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Computer-assisted cognitive remediation therapy for patients with schizophrenia induces microstructural changes in cerebellar regions involved in cognitive functions

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ABSTRACT

Previous studies have reported that cognitive remediation therapy (CRT) improves cognitive deficits in patents with schizophrenia. However, few studies have focused on the underlying structural alterations in the brain following Vocational Cognitive Ability Training by the Japanese Cognitive Rehabilitation Program for Schizophrenia (VCAT-J). In this study, we analyzed changes in diffusion tensor imaging parameters in 31 patients with schizophrenia after 12 weeks of intervention consisting of standard treatment alone or standard treatment plus VCAT-J, in order to determine the effect of the latter on white matter microstructural plasticity. Cognitive function was evaluated using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J) scale. The CRT group exhibited significant improvements in verbal fluency and composite BACS-J scores, relative to the treatment-as-usual (TAU) group. In addition, the CRT group exhibited significantly increased fractional anisotropy (FA) values, along with significantly decreased radial (RD) and mean diffusivity (MD) values, in the posterior lobe of the left cerebellum. Changes in RD and MD values were negatively correlated with changes in BACS-J composite scores. These suggest that VCAT-J might mediate improvements in myelin sheath composition in the posterior lobe of the left cerebellum, which may have been associated with improvements in cognitive function.

1. Introduction

In addition to positive and negative symptoms, patients with schizophrenia present with deficits in cognitive function including memory, attention, working memory, and executive function (Lee et al., 2013; Rund and Borg, 1999). These deficits have also been associated with poor social functioning, independently of positive symptoms (Green, 1996; Robinson et al., 2004). Although antipsychotic medication is effective in the treatment of positive schizophrenia symptoms, it exerts little effect on cognitive deficits (Kurachi et al., 2018; Young and Geyer, 2015). Therefore, alternative interventions for cognitive deficits are required to improve clinical and social outcomes among patients with schizophrenia.

As indicated by a meeting of the Cognitive Remediation Experts Workshop (Florence, Italy, April 2010), accumulating evidence has demonstrated that cognitive remediation therapy (CRT) improves cognitive deficits in patients with schizophrenia (Isaac and Januel, 2016; Wykes et al., 2011). Previous studies have also proposed that computer-supported CRT can improve executive dysfunction in patients with schizophrenia (Matsuda et al., 2018; Sato et al., 2013).

Recently, studies have increasingly focused on the mechanisms underlying the neural changes after CRT in patients with schizophrenia (Thorsen et al., 2014). Furthermore, some magnetic resonance imaging (MRI) studies have suggested that CRT induces alterations gray matter volume and white matter microstructural plasticity. Eack et al. reported that gray matter volume in the left hippocampus, parahippocampal gyrus, and fusiform gyrus was preserved in patients with schizophrenia and schizoaffective disorder undergoing a two-year integrated

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intervention consisting of computer-assisted neurocognitive training (i.e., CRT) and group-based social-cognitive exercises (Eack et al., 2010). A recent study further reported that patients with schizophrenia who underwent Vocational Cognitive Ability Training provided by the Japanese Cognitive Rehabilitation Program for Schizophrenia (VCAT-J) exhibited increases in right hippocampal volume (Morimoto et al., 2018). In one diffusion tensor imaging (DTI) study, patients with schizophrenia exhibited increased fractional anisotropy (FA) values in the genu and body of the corpus callosum and in the right posterior thalamic radiation after 4 weeks of CRT, whereas social skills training was associated with decreased FA values in the bilateral superior longitudinal fasciculus and left inferior longitudinal fasciculus (Penades et al., 2013). In the present study, we analyzed changes in DTI parameters in patients with schizophrenia after 12 weeks of intervention consisting of standard treatment alone or standard treatment plus VCAT-J, in order to determine the effect of the latter on white matter microstructural plasticity.

2. Methods

2.1. Patients

The study design is described in detail elsewhere (Morimoto et al., 2018). The present study included individuals with schizophrenia treated on an outpatient basis at the Department of Psychiatry at Nara Medical University and affiliated hospitals. Inclusion criteria were as follows: (1) diagnosis of schizophrenia based on the criteria established by the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (Text Revision); (2) outpatient status; (3) age between 20 and 60 years at the time of registration. Patients with evidence of an organic central nervous system disorder, a history of drug or alcohol abuse, or intellectual disability were excluded.

Thirty-three patients consented to participate in the present study. Two patients, however, were excluded because one exhibited organic disease (subdural hygroma), while the other declined MRI examination. Consequently, the randomized controlled trial was conducted with 31 patients divided into two groups: a treatment-as-usual (TAU) group and a CRT group. The TAU group (n = 15) received standard outpatient treatment for 12 weeks, while the CRT group (n = 16) received standard treatment plus CRT for 12 weeks. All participants underwent MRI scans, clinical evaluation, and neuropsychological assessments at baseline and after the 12-week intervention. All assessments were performed by personnel blinded to the group assignments. The study was approved by the appropriate institutional review board in Nara Medical University. Written informed consent was obtained from all patients prior to enrollment.

2.2. Treatment

All patients in this study underwent standard outpatient treatment including medication and assistance by social workers and social welfare services as needed. In addition, patients in the CRT group completed VCAT-J training procedures using the Japanese Cognitive Rehabilitation Program for Schizophrenia (Jcores; http://vcat-j.jp/), developed by the VCAT-J group. VCAT-J training procedures were identical to those described in a previous study (Matsuda et al., 2018). Briefly, Jcores is a computer-assisted cognitive remediation program designed to target attention, psychomotor speed, learning, verbal fluency, memory, and executive function. After selecting a specific cognitive domain, participants can choose from among three to seven game types and five degrees of difficulty. VCAT-J training consists of twice-weekly, hour-long computerized training sessions using Jcores and weekly, hour-long group sessions over 12 weeks. Psychiatrists or psychologists with ample experience in computer-assisted treatment (Sato et al., 2013) monitored all VCAT-J sessions.

2.3. Clinical assessments

The severity of schizophrenia was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The PANSS is a 30-item standardized clinical interview designed to assess the presence and severity of positive symptoms (seven items), negative symptoms (seven items), and general psychopathology (16 items). All items are scored from 1 to 7 points according to severity. Cognitive function was assessed using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J) (Kaneda et al., 2013). The BACS was developed to evaluate several aspects of cognition correlated with outcomes in patients with schizophrenia, including verbal memory, working memory, motor speed, verbal fluency, attention, and executive function (Keefe et al., 2004). We also calculated BACS-J composite scores by averaging z-scores from the six subcomponents, which were calculated from the means and standard deviations extracted from a dataset of healthy Japanese controls. Functioning in daily life and community interactions was evaluated using the Life Assessment Scale for the Mentally Ill (LASMI) (Iwasaki et al., 1994). The LASMI evaluates functioning across five social skills: 1) daily living, 2) interpersonal relations, 3) work skills, 4) endurance and stability, and 5) self-recognition. Items in each category are scored from 0 (no difficulty) to 4 points (severe difficulty). In the present study, we used scores for the interpersonal relations and work skills categories. All neuropsychological assessments were performed by psychiatrists or psychologists uninvolved in CRT or regular outpatient treatment.

2.4. MRI data acquisition

All MRI scans were performed using a 3.0-Tesla clinical scanner (Magnetom Verio; Siemens, Erlangen, Germany) equipped with a 32-channel phased-array brain coil. High-resolution, three-dimensional T1-weighted images were acquired using a magnetization-prepared rapid gradient-echo sequence (repetition time (TR) = 1800 ms; echo time (TE) = 2.4 ms; flip angle = 10°; field-of-view (FOV) = 256 mm; 208 sections in the sagittal plane; acquisition matrix = 256 × 256; acquired resolution = 1 × 1 × 1 mm). DTIs were acquired using an echo-planar imaging sequence with a GeneRalized Autocalibrating Partially Parallel Acquisition (GRAPPA) factor of 2. Imaging parameters were as follows: TR = 14 s; TE = 89 ms; b = 0, 1000 s/mm^2; acquisition matrix = 128 × 128; FOV = 256 mm; section thickness = 2.0 mm; no intersection gap; 79 sections. The reconstruction matrix was the same as the acquisition matrix, and 2 mm × 2 mm × 2 mm isotropic voxel data were obtained. A motion probing gradient was applied in 12 directions.

2.5. Analysis of imaging data

FA images and three eigenvalues (λ1, λ2, and λ3) were generated from each individual using Functional Magnetic Resonance Imaging of the Brain (FMRIB) software version 5.0.6 (FMRIB Center, Department of Clinical Neurology, University of Oxford, Oxford, England; http://www.fmrib.ox.ac.uk/fsl/). First, brain tissue was extracted using the Brain Extraction Tool in FSL. Diffusion-weighted images for each of the 12 directions were corrected for eddy current and head motion, and FA values/three eigenvalues (λ1, λ2, and λ3) were calculated at each voxel using FMRIB's Diffusion Toolbox.

Image preprocessing and statistical analysis were carried out using Statistical Parametric Mapping package (SPM12; Wellcome Department of Imaging Neuroscience, London, UK), using methods similar to those described in our previous study (Matsuoka et al., 2017). Each participant's echo planar image was spatially normalized to the Montreal Neurological Institute echo planar image template using parameters determined from the normalization of the image with a b value of 0 s/mm^2 and the echo planar image template in SPM12. Normalized images were spatially smoothed using an isotropic Gaussian filter (6-mm full-width at half-maximum).

Exploratory voxel-based analysis was performed using SPM12 software. We investigated changes in FA values induced by VCAT-J training, utilizing a two-time (baseline versus 12-week follow-up) × two-group (CRT group versus TAU group) flexible factorial design in SPM12. We thus examined four conditions: CRT group at baseline, CRT group at follow-up, TAU group at baseline, and TAU group at follow-up. To avoid possible effects between different tissue types, we excluded all voxels with FA values <0.1 (absolute threshold masking). We applied a liberal significance threshold of $p < .001$ with an 80-voxel whole-brain extent. Volumes of interest (VOIs) were determined from clusters in which significant interactions were observed. Regional FA values were calculated by averaging the values for all voxels within the VOIs. The same VOIs were applied to λ1, λ2, and λ3 images. We then extracted λ1–λ3 values and calculated mean diffusivity (MD) [(λ1 + λ2 + λ3)/3], axial diffusivity (AD) (λ1), and radial diffusivity (RD) ([λ2 + λ3]/2), which provided more specific information regarding the neuropathology underlying the anisotropy changes reflected by FA values (Alexander et al., 2007).

2.6. Statistical analysis

Two-sample *t*-tests and Pearson χ^2-tests were used to compare baseline demographic and clinical characteristics between the two groups. Analyses of variance (ANOVA) were performed to identify post-intervention changes in the mean FA, MD, AD, and RD values of VOIs in which significant changes in FA values were identified, as well as changes in psychiatric symptoms, neurocognitive functioning, and social functioning. Paired *t*-tests were used to separately examine changes in FA values in the CRT and TAU groups. All statistical tests were two-tailed and reported at $p < .05$. All statistical analyses were performed using SPSS for Windows 25.0 (IBM Japan Inc., Tokyo, Japan).

3. Results

3.1. Demographic characteristics at baseline

As reported in our previous study (Morimoto et al., 2018), the demographic characteristics of the included participants at baseline are summarized in Table 1. There were no significant differences in demographic characteristics or psychometric scores between the CRT and TAU groups ($p > .05$). There was no significant difference in the main type of prescribed antipsychotics between the CRT group (atypical; $n = 15$, typical; $n = 1$) and the TAU group (atypical; $n = 12$, typical; $n = 3$) ($\chi^2 = 1.30$, $p = .25$).

3.2. Changes in psychometric scores over each 12-week intervention

There was no participant who dropped out from the study through the 12-week intervention in the CRT group. Following the 12-week intervention period, improvements in the *z*-scores for verbal fluency and BACS-J composite scores were significantly greater in the CRT group than in the TAU group (verbal fluency: $F = 7.12$, $p = .012$; composite score: $F = 4.21$, $p = .049$). No significant differences in PANSS domains or LASMI scores were observed between the groups (Table 2). We previously reported these improvements following VCAT-J (Morimoto et al., 2018).

3.3. Comparison of changes in FA, AD, RD, and md values between the crt and tau groups

In the exploratory voxel-based analysis, the CRT group exhibited significant elevation of mean FA values in the posterior lobe of left cerebellum when compared to the TAU group ([x, y, z] = [- 32, - 66, - 46], cluster voxel size = 89, $T = 4.38$; Fig. 1). In contrast, the TAU group exhibited no increases in FA values in any brain region. FA, AD, RD, and MD values were determined in the VOIs of the posterior lobe of the left cerebellum. Changes in FA values were significantly greater ($p < .001$), while changes in RD ($p = .003$) and MD values ($p = .038$) were significantly less pronounced, in the CRT group than in the TAU group (Table 3). Over the 12-week intervention period, FA values in the

Table 1
Demographic characteristics at baseline.

	CRT group ($n = 16$) Mean (SD)	TAU group ($n = 15$) Mean (SD)	*t* or χ^2	*p*
Gender, male/female	10/6	9/6	$\chi^2 = 0.02$	.59
Age, years	36.1 (7.7)	37.4 (11.0)	$t = -0.39$	.70
Handedness, right/left	16/0	13/2	$\chi^2 = 2.28$	.23
Education, years	14.3 (2.4)	13.0 (2.0)	$t = 1.69$	.10
Duration of illness, years	12.1 (7.8)	13.9 (13.2)	$t = -0.47$	.65
Hospitalization, times	1.0 (1.2)	2.1 (1.9)	$t = -2.00$	.056
JART	102.6 (11.8)	97.8 (12.2)	$t = 1.10$	.28
Drug treatment				
Mean dosage of antipsychotics[a]	440.3 (265.1)	680.3 (530.9)	$t = -1.61$	.12
Mean dosage of anticholinergics[b]	0.75 (1.65)	1.30 (1.51)	$t = -0.97$	.34
PANSS				
Positive symptoms	14.8 (4.9)	14.3 (4.2)	$t = 0.26$	.80
Negative symptoms	20.7 (4.4)	20.6 (7.2)	$t = 0.04$	.97
General psychopathology	39.6 (7.8)	41.5 (10.5)	$t = -0.57$	.57
LASMI				
Interpersonal relations	11.1 (3.9)	11.5 (7.9)	$t = -2.13$	.83
Work	10.6 (3.4)	12.6 (5.7)	$t = -1.22$	.23
BACS-J (*z*-score)				
Verbal memory	−1.8 (1.0)	−2.0 (1.1)	$t = 0.56$	.58
Working memory	−1.3 (1.2)	−1.3 (1.2)	$t = -0.18$	.86
Motor speed	−2.4 (1.4)	−2.8 (1.6)	$t = 0.76$	.45
Verbal fluency	−1.4 (0.8)	−0.9 (0.8)	$t = -1.68$	.10
Attention and speed of information processing	−1.6 (0.8)	−2.1 (0.9)	$t = 1.45$	.16
Executive function	−0.4 (2.3)	−1.1 (1.6)	$t = 0.97$	.34
Composite score	−1.5 (0.9)	−1.7 (0.9)	$t = 0.63$	.53

Abbreviations: CRT, cognitive remediation therapy; TAU, treatment-as-usual; SD, standard deviation; JART, National Adult Reading Test, Japanese Version; PANSS, Positive and Negative Syndrome Scale; LASMI, Life Assessment Scale for the Mentally Ill; BACS-J, the Japanese version of the Brief Assessment of Cognition in Schizophrenia.
[a] Chlorpromazine-equivalent dose (mg/day).
[b] Biperiden-equivalent dose (mg/day).

Table 2
Changes in clinical variables.

	CRT Group ($n = 16$) Mean (SD)	TAU Group ($n = 15$) Mean (SD)	*F*	*p*
PANSS				
Positive symptoms	−0.88 (2.16)	0.33 (3.09)	1.61	.21
Negative symptoms	−2.63 (2.03)	−0.67 (5.04)	2.06	.16
General psychopathology	−2.38 (4.13)	0.40 (8.17)	1.45	.24
LASMI				
Interpersonal relations	−1.75 (2.18)	−0.33 (5.02)	1.06	.31
Work	−0.69 (1.85)	−0.33 (1.29)	0.38	.54
BACS-J (*z*-score)				
Verbal memory	1.02 (0.85)	0.55 (0.81)	2.40	.13
Working memory	0.24 (0.66)	−0.13 (0.98)	1.56	.22
Motor speed	0.38 (1.18)	0.08 (1.41)	0.41	.53
Verbal fluency	0.56 (0.82)	−0.08 (0.47)	7.12	.012
Attention and speed of information processing	0.25 (0.52)	0.04 (0.50)	1.33	.26
Executive function	0.48 (1.85)	0.42 (1.37)	0.01	.92
Composite score	0.49 (0.42)	0.15 (0.50)	4.21	.049

Abbreviations: CRT, cognitive remediation therapy; TAU, treatment-as-usual; SD, standard deviation; PANSS, Positive and Negative Syndrome Scale; LASMI, Life Assessment Scale for the Mentally Ill; BACS-J, the Japanese version of the Brief Assessment of Cognition in Schizophrenia.

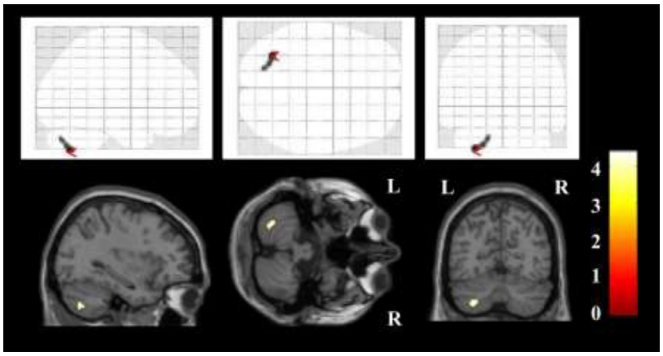

Fig. 1. Regions exhibiting significant differences in fractional anisotropy (FA) values between the cognitive remediation therapy (CRT) and treatment-as-usual (TAU) groups. Sagittal, coronal, and transverse views show voxels with significantly higher FA values in the CRT group than in the TAU group. Detected areas shown in this figure exceed an uncorrected p value of 0.001 with 80 or more contiguous voxels. These statistical parametric mapping projections were then superimposed on representative sagittal ($x = -32$), coronal ($y = -66$), and transverse ($z = -46$) magnetic resonance images.

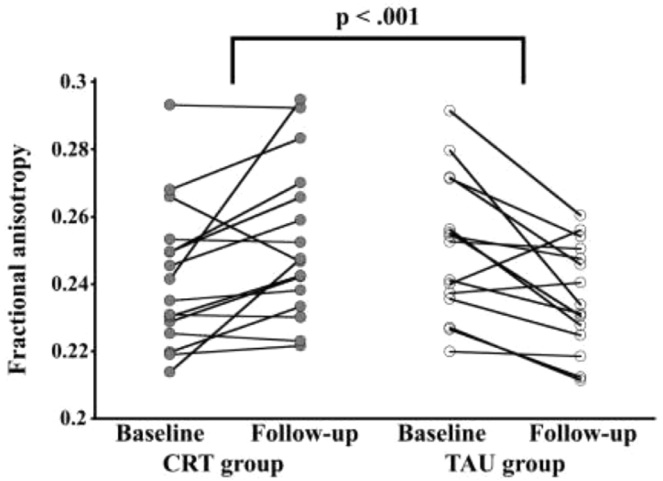

Fig. 2. Scatterplots showing fractional anisotropy (FA) changes in the posterior lobe of the left cerebellum over the 12-week intervention period in the cognitive remediation therapy (CRT) and treatment-as-usual (TAU) groups. Cluster volumes of interest (VOIs) were determined in the regions exhibiting significant increases in FA values in the CRT group, relative to those observed in the TAU group.

VOIs were significantly increased in the CRT group ($p = .019$) and significantly decreased in the TAU group ($p = .003$) when analyses were performed separately (Fig. 2).

3.4. Correlations between changes in dti parameters and psychometric scores over the 12-week intervention period

Changes in BACS-J composite scores were significantly negatively correlated with RD ($r = -0.37$, $p = .039$) and MD values ($r = -0.38$, $p = .034$) in all participants (Fig. 3). There was no correlation between changes in BACS-J composite scores and FA values. In addition, we observed no correlation between verbal fluency on the BACS-J and FA, RD, or MD values over the 12-week intervention period.

4. Discussion

In the present study, we analyzed changes in DTI parameters in patients with schizophrenia after 12 weeks of TAU or CRT-based interventions. Exploratory voxel-based analysis revealed a significant increase in mean FA values, which was accompanied by decreases in RD and MD values, in the posterior lobe of the left cerebellum in the CRT group, relative to values observed in the TAU group. Furthermore, no brain region exhibited significant decreases in mean FA in the CRT group when compared with the TAU group. Moreover, decreases in mean RD and MD values for the posterior lobe of the left cerebellum were negatively correlated with changes in BACS-J composite scores in all patients. These findings suggest that VCAT-J using Jcores may have induced microstructural changes in the posterior lobe of the left cerebellum, and that this area is associated with cognitive functions in patients with schizophrenia.

The current findings indicated that changes in mean MD and RD values were significantly correlated with changes in cognitive recovery. The FA value is considered to represent white matter tract integrity, and several previous studies have reported that FA values are decreased in patients with neuropsychiatric disorders (Kehoe et al., 2014; Teipel et al., 2014). MD and RD values indicate the degree of water diffusion, and additional studies have reported that such values are increased in patients with various neuropsychiatric disorders (Fieremans et al., 2013; Kehoe et al., 2014; LeWinn et al., 2014; Wang et al., 2014). Increases in these parameters are considered to reflect increased intracellular or extracellular water diffusion in affected neural cell membranes. The former is a comparatively global parameter indicating white matter disruption, while the latter is the perpendicular diffusion component, reflecting the severity of demyelination (Alexander et al., 2007). In accordance with our findings, some studies have reported that cognitive training induces increases in FA values that are associated with decreases in RD values (Engvig et al., 2012; Keller and Just, 2009).

Although the white matter microstructural changes underpinning alterations in diffusion parameters remain to be fully understood, non-human primate studies have contributed to our interpretation of such changes. Some studies have indicated that the RD value is associated with changes in myelin structure (Beaulieu, 2002; Song et al., 2002). Song et al. reported that increases in RD values reflect the severity of demyelination, and that decreases in RD values are accompanied by the progression of remyelination (Song et al., 2005). Additional studies have suggested that decreases in MD values are correlated with increases in cellular density (Alexander et al., 2007). There is a possibility that our findings represent that CRT induces plasticity of the myelin sheath in the cerebellum, thereby improving executive function in patients with schizophrenia.

To date, the cerebellum is known to be involved in coordination/

Table 3
Changes in FA, AD, RD, and MD values in the two groups.

	CRT group ($n = 16$)		TAU group ($n = 15$)		F	p
	Baseline	Follow-up	Baseline	Follow-up		
FA	0.24 (0.02)	0.25 (0.02)	0.25 (0.02)	0.24 (0.02)	19.08	< 0.001
AD ($\times 10^{-4}$)	8.33 (0.31)	8.34 (0.30)	8.47 (0.23)	8.48 (0.43)	0.01	.91
RD ($\times 10^{-4}$)	5.91 (0.31)	5.82 (0.32)	5.94 (0.29)	6.08 (0.33)	10.94	.003
MD ($\times 10^{-4}$)	6.71 (0.30)	6.66 (0.30)	6.78 (0.26)	6.88 (0.35)	4.70	.038

Abbreviations: CRT, cognitive remediation therapy; TAU, treatment as usual; FA, fractional anisotropy; AD, axial diffusivity; RD, radial diffusivity; MD, mean diffusivity.

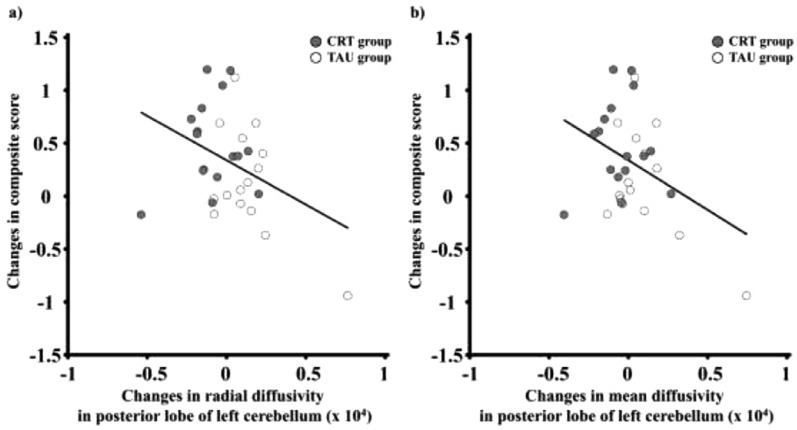

Fig. 3. Scatterplots showing the association between changes in radial diffusivity (RD) values (a)/mean diffusivity (MD) values (b) in the posterior lobe of the left cerebellum and changes in composite scores on the Japanese version of the Brief Assessment of Cognition in Schizophrenia in the cognitive remediation therapy (CRT) and treatment-as-usual (TAU) groups. Significant negative correlations were observed between changes in composite scores and RD values (r = - 0.37, p = .039)/MD values (r = - 0.38, p = .034) in the posterior lobe of the left cerebellum.

balance, gait, extremity movements, and eye movements (Holmes, 1917). Accumulating evidence further indicates that the cerebellum plays a crucial role in various cognitive functions (Koziol et al., 2014). Cerebellar cognitive affective syndrome is characterized by impairments in spatial cognition and language, executive dysfunction, and personality changes, resulting from damage to the lateral hemisphere of the posterior cerebellum or vermis (Schmahmann, 2004). The cerebellum has also been associated with cognitive functions in patients with schizophrenia (Andreasen and Pierson, 2008). Structural MRI studies have revealed that cerebellar volume is positively correlated with poor cognitive function in patients with schizophrenia (Nopoulos et al., 1999). Previous DTI studies have reported that FA values in the cerebellum are lower in patients with schizophrenia than in healthy controls (Kubicki et al., 2007; Samartzis et al., 2014; Tamnes and Agartz, 2016). Our results indicate that favorable white matter microstructural changes in the posterior lobe of the left cerebellum in patients with schizophrenia are associated with improvements in executive function as determined using the BACS-J. Previous studies have indicated that the cerebellum plays a role in executive function by adjusting activity in the frontal cortex (Andreasen et al., 1996). Therefore, our results suggest that network dysfunction between the cerebellum and central-to-frontal cortical regions contributes to the deterioration of cognitive functions in patients with schizophrenia, and that CRT improves such network abnormalities.

The present study possesses some limitations of note. First, all patients with schizophrenia had been exposed to antipsychotic medications. The potential effects of antipsychotic medications on brain structures remain controversial. Some studies have failed to show any significant correlation, although others have reported significant correlations between the use of antipsychotic medication and changes in both gray and white matter structures (Roiz-Santianez et al., 2015). Indeed, one study has suggested that white matter microstructural changes can occur after only 6 weeks of treatment (Wang et al., 2013). Thus, the decreased FA values observed in the posterior lobe of the left cerebellum in the TAU group may have resulted from the use of antipsychotic medications. The difference in the dose of antipsychotics between the two groups did not reach statistical significance probably due to the small number of patients. This difference could potentially affect the study's results. Second, the small number of patients and the relatively short VCAT-J intervention period may limit the interpretation of our results. Further studies involving larger numbers of patients and long-term interventions are required to obtain definitive results. Third, although we observed increased FA values in the posterior lobe of the left cerebellum following CRT, a previous DTI study reported increased FA values in the genu and body of the corpus callosum and in the right posterior thalamic radiation following CRT (Penades et al., 2013). Such differences may be due to differences in the CRT program or interventions used in the control group.

In conclusion, the findings of the present study demonstrate that VCAT-J using Jcores may have induced microstructural changes in the posterior lobe of the left cerebellum, where changes in myelin structures (indicated by RD values) were associated with changes in cognitive function (indicate by BACS-J composite scores) in patients with schizophrenia. We believe that our findings shed light on the mechanisms underlying the effects of VCAT-J on cognitive function.

Declaration of Competing Interest

All authors declare that there are no proprietary interests or conflicts of interest related to this study

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Contributors

KM, FY, TM, and YM designed the study, analyzed the results, and interpreted the data. TK designed the study and interpreted the data. TM, TT, and KK collected and analyzed the MRI data. HY, MT, and SK analyzed and interpreted the data. KM wrote the manuscript. All authors reviewed and edited the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.09.001.

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