




Corpus callosal involvement is correlated with cognitive impairment in multiple system atrophy

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Abstract

Objective We examined the anatomical involvement related to cognitive impairment in patients with multiple system atrophy (MSA).

Methods We examined 30 patients with probable MSA and 15 healthy controls. All MSA patients were assessed by the Unified MSA-Rating scale and Addenbrooke's Cognitive Examination-Revised (ACE-R). We classified 15 MSA patients with ACE-R scores > 88 as having normal cognition (MSA-NC) and 15 with scores ≤ 88 as having cognitive impairment (MSA-CI). All subjects underwent 3 T MRI scanning and were investigated using voxel-based morphometry and diffusion tensor imaging.

Results Both the MSA-NC and MSA-CI patients exhibited cerebellar but not cerebral atrophy in voxel-based morphometry compared to controls. In contrast, tract-based spatial statistics revealed widespread and significantly decreased fractional anisotropy (FA) values, as well as increased mean diffusivity, radial diffusivity, and axial diffusivity in both the cerebrum and cerebellum in MSA-CI patients compared to controls. MSA-NC patients also exhibited similar involvement of the cerebellum but less extensive involvement of the cerebrum compared with the MSA-CI patients. In particular, FA values in MSA-CI patients were significantly decreased in the anterior part of the left corpus callosum compared with those in MSA-NC patients. The mean FA values in the left anterior part of the corpus callosum were significantly correlated with total ACE-R scores and subscores (memory, fluency, and language) in MSA patients.

Conclusions Decreased FA values in the anterior corpus callosum showed a significant correlation with cognitive impairment in MSA.

Keywords Multiple system atrophy · Diffusion tensor imaging · Cognitive impairment

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Introduction

Multiple system atrophy (MSA) is a sporadic neurodegenerative disease characterized by cerebellar ataxia, parkinsonism, and autonomic failure to various degrees during the course of the illness [1, 2]. Pathologically, glial cytoplasmic inclusion (GCI) with immunoreactivity for α -synuclein is a pathological hallmark of MSA [2, 3]. Although dementia that fulfills the criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders is not a supporting feature [4], it has been widely recognized that patients with MSA often present significant declines in attentional function, working memory, recognition, delayed recall, and visuospatial functions [5]. Imaging studies revealed that MSA

patients with cognitive decline have frontal lobe-dominant atrophic changes as well as reduced blood flow in the frontal, temporal, and parietal lobes [5]. Nevertheless, the anatomical background of cognitive impairment in MSA patients remains unclear.

Diffusion tensor imaging is a promising neuroimaging technique that can assess the microstructural white matter tract in healthy and diseased populations [6]. Because MSA patients exhibit both gray and white matter involvement [7–9], combination studies of brain structural changes and anatomical network abnormalities have the potential to provide a new insight into the anatomical alterations causing cognitive impairment in MSA. In this study, we examined differences in the findings of voxel-based morphometry (VBM) and diffusion tensor imaging between MSA patients with cognitive impairment and those with normal cognition.

Methods

Study population and patient selection

We initially examined 39 consecutive MSA patients from August 1, 2013 to December 31, 2016, at Nagoya University Hospital. The diagnosis was based on the clinical criteria of the second consensus statement on the diagnosis of MSA [4]. We then excluded nine of these patients who did not fulfill the diagnostic criteria for probable MSA or did not complete all cognitive function and imaging tests due to severe motor dysfunction. Thus, 30 MSA patients were included in this study. All participants were assessed by the unified MSA rating scales (UMSARS) [10], Mini-Mental State Examination (MMSE), and Addenbrooke's Cognitive Examination-Revised (ACE-R) [11]. ACE-R is an established battery of tasks that evaluates five cognitive domains: orientation/attention, memory, verbal fluency, language, and visuospatial ability [11]. ACE-R is comparable to MoCA, and there is a significant correlation of scores between the two batteries [12]. A systematic review and meta-analysis showed that ACE-R is one of the best screening tests for dementia compared to the Montreal Cognitive Assessment [13]. The optimal cut-score of the ACE-R for discriminating mild cognitive impairment and normal cognition was 89 (impairment = score of 88 or less) [11]. The translated versions of the ACE-R, including the Japanese version, showed good to excellent sensitivity and specificity for detecting dementia [14]. The MMSE score could be obtained simultaneously. Recently, ACE-R has been used for the assessment of cognitive impairment in MSA patients [15, 16].

In this study, 15 MSA patients showed ACE-R scores > 88 and were defined as having MSA–normal cognition (MSA–NC) (8 males and 7 females; mean age, 61.5 ± 8.0 years; disease duration, 2.7 ± 1.2 years), and

15 patients showed scores ≤ 88 and were defined as having MSA–cognitive impairment (MSA–CI) (10 males and 5 females; mean age, 65.5 ± 6.7 years; disease duration, 2.9 ± 1.7 years) [17]. Of the patients with MSA–NC, nine had MSA with predominant cerebellar ataxia (MSA–C) and six had MSA with predominant parkinsonism (MSA–P). Of the MSA–CI patients, eight had MSA–C and seven had MSA–P. We also investigated 15 age- and gender-matched non-demented control subjects who had a normal neurological examination and no medical history of stroke, traumatic brain injury, psychiatric disorder, or neurological disorders (9 males and 6 females; mean age, 63.3 ± 7.9 years).

This study conformed to the Ethical Guidelines for Medical and Health Research Involving Human Subjects endorsed by the Japanese government and was approved by the ethics committee of the Nagoya University Graduate School of Medicine, and written informed consent was obtained from all participants before participating in the study.

Magnetic resonance imaging

All MRI scans were performed using a Siemens Magnetom Verio (Siemens, Erlangen, Germany) 3.0 T scanner with a 32-channel head coil at Nagoya University's Brain and Mind Research Center. A high-resolution T1-weighted image (TR = 2.5 s, TE = 2.48 ms, 192 sagittal slices with a distance factor of 50% and 1 mm thickness, FOV = 256 mm, 256×256 matrix size, and an in-plane voxel resolution of $1 \times 1 \text{ mm}^2$) was acquired from each participant. Diffusion tensor images were also acquired using the following parameters: TR = 13,600 ms, TE = 92 ms, Voxel size $2.0 \times 2.0 \times 2.0 \text{ mm}$, FOV = 196 mm, $b = 0$, 1000 s/mm^2 , 64 directions.

Voxel-based morphometry

Three-dimensional T1-weighted images were analyzed using Statistical Parametric Mapping (SPM8; Wellcome Trust Center for Neuroimaging, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software/spm8>) running on MATLAB (R2014a, Math Work, Natick, Mass, USA). The T1-weighted images were first segmented into component images including gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), among others, using SPM8's new segmentation approach. The segmented images were then normalized to the standard Montreal Neurological Institute space using DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) [18]. Normalized images were modulated to preserve the total amount of signal from each region and resampled to an isotropic voxel resolution of $2 \times 2 \times 2 \text{ mm}^3$. To facilitate an unbiased comparison among regions of interest in different patients, the GM images were spatially smoothed using an 8-mm

full-width-at-half-maximum isotropic Gaussian filter. The preprocessed GM images were further corrected for age and gender before group comparisons were performed. In all comparisons, we included the total intracranial volume, computed as the sum of gray matter, white matter, CSF volumes, and age as covariates of no interest to account for differences in brain sizes. The obtained statistical maps were thresholded at $p < 0.05$ and corrected for multiple comparisons using a cluster-level family wise error correction (FWEc) with a cluster-forming threshold set at $p = 0.001$. From the VBM results, we generated ROIs (sphere, 4 mm radius) centered at the peak coordinates from all comparisons and then extracted the mean GM value within the ROI and computed Pearson's correlations with behavioral measures.

Tract-based spatial statistics

Voxel-wise statistical analysis of the fractional anisotropy (FA) data was carried out using the tract-based spatial statistics (TBSS) [19] part of FSL [20]. First, the brain image was skull stripped using BET [21]. FA images were then created by fitting a tensor model to the raw diffusion data using FDT. All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT [22, 23], which uses a b-spline representation of the registration warp field [24]. Next, a mean FA image was created and projected into the main cortical tracts to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and the resulting data fed into voxel-wise, cross-subject statistics. TBSS analysis was repeated for mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) maps. The results were overlaid on the mean FA image. We performed two-sample t tests using randomization with 5000 permutations. Specifically, the following comparisons were made: controls vs MSA-NC, controls vs MSA-CI, and MSA-NC vs MSA-CI. Using an in-house Matlab script, a mask was created that included only voxels showing a significant difference in the TBSS results. Using this mask, the FA values from each participant's processed FA data were then extracted and averaged. The mean FA values were correlated with ACE-R scores.

Statistical analysis

Group results were expressed as the mean \pm standard deviation. Comparisons of the differences in gender and motor type (MSA-C or MSA-P) were performed using the Chi-square test. The Shapiro-Wilk test was used to assess the normality of continuous variables. To compare the age at examination, we used one-way analysis of variance. The UMSARS I and UMSARS II scores were compared using

Student's t test. To assess differences in disease durations and UMSARS IV scores, we used the Mann-Whitney U test. To evaluate differences in the total scores or five subdomains of the ACE-R and the MMSE scores among controls and MSA-NC and MSA-CI patients, we used the Kruskal-Wallis test. When the p value was significant (< 0.05), post hoc tests were conducted with the Tukey's test for data with normal distributions or the Bonferroni test for data with non-normal distributions. Statistical analyses were performed in PASW Statistics 18.0 for Windows using SPSS version 18 (SPSS Inc., Chicago, IL, USA).

Results

Comparisons of neuropsychological tests in patients with MSA-NC, those with MSA-CI, and controls

Table 1 shows the demographic and clinical data of the subjects studied. There were no significant differences in age; sex; scores on the UMSARS I, UMSARS II, and UMSARS IV; or the proportion of MSA-C and MSA-P between the MSA-NC and MSA-CI groups. The average MMSE and ACE-R scores of the MSA-CI patients were significantly lower than those of controls and MSA-NC patients. ACE-R attention/orientation, memory, fluency,

Table 1 Demographic and clinical data of subjects studied

Group (n)	Controls (15)	MSA-NC (15)	MSA-CI (15)
Sex (M/F)	9/6	8/7	10/5
MSA-C/MSA-P		9/6	8/7
Age (years)	63.3 \pm 7.9	61.5 \pm 8.0	65.5 \pm 6.7
Duration (years)		2.7 \pm 1.2	2.9 \pm 1.7
UMSARS I		17.7 \pm 7.2	19.7 \pm 7.8
UMSARS II		19.7 \pm 8.0	22.1 \pm 8.1
UMSARS IV		2.5 \pm 0.8	2.4 \pm 1.0
MMSE	29.5 \pm 1.4	28.7 \pm 0.9	25.3 \pm 2.5 ^{a,b}
ACE-R	96.6 \pm 2.8	93.1 \pm 2.7	78.6 \pm 6.2 ^{a,b}
Attention and orientation	17.9 \pm 0.3	17.6 \pm 0.6	16.5 \pm 1.4 ^{a,b}
Memory	24.2 \pm 2.0	23.3 \pm 1.9	17.3 \pm 4.4 ^{a,b}
Fluency	13.7 \pm 0.7	12.1 \pm 1.8	8.0 \pm 2.5 ^{a,b}
Language	25.2 \pm 1.0	25.0 \pm 1.1	23.1 \pm 2.4 ^{a,b}
Visuospatial	15.6 \pm 0.9	15.1 \pm 1.0	13.6 \pm 2.4 ^a
Atrophy of putamen or pons		15/15	15/15

MSA-NC multiple system atrophy with normal cognitive, MSA-CI multiple system atrophy with cognitive impairment, MMSE Mini-Mental State Examination, ACE-R Addenbrooke's Cognitive Examination Revised

^a $p < 0.05$ vs controls

^b $p < 0.05$ vs MSA-NC

and language subdomain scores in MSA–CI patients were significantly lower than those of controls and MSA–NC patients ($p < 0.05$). The visuospatial subdomain scores of the ACE-R were significantly lower in MSA–CI patients than in the controls ($p < 0.05$).

VBM findings in MSA–NC and MSA–CI patients compared with controls

The VBM findings demonstrated that both MSA–NC and MSA–CI patients exhibited significant reductions in gray matter volume in the cerebellum compared to controls (FWEc $p < 0.05$, cluster defining threshold $p = 0.001$, Fig. 1). There was no significant relationship between ACE-R scores and gray matter volume changes. Neither MSA–NC nor MSA–CI patients exhibited any significant reductions in cerebral gray matter volume.

FA, MD, RD and AD values in MSA–NC and MSA–CI patients compared with controls

There were widespread significantly decreased FA values and increased MD, RD, and AD values in the cerebral and cerebellar white matter tracts in patients with MSA–CI compared with controls (FWE $p < 0.05$, Fig. 2). Patients with MSA–NC also showed abnormal MD, RD, and AD values compared to controls. However, patients with MSA–NC had more limited MD, RD, and AD values in the cerebral hemisphere than those with MSA–CI. Particularly, there were no significant differences in FA values in the cerebral hemisphere between MSA–NC patients and controls. Cerebral hemispheres showed abnormal MD,

RD, and AD values that were similar but more restricted in MSA–NC than MSA–CI. There were no significant differences in FA values in the cerebral hemispheres between MSA–NC patients and controls.

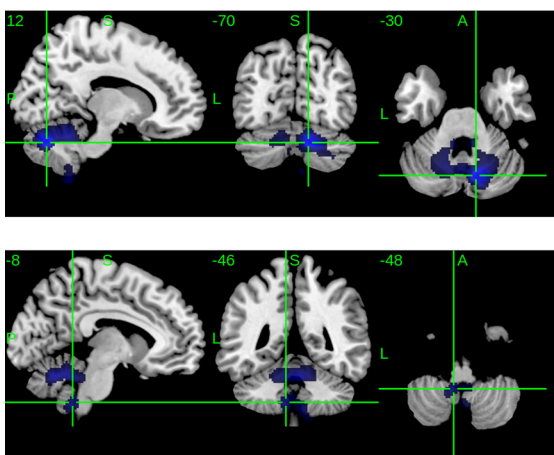
FA, MD, RD and AD values in MSA–NC compared with MSA–CI patients

Comparing MSA–CI to MSA–NC, there were significant reductions in FA values in the left corpus callosum in patients with MSA–CI (FDR $q < 0.05$ Fig. 3a). However, MD, RD, and AD values did not show any significant differences between MSA–CI and MSA–NC.

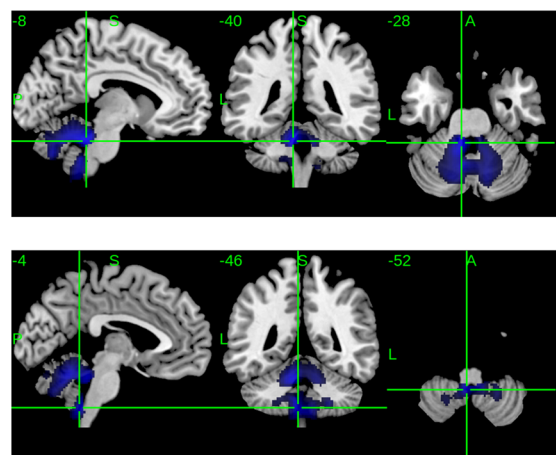
Relationship between FA values in the corpus callosum and ACE-R scores in MSA patients

We investigated the relationship between ACE-R scores and mean FA values in the left corpus callosum, which were significantly different in MSA–CI and MSA–NC patients. There was a significant association between mean FA values of these areas in the left anterior part of the corpus callosum and the total ACE-R scores ($r = 0.69$, $p = 2.60 \times 10^{-5}$) as well as the subscores for memory ($r = 0.55$, $p = 0.0015$), fluency ($r = 0.59$, $p = 6.47 \times 10^{-4}$), and language ($r = 0.46$, $p = 0.0099$) (Fig. 3b–e) but not attention and orientation in all MSA patients. There was no significant association between the mean FA values and age or disease duration.

(A) Controls > MSA–NC



(B) Controls > MSA–CI



FWEc $p < 0.05$ (CDT $p = 0.001$)

Fig. 1 Voxel-based morphometry analyses. **a** Blue areas indicate regions with brain atrophy in patients with MSA–NC compared to controls (controls > MSA–NC). **b** Blue areas indicate regions with

brain atrophy in patients with MSA–CI compared to controls (controls > MSA–CI). *MSA–NC* multiple system atrophy– normal cognition, *MSA–CI* multiple system atrophy– cognitive impairment

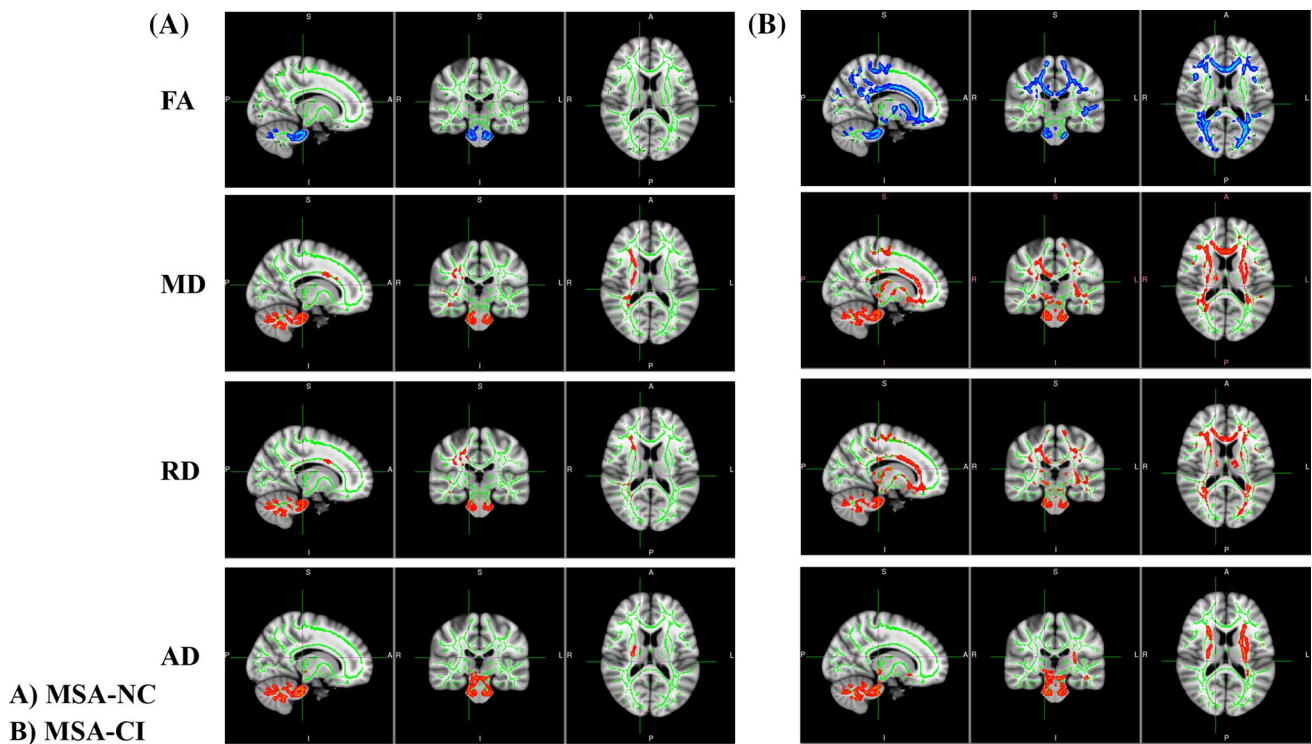


Fig. 2 Tract-based spatial statistics analyses. Maps of differences in fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) for MSA-NC (a) and MSA-CI (b) patients compared to controls. Blue lines indicate reduced FA values

(controls > MSA-NC) and red lines indicate increased MD, RD, and AD values (controls < MSA-CI), compared to controls. *MSA-NC* multiple system atrophy– normal cognition, *MSA-CI* multiple system atrophy– cognitive impairment

(A) MSA-NC > MSA-CI

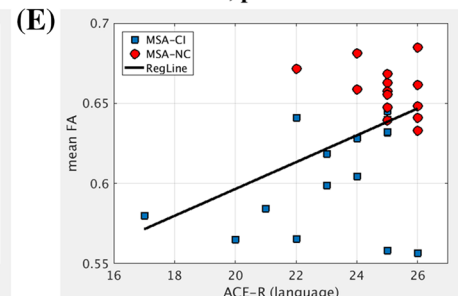
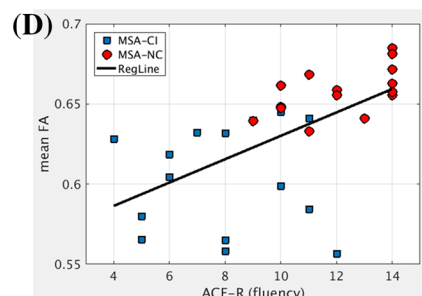
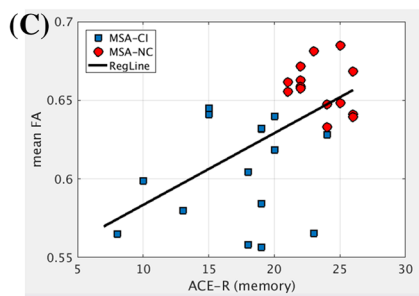
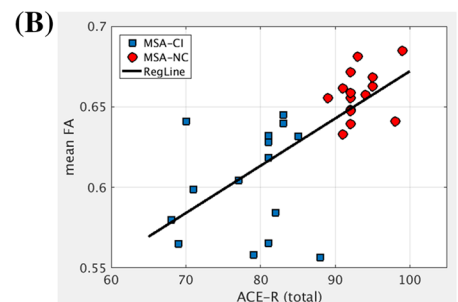
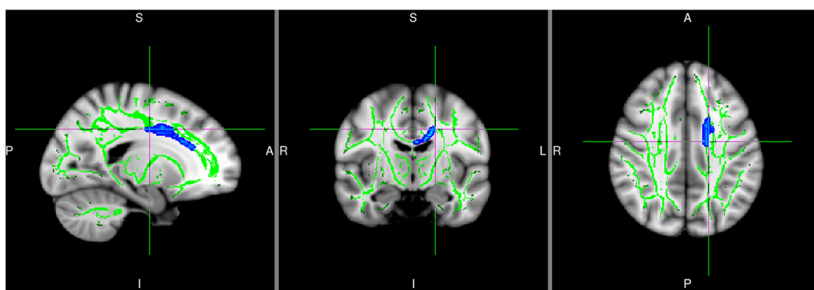


Fig. 3 Associations between mean fractional anisotropy in the corpus callosum and cognition scores. **a** Maps of differences in mean fractional anisotropy (FA) in the corpus callosum for MSA-NC patients compared to MSA-CI patients. **b–e** Correlations between mean FA

values in the corpus callosum and the ACE-R total (**b**) and subdomain scores for memory (**c**), fluency (**d**), and language (**e**) in MSA-CI (blue) and MSA-NC (red) patients

Discussion

VBM findings showed that both MSA–NC and MSA–CI patients exhibited significant reductions in gray matter volume in the cerebellum compared to controls. Neither MSA–NC nor MSA–CI patients exhibited any significant reductions in cerebral gray matter volume. On the other hand, TBSS images indicated that there were widespread significantly decreased FA values and increased MD, RD, and AD values in cerebral and cerebellar white matter tracts in patients with MSA–CI compared with controls. There were also decreased FA in the cerebellum in patients with MSA–NC. They also showed abnormal MD, RD, and AD values compared to controls, although they were less extensive compared with MSA–CI. In other words, compared with controls, MSA–CI patients exhibited significant widespread microstructural cerebral white matter involvement assessed by FA, MD, RD, and AD values in contrast to reduced cerebral gray matter volume. In particular, FA values were significantly decreased in the anterior part of the left corpus callosum in MSA–CI patients compared with MSA–NC patients. Moreover, the mean FA values in the anterior part of the left corpus callosum were significantly correlated with both total and subscores (memory, fluency, and language) of the ACE-R in MSA patients.

The corpus callosum is the largest collection of white matter in the brain and is composed of axons directly connecting the bilateral cerebral hemispheres. Moreover, there was a significant correlation between the severity of the anterior part of the corpus callosum involvement assessed by FA values and ACE-R scores. Although other demented patients also show decreased FA values in the corpus callosum, this is the first study to demonstrate the significant correlation between FA values in the corpus callosum and ACE-R scores in MSA patients [25]. Previously, we reported progressive atrophic changes in the corpus callosum of MSA patients based on MR images analyzed via region-of-interest methods [26]. MSA is thought to be a primary oligodendroglialopathy with abundant GCI and secondary neuronal multisystem degeneration. A pathological study of MSA revealed myelin involvement and Wallerian degeneration in the cerebrum [27]. Thus, it is plausible that the corpus callosum is a vulnerable region in MSA involved not only via primary involvement but also via secondary pathological changes due to widespread cerebral white matter involvement, contributing to cognitive impairment.

Frontal lobe atrophy may be associated with dementia in advanced MSA cases, as previously reported [28–31]. It was reported that reduced gray matter volume was observed in orbitofrontal and mid-frontal regions as well as in temporomesial and insular areas of both hemispheres

in MSA–C patients [28], while in MSA–P patients, reduced gray matter volume was reported in the primary bilateral sensorimotor cortices, supplementary bilateral motor areas, right premotor cortex, prefrontal cortex bilateral (middle frontal gyri), and bilateral insular cortices [29]. A longitudinal study of MSA–P patients revealed that cortical atrophy increased during the course of the illness [30]. The left superior and inferior frontal regions, left caudate, right hippocampus, and right inferior temporal regions were correlated with memory scores [31]. This paper mostly complemented these findings, showing that diffusion changes in the anterior corpus callosum connecting the frontal lobes were correlated with cognitive impairment. These underlying mechanisms may be associated with reduced FA values in the left corpus callosum in MSA–CI.

In this study, the changes between MSA–CI and MSA–NC were only observed in the left, but not the right, corpus callosum. It is unclear why the left, but not right, contributed to the cognitive decline in MSA. A section of the anterior part of the body of the corpus callosum can be associated with the deficits of memory, the dysexecutive cognitive and behavioral syndrome, and disturbances in interhemispheric transfer of learning [32]. However, it has not been determined whether the left and right corpus callosum work in different ways. Further longitudinal study will be needed to clarify the meanings of the laterality.

Detailed relationships between FA, MD, AD, and RD values and pathological conditions have not been elucidated. Although we should consider the influence of the non-Gaussian behavior water motion on these parameters, the reduced FA values we observed were considered to correspond to several pathological conditions, including chronic white matter degeneration, demyelination, subtle microstructural alterations, secondary Wallerian degeneration, and gliosis or early axonal injury [6]. In contrast, increased MD is observed in chronic white matter degeneration, while AD and RD mainly express axonal and myelination involvement, respectively [6]. Since the relationships between FA, MD, RD, and AD values and pathological conditions are not so simple, further comparative study between pathological and radiological findings will be needed to clarify this issue.

Recent neuropsychological studies report dementia in MSA patients [33–35]. Fiorenzato et al. reported that at a 15-month follow-up, the proportion of mild cognitive impairment increased up to 80% [36]. Executive dysfunction, including semantic and phonemic word list generation, is a prominent cognitive disturbance in MSA patients [35, 36], and memory disturbances are also observed, presenting with delayed recall [35]. In this study, patients with MSA–CI had significantly lower ACE-R subscores in the four domains of attention and orientation, memory, fluency, and language, in accordance with previous findings [35, 36].

The interval from MSA diagnosis to clinical cognitive symptoms is estimated to be 6.2 ± 2.4 years [33]; however, earlier cognitive impairments have also been described [34]. The mean disease duration in this study was 2.9 ± 1.7 years in the MSA–CI patients and 2.7 ± 1.2 years in the MSA–NC patients. Interestingly, there were no significant differences in disease duration, motor phenotype, or UMSARS scores between the MSA–CI and MSA–NC patients. Since the mean age at the onset of MSA–CI was 4 years older than the onset of MSA–NC, although not significant, we might consider the influence of aging on the results. However, according to previous studies, widespread white matter can show a significant decline in FA values with age in normal healthy subjects [6], but there were significant differences to a limited extent in the corpus callosum between MSA–CI and MSA–NC in this study. Thus, it would be difficult to explain our results exclusively based on the aging effect. Our results indicate that there may be a discrete phenotype showing mild cognitive involvement during the early course of the illness in MSA.

Limitation

There are several limitations in our study. First, the number of MSA–CI patients was relatively low and influenced on VBM and TBSS results. Particularly, this could be due to no significant cortical gray matter in patients with MSA–CI compared to controls by VBM, although some previous studies showed the relationship between cognitive decline and cortical atrophy in MSA. Second, analysis techniques in this study are rather complex and operator dependent. Some types of blinding of the assessors and future development of automated and observer-independent methods will be needed for clinical use and individual assessment. Finally, because our MSA cases were not pathologically confirmed, concomitant pathology such as tau and β amyloid may be associated with cognitive decline. Further study will be needed to clarify these issues.

Conclusion

In MSA, cognitive impairment appears to be associated with white matter tract involvement, and the anterior part of the corpus callosum in particular may be the target for neuroimaging and pathological study to detect early cognitive impairment.

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Author contributions (1) Research project: (A) conception, (B) organization, (C) execution; (2) statistical analysis: (A) design, (B) execution, (C) review and critique; (3) manuscript: (A) writing of the first draft, (B) review and critique. KH: 1A, 1B, 1C, 2A, 2B, 2C, 3A. HW: 1A, 1B, 1C, 2A, 2C, 3B. EB: 1B, 1C, 2A, 2B, 2C. KK: 1A, 1C. NY: 1A, 1C. RO: 1B, 1C. KI: 1B, 1C. MM: 1B, 1C. TY: 1B, 1C. AO: 1B, 1C. TT: 1A, 1B, 1C. MI: 1A, 1B, 1C, 2A. NA: 1A, 1B, 2A. HN: 1C. TT: 1C, 2A, 2B, 2C. SM: 1B, 1C. SN: 1C, 2A, 2B, 2C, 3A. MK: 1A, 2C, 3B. GS: 1A, 2A, 2C, 3B.

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Compliance with ethical standards

Conflicts of interest All authors declared no conflict of interest.

Ethical standards This study conformed to the Ethical Guidelines for Medical and Health Research Involving Human Subjects endorsed by the Japanese government and was approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

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