



## Impaired empathic abilities and reduced white matter integrity in schizophrenia



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### ABSTRACT

Empathic abilities are impaired in schizophrenia. Although the pathology of schizophrenia is thought to involve disrupted white matter integrity, the relationship between empathic disabilities and altered white matter in the disorder remains unclear. The present study tested associations between empathic disabilities and white matter integrity in order to investigate the neural basis of impaired empathy in schizophrenia.

Sixty-nine patients with schizophrenia and 69 age-, gender-, handedness-, education- and IQ level-matched healthy controls underwent diffusion-weighted imaging. Empathic abilities were assessed using the Interpersonal Reactivity Index (IRI). Using tract-based spatial statistics (TBSS), the associations between empathic abilities and white matter fractional anisotropy (FA), a measure of white matter integrity, were examined in the patient group within brain areas that showed a significant FA reduction compared with the controls.

The patients with schizophrenia reported lower perspective taking and higher personal distress according to the IRI. The patients showed a significant FA reduction in bilateral deep white matter in the frontal, temporal, parietal and occipital lobes, a large portion of the corpus callosum, and the corona radiata. In schizophrenia patients, fantasy subscales positively correlated with FA in the left inferior fronto-occipital fasciculi and anterior thalamic radiation, and personal distress subscales negatively correlated with FA in the splenium of the corpus callosum.

These results suggest that disrupted white matter integrity in these regions constitutes a pathology underpinning specific components of empathic disabilities in schizophrenia, highlighting that different aspects of empathic impairments in the disorder would have, at least partially, distinct neuropathological bases.

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### 1. Introduction

Empathy is a set of constructs that enable us to understand and respond to the emotional experiences of others, and thus has a central role in successful interpersonal engagement and higher social functioning (Davis, 1983; Decety and Moriguchi, 2007). Empathy is considered to be multifaceted and to comprise at least two key components: cognitive empathy and emotional empathy. Cognitive empathy consists of the ability to understand and explain mental states of others, while emotional empathy comprises the experience of an appropriate

emotional response as a consequence of the emotional state in others (Davis, 1983).

A number of studies have reported that empathic impairments were present in schizophrenia (Derntl et al., 2009; Fujiwara et al., 2008; Haker and Rossler, 2009; Montag et al., 2007; Shamay-Tsoory et al., 2007a, 2007b), and that such deficits lead to social dysfunction (Shamay-Tsoory et al., 2007b). In these studies, impairments in empathic abilities were assessed by the Interpersonal Reactivity Index (IRI) (Davis, 1983), which is a widely used self-report instrument to assess empathic abilities on four subscales; Perspective Taking (PT), Fantasy (FS), Empathic Concern (EC), and Personal Distress (PD). PT and FS were designed to measure the cognitive aspects of empathy, and EC and PD the emotional aspects of empathy. Previous studies have revealed decreases in cognitive empathy in schizophrenia (Fujiwara et al., 2008; Montag et al., 2007; Shamay-Tsoory et al., 2007b). In addition, most studies on schizophrenia have reported increases in PD resulting from observing another's negative experience (Derntl et al., 2009; Fujiwara et al., 2008; Montag et al., 2007).

As for the neural basis of empathy in healthy subjects, several functional neuroimaging studies (Hooker et al., 2008; Lamm et al., 2011; Mar, 2011; Singer et al., 2004) and a volumetric study (Banissy et al.,

*Abbreviations:* ACC, anterior cingulate cortex; ANOVAs, analyses of variance; ATR, anterior thalamic radiation; CC, corpus callosum; DTI, diffusion tensor imaging; EC, Empathic Concern; FA, fractional anisotropy; FS, Fantasy; FSL, FMRIB Software Library; GM, gray matter; HPD, haloperidol; IFOF, inferior fronto-occipital fasciculus; IRI, Interpersonal Reactivity Index; JART, the Japanese Version of the National Adult Reading Test; MNI, Montreal Neurological Institute; PANSS, Positive and Negative Syndrome Scale; PD, Personal Distress; PT, Perspective Taking; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders; TBSS, tract-based spatial statistics; TFCE, threshold-free cluster enhancement; WM, white matter.

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2012) have suggested the importance of critical roles of gray matter (GM) regions including the anterior cingulate cortex (ACC), inferior frontal gyrus, precuneus, anterior insula, somatosensory cortex, and dorsolateral prefrontal cortex in terms of empathy processing. Furthermore, a recent study has reported that emotional empathy associates with white matter (WM) integrity in the clusters including the inferior fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus and uncinate fasciculus (Parkinson and Wheatley, 2012).

As for the neural basis of impaired empathic abilities in schizophrenia, recent fMRI studies reported functional abnormalities in cortical and subcortical regions including the ACC, inferior frontal gyrus, precuneus, and insula during a task-related empathy in schizophrenia (Derntl et al., 2012; Lee et al., 2010). In addition to the functional abnormalities, our previous study showed that the GM volume of the left dorsal ACC was negatively correlated with PD scores of the IRI in female schizophrenia patients (Fujiwara et al., 2008). These GM regions largely overlap with those that are reportedly important in empathy in normal subjects.

Considering the neuropathology in schizophrenia, not only GM abnormalities in the frontal, temporal and parietal cortical regions, media temporal lobe structures, basal ganglia, and thalamus (Ellison-Wright et al., 2008), but also disrupted WM integrity among these GM regions has a key role (Walterfang et al., 2006). Since the complicated process of empathy requires the coordinated functioning of a widely distributed network of GM regions, empathic disabilities in schizophrenia may be caused by disrupted WM integrity. However, to the best of our knowledge, no study has directly investigated the relationship between empathic impairments and WM connectivity in schizophrenia.

Here, we investigated the association between empathic disability and WM integrity in schizophrenia, using diffusion tensor imaging (DTI). We used the IRI to evaluate empathic ability. We also utilized a widely used robust voxelwise analysis technique for DTI data called tract-based spatial statistics (TBSS) (Smith et al., 2006), and fractional anisotropy (FA) was used as an index of WM integrity. We hypothesized that empathic disabilities in patients would be correlated with FA reduction in regions that connect GM regions relevant to the process of empathy. Furthermore, it was predicted that different aspects of empathic impairments would be associated with distinct WM disconnectivity in schizophrenia. Emotional empathy comprises the experience of an appropriate emotional response as a consequence of the emotional state in others (Davis, 1983). These abilities appear to rely on the interactions of sensory and emotional processing (Parkinson and Wheatley, 2012). Therefore, emotional aspects of empathic impairments might be more strongly related to FA in the WM regions involved in sensory and emotional processing. On the other hand, the cognitive aspects of empathy require considerable cognitive ability to understand and explain the mental states of others (Davis, 1983). Thus, these impairments would be preferentially associated with FA reduction in the WM regions implicating cognitive processing, which connects to GM regions reported to be associated with cognitive empathy, such as the prefrontal cortices (Banissy et al., 2012).

## 2. Materials and methods

### 2.1. Participants

Sixty-nine schizophrenia patients, diagnosed based on the patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), participated in this study. None of the patients was comorbid with other psychiatric disorders. Predicted premorbid IQ was measured with the Japanese Version of the National Adult Reading Test short form (Matsuoka and Kim, 2007). The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess the severity of clinical symptoms. All patients were receiving antipsychotic medication (typical [ $n = 4$ ], atypical [ $n = 50$ ], typical and atypical [ $n = 15$ ]). Sixty-nine healthy controls, matched with the patient group in age, gender,

handedness, education and predicted IQ levels were recruited. The controls had no history of psychiatric illness, as determined by the non-patient edition of the SCID, and there was no history of psychotic disorders among their first-degree relatives. Exclusion criteria for all individuals included a history of head trauma, any neurological illness, serious medical or surgical illness, and substance abuse. All participants were physically healthy at the time of scanning and psychological tests.

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

### 2.2. The Interpersonal Reactivity Index (IRI)

The Japanese version of the Interpersonal Reactivity Index (IRI) (Davis, 1983; Sakurai, 1988) was administered. It consists of four 7-item subscales to assess different aspects of empathic abilities. PT contains items that assess spontaneous attempts to adopt the perspective of other people and see things from their point of view. FS assesses shifting oneself into feelings of fictional characters. As to the other two subscales, EC inquires about own feelings of compassion and concern for others, while PD measures the personal feelings of anxiety and discomfort resulting from observing another's negative experience. Higher scores of each subscale mean higher empathic tendency. However, it should be noted that four subscale scores are not all positively correlated (Davis, 1980, 1983). Specifically, the PD subscale was negatively correlated with the other measures of empathy and social competence (Davis, 1983). Higher PD scores indicate a greater tendency to have self-oriented feelings of anxiety and discomfort in response to tense interpersonal settings (Davis, 1983), which suggests abnormally enhanced emotional reaction in embarrassing social situations (Decety and Moriguchi, 2007). Such tendency was associated with higher levels of social dysfunction (Davis, 1983), and elevated levels of PD were often seen in various psychiatric disorders (Cusi et al., 2010; Montag et al., 2007). Therefore, higher PD scores can be interpreted as indicating dysfunction.

### 2.3. MRI acquisition and pre-processing

Diffusion-weighted data were acquired using single-shot spin-echo echo-planar sequences with a 3.0-T MRI unit (Trio; Siemens, Erlangen, Germany) with a 40-mT/m gradient and a receiver-only eight-channel phased-array head coil. The scanning parameters were as follows: echo time = 96 ms, repetition time = 10,500 ms,  $96 \times 96$  matrix, field of view =  $192 \times 192$  mm, 70 contiguous axial slices of 2.0-mm thickness, 81 non-collinear motion-probing gradients, and  $b = 1500$  s/mm<sup>2</sup>. The  $b = 0$  images were scanned before every nine diffusion-weighted images, thus consisting of 90 volumes in total.

DTI data were processed using programs in the FMRIB Software Library (FSL) version 4.1 (Smith et al., 2004). Source data were corrected for eddy currents and head motion by registering all data to the first  $b = 0$  image, with affine transformation. The FA maps were calculated using the DTIFIT program implemented in FSL. For voxelwise statistical analysis, TBSS version 1.2 was used. All FA data were normalized into a common space using the nonlinear registration tool FNIRT; normalized FA images were averaged to create a mean FA image, which was then thinned to create a mean FA skeleton, taking only the centers of WM tracts common to all the subjects. Voxel values of each subject's FA map were projected onto the skeleton by searching the local maxima along the perpendicular direction from the skeleton. The resultant skeletonized FA data were used in the following voxelwise statistical analyses.

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