selection, such as the inclusion of patients with additional extracerebellar damage. Although regional cerebral blood flow (rCBF) and cognitive function in spinocerebellar ataxia patients have been examined before genetic analysis became available [7,8], these studies were controversial since they included many types of spinocerebellar ataxia with additional extracerebellar damage.

Neuropathologically, SCA6 is characterized by almost exclusive cerebellar involvement particularly selective loss of the cerebellar Purkinje cells [9]. Degeneration is mostly restricted to the cerebellum in SCA6 patients while cortical structures and basal ganglia are spared. SCA6 therefore represents an excellent model for investigating the cerebellar contribution to cognition. So far, however, only a few studies have examined the rCBF of SCA6 patients [10]. Globas et al. failed to provide clear evidence for cognitive deficits in SCA6 patients [11]. However, we recently revealed significant impaired visual memory and verbal fluency in genetically confirmed SCA6 patients [12], suggesting that SCA6 patients have prefrontal dysfunction. Previous studies have indicated hypoperfusion restricted to the cerebellum [10], however these results may be attributable to the small sample size of the SCA6 patients used. In previous studies, VOI analysis methods was used [10], and they may be not entirely objective because we could not examine the perfusion of whole brain by VOI analysis methods.

The aims of this study were to clarify the rCBF and to evaluate the relationships between rCBF and cognitive dysfunction in genetically confirmed SCA6 patients.

2. Methods

2.1. Subjects (Table 1)

Thirteen genetically confirmed SCA6 patients from thirteen families and 21 control subjects were enrolled in this study (Table 1). These 13 SCA6 patients were from the same pool of 18 patients who were examined in our previous report [12]. All were native Japanese speakers. Severity of ataxia was rated on the International Cooperative Ataxia Rating Scale (ICARS) [13]. Genomic DNA was extracted from the peripheral blood of the SCA6 patients using a conventional technique [14]. PCR amplification of the CAG repeat in the CACNA1A gene was performed using a fluorescein-labelled forward primer (5′-AGCCCCCTCAACATCTGGTA-3′) and a non-labelled reverse primer (5′-GACCCGCCTCTCCATCCT-3′). PCR conditions after a 3-min initial denaturation at 94 °C, were 35 cycles of 94 °C for 1 min, annealing at 64 °C for 1 min, and elongation at 72 °C for 1 min. Aliquots of PCR products were combined with loading dye and separated by electrophoresis with an autoread sequencer SQ-5500 (Hitachi Electronics Engineering, Tokyo, Japan). The size of the CAG repeat was analyzed on Fraglys software version 2.2 (Hitachi) by comparison with co-electrophoresed PCR standards with known repeat sizes. The CAG-repeat size of the PCR standard was determined by direct sequence using a sequence primer (5′-ACATCTGGTACCAGCACTCC-3′). No SCA6 patient included in this study had neurological signs and symptoms suggestive of other neurological or psychiatric diseases. Age- and education-matched paid volunteers were recruited as control subjects for neuropsychological tests and perfusion studies. Control subjects had no history of any neurologic or psychiatric disease that affected cognition. Written informed consent was received in advance from SCA6 patients and control subjects. The study was approved by the ethics committee of the Nagoya University Hospital.

Table 1
SPM results for group comparison between SCA6 patients and control subjects

Region	k_E	Coordinates {mm}			Z
		x	y	z	
Cerebellum, brain stem	18,462	−6	−56	−12	Inf
		8	−58	−12	Inf
		−18	−68	−18	6.93
Left middle frontal gyrus, medial frontal gyrus	325	−28	8	42	3.16
		−8	0	50	2.71
		−24	0	40	2.50

SPM, statistical parametric mapping; SCA6, spinocerebellar ataxia type 6.

2.2. Neuropsychological tests

Based on our previous study [12], we selected neuropsychological tests on which SCA6 patients might have impairments. Each patient underwent a standard cognitive status assessment. All of the patient's neuropsychological tests were given on the same day. The Mini-Mental State Examination (MMSE) was used as a screen [15]. Visual memory was examined using the Visual Paired Associates Subtests 1 and 2 of the Revised Wechsler Memory Scale (WMS-R) [16]. Verbal memory was examined using the Logical Memory Subtests 1 and 2 of the WMS-R [16]. To evaluate verbal fluency as a measure of language function, subjects were asked to name as many items as possible within 1 min from a semantic category (animals) and from a phonemic category (Japanese nouns starting with the Japanese Kana character "Ka"). To evaluate executive function, the Rule Shift Cards test of the Behavioural Assessment of the Dysexecutive Syndrome (BADS) was used [17]. In trial 1 of this test, 21 spiral-bound non-court playing cards are turned over one by one, and the subject is asked to say "yes" to a red card and "no" to a black card. In trial 2, the subject is asked to say "yes" if the card is the same color as the previous one and "no" if it not. We statistically analyzed the relationships between results of the neuropsychological tests and their characteristics, including disease duration, degree of ataxia (ICARS), and CAG-repeat length. For the neuropsychological tests in which rapid speech was an important aspect of performance (e.g., the phonemic and

semantic fluency task), we analyzed the correlations to the dysarthria subscore of the ICARS.

2.3. Assessment of regional brain perfusion with SPECT

600 MBq of ^{99m}Tc-Ethylcysteine dimer (ECD) (Neurolite, Daiichi Radioisotope Laboratories, Ltd, Tokyo, Japan) was injected intravenously while the subjects were in a supine position with eyes closed in a quiet dimly lit room. SPECT scanning was carried out between 5 and 30 min after injection using a triple-head GCA 9300A gamma camera (Toshiba, Tokyo, Japan) equipped with low energy, super high resolution, fan-beam collimators. The data were acquired in a 128×128 matrix through a 120° rotation at an angle interval of 4°. The projection data were prefiltered through a Butterworth filter, and reconstructed using filtered backprojection with a Ramp filter. No attenuation correction was performed. The in-plane spatial resolution was 8 mm in full width at half maximum (FWHM). The final image slices were set up parallel to the orbitomeatal line and were obtained at an interval of 6.9 mm through the entire brain.

2.4. Data analysis

For the statistical analysis of the neuropsychological tests, SPSS version 11.0 for Windows (SPSS Japan, Tokyo, Japan) was used. The Shapiro–Wilk test was used to assess the normality of continuous variables. For comparison between the SCA6 group and the control group, we performed an unpaired t test for normally distributed data or a non-parametric Mann–Whitney U test for non-normally distributed data. Statistical significance was chosen at a P value of 0.05, with the correction for multiple comparisons using Holm–Sidak method. For correlation studies we used the Pearson product moment correlation test for normally distributed variables or the Spearman rank correlation test for non-normally distributed variables.

The SPECT data were analyzed using Statistical Parametric Mapping version 2 (SPM2; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) implemented in MATLAB version 6.5.1 (Math Works, Sherborn, MA, USA). In a pre-processing step, datasets were spatially normalized to a standard stereotactic three dimensional space and smoothed with an isotropic Gaussian kernel of FWHM 12 mm. All of the images resulting from the normalization procedure were visually acceptable. In the following analyses, proportional scaling was applied to adjust the mean whole brain activity to 50 ml/100 g/min to avoid inter-individual variation in global cerebral blood flow. The grey matter threshold was 0.8. The normalized images of the SCA6 patients and control subjects were compared with voxel by voxel t statistics. Confounding effects may arise from age or education differences, which could influence regional cerebral blood flow change in SCA6. Therefore, age and education were inserted as covariates in the statistical parametric mapping (SPM) analyses. In addition, we compared the images of the SCA6 patients to detect voxels in which the rCBF was significantly correlated with the scores of neuropsychological tests on which SCA6 patients showed impairment. Each value of the neuropsychological tests was used as a covariate of interest, and the values of the global rCBF, age, education and ICARS, which are the relevant factors associated with cognitive performance, were excluded as nuisance variables [18]. Regions were reported as significant if they contained voxels with a value of at least $P<0.01$, uncorrected for multiple comparisons, with cluster extent threshold (k_E)=100.

3. Results

3.1. Neuropsychological features

We assessed the neuropsychological features of 13 patients out of 18 patients who were examined in our previous study [12], since these patients could receive both neuropsychological tests and SPECT. The test results were similar to our previous report [12]. SCA6 patients did not differ significantly from controls with regard to MMSE, but showed significant cognitive impairment in several other tasks (Supplemental Table 1). Performance on the Visual Paired Associates Subtest 1 was significantly reduced in SCA6 patients compared with controls (P=0.003), while performance on the Visual Paired Associates Subtest 2 was not. Verbal fluency tasks in semantic and phonemic

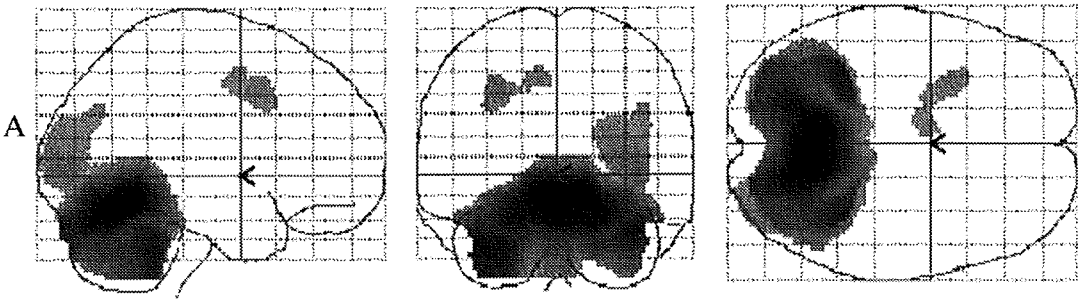

Fig. 1. SPM maps comparing brain perfusion between SCA6 patients and control subjects (uncorrected $P<0.01$). Sagittal (left column), coronal (middle column) and transverse (right column) views of the standard brain.

categories were remarkably impaired in SCA6 patients (P=0.006, P=0.006, respectively). The result of the Rule Shift Cards test tasks showed a tendency to be impaired in SCA6 patients compared with controls, although not significant. These neuropsychological impairments in SCA6 patients did not show any significant correlation to CAG-repeat length and disease duration, nor to ICARS dysarthria subscores. No significant differences were observed between SCA6 patients and control subjects in verbal memory function as tested using Logical Memory Subtests 1 and 2 of the WMS-R.

3.2. Correlation between rCBF and cognitive dysfunction in SCA6 patients

According to SPM analyses, SCA6 patients showed reduced brain perfusion in the left middle frontal and medial frontal cortices, as well as in the cerebellum and brain stem, compared to control subjects (uncorrected $P<0.01$; Fig. 1 and Table 1).

We examined the correlation between rCBF and cognitive dysfunction after age, education, and severity of cerebellar ataxia were excluded statistically (Fig. 2 and Table 2). There

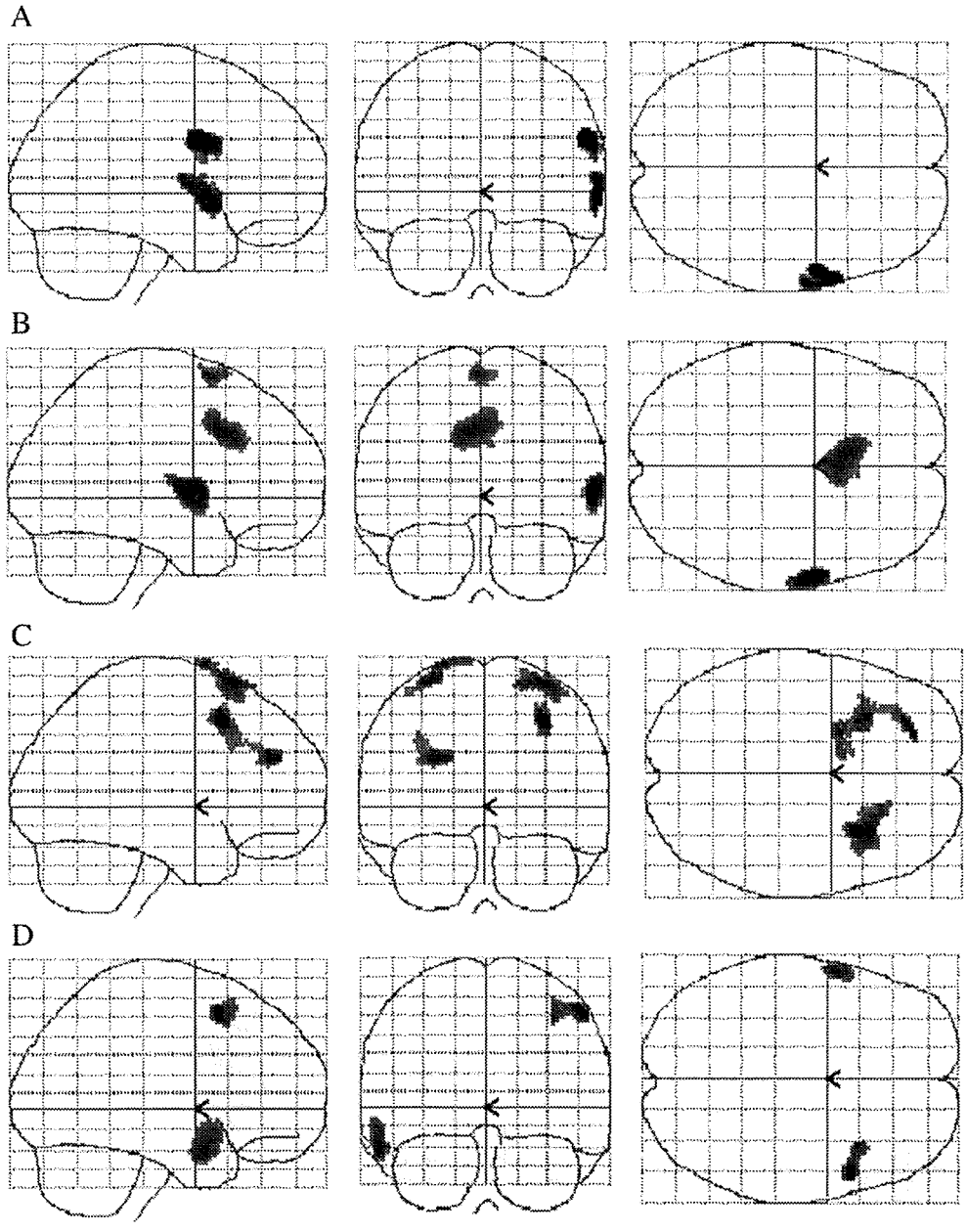

Fig. 2. SPM maps of the correlation between brain perfusion in SCA6 patients and cognitive performance (uncorrected $P<0.01$). Sagittal (left column), coronal (middle column) and transverse (right column) views of the standard brain. A: Visual Paired Associates 1 test, B: phonemic fluency test, C: semantic fluency test, D: Rule Shift Cards test.

Table 2
SPM results of correlations between the results of the neuropsychological tests and brain perfusion in SCA6 patients

Region	k_E	Coordinates			Z
		x	y	z	
		{mm}			
Perfusion positively correlated with the score of the Visual Paired Associates 1					
Right inferior frontal gyrus	163	56	2	30	2.94
		60	10	28	2.79
Right superior temporal gyrus	143	62	8	−2	2.78
		64	−4	6	2.65
Perfusion positively correlated with the score of the phonemic fluency					
Right superior temporal gyrus	270	60	2	4	3.91
Cingulate gyrus	521	−4	14	38	3.11
		4	12	40	2.91
		−10	24	34	2.91
Medial frontal gyrus	115	−2	8	68	2.96
		−2	18	68	2.69
		8	14	66	2.46
Perfusion positively correlated with the score of the semantic fluency					
Right middle frontal gyrus	110	32	16	48	3.80
		30	24	40	2.34
Right superior frontal gyrus	168	32	20	68	3.39
		22	28	66	2.82
		22	26	74	2.44
Left superior frontal gyrus	113	−22	6	78	3.19
		−32	20	68	3.14
		−24	16	72	2.88
Left middle frontal gyrus	103	−30	40	26	3.05
		−36	22	36	2.49
		−34	30	34	2.45
Perfusion positively correlated with the score of the Rule Shift Cards test					
Right superior frontal gyrus	130	52	12	52	3.67
		36	18	48	2.73
		38	18	56	2.70
Left superior temporal gyrus	126	−58	6	−20	2.98
		−60	10	−10	2.73

SPM, statistical parametric mapping; SCA6, spinocerebellar ataxia type 6.

was a positive correlation between the score of the Visual Paired Associates 1 test and the perfusion in the right inferior frontal and right superior temporal gyri in SCA6 patients. In SCA6 patients, there was a positive correlation between the phonemic fluency score and the perfusion in the medial frontal and superior temporal gyri, between the semantic fluency score and the perfusion in the bilateral superior and middle frontal gyri, and between the Rule Shift Cards test score and the perfusion in the right middle frontal and superior temporal gyri.

4. Discussion

In this study, we demonstrate that SCA6 patients have a reduction of rCBF in not only the cerebellum but also prefrontal cortices. In our previous study, we documented that visual memory, verbal fluency, and executive function were significantly impaired in SCA6 patients [12]. In the present study, we show that the rCBF in prefrontal cortices is significantly correlated to these neuropsychological impairments in SCA6 patients.

rCBF had been examined in patients with various types of spinocerebellar ataxia before we could confirm our diagnosis of spinocerebellar ataxias genetically [7,8]. However several types of diseases might be included in these studies, and the results were not consistent. Recently, one study examined rCBFs in genetically confirmed SCA6 patients and described only cerebellar hypoperfusion [10]. These results agree with results of previous neuropathologic studies showing that lesions of SCA6 are restricted to the cerebellum, where abundant expression of P/Q-type calcium channels has been found [19]. Magnetic resonance imaging analysis of SCA6 patients demonstrated no abnormalities in the central nervous system except for cerebellar atrophy [20]. However, one study showed that crossed cerebello-cerebral diaschisis (CCCD) was derived from the functional deactivation of the cerebello-ponto-thalamo-cerebral pathways [21]. Unilateral impairment of the cerebellum would lead to reduced radioisotope uptake in the contralateral cerebral hemisphere, and CCCD has been established by PET and SPECT studies in various cerebellar diseases [8]. Therefore, CCCD might be also found in SCA6 patients. In previous studies, a statistically significant difference of prefrontal perfusion could not be established between SCA6 patients and controls, which may be due to the small sample size of patients [10]. Recently, new SPECT analysis techniques such as SPM have been developed that allow brain functional images to be studied more easily and accurately than before. It is entirely automated and objective, and completely overcomes the disadvantage of earlier VOI analysis methods. Although imaging studies using SPM have been performed on various diseases recently, there has been only one study examining SCA6 patients by SPM, revealing the reduction of metabolism in frontal and prefrontal cortices [22]. In the present study, we examined the perfusion of whole brain in SCA6 patients using SPM, and revealed hypoperfusion in prefrontal cortices as well as cerebellum. We speculate that the mechanism of rCBF reduction in prefrontal cortices of SCA6 patients is the functional deactivation of the cerebello-ponto-thalamo-cerebral pathways.

In this study, we reveal visual memory deficits, impairments of verbal fluency, and executive dysfunction in SCA6 patients, which are similar to those described in patients with spinocerebellar ataxia type 1 [23], type 2 [24,25], and Machado–Joseph disease [26,27]. Cognitive dysfunction in these diseases is considered to be derived from the disruption of the cortico-cerebellar loop [23,24,26,27]. However, these diseases have extracerebellar involvement with degeneration of frontal lobes, thalamus, brainstem or basal ganglia, [28,29]. Cognitive impairment is therefore likely to result from additional extracerebellar damage as well as cerebellar degeneration itself in these disorders. Because lesions in SCA6 patients are restricted to the cerebellum, we suggest that the cognitive dysfunction in SCA6 patients derives from

the disruption of the cortico-cerebellar loop. There are a few studies that address cognitive function in SCA6 patients, and a previous study could not disclose a significant impairment of attention, working memory, verbal and visuospatial memory, or fronto-executive functions [11]. However, the lack of statistical significance in their study may be due to an insufficient sample size of SCA6 patients or to other methodological issues such as different neuropsychological tests.

We found correlations between the score on the Visual Paired Associates 1 test and the perfusion in the right inferior frontal and right superior temporal gyri, between the score on the phonemic fluency test and the perfusion in the medial frontal and superior temporal gyri, between the score on the semantic fluency test and the perfusion in the bilateral superior and middle frontal gyri, and between the score on the Rule Shift Cards test and the perfusion in the right middle frontal and superior temporal gyri in SCA6 patients. These lesions were mostly consistent with the prefrontal hypoperfusion in SCA6 patients. Previous studies demonstrated that frontal lobe function is associated with visual memory task [30,31]. In addition, impairments of verbal fluency have been considered to reflect frontal lobe damage[32]. The Rule Shift Cards test is used for measuring the executive dysfunction, including frontal lobe dysfunction. Taken together, the cognitive dysfunctions seen in SCA6 patients may suggest prefrontal involvement, although the cerebral cortex is well preserved [9].

In summary, SCA6 patients have mild cognitive impairment, and prefrontal hypoperfusion, and these results are related to each other. These data indicate that cognitive impairment in SCA6 patients may result from prefrontal hypoperfusion.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jns.2008.03.018.

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Fractional anisotropy values detect pyramidal tract involvement in multiple system atrophy

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Abstract

Objective: Pathological studies have shown remarkable pyramidal tract involvement in multiple system atrophy (MSA), while clinical pyramidal signs are relatively rare. We investigated the fractional anisotropy (FA) values to assess the degree of pyramidal tract involvement in MSA, in comparison with amyotrophic lateral sclerosis (ALS) and controls. Furthermore, we compared FA values between MSA patients with or without clinical pyramidal signs and controls, and between MSA patients with or without positive conventional MRI findings and controls.

Methods: We evaluated FA values in the internal capsule, corona radiate and whole pyramidal tract using visualized tractography of 65 subjects (20 probable MSA patients, 28 age-matched ALS patients, and 17 age-matched healthy controls) using a 3.0T magnetic resonance system.

Results: The FA values in the internal capsule, corona radiate, and whole pyramidal tract were significantly lower in MSA patients than in controls and were at a level similar to those of ALS patients. In addition, low FA values were prominent in MSA patients, even in those with short duration of illness, lacking precentral gyrus hyperintensity in FLAIR images, and without pyramidal signs.

Conclusion: FA values could identify pyramidal tract degeneration even in patients with early phase MSA and those without clinical pyramidal signs or abnormal MRI findings. More extensive degeneration of the pyramidal tract occurs in MSA than so far believed.

Keywords: Multiple system atrophy; Pyramidal tract involvement; Fractional anisotropy values; Amyotrophic lateral sclerosis; Small-sized neuron; Tractography

1. Introduction

Multiple system atrophy (MSA) is a sporadic, adult-onset neurodegenerative disease [1,2]. The nigrostriatal, olivopontocerebellar, and autonomic systems are often and prominently impaired; the clinical signs of the degeneration of these systems are major diagnostic criteria for MSA [3]. Although pathological studies have shown widespread pyramidal tract involvement in MSA, [4–6] extensor plantar responses with hyperreflexia occur in about 30–50% of patients [7,8]. Thus, pyramidal signs are thought to be less important in diagnosis than the symptoms seen in the other systems. In addition, electrophysiological or magnetic measures to monitor central motor conduction have not been able to detect pyramidal tract degeneration in MSA [9–11].

Fractional anisotropy (FA) values are quantitative parameters of magnetic resonance imaging (MRI) [12], and have been used to evaluate the degree of tissue degenerations in various disorders. FA values measure the degree of anisotropy of the diffusing water along different axes of the image, and decreasing FA values represent tissue degeneration in normal

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aging [13] or various diseases [14–16]. As for the evaluation of pyramidal tract degeneration using FA values, amyotrophic lateral sclerosis (ALS), in which the pyramidal tract is prominently involved, has been well studied, showing low FA values in some regions of pyramidal tract as a result of neuronal degeneration [14,17].

Recent studies have shown that FA values are reduced in the CNS regions in multiple system atrophy predominated in cerebellar ataxia (MSA-C) [18]. FA values have also been used to discriminate multiple system atrophy predominated in parkinsonism (MSA-P) from Parkinson's disease (PD) [19,20]. However, FA values have not been studied for their usefulness detecting pyramidal tract degeneration in MSA. T1 spine-echo imaging, with an additional magnetization transfer contrast pulse (T1 SE/MCT) sequence has recently shown to detect the pyramidal tract degeneration in MSA [21]. However, the extent and features of pyramidal tract degeneration in MSA have not been well evaluated by neuroimaging including FA values.

The aim of the present study is to examine the pyramidal tract involvement in MSA using FA values, to correlate these findings to clinical signs and MRI findings, and further compare to the extent of those seen in ALS.

2. Methods

We studied 65 subjects in total; 20 patients with probable MSA (10 MSA-C; 10 MSA-P), 28 age- and gender-matched patients with ALS, and 17 age- and gender-matched healthy volunteers (Table 1). This study was approved by the ethics committee of the Nagoya University Graduate School of Medicine, and informed consent was established before participation to the study. Clinical diagnoses of MSA and ALS were established by consensus diagnostic criteria [3,22]. All MSA patients fulfilled the criteria for probable MSA. All ALS patients fulfilled the clinically definite or clinically probable-laboratory supported revised ALS criteria of El Escrial. Healthy controls underwent the same MRI examination as the MSA and ALS patients.

There were no differences in mean age or gender distribution between the MSA, ALS or control populations. There was a significant variation in time from initial symptoms to MRI evaluation among the MSA patients (4±2 years, range: 1 to 10 years) and ALS patients (2±1 years, range: 1 to 5 years), including both MSA and ALS patients in relatively early disease stages in this study.

Table 1
Patients data

	Number of cases	Age (years)	Female/ male	Duration (years)	With/without the pyramidal signs
MSA	20	61±9	8/12	4±2	10/10
MSA-P	10	63±11	4/6	4±3	5/5
MSA-C	10	58±7	4/6	4±2	5/5
ALS	28	62±12	9/19	2±1	28/0
Control	17	61±11	12/5		

MSA; multiple system atrophy, MSA-P; multiple system atrophy predominated in parkinsonism.
MSA-C; multiple system atrophy predominated in cerebellar ataxia, ALS; amyotrophic lateral sclerosis.

Information on the presence of the pyramidal signs was obtained from the neurological examinations or from patient medical records. We defined patients as having pyramidal signs when they showed increased tendon reflexes or extensor plantar responses. Ten MSA patients showed pyramidal signs (five MSA-C patients, five MSA-P patients), the other ten patients did not (five MSA-C patients, five MSA-P patients), and all ALS patients showed pyramidal signs, although the extent and combination of signs varied.

2.1. MRI protocol

All scanning was carried out with a 3.0T magnetic resonance scanner (Trio, Siemens, Erlangen, Germany), using a receive-only 8-channel phased-array head coil. Diffusion weighted imaging (DWI) was obtained with optimal methods [23] using a Stejskal–Tanner sequence with single-shot spin-echo-type echo-planar imaging, a flip angle of 90°, and a repetition time of 7700 ms. Echo times corresponding to respective b-factors were 75 ms for 700 s/mm^2. Echo spacing was 0.79 ms, and the matrix size was 128 × 128 with a readout bandwidth of 1562 Hz/pixel. Sixty axial slices, 2 mm thick with a 0.6-mm interslice gap, were used to image the entire brain with a 23-cm^2 square field of view.

A motion-probing gradient (MPG) was applied in 6 orientations after acquisition of b=700 images. The 128 × 128 data matrix was zero-fill interpolated to 256 × 256. An acceleration factor of two was applied using the parallel imaging technique, generalized autocalibrating partially parallel acquisitions (GRAPPA), [24] which is an extension of the simultaneous acquisition of spatial harmonics technique. Eddy current-related geometric distortions were not prominent between the images of each MPG directions; thus, distortion correction post-processing was not applied.

2.2. Data analyses

FA values and tractography were obtained using public domain software dTV II for DWI analysis developed by the Imaging Computing and Analysis Laboratory, Department of Radiology, University of Tokyo Hospital, Japan, and made available at http://www.ut-radiology.umin.jp/people/masutani/dTV.htm.

To set regions of interest (ROIs), we visualized the pyramidal tract using tractography. In this study, we determined the pyramidal tract as visualized fibers by tractography that the seed area was defined as the cerebral peduncle and the target area as the precentral gyrus on T2-weighted axial images (b=0) (Fig. 1A). The ROIs in the internal capsule and corona radiate were placed within closed curves drawn on visualized pyramidal tracts (Fig. 1B, C). In addition, we set ROIs on

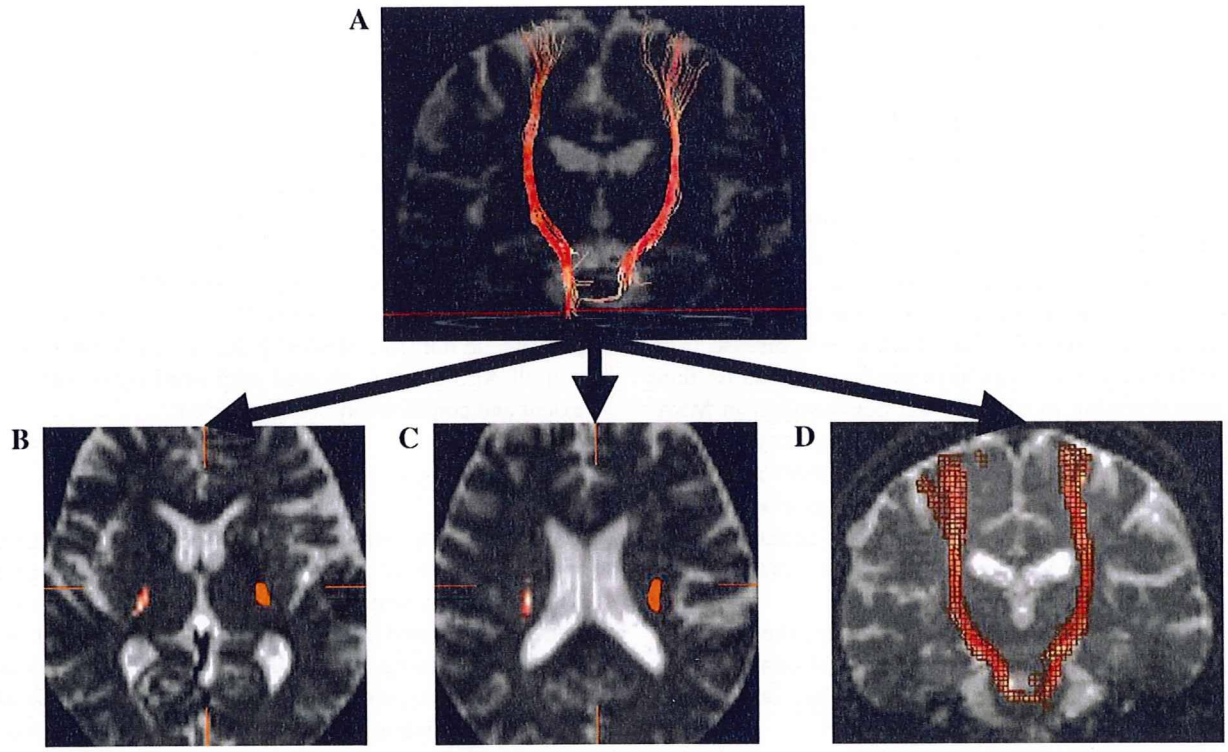

Fig. 1. Regions of interest. Visualizing the pyramidal tract using tractography (A). Regions of interest in the internal capsule (B), corona radiate (C) and whole pyramidal tract (D).

whole pyramidal tract visualized by tractography (Fig. 1D). Regional FA values were calculated for each region of interest. Mean FA values were adapted as representative indices of FA values.

In addition, the presence or absence of precentral gyrus hyperintensity on fluid attenuated inversion recovery (FLAIR) images was determined [21].

Statistical analyses were performed using SPSS 11.0 for Windows (SPSS Inc, USA). The Kruskal–Wallis test was used for comparisons of FA values among MSA and ALS patients, and controls, as well as MSA patients with and without pyramidal signs. The significance level was set at $p<0.05$.

3. Results

3.1. FA values in the internal capsule, corona radiate, and whole pyramidal tract

The tractography of the pyramidal tract was not visualized in one MSA-C and two ALS patients. The MSA-C patient's disease had been ongoing for 10 years and the advanced stage requiring confinement to bed. There was nothing particularly distinctive in the two ALS patients. As a result, we evaluated 19 MSA and 26 ALS patients. We adjusted the FA threshold to visualize tractography clearly. FA values in these three patients were too low to allow the reconstruction of the tractography.

FA values in all three regions of the MSA or ALS patients' brains were significantly lower ($p<0.05$–0.001) than those in controls (Fig. 2A–C). FA values were indistinguishable between MSA and ALS patients in the internal capsule and the corona radiate (Fig. 2A–C), however, FA values in the whole pyramidal tract were significantly lower in MSA patients than ALS patients. With respect to MSA phenotypes, FA values in the internal capsule and whole pyramidal tract were significantly lower ($p<0.01$–0.001) to a similar extent for both MSA-P and MSA-C patients (Fig. 2D, F), while those in the corona radiate tended to be lower in MSA-P and MSA-C patients, although the difference was not statistically significant (Fig. 2E). The FA values in the whole pyramidal tract were significantly lower ($p<0.05$–0.01) in MSA-C and MSA-P patients than ALS patients (Fig. 2F). The FA values in all three regions were similarly decreased in both MSA-C and MSA-P patients.

3.2. Correlation of FA values to precentral gyrus hyperintensity on FLAIR images and clinical pyramidal signs

Six MSA patients (30%) showed the precentral gyrus hyperintensity on FLAIR images, which is considered to be cortical pyramidal neuron involvement [21]. MSA patients both with or without precentral gyrus hyperintensity showed lower FA values in all three areas than seen in controls (Fig. 3A–C). The FA values in the internal capsule and whole pyramidal tract were significantly lower in MSA patients than in controls independent of those with or without precentral gyrus hyperintensity, while those in the corona radiate were

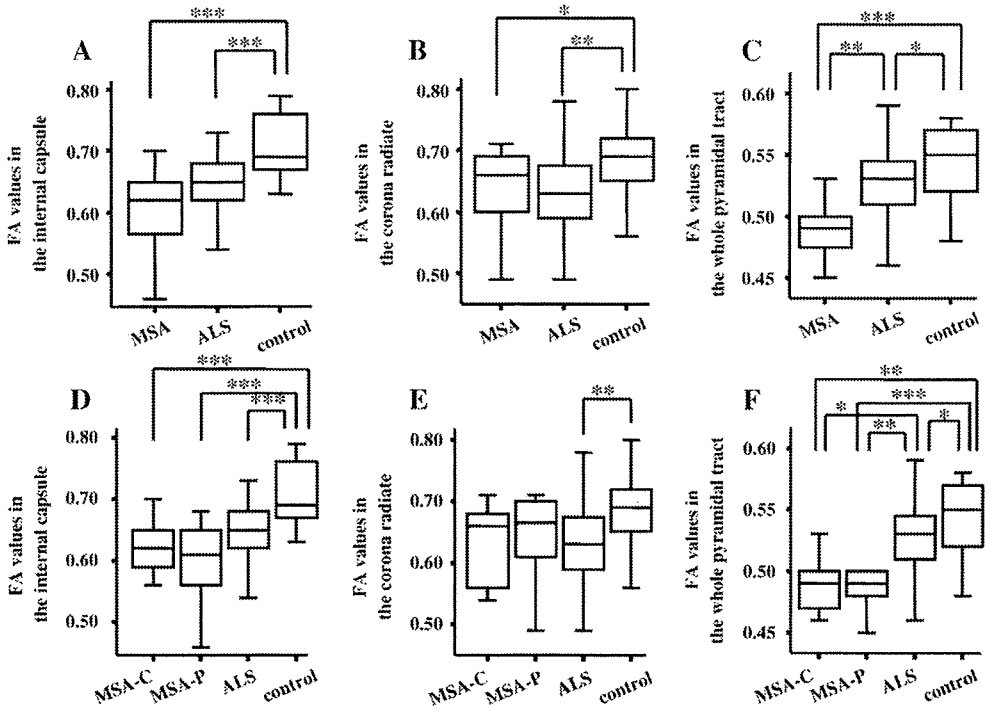

Fig. 2. FA values in the internal capsule, corona radiate, and whole pyramidal tract. FA values in MSA patients, ALS patients and controls or in MSA-C, MSA-P and ALS patients are shown in the internal capsule (A/D), corona radiate (B/E), and whole pyramidal tract (C/F). ***: $p<0.001$, **: $p<0.01$, *: $p<0.05$.

significantly lower in only the MSA patients with precentral gyrus hyperintensity. In addition, FA values in all three regions of interest were more decreased in MSA patients with precentral gyrus hyperintensity than those without it. Especially, FA values with precentral gyrus hyperintensity in the internal capsule were significantly lower than those without it. However, there were no significant differences between FA values with and without precentral gyrus hyperintensity in the corona radiate and whole pyramidal tract. These observations suggested that the FA values were likely decreased in almost all three anatomical regions even in the MSA patients without central gyrus hyperintensity.

We further examined the correlation between FA values and pyramidal signs in MSA patients. The MSA patients, both with or without pyramidal signs, showed lower FA values than controls in all three areas (Fig. 4A–C). FA values in the internal capsule and whole pyramidal tract were significantly lower in MSA patients with or without pyramidal signs than seen in controls, while FA values in the corona radiate were significantly lower in MSA patients

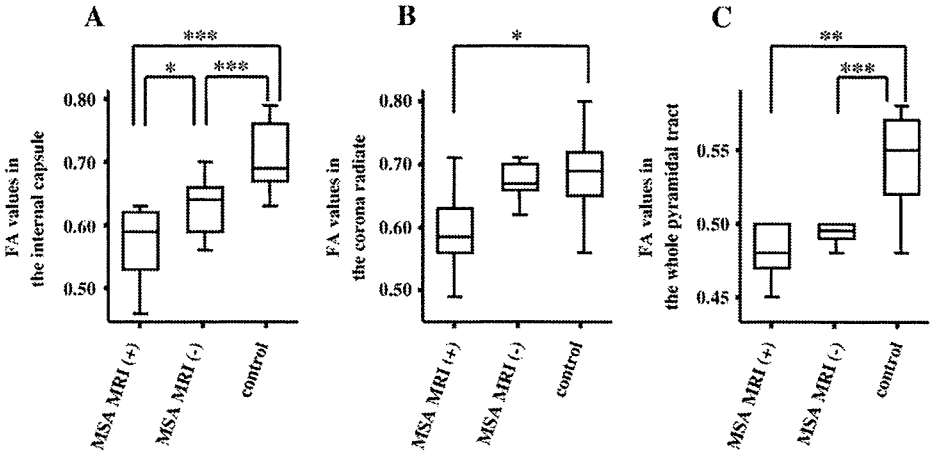

Fig. 3. Correlation between FA values and precentral gyrus hyperintensity on FLAIR images. FA values in MSA patients with or without precentral gyrus hyperintensity, and controls are shown for the internal capsule (A), corona radiate (B), and whole pyramidal tract (C). MSA MRI (+): MSA with precentral gyrus hyperintensity. MSA MRI (−): MSA without precentral gyrus hyperintensity. ***: $p<0.001$, **: $p<0.01$, *: $p<0.05$.

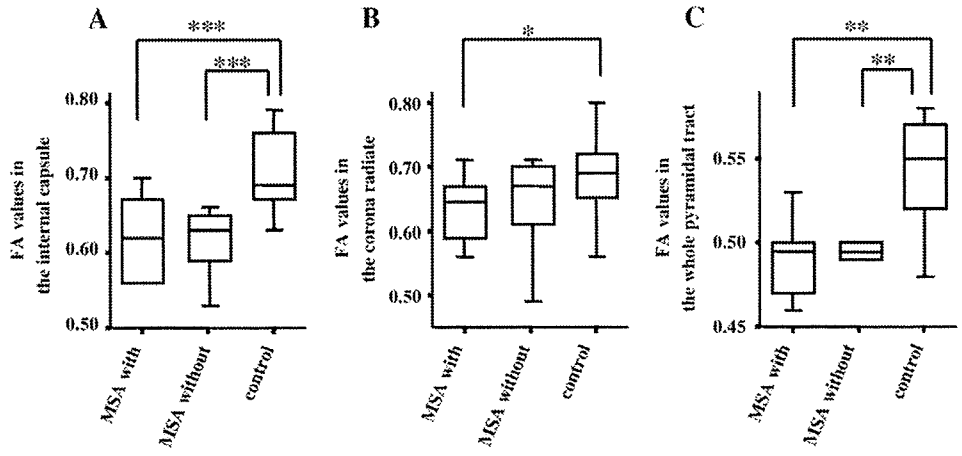

Fig. 4. Correlation between FA values and clinical pyramidal signs. FA values in MSA patients with or without pyramidal signs, and controls are shown for the internal capsule (A), corona radiate (B), and whole pyramidal tract (C). MSA with: MSA with pyramidal signs. MSA without: MSA without pyramidal sings. ***: $p<0.001$, **: $p<0.01$, *: $p<0.05$.

with only pyramidal signs. Although FA values in all three regions of interest were slightly more decreased in MSA patients showing pyramidal signs than those without these signs, however, there were no significant differences between the two groups in all three areas. FA values were decreased even in the MSA patients without pyramidal signs.

4. Discussion

FA values specifically measure the degree of anisotropy of the diffusing water along different axes of an image, enabling useful quantitative estimation of decreased tissue anisotropy reflecting degeneration [12]. Decreased FA values could reflect destruction of this tissue architecture resulting from neuronal loss or gliosis, enhancing random mobility of free water molecules within the tissue; decreasing FA values can be interpreted to show tissue degeneration in normal aging [13] or various diseases [14–17], and demyelination is a possible process underlying FA changes [25]. More recently, decreased FA values in cerebellopetal fibers and the pyramidal tract have been reported in some MSA-C patients [18]. In addition, it was reported that FA values in the pons, cerebellum, putamen and middle cerebellar peduncles were useful in distinguishing MSA from PD [19,20]. FA values were useful in detecting tissue architecture degenerations in MSA; and our results supported these previous observations.

To our knowledge, this is the first systematic study to demonstrate the beneficial utility of FA values in identifying pyramidal tract degeneration in MSA. We evaluated FA values in the internal capsule, corona radiate, and whole pyramidal tract to identify pyramidal tract degeneration; FA values in MSA patients were significantly lower than in controls in all anatomical regions. Especially, FA values in the whole pyramidal tract analyses were more useful in detecting pyramidal tract degeneration than analyses of the internal capsule and the corona radiate. FA values in the internal capsule and the corona radiate evaluated one region in the pyramidal tract. However, in the whole pyramidal tract analyses, we evaluated multiple regions constituting the pyramidal tract. Thus, the whole pyramidal tract analyses could detect more sensitive values than the internal capsule and the corona radiate.

A limitation of the present study is that correction of brain atrophy was not assessed for analysis of FA values. Further comparative study with or without correction will strengthen our result.

In addition, though FA values in cases of MSA were similar to those seen in ALS patients' internal capsule and corona radiate, they were lower than in ALS in the whole pyramidal tract of ALS patients. These results suggest that pyramidal tract degeneration in MSA is more severe than reported to date. Previous pathological studies have demonstrated more frequent and extensive involvement of the pyramidal tract than that observed at clinical examination in MSA [4–6,9], and the level was similar to that of ALS. Despite previous findings of extensive pathological involvement in MSA, it has been noted that it is more difficult to detect pyramidal tract degeneration in MSA by clinical examinations or electrophysiological techniques (such as central motor nerve conduction study) compared with evaluations of degeneration in ALS patients [9–11]. These discrepancies may be explained by the size of the neurons and axons which degenerate in MSA. According to our previous pathological studies of the lateral corticospinal tracts or precentral gyrus in MSA, small- or middle-sized neurons and small-sized axons are predominantly affected, while large-sized neurons and axons are relatively well preserved [9], leading to normal central motor conduction. On a theoretical basis, the smaller the fiber diameter, the higher the FA values in those fibers, particularly as compared to large diameter fibers. Hence, degeneration of small-sized neuron and axon in MSA may readily show low FA values. In contrast to electrically detected central motor

conduction, FA values can detect the small-sized neuron and axon involvement characteristic to pyramidal tract pathology in MSA. Extensive involvement including large-sized neurons may lead to a significant reduction of FA values, but excessive FA values reduction would not be enough to visualize pyramidal tracts as documented in our one patient with severe MSA-C. However, to our knowledge, there were no references that suggested smaller axons had higher FA values and degenerating smaller axons showed lower FA values compared with larger axons. We speculated that small-diameter axons would lead to higher anisotropy of the diffusing water than large-sized axons based on our present observations. In future, we intended to examine the correlation between this point and pathological study.

In this study, only 50% of MSA patients showed pyramidal signs; this frequency is almost consistent with previous reports [7,8]. It is worth nothing that not only the MSA groups with pyramidal signs, but also those without these signs, showed significant low FA values in the pyramidal tract. The mechanism behind the Babinski sign is still unclear [26,27], and a corticospinal tract lesion is not always sufficient to produce a Babinski sign, as previously reported [26,27]. Furthermore, it is not known whether involvement of small fibers in the pyramidal tract contributes to manifestation of a Babinski sign or hyperreflexia. Thus, discrepancies between clinical pyramidal signs and pathological changes of the corticospinal tracts could present in these patients. Our findings suggest that several underlying factors could contribute to elicit clinical pyramidal signs, even in MSA patients with extensive pathological pyramidal tract involvement. Determination of FA values may enable us to detect pyramidal tract damage with higher sensitivity, particularly when we compare this measurement to current clinical and electrophysiological procedures.

In our study, there were six MSA patients with precentral gyrus hyperintensity in FLAIR images; this frequency is almost consistent with previous reports [21]. Strikingly, MSA patients even without precentral gyrus hyperintensity showed lower FA values than controls. In addition, FA values with precentral gyrus hyperintensity in the internal capsule were significantly lower than those without it. These findings suggest that FA values can be used to detect early pyramidal tract degeneration and that precentral gyrus hyperintensity appears when pyramidal tract degeneration becomes more advanced.

In summary, pyramidal tract involvement in MSA was present at a similar level to ALS using FA values measures. In addition, FA values could detect early pyramidal tract degeneration prior to the appearance of clinical pyramidal signs or MR signal changes in MSA. Our findings further support the view that more extensive degeneration of the pyramidal tract occurs in MSA than so far believed.

Acknowledgement

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Cognitive impairments in multiple system atrophy

MSA-C vs MSA-P

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ABSTRACT

Objective: We evaluated comprehensive neuropsychological tests and regional brain blood flow to compare cognitive dysfunction between two types of multiple system atrophy: predominant cerebellar ataxia (MSA-C) and predominant parkinsonism (MSA-P).

Methods: Twenty-one patients with MSA-C, 14 patients with MSA-P, and 21 age- and education-matched control subjects were subjected to neuropsychological tests and SPECT. The neuropsychological tests examined general cognition, verbal and visual memory, working memory, visuospatial and constructional ability, language, executive function, depression, and anxiety, while SPECT analysis examined brain perfusion.

Results: Patients with MSA-P showed severe involvement of visuospatial and constructional function, verbal fluency, and executive function compared with control subjects. Patients with MSA-C showed involvement only in visuospatial and constructional function compared with control subjects and a milder degree of involvement compared with patients with MSA-P. Patients with MSA-P tended toward a wide and severe impairment in cognitive function compared with patients with MSA-C. In addition, neuropsychological impairment in patients with MSA-P was significantly correlated with a decrease in prefrontal perfusion. This significant relation was not correlated to other factors such as age, education, and severity of cerebellar ataxia and parkinsonism, which are relevant factors associated with cognitive performance.

Conclusions: Patients with multiple system atrophy-parkinsonism show more severe and more widespread cognitive dysfunctions than patients with multiple system atrophy-cerebellar ataxia. Our results also indicate that cognitive dysfunction in patients with multiple system atrophy-parkinsonism may be associated with prefrontal involvement. ***Neurology*® 2008;70:1390-1396**

GLOSSARY

MSA = multiple system atrophy; **MSA-C** = MSA-cerebellar; **MSA-P** = MSA-parkinsonism.

Multiple system atrophy (MSA) is a sporadic neurodegenerative disease that presents with parkinsonism, cerebellar ataxia, autonomic failure, and pyramidal signs of varying severity during the course of the illness.[1-3] Neuronal loss, gliosis, and demyelination with widespread involvement—particularly in the striatonigral region, olivopontocerebellar region, and autonomic nervous system—are characteristic. Diagnostic criteria for MSA proposed by a Consensus Conference in 1998[4] recommend designating patients as having MSA-P if parkinsonian features are predominant or MSA-C if cerebellar features are predominant.

Although dementia consistent with the *Diagnostic and Statistical Manual of Mental Disorders* is an exclusion criterion for the diagnosis of MSA,[4] some studies have reported that patients with MSA reveal a cognitive decline when compared with control subjects.[5-9] Furthermore, several studies reported that patients with MSA exhibited more severe cognitive impairment, particularly with executive function, compared with that of

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Table 1 Clinical characteristics of patients with MSA (MSA-C and MSA-P) and control subjects

	MSA (n = 35)	MSA-C (n = 21)	MSA-P (n = 14)	Control subjects (n = 21)
Sex (male/female)	19/16	12/9	7/7	7/14
Age at examination, y	61.0 ± 8.1 (47-76)	60.3 ± 8.3 (48-74)	62.0 ± 7.9 (47-76)	63.1 ± 9.4 (48-79)
Age at onset, y	58.0 ± 8.1 (41-73)	58.1 ± 8.8 (45-73)	57.9 ± 7.2 (41-68)	
Disease duration, y	2.9 ± 1.7 (1-7)	2.6 ± 1.6 (1-7)	3.2 ± 2.0 (1-7)	
Education, y	11.8 ± 2.4 (9-17)	12.1 ± 2.2 (9-17)	11.3 ± 2.5 (9-16)	12.5 ± 2.9 (8-16)
UPDRS part-III	24.2 ± 13.0 (4-54)	16.5 ± 8.8* (4-34)	35.2 ± 9.7* (22-54)	
ICARS	26.1 ± 11.9 (7-51)	27.7 ± 11.8 (11-48)	23.8 ± 12.2 (7-51)	
MMSE	27.4 ± 2.6 (21-30)	28.1 ± 2.4 (21-30)	26.4 ± 2.7† (22-30)	29.1 ± 1.0 (27-30)

Data are presented as mean ± SD (range).
*$p < 0.001$: MSA-P vs MSA-C.
†$p < 0.01$ compared with control.
MSA = multiple system atrophy; MSA-C = MSA-cerebellar; MSA-P = MSA-parkinsonism; UPDRS = Unified Parkinson's Disease Rating Scale; ICARS = International Cooperative Ataxia Rating Scale; MMSE = Mini-Mental State Examination.

severity- and age-matched patients with Parkinson disease.[6-11] In addition, neuroradiologic and pathologic studies have documented a variable extent of frontal and/or temporal lobe involvement in patients with MSA.[12-22] These observations suggest that cognitive function may be more widely and more severely impaired in patients with MSA than has been considered.[5-11] However, the differences in the degree and features of cognitive dysfunction between patients with MSA-C and those with MSA-P are not well understood. Furthermore, the relation between these cognitive dysfunctions and regional cerebral perfusion has not been clarified.

In the present study, we evaluated a wide range of cognitive functions and examined the relation between these impairments and brain regional perfusion, as assessed by SPECT, to reveal the background mechanism of cognitive dysfunction in patients with MSA-C and those with MSA-P.

METHODS

Subjects. Twenty-one patients with MSA-C (12 male, 9 female; age, 60.3 ± 8.3 years; range, 48–74 years), 14 patients with MSA-P (7 male, 7 female; age, 62.0 ± 7.9 years; range, 47–76 years), and 21 control subjects (7 male, 14 female; age, 63.1 ± 9.4 years; range, 48–79 years) were enrolled in this study (table 1). Diagnoses of all patients with MSA were "probable" according to established diagnostic criteria.[4] We examined all patients with MSA by MRI before inclusion, and other neurologic diseases were excluded by MRI. We observed a hyperintense rim at the lateral edge of the dorsolateral putamen and a "hot cross bun" sign in the pontine basis in most of the patients with MSA. All subjects were native Japanese speakers. The severity of ataxia and parkinsonism was rated on the International Cooperative Ataxia Rating Scale[23] and the Unified Parkinson's Disease Rating Scale part-III.[24] Age- and education-matched paid volunteers were recruited as control subjects for neuropsychological tests and the perfusion study. Control subjects had no history of any neurologic or psychiatric disease that influenced cognition. Written informed consent was received in advance from both patients with MSA and control subjects. This study was approved by the ethics committee of the Nagoya University Hospital.

Neuropsychological tests. Each subject underwent a standard cognitive status assessment. All of a subject's neuropsychological tests were given on the same day. The Mini-Mental State Examination (MMSE) was used for overall assessment of cognition.[25] To evaluate attention, the Digit Span Subtest of the Revised Wechsler Adult Intelligence Scale was used.[26] Visual memory was examined using Visual Paired Associates Subtests 1 and 2 of the Revised Wechsler Memory Scale.[27] Verbal memory was examined using Logical Memory Subtests 1 and 2 of the Revised Wechsler Memory Scale.[27] To evaluate verbal fluency as measures of language functions, we asked subjects to name as many items as possible within 1 minute from a semantic category (animals) and from a phonemic category (Japanese nouns starting with the Japanese Kana character "Ka"). To assess executive function, simplified versions of the Wisconsin Card-Sorting Test[28] and the Rule Shift Cards test of the Behavioral Assessment of the Dysexecutive Syndrome[29] were used. Constructional ability was tested using the Block Design Subtest of the Revised Wechsler Adult Intelligence Scale.[26] All subjects completed a self-reporting instrument concerning anxiety and depression (Hospital Anxiety and Depression scale).[30]

Assessment of regional brain perfusion with SPECT. ^{99m}Tc-Ethylcysteine dimer (Neurolite; Daiichi Radioisotope Laboratories, Ltd., Tokyo, Japan), 600 MBq, was injected IV while the subjects were in a supine position with eyes closed in a quiet dimly lit room. SPECT scanning was carried out between 5 and 30 minutes after injection using a triple-head GCA 9300A gamma camera (Toshiba, Tokyo, Japan) equipped with low-energy, super high-resolution, fan-beam collimators. The data were acquired in a 128 × 128 matrix through a 120° rotation at an angle interval of 4°. The projection data were prefiltered through a Butterworth filter and reconstructed using filtered backprojection with a Ramp filter. No attenuation correction was performed. The in-plane spatial resolution was 8 mm in full width at half maximum. The final image slices were set parallel to the orbitomeatal line and were obtained at an interval of 6.9 mm through the entire brain.

Data analysis. For the statistical analysis of the neuropsychological tests, SPSS version 11.0 for Windows was used.

Table 2 Results of neuropsychological tests in patients with MSA (MSA-C and MSA-P) and control subjects

	MSA (n = 35)	MSA-C (n = 21)	MSA-P (n = 14)	Control subjects (n = 21)
Logical memory 1	16.5 ± 8.3	17.5 ± 7.2	14.8 ± 9.9	18.7 ± 4.8
Visual paired associates 1	9.7 ± 4.3	10.5 ± 4.5	8.6 ± 4.0	11.4 ± 4.0
Logical memory 2	12.0 ± 7.3	13.3 ± 6.7	9.9 ± 8.0	13.8 ± 5.0
Visual paired associates 2	4.3 ± 1.7	5.0 ± 1.3	3.3 ± 1.7	4.6 ± 1.7
Block Design	27.8 ± 11.6†	28.9 ± 12.1*	26.0 ± 11.1*	38.4 ± 7.5
Phonemic fluency	7.2 ± 3.0*	7.6 ± 2.9	6.6 ± 3.1*	9.8 ± 2.7
Semantic fluency	12.4 ± 3.9*	13.0 ± 3.5	11.4 ± 4.4*	15.9 ± 3.4
Wisconsin Card Sorting Test				
Categories	2.8 ± 2.0	3.1 ± 2.2	2.4 ± 1.6	2.8 ± 1.8
Total errors	23.1 ± 10.0	22.8 ± 11.2	23.8 ± 7.7	22.7 ± 8.1
Perseverative errors	8.6 ± 8.5	8.3 ± 9.5	9.1 ± 6.8	5.7 ± 4.6
Rule Shift Cards test	2.7 ± 1.6*	3.1 ± 1.2	2.1 ± 1.9*‡	3.8 ± 0.7
Digit Span	12.5 ± 5.0	12.7 ± 4.8	12.1 ± 5.4	12.5 ± 2.8
Depression	8.9 ± 3.4†	9.1 ± 3.2†	8.7 ± 3.8*	4.6 ± 2.7
Anxiety	5.7 ± 3.8	5.8 ± 4.0	5.4 ± 3.6	5.2 ± 3.6

Data are presented as mean ± SD. Unpaired t test for normally distributed data or Mann-Whitney U test for non-normally distributed data between MSA and control group. One-way analysis of variance and Tukey-Kramer test for data with normal distribution or the Kruskal-Wallis test and Steel-Dwass test for data with non-normal distribution among MSA-C, MSA-P, and control groups.

*$p < 0.01$.

†$p < 0.001$ compared with control.

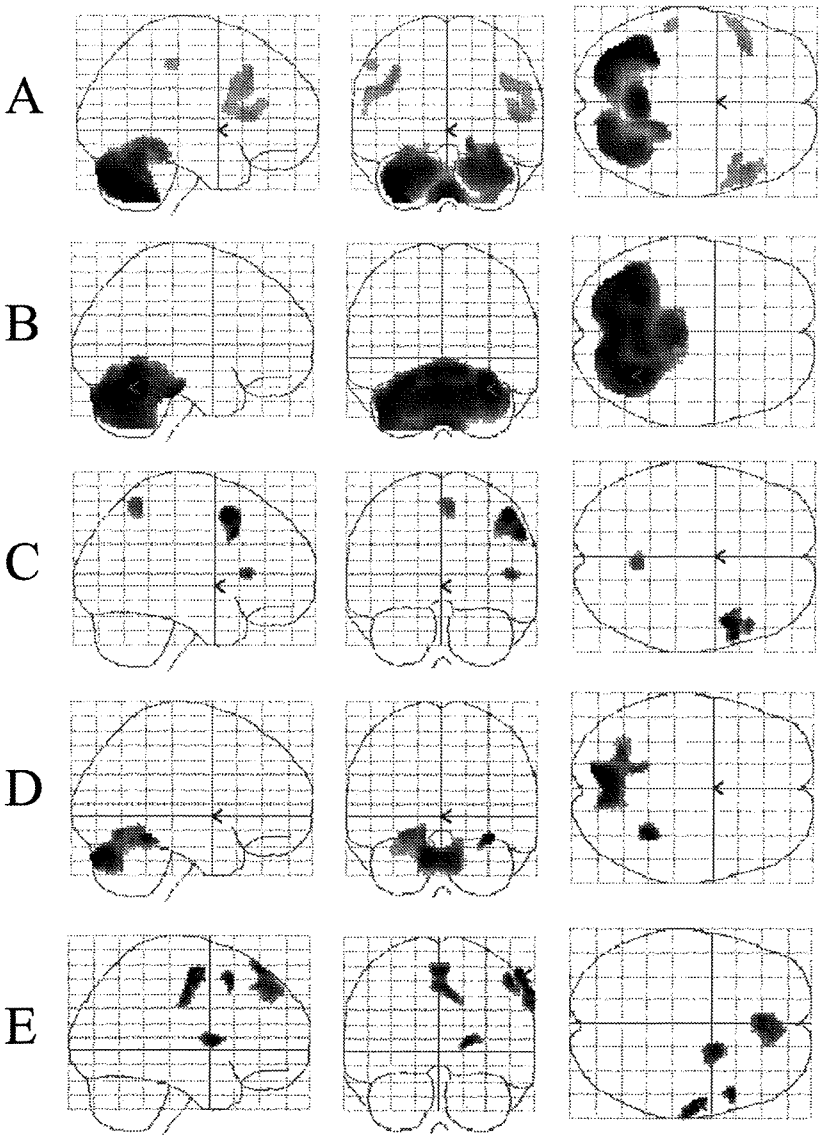
‡$p < 0.05$ compared with MSA-C.

MSA = multiple system atrophy; MSA-C = MSA-cerebellar; MSA-P = MSA-parkinsonism.

The Shapiro-Wilk test was used to assess the normality of continuous variables. For comparison between the MSA group and the control group, we performed the unpaired t test for normally distributed data or the nonparametric Mann-Whitney U test for non-normally distributed data. For comparison among the MSA-C group, MSA-P group, and control group, we performed one-way analysis of variance for data with normal distribution or the Kruskal-Wallis test for data with non-normal distribution. When the p value for this overall comparison was significant (< 0.05), post hoc tests were done with the Tukey-Kramer test for data with normal distribution or Steel-Dwass test for data with non-normal distribution. The p values were subsequently adjusted for multiple comparisons using the Holm-Sidak method. In an attempt to assess the cognitive components of performance independently of motor skills and speed, we created a composite measure of processing speed for each subject by averaging T-transformed values of the time (seconds) demanding Design 1 on the Block Design task and the time (seconds) demanding the preshift phase of the Rule Shift Cards test.[31] Analyses of covariance were also conducted with this composite measure as a covariate when analyzing group differences on those tests in which speed, motor skill, or rapid speech was an important aspect of performance (e.g., Block Design task, phonemic and semantic fluency task). The SPECT data were analyzed using Statistical Parametric Mapping 2 (SPM2; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) implemented in MATLAB 6.5.1 (Math Works, Sherborn, MA). In a preprocessing step, data sets were spatially normalized to a standard stereotactic three-dimensional space and smoothed with an isotropic Gaussian kernel of full width at half maximum 12 mm. All images resulting from the normalization procedure were visually acceptable. In the following analyses, proportional scaling was applied to adjust the mean whole brain activity to 50 mL/100 g per minute to avoid interindividual variation in global cerebral blood flow. The gray matter threshold was 0.8. The normalized images of the patients with MSA-C, patients with MSA-P, and control subjects were compared by voxel-by-voxel t statistics. Confounding effects may arise from age or education differences, which could influence the regional cerebral blood flow change in MSA. Therefore, age and education were inserted as covariates in the SPM analyses. In addition, we compared the images of the patients with MSA-C and those with MSA-P to detect voxels in which the regional cerebral blood flow was significantly correlated with the scores of neuropsychological tests on which patients with MSA-C and those with MSA-P showed impairment. Each value of the neuropsychological tests was used as a covariate of interest, and the values of the global regional cerebral blood flow, age, education, International Cooperative Ataxia Rating Scale, and Unified Parkinson's Disease Rating Scale part-III, which are the relevant factors associated with cognitive performance, were excluded as nuisance variables. Regions were reported as significant if they contained voxels with a value of at least $p < 0.001$, uncorrected for multiple comparisons, with cluster extent threshold (k_E) <10.

RESULTS Comparisons of neuropsychological tests in MSA-C and MSA-P patients. Patients with MSA did not differ significantly from control subjects with regard to MMSE (table 2). However, patients with MSA as a whole showed significant cognitive impairment in several tasks compared with control subjects. Visuospatial and constructional function as tested using Block Design, naming nouns from phonemic and semantic categories, and the Rule Shift Cards test of the Behavioral Assessment of the Dysexecutive Syndrome showed significant impairment. No significant differences were observed between patients with MSA and control subjects in attention (Digit Span) or memory functions, including Logical Memory Subtests 1 and 2 and Visual Paired Associates 1 and 2 of the Revised Wechsler Memory Scale as well as Wisconsin Card-Sorting Test. Scores for depression in patients with MSA were also significantly higher than those of control subjects. The visuospatial and constructional function test assessed by the Block Design task were impaired in both patients with MSA-P and those with MSA-C; however, the corrected p values did not reach the significance level in patients with MSA-C. Visuospatial and constructional function tended to be more severely impaired in patients with MSA-P, although the difference was insignificant. Patients with MSA-P showed signif-

Figure 1 SPM maps comparing brain perfusion among patients with MSA-C, patients with MSA-P, and control subjects (uncorrected $p < 0.001$)



(A) MSA < control, (B) MSA-C < control, (C) MSA-P < control, (D) MSA-C < MSA-P, (E) MSA-P < MSA-C. MSA = multiple system atrophy; MSA-C = MSA-cerebellar; MSA-P = MSA-parkinsonism.

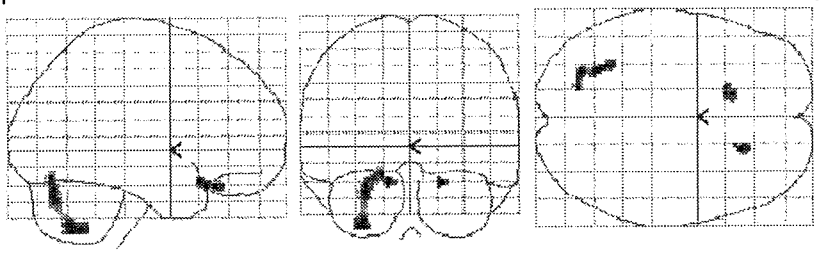
icant impairment of phonemic fluency, semantic fluency, and the Rule Shift Cards test compared with control subjects, whereas patients with MSA-C did not show any significant decrease in these tasks. The score of the Rule Shift Cards test in patients with MSA-P was lower than that of patients with MSA-C ($p < 0.05$). All of the 12 cognitive function tests performed in this study showed a tendency of more severe impairment in patients with MSA-P as compared with patients with MSA-C, although they did not show a significant difference (table 2). After a composite measure of processing speed by averaging T-transformed values of the time (seconds) demanding Design 1 on the Block Design task and the time (seconds) demanding the preshift phase of the Rule Shift Cards test were excluded, patients with MSA still showed impairments on the Block Design, phonemic fluency, and semantic fluency compared with control subjects. After removal of effects of processing speed, the Block Design, phonemic, and semantic fluency tests were impaired in patients with MSA-P compared with control subjects, whereas the impairment of the Block Design test in patients with MSA-C was not significant. Taken together, these results indicate that patients with MSA as a whole are impaired in wide-ranging cognitive functions, whereas patients with MSA-P show more severe and more widespread impairment in cognitive function than patients with MSA-C.

Regional brain perfusions and cognitive dysfunction in MSA-C and MSA-P patients. See tables e-1, e-2, and e-3 (on the *Neurology*® Web site at www.neurology.org) and figures 1, 2, and 3. According to SPM analyses, cerebellar and dorsolateral prefrontal perfusion in patients with MSA was significantly lower than that of the control subjects. Patients with MSA-C showed significantly reduced perfusion in the cerebellar hemisphere compared with control subjects. In contrast, patients with MSA-P showed reduced brain perfusion in the medial frontal cortices and the right dorsolateral prefrontal cortex compared with control subjects. The putamen, pallidum, and caudate nucleus also showed lower perfusion, but the differences were not significant.

When we compared brain perfusion between patients with MSA-C and those with MSA-P, cerebellar perfusion of the patients with MSA-C was decreased significantly compared with that of patients with MSA-P, whereas perfusion in the medial frontal cortices, right motor cortex, and right putamen of patients with MSA-P was decreased significantly compared with that of patients with MSA-C.

When cognitive dysfunction was correlated with regional brain perfusion, there was a positive correlation between the Block Design score and the perfusion in the bilateral prefrontal cortices and left cerebellar hemisphere in patients with MSA-C after age, education, and severity of cerebellar ataxia and parkinsonism were excluded statistically (figure 2). In patients with MSA-P, there was a positive correlation between the Block Design score and the perfusion in the dorsolateral prefrontal cortex, between phonemic fluency score and the perfusion in the dorsolateral prefrontal cortex, and

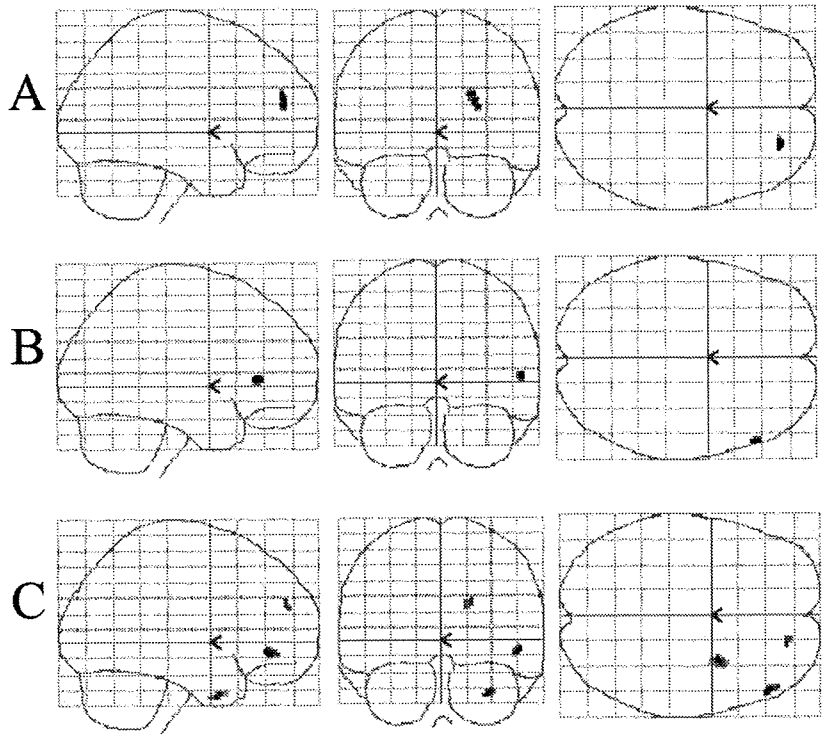
Figure 2 SPM maps of correlation analysis between brain perfusion in patients with multiple system atrophy-cerebellar and cognitive performance (uncorrected $p < 0.001$): Block Design



between the score of the Rule Shift Cards test and the perfusion in the prefrontal and temporal cortices (figure 3).

DISCUSSION Our results show that MSA patients possess visuospatial and constructional dysfunction (Block Design), impairment of verbal fluency, dysexecutive syndrome (Rule Shift Cards test), and depression (Hospital Anxiety and Depression scale); these results are fairly consistent with the results of previous studies.[5-11] In most of the patients with MSA, the MMSE score was not reduced. Therefore, we consider that MMSE is not useful to prove cognitive disturbances in MSA. When we evaluated cognitive impairment separately in patients with MSA-C and those with MSA-P, patients with MSA-P showed wide-ranging cognitive dysfunctions such as visuospatial and constructional dysfunction, impairment of verbal fluency, dysexecutive syndrome, and depression, while patients with MSA-C showed only visuospatial and constructional dysfunction and depression. Furthermore, the cognitive dysfunction in patients with MSA-P showed a tendency to be more severe than that of patients with MSA-C, particularly in executive functions. Thus patients with MSA-P may have more widespread and severe cognitive impairments than patients with MSA-C, although both showed a similar profile of cognitive dysfunction.

Figure 3 SPM maps of correlation analysis between brain perfusion in patients with multiple system atrophy-parkinsonism and cognitive performance (uncorrected $p < 0.001$): (A) Block Design, (B) phonemic fluency, (C) Rule Shift Cards test



Several neurophysiologic reports have shown significant cognitive decline suggesting frontal lobe impairment in patients with MSA. However, it has not been clarified whether frontal lobe or basal ganglia plays a primary role in the manifestation of cognitive impairment, because basal ganglia, which are associated with executive dysfunction, and the frontal or prefrontal area are both involved in MSA, particularly in MSA-P.[32,33] Our results show clearly that patients with MSA-P have significant hypoperfusion in the medial frontal cortices and dorsolateral prefrontal cortex, and the severity of cognitive impairments was significantly correlated with the hypoperfusion in the dorsolateral prefrontal cortex. Furthermore, the scores on the Block Design, phonemic and semantic fluency, and the Rule Shift Cards test were significantly correlated with brain perfusion in the prefrontal cortices after age, education, and severity of cerebellar ataxia and parkinsonism were excluded statistically. Our results support the view that frontal lobe involvement is responsible for the cognitive dysfunction in patients with MSA-P.

In patients with MSA-C, cognitive impairment in visuospatial and constructional dysfunction, assessed by Block Design task, was revealed, although the tendency to be more severely impaired in MSA-C was insignificant after age, education, and severity of cerebellar ataxia and parkinsonism were excluded. Removing only the effect of motor and speech on neuropsychological performances is difficult, because movement disorders and cognitive dysfunctions may progress simultaneously in neurodegenerative diseases and no established method exists. In patients with MSA-C, cognitive impairment in visuospatial and constructional function, assessed by the Block Design task, was correlated with the perfusion in the prefrontal cortex and cerebellum. Involvement of cerebellocortical circuits may also have influence

on the cognitive decline in patients with MSA-C as demonstrated in patients with pure cerebellar involvement.[32-36] The Block Design task is related to spatial visualization, visual–motor coordination, and abstract conceptualization, which require frontal lobe function. Voxel-based morphometry revealed that the frontal lobes, including Brodmann areas 8, 10, 11, 46, and 47, were significantly correlated with the Wechsler Adult Intelligence Scale subtest, including the Block Design.[37] These previous results are consistent with our results, indicating that frontal lobe involvement can be responsible for cognitive dysfunction in patients with MSA-C. We suggest that the performance on cognitive tasks in patients with MSA-C was influenced by various lesions, including those in the cerebellum, cerebellocortical circuits, and the frontal lobe.

In this study, we showed that not only the frontal lobe, but also the posterior parietal lobe, exhibited a significant hypoperfusion in patients with MSA compared with that in control subjects. We also reported a varying degree of progressive cerebral atrophy, particularly in the frontal and temporal lobe, in patients with MSA in an advanced phase.[3] Furthermore, variable atrophy of the corpus callosum is present in a subgroup of patients even at a relatively early course of the illness.[3] More recently, a study based on longitudinal voxel-based morphometry demonstrated brain atrophy of widespread cortical regions such as the primary sensorimotor cortex, supplementary motor area, lateral premotor cortex, medial frontal gyrus, middle frontal gyrus, orbitofrontal cortex, insula, posterior parietal cortex, and hippocampus.[38] In addition, a recent pathologically confirmed case of MSA presenting with frontal executive and semantic language deficits was demonstrated.[39] Taken together, much earlier and more widespread cerebral involvement is present in patients with MSA than has been understood. The present study strongly suggests that parkinsonism, cerebellar ataxia, autonomic failure, and pyramidal tract sign are early and cardinal features of MSA, but cognitive decline is also present widely in MSA, particularly in MSA-P. The pathologic background of these cognitive impairments would be the widespread cortical involvement. Our study also demonstrated that the extent of cognitive involvement is significantly variable among the individual patients, even in those of MSA-P. Factors determining the evolution of cognitive involvement and cerebral involvement in MSA are not clear at present, but certain genetic factors need further study.

It is important to determine whether the cognitive impairments in patients with MSA have any influence on daily life activities. Because many neuropsychological tests and questionnaires are a significant burden to patients with MSA, we can evaluate only limited items at one time. In this study, we evaluated the differences in the cognitive function between patients with MSA-C and patients with MSA-P and the relation to brain perfusion; thus, we could not include the questionnaires to assess daily life activities, particularly in relation to cognitive functions. This relation of daily life activity to cognitive function is an important study to be performed.

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