipital gyrus, and right precentral gyrus/postcentral gyrus. By contrast, UHR subjects showed decreased PAS in the left thalamus relative to healthy

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controls. A negative correlation was observed between decreased PAS in the right hippocampus/parahippocampus and Brief Visuospatial Memory Test-Revised (BVMT-R) scores in the patients ($r = -0.364$, $p = 0.002$). Moreover, the PAS values in the left thalamus could discriminate the patients/UHR subjects from the controls with acceptable sensitivities (68.42%/81.08%). First-episode patients and UHR subjects shared decreased PAS in the left thalamus. This observed pattern of functional asymmetry highlights the involvement of the thalamus in the pathophysiology of psychosis and may also be applied as a very early marker for psychosis.

1. Introduction

The pathophysiology of schizophrenia is hypothesized to include abnormal functional connectivity (FC) between the thalamus and cortex, which topographically organizes as the thalamocortical networks (Swerdlow, 2010; Woodward et al., 2012). Parallel circuits link specific thalamic nuclei to distinct regions in the cerebral cortex (Alexander et al., 1986; Haber, 2003). For example, the prefrontal cortex links preferentially to the anterior and dorsomedial thalamus (Alexander et al., 1986). Thalamocortical dysfunction has been reported by several structural and functional imaging studies (Glahn et al., 2008; Minzenberg et al., 2009; Shenton et al., 2001; Welsh et al., 2010), which may account for clinical and cognitive symptoms observed in schizophrenia (Andreasen et al., 1998).

Healthy human subjects are known to demonstrate several significant functional asymmetries. For example, the right visual hemisphere is more specialized for low spatial frequencies, whereas the left hemisphere prefers to treat high spatial frequencies (Sergent and Bindra, 1981). However, the pattern of normal asymmetry in healthy subjects is disrupted in schizophrenia (Ke et al., 2010). Several investigations indicate that schizophrenia may be associated with abnormal development of the left hemispheric dominance for language (Artiges et al., 2000; Dollfus et al., 2005; Sommer et al., 2001b). Some visual task-related functional magnetic resonance imaging (fMRI) studies have observed the right hemispheric asymmetry in patients with schizophrenia to process sensory information (Gur and Chin, 1999; Heckers et al., 2002). Furthermore, right-sided pathophysiology has been revealed in schizophrenia by diffusion tensor imaging (DTI) studies (Federspiel et al., 2006; Guo et al., 2012; Matsumoto et al., 2001). In addition, decreased interhemispheric FC in patients with schizophrenia and their unaffected siblings have been observed by our group and others (Guo et al., 2014a, 2018, 2014b; Hoptman et al., 2012; Liu et al., 2018). As a result, the lack of normal asymmetry may be related to damage to intrinsic neural circuits (Malaspina et al., 2004; Sears et al., 2000). However, the importance of damage to the functional asymmetry of specific networks (for example, the thalamocortical networks), remains unclear. Moreover, the two hemispheres have functional interaction via the corpus callosum (Lamantia and Rakic, 1990), and thus a single brain region has FCs associated with both intra-hemispheric and inter-hemispheric connections. It is also unknown whether disrupted asymmetry of the thalamocortical networks in schizophrenia results from intra-hemispheric or inter-hemispheric FCs.

Furthermore, schizophrenia is considered as a neurodevelopmental disorder (Fair et al., 2010), and thus the question is raised whether disrupted functional asymmetry of the thalamocortical networks starts at very early stage of psychosis. To answer this question, it is critical to recruit a group of subjects at ultra-high risk for psychosis (UHR). Compared with patients with schizophrenia, UHR subjects exhibit similar but more attenuated abnormalities, including clinical symptoms (Yung et al., 1996), cognitive impairments (Fusar-Poli et al., 2012; Hur et al., 2012; Kim et al., 2011), structural (Han et al., 2012; Jung et al., 2012, 2011; Smieskova et al., 2010) and functional changes (Choi et al., 2012; Fusar-Poli et al., 2010; Li et al., 2018; Wang et al., 2016a, 2016b). Moreover, UHR subjects are related to an increased risk of transferring to frank psychosis within two years (Cannon et al., 2008; Yung et al., 2008). Therefore, it is important to identify early biomarkers that can be applied to discriminate UHR subjects from healthy controls (Peters et al., 2009).

Previous studies have employed independent component analysis (ICA) and resting-state FC strength to assess functional asymmetry (Guo et al., 2018, 2014b; Sommer et al., 2001a). However, the human brain exhibits both inter-hemispheric and intra-hemispheric interactions when reacting to a stimulus. Hence, both inter-hemispheric and intra-hemispheric FC can be used to assess brain functional asymmetry. Previously, Mueller et al. proposed an 'autonomy index' (AI) to assess brain functional asymmetry by counting the numbers of abnormal voxels in each hemisphere (Mueller et al., 2015). While the AI can assess functional asymmetry, it neglects the actual observed magnitude of the correlation coefficients of the abnormal voxels, which is an important characteristic of functional asymmetry. By contrast, we proposed another analysis metric, the 'parameter of asymmetry' (PAS), to assess correlation coefficients of abnormal voxels in a previous study (Zhu et al., 2018). PAS is a voxel-wise method which is not affected by pre-selected regions of interest (ROIs) or thresholding. In addition, the potential confounding effects of ROI-selection bias and structural asymmetry can be minimized.

Given this background, a resting-state fMRI study was conducted in drug-naive, first-episode schizophrenia patients (FEPs), UHR subjects and healthy controls. FEPs and UHR subjects were recruited in order to limit confounding effects caused by long illness duration and medication use, and to document a progressive aspect in psychosis onset. The images were analyzed by using a voxel-wise whole-brain FC method. FC was further divided into intra-hemispheric and inter-hemispheric FCs to determine the magnitude of functional asymmetry observed using the PAS method. Based on the abovementioned studies, functional asymmetry was hypothesized to be altered in the thalamocortical networks in both FEPs and UHR subjects, which could be used to discriminate FEPs/UHR subjects from controls.

2. Experimental procedures

2.1. Participants

The sample included 76 FEPs, 74 UHR subjects and 71 healthy controls from the Second Xiangya Hospital, Central South University, China. All participants were right-handed and aged from 13 to 43 years old with more than 6 years of formal education. All patients were diagnosed with the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders-IV (SCID) criteria, patient edition (First et al., 1997). The positive and negative syndrome scale (PANSS) was used to assess symptom severity in the patients. UHR subjects were confirmed with the structured interview for prodromal syndromes (SIPS) and scale of prodromal syndromes (SOPS) including: (1) brief intermittent psychotic syndrome, (2) attenuated positive symptom syndrome, and (3) genetic risk and deterioration syndrome (Miller et al., 2003). The SIPS (19 items) comprises four symptom clusters: positive symptoms, negative symptoms, disorganized symptoms, and general symptoms. The SOPS was applied to decide the presence of a psychotic syndrome that was either (1) disorganizing or dangerous or (2) occurring at least an hour a day on average four days a week for at least one month. The SIPS/SOPS has showed acceptable reliability and validity (Miller et al., 2003, 2002). Healthy controls were screened by using the SCID, non-patient edition (First et al., 1997). All participants shared the following exclusion criteria: severe medical disorders, neurological disorders, substance abuse, mental retardation, or any contraindications for MRI. In addition, potential controls were excluded if they had a first-degree relative with a psychiatric disorder. Cognitive function was examined in all participants by using trail making test, part A (TMT-A); brief assessment of cognition in schizophrenia (BACS), symbol coding; Hopkins verbal learning test-revised (HVLT-R); brief visuospatial memory test-revised (BVMT-R); Stroop-word, color, color and word; and continuous performance test (CPT).

The study was approved by the local ethics committees of the Second Xiangya Hospital of Central South University. Written informed consent was signed by all participants.

2.2. Scan acquisition and preprocessing

MRI scans were acquired on a Siemens 3T scanner (General Electric, Fairfield, Connecticut, USA). The participants were directed to keep motionless and awake with their eyes closed. Soft earplugs and foam pads were applied to reduce scanner noise and head motion. Resting-state functional magnetic resonance imaging (fMRI) scans were obtained with a gradient echo-planar imaging (EPI) sequence. The following parameters were used during the scan: repetition time/echo time = 2000 ms/30 ms, 33 slices, 64×64 matrix, 90° flip angle, 22 cm field of view, 4 mm slice thickness, no slice gap, and 240 volumes. Each scan lasted for 480 s for a participant.

The DPABI software (Yan et al., 2016) was applied to preprocess the scans. After slice timing and head motion correction, the scans were discarded if the participants had over 2 mm maximal translation and 2° maximal rotation during the scan. Several covariates were removed, including the Friston-24 head motion parameters acquired via rigid body correction (de Kwaasteniet et al., 2013), signal from a ventricular region of interest, and signal from a region centered in the white matter. In addition, framewise displacement (FD) was computed as described in a previous study (Power et al., 2012). The mean FD was used to address the residual effects of head motion as a covariate of no interest in the group analyses. Scrubbing (removing time points with FD > 0.2 mm) was also used as an aggressive head motion control strategy. The global signal was not removed as it is still a controversial practice in the resting-state fMRI analysis (Hahamy et al., 2014). The data were then spatially normalized to the conventional EPI template in the Montreal Neurological Institute (MNI) space and resampled to $3 \times 3 \times 3\,mm^3$ voxels. Finally, the scans were bandpass-filtered (0.01–0.08 Hz) and linearly detrended.

2.3. Calculation of PAS

The calculation of PAS was described in our previous study (Zhu et al., 2018). Briefly, for each participant, correlation coefficients were computed between a given voxel and other voxels from the same hemisphere (intra-hemispheric coefficients) or from the opposite hemisphere (inter-hemispheric coefficients). The mean intra-hemispheric and inter-hemispheric coefficients were defined as the intra-hemispheric and inter-hemispheric FCs of this given voxel. After that, intra-hemispheric and inter-hemispheric FCs were z-transformed as described in a previous study (Buckner et al., 2009). PAS was calculated with the following formula:

$$PAS = FC_{inter} - FC_{intra}$$

Here, FC_{inter} is inter-hemispheric FC, and FC_{intra} refers to intra-hemispheric FC. From the formula, positive PAS values indicate that inter-hemispheric FC is the dominant signal, whereas negative PAS values may result from a dominance of the intra-hemispheric FC. Finally, PAS maps were generated from the resultant PAS values.

2.4. Statistical analyses

A chi-square test and analysis of variance (ANOVA) were used to analyze the demographic and clinical data when necessary.

Analysis of covariance (ANCOVA), followed by post hoc *t* tests, was performed to compare group differences of the PAS maps. The mean FD, age, and years of education were used as covariates of no interest in group comparisons. The significance level was corrected to $p < 0.05$ using the Gaussian random field (GRF) theory (voxel significance: $p < 0.001$, cluster significance: $p < 0.05$) with the REST software (Song et al., 2011).

2.5. Correlation analyses

The PAS values were extracted from abnormal clusters detected by group comparisons. Pearson's correlations were performed between abnormal PAS and clinical or cognitive variables in the patients and UHR subjects after the normality of these variables was confirmed. The significance level was set at $p < 0.05$ (Bonferroni corrected).

2.6. Support vector machine (SVM) analysis

To test the possibilities whether abnormal PAS shared by patients and UHR subjects could be applied to discriminate patients/UHR subjects from healthy controls, SVM was conducted with the LIBSVM software (http://www.csie.ntu.edu.tw/~cjlin/libsvm/). A "leave-one-out" method was used to conduct the SVM.

To validate the SVM results, a five-fold cross-validation method was employed. Each sample (FEPs/controls or UHR subjects/controls) was randomly divided into five subgroups. The first

Table 1 Characteristics of participants.

	First-episode Patients ($n = 76$)	UHR Subjects ($n = 74$)	Controls ($n = 71$)	p value
Sex (male/female)	40/36	43/31	36/35	0.648[a]
Age (years)	23.30 ± 6.00	22.04 ± 5.25	21.37 ± 2.83	0.054[b]
Years of education (years)	11.62 ± 2.70	11.82 ± 2.88	15.00 ± 2.03	<0.001[b]
FD	0.026 ± 0.008	0.029 ± 0.012	0.026 ± 0.009	0.144[b]
Illness duration (months)	10.86 ± 9.54			
PANSS				
Positive scores	19.73 ± 6.77			
Negative scores	20.65 ± 8.59			
General scores	41.04 ± 13.94			
Total scores	84.86 ± 20.69			
SIPS				
positive symptoms		9.51 ± 4.53		
negative symptoms		11.39 ± 6.03		
disorganized symptoms		5.05 ± 2.93		
general symptoms		5.72 ± 3.17		
total scores		32.00 ± 11.08		
TMT-A	52.41 ± 26.07	39.53 ± 17.11	34.11 ± 10.31	<0.001[b]
BACS: Symbol Coding	43.63 ± 14.05	54.39 ± 10.18	61.97 ± 9.32	<0.001[b]
HVLT-R	18.70 ± 6.42	24.23 ± 5.84	26.93 ± 3.97	<0.001[b]
BVMT-R	17.82 ± 9.25	22.95 ± 10.04	28.56 ± 4.89	<0.001[b]
Stroop-Word	77.05 ± 24.97	86.56 ± 27.19	97.68 ± 17.29	<0.001[b]
Stroop-Color	52.11 ± 19.52	56.53 ± 19.21	72.90 ± 13.67	<0.001[b]
Stroop-Color and Word	31.55 ± 13.07	33.24 ± 13.41	43.63 ± 8.43	<0.001[b]
CPT	1.93 ± 0.78	2.40 ± 0.79	2.84 ± 0.56	<0.001[b]

FD = framewise displacement; PANSS = positive and negative syndrome scale; UHR = ultra high-risk; SIPS = structured interview for prodromal syndromes; TMT-A = trail making test, part A; BACS = brief assessment of cognition in schizophrenia; HVLT-R = Hopkins verbal learning test-revised; BVMT-R = brief visuospatial memory test-revised; CPT = continuous performance test.

[a] The p value for sex distribution was obtained by a chi-square test.

[b] The p values were obtained by analyses of variance (ANOVA).

four subgroups were used as training sets, whereas the fifth subgroup was used as a test set. The SVM was conducted, and a global accuracy was obtained.

The SVM results were also validated by a permutation test, which ran 10,000 times for each sample (FEPs/controls or UHR subjects/controls). Then, a global accuracy could be obtained for each sample.

3. Results

3.1. Characteristics of the participants

No significant differences were observed regarding age, sex ratio, and the mean FD across groups (Table 1). However, healthy controls obtained higher education level than FEPs and UHR subjects. As expected, FEPs presented a worse performance in cognitive assessments than healthy controls, whereas the UHR subjects exhibited a cognitive performance midway between FEPs and healthy controls.

3.2. Group differences in PAS

Significant differences in PAS were observed in the frontal, temporal, parietal, and occipital cortices across groups revealed by ANCOVA analysis (Figure S1).

Compared with healthy controls, FEPs showed decreased PAS in the left thalamus/pallidum, right hippocampus/parahippocampus, right inferior frontal gyrus/insula, right thalamus, and left inferior parietal lobule, and increased PAS in the left calcarine, right superior occipital gyrus/middle occipital gyrus, and right precentral gyrus/postcentral gyrus (Fig. 1, Fig. S2, and Table 2). By contrast, UHR subjects exhibited decreased PAS in the left thalamus (Fig. 1 and Table 2).

3.3. Correlation results

For the patient group, the significance level was Bonferroni corrected at $p < 0.05/8 = 0.00625$ (for the eight brain regions with abnormal PAS). A significantly negative correlation was observed between the PAS values in the right hippocampus/parahippocampus and the BVMT-R scores ($r = -0.364$, $p = 0.002$, Fig. 2). There were no other correlations between abnormal PAS and clinical/cognitive variables in the patients.

There were no correlations between abnormal PAS in the left thalamus and clinical/cognitive variables in the UHR subjects at Bonferroni corrected $p < 0.05/1 = 0.05$.

3.4. SVM results

From the results of group differences in PAS, FEPs and UHR subjects shared decreased PAS in the left thalamus. SVM

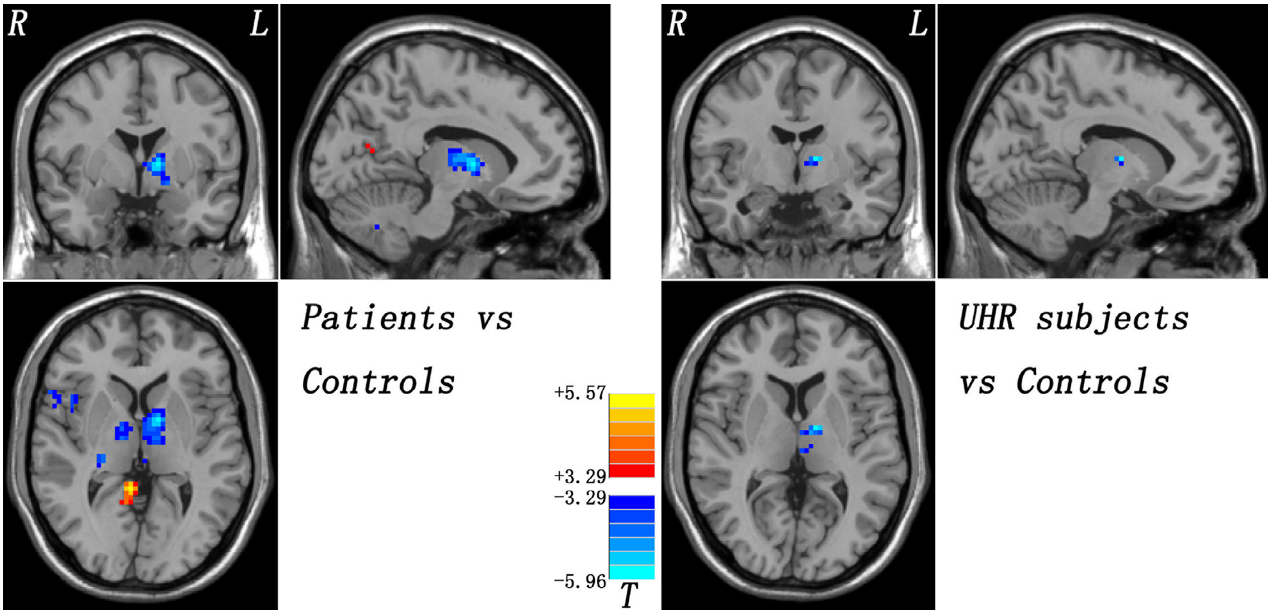

Fig. 1 First-episode patients and UHR subjects shared decreased PAS in the left thalamus relative to healthy controls. PAS = parameter of asymmetry; UHR = ultra-high risk for psychosis.

Table 2 Groups differences in PAS revealed by post hoc *t*-tests.

Cluster location	Peak (MNI)			Number of voxels	*T* value
	x	*y*	*z*		
Patients vs controls					
Left thalamus/pallidum	−12	0	3	153	−5.9590
Right hippocampus/parahippocampus	24	−27	−6	58	−5.7283
Right inferior frontal gyrus/insula	39	15	9	62	−4.5632
Right thalamus	12	−6	6	48	−4.8372
Left inferior parietal lobule	−57	−57	42	46	−4.9015
Left Calcarine	−27	−63	12	77	4.4272
Right Superior Occipital Gyrus/Middle Occipital Gyrus	21	−87	42	48	4.8396
Right precentral gyrus/postcentral gyrus	45	−30	60	49	4.2338
UHR subjects vs controls					
Left thalamus	−12	−6	6	24	−4.0143

PAS = parameter of asymmetry; UHR = ultra-high risk for psychosis.

was conducted by using the PAS values of the left thalamus. The results demonstrated that the PAS values of the left thalamus could discriminate the patients from the controls with a sensitivity of 68.42% (52 out of 76 patients were correctly classified), a specificity of 81.69% (58 out of 71 controls were correctly classified), and a balanced accuracy of 74.83% (110 out of 147 participants were correctly classified) (Fig. 3), whereas the sensitivity, specificity, and balanced accuracy were 81.08% (60 out of 74 UHR subjects were correctly classified), 42.25% (30 out of 71 controls were correctly classified), and 62.07% (90 out of 145 participants were correctly classified) for discriminating UHR subjects from healthy controls (Fig. 4).

The SVM results were validated using the five-fold cross-validation and permutation test methods. The global balanced accuracy was 73.37% for classifying FEPs from healthy controls using the five-fold cross-validation method, whereas the global balanced accuracy was 62.38% for classifying UHR subjects from healthy controls (Fig. 5). By contrast, the global accuracy was 0.7347 ($p < 0.001$) for classifying FEPs from healthy controls using the permutation test, whereas the global accuracy was 0.6207 ($p = 0.001$) for classifying UHR subjects from healthy controls.

4. Discussion

The predominant finding is that UHR subjects and FEPs share decreased PAS in the left thalamus, which can be used to discriminate UHR subjects/FEPs from healthy controls with acceptable sensitivities. Furthermore, a negative correlation is observed between decreased PAS in the right hippocampus/parahippocampus and BVMT-R scores in the FEPs.

Thalamocortical dysconnectivity has been reported in schizophrenia (Woodward et al., 2012). Reduced white matter connectivity between the thalamus and the prefrontal

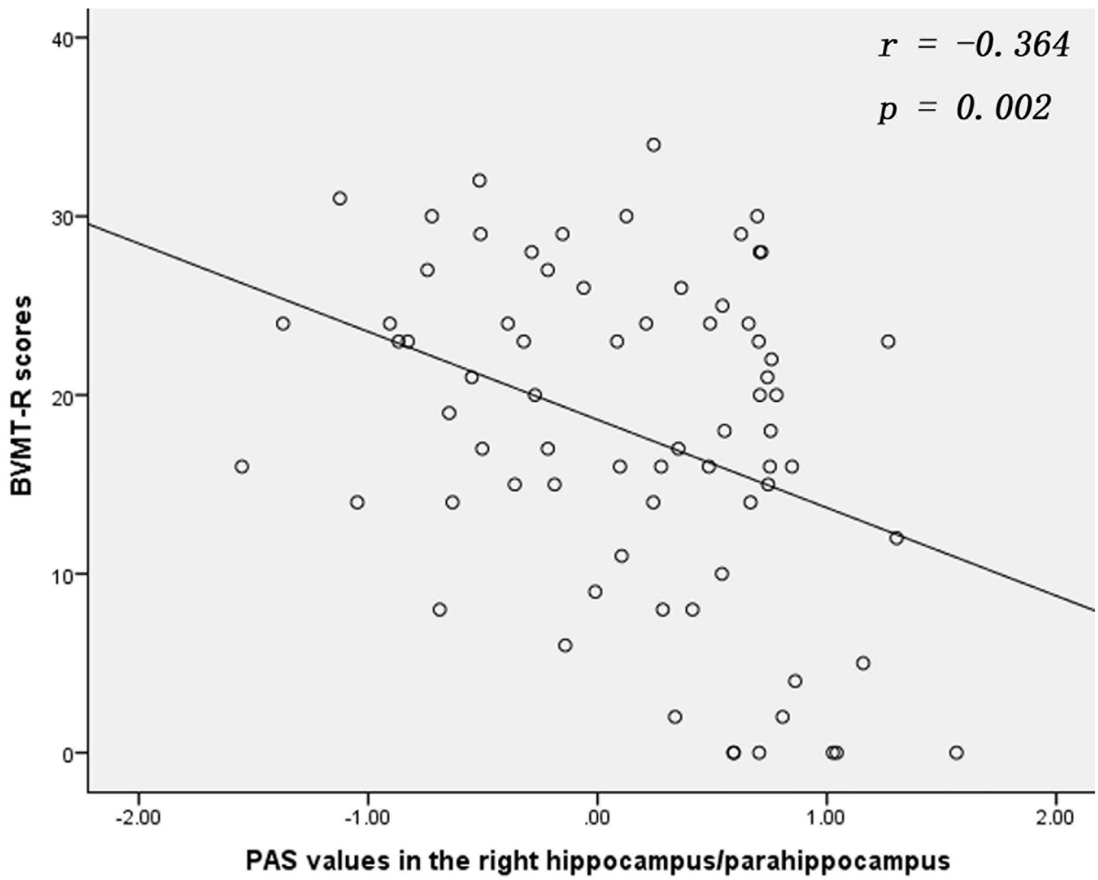

Fig. 2 A significantly negative correlation was observed between the PAS values in the right hippocampus/parahippocampus and the BVMT-R scores in the patients. PAS = parameter of asymmetry; BVMT-R = brief visuospatial memory test-revised.

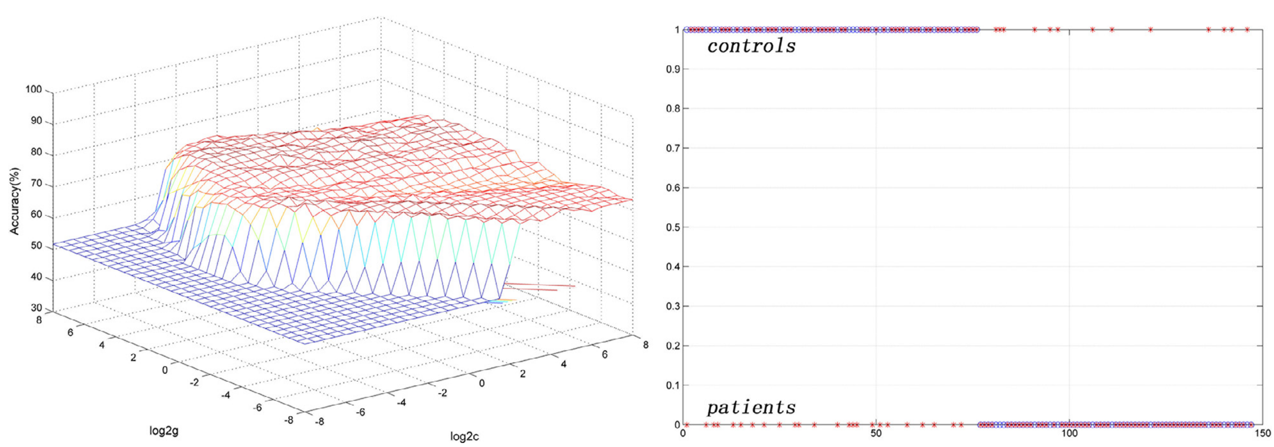

Fig. 3 Visualization of the SVM results for discriminating patients from controls using the PAS values in the left thalamus. Left: 3D view of the classified accuracy with the best parameters; Right: Classified map of the PAS values in the left thalamus. SVM = support vector machine; PAS = parameter of asymmetry.

cortex has also been observed (Cho et al., 2016; Kubota et al., 2013; Marenco et al., 2012). Consistent with these studies, the present study reveals decreased PAS in the left thalamus in both UHR subjects and FEPs, indicating that disrupted functional asymmetry in the left thalamus may start at very early stage of psychosis. However, previous studies do not know whether disrupted functional asymmetry originates from intra-hemispheric or inter-hemispheric FC. In the present study, FC is divided into intra-hemispheric or inter-hemispheric FCs for a given voxel. Then PAS is calculated with the formula ($PAS = FC_{inter} - FC_{intra}$). By using this calculation, decreased PAS in the left thalamus indicates that disrupted functional asymmetry may mainly originate from decreased inter-hemispheric FC in both FEPs and UHR subjects, and thus highlights the involvement of the left thalamus in the pathophysiology of psychosis.

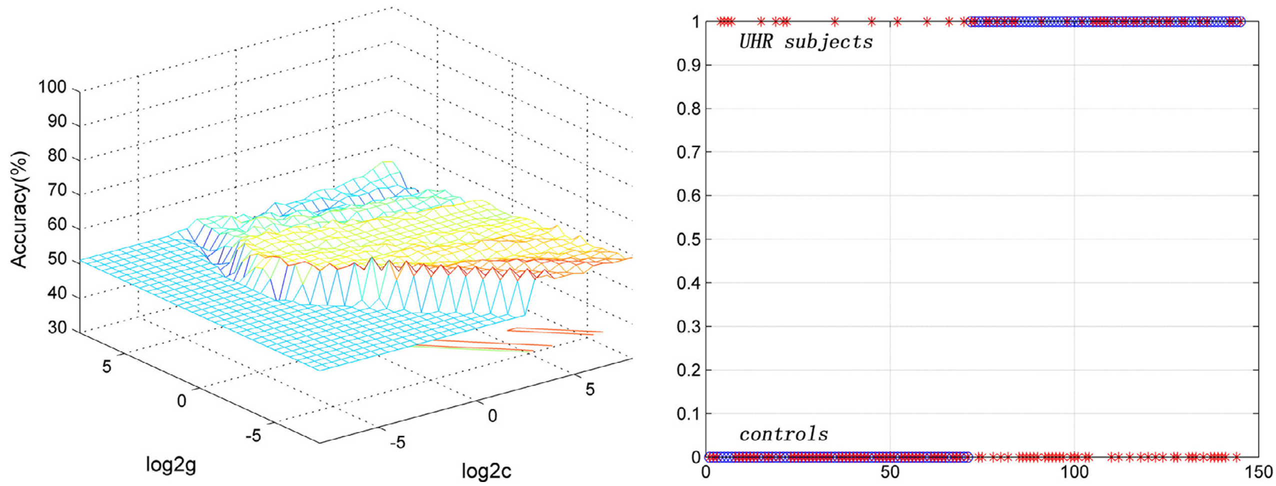

Fig. 4 Visualization of the SVM results for discriminating UHR subjects from controls using the PAS values in the left thalamus. Left: 3D view of the classified accuracy with the best parameters; Right: Classified map of the PAS values in the left thalamus. SVM = support vector machine; UHR = ultra-high risk for psychosis; PAS = parameter of asymmetry.

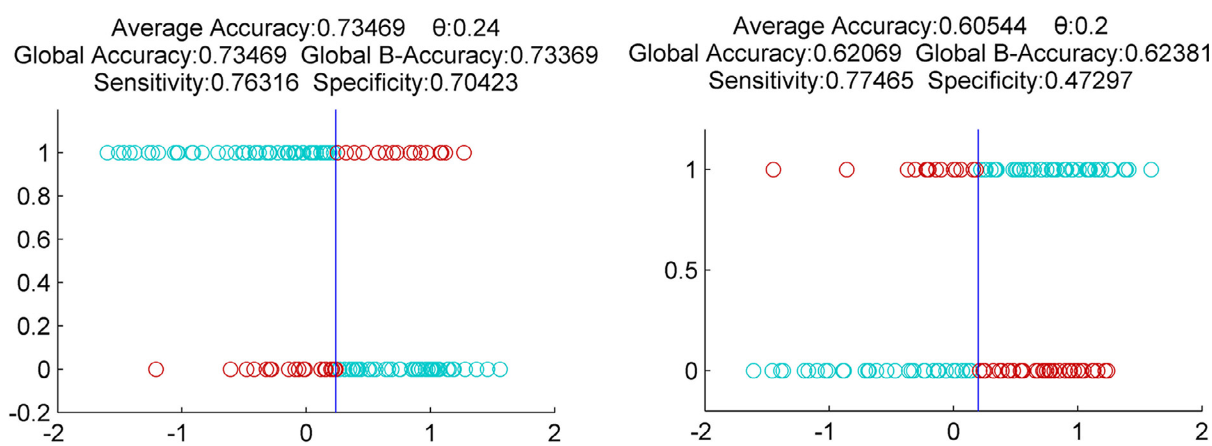

Fig. 5 The SVM results using the five-fold cross-validation method. Left: classifying FEPs from healthy controls; Right: classifying UHR subjects from healthy controls. Cyan circle: correctly classified, Red circle: incorrectly classified, θ: random threshold, B-accuracy: balanced accuracy.

The SVM results further support decreased PAS in the left thalamus as a very early marker for psychosis. Specially, the sensitivities for classifying FEPs/UHR subjects from controls are remarkable. The sensitivities are 68.42% for discriminating FEPs from controls and 81.08% for discriminating UHR subjects from controls, which were validated using the five-fold cross-validation and permutation test methods. Previous study suggests that a sensitivity of 70% is excellent (Gong et al., 2014). According to this criterion, the sensitivities are acceptable in the present study. Therefore, the SVM results further indicate that decreased PAS in the left thalamus may be applied as a very early marker for psychosis. However, the specificity for discriminating UHR subjects from controls is somewhat low. This finding may be partially owing to attenuated symptoms and functional abnormalities in the UHR subjects.

The voxel-wise whole-brain analysis reveals increased PAS in the sensorimotor regions and decreased PAS in other cortical-subcortical regions in the patients relative to the controls. Consistent with our finding, previous studies have observed reduced prefrontal-thalamic FC and enhanced motor/somatosensory-thalamic FC in schizophrenia (Anticevic et al., 2014; Woodward et al., 2012). Similar findings are also revealed in the UHR subjects by a recent meta-analysis (Cooper et al., 2014). The present finding provides evidence that functional asymmetry of schizophrenia may increase inter-hemispheric FC in the sensorimotor regions and decrease inter-hemispheric FC in other cortical-subcortical regions.

Dysfunction of the thalamocortical networks may attribute to clinical and cognitive symptoms observed in schizophrenia (Andreasen et al., 1998). The hippocampus plays major roles in the consolidation of information from short-term memory to long-term memory (Heckers, 2004), and the parahippocampus acts as a key role in memory retrieval and encoding (Ferreira et al., 2003). Reductions in the volume of hippocampus have been found in schizophrenia (Antoniades et al., 2018). Animal investigation suggests that hippocampal dysfunction may introduce abnormal dopamine release in the basal ganglia, thereby indirectly affecting information integration in the prefrontal cortex (Goto and Grace, 2008). Hippocampal dysfunction may account for abnormalities in the long-term memory frequently observed in schizophrenia (Boyer et al., 2007). Consistent with this finding, a negative correlation is found between decreased PAS in the right hippocampus/parahippocampus and BVMT-R scores in the patients, and thus highlights the role of the right hippocampus/parahippocampus in visuospatial memory performance.

Several novel aspects are noted in the present study. First, FC is divided into intra-hemispheric and inter-hemispheric FCs, and thus the origination of functional asymmetry can be determined from intra-hemispheric or inter-hemispheric FCs. Second, voxel-wise whole-brain analysis provides an unbiased FC analysis in the present study, and some critical findings are revealed by this method. Third, a group of UHR subjects is enrolled in the present study. The findings from UHR subjects can help exploring early biomarkers for psychosis. Finally, a group of patients with first-episode, drug-naive schizophrenia is recruited in this study. The recruitment criterion can minimize the confounding effects caused by medication use and long illness duration.

The present paper has some limitations. First, the sample size is hardly sufficient to allow strong conclusions about the anomalies identified. Second, although cross-validation has been used to gauge the reliability of the results, the lack of an independent test set limits the prospective application of the index developed in the clinical setting. Third, the specificity of the UHR classification is very low, meaning that many controls may be ascribed to the UHR group if we were to use these indices for early screening. Fourth, it remains interesting for further neuroimaging investigations that the asymmetry in the thalamo-cortical connections yields some predictive power. The accuracy of the results needs to be carefully considered when interpreting the present results.

In conclusion, FEPs and UHR subjects share decreased PAS in the left thalamus. This observed pattern of functional asymmetry highlights the involvement of the thalamus in the pathophysiology of psychosis and may also be applied as a very early marker for psychosis.

Contributors

Drs. Guo W and Zhao J designed the study. Drs. Liu Y, Li H, and Chen J collected the original imaging data. Drs. Guo W, Liu F, and Yang R managed and analyzed the imaging data. Drs. Guo W, Kennedy DN, and Zhu F wrote the first draft of the manuscript. All the authors contributed to and approved the final manuscript.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.02.006.

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