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Enhanced temporal variability of amygdala-frontal functional connectivity in patients with schizophrenia

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ABSTRACT

Background: The "dysconnectivity hypothesis" was proposed 20 years ago. It characterized schizophrenia as a disorder with dysfunctional connectivity across a large range of distributed brain areas. Resting-state functional magnetic resonance imaging (rsfMRI) data have supported this theory. Previous studies revealed that the amygdala might be responsible for the emotion regulation-related symptoms of schizophrenia. However, conventional methods oversimplified brain activities by assuming that it remained static throughout the entire scan duration, which may explain why inconsistent results have been reported for the same brain region.

Methods: An emerging technique is sliding time window analysis, which is used to describe functional connectivity based on the temporal variability of regions of interest (e.g., amygdala) in patients with schizophrenia. Conventional analysis of the static functional connectivity between the amygdala and whole brain was also conducted.

Results: Static functional connectivity between the amygdala and orbitofrontal region was impaired in patients with schizophrenia. The variability of connectivity between the amygdala and medial prefrontal cortex was enhanced (i.e., greater dynamics) in patients with schizophrenia. A negative relationship was found between the variability of connectivity and information processing efficiency. A positive correlation was found between the variability of connectivity and symptom severity.

Conclusion: The findings suggest that schizophrenia was related to abnormal patterns of fluctuating communication among brain areas that are involved in emotion regulations. Unveiling the temporal properties of functional connectivity could disentangle the inconsistent results of previous functional connectivity studies.

1. Introduction

Schizophrenia is a complex and heterogeneous mental disorder that was recognized approximately 100 years ago. Revealing the underlying neurobiological mechanisms associated with schizophrenia is crucial for effective diagnosis and treatment (McGlashan, 2011). The "dysconnectivity hypothesis" proposes that abnormal communication occurs across distributed brain areas and is crucial for the development of schizophrenia (Vogeley and Falkai, 1998; Bullmore et al., 1997; Zhou et al., 2015). Magnetic resonance image (MRI) studies provided preliminary evidence of alterations in functional and anatomical brain connectivity in patients with schizophrenia, particularly in the fronto-temporal system (Leroux et al., 2014). The amygdala and prefrontal cortex (PFC) play critical roles in the fronto-temporal system. Both regions are involved in affect perception and emotional and cognitive processing (Whitford et al., 2011; Shi et al., 2012; Samartzis et al., 2014; Voineskos, 2014). These functions are impaired in schizophrenia, underscoring the importance of examining the functional integrity of the amygdala and PFC.

Several neuroimaging studies have consistently reported smaller amygdala volumes and alterations of amygdala activity in patients with schizophrenia and their relatives. Imaging studies that analyzed structural data examined brain structures in high-risk offspring of schizophrenia patients and found that the volume of the left-amygdala was

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smaller in high-risk individuals (Keshavan et al., 2002). Amygdala activation has also been assessed during emotion-related tasks. However, since the seminal study by Schneider and colleagues that reported under-recruitment of the amygdala following mood induction in schizophrenia, no consensus has yet been reached on this issue (Schneider et al., 1998; Anticevic et al., 2011). Meta-analyses have shown that schizophrenia patients exhibit modest, albeit statistically significant, and decrease in amygdala recruitment in responses to aversive emotional stimuli (Anticevic et al., 2012; Taylor et al., 2012). Other studies found that functional connectivity between the amygdala and frontal regions is disrupted in schizophrenia (Hoptman et al., 2010; Liu et al., 2014). The present study focused on functional connectivity between the amygdala and whole brain in patients with schizophrenia. Based on the emotion-regulation related symptoms and the specific role of amygdala, our hypothesis was that functional connectivity between the amygdala and PFC was disrupted in patients with schizophrenia.

Conventional approaches that are used to study functional connectivity have an important disadvantage, in which brain activity is assumed to be static throughout the entire duration of scanning. Considering the complexity of the human brain and the ever-changing environment, this assumption that brain activity remains static is an oversimplification, which may omit important information. Brain connectivity should be considered flexible in integrating and transformatting information, in which it varies over time when responding to an ever-changing environment. Emerging studies have attempted to capture the dynamic nature of functional connectivity (Hutchison et al., 2013a; Hutchison et al., 2013b). Several recent studies showed that the dynamics of connectivity can capture uncontrolled but relatively robust patterns of temporal features among networks (Allen et al., 2012; Allen et al., 2014; Sakoğlu et al., 2010), which cannot be detected with static functional connectivity analyses.

One other promising approach to investigate variations in functional connectivity is sliding-time window correlation analysis (Hutchison et al., 2013a; Shakil et al., 2016). In this strategy, a time window with a fixed length is selected and used to calculate the functional connectivity metric. The window then slides by a fixed length to the next time window, which results in many functional connectivity metrics that can elucidate the temporal features of functional connectivity over the entire duration of the scan. Studies of major depression disorder, schizophrenia, and autism have revealed abnormal temporal attributes of functional connectivity (Kaiser et al., 2015; Demirtaş et al., 2016; Damaraju et al., 2014; Nguyen et al., 2016; Mulvey et al., 2013). The results have demonstrated that dynamic functional connectivity that is captured by the sliding time window method can facilitate the interpretation of communication across neural systems. Considering this emerging method and the inconsistent results of functional connectivity analyses between the amygdala and frontal brain areas, the present study investigated variations of functional connectivity, in addition to investigating the static functional connectivity between the amygdala and whole brain. Because of the unstable emotion regulation that is associated with schizophrenia, another hypothesis of the present study was that functional connectivity between the amygdala and PFC would present more variation and less stability in patients with schizophrenia.

2. Methods

2.1. Participants

We assessed a total 67 subjects: 34 healthy controls and 33 schizophrenia patients. The groups were matched for age and sex (age: $p = 0.303$, $t = 1.2031$, df = 2; sex: $p = 0.745$, $\chi^2 = 0.59$, df = 2; Table 1). Diagnoses were based on detailed medical and psychiatric histories and the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*. The exclusion criteria were the following: (i) age < 18 or > 45 years, (ii) left handedness, (iii) history of brain trauma with loss of consciousness, neurological diseases, or serious physical diseases (e.g., respiratory disorders, cardiovascular diseases, and so on), (iv) diagnosis of alcohol/substance abuse within 12 months before participation in the study, and (v) contraindications for MRI. Seven of 33 patients were free of antipsychotic medication (medication-naive: $n = 4$; off antipsychotic medications for at least 2 weeks: $n = 3$), and all of the other patients were on antipsychotic medications at the time of the scan (olanzapine, $n = 8$; risperidone, $n = 9$; aripiprazole, $n = 2$; blonanserin, $n = 5$; amisulpride, $n = 1$; haloperidol, $n = 2$, and one patient received both risperidone and blonanserin at the same time). The Ethics Committee of Beijing Hui-Long-Guan Hospital (Beijing, China) approved the study, and all of the participants provided written informed consents.

Table 1
Demographic and clinical characteristics of the participants in each group.

Characteristic	Schizophrenia group	Healthy control group	*p*
	$n = 33$	$n = 34$	
	Mean (SD)	Mean (SD)	
Age (years)	30.60 (8.13)	28.12 (6.5)	0.171
Sex (male/female)	11/22	14/20	0.51
Education (years)	12.36 (2.68)	12.74 (3.79)	0.686
Age at disease onset (years)	26.21 (8.242)	NA	
Length of illness (years)	4.74 (2.52)	NA	
PANSS score			
Total	78.36 (7.95)	NA	
Positive	25.61 (3.41)	NA	
Negative	17.15 (2.81)	NA	
General	35.60 (4.15)	NA	
Digit coding task	41 (13.1)	64.9 (11.9)	0.00

PANSS, Positive and Negative Symptom Scale.

2.2. Data acquisition and preprocessing

fMRI data were acquired using a 3.0 Tesla Magnetom Trio scanner. The resting-state functional scans were obtained using a gradient-recalled echo-planar imaging sequence that was sensitive to blood oxygen level-dependent contrast (repetition time, 2000 ms; echo time, 30 ms; flip angle, 90°). The slice thickness was 4 mm (no gap), with a matrix size of 64 × 64 and field of view of 220 × 220 mm^2, resulting in a voxel size of 3.4 × 3.4 × 4.0 mm^3. Each brain volume comprised 33 axial slices, and each functional run contained 240 image volumes. During data acquisition, the subjects were instructed to close their eyes, relax, and stay awake. All of the images were checked for artifacts, structural abnormalities, and pathologies by a qualified neuroradiologist.

Image preprocessing was performed using statistical parametric mapping (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). To allow for magnetization equilibrium, the first 20 volumes of the functional images were discarded. The preprocessing procedure included slice-timing correction and head-motion correction. Four patients with schizophrenia were excluded because of head motion (> 2.5 mm). Each fMRI scan was intensity-scaled to yield a whole-brain mean value of 10,000. Temporal band-pass filtering (0.01 < f < 0.08 Hz) was then performed. This range was selected to remove high-frequency activity that is related to cardiac and respiratory activity and low-frequency activity with a period that exceeds the duration of sliding windows that are used in dynamic analyses (Cordes et al., 2001; Leonardi and Van De Ville, 2015). The time series in white matter and cerebrospinal fluid and six affine motion parameters were also regressed from the data. The removal of linear and quadratic trends was also implemented. To obtain results at the group level, single-subject images were nonlinearly normalized to Montreal Neurological Institute (MNI) space using DARTEL in SPM8 and