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Alexithymia and reduced white matter integrity in schizophrenia: A diffusion tensor imaging study on impaired emotional self-awareness

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Abstract

Alexithymia is characterized by deficits in emotional self-awareness. A number of previous studies have revealed impaired emotional self-awareness in schizophrenia. Although the pathology of schizophrenia is thought to involve disrupted white matter integrity, its relationship with alexithymia remains unclear. The present study investigated associations between alexithymia and white matter integrity, to seek the neural basis of impaired emotional self-awareness in schizophrenia. Forty-four patients with schizophrenia and 44 age-, gender- and predicted IQ level-matched healthy controls underwent diffusion-weighted imaging. Alexithymia was assessed using the 20-item Toronto Alexithymia Scale (TAS-20). We applied tract-based spatial statistics to investigate the correlation between the TAS-20 total score and white matter fractional anisotropy (FA). TAS-20 scores were significantly higher in patients than in controls. In the patient group only, FA was negatively correlated with the TAS-20 total score in the corpus callosum, mostly the left part of the superior and inferior longitudinal fasciculi, the inferior occipito-frontal fasciculus, the anterior and posterior thalamic radiation, and the precuneus white matter. These results suggest that schizophrenia is associated with alexithymia, and that reduced white matter integrity within these regions constitutes an important pathology underlying impaired self-emotional awareness in schizophrenia.

Keywords: MRI; Tract-based spatial statistics; TAS-20; Corpus callosum; Superior longitudinal fasciculus; Inferior longitudinal fasciculus

1. Introduction

Alexithymia is characterized by deficits in emotional self-awareness, and refers to a cognitive-affective disturbance that affects the way individuals recognize and verbalize emotions (Sifneos, 1972). Alexithymic individuals show difficulty in recognizing and describing their own feelings, and in discriminating between emotional states and bodily sensations (Taylor, 1984). Their communicative style is characterized by markedly reduced or absent symbolic thinking, so that inner attitudes, feelings, wishes, and drives are not revealed (Taylor, 1984).

The phenomenon was first described in patients with psychosomatic disorders (Sifneos, 1972). A number of subsequent studies reported that alexithymia is shown in other psychiatric disorders, including eating disorders (Bydlowski et al., 2005; Taylor et al., 1996), dissociative disorders (Elzinga et al., 2002; Sayar et al., 2005), posttraumatic stress disorder (Frewen et at., 2008), and pervasive developmental disorders (Fitzgerald and Molyneux, 2004; Szatmari et al., 2008). Alexithymia is also found in schizophrenia (Kubota et al., 2011; Maggini and Raballo, 2004; Stanghellini and Ricca, 1995; Todarello et al., 2005; van 't Wout et al., 2007).

Meanwhile, magnetic resonance imaging (MRI) studies on patients with schizophrenia have consistently reported gray matter (GM) volume reductions in frontal, temporal and parietal cortical regions, medial temporal lobe structures, the basal ganglia, and the thalamus (Ellison-Wright et al., 2008; Shenton et al., 2001). This disorder is thought to arise as a result of disrupted connectivity among these GM regions (Friston, 1998). Diffusion tensor imaging (DTI) techniques have recently been developed to provide

information about white matter (WM) tracts and their organization based on water diffusion. Fractional anisotropy (FA) is the fraction of the total "magnitude" of the diffusion tensor that we can ascribe to anisotropic diffusion (Basser, 1995). FA ranges from 0 to 1, where 0 represents no preferred direction (isotropic diffusion), and 1 represents unidirectional movement (anisotropic diffusion) (Thomason and Thompson, 2011). It is the most commonly used index of DTI, and reduction of FA implies decreased WM tract integrity. A number of studies have demonstrated FA reductions in diverse areas including frontal and temporal WM, the corpus callosum (CC), the cingulum, the fornix, fronto-temporal tracts, and fronto-occipital fascicule in patients with schizophrenia (Kubicki et al., 2007; Walterfang et al., 2006). These findings suggest that WM abnormalities may be an anatomical substrate for the 'disconnection hypothesis' (Friston, 1998) of schizophrenia.

While the neural basis of alexithymia remains a subject of ongoing investigation, previous neuroimaging studies have suggested the importance of the anterior and posterior cingulate cortex, the orbitofrontal cortex, the dorsolateral prefrontal cortex, the insula, and transcallosal interhemispheric transfer in alexithymia of healthy subjects (Borsci et al., 2009; Kano et al., 2003; Mantani et al., 2005; Moriguchi et al., 2007a; Romei et al., 2008). On the other hand, neural underpinnings of alexithymia in schizophrenia remain mostly unclear. To the best of our knowledge, only our previous study has explored such a relationship in the whole brain in schizophrenia, and it demonstrated a negative correlation between alexithymia and GM volume in the left supramarginal gyrus, which is thought to be involved in various cognitive functions (Kubota et al., 2011). However, so far there is no study that has investigated the relationship between alexithymia and WM integrity in

schizophrenia.

The present study sought to examine the association between alexithymia and WM integrity in schizophrenia, using DTI. We employed the Japanese version of the 20-item Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994a,b; Moriguchi et al., 2007b), a well-validated test that has been used to assess alexithymia in many studies on patients with schizophrenia (Kubota et al., 2011; Maggini and Raballo, 2004; Todarello et al., 2005). We also applied a widely developed technique called tract-based spatial statistics (TBSS) (Smith et al., 2006) to perform voxelwise correlational analysis on WM integrity, and FA was used as an index of integrity. TBSS maps each subject's DTI data onto a common WM tract center (‘skeleton’), and is robust to registration confounds. We hypothesized that severity of alexithymia in patients would be correlated with FA reduction in regions that are crucial for impaired cognitive abilities in this disease.

2. Methods

2.1. Participants

The schizophrenia group comprised of 44 patients (26 men and 18 women, all right-handed) who were referred to the Department of Psychiatry, Kyoto University Hospital. Each patient fulfilled the criteria for schizophrenia based on the Structural Clinical Interview for DSM-IV Axis I Disorders-Patient Edition, Version 2.0 (SCID-P). None of the patients were comorbid with other psychiatric disorders. Predicted IQ was measured by the Japanese Version of the National Adult Reading Test short form (Matsuoka et al., 2006; Matsuoka and Kim, 2007), which is considered to reflect the

premorbid IQ of patients with schizophrenia. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). PANSS consists of 30 items, each of which was scored on a 7-point scale ranging from 1 to 7. Levels of psychopathology are as follows: 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate-severe, 6 = severe, and 7 = extreme (Kay et al., 1987). We calculated the average scores for total, positive (7 items), negative (7 items), and general psychopathology (16 items) scales for each patient, and referring to these definitions of symptomatic severity we defined an average score of equal to or less than 3 as mildly symptomatic, more than 3 but less than 5 as moderately symptomatic, and 5 and more as severely symptomatic. All patients were receiving antipsychotic medication (typical [*n*=4], atypical [*n*=31], typical and atypical [*n*=9]) and all were physically healthy at the time of scanning and cognitive tests. None had a history of neurological injury or disease, severe medical diseases, or substance abuse that may affect brain function.

The control comparison group comprised of 44 healthy individuals (26 men and 18 women, all right-handed) matched to the schizophrenia group with respect to age, gender, and predicted IQ level. They were also evaluated using the Structured Clinical Interview for DSM- IV Axis I Disorders-Non-patient Edition, Version 2.0 (SCID-NP), and found to have no history of psychiatric disease. They had no history of neurological injury or disease, severe medical diseases, substance abuse that may affect brain function, or first-degree relatives suffering from psychotic episodes. Table 1 presents the participants' demographic information.

This study was approved by the Committee on Medical Ethics of Kyoto University and

was 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 all participants.

2.2. The 20-item Toronto Alexithymia Scale (TAS-20)

The Japanese version of the TAS-20 was used to assess alexithymia. The TAS-20 is a self-report questionnaire for measuring alexithymia by examining three factors: (a) difficulty identifying feelings (DIF); (b) difficulty describing feelings (DDF); and (c) externally oriented thinking (EOT).

DIF is comprised of 7 items, and assesses difficulty in recognizing one's own feelings (e.g., "I am often confused about what emotion I am feeling"). DDF consists of 5 items, and assesses the inability to communicate one's feelings to other people (e.g., "It is difficult for me to find the right words for my feelings"). EOT consists of 8 items, and assesses an externally-oriented cognitive style, in which little or no reference to a person's inner feelings is contained (e.g., "I prefer talking to people about their daily activities rather than their feelings") (Bagby et al., 1994a).

Each of the 20 items is rated on a five-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). Higher scores overall and for each of these subscales are indicative of alexithymia.

2.3. MRI acquisition and pre-processing

Diffusion-weighted data were acquired using single-shot spin-echo echo-planar

sequences, on 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 × 96 matrix, field of view = 192 × 192 mm, 70 contiguous axial slices of 2.0-mm thickness, 81 non-collinear motion-probing gradients, b = 1,500 s/mm^2. The b = 0 images were scanned before every nine diffusion-weighted images, thus consisting of 90 volumes in total.

All data processing was performed using programs in the FMRIB Software Library (FSL) version 4.1.6 (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 was used in the following voxelwise statistical analysis.

2.4. Data analyses

2.4.1. Group comparison and correlation of TAS-20 score with behavioral data

First, independent sample t-tests were applied to examine group differences in TAS-20 scores. To examine possible gender effects on TAS-20 scores, two-way analyses of

variance (ANOVAs) were applied, with TAS-20 scores (total score and subscale scores of DIF, DDF, and EOT) as dependent variables, and gender and diagnosis as between subject factors.

Second, correlational analyses were performed between TAS-20 total score and demographic variables in each group. In the patient group, correlations between the TAS-20 total score and clinical variables (positive, negative, general psychopathology of PANSS, duration of illness, and medication level (haloperidol-equivalent daily doses)) were also examined. Data were analyzed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p<0.05$ (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. We first performed group comparisons, using an analysis of covariance design, with age and gender as nuisance covariates. Both covariates were centered (demeaned) before being fed into the design matrix, and pre-removed from the data before implementing the permutation tests. Both control–patient and patient–control contrasts were tested, with 10,000 permutations. The statistical threshold was set at $p<0.05$, correcting for multiple comparisons by the threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009). TFCE does not need an arbitrary cluster-forming threshold, while preserving the sensitivity benefits of clusterwise correction.

2.4.3. Voxelwise correlational analyses

Voxelwise multiple regression analyses were performed using TBSS, to explore the WM regions that correlated with the TAS-20 total score in the patient group and control group independently. Age and gender were entered into the model as covariates of no interest. The permutation-based nonparametric inference was undertaken with 10,000 permutations. The statistical threshold was set at $p<0.05$, correcting for multiple comparisons by TFCE. The 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).

3. Results

3.1. Task performance of TAS-20

The demographic and clinical data as well as TAS-20 results are shown in Table 1. Many patients were in the chronic stages. Numbers of patients with mild/moderate/severe symptoms are 41/3/0 for the total score, 39/5/0 for the positive, 35/9/0 for the negative, and 41/3/0 for the general psychopathology subscale scores, respectively, indicating that many patients were with mild symptom severity.

An independent sample t-test revealed that TAS-20 total, and subscale scores of DIF, DDF, and EOT were significantly higher in the patient group than in the controls. The two-way ANOVAs for TAS-20 scores revealed significant main effects of diagnosis in the total and all of the three subscales: $F(1,84) = 33.02$, $p < 0.001$ in TAS-20 total; $F(1,84) = 19.02$, $p < 0.001$ in DIF; $F(1,84) = 13.28$, $p < 0.001$ in DDF; and $F(1,84) = 10.51$, $p = 0.002$

in EOT. There were, however, no significant effects of gender, and no significant diagnosis by gender interaction in any of these analyses.

Correlational analyses revealed that the TAS-20 total score was significantly and negatively correlated with age (Pearson's r=-0.364, p=0.015) in the controls. No other significant correlation was found between TAS-20 total and demographic data in each group. In the patient group, there was no significant correlation between the TAS-20 total and PANSS scores (positive, negative, general psychopathology subscales), duration of illness or medication (haloperidol-equivalent daily doses).

3.2. Group comparison of FA value

Patients with schizophrenia exhibited a widespread cluster of significant FA reductions relative to controls (cluster size: 33686). This cluster extended into the bilateral deep WM in the frontal, temporal, parietal and occipital lobes, a large portion of the CC, and the corona radiata (Fig. 1). These regions included the superior longitudinal fasciculus (SLF), the inferior longitudinal fasciculus (ILF), the superior fronto-occipital fasciculus, the inferior fronto-occipital fasciculus (IFOF), the uncinate fasciculus, the external capsule, the thalamic radiation, the corticospinal tract, and the cerebral peduncle. There was no significant region of FA increase in patients.

3.3. Voxelwise correlational analyses

In the whole-brain correlational analyses, the patient group demonstrated a negative correlation between the FA and TAS-20 total score in four WM clusters (Table 2a; Fig. 2).

Cluster A included the splenium and major forceps of the CC, mostly the left part of the SLF, the ILF, the IFOF, and the posterior thalamic radiation (PTR); cluster B included the trunk of the CC; cluster C included the left precuneus WM; and cluster D included the left anterior thalamic radiation (ATR). Mean FA values from these four clusters were extracted from each subject, and scatter plots of these FA values against the TAS-20 total score are shown in Fig. 3. We further examined if there is a difference of mean FA for each cluster between the patient and control groups. In these analyses, only the largest cluster (cluster A) showed significantly reduced FA in patients compared with controls (Table 2b).

There was no region that showed a significant positive correlation with TAS-20 total. On the other hand, the correlational analyses in the controls revealed no significant positive or negative correlation between FA and TAS-20 total.

4. Discussion

To our knowledge, this is the first study to investigate the relationship between alexithymia and WM connectivity in patients with schizophrenia, using DTI. The results indicate the existence of WM pathology possibly underlying impaired emotional self-awareness in schizophrenia.

The group comparison of TAS-20 revealed an association between schizophrenia and alexithymia, consistent with previous studies (Kubota et al., 2011; Maggini and Raballo, 2004; Stanghellini and Ricca, 1995; Todarello et al., 2005; van 't Wout et al., 2007). Significantly higher scores for the total and all the subscale scores (DIF, DDF, and EOT) in the patient group suggest that schizophrenia patients have difficulties in various aspects of

self emotional processing.

In the control group, the TAS-20 total score was significantly and negatively correlated with age. Although previous studies have yielded mixed results as to the relationship between alexithymia and age (Bagby et al., 1994a; Mattila et al., 2006; Moriguchi et al., 2007b; Parker et al., 1989; Pasini et al., 1992), studies that employ young participants (from teenagers to around mid 30's) are more likely to find negative correlation between alexithymia and aging within such an age range (Bagby et al., 1994a; Moriguchi et al., 2007b), fairly consistent with our results. On the other hand, the TAS-20 in patients were not associated with age, predicted IQ, PANSS (positive, negative and general psychopathology subscales), the duration of illness or medication, suggesting that alexithymia is not simply an epiphenomenon of symptomatology, but instead may constitute a trait marker of schizophrenia.

The results of the group comparison of FA were largely in accord with earlier DTI studies, indicating robust multiregional reduction of WM integrity in schizophrenia (Kubicki et al., 2007; Walterfang et al., 2006).

The results of correlational analyses between alexithymia and WM integrity constitute the major findings of this study. In the patient group only, FA was negatively correlated with alexithymia in four clusters, and mean FA of the largest cluster was reduced in patients compared with controls. This cluster included the splenium and major forceps of the CC, mostly the left part of the SLF, the ILF, the IFOF, and the PTR. Other clusters included the trunk of the CC, the precuneus WM and the ATR.

Past studies on schizophrenia have revealed structural abnormalities of the CC (Patel et

al., 2011; Walterfang et al., 2006). The role of the CC is to transmit the vast bulk of axonal communication between the two cerebral hemispheres (Paul et al., 2007; van der Knaap and van der Ham, 2011), and thus structural alteration of the CC in schizophrenia is thought to reflect dysfunctional interhemispheric information transfer (David, 1994; Knöchel et al., 2012; Patel et al., 2011). Considering the previous findings of transcallosal interhemispheric transfer deficit in alexithymic subjects (Romei et al., 2008), our results indicate that the impaired interhemispheric transfer, caused by the reduced WM integrity at the CC, might lead to impaired emotional processing in schizophrenia.

On the other hand, reduced structural connectivity of the SLF, the ILF, the IFOF, and the thalamic radiation has been repeatedly reported in schizophrenia (Kyriakopoulos and Frangou, 2009, Walterfang et al., 2006). Although the functions of these WM fibers have not been fully understood, studies have demonstrated the role of the SLF (especially the left arcuate fasciculus) as language processing and verbal working memory (Karlsgodt et al., 2008; de Weijer et al., 2011), associations of the ILF with visual-spatial integration, visual representation and social cognition (Ashtani et al., 2007; Miyata et al., 2010; Phillips et al, 2009), and possible involvement of the IFOF into language and semantic processing network (Duffau, 2008; McDonald et al., 2008; de Zubicaray et al., 2011). Moreover, thalamo-cortical connectivity is thought to be an important underlying mechanism of impaired multiple cognitive abilities in schizophrenia (Andreasen et al., 1998; Das et al., 2005; Kim et al., 2008; Marenco et al., 2012).

Previous studies have suggested the associations between these cognitive abilities and alexithymia. Language is thought to be an important component underlying alexithymia. It

is indicated that subjects with lower linguistic abilities might not look much into their inner experiences or cultivate much imagination, while those with higher linguistic ability might attempt to describe their feelings with appropriate words (Nishimura et al., 2009). In addition, impairment in language capacity is shown to be associated with alexithymia in schizophrenia (Maggini and Raballo, 2004; Stanghellini and Ricca, 1995). Conversely, empathic ability, which is involved in the ability to process the emotional valence of visual stimuli, is reported to be inversely related to alexithymia, as well as facial emotion recognition (Guttman and Laporte, 2002; Parker et al., 1993). Thus, together with these findings, our results might indicate that impaired emotional self-awareness in schizophrenia shares a neural underpinning with impaired multiple cognitive domains, such as language processing and social cognition.

Regarding the precuneus, this region is considered to play an important role in neuropsychological processes, such as insight and self-processing (Antonius et al., 2011: Cavanna and Trimble, 2006; Cooke et al., 2008). It might be that such processes have also important links to emotional self-awareness in schizophrenia.

Several limitations of the current study should be considered. First, because all the patients were taking medication, we could not exclude the effect of medication. Second, all the patients had mild and stable symptoms, which could lead to small variances in PANSS scores and apparent negative results in correlational analyses between alexithymia and psychopathological symptoms. Finally, it is difficult to tell exactly which fiber tract is in the largest cluster of the main correlational analysis in the patients, as multiple fiber tracts are contained in the region. Therefore, caution needs to be exercised for interpretation of

these results. Future studies will be needed to validate and generalize the results of this study.

In conclusion, the present study suggested an association between alexithymia and schizophrenia. In the patients only, alexithymia was negatively correlated with WM integrity in several regions including the CC, mostly the left part of the SLF, the ILF, the IFOF, the thalamic radiation and the precuneus WM. Our results suggest that these WM regions might be an important underlying pathology of impaired emotional self-awareness in schizophrenia, sharing the neural bases with interhemispheric transfer deficits and impaired cognitive domains, including language processing, social cognition, and self-related processing in this disease.

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Figure captions

Fig. 1.

Regions of significant FA reduction in patients with schizophrenia relative to controls (p<0.05, corrected by TFCE). Patients with schizophrenia exhibit reductions in bilateral deep white matter in the frontal, temporal, parietal and occipital lobes, a large portion of the corpus callosum, and the corona radiata. 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 (yellow). Left-right orientation is according to the radiological convention. Axial slices from Z = -14 to 52 in MNI coordinate are shown.

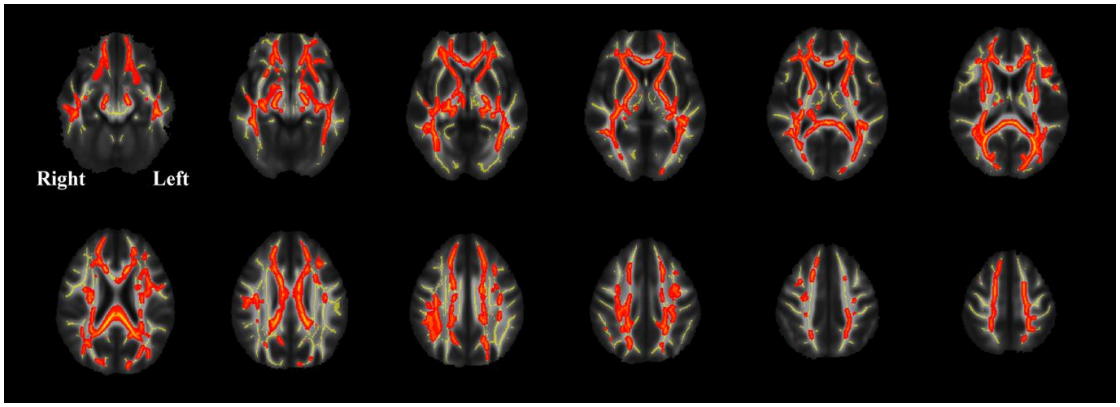

Fig. 2.

Significant negative correlation between TAS-20 total score and FA in the patient group (p<0.05, corrected by TFCE). To aid visualization, results are thickened using the tbss_fill script implemented in FSL. Results are shown overlaid on the mean FA maps and the FA skeleton (yellow), for each cluster separately:

cluster A (blue-light blue): the splenium and major forceps of the corpus callosum, mostly the left part of the superior and inferior longitudinal fasciculi, the inferior fronto-occipital fasciculus, and the posterior thalamic radiation

cluster B (green): the trunk of the corpus callosum

cluster C (pink): the left precuneus white matter

cluster D (red): the left anterior thalamic radiation

Left-right orientation is according to the radiological convention.

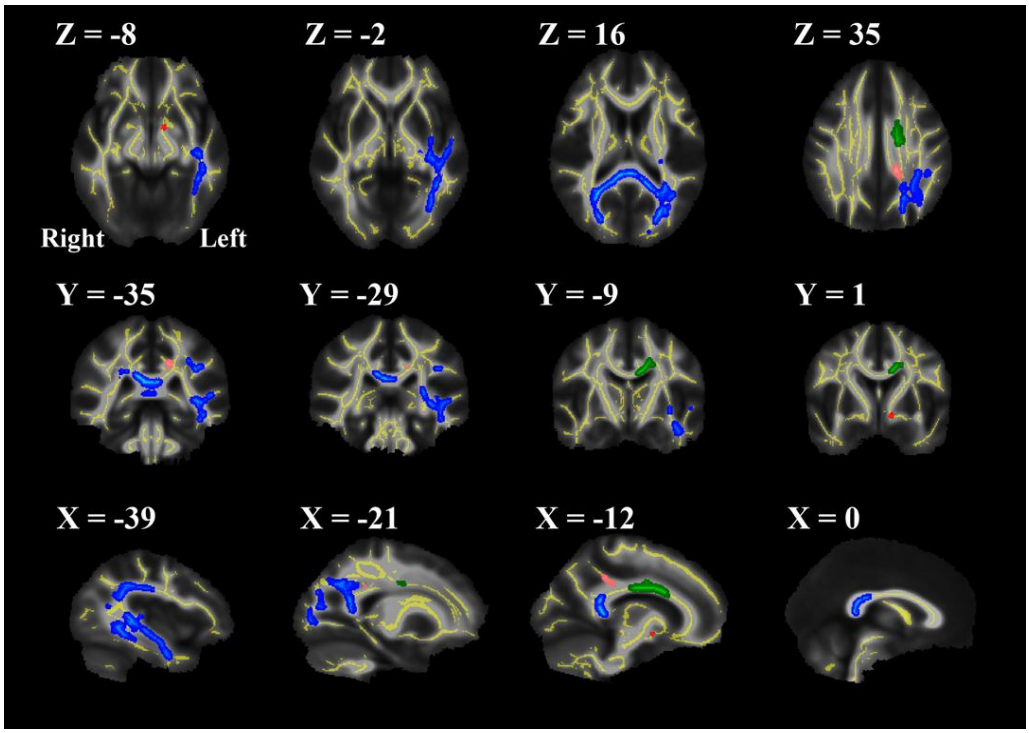

Fig. 3.

Scatter plots of mean FA against TAS-20 total score for the four clusters.

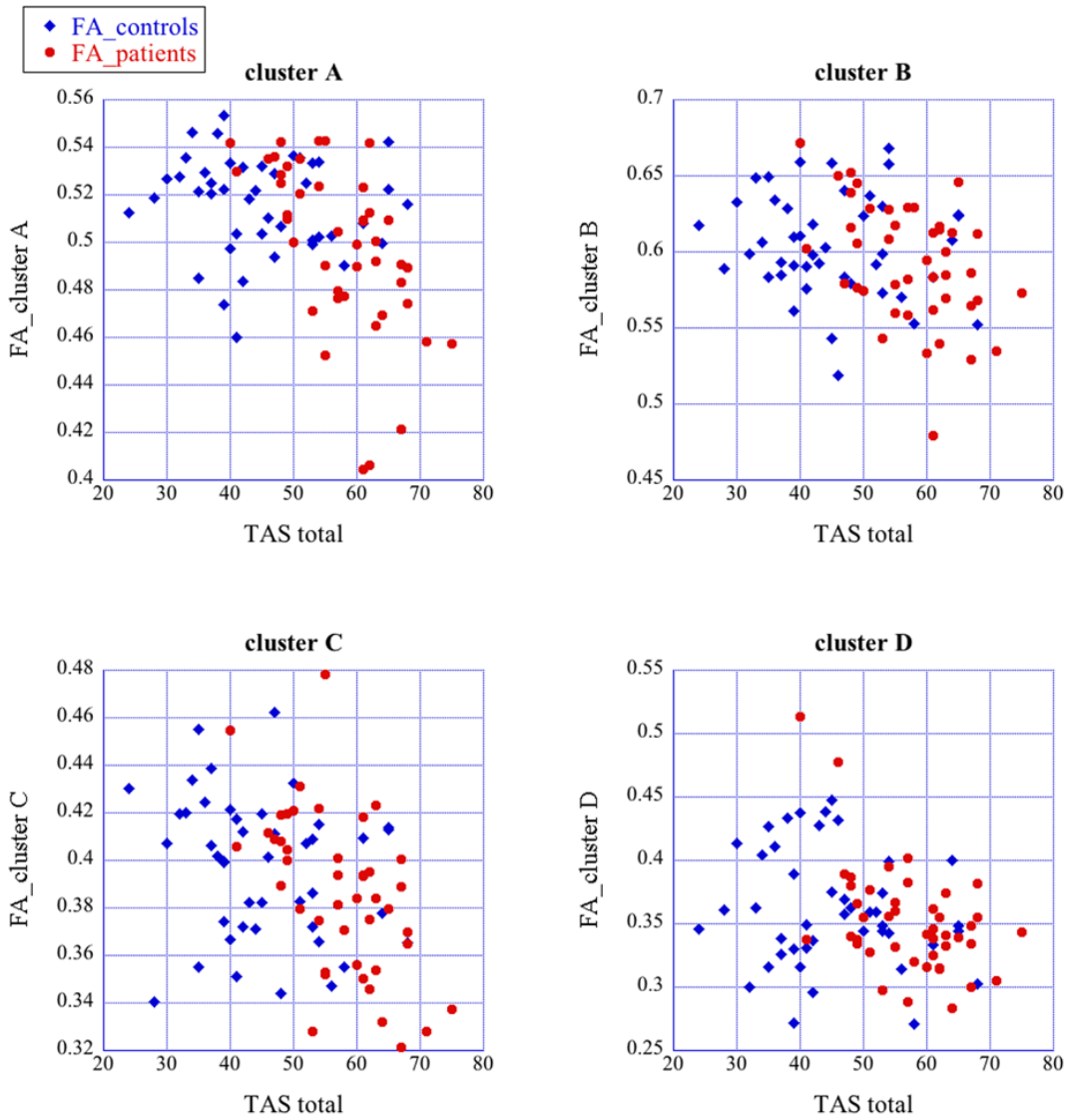

Table 1 Demographic, clinical data and TAS-20 scores in the patient and control groups.

	Patient group (n=44)		Control group (n=44)		Statistics	
	Mean	S.D.	Mean	S.D.	t	p
Age (years)	36.3	10.1	34.4	12.4	0.792	0.431
Gender (male/female)	26/18		26/18			
Predicted IQ (JART)	103.5	7.9	106.8	9.4	-1.783	0.078
Age of onset	23.2	5.6				
Duration of illness (years)	13	9.8				
Drug (mg/day, haloperidol equivalent)[a]	12	8.4				
PANSS total	62.2	16.6				
PANSS positive	14.3	4.6				
PANSS negative	16.2	5.1				
PANSS general	31.8	10.1				
TAS-20 total	57.34	8.08	45.09	10.54	6.12	<0.001
DIF	19.70	6.03	13.75	5.92	4.67	<0.001
DDF	16.95	3.00	13.70	4.55	3.95	<0.001
EOT	20.68	4.53	17.64	3.74	3.43	0.001

Abbreviation: DIF = difficulty identifying feelings; DDF = difficulty describing feelings; EOT = externally oriented thinking; JART = the Japanese Version of the National Adult Reading Test (Matsuoka et al., 2006; Matsuoka and Kim, 2007); PANSS = Positive and Negative Syndrome Scale.

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

Table 2a Results of correlational analyses.

cluster	t	MNI coordinate			Cluster size
		X	Y	Z	
cluster A (the splenium and major forceps of the CC, mostly left part of the SLF and the ILF, the IFOF and the PTR)	3.92	-33	-46	31	5914
cluster B (the trunk of the CC)	3.43	-12	-10	30	456
cluster C (the left precuneus white matter)	3.53	-17	-40	32	117
cluster D (the left ATR)	2.98	-9	2	-9	9

Table 2b Group comparison of mean FA for each cluster

cluster/ FA	Patient group (n=44)		Control group (n=44)		Statistics	
	Mean FA	S.D.	Mean FA	S.D.	t	p
cluster A	0.498	0.035	0.516	0.201	2.966	0.004
cluster B	0.594	0.040	0.604	0.034	1.382	0.171
cluster C	0.386	0.034	0.397	0.030	1.558	0.123
cluster D	0.352	0.043	0.361	0.046	0.999	0.321

Abbreviation: CC = corpus callosum, ATR = anterior thalamic radiation, RTR = posterior thalamic radiation, IFOF = inferior fronto-occipital fasciculus, SLF = superior longitudinal fasciculus, ILF = inferior longitudinal fasciculus, FA = fractional anisotropy.

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Contributors

Manabu Kubota designed the study and wrote the protocol, and also managed the literature searches and analyses and wrote the first draft of the manuscript. Manabu Kubota, Jun Miyata, Akihiko Sasamoto, Ryosaku Kawada, Shinsuke Fujimoto, and Yusuke Tanaka undertook the analysis and interpretation of clinical and psychological data. Manabu Kubota performed data processing and statistical analyses, under technical supervision by Jun Miyata, Nobukatsu Sawamoto, Hidenao Fukuyama, Hidehiko Takahashi, and Toshiya Murai. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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