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ORIGINAL RESEARCH

Functional abnormalities of striatum are related to the season-specific effect on schizophrenia

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Abstract

Schizophrenia is a syndrome that is typically accompanied by delusions, hallucinations and cognitive impairments. Specifically, abundant evidences support the notion that more people diagnosed with schizophrenia are born during fall-winter than spring-summer. Although pathophysiological of schizophrenia might be associated with abnormal brain functional network, little is currently known the relationship between season and deficient brain functional network of schizophrenia. To investigate this issue, in this study 51 schizophrenic subjects and 72 healthy controls underwent MRI scanning to detect the brain functional mapping, each at spring-summer and fall-winter season throughout the year. The data-driven method was used to measure the blood oxygen metabolism variability (BOMV). Decreased BOMV in spring-summer while increased in fall-winter were observed within dopaminergic network of schizophrenic subjects, including striatum, thalamus, and hippocampus. The post hoc analysis exploring the coupling among changed BOMV regions, confirmed that a positive relationship, between pallidum and hippocampus existed in fall-winter healthy controls, but not in fall-winter schizophrenic subjects. These findings identified that seasonal effect on striatum might be associated with modulation of striatum-hippocampus. Our results provide a new insight into the role of season in understanding the pathophysiological of schizophrenia.

Keywords Schizophrenia · Seasonal effect · Blood oxygen metabolism variability · Striatum · Hippocampus

Introduction

Schizophrenia is a complex psychiatric illness, which is always characterized by positive symptoms, such as delusions and hallucinations, together with negative symptoms and cognitive impairments (Freedman 2003). Moreover, it is worth noting that schizophrenia prevalence is associated with the change of season. Research literatures have provided abundant evidences demonstrated that more people diagnosed with schizophrenia are born during the winter than other seasons (Battle et al. 1999; Hare 1975; Pulver et al. 1983). However, the mechanism behind this phenomenon is still poorly understand. Recent excellent study has indicated that schizophrenia is referred to as a 'dysconnection' syndrome, which might relate with altered functional interaction across brain regions or networks (Dong et al. 2020). Investigating the relationship between seasonal effect and brain functional mapping might contribute the knowledge related to neuropathology of seasonal schizophrenia prevalence.

Organisms undergo seasonal changes in their metabolism and behavior. It is one necessary evolutionary adaptation for coping with seasonal changes in temperature, lighting condition and food availability. There are a wide range of behaviors, such as sleep, mood and energy balance, which vary with seasons in humans. Individuals with high seasonality scores

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are highly vulnerable for schizophrenia. Specifically, the relationship between season of birth and schizophrenia has been examined extensively. Hare et al. found English patients with schizophrenia were most likely to be born between January and March (Hare 1975). Letis and Griffin also found that majority of excess schizophrenia births were those subjects born in the winter (Lewis and Griffin 1981). With data collected from the Midwest, Watson et al. concluded that there was a plausible relationship between winter births and prevalence of schizophrenia diagnoses in response to Lewis et al. results (Watson et al. 1982). These findings conclude that seasonality maybe associated with the etiology of schizophrenia. While, an explanation for this relationship remains unclear.

Several lines of evidence suggest that circannual changes in circadian rhythms might impact the central dopaminergic systems. Striatal dopamine receptor binding of rodents shows a season-specific pattern (Naber et al. 1981). Seasonal effect on dopamine synthesis was also observed in human (Eisenberg et al. 2010). The dopamine metabolite concentrations in cerebrospinal fluid is higher in fall and winter than spring and summer (Hartikainen et al. 1991). Moreover, several researches go the finding that season-specific dopaminergic system might be related with circadian variation of melatonin secretion (Bersani et al. 2003; Eisenberg et al. 2010; Monteleone et al. 1992; Robinson et al. 1991). Importantly, the abnormal dopamine hypothesis is the dominant theory to state the clinical symptoms of patients with schizophrenia (Abi-Dargham 2004). It might gain a better understanding the potential neuropathology of schizophrenia and new treatment approaches through elucidating the association between seasonal effect and alteration dopamine synthesis of schizophrenia.

Functional magnetic resonance imaging (fMRI) has been employed in assessing the neuropathology of schizophrenia. Static functional connectivity has been commonly used to measure the symptom related functional networks in schizophrenia, such as basal ganglia, default mode network, sensorimotor network and salience network (Dong et al. 2018a; He et al. 2019; Javitt 2009; Jiang et al. 2019; Mier and Kirsch 2015). Importantly, recent excellent researches reported that there has been a major paradigm shift from assessing the static functional connectivity to additional exploration of the time-varying or dynamic nature of the underlying fluctuations (Abrol et al. 2017; Chang and Glover 2010; Hansen et al. 2015; Liu et al. 2017). Douglas D. Garrett and colleague reported blood oxygen level dependent (BOLD) variability is necessary for brain function, associated with chronological age (Garrett et al. 2010) and individual differences in behavioral performance (Garrett et al. 2011). Together, these perspectives posit that blood oxygen metabolism variability (BOMV) is one critical component of brain function.

In this study, we assessed the variability of season-specific BOLD signal in chronic schizophrenic subjects, and determined whether the altered BOMV was associated with the symptoms of schizophrenic subjects. Based on the findings of previous studies, we hypothesized that season change would abnormally impact the functional variability on brain regions within dopaminergic network of schizophrenia. We posit that these reflect functional variability changes are an important driving factor in season related function changes on schizophrenia.

Materials and methods

Demographic characteristics and study design

Fifty-one schizophrenic subjects were recruited in this study from the clinical hospital of Chengdu Brain Science Institute (CBSI). The inclusion criteria for the inpatients was a diagnosis of schizophrenia based on the structured clinical interview for the DSM-IV axis I disorders-clinical version (SCID-I-CV). Seventy-two matched healthy controls were also recruited in this study without psychiatric, neurological and major medical illness. Sessions were scheduled throughout the calendar year. The autumnal and vernal equinoxes were delineated whether the related seasonal data was fall-winter or spring-summer (Karson et al. 1984). There were 32 spring-summer and 19 fall-winter scans of schizophrenia, 27 spring-summer and 45 fall-winter scans of healthy control in this study. The study was approved by the Ethics Committee of the clinical hospital of CBSI in accordance with the Helsinki Declaration. All the methods were carried out in accordance with the approved guidelines.

Data acquisition and image preprocessing

Imaging was conducted on a 3 T MRI scanner (GE DISCOVERY MR750). During scanning, we used foam padding and ear plugs to reduce head motion and scanner noise, respectively. High-resolution T1-weighted images were acquired using a 3-dimensional fast spoiled gradient echo sequence (repetition time [TR] = 6.008 ms, flip angle [FA] = 9°, matrix = 256 × 256, field of view [FOV] = 256 × 256 mm^2, slice thickness = 1 mm, no gap, 152 slices). Subsequently, resting state functional MRI data were acquired using gradient-echo echo planar imaging sequences (TR = 2000 ms, echo time [TE] = 30 ms, FA = 90°, matrix = 64 × 64, FOV = 240 × 240 mm^2, slice thickness/gap = 4 mm/0.4 mm, number of slices = 35), with an eight channel-phased array head coil. All subjects underwent a 510-s resting state scan to yield 255 volumes. During resting-state fMRI, all subjects were instructed to have their eyes-closed without falling asleep.

Functional image preprocessing was performed using NIT (Neuroscience Information Toolbox) (Dong et al. 2018a, b) according to a standard pipeline and briefly described here. Slice time and head motion correction, segmented normalization (3 mm * 3 mm * 3 mm) using T1 image were performed. Detrending analysis was performed. Then the sources of nuisance signals were removed from the smoothed images, including six motion parameters and their first temporal derivative, white matter signal and cerebrospinal fluid signal. The global signal was not regressed out (Yang et al. 2014). Subjects who had a maximum translation in any of orthogonal direction larger than 3 mm or rotation larger than 3 degree were excluded. Moreover, we calculated the framewise displacement (FD) score of each subject by using the following formula:

$$\mathrm{FD} = \frac{1}{M-1}\sum_{i=2}^{M}\sqrt{|\Delta t_{x_i}|^2 + |\Delta t_{y_i}|^2 + |\Delta t_{z_i}|^2 + |\Delta d_{x_i}|^2 + |\Delta d_{y_i}|^2 + |\Delta d_{z_i}|^2},$$

where M is the length of time courses, x_i, y_i and z_i are translations/rotations at ith time point in the x, y and z directions,$\Delta t_{x_i} = \Delta x_i - x_{i-1}$, similar for Δt_{y_i} and Δt_{z_i}; Δt represents the FD rotations, Δd represents the FD translations. Then we also examined group-level FD difference between four groups using two-way ANOVA.

Structural images were processed using SPM8 toolbox. The structural image was spatial normalized to MNI-space using a diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL), and segmented in to gray matter (GM), white matter and cerebrospinal fluid. Then the segmented GM was modulated using nonlinear deformation. The GM score of subjects was as a variable in the statistical analysis to correct for the global GM volume of different subjects.

Season-specific blood oxygen metabolism variability

At every voxel, BOMV was defined as the mean square successive difference of preprocessed time series in subject space respectively (Fig. 1). BOMV was calculated by subtracting time point t from $t \pm 1$, squaring the results, and then averaging all resulting values acquired from the entire voxel time course as follows:

$$\delta^2 = \frac{\sum_{i=1}^{n-1}(x_{i+1} - x_i)^2}{n-1}$$

Then, $\mathrm{BOMV_{BOLD}}$ maps were masked with grey matter template. Moreover, individual voxel-wise BOMV maps were standardized by dividing the whole-brain mean values and furthermore spatially smoothed (6-mm FWHM Gaussian kernel).

For four groups' data, the two-way ANOVA were used to assess the group * season interaction and main effects of group and season on the $\mathrm{BOMV_{BOLD}}$ maps. Age, gender, education years and GM score were used as the potential confounding covariates in the statistical analysis. The significance threshold of the group difference for the ANOVA was set to GRF corrected ($p < 0.005$with cluster-lever $p < 0.05$).

Coupling among altered functional BOMV regions

To investigate the covariant relationship across subjects among the group * season interaction regions through two-way ANOVA. In each group, we calculated correlation between average BOMV value of each altered region. Then, the association was obtained using the permutation testing between schizophrenic group and healthy group. Using the correlation in healthy group as baseline, negative difference between schizophrenic and healthy subjects implied a relative loss of dynamic functional coupling. Positive difference might reflect a compensatory mechanism.

Coupling between altered functional BOMV and its structural features

To investigate the covariant relationship between altered functional BOMV and its structural feature across subject, we measured correlation between BOMV score and its gray matter volume in each group respectively. Then permutation testing was used to assess the difference of structure-function relationship between fall-winter specific healthy group and fall-winter specific schizophrenic group, as well as spring-summer specific healthy group and spring-summer specific schizophrenic group.

Correlations with pathological factors

The partial correlation analysis was performed between the mean altered BOMV score with symptom scores of schizophrenic subjects with age, gender, education years, GM and medication dosage as covariates in spring-summer and fall-winter groups respectively.

Results

Demographic and clinical data

There is no significant difference among four groups in terms of age, gender and education years. PANSS scores were also no significant difference between two schizophrenia groups (spring-summer group and fall-winter group). Details of demographic characteristics of schizophrenia and healthy groups

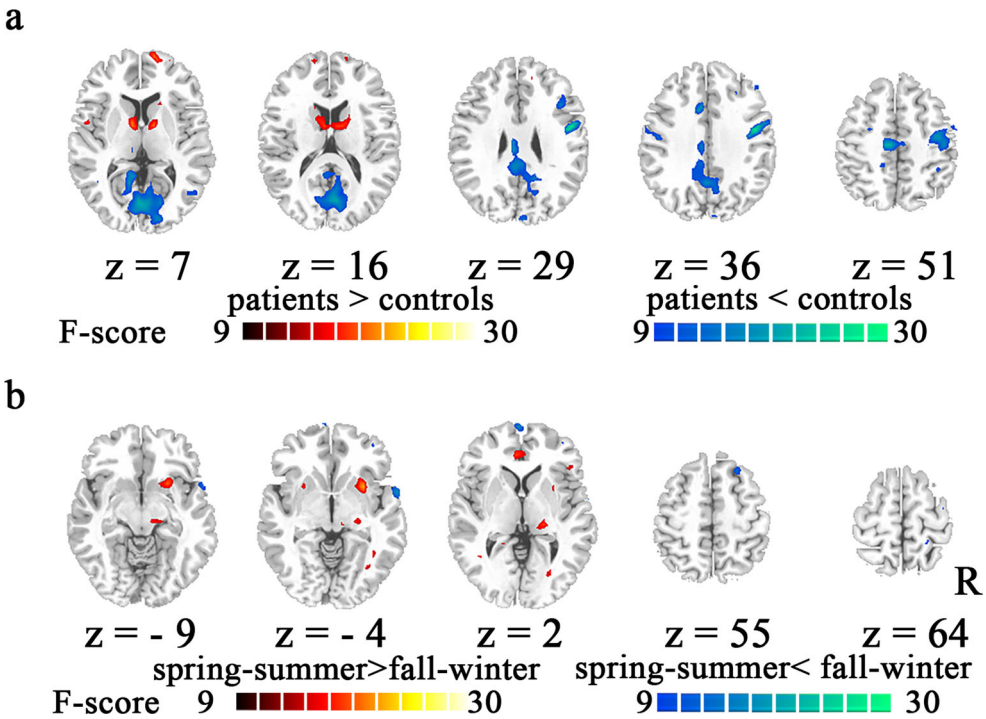

Fig. 1 The main effects of group and season. '*a*' denotes that significant main effect of group on BOMV through repeated measured ANOVA analysis. The red color represents schizophrenic subjects higher than healthy controls; blue color represents opposite. '*b*' denotes that significant main effect of season on BOMV. The red color represents spring-summer season higher than fall-winter season; blue color represents opposite

are showed in Table 1. Difference of FD was also not observed among four groups (Table 1).

Season-specific alteration of BOMV in schizophrenia

The BOMV across brain regions showed a non-uniform spatial distribution. The limbic network is mainly lowest BOLD variability. The primary sensorimotor network and visual cortices were showed a moderate level BOLD variability. The high BOMV displayed in prefrontal and posteromedial cortex.

The main effects of group were observed in schizophrenic subjects compared to healthy controls, including decreased BOMV score in primary sensorimotor and visual networks and increased BOMV in caudate and thalamus (Fig. 1a). We also found the main seasonal effect on BOMV of human brain, including increased variability in right putamen and anterior cingulate cortex during spring-summer season compared to fall-winter season (Fig. 1b). Moreover, group*season interaction was found on BOMV in right pallidum, right putamen, right thalamus and left hippocampus (Fig. 2, Table 2). *Post-hoc* analysis found there were no difference in spring-summer while increased BOMV in left hippocampus (Fig. 2a) and right pallidum (Fig. 2b) of fall-winter schizophrenic subjects

Table 1 Participant fundamental information

	SZ spring-summer	SZ fall-winter	HC spring-summer	HC fall-winter	p
Gender(Male/Female)	27/5	13/6	19/8	25/20	0.064[a]
Age (years)	41.25 ± 10.411	41.95 ± 11.764	33.89 ± 17.818	39.07 ± 7.114	0.062[b]
Education level (years)	11.69 ± 2.729	10.89 ± 2.258	11.74 ± 2.363	11.11 ± 3.221	0.609[b]
Duration of illness (years)	17.39 ± 10.285	16.88 ± 9.215	–	–	0.868[c]
PANSS-positive score	11.71 ± 3.740	9.21 ± 4.003	–	–	0.053[c]
PANSS-negative score	20.89 ± 5.659	21.14 ± 4.912	–	–	0.889[c]
PANSS-general score	26.89 ± 5.915	30.86 ± 7.026	–	–	0.062[c]
PANSS-total score	59.50 ± 10.769	60.79 ± 13.729	–	–	0.741[c]
FD	0.043 ± 0.021	0.062 ± 0.042	0.042 ± 0.028	0.049 ± 0.029	0.109[b]

Abbreviations: *SZ* schizophrenia, *HC* healthy control, *FD* framewise displacement; Indicated values are shown mean ± standard deviation

[a] indicates the *p* values for the comparisons (Chi-square test) among SZ spring-summer, SZ fall-winter, HC spring-summer, HC fall-winter group

[b] indicates the *p* values for the comparisons (Analysis of variance) among SZ spring-summer, SZ fall-winter, HC spring-summer, HC fall-winter group

[c] indicates the *p* values for the comparisons (two-sample t-test) among SZ spring-summer, SZ fall-winter

compared to healthy controls. Additionally, there were decreased BOMV regions in spring-summer, including right thalamus (Fig. 2c), right putamen (Fig. 2d), while increase in fall-winter schizophrenic subjects compared to healthy controls. The detail information was showed in Table 3.

Coupling between hippocampus and striatum

The extent of difference in BOMV of hippocampus was decreased correlated with impaired BOMV of pallidum in fall-winter specific schizophrenia subjects compared to fall-winter specific healthy subjects (Fig. 3, $p < 0.005$). We found positive relationship ($r = 0.419$, $p = 0.004$) between extent of BOMV of hippocampus-pallidum in the controls. Whereas, this correlation was not observed in schizophrenic subjects ($r = 0.152$, $p = 0.53$).

Decreased coupling between structure-function feature of patients' hippocampus

The functional BOMV of hippocampus was decreased correlated with GM score of hippocampus in spring-summer specific schizophrenia subjects compared to spring-summer specific healthy subjects (Fig. 4, $p < 0.001$). We found positive structure-function relationship ($r = 0.496$, $p = 0.008$) of hippocampus in controls. Whereas, negative correlation was observed in schizophrenic subjects ($r = -0.392$, $p = 0.026$).

Relationship between BOMV and positive symptom of schizophrenia

The BOMV score of right thalamus showed a significant negative correlation with the positive score ($r = -0.519$, $p = 0.009$, uncorrected result) of PANSS in spring-summer schizophrenic subjects (Fig. 5). Moreover, no significant correlation was observed between altered BOMV with medication dosage, gender and age in schizophrenia group respectively.

Table 2 Significant season*time interaction on the BOMV value

MNI coordinates					
Regions	x	y	z	F-score$_{(df),}$	Cluster voxels
left Hippocampus	−29	−16	−11	16.98 $_{(1119)}$	20
right Putamen	23	1	10	16.62 $_{(1119)}$	50
right Thalamus	9	−28	5	16.62 $_{(1119)}$	40
right Pallidum	19	−1	4	16.62 $_{(1119)}$	27

Discussion

Though previous researches in rodents and evidence from human have indicated that dopamine-biorhythm interactions, to our knowledge, this is the first study characterize a seasonal effect on dynamic brain functional network of chronic schizophrenic subjects alongside the use of antipsychotic therapy. Decreased BOMV in spring-summer while increase in fall-winter were observed in schizophrenic subjects within striatum and thalamus. Hippocampus and primary visual regions also showed similar difference. The functional BOMV of hippocampus was decreased positively correlated with its GM value in spring-summer specific schizophrenia. Moreover, psychiatric symptom analysis found altered BOMV of thalamus negatively related with the positive symptom score of spring-summer schizophrenic subjects. Consistent with our hypothesis, season change might be related with altered functional variability of dopaminergic system in schizophrenia. These season-specific alterations might be the driving factor that is associated with pathological function changes of schizophrenia.

As yearly fluctuations in circadian rhythms underlie circannual changes (Lewy et al. 2006), it is notable that the deficient circadian rhythms of schizophrenia is associated with melatonin (Bromundt et al. 2011; Monti et al. 2013; Rao et al. 1994), which is a scotoperiod-specific pineal hormone central to seasonal and circadian cycles (Wehr 1997). Furthermore, within dopaminergic midbrain and striatum, there are abundant receptors for melatonin (Uz et al. 2005). Venero et al. also indicated that melatonin upregulates dopamine synthesis in neuronal populations that project to striatum (Venero et al. 2002). Specific, when circadian cycles feature longer scotoperiods and thereby more cumulative melatonin release (Kivelä et al. 1988; Morera and Abreu 2006; Stokkan and Reiter 1994). Thus, greater melatonin release might be likely to appear during fall-winter season, and lead to more upregulation to dopaminergic systems of human brain. In contrast, lesser melatonin release might happen during spring-summer season. In this study, we found abnormal increased BOMV in striatum and thalamus of schizophrenic subjects during fall-winter, while deficient BOMV during spring-summer. The BOMV score of thalamus negative related to the positive symptom of spring-summer schizophrenic subjects. More and lesser melatonin release might add and reduce the modulation on dopaminergic system respectively in schizophrenia. The dopamine hypothesis is the dominant theory to interpret the symptoms of schizophrenia (Abi-Dargham 2004). Thus, compared to healthy controls inverse modulation on abnormal dopamine might lead to season-specific alteration function of striatum in schizophrenia.

Except for melatonin, Grace et.al revealed that pathophysiology of schizophrenia might be associated with abnormal modulation for dopaminergic system by other brain regions

Table 3 The post-hoc results of group*season interaction on BOMV value

	HC(spring-summer group min fall-winter group)	SZ(spring-summer group min fall-winter group)	SZ min HC (spring-summer group)	SZ min HC (fall-winter group)
Regions	T-score$_{(df)}$, P-score	T-score$_{(df)}$, P-score	T-score$_{(df)}$, P-score	T-score$_{(df)}$, P-score
left Hippocampus	$T = 2.841_{(70)}$; $P = 0.006$**	$T = -0.474_{(49)}$; $P = 0.638$	$T = 0.173_{(57)}$; $P = 0.863$	$T = 3.575_{(62)}$; $P = 7 \times 10^{-4}$***
right Putamen	$T = 4.975_{(70)}$; $P < 10^{-4}$***	$T = -0.730_{(49)}$; $P = 0.469$	$T = -2.865_{(57)}$; $P = 0.006$**	$T = 2.463_{(62)}$; $P = 0.017$*
right Thalamus	$T = 3.476_{(70)}$; $P = 9 \times 10^{-4}$***	$T = -1.571_{(49)}$; $P = 0.123$	$T = -2.942_{(57)}$; $P = 0.005$**	$T = 1.840_{(62)}$; $P = 0.071$
right Pallidum	$T = 3.900_{(70)}$; $P = 2 \times 10^{-4}$ ***	$T = -1.267_{(49)}$; $P = 0.211$ *	$T = -1.677_{(57)}$; $P = 0.099$	$T = 3.355_{(62)}$; $P = 0.001$***

HC healthy control, *SZ* schizophrenia. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

(Grace 2012). Researches have indicated converging lines of results highlighting hippocampus contributes to regulate dopamine neuron responsivity as one of central regions (Floresco et al. 2001; Valenti and Grace 2009). The functional activity of hippocampus could drive nucleus accumbens to inhibit dopamine release from pallidum (Floresco et al.

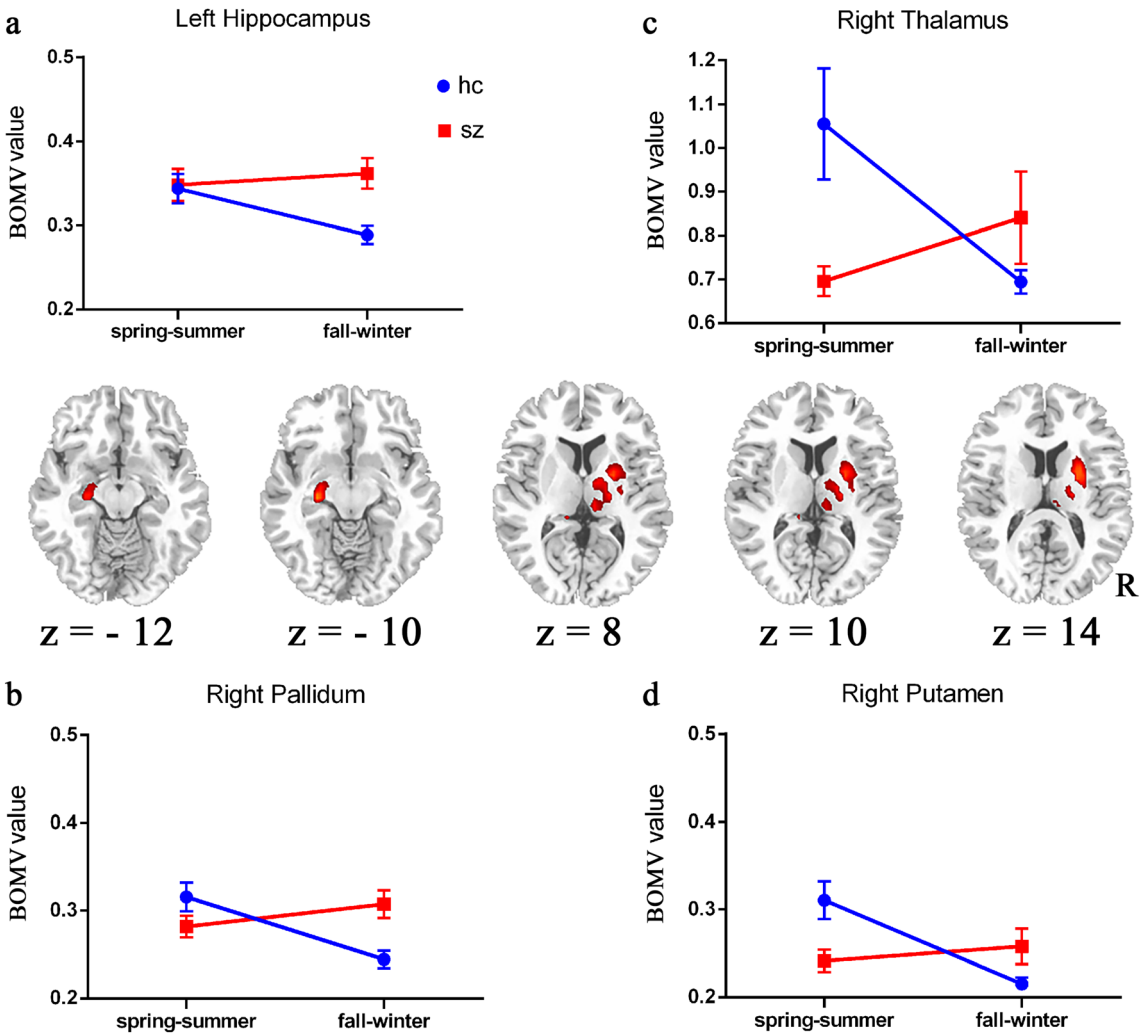

Fig. 2 The group*season interaction effect on BOMV. '*a*', '*b*', '*c*', '*d*' denote the post-hoc results of hippocampus, pallidum, thalamus and putamen respectively. Red node and line represent schizophrenia group, blue node and line denote healthy group.

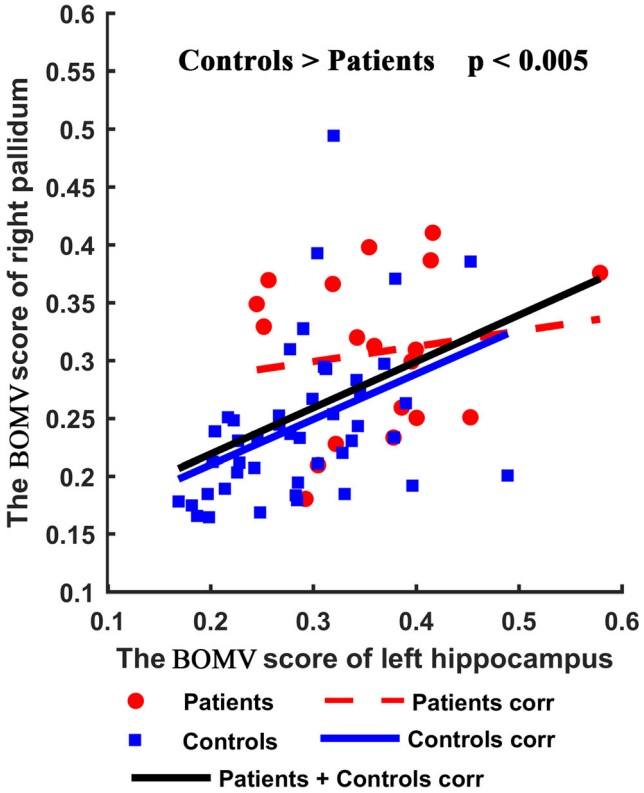

Fig. 3 The difference result of coupling analysis. Positive relationship ($r = 0.419$, $p = 0.004$) between extent of BOMV of hippocampus-pallidum in the fall-winter specific healthy group (blue node and line). Whereas, this correlation was not observed in fall-winter specific schizophrenic subjects ($r = 0.152$, $p = 0.53$, red node and line)

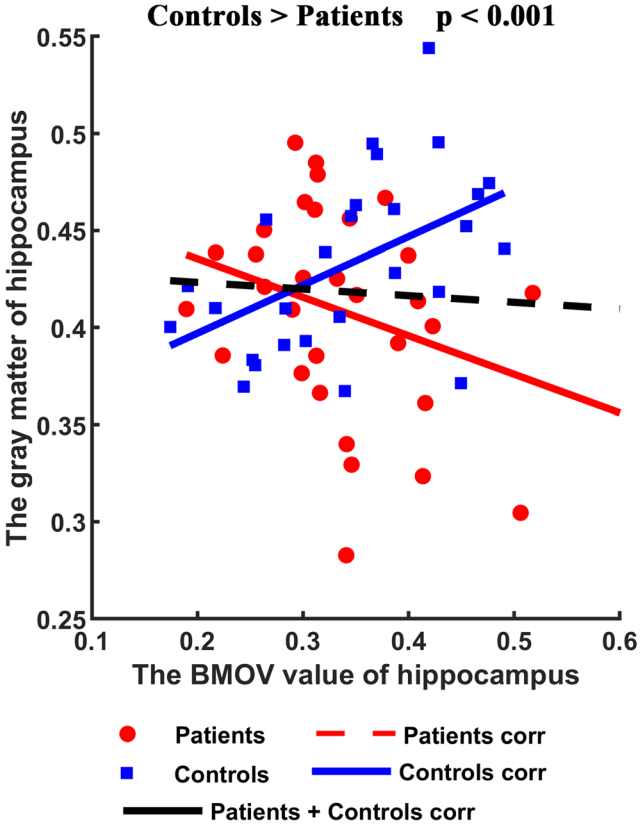

Fig. 4 The difference result of structure-function coupling analysis. Positive structure-function relationship (r = 0.496, $p = 0.008$) of hippocampus in healthy group (blue node and line). Whereas, negative correlation was observed in schizophrenic subjects (r = −0.392, $p = 0.026$, red node and line)

2001). In this study, the increased BOMV of hippocampus was observed in fall-winter schizophrenia group compared to healthy group. Based on these dopaminergic modulation findings, our results demonstrate that the modulation from hippocampus to striatum might be affected during fall-winter season in schizophrenic subjects. Moreover, a reduction in the positive relationship of local dynamic function was observed between hippocampus and pallidum in fall-winter schizophrenia group. This result might reveal that the disrupted hippocampus-pallidum coupling was related with greater melatonin release during fall-winter season.

Hippocampus is one key region of default model network (DMN) in human brain. In monkey, the electrophysiological signals of hippocampus could trigger distributed subregions' neuro activity within DMN (Kaplan et al. 2016). Importantly, recent excellent study has reported that functional connectivity of hippocampus-neocortex would affect the information flow across multi-networks (Kernbach et al. 2018). Thus, the seasonal effects on hippocampus would likely impact the function of DMN, further affect the other network's function.

Several limitation issues need to be considered when interpreting the results of this study. First, a longitudinal design, which each schizophrenic subject undergo MRI scans throughout the year, would be a preferable and more sensitive approach. Second, all inpatients we chose is medically treated chronic schizophrenic subjects. The altered BOMV might be associated with antipsychotic treatment. Moreover, the

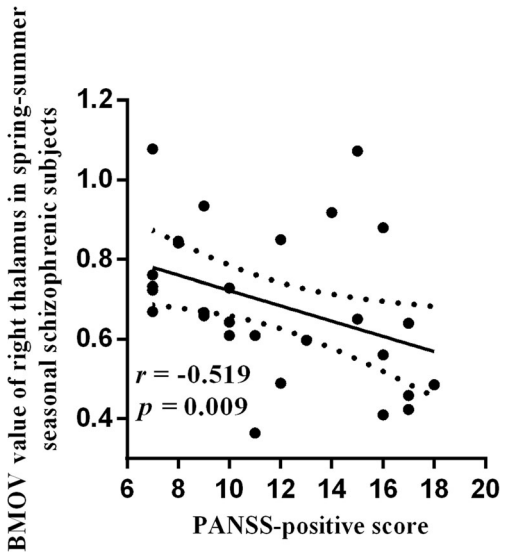

Fig. 5 The significant relationship between BOMV score of right thalamus and positive symptom score of spring-summer season schizophrenic subjects

education years of healthy group is higher than schizophrenia group. Although there is no significant relationship between BOMV score and medication dosage, and education years in schizophrenic group, the effects of antipsychotic therapy on seasonal related functional network should be further assessed in schizophrenia. Finally, we did not find the significant relationship between altered BOMV and PANSS score in fall-winter schizophrenia group. This may be related with a small number of schizophrenic subjects during fall-winter season. Thus, the results should be validated and expanded through large number of patients in the further research. These results might support and expand current knowledge about the underlying neural mechanisms of seasonal effect on schizophrenia.

Conclusion

By BOLD variability approaches, our findings reveal the prominent season-specific BOMV changes within striatum and hippocampus in schizophrenic subjects, which highlighting the fact that seasonal effect might impact the dopaminergic system, and contribute the knowledge related to neuropathology of seasonal schizophrenia prevalence.

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Author contributions Hui He, Mingjun Duan, Cheng Luo, Manxi He and Dezhong Yao had made a substantial contribution to the conception and drafting and revising the article; Gang Yao and Chi Ma acquired the data; Hui He, Huan Cao, Binxin Huang had made a substantial contribution to the analysis and interpretation of the data. All of the authors gave final approval of the version to be published.

Compliance with ethical standards

Conflict of interest No conflicts of interest to declare.

Ethical approval All procedures performed in study involving participants were in accordance with the Ethics Committee of the Chengdu Mental Health Center in accordance with the Helsinki Declaration.

Informed consent Informed consent was obtained from all subjects included in the study.

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