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Functional Connectivity Between Sensory-Motor Subnetworks Reflects the Duration of Untreated Psychosis and Predicts Treatment Outcome of First-Episode Drug-Naïve Schizophrenia

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ABSTRACT

BACKGROUND: Somatic symptoms and motor abnormalities have been consistently reported as typical symptoms of schizophrenia, but evidence linking impaired functional connectivity among the primary sensory-motor network and its associations to schizophrenia is largely lacking. The present study aims to examine abnormal functional connectivity in the sensory-motor network in schizophrenia and its associations with the duration of untreated psychosis and medication treatment effects. We hypothesize that patients with schizophrenia suffer from disrupted functional connectivity between the sensory-motor subnetworks. The degree of impairment in the connectivity could reflect the duration of untreated psychosis and predict outcomes of medication treatment.

METHODS: At baseline, resting-state functional magnetic resonance imaging data were acquired from 60 first-episode patients with drug-naïve schizophrenia (36 were female) and 60 matching normal control subjects (31 were female). After 2 months, 23 patients who received medication treatment and 32 normal control subjects were rescanned. Functional connectivity among subnetworks in the sensory-motor system was compared between the groups and correlated with the duration of untreated psychosis and the treatment outcome.

RESULTS: Patients with schizophrenia showed significantly disrupted functional connectivity in the sensory-motor network. The degree of impairment reflected the duration of untreated psychosis and motor-related symptoms. It further predicted the improvement of positive scores after medication.

CONCLUSIONS: These findings suggest that functional connectivity in the sensory-motor network could indicate the severity of neural impairment in schizophrenia, and it deserves more attention in the search for neuroimaging markers for evaluating neural impairment and prognosis.

Keywords: Duration of untreated psychosis, Schizophrenia, Sensory-motor, fMRI, Functional connectivity, Treatment outcome

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Somatic symptoms and motor abnormalities have been consistently reported as typical symptoms of schizophrenia (1–3), but the roles of sensory-motor abnormalities in schizophrenia have not been systematically examined. Existing findings have linked genetic (4,5), neurophysiological (6), neuroanatomical (7,8), and neurodevelopmental factors (9,10) to sensory-motor abnormalities in schizophrenia. Motor abnormalities, including three distinct domains (catatonia, extrapyramidal symptoms, and neurological soft signs) in the schizophrenia spectrum (11,12) have been proposed as a putative domain within the National Institute of Mental Health Research Domain Criteria framework (13,14). Particularly, Northoff *et al.* (15–18) and other researchers (19,20) have provided solid evidence for catatonia as a cross-disorder symptom and demonstrated its association with clinical diagnosis (15–17) and cortical dysfunctions (18–20). Yet the underlying associations between schizophrenia and impairments in sensory-motor neurocircuits still need to be clarified (2,12).

A large number of imaging studies have focused on the functional connectivity among the "high-order" functional networks that seem to show closer relevance to cognitive deficits in schizophrenia (21–26), such as the default mode network and the frontoparietal network. Findings from previous studies support a "disconnection hypothesis" that suggests that the cognitive deficits and clinical symptoms in schizophrenia are associated with impairment in functional connectivity among distinct brain regions and networks (24,27–29). However, evidence regarding impaired functional connectivity among the primary sensory-motor network and its associations to schizophrenia is largely lacking. Importantly, compared with the high-order networks that are mainly involved in complex cognitive processes, the functional connectivity in the primary sensory-

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motor network is at the most primary end of the cerebral cortex, which could be more state independent than other high-order systems and could more clearly reflect the deficits in neural circuits.

The present study aims to examine abnormal functional connectivity in the sensory-motor network in schizophrenia and its associations with medication treatment effects. In whole-brain functional connectivity network studies, the sensory-motor network commonly covers a large area containing functionally heterogeneous brain regions (30). A fine-grained parcellation of the sensory-motor network into subsystems facilitates an in-depth investigation of aberrant functional connectivity in the system (31). Linking previous findings of impaired sensory-motor function to disrupted brain connectivity in schizophrenia, we hypothesize that patients with schizophrenia suffer from disrupted functional network connectivity (FNC) between the sensory-motor subnetworks. An implication of this hypothesis is that functional connectivity in the sensory-motor network could serve as an indicator for the severity of neural impairment in schizophrenia, which helps to predict symptom improvement after treatment.

Furthermore, the duration of the untreated psychosis (DUP) has been found as a factor that influences the severity of psychosis (32) and the treatment effect (33). Studies have shown that a longer DUP leads to worse treatment outcomes and that a DUP of 23 weeks may be a critical cut-off point for the prognosis of treatments (34). However, the relationships among DUP and clinical symptoms and treatment outcomes are complex and inconclusive (35), and it is possible that the hypothesized "neurotoxic effect" of DUP (36,37) is reflected by biological deficits. Indeed, previous findings have suggested that long DUP affects gray matter volume (38,39) and functional connectivity (40–42). We therefore further hypothesize that more severely impaired FNC in the sensory-motor subnetworks accompanies a longer DUP in individuals with schizophrenia.

To examine these hypotheses, we investigated the changes in FNC between sensory-motor subnetworks in 65 first-episode patients with drug-naïve schizophrenia (hereafter referred to as patients with SZ) and 65 matching normal control (NC) subjects. We examined the links among clinical symptoms, impairment of the FNC, and DUP. Furthermore, with a follow-up sample, we examined the predictive effects of impairment of the FNC and DUP on improvements of clinical symptoms after 2-month medication treatment.

METHODS AND MATERIALS

Participants

Sixty-five first-episode patients with drug-naïve schizophrenia and 65 normal control subjects participated in the first magnetic resonance imaging (MRI) scan. Two months later, 35 NC subjects and 29 patients with SZ completed the follow-up interview and the second MRI scan. The patients with SZ were recruited from Shanghai Mental Health Center, Shanghai, China. The NC participants were recruited from local communities in Shanghai. Each participant (or participant's guardian) signed the informed consent before data acquisition. This study was approved by the Local Research Ethics Committee, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine. The inclusion criteria for the SZ group were 1) consensus diagnosis of first-episode schizophrenia assigned by two psychiatrists, according to the DSM-IV, on the basis of Structured Clinical Interview for DSM-IV; 2) being medication free; and 3) education level higher than primary school and capability of finishing the tests. The exclusion criteria were 1) too agitated or aggressive to finish the assessments; 2) presence of another Axis I psychiatric disorder; 3) rated 7 or higher in the Calgary Depression Scale for Schizophrenia; 4) history of suicidal behavior; 5) history of antipsychotic medication; 6) history of substance abuse; 7) pregnancy; 8) history of serious physical diseases; and 9) unsuitability for MRI scans, for instance, having metal implants. The NC group was matched with an SZ group for age, gender, and education level. None of the NC participants had a positive family history for any psychiatric disorder. Participants were screened with the Chinese version of the Mini-International Neuropsychiatric Interview, Version 5.0 (43,44) and were excluded if they met the criteria for any mental disorder according to the DSM-IV or had a history of serious physical diseases, pregnancy, taking any antipsychotic drugs, or substance abuse.

Clinical Measurements

A trained psychiatrist assessed the clinical symptoms of all patients. The baseline assessment was conducted before drug medication, and the follow-up assessment was conducted after 8 weeks of antipsychotic treatment. Each patient was clinically evaluated using the 24-item Brief Psychiatric Rating Scale (BPRS) Expanded Version and the Scale for Assessment of Negative Symptoms (SANS). These assessments were conducted at both the baseline and follow-up examinations. DUP reflected the length of time an individual was affected by the psychotic symptoms without receiving medication treatment and was acquired at the baseline exam. The duration of illness was also acquired for 23 of the patients because the other patients could not provide precise information owing to the lack of relevant knowledge or neglect of the early signs.

MRI Acquisition, Data Preprocessing, and Quality Control

All participants completed functional MRI (fMRI) and structural MRI on a 3.0T Siemens Verio MRI scanner (Siemens Medical Solutions, Erlangen, German) at Shanghai Mental Health Center. A T1-weighted structural image and a resting-state fMRI (rs-fMRI) scan were acquired (the detailed scan parameters are described in Supplemental Methods). Participants were instructed to close their eyes and remain awake during the MRI scan. The awake state during the resting-state scan was confirmed in a brief interview after the scans.

The detailed preprocessing steps are described in Supplemental Methods. Briefly, the preprocessing of the fMRI images included dropping the first 10 volumes, slice timing correction, motion correction, spatial registration and normalization, signal intensity normalization, and bandpass filtering (0.01–0.1 Hz). The nuisance regression (24-head motion parameters, mean white matter signal, mean ventricle signal, and motion outliers) was only applied before the bandpass

filtering step for a region-of-interest–based analysis, but it was not applied to the data for independent component (IC) analysis (see Supplemental Methods for rationales).

The quality of the image and spatial registration were visually inspected. Five NC and 5 SZ participants were excluded for further analysis owing to poor image quality. The head motion in rs-fMRI data was evaluated using mean framewise displacement (meanFD) (30), and all data had meanFD <0.5 mm, <3 mm of displacement, or <3 degrees of rotation in any direction. Finally, 60 SZ (25.60 ± 6.99 years, 36 female) and 60 NC (25.03 ± 6.41 years, 31 female) participants were included in the analysis of the baseline scan, of which 32 NC and 23 SZ participants were included in the longitudinal analysis.

Probabilistic IC Analysis and Identification of Sensory-Motor Network Components

For the baseline scan, the preprocessed rs-fMRI images of all participants were concatenated across time into a single 4-dimensional image and then decomposed into a set of group ICs using the MELODIC module of the FSL package (31). The number of components was automatically estimated to be 53. By matching against a predefined spatial template of the sensory-motor (i.e., somatomotor) network proposed by Yeo *et al.* (32), 5 ICs were selected to represent subnetworks within the sensory-motor network because they exhibited high correlation coefficients with the template (ranged between 0.37 and 0.49) and their core regions fall into the spatial boundary of the sensory-motor network

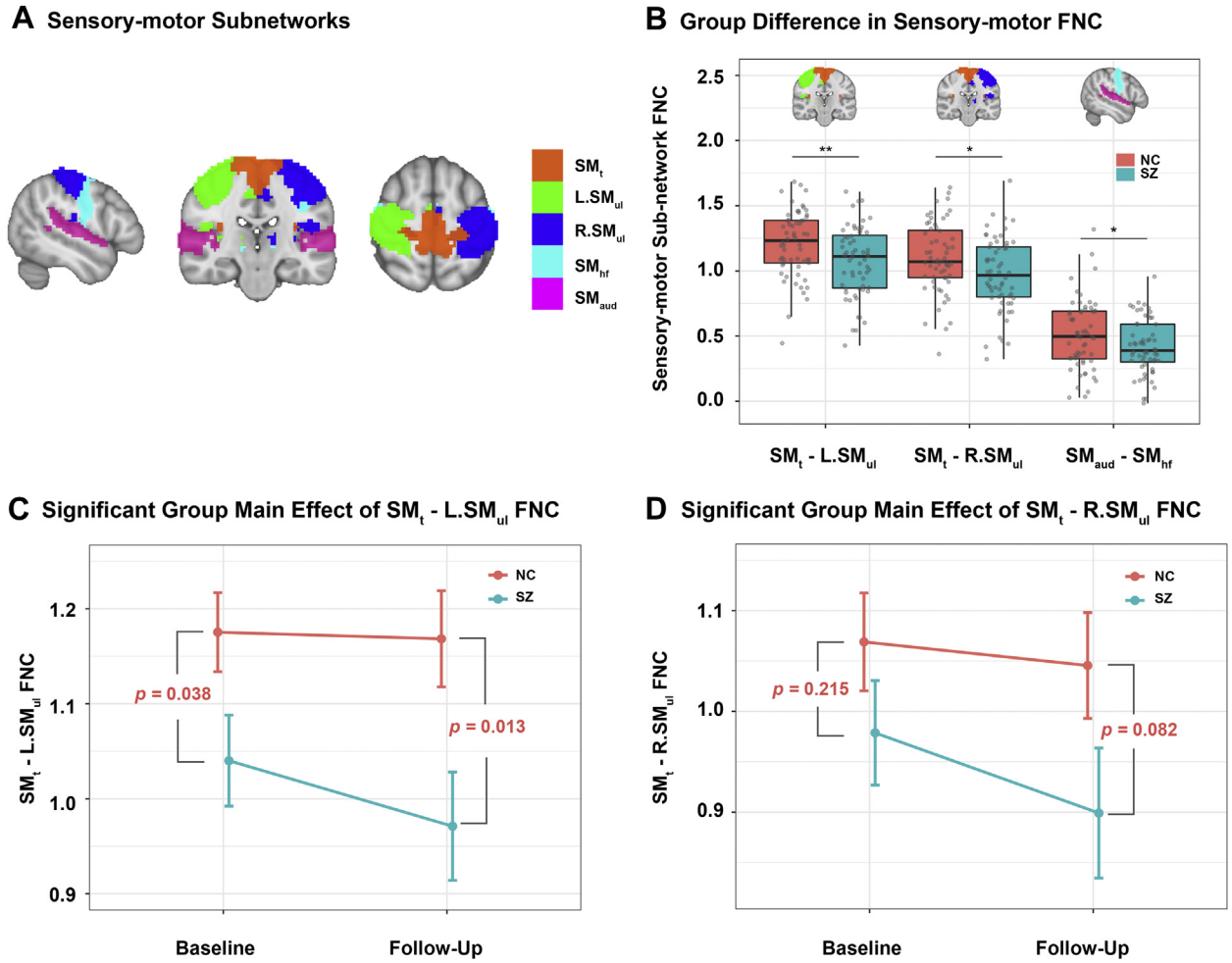

Figure 1. Disrupted sensory-motor subnetwork functional connectivity in patients with schizophrenia (SZ). **(A)** A brain map showing sensory-motor subnetworks obtained in the independent component analysis. These subnetworks all fall in the sensory-motor functional connectivity network that has been commonly used in resting-state functional magnetic resonance imaging studies. **(B)** Group difference in sensory-motor subnetwork connectivity. Three pairs of subnetworks are significantly lower in the SZ group. Significance markers: *$p < .05$; **$p < .01$. **(C)** Significant group difference in the SM_t-$L.SM_{ul}$ connectivity revealed in the longitudinal analysis. The SZ group shows significantly lower functional connectivity in both the baseline and follow-up scans. There is no significant interaction effect. **(D)** The SMt-$R.SM_{ul}$ connectivity also has a significant group main effect but not interaction effect in the longitudinal analysis, and the post hoc tests (two-tailed) reveal trending significant difference in both the baseline and follow-up scans. FNC, functional network connectivity; NC, normal control (group); $L.SM_{ul}$, left upper limb area; $R.SM_{ul}$, right upper limb area; SM_{aud}, bilateral auditory area; SM_{hf}, bilateral head and face area; SM_t, bilateral trunk area.

template (Figure 1A). These 5 subnetworks were further identified with a more detailed atlas from work by Fan *et al.* (33), and these subnetworks represented bilateral trunk area (SM_t), left upper limb area ($L.SM_{ul}$), right upper limb area ($R.SM_{ul}$), bilateral head and face area (SM_{hf}), and bilateral auditory area (SM_{aud}), respectively. Dual regression was applied to obtain individual IC maps and time courses for every participant (34). In brief, for each participant, the spatial maps of the group-level ICs were used as regressors, and the contributions of these maps to the participant's rs-fMRI data were estimated using a linear model. The contributions were depicted using time courses. These time courses were further used as regressors, and the contributions of these time courses to the same rs-fMRI dataset were estimated and represented as a set of spatial maps. These spatial maps represented resting-state functional networks (or image artifacts) in individual participants.

Statistical Analyses

Statistical analyses were conducted using R, version 3.5.2 (35). To evaluate the effectiveness of treatment, a *t* test (two-tailed, same below) was employed to compare the pre- and posttreatment clinical symptoms in the SZ group. To characterize the functional connectivity among the five sensory-motor subnetworks, pairwise FNC was computed by regressing the time courses of the subnetworks, with the FD time course as a covariate, yielding 10 FNC metrics for each participant. The FNC metrics were then converted into Fisher's *Z* values, and a *t* test was performed to compare the group difference between NC and SZ groups at the baseline scan. For the FNC showing significant group difference, we used stepwise regression to examine the associations between the disrupted FNC and clinical symptoms in the SZ participants. The FNC metrics were used to predict the positive and negative symptom scores in the BPRS and motor symptom-relevant scores in the BPRS and SANS. The age, education level, and gender were used as covariates.

To examine whether longer DUP can lead to more impaired sensory-motor FNC in patients with schizophrenia, linear regression was used to model the contribution of DUP to the subnetwork FNC measured at the baseline, with age, education level, and gender as covariates. To correct for the long-tailed distribution of DUP, the DUP values were first transformed into logarithmic values before entering the model.

In the longitudinal analyses, we examined whether the abnormal sensory-motor subnetwork FNC before the medication could predict the treatment outcome. Paired *t* tests were first adopted to examine the changes in the positive and negative scores after medication in the SZ group. Stepwise regression analyses were then performed to predict the improvement of clinical symptoms after medication using the subnetwork FNC measured before medication, with age, education level, and gender as covariates. Finally, we examined the relationships among the baseline FNC and the improvement of clinical symptoms using correlation analyses.

Additionally, we performed region-of-interest–based functional connectivity analyses focusing on the deficits of the sensory-motor areas and the clinical associations. Details of the methods are described in Supplemental Methods.

Table 1. Demographic and Clinical Characteristics for First-Episode Schizophrenia and Normal Control Subjects

	First-Episode Patients With Schizophrenia	Normal Control Subjects	Statistical Test (*p* Value)
Gender, Male/Female, *n*	24/36	29/31	$\chi^2 = 0.84$ (.358)
Age, Years	25.60 ± 6.99	25.03 ± 6.41	$t = -0.46$ (.645)
Education Level, Years	12.63 ± 2.85	12.70 ± 2.82	$t = 0.13$ (.898)
MeanFD	0.08 ± 0.04	0.10 ± 0.06	$t = 1.62$ (.108)
DUP, Weeks	34.18 ± 37.87	—	—
DUP, log(weeks)	3.13 ± 0.86	—	—
BPRS Total	46.17 ± 8.27	—	—
BPRS Positive	15. 45 ± 4.22	—	—
BPRS Negative	7.77 ± 2.90	—	—
SANS	20.40 ± 12.50	—	—

Values are mean ± SD unless otherwise indicated.

BPRS, Brief Psychiatric Rating Scale; DUP, duration of untreated psychosis; FD, framewise displacement; SANS, Scale for Assessment of Negative Symptoms.

RESULTS

Demographic and Clinical Characteristics

At both the baseline and follow-up scans, demographic data did not differ in age, gender, or education level among the NC and SZ groups (Table 1). DUP of the patients was 34.18 ± 37.87 weeks, and the available duration of illness was 48.77 ± 44.13 weeks ($n = 23$). Furthermore, the longitudinal analysis showed no significant difference in these demographic variables between the patients with SZ and the normal control subjects who were successfully followed-up (Table 2). With 2-months' medication, the SZ group showed significant decrease in BPRS total scores ($t = 7.38$, $p < .0001$) and positive symptoms of BPRS score ($t = 7.46$, $p < .0001$). However, the negative symptom scores in BPRS ($t = 1.11$, $p = .271$) and SANS ($t = 1.05$, $p = .298$) did not show significant improvement after medication.

Disrupted Sensory-Motor Subnetwork FNC in Schizophrenia

Figure 1A presents the above-mentioned five subnetworks (SM_t, $L.SM_{ul}$, $R.SM_{ul}$, SM_{hf}, SM_{aud}) of the sensory-motor functional connectivity network according to the brain atlas by Fan *et al.* As presented in Figure 1B, the SZ group exhibited (marginally) significantly lower sensory-motor subnetwork FNCs than did the NC group in the SM_t-$L.SM_{ul}$ measure ($t = -2.89$, $p = .046$, false discovery rate corrected, uncorrected $p = .004$), the SM_t-$R.SM_{ul}$ measure ($t = -2.51$, $p = .067$, uncorrected $p = .013$), and the SM_{aud}-SM_{hf} measure ($t = -2.08$, $p = .131$, uncorrected $p = .039$) at baseline. The stepwise regression analysis did not reveal any significant correlation between the significantly decreased subnetwork

Table 2. Clinical Characteristics for Patients With Schizophrenia and Normal Control Subjects After 2-Month Medication Treatment

Characteristics	Patients With Schizophrenia		Normal Control Subjects	Statistical Test (*p* Value)
Gender, Male/Female, *n*	10/13		15/17	$\chi^2 = 0.06$ (.803)
Age, Years	24.00 ± 5.49		26.19 ± 7.25	$t = -1.27$ (.209)
Education Level, Years	12.91 ± 2.95		12.47 ± 2.99	$t = 0.55$ (.586)
MeanFD	0.07 ± 0.36		0.09 ± 0.37	$t = 1.30$ (.199)
DUP, Weeks	25.48 ± 14.95		–	–
DUP, log(weeks)	3.07 ± 0.61		–	–
	Baseline	Follow-up		
BPRS Total	49.35 ± 7.33	33.43 ± 7.30	–	<.0001
BPRS Positive	16.35 ± 3.11	8.52 ± 3.95	–	<.0001
BPRS Negative	7.96 ± 3.11	6.95 ± 2.98	–	.271
SANS	20.74 ± 14.68	16.70 ± 11.11	–	.298

Values are mean ± SD unless otherwise indicated.

BPRS, Brief Psychiatric Rating Scale; DUP, duration of untreated psychosis (at baseline); FD, framewise displacement; SANS, Scale for Assessment of Negative Symptoms.

FNC metrics (SM_t-$L.SM_{ul}$, SM_t-$R.SM_{ul}$, and SM_{aud}-SM_{hf}) and positive/negative symptom scores in the SZ group.

We also found a significant negative correlation between the motor-related items in the SANS and the sensory-motor subnetwork FNC measures. Specifically, the Spearman correlation coefficients between the "decreased spontaneous movements" and the SM_t-$R.SM_{ul}$ and SM_t-$R.SM_{ul}$ FNC measures were $r = -.34$ ($p = .009$) and $r = -.33$ ($p = .013$); the Spearman correlation coefficients between the "paucity of expressive gestures" and these FNC measures were $r = -.30$ ($p = .023$) and $r = -.29$ ($p = .029$), respectively. These results indicated to us that impaired FNCs are associated with motor abnormalities in patients with schizophrenia. Our region-of-interest–based functional connectivity analysis that better separated the sensory and motor areas partially confirmed these observations (see Supplemental Figures S2 and S3).

As presented in Figure 1C and D, both the SM_t-$L.SM_{ul}$ FNC and the SM_t-$R.SM_{ul}$ FNC exhibited significant or marginally significant group main effects ($F = 8.02$, $p = .007$ for the left hemisphere; $F = 3.29$, $p = .076$ for the right hemisphere), but no significant effect of scan sessions ($F = 0.756$, $p = .389$ for the left hemisphere; $F = 1.32$, $p = .256$ for the right hemisphere). The interaction effects were not significant ($F = 0.64$, $p = .428$ for the left hemisphere; $F = 0.45$, $p = .504$ for the right hemisphere). These results indicate that the FNC metrics in the SZ group were consistently lower than for the NC group in both baseline and follow-up scans.

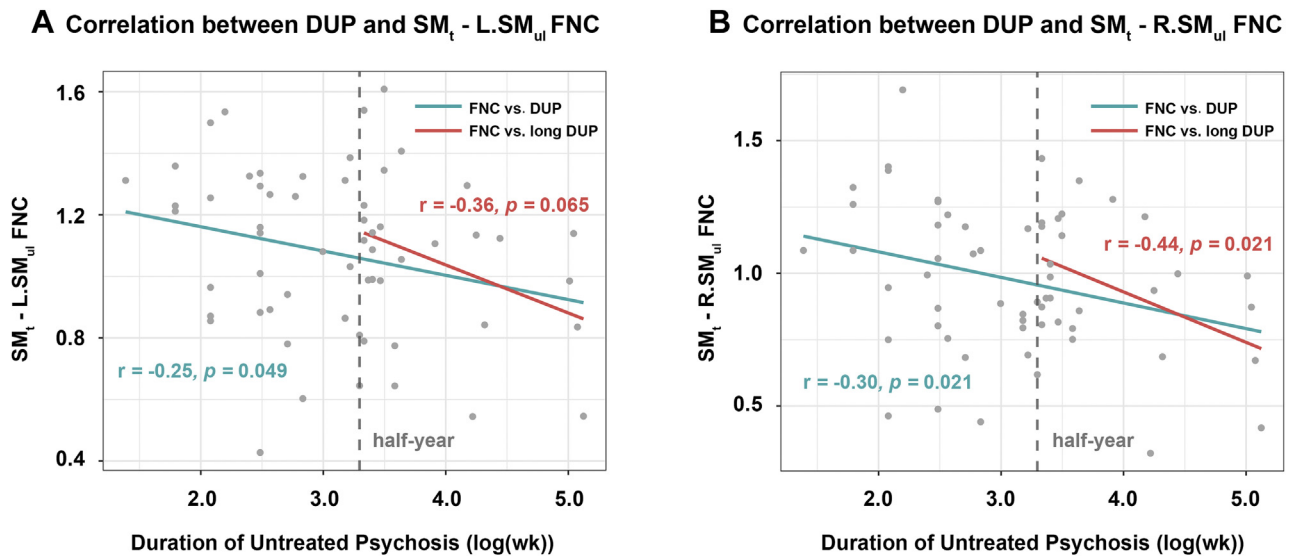

Figure 2. Correlation between duration of untreated psychosis (DUP) and functional connectivity in sensory-motor subnetworks. The functional network connectivity (FNC) in both SM_t-$L.SM_{ul}$ **(A)** and SM_t-$R.SM_{ul}$ **(B)** significantly correlate with DUP. For DUP longer than half a year (starting from the gray dashed lines), the correlation coefficients seem to become larger. $L.SM_{ul}$, left upper limb area; $R.SM_{ul}$, right upper limb area; SM_t, bilateral trunk area.

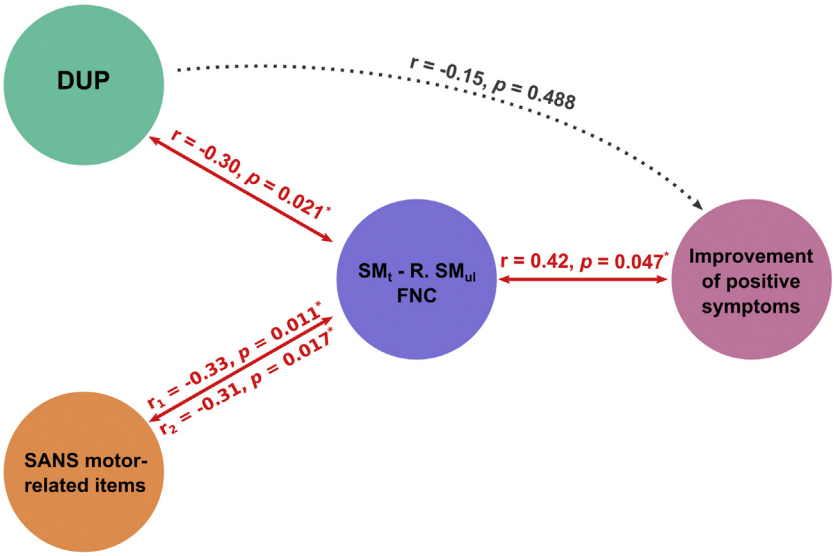

Figure 3. Correlations among symptom improvement, duration of untreated psychosis (DUP), and sensory-motor subnetworks functional connectivity (FNC). The SM_t-R.SM_{ul} FNC measured at baseline is significantly correlated with the improvement of the positive symptoms after medication. The baseline SM_t-R.SM_{ul} FNC also reflects a significantly negative correlation with DUP, and motor-related symptom scores such as decreased spontaneous movements (r_1) and paucity of expressive gestures (r_2). DUP does not have a significant correlation with the improvement of positive symptoms (dashed line). These relationships indicate that the SM_t-R.SM_{ul} FNC measured at the baseline is associated with DUP and motor abnormalities and predicts treatment outcome. R.SM_{ul}, right upper limb area; SANS, Scale for Assessment of Negative Symptoms; SM_t, bilateral trunk area.

DUP Predicts Degree of Impairment in Sensory-Motor Subnetwork FNC

In the regression analysis, we found that DUP (logarithmic values, same below) significantly affected the SM_t-L.SM_{ul} FNC ($t = -2.00$, $p = .050$, adjusted for age, education, and gender, same below) and SM_t-R.SM_{ul} FNC ($t = -2.46$, $p = .017$) in schizophrenia, but not SM_{aud}-SM_{hf} FNC ($t = -0.42$, $p = .674$). Figure 2 illustrates the significant correlation coefficient between the DUP and the SM_t-L.SM_{ul} FNC ($r = -.25$, $p = .049$) (Figure 2A) and SM_t-R.SM_{ul} FNC ($r = -.30$, $p = .021$) (Figure 2B). Furthermore, we found that long DUP (longer than half a year) seemed to exhibit stronger correlation with the disruption of the SM_t-R.SM_{ul} FNC ($r = -.44$, $p = .021$) and the SM_t-L.SM_{ul} FNC ($r = -.36$, $p = .065$), suggesting that longer DUP is associated with more severely impaired sensory-motor subnetwork FNC. In contrast, no significant correlation between DUP and positive ($r = -.16$, $p = .209$) and negative symptoms ($r = -.14$, $p = .303$) were observed in patients with SZ. The above findings indicate that patients with SZ suffer from impaired subnetwork FNC in the sensory-motor system, and the DUP, which has been found relating to the severity and outcomes of psychosis, plays a role in the impairment of the sensory-motor subnetworks.

To further rule out the potential impact of age on FNC, we first investigated the distribution of the age of patients with SZ and found that it was unimodal with 3 individuals > 40 years of age as outliers (Supplemental Figure S1A). The unimodal distribution ensures that including age as a covariate in the above regression analyses could effectively remove the linear confound of age. Supplemental Figure S1B and C presents scatter plots showing that the correlation between age and the FNC metrics of interest were not significantly correlated. Furthermore, splitting the SZ sample into two age groups (< 25.6 and ≥ 25.6 years) did not alter the relationship between DUP and FNC (Supplemental Figure S1D, E).

Disrupted Sensory-Motor Subnetwork FNC Predicts Treatment Outcome

Longitudinal analysis revealed that the disrupted SM_t-R.SM_{ul} FNC at the baseline could predict the improvement of positive symptoms after 2 months' medication ($r = .43$, $p = .039$) (Figure 3), adjusted for age, education level, and gender. Although the negative symptom did not show significant improvement, we repeated the analysis but did not find any significant correlation between disrupted sensory-motor FNC and negative score improvement. We did not find a significant correlation between the DUP and the improvement of positive symptoms ($r = .18$, $p = .394$) (Figure 3). As Figure 3 shows, these findings seem to imply a mediation effect of the SM_t-R.SM_{ul} FNC between DUP and the improvement of positive symptoms after medication.

DISCUSSION

We obtained two main findings in this study. First, motor abnormality-related decreased FNCs among the sensory-motor subnetworks were observed in patients with SZ, and the severity of impairment of the bilateral SM_t-SM_{ul} FNC is related to DUP and motor-related symptoms. Second, the SM_t-R.SM_{ul} FNC measured at the baseline could predict the improvement of positive symptoms after a 2-month treatment, so that lower FNC predicted poorer improvement after treatment. Given that DUP had no significant correlation with symptom improvement, our results suggest that the impairment of the subnetwork FNC seems to be a linkage between the environmental factor DUP and the clinical symptom, which implies that longer DUP leads to more severely disrupted FNC, and the latter leads to difficulties in the treatment of the positive symptoms.

Impaired Sensory-Motor FNCs in Schizophrenia

Our findings that patients with schizophrenia exhibited significantly decreased sensory-motor FNCs (SM_t-L.SM_{ul}, SM_t-R.SM_{ul}, and SM_{aud}-SM_{hf}) enriched the neuroimaging evidence

of functional disconnection among sensory-motor subnetworks in schizophrenia. For a long time, researchers have noticed motor abnormality and corresponding aberrant sensory-motor and supplementary motor cortex activities in schizophrenia (36–38), and abnormal sensory-motor FNCs were often mentioned as complementary evidence to supported various theories of schizophrenia. For example, Pinault (39) reported dysfunctional thalamus-sensorimotor circular in schizophrenia. Berman *et al.* (40) observed disrupted FNC in the sensory-motor network and hypothesized that the disruption represented the abnormal integration of sensory-motor and social-cognitive processing in the pathophysiology and symptomatology of schizophrenia. Using diffusion tensor imaging method, Bracht *et al.* (7) revealed a white matter pathway alteration, from subcortical nuclei to important cortical motor regions, including dorsolateral prefrontal cortex, anterior cingulate cortex, presupplementary and supplementary motor areas, and primary motor cortex in patients with schizophrenia.

The observed negative correlations between the sensory-motor subnetwork FNC and the motor-related symptoms, such as decreased spontaneous movements and the paucity of expressive gestures, further support the clinical relevance of the impairment of the sensory-motor networks. This evidence echoes the arguments of the previous works that call for more attention to the sensory-motor deficits in patients with schizophrenia (12). In future studies, the motor-related symptoms should be more thoroughly evaluated using specific tools such as Northoff Catatonia Scale or Bush-Francis Catatonia Rating Scale (15,17,41).

A Potential Imaging Marker for Brain Impairment in Schizophrenia

Clinical studies have consistently reported treatment resistance in schizophrenia (42–45). In our study, after 2-month medication treatment, the positive symptoms were controlled, but the negative symptoms did not show significant change. Our finding that the sensory-motor subnetwork FNC in the SZ group was consistently lower than that in the NC group echoed the behavioral observation, suggesting that the impairment in brain function had not been fully recovered by the 2-month medication treatment. On the other hand, the improvement of the positive symptom significantly correlated with the degree of impairment in the sensory-motor FNC measured at the baseline (Figure 3), indicating that the degree of FNC impairment before the medication could affect the treatment effect. Combining the above arguments, the disrupted sensory-motor FNC has the potential to be a neuroimaging marker for representing the degree of brain function impairment in schizophrenia and for the prognosis of treatment outcome in drug-naïve patients with SZ.

The effects of the drug treatment on the patient's symptoms and the underlying brain mechanisms are complex and unclear (46–48). A number of studies have reported disrupted FNC in high-order cognitive networks in schizophrenia (26,49–52). Nonetheless, the intrinsic flexibility in these high-order brain networks and the complex between-network interactions (53,54) may increase their sensitivity to the transient environmental factors or the mental states of the patient. In contrast, the functional connectivity within the sensory-motor system is relatively independent of the transient factors, and stably reflects the status of the neural networks. The evidence reported in this study suggests a new possibility to use the relatively stable functional connectivity within the sensory-motor system as a marker to indicate the severity of brain impairment due to schizophrenia. Our findings support the effectiveness of this brain impairment index because it helps to predict treatment outcomes.

DUP Affects the Impairment of Sensory-Motor Subnetwork FNC

Evidence has supported that DUP has a significant impact on both clinical symptom severity (55–57) and prognosis (58,59). Longer DUP suggests more severe psychosis symptoms and greater difficulties in treatment (60). In the present study, we found that DUP is significantly related to disrupted sensory-motor FNC in schizophrenia (Figure 2). Furthermore, these associations were more pronounced when DUP was longer than half a year (Figure 2). Again, these findings support our argument that impaired sensory-motor FNC can be used as a stable indicator of the severity of brain impairment in schizophrenia.

Our findings are not the only evidence linking DUP and abnormal functional connectivity. In fact, a number of previous studies have demonstrated associations between DUP and abnormal FNC (61–63). However, our findings can stand on their own from two perspectives. First, owing to the relatively low-level role in the cerebral cortex, the sensory-motor subnetwork FNC found in our study is less affected by transient environmental factors or mental states, making it a reasonable candidate as an indicator of neural circuit impairment in schizophrenia. On the other hand, our results implied a mediation role of the sensory-motor FNC between the DUP and the treatment effects. In our sample, the relationship between DUP and treatment outcome was not explicit, but it could be bridged with the degree of impairment in sensory-motor FNC, suggesting that the sensory-motor FNC may be a more precise indicator for the evaluation of the severity of neural impairment and for the treatment prognosis.

Limitations

First, our 2-month follow-up sample had a relatively small sample size that did not allow us to apply a formal statistical analysis to elaborate on the mediation of the sensory-motor FNC between the DUP and the treatment outcome. Second, one stage of follow-up could not fully explain the treatment outcome. The treatment-resistant negative symptom and relatively stable impaired sensory-motor FNC may be improved after longer treatment (64). Finally, we did not apply specific scales, such as the Northoff Catatonia Scale (17), to assess the motor abnormalities of the patients owing to the lack of validated Chinese version. Future studies should introduce these assessments.

Conclusions

Taken together, this study reports disrupted functional connectivity in the sensory-motor system in patients with schizophrenia. The degree of impairment in the sensory-motor functional connectivity reflects the duration of untreated psychosis and predicts the treatment outcome after 2 months' medication. These

findings support that functional connectivity in the sensory-motor network reflects the hypothesized "neurotoxic effect" of untreated psychosis, and this network deserves more attention in the search for neuroimaging markers for evaluating neural impairment and prognosis in schizophrenia.

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ARTICLE INFORMATION

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