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Lateralization of intrinsic frontoparietal network connectivity and symptoms in schizophrenia

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ABSTRACT

It has been frequently reported that schizophrenia patients have reduced functional lateralization in the areas related to language processing. Furthermore, there is evidence supporting that schizophrenia patients have disrupted functional connectivity in the bilateral frontoparietal networks (FPNs), of which the left is strongly associated with a cognition-language paradigm, using resting-state functional magnetic resonance imaging (rsfMRI). To examine the laterality of resting-state functional connectivity in schizophrenia, we investigated the bilateral FPNs. We investigated 41 schizophrenia and 35 healthy participants using independent component analysis for rsfMRI. We extracted mean connectivity values of both left and right FPNs and calculated their laterality index by (left - right)/(left + right). Subsequently, we investigated group differences of these values and the correlation between these values and symptoms. In schizophrenia, mean connectivity values of both left and right FPNs were significantly lower than in healthy controls, whereas their laterality indices were not significantly different. However, correlation analyses revealed that the laterality index was negatively correlated with positive symptoms, and that mean connectivity of left FPN was negatively correlated with depressive symptoms in schizophrenia. Our results suggest that language-related networks and their laterality might be one of the neural correlates of schizophrenia symptoms.

1. Introduction

Structural and functional asymmetry has been shown in human brain, and it is known that left is greater than right in the areas related to language processing such as Broca's area and Wernicke's area (Toga and Thompson, 2003). These asymmetries have also been considered to be related to a number of factors such as gender and handedness (Toga and Thompson, 2003), and also to schizotypy (Lindell, 2014).

Abnormal asymmetry has been one of the main hypotheses for explaining the pathophysiology of schizophrenia (Crow, 1997, 2000). A number of magnetic resonance imaging (MRI) studies have investigated functional as well as structural asymmetry in schizophrenia (Oertel-Knochel and Linden, 2011). It has been frequently reported that schizophrenia patients have reduced functional and structural asymmetry in areas related to language processing such as Broca's area, Wernicke's area, Heschl's gyrus, or planum temporale (Oertel-Knochel and Linden, 2011).

A number of structural studies of schizophrenia have revealed reduced or reversed cerebral gray matter asymmetry in the planum temporale (Barta et al., 1997; Clark et al., 2010; Hirayasu et al., 2000; Kasai et al., 2003; Kawasaki et al., 2008; Kwon et al., 1999; Oertel et al., 2010; Petty et al., 1995) and Heschl's gyrus (Asami et al., 2012; Kasai et al., 2003; Oertel et al., 2010; Takahashi et al., 2009).

In addition to cortical morphology, a number of studies have assessed asymmetries in white matter integrity (Catani et al., 2011; Curcic-Blake et al., 2015; Kubicki et al., 2002; Kunimatsu et al., 2008;

Abbreviations: rsfMRI, resting-state functional magnetic resonance imaging; ROI, region-of-interest; ICA, independent component analysis; FPN, frontoparietal network; SCID-P, Structured Clinical Interview for DSM-IV Axis I Disorders Patients Edition, Version 2.0; JART, the Japanese Version of the National Adult Reading Test; PANSS, Positive and Negative Syndrome Scale; SCID-NP, Structured Clinical Interview for DSM-IV Axis I Disorders - Non-patient Edition, Version 2.0; 3D-MPRAGE, 3-dimensional magnetization-prepared rapid gradient echo; EPI, echo planar imaging; TE, echo time; TR, repetition time; FOV, field of view; MELODIC, Multivariate Exploratory Linear Optimized Decomposition into Independent Components; FWHM, full width at half maximum; LI, laterality index, HP, haloperidol; Hc, healthy control group; Sc, schizophrenia group

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Miyata et al., 2012; Park et al., 2004; Ribolsi et al., 2014; Voineskos et al., 2010). Although the results are varied, some studies have reported asymmetrical white matter disruption in arcuate fasciculus in schizophrenia (Catani et al., 2011; Curcic-Blake et al., 2015), which is a well-known white matter bundle connecting Broca's and Wernicke's areas (Takaya et al., 2015). In addition, our previous study demonstrated rightward shift of white matter integrity in the external capsule, which has a connection to orbitofrontal cortex through uncinate and inferior occipitofrontal fasciculi (Miyata et al., 2012).

While a number of studies have focused on structural asymmetry, some researchers have also focused on functional laterality in schizophrenia. Several neural imaging studies using language task also reported that reduced functional laterality is correlated with schizophrenia symptoms. A study using auditory stimuli has reported that reduced functional laterality in auditory cortex, planum temporale, and Heschl's gyrus is correlated with increased positive symptoms and that planum temporale and Heschl's gyrus are correlated with hallucination (Oertel et al., 2010). Another study using the verbal fluency task has shown that reduced laterality of activation in Broca's area is correlated with increased hallucinations (Weiss et al., 2006). Yet another studies using the verb-generation task (Warburton et al., 1996) and the reverse-reading task (Benson et al., 1996) have reported that the laterality of activation within areas with language processing (Brodman area, superior temporal gyrus, or middle temporal gyrus) is correlated with hallucinations (Sommer et al., 2001) and delusions (Sommer et al., 2003). A few studies reported a correlation of functional laterality with negative symptoms (Artiges et al., 2000). In contrast, some other studies found no association between functional laterality and schizophrenia symptoms (Alary et al., 2013; Royer et al., 2015).

Recently, several studies have investigated the functional connectivity lateralization of schizophrenia using resting-state functional magnetic resonance imaging (rsfMRI) (Ribolsi et al., 2014). One study, using whole brain analysis, reported that schizophrenia patients with positive symptoms had increased leftward asymmetry and patients with negative symptoms had increased rightward asymmetry (Ke et al., 2010). In another study, using region-of-interest (ROI) -based analysis, schizophrenia patients were shown to have reduced leftward asymmetry that was correlated with increased hallucination (Oertel-Knochel et al., 2013, 2014). In yet another study, using independent component analysis (ICA), schizophrenia patients showed decreased rightward laterality that was correlated with increased disorganization symptom only for the right frontoparietal network (FPN) (Rotarska-Jagiela et al., 2010). These apparently inconsistent findings might be due to different rsfMRI analysis methods used, as different methods focus on different aspects of functional connectivity.

Left and right FPNs constitute one of the well-known intrinsic networks identified in rsfMRI studies, which are bilaterally distributed almost like mirror images. Left FPN includes Broca's and Wernicke's areas (Smith et al., 2009) and has also been shown to be strongly correlated with cognition-language paradigm (Smith et al., 2009). Moreover, FPNs are known to form an important intrinsic network for appropriate executive control function (Dosenbach et al., 2008, 2007), whose impairment is a core feature of schizophrenia (Minzenberg et al., 2009). In schizophrenia, it is known that this network is disrupted (Baker et al., 2014; Chang et al., 2014; Manoliu et al., 2014), as well as in other intrinsic networks such as the Default Mode Network (Chang et al., 2014; Manoliu et al., 2014; Orliac et al., 2013; Pearlson et al., 2014; Rotarska-Jagiela et al., 2010) and the Salience Network (Manoliu et al., 2014; Orliac et al., 2013). Importantly, FPNs comprise the only intrinsic network revealed by ICA that is lateralized rather than symmetrical. Comparison between the left and right FPNs would provide considerable information in the research of functional laterality. Although there have been several studies assessing language-specific regions as shown above, no studies have investigated abnormal lateralization between left and right FPN connectivity in schizophrenia. Because FPNs are identified in ICA, study on FPNs must rely on the use of ICA. In addition, as rsfMRI does not require tasks, it can be readily performed on schizophrenia patients, and it is basically free from the issue of task performance.

Based on these results, it is natural to hypothesize that schizophrenia patients have abnormal lateralization between the left and right FPN connectivity, and that these abnormalities are associated with symptomatology, especially positive symptoms as shown in several previous fMRI studies. In this study we investigated the lateralization of functional connectivity of bilateral FPNs in schizophrenia by applying ICA for rsfMRI in order to clarify the possible neural correlates explaining the symptomatology of schizophrenia.

2. Methods

2.1. Participants

Forty-one patients with schizophrenia (20 men and 21 women, age =37.51 ± 8.64), who were referred to the Department of Psychiatry, Kyoto University Hospital, Japan, were recruited. Each patient fulfilled the criteria for schizophrenia based on the Structured Clinical Interview for DSM-IV Axis I Disorders Patients Edition, Version 2.0 (SCID-P). None of the patients were comorbid with other mental disorders. Predicted IQ was measured using the Japanese Version of the National Adult Reading Test (JART) short form (Matsuoka and Kim, 2007; Matsuoka et al., 2006), which is thought to reflect the premorbid IQ of schizophrenia patients. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Because PANSS has been revealed to have five dimensional symptoms, we employed the five-factor model of Lancon et al. (Lancon et al., 1998), which consists of 24 items from the original 30 items of PANSS and has subscales comprised of 7 items for negative factor, 5 items for positive factor, 5 items for activation factor, 4 items for depressive factor, and 3 items for cognitive factor. All patients were receiving antipsychotic medication (typical [n=3], atypical [n =30], typical and atypical [n=8]). Haloperidol equivalents were calculated according to the practice guideline for the treatment of schizophrenia patients (Inada and Inagaki, 2015; Lehman et al., 2004).

Thirty-five age-, gender-, handedness-, and predicted IQ-matched healthy individuals (24 men and 11 women, age =34.20 ± 8.57) were recruited as control group. They were also evaluated using the Structured Clinical Interview for DSM-IV Axis I Disorders - Non-patient Edition, Version 2.0 (SCID-NP). They had no history of psychiatric disorders, and their first-degree relatives had not experienced any psychotic episodes. Exclusion criteria for both groups were: a history of head trauma, neurological disease, severe medical or surgery-related illness, or substance abuse that could affect brain function. Handedness was assessed by Edinburgh handedness inventory (Oldfield, 1971).

After receiving a complete description of the study, written informed consent was obtained from each participant. This study was approved by the Committee on Medical Ethics of Kyoto University, and was conducted in accordance with The Code of Ethics of the World Medical Association.

2.2. MRI acquisition

Structural MRI data were acquired using 3-dimensional magnetization-prepared rapid gradient echo (3D-MPRAGE) sequences, and resting-state data were acquired while the subjects kept their eyes open using a single-shot gradient-echo echo planar imaging (EPI) pulse sequence on a 3-Tesla MRI unit (Trio; Siemens, Erlangen, Germany) with a 40-mT/m gradient and a receiver-only 8-channel phased-array head coil. At the resting state data acquisition, we instructed participants to visually concentrate on a fixation cross in the center of the screen while thinking nothing else at all. Parameters for the 3D-MPRAGE images were as follows: echo time (TE), 4.38 ms; repetition