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Patterns of brain atrophy in Parkinson's disease, progressive supranuclear palsy and multiple system atrophy☆

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ABSTRACT

Background and purpose: Quantitative analysis of brain atrophy may be useful in differentiating Parkinson's Disease (PD) from Progressive Supranuclear Palsy (PSP) and parkinsonian variant of Multiple System Atrophy (MSA-P); the aim of this study was to identify the volumetric differences of subcortical structures in patients with PD, PSP and MSA-P using a novel and validated fully-automated whole brain segmentation method.
Methods: Volumetric MRIs were obtained in 72 patients with PD, 32 patients with PSP, 15 patients with MSA-P, and in 46 control subjects. Subcortical volume was measured automatically by FreeSurfer. Multivariate analysis of covariance, adjusted for intracranial volume (ICV), sex and age, was used to explore group differences.
Results: No volumetric differences were found between PD and controls group; otherwise the volumes of the cerebellum, the thalamus, the putamen, the pallidum, the hippocampus, and the brainstem were significantly reduced in PSP and MSA-P compared to patients with PD and control subjects. PSP and MSA-P patients only differed in thalamus volume which was smaller in PSP group ($p < 0.001$). Moreover, patients with PSP and MSA-P showed a ventricular system (including lateral, third and fourth ventricles) larger than that detected in PD and controls ($p < 0.001$).
Conclusions: Volumetric data obtained with automated segmentation of cerebral regions show a significant atrophy of different brain structures in parkinsonisms rather than in PD. Our study also demonstrates that the atrophy of the thalamus only occurs in PSP while the enlargement of the whole ventricular system characterizes both PSP and MSA-P.

1. Introduction

Progressive Supranuclear Palsy (PSP) and parkinsonian variant of Multiple System Atrophy (MSA-P) are neurodegenerative disorders that result clinically difficult to differentiate from idiopathic Parkinson's Disease (PD) particularly in the early stages of the diseases, when the clinical typical signs are not clearly evident [1]. Magnetic Resonance Imaging (MRI) is considered helpful to facilitate the diagnosis *in vivo* of patients with PSP, MSA-P or PD, revealing either signal changes or atrophy of specific brain regions [2,3].

In the last few years, several volumetric studies using reliable manual or semi-automated region of interest (ROI) techniques [4,5] have been performed to characterize regional brain volume differences in parkinsonian degenerative disorders. Some of these MRI studies, however, either provided contradictory results [6,7] or failed to discriminate patients with PD from those with other parkinsonian syndromes mainly due to the limitations of structural imaging techniques. The main concerns with manual volumetry are the following: a) this technique is traditionally time-consuming and dependent on rater experience; b) this method provides individual data obtained for each ROI in the native space, without image transformation; c) the precise measurement of subcortical structures requires considerable prior knowledge to select the regions that should be analyzed and therefore constrains the target of the

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study, thus limiting measurements to few selected brain regions. For these reasons, fully automated and reliable methods for measuring the volume of cortical and subcortical regions are highly desirable.

In the present study, we evaluated on MRI the volume of several cerebral regions in patients with PD, MSA-P, PSP and healthy controls by using a relatively new fully-automated segmentation software (FreeSurfer) [8]. This software is a highly reliable method for automated MRI-based measurements of human brain volumes that provides novel insights into abnormal neuroanatomy and may be a useful tool for the investigation of brain changes in patients with neurodegenerative diseases, *in vivo* [9]. The segmentation method provided by this software directly subdivides the image into a series of neuroanatomically defined structures with a priori knowledge of their individual intensity properties, atlas location, and location relative to each other.

2. Methods

2.1. Patients

Clinical diagnosis of PSP, PD, and MSA-P was determined by one of the authors (G.N., with more than 10 years of experience in movement disorders) according to established consensus criteria. The patients were included in the study only whether they fulfilled the proposed criteria for possible or probable PSP, probable PD and probable MSA-P [10–12]. All subjects were recruited from the Neurology Unit of the University "Magna Graecia" of Catanzaro. The controls were partners of the patients or subjects who underwent MRI for mild neurological disorders (i.e. headache) with normal neurological examination and without a history of central nervous system (CNS) diseases.

Thirty-two patients with PSP (21 men, mean age 70.6, mean of disease duration 3.5 y), 15 patients with MSA-P (5 men, mean age 64.2, mean of disease duration 3.0 y), 72 patients with PD (40 men, mean age 63.7, mean of disease duration 6.2 y) and 46 age matched healthy subjects (20 men, mean age 66.7 y) were included in our study. All patients were evaluated clinically by Hoehn–Yahr (HY) staging assessed in "off" condition and examined with MR imaging. All images were before evaluated by a neuroradiologist (P.L.) to detect the presence of signs typically occurring in parkinsonisms, and to exclude abnormal signs in controls. All participants gave their written informed consent to participate in the study, which was approved by the local ethics committee.

2.2. MR imaging scanning and image processing

Brain MRI was performed according to our routine protocol by a 1.5-T unit (Signa NV/I; GE Medical Systems, Milwaukee, WI, USA). All MR imaging examinations included transverse intermediate-weighted and T2-weighted dual-echo fast spin-echo (repetition time ms/echo time ms, 3500/10.2, 85; section thickness, 4 mm; frequency- and phase-encoding matrix, 288 × 224), transverse fluid-attenuated inversion-recovery (repetition time ms/echo time ms/inversion time ms, 8000/120/2000; section thickness, 4 mm; frequency- and phase-encoding matrix, 256 × 224) and transverse T2-weighted gradient-echo (500/15; section thickness, 4 mm; frequency- and phase-encoding matrix, 256 × 192; flip angle, 20°). Structural MRI data were acquired using a 3D T1-weighted spoiled gradient-echo (SPGR) sequence with the following parameters: TR = 15.2 ms; TE = 6.7 ms; flip angle 15°; matrix size 256 × 256; FOV = 24 cm; slice thickness = 1.2 mm. Each SPGR image was visually inspected, and only scans deemed to have no or minimal movement artefacts were included in analyses.

The image protocol was identical for all subjects studied. The image files in DICOM format were transferred to a Linux workstation for morphological analyses. Subcortical volume analysis was measured automatically by FreeSurfer 4.05 installed on a Red Hat Enterprise Linux v.5. This technique has been validated against manual tracings in healthy individuals and in patients with neurological diseases demonstrating high reliability and accuracy in quantifying subcortical structures such as ventricular volumes [13,14]. The automated procedures for volumetric measures of these several subcortical regions have been previously described [8]. This procedure automatically provided segments and labels for up to 40 unique structures and assigned a neuroanatomical label to each voxel in an MRI volume based on probabilistic information estimated automatically from a manually labeled training set. The segmentation used three pieces of information to disambiguate labels: (1) the prior probability of a given tissue class occurring at a specific atlas location, (2) the likelihood of the image given that tissue class, and (3) the probability of the local spatial configuration of labels given the tissue class. Intracranial volume (ICV) was automatically calculated and used to correct the regional brain volumes analyses also considering age and gender.

2.3. Statistical analysis

Group differences in automatically segmented brain regions were analyzed using multivariate analysis of covariance (MANCOVA) adjusted for age, sex and ICV. The difference in sex distribution among groups was evaluated with χ^2-test. One-way analysis of variance was performed for comparison of the age at examination, disease duration, ICV, and age at onset among groups, followed by unpaired *t*-test. To assess the differences in HY "off" stages Kruskall–Wallis test was used, followed by Mann–Whitney U-test. For all pairwise comparisons, the resulting *p*-values were corrected according to Bonferroni method. All tests were two tailed and the *p* level was set at 0.01. Statistical analysis was performed with Statistical Package for Social Science Software (SPSS, version 17.0, Chicago, IL) for Windows.

3. Results

Clinical and demographic data of patients with PSP, MSA-P, PD and control subjects are shown in Table 1. No significant difference was found in gender between all the groups. On the contrary, significant differences in age were identified between PD patients and PSP patients, while disease duration was longer in PD group than in atypical parkinsonism groups. The HY scores were higher in patients with PSP and MSA-P than in patients with PD. All PD patients had a positive response to levodopa whereas only six of 17 patients with MSA-P and three of 25 patients with PSP had a transient positive levodopa response which was short lasting and disappearing within a few months, according to similar results that have been already reported in patients with atypical parkinsonian disorders with pathological confirmation [15].

Table 2 shows the volumes of different brain structures in all subjects. All analyses were corrected for age, gender and ICV. No significant differences in intracranial volume, cerebral cortex, caudate nucleus and amygdala were detected among groups. Otherwise, significant volumetric differences among groups were detected in several brain regions including: cerebellar cortex, thalamus, putamen, pallidum, hippocampus, lateral ventricles, 3th and 4th ventricles and brainstem. Table 3 shows *p*-values for post-hoc comparisons between groups.

3.1. PD vs. controls

Multivariate analysis did not reveal any significant difference in the volumes of different brain structures between PD and control

Table 1
Clinical and demographic characteristics of patients and controls.

	Controls	PD	PSP	MSA-P	*p*-value
Sex, M/F	20/26	40/32	21/11	5/10	0.103
Age, mean ± SD	66.78 ± 6.7	63.78 ± 9.0	70.63 ± 5.3	64.27 ± 4.3	<0.001[a]
Onset, mean ± SD	–	57.58 ± 9.0	67.09 ± 6.8	61.20 ± 4.3	<0.001[a]
Duration disease, mean ± SD	–	6.19 ± 4.5	3.53 ± 3.5	3.07 ± 2.2	0.002[b]
HY, median (range)	–	2 (2–5)	4 (3–5)	4 (2–4)	<0.001[c]

PD = Parkinson's disease; PSP = progressive supranuclear palsy; MSA-P = multiple system atrophy, parkinsonian type.
[a] PD vs. PSP: $p < 0.001$ (unpaired t-test corrected according to Bonferroni).
[b] PD vs. PSP: $p = 0.008$; PD vs. MSA $p = 0.024$ (unpaired t-test corrected according to Bonferroni).
[c] PD vs. PSP: $p < 0.001$; PD vs. MSA $p < 0.001$ (Mann–Whitney test corrected according to Bonferroni).

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Table 2
Volumes [cm^3] of different brain structures measured with an automated volumetric method (FreeSurfer).

	PD	PSP	MSA-P	Controls	*p*-value
Intracranial Volume	1493.30 ± 178.1	1461.08 ± 144.5	1407.06 ± 127.3	1418.89 ± 113.9	n.s.
Cerebral Cortex	405.26 ± 36.0	389.93 ± 38.4	393.14 ± 37.4	401.09 ± 30.1	n.s.
Cerebellar cortex	91.03 ± 10.9	80.90 ± 9.5	73.02 ± 10.4	88.20 ± 8.6	<0.001
Thalamus	12.07 ± 1.3	9.88 ± 1.0	11.20 ± 1.1	11.55 ± 1.1	<0.001
Caudate	6.92 ± 1.1	6.35 ± 0.8	6.13 ± 0.7	6.49 ± 0.7	n.s.
Putamen	9.34 ± 1.2	8.19 ± 0.7	7.14 ± 1.4	9.01 ± 1.1	<0.001
Pallidum	3.12 ± 0.4	2.12 ± 0.2	2.44 ± 0.4	2.93 ± 0.3	<0.001
Hippocampus	6.99 ± 0.8	6.06 ± 0.6	6.31 ± 0.6	6.87 ± 0.7	<0.001
Amygdala	2.59 ± 0.3	2.30 ± 0.3	2.40 ± 0.3	2.44 ± 0.3	n.s.
Lateral ventricles	24.05 ± 14.4	40.35 ± 18.8	27.40 ± 13.4	20.44 ± 12.4	<0.001
3rd ventricle	1.56 ± 0.7	2.48 ± 0.8	1.88 ± 0.5	1.40 ± 0.5	<0.001
4th ventricle	1.91 ± 0.6	2.59 ± 0.6	2.72 ± 1.1	1.69 ± 0.5	<0.001
Brainstem	19.87 ± 2.4	15.51 ± 1.9	14.92 ± 2.8	19.12 ± 2.0	<0.001

Data were expressed as mean ± SD. For each structure, multivariate analysis of covariance (MANCOVA) adjusted for age, sex and ICV was performed. PD = Parkinson's disease; PSP = progressive supranuclear palsy; MSA-P = multiple system atrophy, parkinsonian type.

subjects. Moreover, to confirm whether the gender could have an impact on the detected volume results, we performed a further analysis within the PD group comparing males vs. females. No significant difference was detected for all the examined brain regions.

3.2. PSP patients vs. PD patients and controls

There were several significant volumetric differences that distinguished patients with PSP from patients with PD and healthy controls. The atrophy pattern predominantly involved the cerebellar cortex, the thalamus, the putamen, the pallidum, the hippocampus and the brainstem. Significant differences (all $p < 0.001$) were also found for the lateral ventricles size, for the 3th ventricle size and for the 4th ventricle size. Similar findings resulted also from the comparison of PSP with controls.

3.3. MSA-P patients vs. PD patients and controls

The cerebral regions that resulted more atrophied in MSA-P patients compared with either PD or controls were the cerebellar cortex, the putamen, the pallidum, the hippocampus, the 4th ventricle and the brainstem. Similar findings resulted also from the comparison between PSP and healthy controls, although the 3th ventricle resulted to be significantly enlarged only in the comparison with controls.

3.4. PSP patients vs. MSA patients

The only significant finding that differentiated patients with PSP from those with MSA-P was the atrophy of the thalamus (Fig. 1). No significant differences were found for all other structures.

4. Discussion

To our knowledge, this is the first study to quantify *in vivo* the regional brain atrophy in parkinsonian syndromes using a fully-automated whole brain segmentation method. The main findings of our study are: a) patients with parkinsonian syndromes (PSP and MSA-P) showed marked atrophy in several brain structures including basal ganglia and a marked enlargement of cerebral ventricular system; b) patients with PD did not show evidence of volumetric change in the investigated brain areas with respect to healthy controls; c) the atrophy of the thalamus only occurred in PSP; d) the enlargement of the third ventricle was not a marker suggestive of PSP, because its volume resulted increased in MSA-P patients as well. Furthermore, in addition to the third ventricle, the fourth ventricle and the lateral ventricles volumes were all larger in PSP patients than in PD and controls.

In agreement with previous qualitative and quantitative studies [2,3] our results demonstrated that patients with atypical parkinsonism showed a volume loss in several brain regions. In particular, in patients with PSP and MSA-P with respect to patients with PD or healthy subjects, we found a significant atrophy of the cerebellar cortex, the putamen, the pallidum, the thalamus, the hippocampus and the brainstem and a larger volume of the whole ventricular system. No significant differences were found for intracranial volume, cerebral cortex, caudate nucleus and amygdala among the different groups.

By contrast, according to other VBM studies carried out in PD patients without evidences of dementia [16] or depression [17], the

Table 3
Post-hoc analysis between groups.

	PD vs. Controls	PSP vs. Controls	PSP vs. PD	MSA-P vs. Controls	MSA-P vs. PD	PSP vs. MSA-P
Cerebral Cortex	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Cerebellar cortex	n.s.	0.001	0.001	<0.001	<0.001	n.s.
Thalamus	n.s.	<0.001	<0.001	n.s.	n.s.	<0.001
Caudate	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Putamen	n.s.	0.002	0.002	0.002	<0.001	n.s.
Pallidum	n.s.	<0.001	<0.001	<0.001	<0.001	n.s.
Hippocampus	n.s.	<0.001	<0.001	0.007	n.s.	n.s.
Amygdala	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Lateral ventricles	n.s.	<0.001	<0.001	n.s.	n.s.	n.s.
3rd ventricle	n.s.	<0.001	<0.001	0.005	n.s.	n.s.
4th ventricle	n.s.	<0.001	<0.001	<0.001	<0.001	n.s.
Brain Stem	n.s.	<0.001	<0.001	<0.001	<0.001	n.s.

PD = Parkinson's disease; PSP = progressive supranuclear palsy; MSA-P = multiple system atrophy, parkinsonian type.

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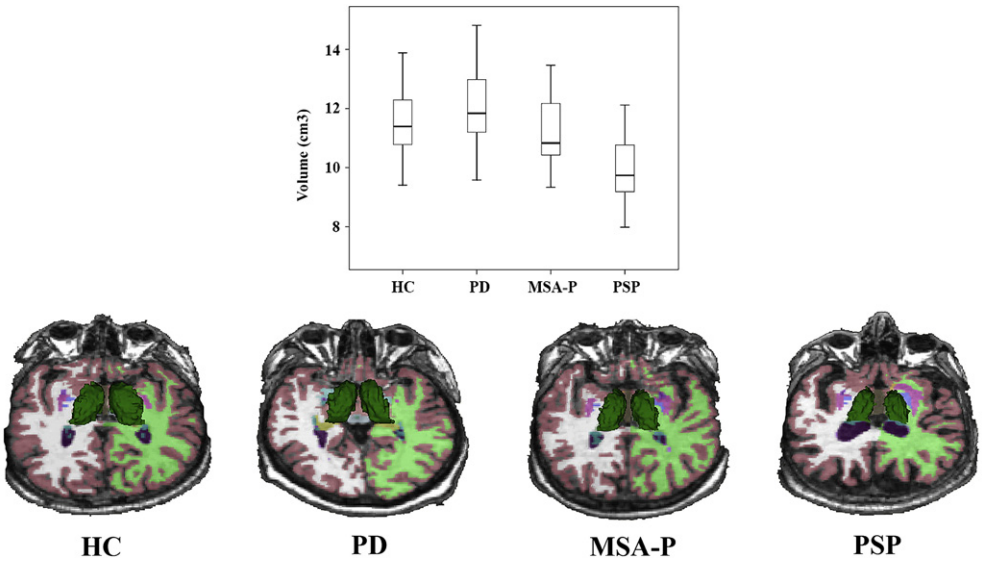

Fig. 1. Three-dimensional surface models created with 3D Slicer v.3 (www.slicer.org) are derived from the *FreeSurfer* subcortical segmentation of the thalamus for a single subject of each group (for display purpose only). Box plots in patients with PSP, patients with MSA-P, patients with PD, and in control participants were showed. Vertical solid lines (whiskers) showed lower and upper values. Box stretches from lower hinge (25th percentile) to upper hinge (75th percentile). Median was shown as line across each box. MANCOVA analysis revealed that the atrophy of the thalamus was the only finding that differentiated patients with PSP from those with MSA-P. HC = healthy controls; PD = Parkinson's disease; PSP = progressive supranuclear palsy; MSA-P = multiple system atrophy, parkinsonian type.

current study demonstrates that brain volumes of patients with idiopathic PD did not differ from those detected in healthy controls.

Furthermore, our study demonstrates that patients with PSP showed the atrophy of the thalamus, a finding not evident in patients with MSA-P and PD. The neuronal loss of the thalamus in patients with PSP was already highlighted by previous neuropathological [18] and voxel based morphometry (VBM) [19] studies which showed atrophy of the thalamus in association with atrophy of different brain areas. In addition, other MRI studies demonstrated thalamus atrophy in PSP in comparison with healthy subjects or with patients affected by corticobasal degeneration [20], and a marked progression of thalamus atrophy was also observed in MSA-P compared to PD [21]. However no volumetric study reported the thalamus as region of interest to differentiate patients with PSP from those with MSA-P. More recently, some authors demonstrated a thalamic involvement, prevalent in the anterior region, by using a diffusion tensor imaging (DTI) study in patients with PSP [22]. At the present time we do not have a valid explanation for our finding.

Third ventricle dilatation is considered a simple and accurate MRI marker of PSP, and it has been reported to occur in 75%–100% of cases [23] based prevalently on a subjective observations. Our data, although confirming the dilation of the third ventricle in PSP patients in respect with PD and healthy subjects, demonstrated that its measurement did not allow to distinguish PSP from MSA-P. Furthermore the whole ventricular system resulted enlarged in both PSP and MSA-P in comparison with PD and controls, a finding already reported by other authors [7]. This result suggests caution in considering third ventricle dilatation as a diagnostic marker of PSP.

There were some limitations in this study. We used clinical criteria for the diagnosis of the diseases, and we did not have pathologic confirmation. Thus, it is possible that in some patients the clinical diagnosis may be in error. However, all patients included in our study were evaluated in a standardized approach by one of the authors (G.N.) who had more than 10 years of experience in movement disorders.

In conclusion, our data suggest that the brain of patients with PSP was diffusely atrophied compared with PD patients and healthy controls. The atrophy involved different brain structures already known as target of this neurodegenerative disorder. With exception of the thalamus, the brain of patients with MSA-P showed a distribution of the atrophy and an enlargement of the ventricular system similar to those detected in PSP, thus explaining the common clinical features of both diseases. These findings may prove the clinical utility of this fully-automated whole brain segmentation method and should stimulate further studies to clarify the role of several brain structures, such as the thalamus, in parkinsonian disorders. A prospective study in a larger cohort of patients to confirm the accuracy of FreeSurfer for identifying cerebral regional atrophy in parkinsonian syndromes is warranted.

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