

**Title**

Impaired empathic abilities and reduced white matter integrity in schizophrenia

**Author names and affiliations**

Junya Fujino<sup>a</sup>, Hidehiko Takahashi<sup>a\*</sup>, Jun Miyata<sup>a</sup>, Genichi Sugihara<sup>a</sup>, Manabu Kubota<sup>a</sup>, Akihiko Sasamoto<sup>a</sup>, Hironobu Fujiwara<sup>a</sup>, Toshihiko Aso<sup>b</sup>, Hidenao Fukuyama<sup>b</sup>, Toshiya Murai<sup>a</sup>

- a. Department of Psychiatry, Graduate School of Medicine, Kyoto University, Shogoin-Kawaracho 54, Kyoto 606-8507, Japan
- b. Human Brain Research Center, Graduate School of Medicine, Kyoto University, Shogoin-Kawaracho 54, Kyoto 606-8507, Japan

**\* Corresponding author**

Tel: +81-75-751-3386, Fax: +81-75-751-3246

E-mail: [hidehiko@kuhp.kyoto-u.ac.jp](mailto:hidehiko@kuhp.kyoto-u.ac.jp) (H. Takahashi)

1

---

*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

## 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.

**Keywords:** Schizophrenia; Empathy; White matter; Corpus callosum; Inferior fronto-occipital fasciculus

## 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; Lam et al., 2011; Mar, 2011; Singer et al., 2004) and a volumetric study (Banissy et al., 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., 2011; 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., 2007). 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,  $b = 1,500 \text{ s/mm}^2$ . 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.

## 2.4. Data analyses

### 2.4.1. Scores of each IRI subscale

First, to examine group differences and possible gender effects on each IRI subscale, we applied two-way analyses of variance (ANOVAs) with each IRI subscale as dependent variables, and gender and diagnosis as between-subject factors.

Second, to explore possible influences of clinical characteristics on IRI scores, correlational analyses were performed between each IRI subscale and clinical variable (i.e., scores in positive, negative, general psychopathology of PANSS, duration of illness, medication) in the patient group. Since some of the data were not normally distributed (Shapiro-Wilk test,  $p < 0.05$ ), we chose Spearman's rank correlation. Data were analyzed using SPSS 21 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at  $p < 0.05$  (two-tailed) in all analyses.

### 2.4.2. Group comparison of FA

Voxelwise permutation-based nonparametric inference ([Nichols and Holmes, 2002](#)) was performed on skeletonized FA data, using FSL Randomize ver. 2.5. Firstly, we performed group comparisons, with age and gender as nuisance covariates. Both control–patient and patient–control contrasts were tested, with 10,000 permutations. The statistical threshold was defined at  $p < 0.05$ , correcting for multiple comparisons by threshold-free cluster enhancement (TFCE) ([Smith and Nichols, 2009](#)). The resultant significant FA reduction/increase areas in patients were used as inclusion masks in the following voxelwise correlational analyses.

### 2.4.3. Voxelwise correlational analyses

Voxelwise multiple regression analyses were carried out using TBSS to explore the WM regions that correlated with each IRI subscale in schizophrenia patients. Age and gender were entered into the model as covariates of no interest. The above-mentioned masks were applied to include only those voxels with significant group differences. Permutation-based nonparametric inference was undertaken with 10,000 permutations. The statistical threshold was defined at  $p < 0.05$ , correcting for multiple comparisons by TFCE. Fiber tracts corresponding to the clusters were identified with reference to the

Johns Hopkins University DTI-based White Matter Atlas (<http://cmrm.med.jhmi.edu>) (Mori et al., 2005).

The same correlational analyses were performed on healthy subjects for the whole skeleton. The threshold for statistical significance was also defined at  $p < 0.05$ , TFCE-corrected for multiple comparisons.

### 3. Results

Demographic and clinical data are shown in Table 1. The patient group consisted mainly of chronic patients with relatively mild symptom severity.

#### 3.1. Scores of each IRI subscale

The two-way ANOVAs revealed significant main effects of diagnosis in the PT and PD subscales [PT,  $F(1,134) = 9.782$ ,  $p = 0.002$ ; PD,  $F(1,134) = 11.188$ ,  $p = 0.001$ ]. Schizophrenia patients showed significantly lower scores on the PT subscale and significantly higher PD compared to controls (Table 2). There were, however, no significant effects of gender, and no significant diagnosis  $\times$  gender interaction in any of these analyses. There were no significant main effects of diagnosis and gender, and no significant diagnosis  $\times$  gender interaction in the FS and EC subscales. No significant correlations were found between IRI subscales and PANSS subscale scores, duration of illness, or medication in the patient group.

#### 3.2. Group comparison of FA value

Schizophrenia patients displayed a cluster of widely distributed significant FA reduction relative to controls. This cluster extended to the bilateral deep WM in the frontal, temporal, parietal and occipital lobes, a large portion of the corpus callosum (CC), and the corona radiata (Fig. 1). There was no region in which the patients showed increased FA compared to the controls. Thus, we used the cluster in which FA was reduced in the patients as a mask in the following correlational analyses.

#### 3.3. Voxelwise correlational analyses

In the patient group, there was a significant positive correlation between FS subscales and FA in a cluster including the left IFOF and the anterior thalamic radiation (ATR). In

addition, patients' PD subscale showed negative correlation with FA in a cluster including the splenium of the CC (Table 3, Fig. 2 and 3). Spearman's rank correlation coefficients between FS/PD and mean FA of these clusters were 0.544 and -0.312, respectively. The other two subscales showed no significant correlations with FA reduction. We tested possible effects of major clinical characteristics on these significant correlations [FS/PD and mean FA of the clusters ( $p < 0.05$ , TFCE)], using partial correlation. The correlation between FS subscales and FA in the cluster including the left IFOF and ATR, and the correlation between PD subscales and FA in the cluster including the splenium of the CC remained significant after controlling for age, gender, education and premorbid IQ (FS,  $\rho = 0.517$ ,  $p < 0.001$ ; PD,  $\rho = -0.372$ ,  $p = 0.002$ ). Moreover, both correlations were still significant even after controlling for positive, negative and general psychopathology subscales of PANSS (FS,  $\rho = 0.505$ ,  $p < 0.001$ ; PD,  $\rho = -0.367$ ,  $p = 0.003$ ), duration of illness (FS,  $\rho = 0.501$ ,  $p < 0.001$ ; PD,  $\rho = -0.331$ ,  $p = 0.009$ ), and medication (FS,  $\rho = 0.498$ ,  $p < 0.001$ ; PD,  $\rho = -0.324$ ,  $p = 0.012$ ).

On the other hand, there was no significant correlation of FA with any of the IRI subscales in healthy controls.

#### 4. Discussion

To the best of our knowledge, this is the first study to examine the relationship between empathic disabilities and disrupted WM integrity in schizophrenia. The results suggest that disrupted white matter integrity in two regions constitutes a pathology underpinning specific components of empathic disabilities in schizophrenia; PD negatively correlated with FA in a cluster including the splenium of the CC, and FS positively correlated with FA in a cluster including the left IFOF/ATR.

The results of IRI generally replicated the previous literature. The schizophrenia group showed lower PT and higher PD, consistent with the previous studies (Haker and Rossler, 2009; Montag et al., 2007). Although we did not find a significant difference in FS score between the two groups in this study, a number of previous studies showed lower FS in schizophrenia compared with healthy subjects (Derntl et al., 2009; Fujiwara et al., 2008). The lack of a group difference in EC score is consistent with most previous reports (Derntl et al., 2009; Fujiwara et al., 2008; Haker and Rossler, 2009;

[Montag et al., 2007](#); [Shamay-Tsoory et al., 2007a, 2007b](#)). In correlational analyses, we found no associations between IRI subscales and clinical variables (positive, negative, general psychopathology of PANSS and duration of illness) in schizophrenia. It is controversial whether empathic impairments in schizophrenia reflect a state or a trait ([Achiem et al., 2010](#); [Haker H et al., 2012](#)), however our results support that empathic disabilities may constitute a trait marker of schizophrenia.

Patients showed a significant FA reduction in bilateral deep white matter in the frontal, temporal, parietal and occipital lobes, a large portion of the CC, and the corona radiata. The results of the group comparison of FA were largely consistent with previous studies, indicating robust multiregional reduction of WM integrity in schizophrenia ([Walterfang et al., 2006](#); [Miyata et al., 2010](#)).

In these areas, PD subscale negatively correlated with FA in a cluster including the splenium of the CC, whereas FS subscale positively correlated with FA in a cluster including the left IFOF and ATR, suggesting that distinct WM disconnectivity might underlie different facets of empathic impairments in schizophrenia. A possible interpretation of the correlation between PD and the cluster including the splenium of CC is as follows. Previous studies have suggested that structural alteration of the CC in schizophrenia reflects dysfunctional interhemispheric information transfer and can cause a disturbed integration of information concerning self and environment ([David, 1994](#); [Knöchel et al., 2012](#); [Patel et al., 2011](#); [van der Knaap and van der Ham, 2011](#)). Difficulties in self-other distinction may result in abnormally enhanced empathic responding in embarrassing social situations ([Decety and Moriguchi, 2007](#)). Interestingly, the cluster in the CC in which FA was correlated with PD was located in the posterior part of the CC, which includes the transcallosal fibers connecting the bilateral somatosensory cortex ([Fabri et al., 2001](#); [van der Knaap and van der Ham, 2011](#)). Therefore, our findings are consistent with the results of the previous study, namely, that the GM volume in the somatosensory cortex was associated with PD subscales in healthy subjects ([Banissy et al., 2012](#)). In addition, the results might support the recent studies that have indicated a key role for somatosensation in social perception ([Hooker et al., 2008](#), [Keysers et al., 2010](#)).

We also found a correlation between FS and the cluster including IFOF/ATR in schizophrenia. FS subscale, a measure of the capability of shifting oneself into feelings of fictional characters, was reported to be positively correlated with verbal ability and

vocabulary (Davis, 1983). Several studies have indicated the importance of the IFOF in language and semantic processing network (deZubicaray et al., 2011; Duffau, 2008). Thus, disrupted WM integrity in the IFOF is associated with this specific aspect of empathy. In addition, the ATR was contained in this cluster. Thalamo-cortical connectivity is also considered to be a key underpinning of impaired multiple cognitive abilities in schizophrenia (Kim et al., 2008; Marengo et al., 2012). In the same vein, the ATR may play an important role in FS ability in schizophrenia. Furthermore, GM volume in the dorsolateral prefrontal cortex was associated with FS subscale scores in healthy subjects (Banissy et al., 2012). As the dorsolateral prefrontal cortex is the region in which both IFOF and ATR are partially connecting (Mori et al., 2005), the study by Banissy et al. again corroborates our interpretation.

On the other hand, PT and EC subscales showed no significant correlations with FA reduction in schizophrenia. One possible explanation is that the neural network for PT may not be specific for this function, as PT may depend on domain-general mechanisms underlying a broad range of cognitive abilities rather than domain-specific mechanisms for empathy or social cognition (Decety and Lamm, 2007; Parkinson and Wheatley, 2012). Concerning EC, it is intact in schizophrenia, and thus it may not be related to reduced WM integrity.

With respect to healthy subjects, we did not find associations between FA and any of the IRI subscales, while a previous study showed an association between EC subscale and WM microstructure (Parkinson and Wheatley, 2012). This discrepancy might be due to different characteristics of participants, as for example, the older age of our subjects.

There are several limitations to this study. First, most patients participating in this study had relatively mild and stable symptoms, and therefore, our sample may not be representative of the general population of patients with schizophrenia. Secondly, it is difficult to exactly identify the fiber tracts in the clusters that emerged in the correlational analyses. To overcome this issue, detailed tractography analyses would be necessary in future studies. Thirdly, all the patients were receiving antipsychotic medications. Although we confirmed that the results of two correlational analyses were still significant even after controlling for dosage of antipsychotic medications, we cannot exclude completely the possibility of confounding effects of antipsychotics. Most previous studies showed no significant findings regarding correlational analyses

between the level of antipsychotic medications and DTI data (Kalus et al., 2005, Kubicki et al., 2005, Kumra et al., 2005, Kyriakopoulos et al., 2008). However, several studies reported significant correlations between antipsychotic doses and FA in some WM regions of the brain in schizophrenia (Miami et al., 2003, Okugawa et al., 2004). To address the effect of medication on brain structure, systematic studies with a larger sample size, which can analyze the associations between FA and the level of various medication subtypes, would be needed. Finally, the focus of this study was restricted to the WM abnormalities. In the neuropathology of schizophrenia, GM abnormalities also have key roles. Future research utilizing multimodal MRI will need to investigate the interplay between GM and WM abnormalities on empathic impairments to better understand the pathophysiology of the deficits in schizophrenia.

Despite these limitations, the present study is noteworthy because it indicates, for the first time, the existence of WM pathology underlying impaired empathy in schizophrenia. Furthermore, the results also showed that distinct WM disconnectivity might underlie different aspects of empathic impairments in schizophrenia; disrupted WM connectivity in the left IFOF/ATR, and the splenium of the CC is associated with FS and PD of IRI, respectively, in the disorder. These neurobiological findings highlight the view that empathy is not a unitary but rather a multifaceted construct, and they add to our understanding of the neural basis of impaired empathic abilities in schizophrenia. This multidimensionality of empathic impairments should be considered when developing interventions for improving empathic abilities in schizophrenia.

## **5. Conclusions**

In summary, this study demonstrates disrupted WM connectivity in the left IFOF/ATR, and the splenium of the CC is associated with FS and PD of IRI, respectively, in schizophrenia. Our neurobiological findings emphasize the multidimensionality of empathic impairments in schizophrenia. Taking this into account, strengthening these connections would be a possible target of pharmacological as well as non-pharmacological therapies, to improve empathic abilities and social functioning in schizophrenia.

## **Conflict of interest**

All authors declare that they have no conflicts of interest.

## **Acknowledgements**

This work was supported by grants-in-aid for scientific research B (23390290), S (22220003), and on Innovative Areas (23118004, 23120009), from the Ministry of Education, Culture, Sports, Science and Technology of Japan; Grants-in-Aid for Young Scientists A (23680045), B (23791329) from the Japan Society for the Promotion of Science. These agencies had no further role in the study design, the collection, analysis and interpretation of data, the writing of the report, or in the decision to submit the paper for publication. All authors declare that they have no conflicts of interest.

The authors wish to extend their gratitude to Ryosaku Kawada, Yusuke Tanaka, Shiho Ubukata, Yukiko Matsumoto, Masanori Isobe, Shuraku Son, Kousuke Tsurumi, Yasuo Mori, Naoto Yokoyama, Kimito Hirose, Shisei Tei, Miki Ono, Naho Saito, Tomomi Noda, Hitoshi Sasaki, Hideaki Takeuchi, Ariyoshi Takemura, Noriko Matsukawa, Ema Murao and Takuro Murao for their assistance in data acquisition and processing, and, most of all, to the patients and volunteers for participating in the study.

## References

Achim AM, Ouellet R, Roy MA, Jackson PL. Assessment of empathy in first-episode psychosis and meta-analytic comparison with previous studies in schizophrenia. *Psychiatry Res.* 2011;190:3-8.

Banissy MJ, Kanai R, Walsh V, Rees G. Inter-individual differences in empathy are reflected in human brain structure. *Neuroimage.* 2012;62:2034-9.

Cusi A, Macqueen GM, McKinnon MC. Altered self-report of empathic responding in patients with bipolar disorder. *Psychiatry Res.* 2010;178:354-8.

David AS. Schizophrenia and the corpus callosum: developmental, structural and functional relationships. *Behav Brain Res.* 1994;64:203-11.

Davis MH. A multidimensional approach to individual differences in empathy. *JSAS Catal. Sel. Doc. Psychol.* 1980;10:85.

Davis MH. Measuring individual differences in empathy: evidence for a multidimensional approach. *J. Person. Soc. Psychol.* 1983;44:113–26.

de Zubicaray GI, Rose SE, McMahon KL. The structure and connectivity of semantic memory in the healthy older adult brain. *Neuroimage.* 2011;54:1488-94.

Decety J, Lamm C. The role of the right temporoparietal junction in social interaction: how low-level computational processes contribute to meta-cognition. *Neuroscientist.* 2007;13:580-93.

Decety J, Moriguchi Y. The empathic brain and its dysfunction in psychiatric populations: implications for intervention across different clinical conditions. *Biopsychosoc Med.* 2007;1:22.

Derntl B, Finkelmeyer A, Toygar TK, Hulsmann A, Schneider F, Falkenberg DI, et al.

Generalized deficit in all core components of empathy in schizophrenia. *Schizophr Res.* 2009;108:197-206.

Derntl B, Finkelmeyer A, Voss B, Eickhoff SB, Kellermann T, Schneider F, et al. Neural correlates of the core facets of empathy in schizophrenia. *Schizophr Res.* 2012;136:70-81.

Duffau H. The anatomo-functional connectivity of language revisited. New insights provided by electrostimulation and tractography. *Neuropsychologia.* 2008;46:927-34.

Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *Am J Psychiatry.* 2008;165:1015-23.

Fabri M, Polonara G, Del Pesce M, Quattrini A, Salvolini U, Manzoni T. Posterior corpus callosum and interhemispheric transfer of somatosensory information: an fMRI and neuropsychological study of a partially callosotomized patient. *J Cogn Neurosci.* 2001;13:1071-9.

Fujiwara H, Shimizu M, Hirao K, Miyata J, Namiki C, Sawamoto N, et al. Female specific anterior cingulate abnormality and its association with empathic disability in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32:1728-34.

Haker H, Rossler W. Empathy in schizophrenia: impaired resonance. *Eur Arch Psychiatry Clin Neurosci.* 2009;259:352-61.

Haker H, Schimansky J, Jann S, Rossler W. Self-reported empathic abilities in schizophrenia: a longitudinal perspective. *Psychiatry Res.* 2012;200:1028-31.

Hooker CI, Verosky SC, Germine LT, Knight RT, D'Esposito M. Mentalizing about emotion and its relationship to empathy. *Soc Cogn Affect Neurosci.* 2008;3:204-17.

Inagaki, A., Inada, T. Dose equivalence of psychotropic drugs. *Jpn. J. Clin.*

Psychopharmacol. 2008;11:887–890.

Kalus P, Slotboom J, Gallinat J, Federspiel A, Gralla J, Remonda L, et al. New evidence for involvement of the entorhinal region in schizophrenia: a combined MRI volumetric and DTI study. *Neuroimage*. 2005;24:1122-9.

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261-76.

Keysers C, Kaas JH, Gazzola V. Somatosensation in social perception. *Nat Rev Neurosci*. 2010;11:417-28.

Kim DJ, Kim JJ, Park JY, Lee SY, Kim J, Kim IY, et al. Quantification of thalamocortical tracts in schizophrenia on probabilistic maps. *Neuroreport*. 2008;19:399-403.

Knöchel C, Oertel-Knöchel V, Schönmeier R, Rotarska-Jagiela A, van de Ven V, Prvulovic D, et al. Interhemispheric hypoconnectivity in schizophrenia: fiber integrity and volume differences of the corpus callosum in patients and unaffected relatives. *Neuroimage*. 2012;59:926-34.

Kubicki M, Park H, Westin CF, Nestor PG, Mulkern RV, Maier SE, et al. DTI and MTR abnormalities in schizophrenia: analysis of white matter integrity. *Neuroimage*. 2005;26:1109-18.

Kumra S, Ashtari M, Cervellione KL, Henderson I, Kester H, Roofeh D, et al. White matter abnormalities in early-onset schizophrenia: a voxel-based diffusion tensor imaging study. *J Am Acad Child Adolesc Psychiatry*. 2005;44:934-41.

Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S. Diffusion tensor imaging in schizophrenia. *Eur Psychiatry*. 2008;23:255-73.

Lamm C, Decety J, Singer T. Meta-analytic evidence for common and distinct neural

networks associated with directly experienced pain and empathy for pain. *Neuroimage*. 2011;54:2492-502.

Lee SJ, Kang do H, Kim CW, Gu BM, Park JY, Choi CH, et al. Multi-level comparison of empathy in schizophrenia: an fMRI study of a cartoon task. *Psychiatry Res*. 2010;181:121-9.

Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*. 2004;161:1-56.

Mar RA. The neural bases of social cognition and story comprehension. *Annu Rev Psychol*. 2011;62:103-34.

Marenco S, Stein JL, Savostyanova AA, Sambataro F, Tan HY, Goldman AL, et al. Investigation of anatomical thalamo-cortical connectivity and FMRI activation in schizophrenia. *Neuropsychopharmacology*. 2012;37:499-507.

Matsuoka K, & Kim Y. Japanese Adult Reading Test (JART). Tokyo: Shinko-Igaku, 2007.

Minami T, Nobuhara K, Okugawa G, Takase K, Yoshida T, Sawada S, et al. Diffusion tensor magnetic resonance imaging of disruption of regional white matter in schizophrenia. *Neuropsychobiology*. 2003;47:141-5.

Miyata J, Yamada M, Namiki C, Hirao K, Saze T, Fujiwara H, et al. Reduced white matter integrity as a neural correlate of social cognition deficits in schizophrenia. *Schizophr Res*. 2010;119:232-9.

Montag C, Heinz A, Kunz D, Gallinat J. Self-reported empathic abilities in schizophrenia. *Schizophr Res*. 2007;92:85-9.

Mori S, Wakana S, Nagae-Poetscher L, & van Zijl P.C.M. MRI Atlas of Human White

Matter. Amsterdam: Elsevier, 2005.

Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp.* 2002;15:1-25.

Okugawa G, Nobuhara K, Minami T, Tamagaki C, Takase K, Sugimoto T, et al. Subtle disruption of the middle cerebellar peduncles in patients with schizophrenia. *Neuropsychobiology.* 2004;50:119-23.

Parkinson C, Wheatley T. Relating Anatomical and Social Connectivity: White Matter Microstructure Predicts Emotional Empathy. *Cereb Cortex.* 2012.

Patel S, Mahon K, Wellington R, Zhang J, Chaplin W, Szeszko PR. A meta-analysis of diffusion tensor imaging studies of the corpus callosum in schizophrenia. *Schizophr Res.* 2011;129:149-55.

Sakurai S. Association of empathy and supportive behaviors in college students: a study using Interpersonal Reactivity Index. Nara University of Education Press. 1988;37:149–54.

Shamay-Tsoory SG, Shur S, Barcai-Goodman L, Medlovich S, Harari H, Levkovitz Y. Dissociation of cognitive from affective components of theory of mind in schizophrenia. *Psychiatry Res.* 2007a;149:11-23.

Shamay-Tsoory SG, Shur S, Harari H, Levkovitz Y. Neurocognitive basis of impaired empathy in schizophrenia. *Neuropsychology.* 2007b;21:431-8.

Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science.* 2004;303:1157-62.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage.* 2006;31:1487-505.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004;23 Suppl 1:S208-19.

Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage*. 2009;44:83-98.

van der Knaap LJ, van der Ham IJ. How does the corpus callosum mediate interhemispheric transfer? A review. *Behav Brain Res*. 2011;223:211-21.

Walterfang M, Wood SJ, Velakoulis D, Pantelis C. Neuropathological, neurogenetic and neuroimaging evidence for white matter pathology in schizophrenia. *Neurosci Biobehav Rev*. 2006;30:918-48.

**Table 1**

Demographic and clinical characteristics of participants

|                             | Schizophrenia<br>(n=69) |      | Control<br>(n=69) |      | Statistics        |
|-----------------------------|-------------------------|------|-------------------|------|-------------------|
|                             | Mean                    | S.D. | Mean              | S.D. | p                 |
| Age (years)                 | 36.6                    | 9.2  | 34.2              | 12.4 | 0.16 <sup>b</sup> |
| Gender (male/female)        | 40/29                   |      | 35/34             |      | 0.40 <sup>c</sup> |
| Handedness (right/left)     | 64/5                    |      | 65/4              |      | 0.73 <sup>c</sup> |
| Education years             | 13.9                    | 2.2  | 14.5              | 2.5  | 0.21 <sup>b</sup> |
| Predicted IQ (JART)         | 103.1                   | 9.0  | 105.3             | 9.0  | 0.13 <sup>b</sup> |
| Age at onset                | 24.2                    | 7.0  |                   |      |                   |
| Duration of illness (years) | 13.1                    | 9.7  |                   |      |                   |
| PANSS total                 |                         |      |                   |      |                   |
| PANSS positive              | 61.6                    | 17.8 |                   |      |                   |
| PANSS negative              | 14.2                    | 4.7  |                   |      |                   |
| PANSS general               | 15.9                    | 5.5  |                   |      |                   |
| Drug (mg/day, HPD           | 31.4                    | 10.1 |                   |      |                   |
| equivalent) <sup>a</sup>    | 11.5                    | 9.3  |                   |      |                   |

<sup>a</sup> Haloperidol equivalents were calculated according to the practice guidelines for the treatment of patients with schizophrenia (Lehman et al., 2004; Inagaki and Inada, 2008).

<sup>b</sup> Mann-Whitney test

<sup>c</sup> Two-tailed chi-square test

Abbreviations; JART = Japanese Version of the National Adult Reading Test, PANSS = Positive and Negative Syndrome Scale, HPD = haloperidol

**Table 2**

Scores of each IRI subscale for the participants

| IRI | Schizophrenia |      | Control |      | Statistics           |                    |                    |
|-----|---------------|------|---------|------|----------------------|--------------------|--------------------|
|     | (n=69)        |      | (n=69)  |      | Diagnosis            | Gender             | Diagnosis x Gender |
|     | Mean          | S.D. | Mean    | S.D. | df=1, 134            | df=1, 134          | df=1, 134          |
| PT  | 18.2          | 3.6  | 20.1    | 3.5  | F=9.782<br>p=0.002*  | F=1.328<br>p=0.251 | F=1.120<br>p=0.292 |
| FS  | 17.7          | 3.4  | 18.7    | 3.4  | F=2.306<br>p=0.131   | F=1.488<br>p=0.225 | F=0.296<br>p=0.587 |
| EC  | 20.8          | 2.7  | 20.9    | 2.4  | F=0.064<br>p=0.800   | F=0.063<br>p=0.803 | F=2.458<br>p=0.119 |
| PD  | 18.8          | 3.9  | 16.7    | 3.5  | F=11.188<br>p=0.001* | F=0.327<br>p=0.568 | F=0.396<br>p=0.530 |

\*  $p < 0.05$ 

Abbreviations; IRI = Interpersonal Reactivity Index, PT = Perspective Taking, FS = Fantasy, EC = Empathic Concern, PD = Personal Distress

**Table 3**

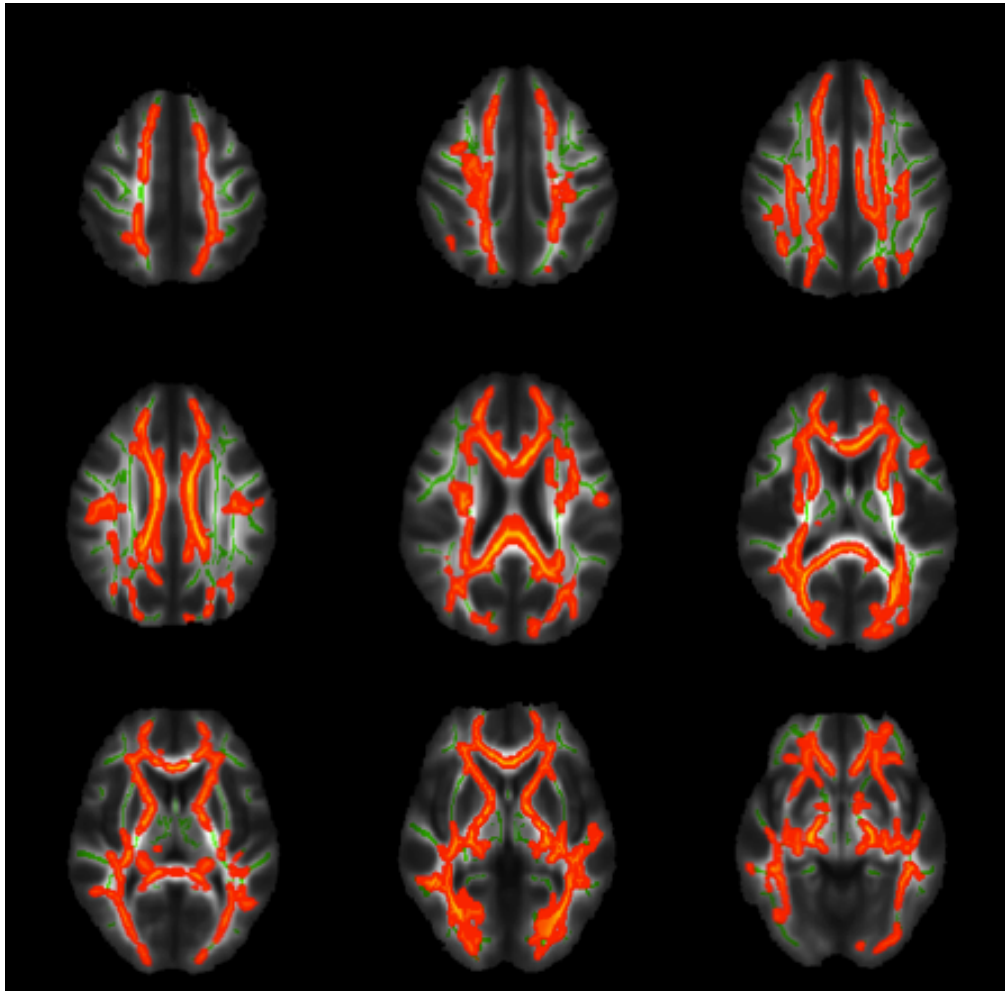
Significant correlation between the IRI subscale score and FA in patients

| Anatomical region    | IRI | t    | rho    | MNI coordinate <sup>a</sup> |     |    | Cluster size |
|----------------------|-----|------|--------|-----------------------------|-----|----|--------------|
|                      |     |      |        | X                           | Y   | Z  |              |
| Left ATR and IFOF    | FS  | 4.67 | 0.544  | -15                         | 8   | 5  | 65           |
| Right splenium of CC | PD  | 3.68 | -0.312 | 11                          | -38 | 23 | 88           |

<sup>a</sup> Coordinates for the peak voxels are displayed.

Abbreviations: ATR = anterior thalamic radiation, IFOF = inferior fronto-occipital fasciculus, CC = corpus callosum. FS = Fantasy, PD = Personal Distress, MNI = Montreal Neurological Institute

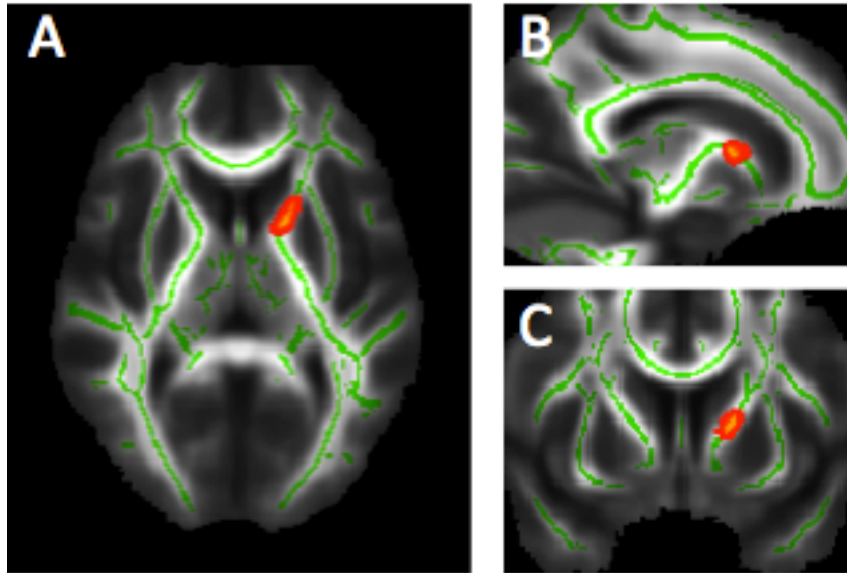
**Fig.1**



Regions of significant FA reduction in patients with schizophrenia relative to controls ( $p < 0.05$ , corrected by TFCE). To aid visualization, results are thickened using the `tbss_fill` script implemented in FSL (red-yellow). Results are shown overlaid on the mean FA maps and the FA skeleton (green). Left-right orientation is according to radiological convention. Axial slices from  $Z = -6$  to 50 in MNI coordinate are shown.

Abbreviations; FA = fractional anisotropy, TFCE = threshold-free cluster enhancement, FSL = FMRIB Software Library, MNI = Montreal Neurological Institute

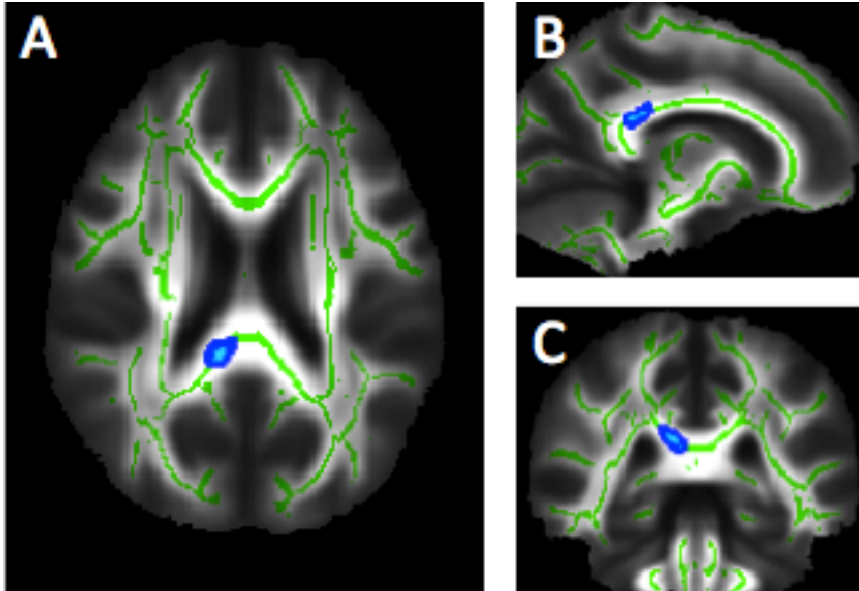
**Fig. 2**



Significant positive correlation between FS subscale score and FA in schizophrenia patients ( $p < 0.05$ , corrected by TFCE). To aid visualization, results are thickened using the `tbss_fill` script implemented in FSL (red–yellow). The results are shown overlaid on the mean FA map and the FA skeleton (green). A: axial slice; B: sagittal slice; C: coronal slice.

Abbreviations; FS = Fantasy, FA = fractional anisotropy, TFCE = threshold-free cluster enhancement, FSL = FMRIB Software Library

**Fig. 3**



Significant negative correlation between PD subscale score and FA in schizophrenia patients ( $p < 0.05$ , corrected by TFCE). To aid visualization, results are thickened using the `tbss_fill` script implemented in FSL (blue–light blue). The results are shown overlaid on the mean FA map and the FA skeleton (green). A: axial slice; B: sagittal slice; C: coronal slice.

Abbreviations; PD = Personal Distress, FA = fractional anisotropy, TFCE = threshold-free cluster enhancement, FSL = FMRIB Software Library