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RESEARCH ARTICLE

Progressive Brain Atrophy in Multiple System Atrophy: A Longitudinal, Multicenter, Magnetic Resonance Imaging Study

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ABSTRACT: Objective: To determine the rates of brain atrophy progression in vivo in patients with multiple system atrophy (MSA).
Background: Surrogate biomarkers of disease progression are a major unmet need in MSA. Small-scale longitudinal studies in patients with MSA using magnetic resonance imaging (MRI) to assess progression of brain atrophy have produced inconsistent results. In recent years, novel MRI post-processing methods have been developed enabling reliable quantification of brain atrophy in an automated fashion.
Methods: Serial 3D-T1-weighted MRI assessments (baseline and after 1 year of follow-up) of 43 patients with MSA were analyzed and compared to a cohort of

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early-stage Parkinson's disease (PD) patients and healthy controls (HC). FreeSurfer's longitudinal analysis stream was used to determine the brain atrophy rates in an observer-independent fashion.

Results: Mean ages at baseline were 64.4 ± 8.3, 60.0 ± 7.5, and 59.8 ± 9.2 years in MSA, PD patients and HC, respectively. A mean disease duration at baseline of 4.1 ± 2.5 years in MSA patients and 2.3 ± 1.4 years in PD patients was observed. Brain regions chiefly affected by MSA pathology showed progressive atrophy with annual rates of atrophy for the cerebellar cortex, cerebellar white matter, pons, and putamen of −4.24 ± 6.8%, −8.22 ± 8.8%, −4.67 ± 4.9%, and − 4.25 ± 4.9%, respectively. Similar to HC, atrophy rates in PD patients were minimal with values of −0.41% ± 1.8%, −1.47% ± 4.1%, −0.04% ± 1.8%, and −1.54% ± 2.2% for cerebellar cortex, cerebellar white matter, pons, and putamen, respectively.

Conclusions: Patients with MSA show significant brain volume loss over 12 months, and cerebellar, pontine, and putaminal volumes were the most sensitive to change in mid-stage disease. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: multiple system atrophy; MRI; brain atrophy; progression

Multiple system atrophy (MSA) is a rare and rapidly progressive neurodegenerative movement disorder.[1,2] The clinical presentation is variable and includes parkinsonian, cerebellar, autonomic, and pyramidal symptoms. MSA can be subdivided according to the main motor features into a parkinsonian (MSA-P) and a cerebellar (MSA-C) variant.[3] Despite the occurrence of motor symptoms generally thought to be symmetric in MSA patients, asymmetric presentations appear to be common and have been reported in up to 41% of cases in a clinicopathological study[4] and radiotracer imaging studies suggest that lateralized dopamine transporter uptake may not discriminate MSA from related diseases including Parkinson's disease (PD).[5] The lack of therapies that slow or prevent progression in MSA is a major unmet medical need.[6] The use of sensitive and reliable surrogate markers of disease progression and the availability of early markers of target engagement are critical to the success of trials of therapies with putative disease-modifying efficacy. Magnetic resonance imaging (MRI)-based assessments in neurodegenerative diseases include a variety of measures like volumetry, diffusion tensor imaging, and iron quantification, as well as multimodal approaches combining different techniques. Some of these have also been used in clinical trials in MSA to determine biological effects of investigational products.[7,8] Previous longitudinal observational MRI studies in MSA have revealed progressive changes in different parameters and brain regions over time.[9-15] In a study involving nine MSA patients, Paviour et al. were able to demonstrate that pontine atrophy appears to be specific for MSA with annual percent changes reaching 4.5%.[9] Other brain regions showing marked atrophy were the cerebellum and the lateral as well as the third ventricles; however, latter brain regions also showed substantial atrophy in other diseases, including PD, as well as in healthy controls (HC).[9] Another MRI study confirmed the greater volume loss in the pons in a group of 12 MSA patients as compared with HC.[10] A functional MRI study in 13 MSA patients reported that changes over the course of 1 year are exclusively extrastriatal in MSA patients and include a reduction in functional activity in the primary motor cortex, the supplementary motor area, and the superior cerebellum.[11] This finding is also supported by a voxel-based morphometry study showing reduced cortical thickness in the primary motor cortex and the supplementary motor area.[14] In addition to macrostructural changes,[9,10,12,14] changes in iron-sensitive sequences[12] and diffusion-tensor imaging[10,13] have been reported. Overall, pontine, putaminal, and cerebellar atrophy were the most commonly reported areas affected by progressive MSA pathology.

A major limitation of these studies is their single-center design and the resultant small sample sizes. In addition, most studies used methods that were developed to analyze MRI cross-sectionally which likely introduces inherent noise and may obscure individual differences resulting in biased and heterogeneous measurements.[16] In recent years, novel MRI post-processing methods have been developed to provide more reliable longitudinal quantification of brain atrophy.[16]

In the present work, we sought to establish annual progression rates of brain atrophy exploiting a well-characterized post-processing pipeline. To this end, we analyzed imaging data of MSA patients from a substudy of a large clinical trial and a prospective, observational cohort study and compared these data to HC as well as PD patients.

Methods

Source of Data

MSA Patients

Two independent studies were exploited to recruit 43 MSA patients with possible or probable MSA according to the second MSA consensus diagnostic

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criteria[17]: (1) the MSA-Ras trial[7] and (2) a prospective observational study[18,19] conducted by the French MSA Reference Center. Patients with predominantly parkinsonian features were designated MSA-P, whereas patients with predominantly cerebellar ataxia were designated MSA-C.[17]

The MSA-Ras study was a multicenter, randomized, double-blind, placebo-controlled study (NCT00977665) sponsored by Teva Pharmaceutical Industries, Ltd (Netanya, Israel) and H. Lundbeck (Valby, Denmark) investigating the effects of rasagiline on symptom progression in patients with a diagnosis of possible or probable MSA-P according to consensus criteria.[7,17] The study period was 48 weeks and inclusion criteria were defined to capture early disease stages (<3 years from the time of documented MSA diagnosis, anticipated survival of at least 3 years, and exclusion of patients with severe orthostatic symptoms, severe impairment of speech, swallowing, and ambulation and/or ≥1 falls per week). Clinical progression was assessed at baseline and weeks 12, 24, 36, and 48 using the Unified Multiple System Atrophy Rating Scale (UMSARS) total, motor, and activity of daily living (ADL) scores[20] and did not show an effect of rasagiline 1 mg on clinical progression. Ten of 40 participating study sites met technical requirements (eg, correct equipment and adequate training) and enrolled 40 MSA patients into a MRI substudy. All patients recruited at the MRI sites were invited to participate in the MR substudy[7,21] The study was undertaken in accordance with Good Clinical Practice and the provisions of the International Conference on Harmonisation with all patients providing informed and written consent for both the overall study and the substudy.[7] Only patients who had two scans 48 weeks apart were considered for the present analysis (n = 23).

For the French observational MSA study, MSA patients were consecutively enrolled from the outpatient clinics of the Toulouse/Bordeaux MSA Reference Center (NCT02428816).[18,19] Inclusion criteria were minimal and included: (1) a diagnosis of MSA according to established international diagnostic criteria; (2) Hoehn and Yahr score <4 on treatment; (3) negative history of neurological or psychiatric diseases other than PD or MSA; (4) Mini-Mental State Examination (MMSE) score >24; (5) no treatment with deep brain stimulation; and (6) no evidence of movement artifacts, vascular brain lesions, brain tumor, and/or marked cortical and/or subcortical atrophy on MRI scan (two expert radiologists examined all MRIs to exclude potential brain abnormalities as apparent on conventional fluid-attenuated inversion recovery (FLAIR), T2-weighted, and T1-weighted images).[18,19] Twenty MSA patients underwent serial 3T MRI examinations; at time of inclusion and after 1 year of follow-up. Clinical progression was assessed at these two time points using UMSARS. The Toulouse Clinical Investigation Center and the INSERM U825 MRI technical platform supported this study.

Control Cohort

Some 19 HC and 14 PD patients were retrospectively selected from the MRI database of the Medical University Innsbruck. HC and PD patients having serial 3T MR scans 12 months apart were included in the present study. All PD patients had to fulfill diagnostic criteria for PD.[22]

Clinical Assessments

In MSA patients, the motor examination part of the disease-specific UMSARS was used to evaluate the severity of motor symptoms.[20] The motor subscale of the UMSARS ranges from 0 to 56 points and higher scores indicate greater disability. The motor evaluation part of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was exploited to define the extent of motor impairment in PD patients.[23] MDS-UPDRS motor examination scores range from 0 to 132 points and higher scores indicate greater disease burden. In all patients, the Montreal Cognitive Assessment (MoCA), ranging from 0 to 30 points, was used as a screening assessment for detecting cognitive deficits. PD patients were tested in the ON medication state.[24]

Imaging Analysis

In all participants, the MR scanner (vendor and type), the MR sequence, as well as the head coils were identical at baseline and follow-up. 3D-T1 images were acquired on 1.5T (MSA-Ras study, Siemens Avanto) and 3T machines (Innsbruck PD cohort [Siemens Verio], HC [Siemens Verio], and French MSA patients [Philips]). Details of the MR sequences are provided in Table S1.

Based on previous MRI studies[25] as well as clinicopathological reports,[26] the putamen (both hemispheres separately), the cerebellar white matter (both hemispheres separately), the cerebellar gray matter (both hemispheres separately), the midbrain, and the pons were considered as brain regions chiefly affected by MSA pathology. We have only evaluated longitudinal changes in the aforementioned brain regions for the present study. Longitudinal volume estimates for these regions were derived from the T1 images using the volume and longitudinal streams of FreeSurfer (http://surfer.nmr.mgh.harvard.edu/[27]).

FreeSurfer is a well-established neuroimaging tool which provides quantitative measures of brain morphology. Extensive technical details on FreeSurfer are described in prior publications.[16,28-34] Briefly, the volumetric stream of FreeSurfer consists of five steps (explained in detail in Fischl et al.[30]). First, an affine

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registration to MNI305 space is estimated. Then, an initial labeling of the tissue is performed and a correction for intensity variation caused by the B1 bias field is executed. Finally, a nonlinear alignment of the volume to the MNI305 atlas is obtained and labeling of individual voxels is performed by aligning a probabilistic atlas from MNI305 space to the subject's brain and obtaining the maximum a posteriori segmentation of a Bayesian formulation of the segmentation problem. Volumes estimated are obtained from the regional labels by applying a partial volume correction to account for the contribution of multiple tissue classes to individual voxels and summing the corrected contribution of each class.

FreeSurfer's longitudinal stream is used to obtain unbiased estimates of volume changes over time.[16] The longitudinal T1 images are processed with following three steps. First, a cross-sectional processing is performed with all time points of all subjects being assessed independently and results in a full image segmentation and surface reconstruction for each time point/subject. Second, for each subject a template is created from all time points to estimate average subject anatomy. The software package creates an unbiased within-subject template space and image by using robust, inverse consistent registration as described previously.[31] Finally, several processing steps, such as skull stripping, Talairach transforms, and atlas registration, are then initialized with common information from the within-subject template and the individual runs.[16]

In our analysis, the most affected brain region was defined as the brain region with the largest atrophy rate in each individual participant (considering both hemispheres for putamen, cerebellar white, and grey matter). Atrophy rate per year was estimated using the symmetrized percent change in volume (ie, the rate with respect to the average between the two time points). The asymmetry index (AI) of imaging measures was calculated on annual percent changes of the regions of interest by applying the following formula: $\mathrm{AI} = \frac{(\mathrm{Right}-\mathrm{Left})}{(\mathrm{Right}+\mathrm{Left})}$.

Statistical Analysis

Data analysis was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria). Demographic data are presented as frequencies, means ± standard deviations, or median (interquartile range) according to data distribution. Gaussian distribution was confirmed by visual interpretation of the Q–Q (quantile–quantile) plots and the Kolmogorov–Smirnov test. Participants were assigned to the following diagnostic categories: MSA (subclassification into MSA-P and MSA-C), PD, and HC. Group differences for demographic variables, clinical variables, and imaging measures were assessed using parametric tests (analysis of variance [ANOVA] or Welch's *t*-test as applicable) for continuous and normally distributed variables, nonparametric tests (Kruskal–Wallis one-way ANOVA by ranks or Mann–Whitney U test) for non-normal continuous variables, and Pearson's chi-square tests and Fisher's exact tests for categorical variables. Age and sex were included as covariates in the ANOVA model evaluating group differences in brain atrophy progression. Longitudinal changes (ie, symmetrized percent change deviates from zero) were tested using Wilcoxon's signed-rank test. The UMSARS II (motor examination part) as well as baseline disease duration were correlated with imaging measures (percentage change per year in cerebellar white matter [more affected side], cerebellar cortex [more affected side], pons, putamen [more affected side], and the most affected brain region) using Pearson's or Spearman's correlation coefficients, as appropriate. Holm's correction was used to correct for multiple testing in correlation analyses. Bonferroni's correction for multiple testing was applied to the ANOVA post-hoc tests and Wilcoxon's signed-rank test evaluating longitudinal changes. The distribution of asymmetry indexes against zero was tested using Wilcoxon's signed-rank test.

Results

Fifty-eight evaluable patients (43 MSA and 15 PD subjects) and 19 HC were included in the present analysis. The MSA patients, PD patients, and HC were comparable regarding gender distribution ($P = 0.100$), age at baseline visit (HC: 59.8 ± 9.2, MSA: 64.4 ± 8.30, PD: 60.0 ± 7.5, $P = 0.130$), and age at symptom onset (MSA: 60.3 ± 8.8, PD: 57. 7 ± 7.7, $P = 0.300$). Across the different study cohorts, disease duration at baseline was significantly longer in the French MSA cohort (5.2 ± 2.1 years) as compared with the other two cohorts (MSA-Ras study: 3.1 ± 2.4, PD cohort: 2.3 ± 1.4) and, among the two MSA cohorts, patients in the French cohort were more severely affected as indicated by higher UMSARS scores (26.6 ± 7.7 vs. 17.5 ± 4.5 for the French MSA cohort and the MSA-Ras study, respectively; Table S3). Among MSA subtypes, MSA-C patients had greater severe disease severity as reflected by higher UMSARS scores (MSA-C: 26.3 ± 5.5; MSA-P: 20.2 ± 7.7). Detailed demographics and basic clinical information are summarized in Tables 1 and S2.

Progression Rates

Statistically significant longitudinal changes were observed in most of the studied brain regions in MSA patients (Tables 2, 3, and S3). In detail, there was marked progression of atrophy in MSA patients in infratentorial brain regions (cerebellar cortex, cerebellar

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TABLE 1 *Population characteristics across the different disease categories*

Characteristic	HC (N = 19)	MSA (N = 43)	PD (N = 15)	*P*-value[a]	MSA-C (N = 11)	MSA-P (N = 32)	PD (N = 15)	*P*-value[b]
Sex, n (%)				0.10				0.5
Female	14/19 (74%)	21/43 (49%)	6/15 (40%)		7/11 (64%)	14/32 (44%)	6/15 (40%)	
Male	5/19 (26%)	22/43 (51%)	9/15 (60%)		4/11 (36%)	18/32 (56%)	9/15 (60%)	
Diagnostic certainty at baseline[c], n (%)				>0.9				0.078
Possible MSA	NA	23/43 (53%)	NA		3/11 (27%)	20/32 (63%)	NA	
Probable MSA	NA	20/43 (47%)	NA		8/11 (73%)	12/32 (38%)	NA	
Age at baseline visit, years (baseline)	59.81 (9.19)	64.40 (8.30)	60.00 (7.49)	0.13	62.18 (5.44)	65.17 (9.02)	60.00 (7.49)	0.12
Age at symptom-onset, years (baseline)	NA	60.28 (8.76)	57.67 (7.72)	0.3	56.91 (6.07)	61.44 (9.31)	57.67 (7.72)	0.12
Disease duration, years (baseline)	NA	4.09 (2.45)	2.33 (1.35)	0.014	5.23 (2.02)	3.70 (2.48)	2.33 (1.35)	0.007
UMSARS II (baseline)	NA	21.72 (7.63)	NA		26.27 (5.50)	20.16 (7.69)	NA	0.005
UPDRS III (baseline)	1.42 (1.26)	NA	25.20 (8.01)	<0.001	NA	NA	25.20 (8.01)	
MoCA (baseline)	NA	26.33 (3.48)	25.40 (2.85)	0.14	26.64 (3.11)	26.22 (3.63)	25.40 (2.85)	0.3
Dopaminergic therapy, n (%) (baseline)	NA	27/43 (63%)	15/15 (100%)	0.006	3/11 (27%)	24/32 (75%)	15/15 (100%)	<0.001
Relative contribution of different studies to the disease groups, n (%)								
MSA-Ras study	0/19 (0%)	23/43 (53%)	0/15 (0%)		0/11 (0%)	23/32 (72%)	0/15 (0%)	
French MSA cohort	0/19 (0%)	20/43 (47%)	0/15 (0%)		11/11 (100%)	9/32 (28%)	0/15 (0%)	
PD cohort	0/19 (0%)	0/43 (0%)	15/15 (100%)		0/11 (0%)	0/32 (0%)	15/15 (100%)	
HC cohort	19/19 (100%)	0/43 (0%)	0/15 (0%)		0/11 (0%)	0/32 (0%)	0/15 (0%)	

[a]Pearson's chi-squared test; Fisher's exact test; Kruskal–Wallis rank-sum test.
[b]Fisher's exact test; Kruskal–Wallis rank-sum test.
[c]Diagnostic certainty was classified according to the MSA diagnostic criteria.
Abbreviations: HC, healthy controls; MSA, multiple system atrophy; PD, Parkinson's disease; MSA-C, cerebellar MSA variant; MSA-P, parkinsonian MSA variant; NA, not applicable; UMSARS II, Unified Multiple System Atrophy Rating Scale Part II; UPDRS III, Unified Parkinson's Disease Rating Scale Part III; MoCA, Montreal Cognitive Assessment.

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TABLE 2 *Atrophy rates of selected brain regions by diagnosis*

Characteristic	HC (N = 19)[a]	MSA (N = 43)[a]	PD (N = 15)[a]	*P*-value[b]	*P*-value, age-, and sex-adjusted model[c]	Effect sizes (MSA) (N = 43)[d]
Cerebellum cortex (left)[a]	−0.44 (1.47)	**−3.30 (6.12)**[f]	0.09 (2.23)	0.021 HC vs. MSA: 0.10 HC vs. PD: >0.9 MSA vs. PD: 0.061	0.022	−0.54 (−1.17–0.09)
Cerebellum white matter (left)[a]	−0.62 (2.88)	**−6.15 (8.73)**[f]	−0.52 (3.96)	0.003 HC vs. MSA: 0.015 HC vs. PD: >0.9 MSA vs. PD: 0.025	0.004	−0.70 (−1.34–0.07)
Putamen (left)[a]	−1.17 (1.76)	−2.42 (4.92)	−0.70 (2.96)	0.3 HC vs. MSA: 0.8 HC vs. PD: >0.9 MSA vs. PD: 0.5	0.280	−0.49 (−1.12–0.13)
Cerebellum cortex (right)[a]	−0.24 (1.36)	**−3.29 (6.97)**[f]	−0.12 (1.72)	0.047 HC vs. MSA: 0.13 HC vs. PD: >0.9 MSA vs. PD: 0.2	0.047	−0.47 (−1.10–0.15)
Cerebellum white matter (right)[a]	−0.64 (2.22)	−5.43 (9.52)	−0.68 (4.47)	0.026 HC vs. MSA: 0.071 HC vs. PD: >0.9 MSA vs. PD: 0.12	0.028	−0.57 (−1.20–0.06)
Putamen (right)[a]	−1.01 (1.65)	−2.45 (4.40)	−0.61 (2.14)	0.14 HC vs. MSA: 0.4 HC vs. PD: >0.9 MSA vs. PD: 0.3	0.146	−0.56 (−1.18–0.07)
Cerebellum cortex (more affected hemisphere)[a]	−0.65 (1.37)	**−4.24 (6.78)**[f]	−0.41 (1.76)	0.011 HC vs. MSA: 0.044 HC vs. PD: >0.9 MSA vs. PD: 0.050	0.011	−0.63 (−1.26–0.01)
Cerebellum white matter (more affected hemisphere)[a]	−1.33 (2.57)	**−8.22 (8.80)**[f]	−1.47 (4.10)	<0.001 HC vs. MSA: 0.002 HC vs. PD: >0.9 MSA vs. PD: 0.006	<0.001	−0.93 (−1.58 to −0.29)
Putamen (more affected hemisphere)[a]	**−1.48 (1.69)**[f]	**−4.25 (4.87)**[f]	−1.54 (2.18)	0.011 HC vs. MSA: 0.034 HC vs. PD: >0.9 MSA vs. PD: 0.068	0.012	−0.87 (−1.52 to −0.23)
Midbrain[a]	−0.79 (1.81)	**−1.53 (2.79)**[f]	0.02 (1.55)	0.089 HC vs. MSA: 0.8 HC vs. PD: >0.9 MSA vs. PD: 0.10	0.084	−0.55 (−1.17–0.08)
Pons[a]	−0.42 (0.98)	**−4.67 (4.88)**[f]	−0.04 (1.77)	<0.001 HC vs. MSA: <0.001 HC vs. PD: >0.9 MSA vs. PD: <0.001	<0.001	−0.96 (−1.61 to −0.31)
Most affected brain region[a,e]	**−2.77 (1.49)**[f]	**−11.51 (7.63)**[f]	**−3.45 (3.35)**[f]	<0.001 HC vs. MSA: <0.001 HC vs. PD: >0.9 MSA vs. PD: <0.001	<0.001	−1.51 (−2.21 to −0.81)
UMSARS II	NA (NA)	−4.51 (5.40)	NA (NA)	NA	NA	−0.84 (−1.49 to −0.18)

[a]Percent change per year reported as mean (standard deviation).
[b]One-way ANOVA with Bonferroni-corrected post-hoc tests.
[c]Age- and sex-adjusted ANCOVA model.
[d]Cohen's D (95% confidence interval).
[e]Most affected brain region was defined as the largest rate of decline of the following brain areas: putamen (both hemispheres), cerebellum white matter (both hemispheres), cerebellum gray matter (both hemispheres), brainstem, and pons.
[f]Statistically significant longitudinal changes (also indicated by bold type).
Abbreviations: HC, healthy controls; MSA, multiple system atrophy; PD, Parkinson's disease; UMSARS II, Unified Multiple System Atrophy Rating Scale Part II; NA, not applicable.

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TABLE 3 *Atrophy rates of selected brain regions by multiple system atrophy subtypes*

Characteristic	MSA-P (N = 32)[a]	MSA-C (N = 11)[a]	*P*-value[b]
Cerebellum cortex (left)	−1.80 (2.45)	−7.68 (10.49)	0.094
Cerebellum white matter (left)	−5.91 (7.50)	−6.83 (12.03)	0.8
Putamen (left)	−3.01 (4.93)	−0.73 (4.70)	0.2
Cerebellum cortex (right)	−1.80 (3.32)	−7.62 (11.93)	0.14
Cerebellum white matter (right)	−4.94 (7.03)	−6.83 (14.98)	0.7
Putamen (right)	−2.38 (4.76)	−2.64 (3.32)	0.8
Cerebellum cortex (more affected hemisphere)	−2.60 (2.88)	−9.00 (11.56)	0.10
Cerebellum white matter (more affected hemisphere)	−7.56 (7.60)	−10.14 (11.86)	0.5
Putamen (more affected hemisphere)	−4.70 (5.19)	−2.94 (3.71)	0.2
Midbrain	−1.17 (2.62)	−2.59 (3.15)	0.2
Pons	−3.45 (4.37)	−8.22 (4.71)	**0.009**[d]
Most affected brain region[c]	−10.19 (6.05)	−15.35 (10.43)	0.14
UMSARS II	−4.50 (5.45)	−4.55 (5.50)	>0.9

[a]Percent change per year reported as mean (standard deviation).
[b]Welch's two-sample *t*-test.
[c]Most affected brain region was defined as brain area with the largest rate of decline out of the following disease-specific brain areas: putamen (both hemispheres), cerebellum white matter (both hemispheres), cerebellum gray matter (both hemispheres), brainstem, and pons.
[d]Statistically significant longitudinal changes (also indicated by bold type).
Abbreviations: MSA, multiple system atrophy; MSA-P, parkinsonian MSA variant; MSA-C, cerebellar MSA variant; UMSARS II, Unified Multiple System Atrophy Rating Scale Part II.

white matter, pons) with annual volume loss ranging from −2.60% (more affected side based on the degree of atrophy of the cerebellar cortex, MSA-P patients) to −10.14% (more affected side of the cerebellar white matter, MSA-C patients), while putaminal volume loss over time was less pronounced and ranged from −2.94 (more affected side in MSA-C patients) to −4.70% (more affected side in MSA-P patients) (Tables 2 and 3). In contrast, PD patients and HC showed significantly lower progression rates in the more affected hemisphere of the cerebellar cortex (omnibus test: $P = 0.011$, HC vs. MSA: $P = 0.044$, HC vs. PD: $P > 0.9$, MSA vs. PD: $P = 0.050$), the cerebellar white matter (omnibus test: $P < 0.001$, HC vs. MSA: $P = 0.002$, HC vs. PD: $P > 0.9$, MSA vs. PD: $P = 0.006$), and the putamen (omnibus test: $P = 0.011$, HC vs. MSA: $P = 0.034$, HC vs. PD: $P > 0.9$, MSA vs. PD: $P = 0.068$), as well as the pons (omnibus test: $P < 0.001$, HC vs. MSA: $P < 0.001$, HC vs. PD: $P > 0.9$, MSA vs. PD: $P = <0.001$).

When considering only the most affected brain region across the different regions of interest in every individual patient (any of the infratentorial compartments or the putamen), progression rates of volume loss ranged from −10.19% in MSA-P patients to −15.35% in MSA-C patients, while the progression rate in HC and PD patients were similar and remained low at −2.77% and −3.45%, respectively. Atrophy progression in PD patients did not differ significantly from HC (all P values > 0.9) and observed progression rates were as low as −0.41%, −1.47%, −0.04%, and −1.54% for cerebellar cortex (more affected hemisphere), cerebellar white matter (more affected hemisphere), pons, and putamen (more affected hemisphere), respectively.

Pattern of Atrophy

Furthermore, there was considerable interindividual and intergroup variability in MSA patients in the patterns of atrophy with some patients showing predominant putaminal atrophy, others showing predominant cerebellar atrophy, and some patients having a mixed pattern of atrophy progression (Fig. 1). The latter was also owing to differences between the two MSA cohorts due to the fact that the frequency of MSA subtypes was different between the two cohorts (the French MSA cohort included both MSA-P and MSA-C patients whereas the MSA-Ras cohort was composed of MSA-P patients only; Table S4). While at least one of the infratentorial brain regions showed a numerically larger atrophy rate compared to the putamen in both MSA-C and MSA-P patients, a significant difference between MSA subgroups was only observed in the pons ($P < 0.001$).

Within individual MSA patients, there was significant asymmetry of atrophy progression at the putaminal

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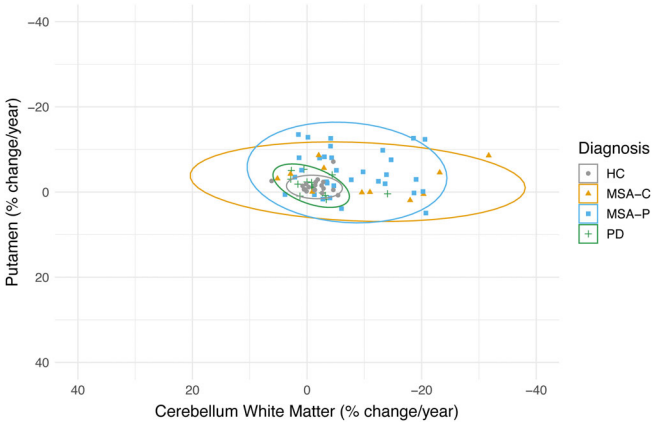

FIG. 1. Pattern of progression of brain atrophy in multiple system atrophy. Rate of change expressed as percent change per year from baseline. Elliptical areas represent the 95% confidence interval of the data for the different groups assuming a Student's *t*-distribution. HC, healthy controls; MSA, multiple system atrophy, MSA-C, cerebellar MSA variant; MSA-P, parkinsonian MSA variant; PD, Parkinson's disease. [Color figure can be viewed at wileyonlinelibrary.com]

level ($P = 0.036$; Fig. 2A), while no asymmetry was observed at the cerebellar level (Fig. 2B).

Effect Sizes in MSA Patients and Correlation Analysis

The effect sizes of progression of brain atrophy in MSA patients exceeded clinical progression in many of the evaluated brain regions (Table 2). Importantly, the effect size of the annual change of the most affected brain region exceeded the effect size of annual UMSARS Part II decline by almost two-fold (Table 2).

In MSA patients, there was a significant correlation between clinical progression as measured by the difference of UMSARS Part II (motor examination) scores between baseline and follow-up and annual volume loss in the most severely affected brain region, the pons and the cerebellar white matter (Fig. 2C). Baseline disease duration was not correlated with progression rates.

Discussion

Biomarkers of disease progression are a critical requirement for the development of disease-modifying interventions in neurodegenerative parkinsonian disorders including MSA. While MRI measures of brain atrophy have been assessed in previous longitudinal studies involving MSA patients,[9-15] sample sizes were small and methodological concerns have limited conclusions about their validity as measures of disease progression. The development of novel post-processing methods meanwhile allows standardized and reliable quantification of brain atrophy in an observer-independent fashion.[16] Using such techniques, we have analyzed annual change rates of brain volume in MSA based on longitudinal MR imaging data from two MSA cohorts: one consisting of participants of the MRI substudy of a multicenter MSA disease modification trial[7] and the other of a prospective, observational cohort from the French MSA reference centre. MRI data from a longitudinally assessed group of PD patients and HC were analyzed for reference. Recapitulating the setting of a multicenter clinical trial, our study used multiple different MRI machines from different vendors for data acquisition. In the first MSA dataset, MR scans had been acquired on a 1.5T MRI machine, while the second MSA study had used a 3T scanner for image acquisition. All PD patients were scanned on a 3T MRI scanner. The present results indicate that infratentorial brain regions are more sensitive to change over time in MSA as compared to the putamen. The annual volume loss of cerebellar regions of interest and the pons was consistent across MSA motor phenotypes and study cohorts, while putaminal atrophy rates showed some discrepancy in the datasets examined here. Not surprisingly, longitudinal changes in the putamen were observed in MSA-P patients, while putaminal volume loss did not differ between patients with MSA-C and PD. With regards to differences between MSA subtypes, MSA-C patients showed numerically larger progression rates, although a statistically significant difference was only observed in the pons. Annual volume loss of the most affected brain region were 10.2%/year and 15.4%/year for MSA-P and MSA-C patients, respectively, and exceeded 11%/year in both datasets (combining motor phenotypes), which is larger than what was observed in previous studies using voxel-based morphometry (VBM) techniques. Paviour et al.[9] reported a maximum decline for the pontine region (−4.5%/year) and Lee et al.[12] for the putamen (5.8%/year). Other longitudinal studies evaluated serial brain MRIs only at a group level which makes it impossible to reliably calculate annual change rates.[10,14] Nonetheless, there is consistency across all longitudinal volumetric MR studies of MSA patients (including the present study) regarding progressive volume loss of brain regions known to be affected by MSA pathology. Intriguingly, the effect size of the observed brain atrophy in the most affected brain region exceeded the effect size of UMSARS progression by almost two-fold. This finding, together with the observation that clinical progression correlates with imaging progression, suggests that the present imaging biomarker anticipates clinical progression and therefore qualifies as at least a medium-grade surrogate marker of disease progression according to a recently published framework proposal for the study of atypical parkinsonism.[35]

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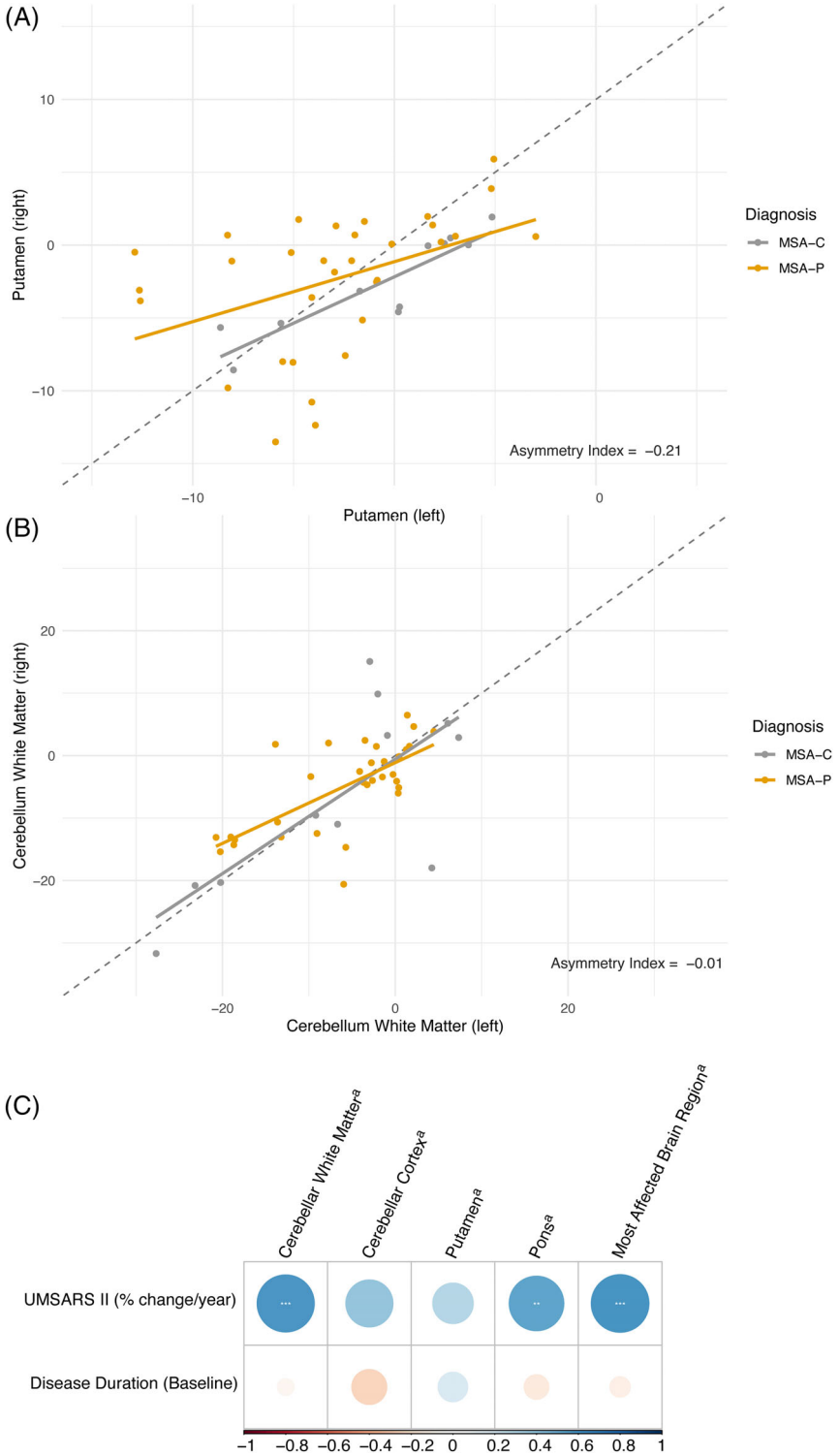

FIG. 2. Asymmetry of percent change per year in individual patients and correlation matrix of UMSARS II progression and baseline disease duration by percent change per year. (A) Symmetry of percent change per year at the putaminal level. (B) Symmetry of percent change per year at the cerebellar level. (C) Correlation matrix of UMSARS II progression and baseline disease duration by percent change per year. Percent changes per year are plotted on the x- and y-axes in (A, B); (C) shows correlation coefficients with the color gradient and the size of the circle reflecting stronger correlation. **P*-value < 0.05, ***P*-value < 0.01, ****P*-value < 0.001. [a]Percent change/year of the more affected side. MSA, multiple system atrophy; MSA-C, cerebellar MSA variant; MSA-P, parkinsonian MSA variant; UMSARS II, Unified Multiple System Atrophy Rating Scale Part II. [Color figure can be viewed at wileyonlinelibrary.com]

By contrast, atrophy rates in our reference sample of PD patients were significantly lower with annual change rates of 1.7%/year for the most affected putamen and of 3.6%/year for the most affected brain region overall. These results in PD are similar to those reported in a previous study exploiting the same post-processing pipeline.[36]

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Overall, brain atrophy observed in MSA patients in our study is multiple folds larger compared to results of a study evaluating brain atrophy in a healthy elderly population,[37,38] which reported annual, region-of-interest (ROI)-based change rates of around 0.5%/year (selected annual change rates: putamen = −0.43%/year, cerebellar white matter = −0.57%/year).

Although motor presentation in MSA patients is commonly considered to show little laterality, our imaging data suggest that there are interindividual differences regarding the more severely affected hemisphere, particularly at the putaminal level (Fig. 2), which is in line with a previous clinicopathological study reporting asymmetry in post-mortem-verified cases.[39] Reasons underlying this asymmetry remain similarly elusive as they are for the motor asymmetry of PD. However, these interindividual differences regarding the predominantly affected hemisphere and brain region (ie, putamen, cerebellar white, or gray matter) as demonstrated by the pattern of atrophy progression (Figs 1 and 2) introduce noise which can negatively affect the calculation of sample sizes for interventional studies using this MRI outcome measure. To reduce between-subject variability, we considered the largest negative change rate value out of the putamen, cerebellar white matter, and cerebellar gray matter to best reflect each patient's individual pattern of disease progression, and using this measure led to a significant reduction of standard deviations. This observation, as well as the consistently large progression rates, support the use of our approach as a sensitive progression marker for future trials. Moreover, progression of the most prominently affected brain region in every individual patient parallels each patient's clinical progression as indicated by correlation analysis.

In the present study, the post-processing of each MRI time point was initiated with common information from an individual subject template for each participant. This approach results in an unbiased longitudinal image analysis through reduction of variability and avoidance of over-regularization.[16] The present work clearly demonstrates that these advanced methods can be applied in MSA research and future clinical studies will benefit from these observations. The reductions in variability increase statistical power and the use of automated analyses will facilitate the central reading of structural MRIs.

Some limitations need to be acknowledged. In the absence of autopsy confirmation, we cannot exclude a possible misdiagnosis as a confounder of interindividual variation of volumetric progression. However, patients had been recruited in highly experienced clinical centers that apply validated diagnostic criteria. In addition, patients' mean duration of disease at time of baseline MRI was between 3 and 5 years. Both factors enhanced the clinical diagnostic accuracy of patients in this cohort. Of note, the present sample had a mean duration of MSA-related symptoms of about 4 years at our study's baseline, and future research is needed to define atrophy rates in patients in earlier clinical stages of MSA or even in prodromal MSA.

In conclusion, patients with MSA show significant brain volume loss over 12 months, and cerebellar, pontine, and putaminal volumes were the most sensitive to change in mid-stage disease. This study's results support the use of MRI as an outcome measure in disease-modification trials in MSA.

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Data Availability Statement

Restrictions apply to the availability of these data, which were used under license for this study.

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Supporting Data

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Financial Disclosures

The authors have nothing to report in relation to this study.

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