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Functional brain lateralization in schizophrenia based on the variability of resting-state fMRI signal

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ABSTRACT

Abnormal brain lateralization has been implicated in schizophrenia but few studies have focused on the variability of resting-state fMRI signal and its lateralization in schizophrenia. Here we utilized standard deviations (SD) to quantify the variability of resting-state fMRI signal and measured the lateralization index (LI), on the basis of SD of the resting-state fMRI signal in order to assess the difference of brain signal variability across the hemispheres. We recruited 180 patients with schizophrenia and 358 age- and sex-matched healthy volunteers. Between-group comparison revealed that in comparison to healthy volunteers, schizophrenia patients have significantly higher SD of resting-state fMRI activity in left inferior temporal, left fusiform, and right superior medial frontal cortex, and lower SD in right precuneus, posterior cingulum on both sides, right lingual, and left calcarine in the occipital region. Using region of interest approach, most brain regions showed increased leftward lateralization in patients with schizophrenia, as compared with healthy controls. SD and LI were also found to be correlated to age of onset or duration of illness. These results provide further evidence that abnormal variability and lateralization exist in schizophrenia patients, and abnormality in fusiform, lingual and inferior temporal could have potential help to identify the dysfunctional brain lateralization in schizophrenia.

1. Introduction

The brain often exhibits asymmetry both in terms of structure and function (Rentería, 2012). This structural and functional asymmetry of the brain, which can be caused by a number of genetic, epigenetic, or neural mechanisms (Concha et al., 2012), is widely observed among vertebrates and invertebrates (Corballis, 2014; Ribolsi et al., 2009a; Rogers et al., 2013). In human beings, the left hemisphere is usually considered to be dominant in terms of language and handedness (MacNeilage, 2013) and the right hemisphere is regarded to be dominant for certain non-verbal functions, including spatial attention (Cai et al., 2013) and the processing of facial recognition (Dundas et al., 2014). Conversely, a change in left-hemisphere dominance has been observed in the case of mental illnesses, such as schizophrenia (Mitchell and Crow, 2005).

A growing body of evidence has revealed that in the case of schizophrenia, altered brain asymmetry is not only structural but also functional (Baker et al., 2014, Friston, 2002, Koch et al., 2008, Ribolsi et al., 2014, Ribolsi et al., 2009a, Zhang et al., 2015). For example, an abnormal asymmetry of functional connections was observed in schizophrenia patients in comparison with healthy subjects. Patients exhibiting positive symptoms displayed significantly increased leftward asymmetry of functional connectivity in the resting-state fMRI, while the patients with negative symptoms exhibited increased rightward asymmetry of functional connectivity (Jalili, 2014; Ke et al., 2010). In another study, decreased asymmetric functional connectivity has been observed in chronic schizophrenia patients, as compared with healthy controls. The degree of this abnormality increases with the increase in the duration of the disease (Jalili et al., 2010). In a study involving the auditory perception network (Gavrilescu et al., 2010; Rotarska-Jagiela et al., 2009; Vercammen et al., 2010), patients displayed a lower degree of right-sided laterality for the right fronto-parietal network, which correlates with increasing symptoms of disorganization. With respect to the regions of the brain that are associated with auditory hallucination

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(Sumich et al., 2005), both hemispheric asymmetry (Oertel et al., 2010b) and leftward asymmetry of intrinsic functional connectivity were reduced in patients with schizophrenia (Oertel-Knöchel et al., 2013).

A limited number of previous studies pertaining to functional analysis have considered brain signal variability as a measure of interest, such as standard deviation (SD). SD is a measure that is used to quantify the amount of variation or dispersion in a set of data values. A low SD indicates that the data tend to be close to the mean of the set, while a high SD signifies that the data are spread out over a wider range of values. In the case of the resting-state fMRI signal, higher SD implies a greater intensity of signal fluctuation, which may indicate a higher level of activation in the given area (Garrett et al., 2011).

Therefore, in this paper, we studied the variability of the resting-state fMRI signal in patients with schizophrenia and in healthy controls. The quantification of asymmetry defined in previous studies is derived from the number of activated voxels, through which the difference in functional connectivity between the left and the right hemispheres can be obtained (Alary et al., 2013; Bach et al., 2009; Wilke and Lidzba, 2007). Thus, we also attempted to study the lateralization of brain activity on the basis of the SD of the resting-state fMRI signal across the brain. Such an investigation may reveal crucial information regarding the neural activation of the resting-state fMRI signal and the laterality of the brain signal variability in the case of schizophrenia. We hypothesized that 1) schizophrenia patients exhibit abnormal SD of the resting-state fMRI signal, compared with healthy controls, and 2) that different lateralization of brain signal variability in certain brain regions can be observed in patients with schizophrenia, relative to healthy controls. We then tested the hypothesis within a large fMRI cohort of schizophrenia patients (N = 180) and healthy controls (N = 358).

2. Materials and methods

2.1. Study participants and image acquisition

The study cohort consisted of 538 Han Chinese participants, who were recruited from the Department of Psychiatry, Taipei Veterans General Hospital, Taiwan. Demographic and clinical data of the participants are presented in Table 1. The patient group consisted of 180 patients with schizophrenia (75 men and 105 women; mean age: 45.1 ± 12.1 years). All schizophrenia patients were evaluated using the same protocol described previously (Yang et al., 2015). Majority of patients were treated with second generation antipsychotics, and chlorpromazine (CPZ) equivalent dose was converted for each patient to measure the dose of antipsychotics use. The comparison group comprised 358 healthy volunteers (145 men and 213 women; mean age: 45.3 ± 15.6 years), who were recruited from a healthy aging cohort and matched according to age and sex at a 2:1 control-to-patient ratio (Yang et al., 2013a, 2014b).

Table 1
Demographics and clinical characteristics.

Variables	Schizophrenia (n = 180)		Healthy control (n = 358)		t or χ^2	P
	Mean	SD	Mean	SD		
Age at scan (years)	45.09	12.10	45.3	15.649	0.17	0.86
Sex, male	75	42%	145	41%	0.06	0.85
Handedness, right	171	95%	344	97%	0.84	0.36
Age of illness onset	27.54	9.41				
(years)	17.57	11.046				
Illness duration	53.07	12.81				
PANSS total	12.41	4.38				
PANSS positive	12.93	4.65				
PANSS negative	27.73	7.16				
PANSS general						

Categorical data are given as number (%).
PANSS, Positive and Negative Syndrome Scale.

Both healthy subjects and schizophrenia patients underwent the same fMRI scanning protocol performed at the National Yang-Ming University with the employment of a 3.0 T Siemens MRI scanner (Siemens, Erlangen, Germany), equipped with a 12-channel head coil (Yang et al., 2013a, 2014b). The resting-state fMRI images included 200 EPI volume images were acquired along the AC-PC plane. The duration of the fMRI scanning procedure was approximately 15 min for each participant. The resting-state fMRI images were preprocessed through the use of Data Processing Assistant for Resting-State fMRI toolbox (Chao-Gan and Yu-Feng, 2010), and the preprocessing procedures were consistent with our previous reports (Yang et al., 2013b, 2014a, 2015). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Taipei Veterans General Hospital.

2.2. Lateralization indices of standard deviation of the resting-state fMRI signal

First, we estimated the SD of the resting-state fMRI signals in every grey matter voxel, and then obtained the average of SD in the regions of the brain, based on 90 ROIs of the Automated Anatomical Labeling (AAL) template (Tzourio-Mazoyer et al., 2002). The lateralization indices (Alary et al., 2013; Wilke and Lidzba, 2007), based on the SD of the resting-state fMRI signal, are defined using the following formula:

$$LI = \frac{SDL - SDR}{SDL + SDR}$$

where LI represents the lateralization indices and SDL and SDR stand for the ROI-wise SD in the left-hemisphere and the corresponding area in the right-hemisphere. The resulting LI ranges from −1 (total rightward) to 1 (total leftward) and reflects the lateralized degree of the variability of the resting-state fMRI signal in a given brain region. If LI is higher than 0, it implies the occurrence of left lateralization, while an LI lower than 0 represents right lateralization. If LI equals 0, there will be an equal variability of the resting-state fMRI signal in the given region of the brain.

2.3. Statistical analysis

Statistical analysis of the SD parametric imaging data was conducted using MATLAB. First, the voxel-wise between-group differences of SD were examined with the use of the general linear model (GLM). Since age and sex were well matched in the patient and control groups, we assessed the main effect of schizophrenia on the SD of the resting-state fMRI signal without introducing the covariates to the GLM. For voxel-wise analyses, significant brain regions with peak coordinates in the MNI space were reported if the P-value corrected for multiple comparisons using the familywise error (FWE) rate was lower than 0.05 at the cluster level. We also studied the association of the SD/LI with psychopathology (e.g., age of onset, duration of illness, or Positive and Negative Syndrome Scale; PANSS scores), and CPZ equivalent dose, with the help of the linear regression method and false discovery rate (FDR) was used to assess statistical significance with multiple comparisons.

Second, we evaluated the lateralization of the SD (i.e., LI of SD) of the resting-state fMRI signal across the brain with the use of the ROI approach. Between-group difference in the LI was evaluated with student t-test for the 45 matched inter-hemispheric pair of AAL regions, with the correction of multiple comparisons using the Bonferroni method. A P-value < 0.0011 (0.05/45) was considered significant in the student t-test. Moreover, we also analyzed the effect of group by sex interaction on LI with GLM. Last, we visualized the difference in the LI

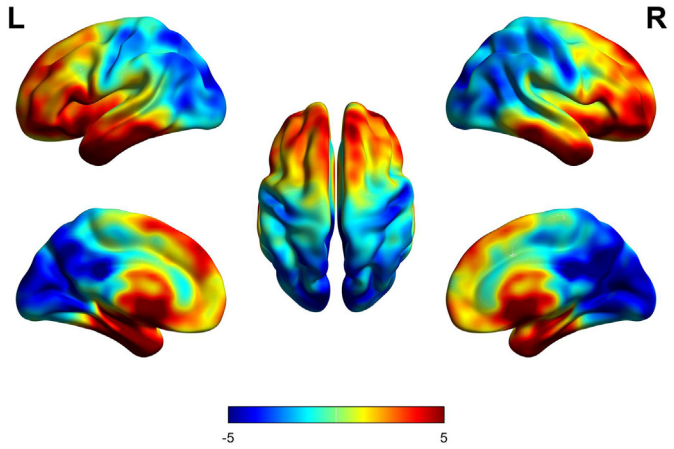

Fig. 1. Reginal differences of the standard deviation (SD) of the resting-state fMRI signal between patients with schizophrenia and healthy subjects are presented here. A positive t-value (warm color spectrum) represents a higher SD in patients with schizophrenia than in healthy subjects, and vice versa for the results with negative t-values (cool color spectrum). Visual inspection suggested that different activity variation occurs in patients with schizophrenia. Most part of the frontal lobe, temporal lobe, basal nucleus, and part of parietal lobe in patients with schizophrenia exhibited a greater variability of brain activity compared with those of the healthy volunteers. By contrast, the occipital lobe and part of the parietal lobe exhibited less variability of brain activity.

of the SD between schizophrenia patients and healthy controls using the rank comparison map by plotting the rank of LI in the schizophrenia patients against that of the healthy controls.

3. Results

3.1. Between-group comparison of resting-state fMRI signal variability

Fig. 1 indicates the regional between-group SD differences of the resting-state fMRI signal at the voxel-wise level. Schizophrenia patients showed a significantly higher SD of the resting-state fMRI activity in the left inferior temporal, left fusiform, and right superior medial frontal cortex, as compared with healthy subjects. In contrast, compared with healthy volunteers, schizophrenia patients displayed a lower SD in the right precuneus, posterior cingulum on both sides, right lingual, and left calcarine in the occipital (refer to Table 2).

Table 2
Regions showing significant SD changes of BOLD signals.

MNI coordinates (mm)			AAL	Lobe
x	y	z		
Regions have higher SD (patient > control)				
−45	−27	−24	Temporal_Inf_L	Temporal Lobe
−45	6	−36	Temporal_Inf_L	Temporal Lobe
−36	−6	−33	Fusiform_L	Limbic Lobe
12	42	42	Frontal_Sup_Medial_R	Frontal Lobe
Regions have lower SD (patient < control)				
3	−63	36	Precuneus_R Cingulum_Post_L	Parietal Lobe
0	−36	27	Cingulum_Post_R	Limbic Lobe
6	−51	27	Lingual_R	Limbic Lobe
21	−99	−18	Calcarine_L	Occipital Lobe
6	−96	−3		Occipital Lobe

All brain clusters have P value < 0.05 corrected for multiple comparisons using familywise error methods.
AAL, Automated Anatomical Labeling.

3.2. Comparison of lateralization indices between schizophrenia patients and controls

Table 3 presents the difference in the LI between patients with schizophrenia and healthy controls in each corresponding AAL brain area. Compared with healthy controls, schizophrenia patients exhibited significantly increased leftward lateralization in the inferior frontal, rolandic, hippocampus, parahippocampal, fusiform, putamen, superior temporal cortex. In contrast, schizophrenia patients showed a significantly decreased rightward lateralization in the supramarginal and inferior temporal cortex, compared with healthy controls. Additionally, schizophrenia patients also displayed significant changes from rightward to leftward lateralization in the precentral, caudate, insula, postcentral and middle temporal regions in comparison with healthy controls.

3.3. Rank comparison of lateralization between patients with schizophrenia and controls

Fig. 2 indicates the level of lateralization difference in the resting state between patients with schizophrenia and healthy controls. The horizontal axis represents the rank of LI for healthy controls in a given AAL region, and the vertical axis denotes the rank of LI of schizophrenia patients in the same region of the brain. Higher rank signifies a greater LI, and vice versa. Therefore, each data point represents the level of lateralization in healthy controls and in patients with schizophrenia. If both healthy controls and schizophrenia patients have the same rank in LI, the data point will be on the diagonal line (dash line). However, the data point will be above the diagonal line if the LI rank in schizophrenia is higher than that in healthy controls, and vice versa if the LI rank in schizophrenia is lower than that in healthy controls.

According to Fig. 2, putamen, superior temporal, hippocampus, inferior frontal opercular, rolandic operculum, fusiform, parahippocampal, middle temporal, precentral, postcentral, insula, inferior temporal, and supramarginal brain regions were all located below the dash line, which indicates the LI rank of these brain regions were higher in patients with schizophrenia than those in healthy controls. Compared to the results presented in Table 3, all these regions of the brain displayed increased leftward lateralization. Other brain regions above the dash line represent lower rank in schizophrenia patients than in healthy controls, but none of them exhibited significant differences in the between-group comparison of LI.

3.4. Correlation between SD/LI and psychopathology

The results of correlation between SD/LI and psychopathology are highlighted in Table 4. Specifically, we examined the correlation between psychopathology and SD/LI of the regions of the brain that showed significant between-group differences. The right lingual ($r = 0.212$), left fusiform ($r = 0.263$), and left inferior temporal cortex ($r = 0.283$) exhibited significant correlation between the SD and the duration of illness. The inferior frontal operculum displayed significant correlation between the LI and age of onset ($r = 0.181$). The parahippocampal brain region showed significant correlation between LI and the duration of illness ($r = 0.199$). All results passed the FDR correction for multiple comparisons with $P < 0.0011$. There was no significant correlation between SD/LI and PANSS scores.

The LI of olfactory, hippocampus, postcentral, caudate, pallidum and thalamus do not have significant group by sex interaction after correction for multiple comparisons using Bonferroni method (all P-values > 0.0011). In addition, none of brain region show significant correlation between LI and CPZ equivalent dose.

4. Discussion

The key findings that have emerged from this study are that 1)

Table 3
Regions showing significant changes in lateralization indices between hemispheres.

Region of the brain	Schizophrenia patients	Healthy control	*p*	Laterality
Central region				
Postcentral cortex*	0.003 ± 0.036	−0.009 ± 0.040	< 0.001	R to L
Precentral cortex*	0.009 ± 0.045	−0.008 ± 0.044	< 0.001	R to L
Rolandic operculum*	0.030 ± 0.046	0.013 ± 0.041	< 0.001	L↑
Frontal lobe				
Inferior frontal cortex, operculum*	0.033 ± 0.045	0.018 ± 0.040	< 0.001	L↑
Paracentral lobule	−0.095 ± 0.051	−0.108 ± 0.058	0.012	R↓
Supplementary motor area	0.011 ± 0.034	0.003 ± 0.029	0.005	L↑
Temporal lobe				
Heschl cortex	0.026 ± 0.060	0.013 ± 0.060	0.009	L↑
Inferior temporal cortex*	−0.027 ± 0.064	−0.056 ± 0.052	< 0.001	R↓
Middle temporal cortex*	0.010 ± 0.044	−0.006 ± 0.033	< 0.001	R to L
Middle temporal cortex, temporal pole	0.125 ± 0.069	0.110 ± 0.062	0.013	L↑
Superior temporal cortex*	0.070 ± 0.048	0.051 ± 0.043	< 0.001	L↑
Superior temporal cortex, temporal pole	0.106 ± 0.057	0.092 ± 0.057	0.011	L↑
Parietal lobe				
Supramarginal cortex*	−0.028 ± 0.043	−0.042 ± 0.043	0.001	R↓
Occipital lobe				
Fusiform cortex*	0.028 ± 0.045	0.007 ± 0.035	< 0.001	L↑
Lingual cortex	−0.032 ± 0.051	−0.045 ± 0.051	0.005	R↓
Superior occipital cortex	0.021 ± 0.041	0.029 ± 0.040	0.030	L↓
Limbic lobe				
Hippocampus*	0.051 ± 0.045	0.035 ± 0.033	< 0.001	L↑
Parahippocampal cortex*	0.024 ± 0.049	0.007 ± 0.038	< 0.001	L↑
Insula*	0.002 ± 0.040	−0.010 ± 0.038	< 0.001	R to L
Sub-cortical grey nuclei				
Amygdala	0.045 ± 0.072	0.032 ± 0.060	0.049	L↑
Caudate nucleus	0.007 ± 0.035	−0.001 ± 0.037	0.016	R to L
Lenticular nucleus, pallidum	0.124 ± 0.028	0.119 ± 0.024	0.043	L↑
Lenticular nucleus, putamen*	0.090 ± 0.025	0.083 ± 0.021	< 0.001	L↑

Asterisk means P value with Bonferroni correction was lower than 0.0011 at the cluster level.
R to L means lateralization in patients with schizophrenia have significant changes from Rightward to leftward compare to healthy controls.
L↑ means lateralization in patients with schizophrenia have significant increased leftward compare to healthy controls.
L↓ means lateralization in patients with schizophrenia have significant decreased leftward compare to healthy controls.
R↓ means lateralization in patients with schizophrenia have significant decreased rightward compare to healthy controls.

compared to healthy controls, schizophrenia patients exhibit a significant increase in the SD of the resting-state fMRI signal in the left inferior temporal, left fusiform, and right dorsal medial prefrontal cortex, and a decrease in the SD of the resting-state fMRI signal in the right precuneus, left/right posterior cingulum, right lingual, and left calcarine cortex; 2) schizophrenia patients display a significantly increased leftward lateralization of the SD of the resting-state fMRI signal in the precentral, operculum inferior frontal, operculum rolandic, insula, hippocampus, parahippocampal, fusiform, postcentral, supramarginal, putamen, superior temporal, middle temporal, and inferior temporal brain regions; and 3) three brain regions, including fusiform, lingual, and inferior temporal cortex, show significant between-group difference in both SD and LI; 4) abnormal SD and LI found in patients with schizophrenia were correlated to the age of onset or the duration of illness.

4.1. Variability of the resting-state fMRI signal

It is clear that the spatial property of the resting-state fMRI activity distinguishes it from random noise. However, interestingly, so does its temporal property (Biswal et al., 1995b; Faisal et al., 2008; Stein et al., 2005). Studies concerning the temporal property, such as those measured through the use of the variability in neural activity, have emerged in recent years, which shows the potential for elucidating the nuances of the human brain function (Halliday et al., 2017; Zöller et al., 2017). Indeed, variability in brain activations may potentially represent the substrate for adaptive and stable neural function (Garrett et al., 2013b). Several studies have demonstrated that the variability of brain signal is higher in better performing younger adults in comparison with lower performing elderly subjects (Garrett et al., 2012, 2013a; Grady and Garrett, 2014). Recent research has yielded an intriguing conclusion that high levels of variability in neuronal processes are beneficial for cognitive functioning in healthy adults. However, cognitive stability, i.e., the ability to maintain a task goal in the face of irrelevant distractors, would suffer under high levels of brain signal variability (Armbruster-Genç et al., 2016). Variability of the resting-state fMRI signal have been observed to be altered in multiple neuropsychiatric disorders, such as autism (Di Martino et al., 2014; Lai et al., 2010), Alzheimer's disease (Han et al., 2011; Liu et al., 2016), and attention deficit hyperactivity disorder (Yu-Feng et al., 2007), as well as schizophrenia (Yang et al., 2014c).

It is noteworthy that the SD of the resting-state fMRI signal is related to methods of amplitude of low-frequency fluctuation (ALFF) or fractional amplitude of low-frequency fluctuation (fALFF) in the frequency-domain. ALFF and fALFF quantify the variability of the resting-state fMRI signal with the help of the spectral method. Mathematically, the sum of the total power in the spectrum of the resting-state fMRI is equivalent to its statistical variance. For purposes of consistency and simplicity of the data analysis, we focused on SD in the present study (Garrett et al., 2017).

4.2. Variability vs. complexity

The term *variability* is used in numerous different contexts, such as descriptions of genetic differences, phenotypic variations, or fluctuations of physiologic signal over time. Analysis and quantification of

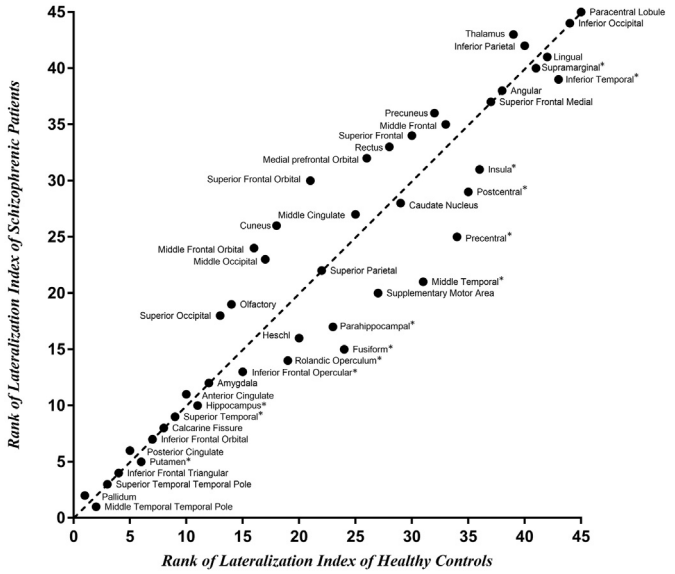

Fig. 2. Rank comparison of the lateralization index between healthy controls and schizophrenia patients is presented here. The horizontal axis represents the rank of the LI of healthy controls in a given AAL region and the vertical axis denotes the rank of the LI of schizophrenia patients in the same brain regions. Asterisk assigned to the brain regions indicates that the LI of the regions have significant difference between healthy controls and schizophrenia patients after the FDR correction. The dash line is y = x. If the LI rank in schizophrenia is higher than that in healthy controls, the point will be above the dash line, and vice versa. The regions of the brain with higher LI rank in schizophrenia than that in healthy controls indicate increased leftward lateralization.

Table 4
Correlation between SD/LI and psychopathology.

	Brain region	Pearson *r*	*P*
SD			
	Duration		
	Lingual_R	0.212	0.011
	Fusiform_L	0.263	0.001
	Inferior Temporal_L	0.283	0.001
LI			
	Age of onset		
	Inferior Frontal, Opercular	0.181	0.005
	Duration		
	Parahippocampal	0.199	0.004

All brain regions had P value < 0.05 corrected for multiple comparisons using FDR methods.
L, left; R, right.
All brain regions show significant SD/LI changes of BOLD signals between patients with schizophrenia and healthy controls.

variability in a manner that our brain activity fluctuates over time may offer new approaches toward the diagnosis and therapeutics of brain dysfunction. The SD is the most fundamental measure of variability. For instance, heart rate variability has been one of the most widely studied application of dynamics to human physiology (van Ravenswaaij-Arts et al., 1993), and alterations in the SD of heart rate has been observed in cardiovascular diseases (Kleiger et al., 1987; Tsuji et al., 1994). It is noteworthy that SD quantifies the variation of the signal but does not capture the dynamics of the signal, which is often referred to as *complexity (Goldberger, 1996)*.

However, we discovered that the results from the SD and quantification of complexity could be complementary. According to our previous study related to brain signal complexity in schizophrenia using the multiscale entropy method (Yang et al., 2015), the fusiform gyrus and middle temporal gyrus, which exhibit a regular pattern of reduction in brain signal complexity, also exhibit a larger resting-state fMRI signal variability (SD) and leftward lateralization in the current study. Previous studies have shown that these regions of the brain are associated with auditory or imaginary hallucinations (Lawrie et al., 2002; Santhouse et al., 2000; Shergill et al., 2000). Our findings from both the SD and the brain signal complexity could support the idea that these regions of the brain are over-active (i.e., increased SD) and becomes too regular (i.e., the absence of complex dynamics). This is related to repetitive and involuntary hallucinatory experiences and fixed delusional thoughts. Additionally, the reduction in complexity in the occipital and postcentral cortices, together with increased leftward lateralization, is consistent with the impaired sensory gating and sensory overload commonly observed in patients with schizophrenia (Braff and Geyer, 1990; Brown et al., 2002; Swerdlow et al., 2016).

4.3. Brain lateralization in schizophrenia

Abnormal brain lateralization has been implicated in schizophrenia in both structural (e.g., grey matter volume, cytoarchitecture and dendritic arborization, or in white-matter integrity) and functional measures (e.g., functional connectivity). In general, schizophrenia patients display lesser anatomical and functional asymmetries than healthy people (Ribolsi et al., 2009b).

A meta-analysis of a large population of schizophrenia patients reveals the reduced asymmetry in grey matter volume in the planum temporale, which is anatomically and functionally related to language processes (Shapleske et al., 1999). This reduced asymmetry of the planum temporale has been observed to be associated with more severe positive symptoms in schizophrenia patients (Oertel et al., 2010a). In another study, a loss of the cerebral torque (greater width of the right frontal and left occipital lobes relative to their contra-lateral counterparts) was found in patients with schizophrenia, compared with healthy controls (Crow, 2013). Conversely, reduced lateralization was also observed in white matter integrity with the help of diffusion tensor imaging (DTI), which revealed a reduction in asymmetry in the cingulum bundle and the anterior corpus callosum (Park et al., 2004). A loss of left-hemisphere dominance and structural anomalies of cerebral asymmetry are related to the progression of the disease (Lam et al., 2012). These points indicate the hypothesis of the failure of left-hemisphere lateralization in the pathophysiology of schizophrenia (Crow, 1997).

However, some studies also found an increase in asymmetry in cases of schizophrenia, particularly in the sub-cortical regions. For example, increased rightward asymmetry of the thalamus (Csernansky et al., 2004) and hippocampus (Wang et al., 2001) have been reported in the investigation of schizophrenia. A recent study discovered a schizophrenia-specific leftward asymmetry in the globus pallidus volume, which suggests the possibility of aberrant laterality in neural pathways and connectivity patterns related to the pallidum in the case of schizophrenia (Okada et al., 2016). Other studies have reported a reversal of lateralization to the right hemisphere in schizophrenia (Aydin et al., 2001; Gruzelier et al., 1999; Gur and Chin, 1999; Kircher et al., 2002; Kwon et al., 1999; Sommer et al., 2001; Sumich et al., 2002). The inconsistency may be attributed to different patient conditions, populations, and methods of analysis (Hallahan et al., 2011; Okada et al., 2016).

Besides the aforementioned evidence supporting the existence of abnormal structural asymmetry in schizophrenia, functional brain activity has been investigated in order to account for possible functional asymmetries in schizophrenia patients. In electrophysiologic studies, the level of asymmetry (predominantly right-sided) in the distribution of the spectral power of the electroencephalogram (EEG) rhythms has been observed to depend on disease severity in schizophrenia. This is owing to the fact that acute patients exhibit a greater asymmetry than chronic patients, in which the power of most EEG rhythms was

significantly lower than in acute schizophrenia and in healthy control groups (Strelets et al., 2006). Such an asymmetry in brain activity may lead to asymmetry in functional connectivity between spatial brain regions. Implementing the resting-state fMRI technique, a generally attenuated asymmetry between the two hemispheres was discovered in chronic schizophrenia, as compared with healthy controls (Jalili et al., 2010). Furthermore, the degree of abnormality of asymmetry increases with the duration of the disease and correlates with the negative symptoms (Jalili et al., 2010). The result of an attenuated asymmetry of functional connectivity was also found by Rotarska-Jagiela et al. (Rotarska-Jagiela et al., 2009), as patients displayed a lower degree of right-sided laterality for the right fronto-parietal network. Collectively, these suggest that abnormal brain asymmetry and connectivity are important determinants of schizophrenia pathophysiology.

The present study revealed a majority of increased leftward lateralization of brain signal variability in patients with schizophrenia, as compared to healthy controls. In particular, we found that three brain regions, including fusiform, lingual, and inferior temporal cortex, show significant between-group difference in both SD and LI, which may implicate in the pathophysiology of schizophrenia.

Lines of evidence suggest that individuals with schizophrenia suffer from face processing deficits. Although fusiform has been shown to function normally in schizophrenia in general face recognition (Yoon et al., 2006), patients demonstrated greater fMRI variability compared to healthy controls (Silverstein et al., 2010). Though hyperactivation in bilateral lingual gyrus of schizophrenia patients has been found in previous work (Birur et al., 2017; Kühn and Gallinat, 2011), the left lingual exhibited more resting-state fMRI variability compared to the right side for the decreased rightward lateralization according to our study. The left inferior temporal gyrus is one of the most important brain regions involved in the pathophysiology of schizophrenia and has a crucial role in social cognition and emotional processes (Wang et al., 2016). In this study, schizophrenia patients exhibited reduced rightward lateralization of resting-state fMRI variability in this brain area, suggesting that impairments in basic integration abilities may be compensated for by relatively increased activity in this region, especially in the left hemisphere.

Additionally, we observed a marginal association of lateralization of brain signal variability with the age of onset and the duration of illness. Although the mechanism underlying this observation is unclear, we speculate that a dysfunctional inter-hemispheric communication, as evidenced by the disrupted inter-hemispheric information transferring in schizophrenia (Beaumont and Dimond, 1973; Ribolsi et al., 2011) may contribute to the asymmetry of brain signal variability in patients. Future studies should investigate the degree of connectivity of regions of the brain in relation to the brain signal variability and their relationship to structural and functional brain lateralization in cases of schizophrenia.

5. Limitation

There are several limitations to this study. First, like most resting-state fMRI study of psychosis, the patients enrolled in this study were medicated and were not in an acute stage wherein they tend to be uncooperative and incompetent. Currently, little is known about the effects of antipsychotic drugs on resting-state fMRI signals. A meta-analysis revealed no common effect of antipsychotics on resting-state fMRI signals. However, antipsychotics with various affinities for the dopamine D2-receptor may influence resting-state fMRI activity (Baker et al., 2014). A future study categorizing patients with schizophrenia according to various outcomes or classes of antipsychotics may clarify this effect. Second, we applied an ROI approach to investigate the lateralization of brain signal variability. Future study is warranted for examining the lateralization of brain signal variability at the voxel-wise level. Third, the method of quantifying brain signal variability using SD is comparable to the amplitude of low-frequency fluctuation derived through spectral analysis (Yang et al., 2007; Zou et al., 2008). However, without the distinct spectral decomposition of resting-state fMRI signal, the SD could be more straightforward and fundamental (Garrett et al., 2017), as demonstrated in other studies pertaining to the physiologic system, such as heart rate variability (Tsuji et al., 1994). Currently, the exact compositions of resting-state fMRI signals and their functional relevance are still under investigation, with the neural component of the resting-state fMRI signal being typically detected at a low-frequency range (< 0.08 or < 0.1 Hz) (Biswal et al., 1995a; Buckner et al., 2009; Zou et al., 2008). The spectral division of the resting-state fMRI signal and the variability underlying specific frequency band may be examined using data with longer scanning time and higher sampling rate, such as those used in the Human Connectome Project (Van Essen et al., 2013).

6. Conclusion

Using brain signal variability as an indicator of functional brain activity, we have evaluated the lateralization of brain signal variability in patients with schizophrenia. We observed abnormal variability of the resting-state fMRI signal and increased leftward lateralization of this variability in cases of schizophrenia. These findings support the notion that abnormal variability in temporal brain signal activity may be related to the pathology of the schizophrenia. On a broader scale, analyzing the variability of the human brain at the temporal dimension may have potential help to identify the dysfunctional brain lateralization in schizophrenia.

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Conflict of interest

All authors declared that there are no conflicts of interest in relation to the subject of this study.

Ethical statement

We confirmed that the data contained in this manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Progress in Neuro-Psychopharmacology and Biological Psychiatry.

The study was conducted in accordance with the Declaration of Helsinki, receiving approval from the local Institutional Review Board. Informed consent was obtained from all subjects prior to commencement of the study.

We confirmed that all authors have reviewed the contents of this manuscript, approve of its contents and validate the accuracy of the data.

All authors reported no biomedical financial interests or potential conflicts of interest.

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