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Association Study Between White Matter Microstructure and Intelligence Decline in Schizophrenia

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Abstract

Patients with schizophrenia can exhibit intelligence decline, which is an important element of cognitive impairment. Previous magnetic resonance imaging (MRI) studies have demonstrated that patients with schizophrenia have altered gray matter structures and functional connectivity associated with intelligence decline defined by a difference between premorbid and current intelligence quotients (IQs). However, it has remained unclear whether white matter microstructures are related to intelligence decline. In the present study, the indices of diffusion tensor imaging (DTI) obtained from 138 patients with schizophrenia and 554 healthy controls were analyzed. The patients were classified into three subgroups based on intelligence decline: deteriorated (94 patients), preserved (42 patients), and compromised IQ (2 patients) groups. Given that the DTI of each subject was acquired using either one of two different MRI scanners, we analyzed DTI indices separately for each scanner group. In the comparison between the deteriorated IQ group and the healthy controls, differences in some DTI indices were noted in three regions of interest irrespective of the MRI scanners, whereas differences in only one region of interest were noted between the preserved IQ group and the healthy controls. However, the comparisons between the deteriorated and preserved IQ groups did not show any reproducible differences. Together with the previous findings, it is thought that gray matter structures and functional connectivity are more promising as markers of intelligence decline in schizophrenia than white matter microstructures.

Keywords

schizophrenia, cognitive impairment, cognitive decline, diffusion tensor imaging, white matter

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Introduction

Schizophrenia is a severe psychiatric disorder characterized by positive symptoms, such as hallucinations and delusions, and negative symptoms, such as avolition.[1] Patients with schizophrenia have difficulty gaining insight.[2,3] They also show cognitive impairments.[4] Cognitive function plays an important role in patients' functional outcomes.[5] In particular, intelligence decline has an adverse impact on functional outcomes, such as maintaining employment.[6]

Previous case-control studies have demonstrated that patients with schizophrenia show abnormal brain structures.[7–12] Patients with schizophrenia who have a compromised intelligence quotient (IQ) have a reduced total brain volume, intracranial volume, cortical gray matter volume, cortical thickness, and insula volume.[13] It was reported that patients with schizophrenia who have severely deteriorated IQ had significantly reduced total hippocampal, lingual gyrus, and superior temporal sulcus gray

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matter volumes relative to patients with schizophrenia who have putatively preserved IQ.[14] Morita and his colleague have shown that the cortical thickness of the left pars opercularis is associated with free-viewing behaviors related to cognitive and social functioning in schizophrenia.[15–17] Recently, a relationship between hippocampal and accumbal volumes and memory function[18] as well as a relationship between right thalamic volume and cognitive impairment and social function[19] have been reported, suggesting that structural abnormalities in subcortical regions may also have clinical significance in schizophrenia. On the other hand, cognitive ability, such as intelligence, is related to the white matter structure.[20] A diffusion tensor imaging (DTI) study demonstrated that structural connectivity of the right frontal white matter and corpus callosum is associated with social functioning in schizophrenia.[21]

In terms of functional connectivity, it has been reported that thalamo-prefrontal connectivity is decreased in schizophrenia, whereas thalamotemporal and thalamo-sensorimotor connectivity is increased.[22,23] In addition, patients with schizophrenia who had deteriorated IQ exhibited hyperconnectivity between the thalamus and a broad range of brain regions compared to healthy subjects.[24] In the same study, patients with schizophrenia who had preserved IQ were observed to have hyperconnectivity between the acccumbens and the superior and middle frontal gyri.[24] Given that studies have demonstrated differences in functional connectivity,[22–24] this raises the question of whether some differences in the cerebral white matter, which is the pathway to that neural network, may exist. However, it is unclear whether any difference exists in the white matter microstructure between groups with and without cognitive impairment. In the present study, we tested this possibility on the entire brain by examining the DTI indices that represent white matter microstructures involving fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD).

Materials and Methods

Subjects

The data from 138 patients with schizophrenia recruited at Osaka University Hospital and 554 healthy individuals recruited at Osaka University were analyzed in this study. These subjects' data were included in our previous studies,[9,19,21,25] and detailed information on the subjects has been described elsewhere. Therefore, we will describe them here only briefly. The patients were diagnosed based on the Structured Clinical Interview for DSM-IV (SCID), and their psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS).[26] Their premorbid IQ was estimated from the Japanese adult reading test (JART) score,[27] and their current IQ was determined using the full-scale IQ of the Wechsler adult intelligence scale third edition (WAIS-III).[28,29] The intelligence decline after disease onset was obtained by subtracting the premorbid IQ from the current IQ.[6,30] Healthy individuals were included only when they never had any current or past contact with psychiatric services, a neurological disease, or any medical conditions that could potentially affect the central nervous system. All participants provided written informed consent.

To study whether there is any difference in white matter microstructure between patients with and without intelligence decline, we classified the patients into three groups as described in a previous study:[24,30] deteriorated, preserved and compromised IQ groups. The patients were classified into the deteriorated group if they exhibited meaningful intelligence decline (≥ 10 points). The remaining patients were classified into the preserved group when they had less than a 10-point difference between their estimated premorbid IQ and their current IQ and their premorbid IQ exceeded 90. Because only two patients were classified into the compromised group (a premorbid IQ less than 90), they were excluded from the analyses.

Diffusion Tensor Imaging (DTI)

DTI was acquired by using two magnetic resonance imaging (MRI) scanners (Osaka A and Osaka B). Whole-brain axial DTI scanning of 60 patients (21 patients with preserved IQ and 38 patients with deteriorated IQ) and 229 healthy individuals was performed using the 3.0 Tesla GE Signa HDxt (Osaka A), and 78 (21 patients with preserved IQ and 56 patients with deteriorated IQ) patients and 325 healthy individuals were scanned with the DISCOVER 750 scanner (Osaka B) (GE Healthcare, Milwaukee, WI) with eight-channel head, neck, and spine coils. The detailed scanning protocols have already been described in Koshiyama et al[21]

As in previous studies,[21,25,31] the DTI indices involving FA, MD, RD, and AD were calculated using dti_fit (FSL 5.0)[32] after preprocessing with head motion correction and distortion correction induced by eddy current using edd_correct.[33] Tract-based spatial statistics (TBSS)[34] using the ENIGMA-DTI template and JHU regions of interest (ROIs) was applied to extract local values (44 ROIs) of the DTI indices based on the ENIGMA-DTI protocols.[7]

In the present study, the data from the two different scanners were dealt with as separate independent cohorts to evaluate the significance and reproducibility of the differences in the DTI indices. Thus, we screened both cohorts using analysis of variance (ANOVA) and performed a post hoc analysis on the combinations of ROIs and indices that showed a significant difference in the mean indices' values in both cohorts. The significance level of the ANOVA was multiplied by 176 ($44 \times 4 = 176$, based on 44 ROIs and four indices). Multiple comparisons were performed using the Bonferroni method among the healthy controls, preserved IQ group, and deteriorated IQ group at the ROIs where ANOVA results were significant (corrected $P < .05$) in both cohorts. As a result, a group difference in the mean of indices for the ROI was considered to exist if it was

Table 1. Demographic and Clinical Characteristics of the Participants.

	HC (N = 554)	P-IQ (N = 42)	D-IQ (N = 94)	*P value*[a] (P-IQ vs D-IQ)
Age (years)	30.8 ± 13.1	36.4 ± 14.3	32.9 ± 10.3	.15
Sex (male/female)	308/246	16/26	48/46	.16
Years of education	14.9 ± 1.8	13.9 ± 2.7	13.6 ± 2.4	.60
Estimated premorbid FIQ[b]	109.8 ± 6.4	103.2 ± 7.3	101.4 ± 10.4	.24
WAIS-III FIQ	114.5 ± 11.8	102.9 ± 10.4	79.4 ± 13.7	5.3×10^{-19}
IQ decline		−.4 ± 7.2	−22.0 ± 8.5	6.3×10^{-27}
Age of onset (years)		25.5 ± 11.6	21.3 ± 8.5	.04
Duration of illness (years)		10.8 ± 9.7	11.6 ± 9.1	.68
PANSS total score		77.5 ± 20.1	89.9 ± 17.1	9.3×10^{-4}
PANSS positive score		17.9 ± 5.9	20.4 ± 5.0	.02
PANSS negative score		19.0 ± 5.0	22.3 ± 4.4	3.5×10^{-4}
PANSS general score		40.7 ± 10.4	47.2 ± 8.8	7.4×10^{-4}
Daily dose of CPZ eq (mg)		595.4 ± 620.6	528.4 ± 526.9	.55

The mean and standard deviation. A total of 229 HC, 21 P-IQ, and 38 D-IQ subjects were Osaka A (GE Signa HDxt scanner), and 325 HC, 21 P-IQ, and 56 D-IQ were Osaka B (DISCOVER 750 scanner) (GE Healthcare, Milwaukee, WI).

[a]Statistical comparisons between the P-IQ and D-IQ were made with a t-test, except for sex (chi-square test).

[b]FIQ was estimated using the Japanese Adult Reading Test. In the healthy controls, the mean estimated premorbid FIQ was calculated from 549 subjects whose Japanese Adult Reading Test data were available. Only two patients were classified into the compromised IQ group, and they were excluded from this table given that the sample number was too small to include statistical analyses.

Abbreviations: CPZ eq: chlorpromazine equivalents; FIQ: full-scale IQ; D-IQ: patients with schizophrenia who have deteriorated IQ; HC: healthy controls; P-IQ: patients with schizophrenia who have preserved IQ; PANSS: positive and negative symptom scale; WAIS-III: Wechsler adult intelligence scale-III.

significant in either cohort. Statistical analyses were conducted using SPSS version 26 (IBM Corp., Armonk, NY).

Results

The demographic data of the subjects are summarized in Table 1. The current IQs of the deteriorated and preserved groups differed by 23.5 points on average, whereas their premorbid IQs were similar. Thus, the deteriorated group was characterized by an intelligence decline after the onset of the disease. These two groups showed differences in symptoms as measured using PANSS total ($P = 9.3 \times 10^{-4}$), PANSS positive ($P = .02$), PANSS negative ($P = 3.5 \times 10^{-4}$), and PANSS general psychopathology scores ($P = 7.4 \times 10^{-4}$). On average, the scores were all higher in the deteriorated group compared with the preserved group. The other unique characteristic was the age of disease onset, which was lower in the deteriorated group ($P = .04$).

Figure 1 compares the averages of the DTI indices among the deteriorated group, preserved group and healthy individuals separately for each MRI scanner (Tables S1 and S2). The deteriorated group had a significantly higher average RD than the healthy individuals based on data from both scanners (Osaka A: $P = 9.33 \times 10^{-3}$ and Osaka B: $P = 1.98 \times 10^{-4}$). Thus, these significant differences were replicated between the two scanner groups. In the data from the Osaka A group, the preserved group had significantly lower average FA ($P = 1.24 \times 10^{-4}$) and higher average RD ($P = 7.32 \times 10^{-4}$) than the healthy individuals, but none of these findings were replicated in the Osaka B group. On the other hand, no detectable differences in any of the average DTI indices were noted between the deteriorated and preserved groups.

The comparisons for the individual ROIs are summarized in Tables S1 and S2. Consistently, in both the Osaka A and B groups, differences in the DTI indices between the deteriorated and healthy controls were detected in the right anterior corona radiata (ACR) for FA (Osaka A: $P = 2.19 \times 10^{-4}$ and Osaka B: $P = 9.81 \times 10^{-6}$) and right anterior limb of the internal capsule (ALIC) for AD (Osaka A: $P = 3.09 \times 10^{-4}$ and Osaka B: $P = 3.56 \times 10^{-4}$). On the other hand, differences between the preserved group and healthy controls were consistently detected in the right ACR for FA (Osaka A: $P = 4.51 \times 10^{-3}$ and Osaka B: $P = 1.77 \times 10^{-2}$) in both scanner groups. Comparing the preserved and deteriorated groups, no differences were detected in either Osaka A or B groups.

Discussion

In this study, we divided schizophrenia patients into three separate groups based on intelligence decline. Reading skills are relatively well preserved in schizophrenia,[35] and the National Adult Reading Test (NART)[36] is useful for premorbid IQ in schizophrenia.[37] Thus, research methods have been used to stratify schizophrenic patients by the difference between IQ and NART for preserved IQ, deteriorated IQ and compiled IQ.[30,38,39] In Japan, the Japanese version of the NART, namely, the JART,[27] is used for premorbid IQ. The comparison of JART and full-scale IQ is also useful for stratifying IQ decline in schizophrenia.[40] The method has been used in studies of stratification of IQ decline in schizophrenia in Japan.[24,41] The same method was

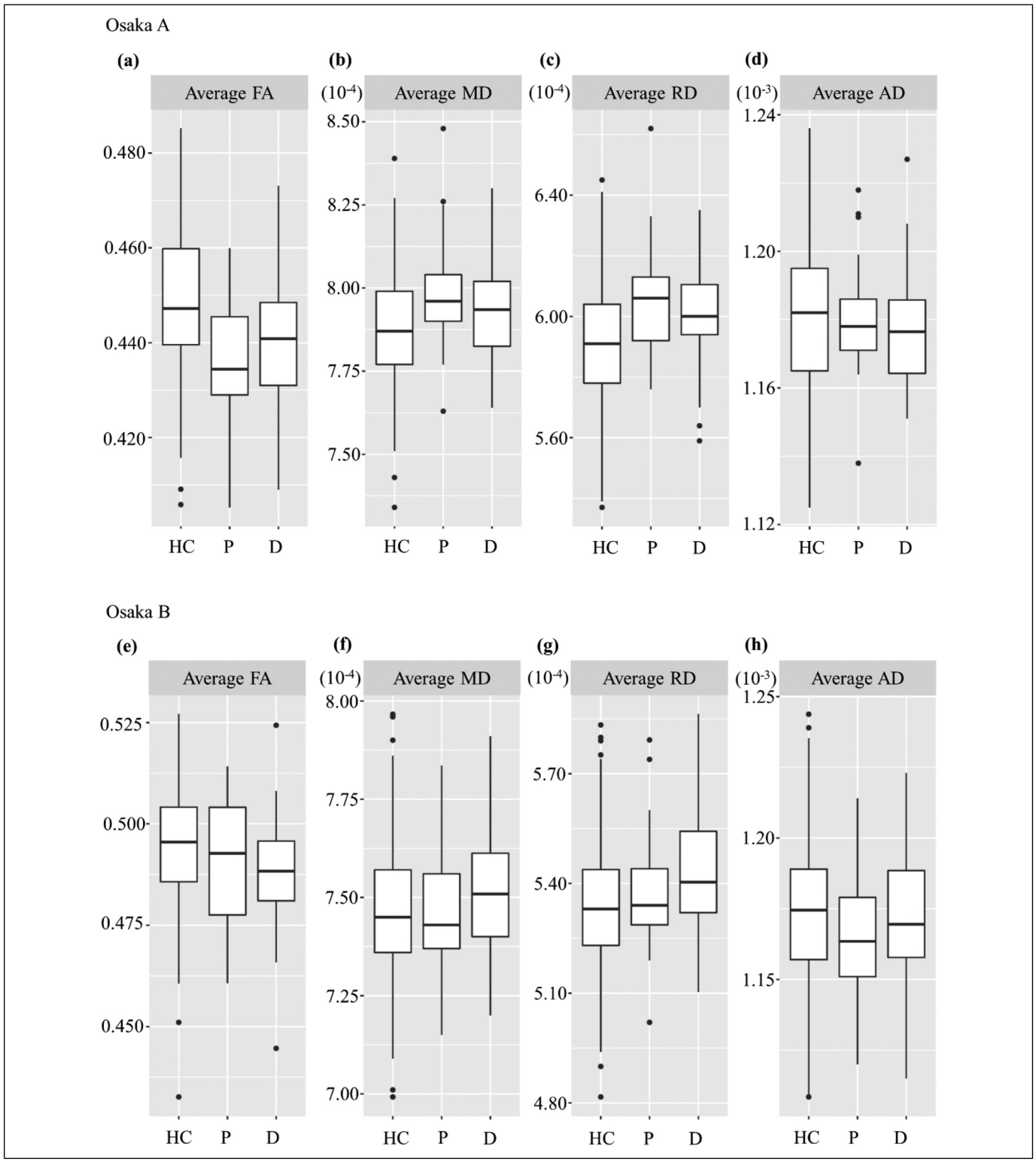

Figure 1. Comparisons of average FA ([a] and [e]), MD ([b] and [f]), RD ([c] and [g]), and AD ([d] and [h]) among healthy controls (HC), patients with schizophrenia who have preserved IQ (P), and patients with schizophrenia who have deteriorated IQ (D). Panels (a) to (d) are data from the Osaka A group, and panels (e) to (h) are from the Osaka B group. The whiskers are the maximum and minimum excluding outliers (dots). The exponential notation (10^{-4}) of the values on the vertical axis for MD and RD is shown above the vertical axis; the exponential part (10^{-3}) of the values on the vertical axis for AD is also shown above the vertical axis.

used in this study. Note that the estimated intelligence level before the onset of disease was similar between the preserved and deteriorated groups. Previous studies with similar stratification criteria[13,14,24] demonstrated that the PANSS negative symptom score was higher in the deteriorated groups compared with the preserved groups, but no significant differences were reported for positive symptoms. Furthermore, in a few of these studies,[14,24] the PANSS total score was also higher in the deteriorated group compared with the preserved group. The present results are consistent with the previous findings for the PANSS total and negative scores, suggesting that intelligence decline is closely associated with the severity of negative and overall symptoms. Here, we also obtained results suggesting that positive symptoms and symptoms of general psychopathology may also be related to intelligence decline. To verify causality, a longitudinal study is needed.

Koshiyama et al[21] reported that the DTI indices of several ROIs were significantly different between patients with schizophrenia and healthy individuals. The ROIs with significant effects for the diagnosis involved the corpus callosum (CC), genu of corpus callosum (GCC), body of corpus callosum (BCC), bilateral ACR, right ALIC, fornix (FX), right posterior thalamic radiation (PTR), right superior fronto-occipital fasciculus (SFO), and left sagittal stratum (SS) for FA; FX and left uncinate fasciculus (UNC) for MD; CC, GCC, BCC, right ACR, FX, and right PTR for RD; and bilateral ALIC and FX for AD. They also reported differences in the average FA and RD. Herein, we found differences between the deteriorated group and healthy controls in right ACR for FA, right ALIC for AD, and average RD. All of these were included in the combination of DTI indices and ROIs that had a diagnostic effect in the comparison between the healthy control group and the schizophrenia group reported above by Koshiyama et al[21] On the other hand, comparisons between the deteriorated and preserved groups did not show robust and reproducible differences in the present study.

Significant differences in structural images, such as cortical thickness and subcortical volume, as well as functional connectivity by resting-state functional MRI have already been reported in the presence and absence of cognitive dysfunction in schizophrenia in a previous study.[24] Here, we did not obtain direct evidence for the effects of intelligence decline on the DTI indices. Taken together, the present findings suggest that cortical thickness, subcortical volume, and functional connectivity are more promising than the DTI indices as markers of cognitive dysfunction in schizophrenia.

Limitations

This study showed that the DTI index was significantly different between the preserved IQ and deteriorated IQ groups; on the other hand, significant group differences in PANSS scores were noted between the preserved IQ and deteriorated IQ groups. Therefore, future analyses are needed to clarify whether the group differences in the DTI index between the preserved IQ and deteriorated IQ groups are related to the severity of the disease.

This study only addresses the intelligence decline estimated with the differences between the JART and WAIS-III scores. There are many domains of cognitive function.[42] Thus, our findings were exclusively limited to the domain of intelligence. Future studies using multiple neurocognitive test batteries may be helpful for investigating the effects of schizophrenia on cognitive impairment and the related neural changes.

Conclusion

Previous studies have demonstrated significant differences in structural images, such as cortical thickness and subcortical volume, as well as functional connectivity, by resting-state functional MRI.[24] In this study, we sought associations of intelligence decline on the FA, MD, RD, and AD values of the DTI indices in each ROI of the patients with schizophrenia, but direct evidence was not obtained. Thus, these structural and functional associations are more promising as markers of cognitive dysfunction in schizophrenia than white matter microstructures.

Author Contributions

JM contributed to conception, data curation, formal analysis, visualization, writing - original draft, and writing - review & editing. KM contributed to conception, validation, formal analysis, software, data curation, formal analysis, visualization, writing - original draft, and writing - review & editing. MF contributed to software, data curation, formal analysis, visualization, and writing - review & editing. KN contributed to formal analysis, software, data curation, and writing - review & editing. DK contributed to software, formal analysis, investigation, data curation, and writing - review & editing. NO contributed to formal analysis, investigation, data curation, and writing - review & editing. KM contributed to formal analysis, investigation, data curation, and writing - review & editing. HY contributed to resources, investigation, methodology, data curation, and writing - review & editing. YY contributed to resources, investigation, methodology, data curation, and writing - review & editing. MF contributed to resources, investigation, methodology, data curation, and writing - review & editing. SI contributed to formal analysis, validation, and writing review & editing. NH contributed to validation, and writing review & editing. YW contributed to data curation, methodology, investigation, resources, and writing - review & editing. KK contributed to formal analysis, investigation, data curation, and writing - review & editing. RH contributed to conceptualization, methodology, validation, investigation, resources, data curation, writing - review & editing, supervision, project administration, and funding acquisition.

Declaration of Conflicting Interests

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Ethical Approval

All procedures were conducted according to the Declaration of Helsinki and approved by the ethical committee of Osaka University and the National Center of Neurology and Psychiatry.

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Supplemental Material

Supplemental material for this article is available online.

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