



Linked functional network abnormalities during intrinsic and extrinsic activity in schizophrenia as revealed by a data-fusion approach



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ABSTRACT

Abnormalities in functional brain networks in schizophrenia have been studied by examining intrinsic and extrinsic brain activity under various experimental paradigms. However, the identified patterns of abnormal functional connectivity (FC) vary depending on the adopted paradigms. Thus, it is unclear whether and how these patterns are inter-related. In order to assess relationships between abnormal patterns of FC during intrinsic activity and those during extrinsic activity, we adopted a data-fusion approach and applied partial least square (PLS) analyses to FC datasets from 25 patients with chronic schizophrenia and 25 age- and sex-matched normal controls. For the input to the PLS analyses, we generated a pair of FC maps during the resting state (REST) and the auditory deviance response (ADR) from each participant using the common seed region in the left middle temporal gyrus, which is a focus of activity associated with auditory verbal hallucinations (AVHs). PLS correlation (PLS-C) analysis revealed that patients with schizophrenia have significantly lower loadings of a component containing positive FCs in default-mode network regions during REST and a component containing positive FCs in the auditory and attention-related networks during ADR. Specifically, loadings of the REST component were significantly correlated with the severities of positive symptoms and AVH in patients with schizophrenia. The co-occurrence of such altered FC patterns during REST and ADR was replicated using PLS regression, wherein FC patterns during REST are modeled to predict patterns during ADR. These findings provide an integrative understanding of altered FCs during intrinsic and extrinsic activity underlying core schizophrenia symptoms.

1. Introduction

Schizophrenia is typically characterized by a range of psychotic symptoms that stem from altered senses of self and reality. These symptoms include auditory verbal hallucinations (AVHs) and delusions. Brain mechanisms underlying these symptoms have been intensely studied using neuroimaging techniques. The neural correlate of AVH has a particularly long history of investigation. Because of its auditory and verbal nature, abnormalities in auditory and speech-related brain regions have long been thought to underlie AVH (Crow, 2008; Jones and Fernyhough, 2007). However, structural or functional alterations associated with AVH have often been found outside auditory and speech-related regions as well (Allen et al., 2012; Jardri et al., 2011). These findings support a more complicated view of AVH, specifically that fundamental abnormalities exist at the network level in multiple

brain regions that subsume auditory and speech-related regions.

Functional imaging researchers have adopted multiple strategies to elucidate the complexities of AVH in schizophrenia. One strategy is to examine extrinsic brain activity while imposing cognitive or perceptual tasks to drive neural systems hypothesized to be relevant to the generation of AVH (e.g., auditory and speech systems). The auditory deviance response (ADR) refers to differential neural responses to an infrequent deviant (oddball) auditory stimulus presented within a train of repeated standard stimuli and is probably one of the best-studied functional indices of the auditory and speech abnormalities in schizophrenia (Light et al., 2015; Naatanen et al., 2011; Nagai et al., 2013; Salisbury et al., 2007). Although the ADR may be largely regarded as a functional probe for sensory processing, its neural generators may not be localized to the auditory cortex, but rather involve large-scale functional connectivity (FC) networks, such as the saliency and central

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executive networks (Kim, 2014).

As a complement to extrinsically evoked activity, a growing number of studies have examined intrinsic activity during the resting state (Rotarska-Jagiela et al., 2010). Resting state activity comprises coordinated activity of multiple functional networks. One of these networks, the default-mode network (DMN), refers to a set of brain regions, including the medial prefrontal cortex (MPFC), cingulate cortex (CC), retrosplenial cortex (RSC), and lateral inferior parietal cortex (LIPC), whose activities rather increase during the resting state when compared to the state in which external tasks are imposed. Abnormalities in DMN have been associated with core symptoms of schizophrenia, including AVH (Garrity et al., 2007). These findings have led to the proposal of a “resting-state hypothesis” of AVH, which proposes that abnormal spontaneous activity in multiple regions, including the DMN, is the putative neural mechanism underlying the experience of AVH (Northoff and Qin, 2011).

Previous functional imaging studies have adopted one of the above two strategies and found abnormalities in specific brain regions and/or systems, some of which (e.g., those in the anterior CC) have also been found in multiple studies (Garrity et al., 2007; Kim et al., 2009). However, as task-evoked and resting-state functional magnetic resonance imaging (fMRI) studies have been conducted independently, the fundamental question of whether and how such multiple patterns of abnormalities are related to each other remains. Given the recent accumulation of findings using a single MRI methodology, the need for the integration of multiple datasets has become a pivotal issue in neuroimaging. Indeed, data-fusion analysis using multivariate statistical techniques has turned out to be effective in revealing latent patterns of brain features that are found in multiple datasets collected from the same individual (Itahashi et al., 2015; Sui et al., 2012). For instance, a recent study adopted the partial least square (PLS) method to integrate diffusion-weighted images and resting-state fMRI data collected from the same individuals and revealed latent patterns of structural and functional connectivity co-occurring in typically developed adults (Misić et al., 2016). This methodology may thus be highly suitable for extracting linked latent patterns of connectivity that are present across multiple datasets.

In this study, we adopted a data-fusion method of PLS and aimed to find links between latent patterns of abnormal FC during intrinsic and extrinsic activity underlying schizophrenia and its psychotic symptoms, including AVH. Hence, we collected fMRI FC data during the resting state (REST) and the ADR from the same patients with chronic schizophrenia (SCZ) and from matched healthy controls (HC). We used PLS to uncover latent FC features in the pairs of fMRI data collected during REST and ADR. Based on previous studies using single fMRI paradigms, we expected that our analysis might reveal an association between the DMN during REST and auditory and attention-related networks during the ADR paradigm. When such an association was indeed identified, we also expected that the loadings of the identified FC components would be significantly different between SCZ and HC. Furthermore, individual loadings of such components might be correlated with the severities of psychotic symptoms, including AVH.

2. Materials and methods

2.1. Participants

Twenty-five patients with SCZ and 25 age- and sex-matched HCs participated in this study. The patients were recruited at Karasuyama Hospital at the Showa University School of Medicine in Tokyo, Japan. Diagnoses were made by 2 experienced psychiatrists, based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Patients were excluded if they had other major psychiatric or neurological disease, severe somatic disorders, alcohol intake within 24 h of the examination, or current or past alcohol abuse. Psychiatric symptoms were assessed using the Positive

Table 1

The demographic and clinical data of the participants.

	HC	SCZ
Number (male/female)	25 (15/10)	25 (15/10)
Age (years)	34.6 ± 8.2 [24–50]	34.4 ± 8.5 [21–53]
Estimated IQ	106.1 ± 10.6 [83–119]	99.5 ± 9.5 [83–119]
Handedness	R = 24, L = 1	R = 24, L = 1
Length of illness (years)	(–)	9.8 ± 7.2 [1–23]
Chlorpromazine equivalents (mg/day)	(–)	758.0 ± 515.9 [0–2000]
PANSS(P) score	(–)	14.4 ± 5.7 [6–27]
PANSS(N) score	(–)	16.3 ± 5.2 [6–24]
PANSS(G) score	(–)	29.7 ± 7.6 [17–43]
PANSS(T) score	(–)	60.4 ± 16.5 [32–90]
AHRS score	(–)	14.6 ± 12.4 [2–35]

Mean ± standard deviation [Range].

HC: Healthy controls, SCZ: schizophrenia patients, PANSS: Positive and Negative Syndrome Scale, P: positive scale, N: negative scale, G: global psychopathology scale, T: total, AHRS: Auditory Hallucination Rating Scale.

and Negative Syndrome Scale (PANSS), and the severities of the auditory hallucinations were rated using the Auditory Hallucination Rating Scale (AHRS) (Hoffman et al., 2003). None of the HCs reported any severe medical problems or neurological or psychiatric histories, and none satisfied the diagnostic criteria for any psychiatric disorder. Written informed consent was obtained from all participants. Handedness of each participant was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). The patient's premorbid intelligence was estimated using the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). Demographic data for the SCZ and HC groups are shown in Table 1. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine of Showa University. The patients' primary physicians determined the patients' ability to provide informed consent before recruitment.

2.2. Data acquisition

All MRI data were acquired using a 1.5-T GE Signa system (General Electric; Milwaukee, WI, USA) with a phased-array whole-head coil. Every participant underwent the two functional imaging runs for the REST and ADR paradigms in a single fMRI session. The functional images were acquired using a gradient echo-planar imaging sequence. Except for parameters of slice thickness and the number of volumes, the following parameters were the same between the two fMRI runs: in-plane resolution = 3.4375 × 3.4375 mm², echo time (TE) = 40 ms, repetition time (TR) = 2000 ms, flip angle = 90°, matrix size: 64 × 64, and 27 axial slices. Slice thickness was 4 mm with a 1-mm slice gap for REST and 4 mm without a gap for ADR. In each fMRI run, the first four volumes were discarded to allow for equilibration effects. At the end of the MRI session, a high-resolution T1-weighted spoiled gradient recalled three-dimensional MRI image was acquired (in-plane resolution: 0.9375 × 0.9375 mm², 1.4 mm slice thickness, TR: 25 ms, TE: 9.2 ms, matrix size: 256 × 256, 128 sagittal slices).

2.3. Task

For the REST run, the participants were instructed to lie in the supine position in the scanner, to remain as still as possible, and to keep their eyes closed, but stay awake in the dim scanner room. In total, 204 volumes were acquired over 6 min 48 s.

For the ADR run, we adopted an auditory oddball paradigm originally used in a previous study wherein the neural sources of ADR were identified (Molholm et al., 2005). In this paradigm, sequences consisting of two types of tones were presented: Tone 1 (TN1) was a

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