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Altered resting-state regional homogeneity after 13 weeks of paliperidone injection treatment in schizophrenia patients

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ABSTRACT

This study aimed to explore the effects of the long-acting antipsychotic drug palmitate paliperidone in resting-state brain activity of schizophrenia patients. Seventeen schizophrenia outpatients were included and received palmitate paliperidone injection (PAL) treatment for 13 weeks. These patients were compared to seventeen matched healthy controls. All subjects underwent two scan sessions of resting-state magnetic resonance imaging (baseline and the 13th week) and regional homogeneity (ReHo) at resting-state where compared. After 13 weeks of treatment, PAL increased ReHo of the prefrontal cortex, anterior cingulate gyrus and orbital frontal gyrus, while PAL decreased ReHo of the thalamus, parahippocampal gyrus and superior temporal gyrus. Furthermore, improvement of psychiatric symptoms correlated with changing amplitude of ReHo: positively correlated with postcentral gyrus and negatively correlated with the occipital cortex. Baseline ReHo values of the middle occipital gyrus were positively correlated with the rate of reduction of psychiatric symptoms and improvement of social function. These results suggested that PAL might achieve its clinical effect in schizophrenia by influencing the resting-state function of the occipital cortex, lateral prefrontal cortex and temporal lobe. Baseline function of the inferior occipital gyrus might potentially predict the short-term effect of PAL in schizophrenia.

1. Introduction

Psychopharmacological treatments for schizophrenia is an important issue in public health given the chronic, relapsing and disabling nature of the disorder (Mayoral-van Son et al., 2015). Typically, treatment of schizophrenia with antipsychotics requires an extended regimen to effectively minimize the symptoms and to reduce the likelihood of relapse (Ascher-Svanum et al., 2006; Jablensky et al., 1992). Although wildly used in clinical treatment, antipsychotics result in variable clinical responses. Moreover, the brain functional changes induced by antipsychotics remain largely unknown.

In recent years, brain functional magnetic resonance imaging (fMRI) has emerged as a useful method to analyze the relationship between symptoms of schizophrenia patients and changes in their brain activity. fMRI might be a key tool in understanding the pathogenesis of schizophrenia and predicting patients' prognosis at the level of brain function (Dazzan et al., 2015). Atypical antipsychotics treated (medicated) schizophrenia patient group displayed higher dorso-lateral prefrontal cortex (DLPFC) activation than unmedicated patient group (Lesh et al., 2015). Clozapine treatment resistance seems to be associated with hyper-activation of the dorso-medial prefrontal cortex (DMPFC) in schizophrenia patients during emotional processing (Potvin et al., 2015). Evaluating the influence of antipsychotics based on measures of brain function is of crucial importance to understanding how these medications affect the brain and illness. An acute dose of aripiprazole or haloperidol is reported to show strong task

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effects with prominent activation in the occipital, parietal and frontal cortices and the thalamus in healthy participants (Bolstad et al., 2015). One recent study using resting-state fMRI provides evidence that baseline striatal functional connectivity can predict the response to antipsychotic treatment in acute psychotic patients (Sarpal et al., 2016). Kraguljac et al. also reported that baseline connectivity between the hippocampus and anterior cingulate cortex, caudate nucleus, auditory cortex and calcarine sulcus in patients might predict the following response to risperidone (Kraguljac et al., 2016). Most of the results gained from the connectivity analysis were derived from the prior proposed region of interests (ROI). As studies examining the change in brain fMRI of patients with schizophrenia before and after treatment with atypical antipsychotic drugs are still rare, a whole-brain based prospective approach is important to fill the current gap in the knowledge of psychotropic drug efficacy and their mechanisms of action beyond neurotransmitter systems level (Rossi et al., 2015).

Regional homogeneity (ReHo) is a measure of the similarity of the time series of a given voxel with its nearest neighbors within a single region and provides important information about the local temporal synchrony in the brain (Zang et al., 2004). Since the blood-oxygenation-level-dependent (BOLD) signal of fMRI reflects neural activity (Logothetis and Wandell, 2004), abnormal ReHo is more likely related to changes in the temporal aspects of the spontaneous neural activity in a specific brain region. Using these methods, abnormal spontaneous neuronal activities in schizophrenia have been reported (Liu et al., 2016; Xu et al., 2015).

As a newly available, long-acting, injectable antipsychotic, paliperidone palmitate injection (PAL) may show an advantage to improve adherence (Kane, 2006) and relapse prevention (Kishimoto et al., 2013) in patients than oral formulations for treating schizophrenia. Paliperidone, the 9-hydroxy main metabolite of risperidone, antagonizes D2 and 5-HT2A receptors (Corena-McLeod, 2015) and has proven effective in the treatment of schizophrenia (Schreiner et al., 2015). In the present study, we investigate the effect of PAL on brain function to better understand the mechanism-of-action of PAL. We examine changes in ReHo with brain resting-state fMRI in patients with schizophrenia before and after treatment with PAL and correlate of ReHo to patient symptoms.

2. Materials and methods

2.1. Participants

Schizophrenia patients 18–50 years old underwent resting-state fMRI scanning and symptom ratings at baseline and after 13 weeks of treatment with PAL (NCT01259232, https://clinicaltrials.gov). All patients did not have any exposure to antipsychotics two weeks before entering this clinical study. We also recruited seventeen gender- and age-matched healthy controls (HC) by advertisement. Healthy controls were scanned at two time points within a 12–14 week interval (Table 1). Patients were diagnosed with the Structured Clinical Interview for Axis I Diagnostic and Statistical Manual-IV Disorders (SCID). All participants or guardians signed informed consent (written consent and written parental/guardian consent for those under 18 years old) after a complete description of the study. The study was approved by the Ethics Committee of First Affiliated Hospital of Kunming Medical University. Patients' legal guardians supervised the processes of consent. Additional details regarding inclusion and exclusion criteria for our study participants are provided in the Supplemental materials.

The 26 patients met the following criteria: (i) DSM-IV diagnosis of schizophrenia according to the SCIDI/P, and no other Axis I diagnosis in their lifetime; (ii) ages 18–60 years old; (iii) Score of PANSS:60–120; (iv) willing to accept the treatment of paliperidone palmitate. Exclusion criteria: (i) any suicide attempt and no serious tendency of acts of suicide and violence in clinical evaluations before 12 months of screen; (ii) had taken non-selective/irreversible monoamine oxidase inhibitor antidepressant drugs within the prior 30 days; (iii) never received electroconvulsive shock treatment; (iv) history of major neurological or physical disorders; (v) history of drug abuse; (vi) pregnant for women or plan of pregnant in the following 3 months; (vii) cannot cooperate with the brain fMRI scan; (viii) Metal in the body; (ix) Abnormal brain structure. We also excluded data due to abnormal brain structure or excessive head motion beyond 1.5 mm. Psychiatric symptoms were rated using the Positive and Negative Symptom Scale (PANSS). And social function was evaluated by Personal Social Performance Scale (PSP).

This study used an open design with variable dose of PAL treatment. Schizophrenia Patients received PAL treatment and underwent resting-state fMRI scanning and symptom ratings at baseline and after 13 weeks of treatment. In this study, PAL was provided as 75, 100, and 150 mg injectable suspensions and was administered using intramuscular gluteal injections of 150 mg at day 1, 100 mg at day 8 and then once every month with subsequent gluteal injections at a flexible dose (75, 100, or 150 mg), according to the clinical effect and tolerance, for the next two months (see Treatment schedule, Supplementary Fig. S1).

2.2. Image acquisition

MRI data acquisition was performed on a GE Signa 1.5T scanner in the department of Radiology of The First People's Hospital of Kunming. Patients lay quietly in the scanner with their eyes closed and remained awake. A black eye-shade and earplugs were used to minimize the inference of light and scanner noise, respectively. Before the scans, subjects were instructed to remain still and stay awake. The functional images were obtained using a fast spoiled gradient-recalled acquisition (FSPGR) sequence with the following parameters in order

Table 1
Demographics and clinical data.

	Healthy controls (N=17)	Patients (N=17)		t	P
		Baseline	13 weeks		
Age (year)	**28.71(5.96)**	**26.00(5.49)**			
Sex (Male/Female)	**14/3**	**14/3**			
Education (year)	**13.65(2.21)**	**10.59(4.24)**			
Duration of illness (month)	**NA**	**40.29(38.03)**			
PANSS total	**NA**	**82.06 ± 12.26**	**61.71 ± 14.55**	**6.139**	**0.000**
Positive symptoms	**NA**	**15.29 ± 5.46**	**10.35 ± 2.89**	**3.917**	**0.001**
Negative symptoms	**NA**	**24.88 ± 6.45**	**21.12 ± 7.98**	**2.984**	**0.009**
Basic symptoms	**NA**	**41.88 ± 7.32**	**30.24 ± 6.04**	**5.84**	**0.000**
Delusion	**NA**	**3.06 ± 1.71**	**1.94 ± 0.97**	**2.613**	**0.019**
Hallucination	**NA**	**2.47 ± 1.74**	**1.47 ± 0.87**	**2.675**	**0.017**
PSP	**NA**	**47.82 ± 9.95**	**61.53 ± 11.71**	**5.713**	**0.000**