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Olanzapine modulation of long- and short-range functional connectivity in the resting brain in a sample of patients with schizophrenia

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Abstract
Treatment effects of antipsychotic drugs on cerebral function are seldom examined. Exploring functional connectivity (FC) in drug-free schizophrenia patients before and after antipsychotic treatment can improve the understanding of antipsychotic drug mechanisms. A total of 17 drug-free patients with recurrent schizophrenia and 24 healthy controls underwent resting-state functional magnetic resonance imaging scans. Long- and short-range FC strengths (FCS) were calculated for each participant. Compared with the controls, the patients at baseline exhibited increased long-range positive FCS (lpFCS) in the bilateral inferior parietal lobule (IPL) and decreased lpFCS in the brain regions of the default-mode network (DMN) regions and sensorimotor circuits of the brain. By contrast, increased short-range positive FCS was observed in the right IPL of the patients at baseline compared with the controls. After treatment with olanzapine, increased FC in the DMN and sensorimotor circuits of the brain was noted, whereas decreased FC was observed in the left superior temporal gyrus (STG). Moreover, the alterations of the FCS values and the reductions in symptom severity among the patients after treatment were correlated. The present study provides evidence that olanzapine normalizes the

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abnormalities of long- and short-range FCs in schizophrenia. FC reductions in the right IPL may be associated with early treatment response, whereas those in the left STG may be related to poor treatment outcome.

1. Introduction

Schizophrenia is a complex, recurrent psychiatric disorder associated with clinical heterogeneity and functional disability (Silveira et al., 2012). Studies have suggested that disrupted functional connectivity (FC) between certain brain regions is associated with clinical symptoms and cognitive deficits (Lawrie et al., 2002; Meyer-Lindenberg et al., 2005), which support the "disconnection" hypothesis in schizophrenia (Friston, 1998). Decreased FC has been reported in widely distributed brain regions, such as the anterior cingulate cortex, frontal and temporal gyri, and other cortical and subcortical regions in both first-episode and chronic schizophrenia (Pettersson-Yeo et al., 2011).

The standard treatment for schizophrenia is the use of antipsychotic drugs, such as olanzapine, risperidone, and quetiapine. Antipsychotic drugs relieve clinical symptoms mainly through their affinity with D_2 dopamine receptors. However, the system-level mechanisms through which antipsychotic drugs execute treatment effects remain unknown. The results of systematic reviews (Abbott et al., 2013; De Rossi et al., 2015) show normalization (Bertolino et al., 2004; Blasi et al., 2009; Keedy et al., 2009; Lui et al., 2010; Sambataro et al., 2010; Snitz et al., 2005; Stephan et al., 2001; van Veelen et al., 2011) and concurrent abnormal activity (Keedy et al., 2009; Lui et al., 2010; Stephan et al., 2001) of the blood-oxygen-level-dependent functional magnetic resonance imaging (fMRI) signal related to antipsychotic treatment compared with baseline brain function. Normalization was reported in the default mode network (DMN), frontoparietal and temporal networks, and sensorimotor circuits after treatment with antipsychotics. By contrast, disrupted connectivity was observed in the cortical (such as the dorsolateral prefrontal cortex and right ventral lateral prefrontal cortex) and subcortical regions (such as the putamen, caudate, and thalamus). In particular, only one study observed a significant correlation between alterations of brain activity and improvement of clinical symptoms (Lui et al., 2010). The aforementioned studies are helpful in improving the understanding of antipsychotic mechanisms beyond neurotransmitter systems. However, two issues remain unresolved. First, the aforementioned studies were conducted with different task designs, and only one study was performed at resting state (Lui et al., 2010). Hence, these studies expectedly acquire varying results with different task designs. Therefore, a "standard" design is urgently required. Second, these studies were conducted at two time points (baseline and after treatment) with a relatively short treatment period (mean: 45 days). Changes in brain activities over a long treatment period (e.g., 6 months) are yet to be studied.

Given the aforementioned reasons, we conducted a "resting-state" fMRI study on schizophrenia patients to examine treatment effects on brain FC. Resting-state fMRI is relatively easy to conduct, avoids performance confounds in clinical studies (Biswal et al., 1995; Callicott et al., 2003; Liu et al., 2013, 2015a), and has the potential to be a "standard" design for fMRI studies. In a preliminary study, Lui et al. (2010) reported that patients with drug-naive first-episode schizophrenia at rest exhibited widespread increased activity in several brain regions, including the bilateral prefrontal and parietal gyri, right caudate nucleus, and left superior temporal gyrus (STG). This study was helpful in clarifying the neural system effects of antipsychotic drugs, but the covered treatment period was short (6 weeks) (Lui et al., 2010).

FC analysis is commonly used to process resting-state fMRI data, which reflect the integration level of local brain activities across regions (Lui et al., 2010). Several studies have applied FC analysis in first-episode (Guo et al., 2015a, 2015b; Lui et al., 2009; Wang et al., 2016) and chronic schizophrenia (Wang et al., 2014). The human brain operates efficiently with both long- and short-range FCs. Long-range FC runs at higher metabolic and time costs (Bullmore and Sporns, 2012; Liang et al., 2013), whereas short-range FC operates at lower metabolic and time costs and exhibits enhanced FC strength (FCS) (Salvador et al., 2005). The brain will not discourage all long-range FCs despite their high metabolic and time costs (Vertes et al., 2012), and will be beneficial for efficient communication (Sepulcre et al., 2010). Studies in schizophrenia indicate that FC can be affected by anatomical distance (Guo et al., 2014, 2015c; Wang et al., 2014). Guo et al. (2014) observed reduced long-range FC in medicated schizophrenia, whereas Wang et al. (2014) reported reduced long- and short-range FCs in chronic schizophrenia. In our previous study (Guo et al., 2015c), we found increased long- and short-range FCs in DMN brain regions in first-episode drug-naive schizophrenia. However, the effects of antipsychotic treatment on long- and short-range FCs in schizophrenia have not yet been explored. Therefore, examining alterations of long- and short-range FCs in schizophrenia after antipsychotic treatment can not only offer new insights into the effects of antipsychotic treatment at the system level, but also help clarify whether FC abnormalities reported in chronic schizophrenia are either the result of treatment or disease-related changes.

In the present study, we recruited a group of drug-free patients with recurrent schizophrenia. The whole-brain FC was constructed and divided into long- and short-range FCs based on their anatomical distance (Achard et al., 2006; He et al., 2007). This study aimed to characterize alterations of long- and short-range FCs after antipsychotic treatment. The correlations between alterations of FC indices and decreases in symptom severity after treatment were also