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Cognitive Impairment in Multiple System Atrophy Is Related to White Matter Damage Detected by the T1-Weighted/T2-Weighted Ratio

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Keywords
Multiple system atrophy · Cognitive dysfunction · Magnetic resonance imaging · Iron · White matter

Abstract
Introduction: This study aimed to use a novel MRI contrast, the standardized T1-weighted/T2-weighted (sT1w/T2w) ratio, to assess damage of the white matter and gray matter in multiple system atrophy (MSA). Furthermore, this study investigated whether the sT1w/T2w ratio was associated with cognitive impairment in MSA. ***Methods:*** The white matter and gray matter sT1w/T2w ratio of 37 MSA patients and 19 healthy controls were measured. Correlation analyses were used to evaluate the relationship between sT1w/T2w ratio values and clinical variables, and a multivariate analysis was used to identify independent factors associated with cognitive impairment in MSA. ***Results:*** MSA patients showed a higher white matter sT1w/T2w ratio value than controls ($p < 0.001$), and the white matter sT1w/T2w ratio value was significantly correlated with the International Cooperative Ataxia Rating Scale score ($r = 0.377$, $p = 0.021$) and the Addenbrooke's cognitive examination III score ($r = -0.438$, $p = 0.007$). Cognitively impaired MSA patients had a significantly higher white matter sT1w/T2w ratio value than cognitively preserved MSA patients ($p = 0.010$), and the multiple logistic regression analysis revealed that the median white matter sT1w/T2w ratio value was independently associated with cognitive impairment in MSA. ***Conclusion:*** The sT1w/T2w ratio is sensitive to degenerative changes in the white matter that is associated with cognitive ability in MSA patients.

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Introduction

Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder characterized by cerebellar ataxia, parkinsonism, and autonomic failure at varying degrees during the course of its natural history. Based on the predominant motor symptomatology, MSA is classified into cerebellar ataxia-predominant MSA (MSA-C) and parkinsonism-predominant MSA (MSA-P). Dementia that fulfills the criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders is considered as a non-supporting feature of MSA diagnosis [1]; however, it has been found that MSA patients often present with a significant decline in executive function, memory, language, and visuospatial functions [2]. Several advanced MRI techniques such as voxel-based morphometry (VBM), cortical thickness measurement, diffusion tensor imaging (DTI), and resting-state functional MRI (fMRI) have been used to explore the underlying anatomical signature of cognitive impairment in MSA patients [2–6]. Several VBM findings demonstrated that MSA patients with cognitive impairment have a frontal lobe-dominant cortical atrophy, suggesting that cortical degeneration play a primary role in cognitive impairment in MSA [2]. Conversely, earlier studies that used DTI and fMRI indicated that subcortical network dysfunction caused by white matter degeneration is an anatomical and pathophysiological background of cognitive impairment in MSA [3–6]. The exact pathogenic mechanism of neural correlates causing cognitive impairment in MSA patients remains unclear. Moreover, the barriers in using advanced MRI techniques in clinical practice and research are complexity of MRI techniques, the expertise required in image post-processing, and the duration in obtaining images.

Recently, an MRI-based method for studying microstructural tissue integrity has been developed. The method is based on the ratio of T1-weighted (T1w) and T2-weighted (T2w) image signal intensities [7], and can yield a new quantitative contrast (T1w/T2w ratio), with high spatial resolution and test-retest reliability [8]. The most significant advantages of the method are the use of common T1w and T2w images that are already obtained by nearly all clinical and research MRI protocols and a simple post-processing procedure. The T1w/T2w ratio has been shown to be associated with cortical myelination patterns [9], and may be used in differentiating myelinated from demyelinated tissue postmortem [10]. Cortical and subcortical T1w/T2w ratio values have also been noted to be correlated with neurodegenerative changes in several neurodegenerative disorders [11, 12]. Recently, it has also been shown that the standardized T1w/T2w (sT1w/T2w) ratio corrects for the receive field bias and is also more sensitive to tissue damage in multiple sclerosis [13, 14].

In this study, the sT1w/T2w ratio was used in the MSA population to assess the gray matter and white matter damage and to investigate their association with cognitive impairment in MSA. In addition, we examined DTI in MSA patients to validate the association between white matter damage and cognitive impairment as well as to explore the underpinning microstructural changes of the white matter in association with cognitive impairment in MSA patients.

Materials and Methods

Subjects

This retrospective study was approved by the Institutional Review Board, and the need for informed consent was waived. Forty-five consecutive MSA patients who were admitted to our institution between September 2017 and July 2019 were identified through our database. Patients with current or previous history of another neuropsychiatric disorder and abnormal MRI due to another etiology were excluded from the study. Patients with disease onset after the age of 80 were also excluded because they have an atypical late-onset age for MSA and are likely to be associated with non-MSA causes of dementia. A total of 8 patients were then not included (two with age at onset above 80 years, 2 with depression, 1 with hemorrhage in the putamen, 1 with brain infarction, 1 with polymicrogyria on brain MRI, and 1 with infantile paralysis). The final study cohort consisted of 37 MSA patients and 19 age- and sex-matched healthy controls (HC).

The patients with MSA were clinically diagnosed in accordance with the second consensus statement by Gilman et al. [1] (probable, 30; possible, 7). The MSA patients were further grouped into MSA-C and MSA-P based on the predominant clinical symptomatology at the time MRI was performed. Among the 37 MSA patients, 20 were classified into the MSA-C group and 17 into the MSA-P group. All of the 20 patients with MSA-C were also included in our previously published study [15]. The medical records of the MSA patients were reviewed for age at disease onset, age at scan, disease duration, the Unified Multiple System Atrophy Rating Scale (UMSARS) part 2 scores, the International Cooperative Ataxia Rating Scale (ICARS) scores, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part 3 scores, the Zung Self-Rating Depression Scale (SDS) scores, and the Addenbrooke's cognitive examination III (ACE-III) scores [16]. In this study, 20 MSA patients with ACE-III scores >88 were classified as cognitively preserved MSA (MSA-CP), and 17 MSA patients with scores ≤88 were classified as cognitively impaired MSA (MSA-CI) [17]. Clinical and neuropsychological evaluations, including UMSARS part 2, ICARS, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part 3, SDS, and ACE-III, were performed in the same way in all MSA patients at the time of admission. All MRI images were obtained using the same MRI scanner using the same imaging parameters for all subjects, except that DTI was obtained only in the patients with MSA.

MRI Acquisition

As a part of routine patient care, DTI, structural T1w, and T2w images were obtained using a single 3 T GE scanner (GE DISCOVERY MR750; GE Healthcare, Milwaukee, WI, USA). The imaging parameters for T1w images were 3D-IR-SPGR, sagittal plane, TR = 8 ms, TE = 3 ms, TI = 420 ms, flip angle of 15°, FOV 256 mm, 256 × 256 matrix, and voxel size of 1 × 1 × 1 mm^3, and for T2w images were 2D-TSE, axial plane, TR = 5,000 ms, TE = 93 ms, field of view of 220 × 220 mm, 352 × 352 matrix, 0.43 × 0.43 × 5 mm resolution, and interslice gap of 1 mm. The diffusion tensor images were also acquired through single-shot echo-planar imaging with the following parameters: TR = 8,500 ms, TE = 61.1 ms, 128 × 128 matrix, 1.875 × 1.875 × 2-mm resolution, *b* value = 1,000 s/mm^2, number of motion-probing gradient directions = 30, number of acquisitions = 2, and acceleration factor = 2.

MRI Preprocessing

Before the sT1w/T2w ratio was measured, the T1w and T2w images were preprocessed as follows; the 3D T1w images were linearly co-registered to the 2D axial T2w images using SPM12 (version 7219), a brain mask was created by skull stripping the co-registered T1w image using the Brain Extraction Tool with FSL version 5.0.11 [18] and binarizing it with FSL tools, and gray matter and white matter masks were generated by thresholding the pseg output from the FMRIB Automatic Segmentation Tool [19].

T1w/T2w Ratio and sT1w/T2w Ratio Calculation

The sT1w/T2w ratios in the gray matter and white matter were measured [14]. Median intensity values in T1w and T2w images in both gray matter and white matter masks of each subject were calculated. Moreover, a scaling factor was calculated by dividing the median gray matter intensity value in the T1w image by the median gray matter intensity value in the T2w image. A scaled T2w image (sT2) was then created by multiplying the T2w image by the scaling factor. Finally, the sT1w/T2w ratio was calculated using the following equation developed by Misaki et al. [13]:

$$\mathrm{s}\frac{\mathrm{T1w}}{\mathrm{T2w}}\ \mathrm{ratio} = \frac{\mathrm{T1w} - \mathrm{sT2w}}{\mathrm{T1w} + \mathrm{sT2w}}.$$

Median sT1w/T2w ratio values in the gray matter and white matter were calculated.

Tract-Based Spatial Statistics

Voxelwise statistical analysis of the fractional anisotropy (FA) data was conducted using tract-based spatial statistics (TBSS) [20]. The brain image was skull stripped using the Brain Extraction Tool. The FA images were then created by fitting a tensor model to the raw diffusion data using FMRIB's diffusion toolbox. Each FA image was registered to the standard MNI space using the nonlinear registration tool in FSL. Next, a mean FA image was created and projected into the main central tracts to prepare the mean FA skeleton, representing the centers of all white matter tracts. Each subject's aligned FA images were then projected onto this skeleton before running the voxelwise cross-subject stats. TBSS analysis was repeated for mean diffusivity, axial diffusivity, and radial diffusivity (RD) maps.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 25.0 (SPSS Japan, Tokyo). Demographic data of the MSA patients and HC were compared using the χ^2 test for sex and the Student's *t* test for age at the time of MRI scan, and sT1w/T2w ratio values in the white matter and gray matter between MSA patients and HC were compared using the Student's *t* test.

Spearman correlation analyses were used to evaluate the relationship between sT1w/T2w ratio values and sex, disease type, disease duration, UMSARS score, ICARS score, UPDRS score, and ACE-III score, whereas Pearson correlation analyses were used to evaluate the relationship between the sT1w/T2w ratio values and age at disease onset, age at the time of MRI scan, and SDS score.

The sex and age at MRI scan of patients with MSA-CP or MSA-CI were compared with those of the controls by the χ^2 test and Kruskal-Wallis test, respectively, with adjustment for multiple testing using the Bonferroni method. Other demographic and clinical variables were compared between patients with MSA-CP and those with MSA-CI through Student's *t* test and Mann-Whitney U test for the continuous variables and the χ^2 test for the categorical variables. Moreover, the sT1w/T2w ratio values in the white matter and gray matter were compared among the controls and MSA-CP and MSA-CI patients by one-way analysis of variance. Tukey's HSD test was used as a post hoc test for pairwise comparisons. Parameters that were found to be statistically significant in univariate analyses were included in a multivariate analysis by logistic regression to identify the independent factors associated with cognitive impairment in MSA. A forward stepwise logistic regression analysis with the likelihood method (probability for stepwise, $p < 0.05$ for entry and $p < 0.10$ for removal) was used. A p value of <0.05 was considered statistically significant.

To determine the diffusion skeleton voxels that were significantly different between the MSA-CP and MSA-CI groups, we estimated 2 contrasts by the FSL tool "General Linear Model." The purpose of the 2 contrasts was to test whether the means of the 2 groups differed. The significance of contrast1 indicated that mean MSA-CP > mean MSA-CI, and that of contrast 2 indicated that mean MSA-CP < mean MSA-CI. The type of disease was entered into the analysis as a covariate. The results were viewed and overlaid onto the standard brain using FSLView at a familywise error-corrected threshold of $p < 0.05$.

Results

The demographic and clinical data of MSA patients and HC are summarized in Table 1. An example of sT1w/T2w ratio map for a MSA patient is depicted in Figure 1. The white matter sT1w/T2w ratio of MSA patients was significantly higher than that of HC (0.17 ± 0.02 vs. 0.14 ± 0.01, $p < 0.001$) (Fig. 1). However, the gray matter sT1w/T2w ratio values between MSA patients and HC were not significantly different (−0.06 ± 0.02 vs. −0.05 ± 0.02. $p = 0.056$) (Fig. 2).

Furthermore, the white matter sT1w/T2w ratio value was significantly correlated with the ICARS score ($r = 0.377$, $p = 0.021$) and ACE-III score ($r = -0.438$, $p = 0.007$) (Fig. 3). There was no significant correlation between the

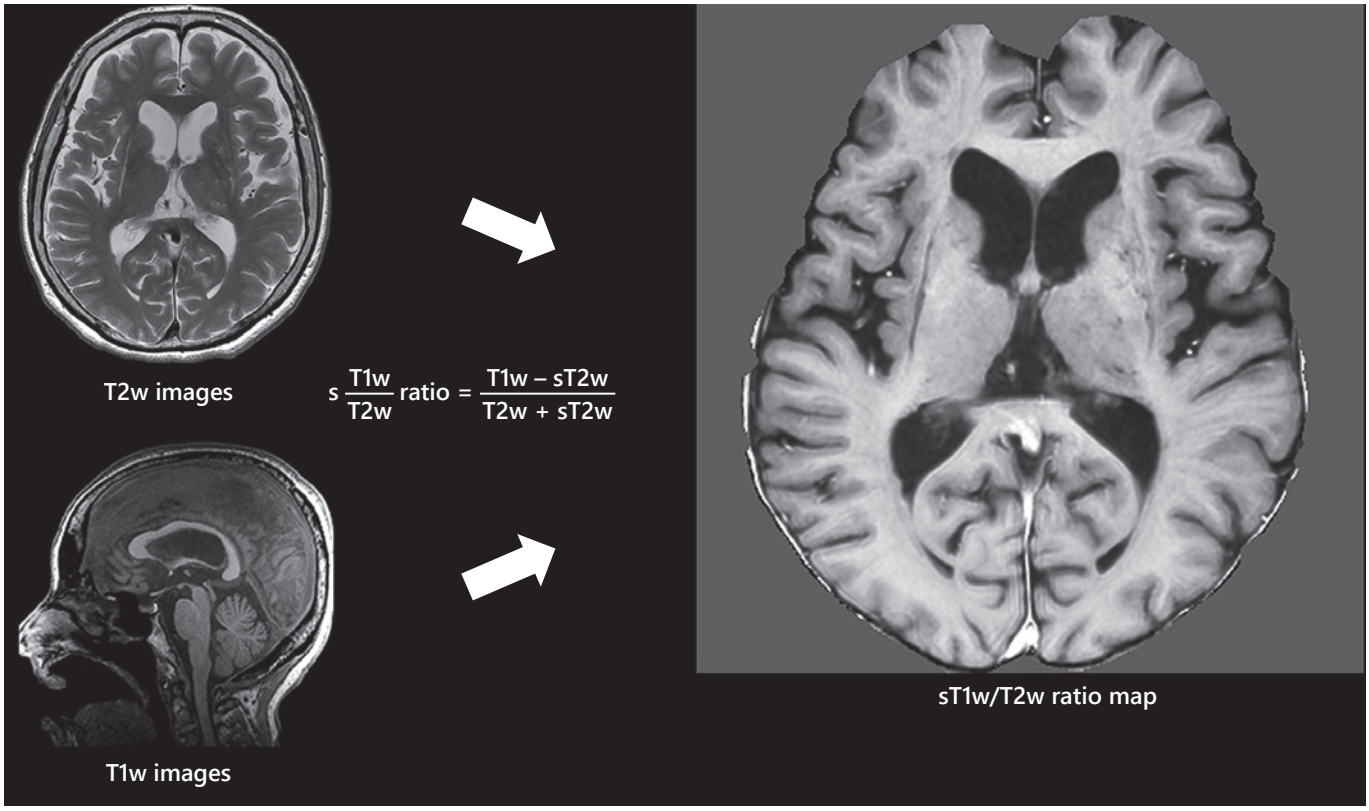

Fig. 1. An example of sT1w/T2w ratio map from an MSA patient. sT2w, a scaled T2w image; sT1w/T2w, standardized T1-weighted/T2-weighted; MSA, multiple system atrophy.

Table 1. Demographic and clinical data of MSA patients and HC

Group	MSA	HC	*p* value
N	37	19	
Sex (male/female)[a]	24/13	8/11	0.103
Age at MRI, years, mean ± SD[b]	63.5±9.7	65.7±9.6	0.586
Age at onset, years, mean ± SD	61.6±9.9	NA	
Disease duration, years, median (range)	1.6 (0.4–5.5)	NA	
UMSARS part 2 score, median (range)	13.0 (6–28)	NA	
ICARS score, median (range)	23.0 (7–63)	NA	
MDS-UPDRS part 3 score, median (range)	23.0 (4–71)	NA	
SDS score, mean ± SD	41.3±6.7	NA	
ACE-III score, median (range)	89.0 (62–98)	NA	

MRI, magnetic resonance imaging; SD, standard deviation; NA, not applicable; MSA, multiple system atrophy; UMSARS, Unified Multiple System Atrophy Rating Scale; ICARS, International Cooperative Ataxia Rating Scale; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SDS, Zung Self-Rating Depression Scale; ACE-III, Addenbrooke's cognitive examination III; HC, healthy controls. [a] χ^2 test. [b]Student's *t* test.

white matter sT1w/T2w ratio value and other clinical variables including age at MRI. The gray matter sT1w/T2w ratio value was significantly correlated with age at disease onset ($r = 0.488$, $p = 0.002$), age at the time of MRI scan ($r = 0.478$, $p = 0.003$), and the ACE-III score ($r = -0.349$, $p = 0.034$). There was no significant correlation between the gray matter sT1w/T2w ratio value and other clinical variables.

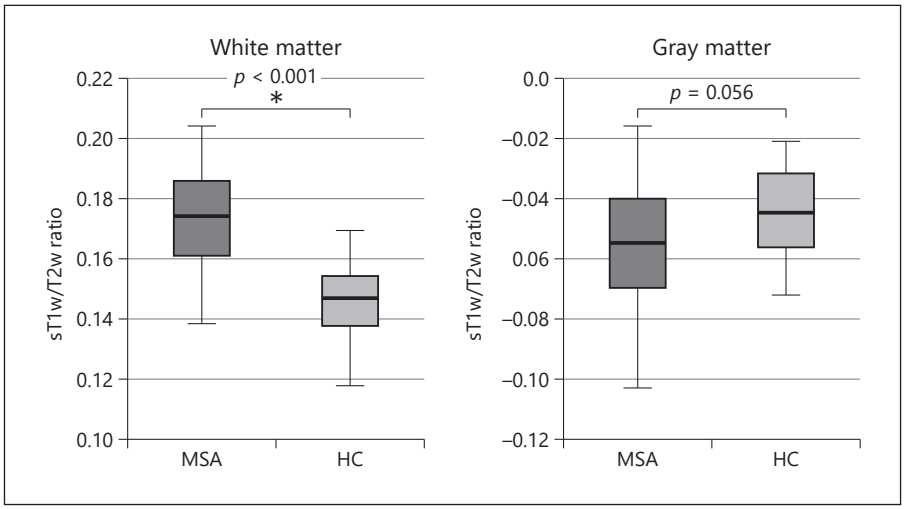

Fig. 2. Group comparison of the sT1w/T2w ratio in the white matter and gray matter between MSA patients and HC. The white matter sT1w/T2w ratio was significantly higher in MSA patients than in HC. There was no significant difference in the gray matter sT1w/T2w ratio between MSA patients and HC. The boxes on the boxplots indicate 25th percentile, median, and 75th percentile values. sT1w/T2w, standardized T1-weighted/T2-weighted; MSA, multiple system atrophy; HC, healthy controls

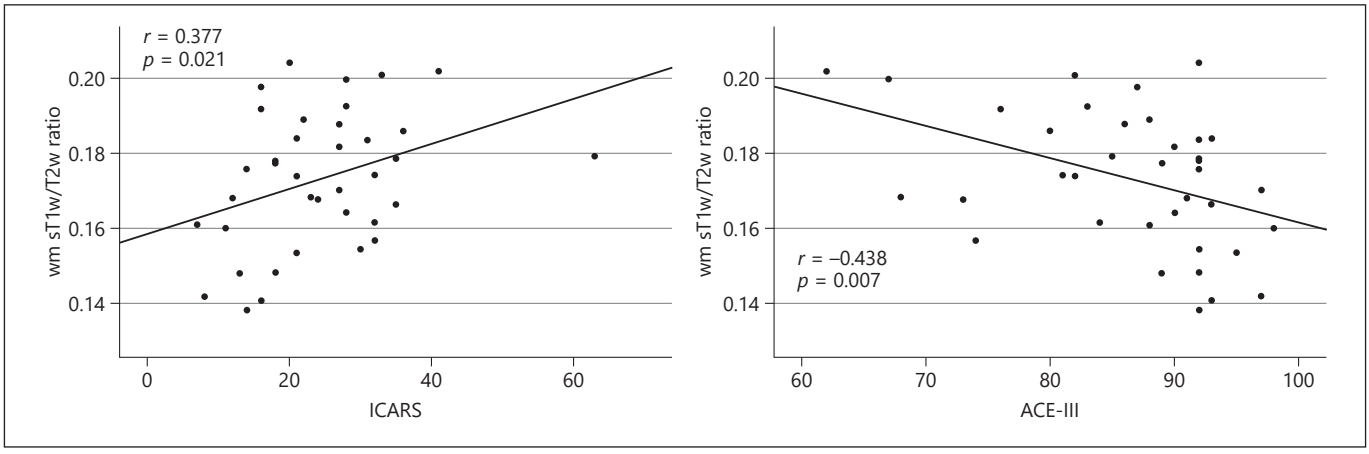

Fig. 3. Correlations between the sT1w/T2w ratio in the cerebral white matter and ICARS and ACE-III in MSA patients. The sT1w/T2w ratio in the cerebral white matter (wm sT1w/T2w ratio) was correlated with ICARS scores and inversely correlated with ACE-III scores in MSA patients. sT1w/T2w, standardized T1-weighted/T2-weighted; MSA, multiple system atrophy; ICARS, International Cooperative Ataxia Rating Scale; ACE-III, Addenbrooke's cognitive examination III.

There were no significant differences among the HC and MSA-CP and MSA-CI patients in terms of sex and age at the time of MRI scan. Table 2 shows a comparison between MSA-CP patients and MSA-CI patients. The proportion of MSA-C characterization and the ICARS score was significantly higher in MSA-CI patients than in MSA-CP patients ($p = 0.012$ and 0.034). Moreover, the MSA-CI patients showed significantly lower ACE-III scores than the MSA-CP patients ($p < 0.001$). However, the MSA-CI patients showed significantly higher white matter sT1w/T2w ratio values than the MSA-CP patients (0.18 ± 0.02 vs. 0.17 ± 0.02, $p = 0.010$) (Fig. 4). Moreover, there was no significant difference between the gray matter sT1w/T2w ratio value of MSA-CI and MSA-CP patients (−0.05 ± 0.02 vs. −0.06 ± 0.02, $p = 0.169$) (Fig. 4). A multivariate logistic regression that included the disease type, ICARS score, and white matter sT1w/T2w ratio value as explanatory variables were performed to determine the independent factors associated with MSA-CI. A stepwise forward method generated a model that included the disease type and white matter sT1w/T2w ratio value as variables. The white matter sT1w/T2w ratio value was found to be the only variable significantly associated with MSA-CI ($p = 0.036$), whereas the disease type was not significantly associated with MSA-CI ($p = 0.052$). The model was significant ($\chi^2 = 11.982$, 2 df, $p = 0.003$), and the Hosmer-Lemeshow χ^2 goodness of

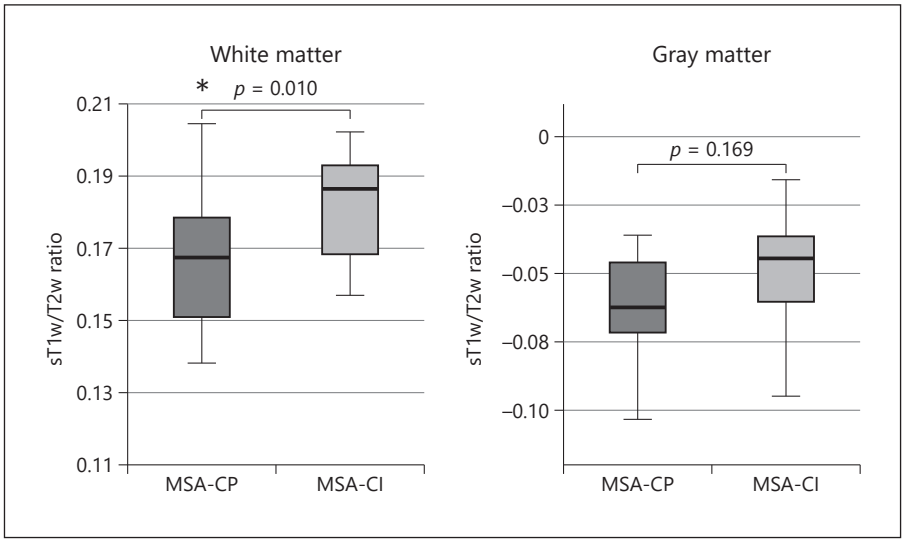

Fig. 4. Group comparison of the sT1w/T2w ratio in the white matter and gray matter between MSA-CP and MSA-CI. The white matter sT1w/T2w ratio was significantly higher in MSA-CI than in MSA-CP. There was no significant difference in the gray matter sT1w/T2w ratio between MSA-CP and MSA-CI. The boxes on the boxplots indicate 25th percentile, median, and 75th percentile values. sT1w/T2w, standardized T1-weighted/T2-weighted; MSA-CP, multiple system atrophy-cognitively preserved; MSA-CI, multiple system atrophy-cognitively impaired.

Table 2. Comparison of MSA patients with and without cognitive impairment

Characteristic	MSA-CI	MSA-CP	*p* value
N	17	20	
Type of disease (MSA-C/MSA-P)[a]	13/4	7/13	**0.012**
Sex (male/female)[a, *]	12/5	12/8	0.501
Age at MRI, years, median (range)[b, *]	68.0 (49–77)	56.0 (46–80)	0.297
Age at onset, years, median (range)[b]	65.0 (47–76)	54.5 (44–79)	0.311
Disease duration, years, median (range)[b]	1.3 (0.8–5.5)	1.8 (0.4–3.7)	0.460
UMSARS part 2 score, median (range)[b]	13.0 (7–28)	14.5 (6–28)	0.390
ICARS score, median (range)[b]	28.0 (7–63)	19.0 (8–35)	**0.034**
MDS-UPDRS part 3 score, median (range)[b]	21.0 (8–65)	28.0 (4–71)	0.141
SDS score, mean ± SD[c]	41.3±8.0	41.4±5.6	0.980
ACE-III score, median (range)[b]	82.0 (62–88)	92.0 (89–98)	**<0.001**

Values in bold indicate $p < 0.05$. MRI, magnetic resonance imaging; SD, standard deviation; MSA, multiple system atrophy; UMSARS, Unified Multiple System Atrophy Rating Scale; ICARS, International Cooperative Ataxia Rating Scale; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SDS, Zung Self-Rating Depression Scale; ACE-III, Addenbrooke's cognitive examination III; MSA-P, parkinsonism-predominant MSA; MSA-C, cerebellar ataxia-predominant MSA; MSA-CP, multiple system atrophy-cognitively preserved; MSA-CI, multiple system atrophy-cognitively impaired. [a] χ^2 test. [b] Mann-Whitney U test. [c] Student's *t* test. * Adjusted for multiple comparisons: $p < 0.05/3 = 0.0167$.

fit statistic was nonsignificant ($p = 0.128$). Nagelkerke and Cox-Snell R^2 values were 0.370 and 0.277, respectively. The model accurately identified 67.6% of MSA-CI patients.

The FA values were significantly decreased, and the RD values were increased in the cerebral white matter tracts in patients with MSA-CI, when compared with those in patients with MSA-CP (Fig. 5). There were no significant differences in the mean diffusivity and axial diffusivity values between the MSA-CI and MSA-CP patients.

Discussion

This study revealed that MSA patients had a significantly higher median white matter sT1w/T2w ratio value than controls. Moreover, the white matter sT1w/T2w ratio was significantly correlated with cerebellar ataxia scores and general cognitive scores. Among patients with MSA, MSA-CI patients had a significantly higher white matter sT1w/T2w ratio value than MSA-CP patients, and

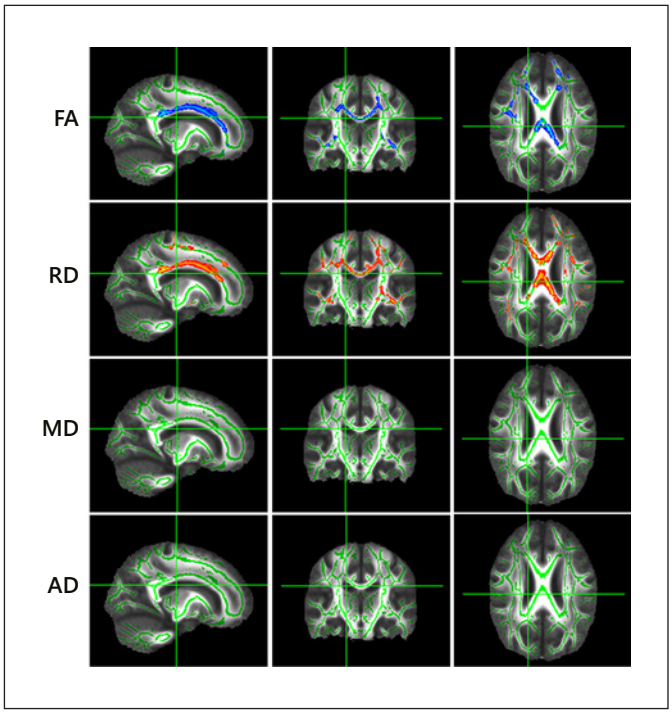

Fig. 5. TBSS results indicating a significant difference in FA and RD values between MSA-CP and MSA-CI patients. The results are superimposed on the fiber skeleton (green) and overlaid on the FMRIB FA 1 mm template. Blue lines indicate decreased FA values in MSA-CI patients compared to that in MSA-CP patients (MSA-CI < MSA-CP). Red lines indicate increased RD values in MSA-CI patients compared to that in MSA-CP patients (MSA-CI > MSA-CP). TBSS, tract-based spatial statistics; MSA-CP, multiple system atrophy-cognitively preserved; MSA-CI, multiple system atrophy-cognitively impaired; FA, fractional anisotropy; RD, radial diffusivity; MD, mean diffusivity; AD, axial diffusivity.

multiple logistic regression analysis showed that only the white matter sT1w/T2w ratio value independently associated with cognitive impairment in MSA. Comparison of MSA-CI with MSA-CP by TBSS revealed decreased FA and increased RD values in the cerebral white matter tracts in patients with MSA-CI, suggesting an association between microstructural cerebral white matter involvement and cognitive impairment in MSA patients.

Previous studies suggested that degenerative white matter changes are associated with cognitive impairment in MSA. Glial cytoplasmic inclusions within oligodendrocytes widely distributed in white matter are considered as the pathological hallmark for the diagnosis of MSA, and are believed to play a key role in the pathogenesis of MSA [21]. An autopsy report described that an MSA patient with dementia and progressive aphasia showed frontal lobe atrophy with mild loss of myelinated fibers and axons, mild gliosis, and abundant glial cytoplasmic inclusions in the white matter [22]. An MRI study using DTI showed a damaged frontal and occipital white matter in MSA-C patients, and suggested that the cerebral white matter changes were related to cognitive disturbances and visuospatial deficits [3]. Another MRI study using DTI revealed that anterior corpus callosal involvement was related to cognitive deficits in MSA [4]. Kawabata et al. [5] reported that gray matter volume was not significantly correlated with global cognitive scores in VBM in MSA patients, and that global cognitive scores were correlated with cerebello-cerebral functional connectivity in resting-state fMRI analysis. These results indicate that cognitive impairment in MSA was due to subcortical network dysfunction associated with white matter degeneration preceding cortical atrophy. In accordance with the reports of these previous studies, comparison of MSA-CI with MSA-CP by TBSS in the current study revealed decreased FA values in the cerebral white matter tracts in patients with MSA-CI. This study also revealed that the median white matter sT1w/T2w ratio value was significantly associated with the ACE-III score. Moreover, the median white matter sT1w/T2w ratio value of MSA-CI patients was significantly higher than that of MSA-CP patients, and the multiple logistic regression analysis showed that the median white matter sT1w/T2w ratio value was the only independent predictor of cognitive impairment in MSA. As mentioned, previous studies noted degenerative changes in the white matter associated with cognitive impairment in MSA patients using advanced MRI techniques such as DTI and fMRI [3–5]. However, the advanced MRI techniques are not commonly included as part of the routine clinical MRI protocol, and the expertise is required in image post-processing. The advantages of using the sT1w/T2w ratio method are that it requires only T1w and T2w scans, and the post-processing procedure is easy.

The underlying biological substrate of T1w/T2w ratio in the white matter is not fully understood. The T1w/T2w ratio method was originally recommended to be sensitive in detecting myelin content [7, 9]. MSA patients showing a higher white matter sT1w/T2w ratio value than HC was contrary to our expected finding. Myelin loss has been reported most commonly in white matter tracts associated with striatonigral and olivopontocerebellar regions [23], and was shown to be correlated with white matter hypointensities on postmortem T2w images in MSA [24]. FA reduction along with RD increase, which was recorded in the white matter of MSA-CI patients by TBSS analysis in the present study, has been reported to reflect de-

myelination [25]. If the sT1w/T2w ratio indicated myelin-related pathological changes, the white matter sT1w/T2w ratio value should be decreased in accordance with the progression of degeneration in MSA. In interpreting the results of this study, it should be considered that the sT1w/T2w ratio may reflect not only the level of demyelination but also other microstructural factors including iron accumulation. Inconsistent correlations with histology [26], myelin water imaging [8, 27], simultaneous tissue relaxometry, and magnetization transfer saturation index [28] suggest that T1w/T2w ratio is sensitive to other microstructural factors such as axonal diameter, iron accumulation, calcium content, and inflammation, in addition to myelin content [8, 26–30]. In a report that described a higher gray matter T1w/T2w ratio value in Alzheimer's disease patients and the correlation between higher T1w/T2w ratio value and impaired cognitive function, microstructural factors including iron accumulation were considered as biological substrates of a higher gray matter T1w/T2w ratio value in Alzheimer's disease [11]. This contribution of additional microstructural factors is supported by recent findings in MSA pathology. Dysregulation of brain iron homeostasis has been shown to be related to the pathophysiology of MSA due to the incidence of oxidative stress and neuroinflammation [31]. An increase in total iron concentration coupled with a disproportionate increase in ferritin in activated microglia and a reduction in ferroportin were observed in the basis pontis (both gray and white matter) of the MSA tissue [32]. A transcriptome study using RNA sequencing revealed increased expressions of alpha and beta hemoglobin genes in the white matter of the MSA tissue, and suggested that increased iron levels in the white matter were related to MSA pathology at the transcriptional level [33]. An MRI pathology correlation study to confirm the pathological underpinning of the white matter sT1w/T2w ratio in MSA is warranted.

This study had the following limitations. One is that MSA patients were clinically diagnosed without postmortem confirmation. The other is that the median white matter and gray matter sT1w/T2w ratios were assessed; hence, the approach used in this study does not enable us to localize changes in the white matter and gray matter to a particular clinical deficit.

Conclusion

In summary, this study demonstrated the sT1w/T2w ratio, a clinically feasible MRI measure, was sensitive to white matter damage, and was related to cognitive impairment in MSA.

Statement of Ethics

This study procedure was approved by the Institutional Review Board of the Chiba University Graduate School of Medicine (reference number: 1222). Written informed consents from the patients were waived because this study collected clinical and imaging data obtained in routine practice.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Study concept and design: Atsuhiko Sugiyama, Graham Cooper, and Satoshi Kuwabara. Data acquisition and analysis: Graham Cooper, Hajime Yokota, Keisuke Shimizu, and Masatsugu Yakiyama. Drafting the manuscript and figures: Atsuhiko Sugiyama, Graham Cooper, Shigeki Hirano, Masahiro Mori, Carsten Finke, Alexander U. Brandt, Friedemann Paul, and Satoshi Kuwabara.

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