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# Hyper-coupling between working memory task-evoked activations and amplitude of spontaneous fluctuations in first-episode schizophrenia

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ABSTRACT

Working memory (WM) deficit is an important component of impaired cognition in schizophrenia. However, between-studies inconsistencies as to the specific functional substrate imply that inter-individual variability (IIV) in the WM performance is associated with IIV in brain activity in schizophrenia. To examine the neural substrate of this WM IIV, we studied whether the neural mechanisms that underlie individual differences in WM capacity are the same in schizophrenia patients and healthy people. We correlated the IIV of the task-evoked brain activity and task performance during an n-back WM task with the IIV of the moment-to-moment variability in intrinsic resting-state activity, as measured by the amplitude of low-frequency fluctuations (ALFFs) and further compared this relationship between 17 patients with first-episode schizophrenia (FES) and 18 healthy controls. Between-group comparisons of the correlation patterns indicated aberrant ALFF-WM activation correlations and ALFF-WM performance correlations in the FES patients, but no significant changes were detected in any single measurement of these three characteristics. Specifically, we found increased positive ALFF-WM activation correlations in the bilateral lateral prefrontal cortices, posterior parietal cortices and fusiform gyri in the FES patients. We also observed significant increases in positive ALFF-WM performance correlations in the bilateral ventromedial prefrontal cortices in the FES patients. This hyper-coupling between the ALFF and fMRI measures during a WM task may indicate that it was difficult for the patients to detach themselves from one state to transition to another and suggests that the inefficient cortical function in schizophrenia stems from the intrinsic functional architecture of the brain.



## 1. Introduction

Working memory (WM) deficits are an important component of impaired cognition in people with schizophrenia (Lee and Park, 2005; Piskulic et al., 2007; Forbes et al., 2009). Cumulative evidence from neuroimaging and physiological studies suggests that functional abnormalities in the prefrontal and posterior parietal cortices are the neural basis for impairedWM in schizophrenia (Goldman-Rakic, 1999; Quintana et al., 2003; Glahn et al., 2005; Tan et al., 2006). However, mixed findings of hyperactivations, hypoactivations, or no differences in the dorsolateral prefrontal cortex (DLPFC) compared with healthy controls have been described during WM tasks (for review, see Manoach, 2003). A recent meta-analysis demonstrated that group differences in DLPFC activations between schizophrenia patients and healthy participants depended on the magnitude of the group differences in WM performance (Van Snellenberg et al., 2006). These findings suggest that inter-individual variability (IIV) in WM performance exists in schizophrenia and that behavioral IIV is associated with IIV in brain activity in schizophrenia.

Experiences shape intrinsic brain activity and intrinsic brain activity in turn impacts behavior (Sadaghiani and Kleinschmidt, 2013). In healthy populations, intrinsic resting-state brain activity effectively reflects the brain's functional architecture when responding to external stimuli (Raichle and Mintun, 2006; Smith et al., 2009), as evidenced by findings that intrinsic resting-state brain activity can predict task-evoked brain activation during different cognitive tasks (Fox et al., 2006, 2007; Mennes et al., 2010; Liu et al., 2011; Mennes et al., 2011; Zou et al., 2012). Researchers have linked intrinsic resting-state brain activity with IIV in WM capacity in a healthy population (Hampson et al., 2006, 2010; Sala-Llonch et al., 2011; Stevens et al., 2012) and continuing efforts are underway (for review, see Barch et al., 2013).

*Abbreviations:* ALFF, amplitude of low-frequency fluctuation; DLPFC, dorsolateral prefrontal cortex; FES, first-episode schizophrenia; fMRI, functional magnetic resonance imaging; IIV, inter-individual variability; PFC, prefrontal cortices; vMPFC, ventromedial prefrontal cortices; WM, working memory.

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However, few studies have investigated the rest–task activity (Salomon et al., 2011; Repovs and Barch, 2012) or rest–task performance (Tu et al., 2011) relationships in schizophrenia.

The amplitude of low-frequency fluctuation (ALFF) is an index of intrinsic resting-state brain activity and has been used in previous schizophrenia studies (Hoptman et al., 2010; Huang et al., 2010; Lui et al., 2010; Yu et al., 2012). ALFF evaluates the amplitude of spontaneous fluctuations of specific voxels (Zang et al., 2007) and reflects signal variability in the frequency domain (Zuo et al., 2010; Garrett et al., 2013). Additionally, as a data-driven approach, ALFF requires no a priori hypothesis and can provide information about the local activity of separate brain regions and thus is appropriate for exploratory analyses, such as the present study. Finally, ALFF shows good reliability across time points and potentially represents a meaningful and stable property of the human brain (Zuo et al., 2010). Therefore, ALFF is a candidate for linking intra-individual moment-to-moment signal variability with key individual difference variables (Garrett et al., 2013). Using this method, Zou et al. (2012) found positive coupling between ALFF and WM task-evoked activation in the middle frontal gyrus and posterior parietal cortex and negative coupling in the default mode network regions. They also observed that the ALFFs in the bilateral posterior parietal cortices were significantly correlated with WM task performance (Zou et al., 2012).

To investigate whether the WM IIV in schizophrenia can be explained by the same neural mechanism that underlies IIV in WM capacity among healthy individuals, we linked both the IIV in the task-evoked activity and task performance during an n-back WM task with the intrinsic resting-state activity measured by ALFF in patients with first-episode schizophrenia (FES) and in healthy participants and compared the patterns observed in the FES patients with those from the healthy participants. Investigating FES is important for providing significant insight into the nature of the disease because the influence of certain potentially confounding factors, such as long-term treatment and chronic illness, may be reduced by studying patients in the early stages of schizophrenia, who have had a minimal exposure to treatment. The recruitment of the FES patients makes it unlikely that the current findings are the products of potentially confounding factors of long-term treatment or chronic illness.

## 2. Methods

### 2.1. Participants

Using the Structured Clinical Interview for DSM-IV patient version (SCID-P), patients were recruited from inpatient and outpatient units of the Department of Psychiatry, the Second Xiangya Hospital of Central South University, Changsha, Hunan province, PR China. The inclusion criteria were: a) age between 18 and 45; b) Han Chinese ethnicity; c) nine years of education or above; d) right-handed by a determination of hand preference; e) met DSM-IV criteria for schizophrenia or schizophreniform disorder; f) the total course of disease ≤18 months. The exclusion criteria were: a) any contra-indications to MRI scanning; b) substance-related disorders; c) loss of consciousness of more than five minutes; d) chronic neurological disorders or severe physical disease. Eighteen patients were recruited in this study, including 14 patients with schizophrenia and 4 patients with schizophreniform disorder. All subjects diagnosed with schizophreniform disorder at the time of the study enrollment were subsequently diagnosed with schizophrenia after 6 months of illness. In order to simplify the paper, we decided to refer to this group simply as "first-episode schizophrenia (FES)" throughout the manuscript.

At the time of image acquisition, the symptoms of these patients were assessed by trained and experienced psychiatrists using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b). All patients were receiving atypical antipsychotic medications at the time of image acquisition (risperidone [n = 8, 0.5–4 mg/day], olanzapine [n = 6, 100–150 mg/day], ziprasidone [n = 3, 40–160 mg/day], and paliperidone [n = 1, 6 mg/day]; among them, two patients received a combined treatment with sulpiride [n = 2, intravenously guttae, 100–300 mg/day]).

Eighteen age-, gender- and education-matched healthy controls were recruited from a community sample in Changsha city (Table 1). The inclusion and exclusion criteria were the same as those of the patients group except that the healthy controls did not meet the DSM-IV diagnostic criteria for any psychiatric disorder by the SCID non-patient version.

All participants gave their written informed consent for participation in the study after the risks and benefits of their participation were explained in detail. The ethics committee of the Second Xiangya Hospital of Central South University approved the study.

### 2.2. Experimental design and task

All participants underwent both a resting-state fMRI scan and a subsequent n-back WM task. The WM paradigm was a block-design letter n-back WM task, which has been used in previous studies (Nystrom et al., 2000; Zhou et al., 2007). This task contained a resting condition and two stimuli conditions: (1) in the "2-back" condition, the participants were required to press a button when the letter they saw equaled the letter seen two letters before; and (2) in the "0-back" condition, the participants had to press a button each time they saw the letter X. The letter stimuli were chosen from a set of 18 letters (all consonants except L, W, Y), ignoring upper- or lowercase. Each letter stimulus appeared for 500 ms, and the inter-stimulus interval was 1500 ms. Each stimulus block consisted of 20 stimuli containing seven targets and was indicated by an instruction cue displayed for 2 s before each block. Stimulus blocks and resting periods alternated within the experiment with a total of four 2-back and four 0-back blocks, with a defined sequence (0-2-0-0-2-2-0-2). During resting periods, the participants were instructed to fixate on a cross in the center of the screen for 20 s.

**Table 1**
Demographic and clinical characteristics of first-episode schizophrenia patients (FES) and normal controls (NC).

| Variable | FES | NC | Group comparisons |
|---|---|---|---|
| Age (year) | 23.71 (6.89) | 24.94 (7.29) | $t = -0.52$, $p = 0.61$ |
| Education (years) | 11.65 (1.96) | 13.03 (2.4) | $t = -1.86$, $p = 0.07$ |
| Gender (male/female) | 10/7 | 9/9 | $X^2 = 0.27$, $p = 0.6$ |
| 0-back (dprime score) | 3.58 (0.76) | 3.91 (0.38) | $t = -1.64$, $p = 0.11$ |
| 2-back (dprime score) | 2.03 (0.85) | 2.32 (0.66) | $t = -1.14$, $p = 0.26$ |
| 0-back (c score) | 0.23 (0.29) | 0.04 (0.14) | $t = -2.46$, $p = 0.02$ |
| 2-back (c score) | 0.53 (0.42) | 0.21 (0.39) | $t = -2.28$, $p = 0.03$ |
| 0-back (RT, ms) | 512.27 (57.00) | 476.52 (55.66) | $t = 1.88$, $p = 0.07$ |
| 2-back (RT, ms) | 691.54 (149.88) | 654.78 (123.12) | $t = -0.80$, $p = 0.43$ |
| Mean FD during rest | 0.10 (0.04) | 0.08 (0.02) | $t = 1.34$, $p = 0.19$ |
| Mean FD during task | 0.11 (0.05) | 0.09 (0.04) | $t = 1.35$, $p = 0.19$ |
| SAPS scores | 17.9 (7.8) | – | – |
| SANS scores | 23.4 (20.8) | – | – |
| Course of disease (days) | 283.0 (145.4) | – | – |
| CPZ equivalents (mg) | 251.0 (279.6) | – | – |

Data reflect mean (SD) unless otherwise stated. CPZ = chlorpromazine; FD = framewise displacement; '–' = no data.

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