

# Differential diagnosis of parkinsonian degenerative disorders in combination manual measurements with automated volumetry of the brain

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## Research article

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manual measurements with automated volumetry of the brain**

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## ABSTRACT

**Background:** To compare brain morphological differences in progressive supranuclear palsy (PSP), multiple system atrophy with the parkinsonian variant (MSA-P), Parkinson's disease (PD) and controls by manual and automated measurements and to explore the feasibility of these measurements in disease differentiation.

**Methods:** Ninety-five PSP patients (48 males, mean age 67.9 y), 32 MSA-P patients (18 males, mean age 63.0 y), 136 PD patients (72 males, mean age 66.6 y) and 100 controls (50 males, mean age 66 y) were included. The 12 manual measurements were acquired. Relative brain structural volumes adjusted according to the intracranial volume (ICV) of different brain regions were also quantified. Differences among and between groups were evaluated. Receiver operating characteristic curve analysis was used to assess diagnostic performance and define cutoff values of these measures.

**Results:** P/M area 2.0 displayed the highest diagnostic performance (AUC: 0.801) for distinguishing PSP from MSA-P or PD (sensitivity 69.5%, specificity 82.1%). Furthermore, the combination of morphological features in manual parameters (P/M area 2.0, MRPI and M/P diameter) and volume atrophy in the midbrain improved the PSP discrimination (AUC: 0.870, sensitivity 76.8%, specificity 83.9%). The relative volume of the putamen can better differentiate MSA-P from PSP and PD (AUC: 0.844, sensitivity 81.3%, specificity 75.3%). Similarly, the ability to differentially diagnose MSA-P increased most significantly (AUC: 0.927, sensitivity 87.5%, specificity 87.9%) when combining volume atrophy in the putamen with the caudate and manual parameter (M/P diameter).

**Conclusion:** Manual and automated MR variables can reveal atrophy features of the brain and be helpful in the differential diagnosis.

Keywords: Parkinson disease, Atypical parkinsonism, Differential diagnosis, Magnetic resonance imaging, Volumetry

## **BACKGROUND**

Progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) are two of the main progressive atypical parkinsonism syndromes (APS) that are frequently misdiagnosed as Parkinson's disease (PD). Up to 24% of patients clinically diagnosed with PD were classified as APS post mortem[1]. Accurate diagnosis of these three degenerative parkinsonian disorders based on clinical features, especially at an early stage, is challenging due to overlapping clinical features. Diagnosis based on a complete medical history includes a timeline of symptoms and recognition of the important clinical signs. Diagnostic accuracy is substantially influenced by clinical experience, and even among movement disorder specialists, the clinical diagnosis may change over time due to emerging clinical signs[2]. However, the correct differential diagnosis of PD, PSP and MSA is important for patient counselling and clinical research purposes. Therefore, supplementary supporting examinations are required for accurate diagnosis. Radiographic signs have been reported to be of importance for differential diagnosis.

Magnetic resonance imaging (MRI) has played a significant role in parkinsonian disorders, and some morphological features that are helpful in differential diagnosis can be revealed on conventional MRI, such as abnormal iron accumulation with the disappearance of the "swallow tail" sign in PD [3], midbrain atrophy with the "hummingbird" sign or the "morning glory flower" sign in PSP [4, 5], and abnormalities in the putamen, middle cerebellar peduncles (MCP), and pons with the presence of the "putaminal rim" sign, the MCP sign and the "hot cross bun" sign in MSA [6, 7]. However, these MRI-based sign assessments have limitations. The disappearance of the "swallow tail" sign is helpful in distinguishing PD from controls[3, 8], but not from APS[9, 10]. Additionally, the "swallow tail" sign is not always visible at 3T, the procedure of imaging acquisition is not yet standardized and the swallow tail

loss is not always bilaterally visible[11]. The “hummingbird” and “morning glory” signs are highly specific to PSP, and the MCP and “hot cross bun” signs are indicative of MSA; however, the detection sensitivity of these signs is low[6]. Additionally, these visual evaluation criteria are highly dependent on image quality, median location selection and the evaluator's experience[12, 13].

Compared with morphological evaluation, quantitative analyses more objectively differentiate PD, PSP and MSA. Manual measures of the midbrain and pons (or their ratio) and calculation of the MR parkinsonism index (MRPI) identified PSP with a sensitivity up to 100% in some early studies[14, 15]. However, the results were not as ideal in the subsequent studies. The sensitivity and specificity can vary widely when using manual measures[16]. MRPI 2.0 was first reported as an updated index for MRPI, which included the measurement of the third ventricle width. It was reported that this new MR index showed higher sensitivity (100%) and similar specificity (94.3%) in differentiating between PSP-P and PD [17]. However, further literature verifying these results is still lacking. MRI-based brain automatic segmentation volumetry can also differentiate parkinsonian disorders. Different patterns of brain atrophy in PSP, MSA and PD have been characterized[18]. It has been reported that both cortical and subcortical volumetry in supra- and infra-tentorial regions can be helpful in differentiating PSP, MSA and PD[16, 19]. As manual measures have unstable diagnostic performance according to the present literature and few studies have combined the manual and automatic volumetric tools for PSP, MSA-P and PD differentiation, the aim of this study was first to further confirm the diagnostic performance of manual brainstem measurements and to determine whether there are more suitable cutoff values for disease differentiation. Second, we evaluated and compared both the automated volumetric differences of specific brain regions and

manual parameters, trying to develop and optimize an efficient combined radiological diagnostic marker for PSP, MSA-P and PD differentiation.

## **METHODS**

### ***Patients***

From January 2017 to June 2019, 447 patients suspected of having Parkinson's syndrome at the Neurology Unit of Peking Union Medical College Hospital underwent an MRI scan. Of these 477 patients, 214 were excluded for the following reasons: (a) lack of complete clinical information (n=128) and (b) clinical diagnosis of another type of Parkinson's syndrome (n=86). A total of 263 patients were retrospectively included in the study who fulfilled the criteria for possible or probable PSP, PD or MSA-P.

Ninety-five PSP patients (48 males, mean age 67.9 y, mean disease duration 3.8 y), 32 MSA-P patients (18 males, mean age 63.0 y, mean disease duration 2.9 y), 136 PD patients (72 males, mean age 66.6 y, mean disease duration 4.8 y) and 100 controls (50 males, mean age 66 y) were included (Table 1). Two of the authors (X.D. and W.H.) with more than 10 years of experience in movement disorders determined the clinical diagnosis of patients together according to the consensus criteria[20-22]. The controls were selected from a community cohort, and the subjects all had a normal neurological examination and with no history of central nervous system diseases.

### ***MRI acquisition***

Brain MRI was performed with two 3.0 T units (Ingenia CX 3.0; Philips Medical Systems, Best, Netherlands, and Discovery MR750 3T, GE Healthcare, Milwaukee, WI, USA). Structural MRI data were acquired using a 3D T1-weighted imaging. Turbo field echo compressed SENSE (TFE-CS) sequence on Philips unit with the following

parameters: repetition time (TR) = 8.1 ms; echo time (TE) = 3.7 ms; flip angle: 8°; FOV: 25 × 25 cm; and voxel size: 1.0 × 1.0 × 1.0 mm. T1WI-prepared fast spoiled gradient echo (i.e., BRAin VOlume acquisition, BRAVO) on the GE unit with the following parameters: TR = 7.1 ms; TE = 3.2 ms; flip angle: 12°; FOV: 25 × 25 cm; voxel size: 1.0 × 1.0 × 1.0 mm.

### ***Image processing***

#### *Morphometric parameters based on manual measurements*

The manual measurements including the third ventricle (3<sup>rd</sup>V) and frontal horns (FH) width, 3<sup>rd</sup>V-FH ratio, diameter of pons (P) and midbrain (M), M/P diameter, area of P and M, M/P area, P/M area 2.0 (P/M area 2.0 = P/M \* 3<sup>rd</sup>V/FH), and MRPI (MRPI = (P/M diameter) \* (MCP/SCP)), and MRPI 2.0 (MRPI 2.0 = MRPI \* 3<sup>rd</sup>V/FH) were calculated on the reconstructed T1-weighted images based on the methodology described in previous literature[14, 15, 17] by one neuroradiologist blinded to the clinical information. Interrater reliability studies were performed with images from ten randomly selected subjects assessed by another neuroradiologist.

#### *Volumetric analysis based on automated segmentation*

Relative brain volume measurements adjusted for the intracranial volume (ICV) of different brain regions were automatically quantified using AccuBrain® IV 1.0 software (BrainNow Medical Technology Limited, China) [23]. The brain regions included the midbrain, pons, cerebellum, putamen, pallidum, caudate, brain parenchyma and grey matter of different brain lobes (Figure 2).

$$\text{Relative volume} = \frac{\text{absolute volume of brain region}}{\text{ICV}}$$

### ***Statistical analysis***

An intraclass correlation coefficient was used to assess the interrater agreement in the manual measurements. Differences across groups were compared by analysis of variance (ANOVA) followed by post-hoc least significant difference (LSD) test. P value  $<0.0083$  was considered statistically significant with the Bonferroni correction for pairwise comparisons. Parameters with significant differences were further evaluated by receiver-operating characteristic (ROC) curves to compare the area under the curve (AUC). The optimal cut-off value balancing sensitivity and specificity was identified as the one corresponding to the maximum value of Youden's index, calculated as [sensitivity + specificity - 1]. The positive predictive value, negative predictive value and overall accuracy were also given. AUC values were interpreted as follows:  $0.5 < \text{AUC} < 0.7$  poor accuracy;  $0.7 < \text{AUC} < 0.9$  moderate accuracy;  $0.9 < \text{AUC} < 1.0$  high accuracy,  $\text{AUC} = 1$  perfect accuracy. We also examined whether diagnostic accuracy was improved by using MR variables in combination and adjusting for patients' age and disease duration using logistic regression analysis with a forward stepwise procedure. MR variables with with  $\text{AUC} \geq 0.7$  in univariate analyses were included one at a time. The forward stepwise procedure stopped when additional variables did not contribute further significant information at the  $P \leq 0.05$  significance level. ROC curves were calculated for combinations of variables. Statistical analysis was performed with the Statistical Package for Social Science Software (SPSS, version 21.0, Chicago, IL) for Mac.

### **RESULTS**

Tables 2 provides the results of the comparison of the quantitative MR parameters, including manual measurements and volumetric analysis, among MSA-P, PSP, PD

patients and healthy controls. Table 3 shows the pairwise comparison of the volumetric parameters across MSA-P, PSP, PD patients and healthy controls. Table 4 demonstrates the diagnostic performance of manual and volumetric parameters with AUC > 0.7 among only parkinsonian groups, including the cut-off values that provide an optimal balance of sensitivity and specificity, positive predictive value, negative predictive value and overall accuracy.

### ***Interrater reliability***

Ten participants were randomly selected from the main cohort for interrater reliability studies between two raters (YW. Z and YH) with no knowledge of the clinical diagnosis, and this analysis indicated high levels of repeatability. (Interrater intraclass coefficient (ICC), two-way random model for consistency: midbrain diameter 0.973 (95% CI: 0.830 - 0.994); pons diameter, 0.894 (95% CI: 0.632 - 0.973); midbrain area, 0.891 (95% CI:0.623-0.972); pons area, 0.952 (95% CI:0.821-0.988), 3rdV width, 0.997 (95% CI:0.986-0.999); FH width, 0.992 (95% CI: 0.967-0.998); MRPI, 0.873 (95% CI: 0.591-0.966); and MRPI 2.0 0.957 (95% CI: 0.833-0.990).

### ***Group Differences***

#### *Morphometric analysis of manual parameters*

Significant differences among parkinsonian groups and healthy controls were found in the manual MR parameters at the group level (Table 2). The midbrain diameter, the M/P diameter, midbrain area, and M/P area in the PSP were significantly smaller compared with those in all the others ( $P < 0.001$  each). The PSP patients displayed the highest P/M area 2.0, MRPI and MRPI 2.0 values among all the groups ( $P < 0.001$  each). The third ventricle was enlarged in the PSP with a larger 3<sup>rd</sup>Vwidth (MSA  $P = 0.003$ ; PD  $P$

$< 0.001$ ; HC  $P < 0.001$ ). The 3<sup>rd</sup>V-FH ratio of PSP was larger than that in the PD ( $P < 0.001$ ) and healthy controls ( $P < 0.001$ ), but not in the MSA-P group ( $P = 0.019$ ). The MSA-P patients had a smaller pons area compared with that in the other three groups (PSP  $P = 0.002$ ; PD  $P < 0.001$ ; HC  $P < 0.001$ ), and a smaller pons diameter compared with that in the PSP ( $P = 0.001$ ) and PD ( $P < 0.001$ ).

### *Volumetric analysis*

Significant difference in the volumetric comparison can be seen among groups in the supra- and infra-tentorial regions except the grey matter of the occipital lobe ( $P = 0.334$ ) (Table 2). The midbrain volume in the PSP group was significantly distinguishable from that in the three other groups (MSA-P  $P = 0.001$ ; PD  $P < 0.001$ ; HC  $P < 0.001$ ). The relative volume of the putamen was smallest in the MSA-P among the groups. The reduced volume in the pons, pallidum and cerebellum was observed in the MSA-P group compared with the PD patients and healthy controls. However, the difference between MSA-P and PSP was not statistically significant. The volume of the caudate was smaller in the MSA-P patients compared with the PSP ( $P < 0.001$ ) and PD ( $P < 0.001$ ) patients but not the healthy controls ( $P = 0.389$ ). The overall brain parenchyma and the grey matter of the frontal lobe were decreased in PSP patients compared with the other three groups. The reduced relative volume of the temporal and parietal lobe grey matter was found in the PSP and PD groups compared with the MSA-P group and healthy controls. The PD patients had a smaller volume of grey matter in the temporal and parietal lobes compared with the healthy controls. The healthy controls did not exhibit differences compared with the three Parkinson syndrome groups with respect to relative volume of the insular cortex. (Table 3.)

## ***Diagnostic performance***

### *Morphometric analysis of manual parameters*

The MRPI 2.0 and P/M area 2.0 measures showed better performance than their original biomarkers (MRPI and M/P area) in differentiating the PSP group from other two parkinsonian groups. Additionally, P/M area 2.0 displayed the highest diagnostic performance for PSP differentiation among all the investigated biomarkers (Table 4).

Regarding the differentiation of the PSP group from the MSA-P, PD and healthy control groups, a midbrain diameter of 9.35 mm, which is the cutoff value of defined and widely accepted in previous literature, had a sensitivity of 66.3% and specificity of 72.6%; the M/P (diameter) of 0.52 had a sensitivity of 51.6% and a specificity of 86.3%; the P/M area 2.0 of 0.88 had a sensitivity of 89.5% and a specificity of 53.0%; and the MRPI of 13.55 had a sensitivity of 41.1% and a specificity of 95.2% and MRPI 2.0 of 2.5 had a sensitivity of 73.7% and a specificity of 72.0% for PSP differentiation from the MSA-P and PD groups. The manual variables including MRPI, M/P (diameter) and M/P (area) helped distinguish MSA-P group from the PSP and PD groups with an AUC > 0.7.

### *Volumetric analysis*

The relative volume of the midbrain showed the highest diagnostic performance in volumetric biomarkers for differentiating PSP from MSA-P and PD, with an AUC of 0.749 (95% CI: 0.687–0.812). Regarding differentiation of the MSA-P from the other two parkinsonian groups, the relative volume of the putamen became the most useful radiological biomarker among the other investigated ones, with an AUC > 0.8.

### *Combinations of manual and volumetric variables*

We carried out a further analysis to determine whether an incremental accuracy could be achieved by a combination of MR variables. The AUC of 0.870 (95% CI: 0.826–0.914) can be achieved when combining the manual index (P/M area 2.0, MRPI, M/P(diameter)) and volumetric parameters (midbrain) to differentiate PSP from MSA-P and PD with 76.8% sensitivity and 83.9% specificity (Figure 3A.). The features of M/P (diameter) and relative volume of the putamen and caudate can help differentiate MSA-P from PSP and PD with an AUC of 0.927 (95% CI: 0.874–0.981), 87.5% sensitivity and 87.9% specificity (Figure 3B.). The combination markers of M/P(diameter), MRPI and relative volume of putamen can differentiate the PSP from the MSA-P with an AUC of 0.936 (95% CI: 0.883–0.989), 84.2% sensitivity and 90.6% specificity. The combined indicators (M/P(diameter), MRPI 2.0, and relative volume of the pallidum and midbrain) can differentiate PSP from PD with an AUC of 0.869 (95% CI: 0.823–0.916), 80.0% sensitivity and 82.4% specificity. The AUC can reach 0.922 (95% CI: 0.865–0.979) with 94.9% sensitivity and 84.4% specificity using combination of M/P(diameter) and relative volume of the caudate to differentiate MSA-P from PD.

### **DISCUSSION**

Our study was a retrospective study with a large cohort applying MR variables of both manual measurements and automated volumetry to investigate the morphometric characteristics between PSP, MSA-P, and PD patients and healthy controls, and for differential diagnosis of parkinsonian disorders in clinical scenarios based on all these parameters. These measurements were based solely on conventional structural MRI and allowed the morphometric analysis of the brain quantitatively. Our study compared 12 manual radiographic biomarkers which included almost all manual measurements reported in the current literature. The measure method of these manual parameters was

consistent with the previous literature and was highly reproducible between experts. Automated volumetry included the super-tentorial (brain parenchyma and grey matter of different brain lobes) and infra-tentorial structures (midbrain, pons, cerebellum). Subcortical volumetric changes in the basal ganglia (putamen, pallidum and caudate) were also discussed in the study.

In this study, the specific structural changes distinguishing PSP from the other two parkinsonian groups and healthy controls included 9 manual measures and 3 volumetric biomarkers. The midbrain atrophy in the PSP patients was significant, which was demonstrated not only in the manual measurements (midbrain diameter, midbrain area, M/P diameter, M/P area) but also in the volumetric analysis of the midbrain. These findings are consistent with the previous studies, which were in general agreement that midbrain measurements are smaller in PSP patients compared with MSA and PD patients. Other regional brain volumetric atrophy was also found in structures including the brain parenchyma and frontal lobe in PSP, which has been demonstrated by a number of group level studies[16]. A previous study showed that discernible frontal atrophy was present in only approximately 60% of PSP-RS patients by visual assessment[6]. This further highlights the value of automated brain volumetry, which may identify cortical atrophy in the early phase of disease. Cordato et al. found a significant reduction of whole brain and frontal lobe volume in PSP compared to PD and healthy controls, but only frontal lobe volume contributed to the differential diagnosis[24]. Unfortunately, the atrophy of brain parenchyma and frontal lobe played a limited role in the differential diagnosis of PSP from MSA-P and PD, both of which showed a poor accuracy ( $AUC < 0.7$ ) in this study. An enlarged third ventricle can be observed in the PSP patients through higher values of manual parameters in 3rdV width and 3rdV-FH ratio. The atrophy of the midbrain, superior cerebellar peduncles and an

enlarged third ventricle were reflected in manual biomarkers, such as P/M area 2.0, MRPI, and MRPI 2.0, which represented various combinations of these structural changes.

We did not include the healthy controls in the analysis of the diagnostic performance of all different MR parameters. The inclusion of controls will make the AUC values better, but it obscures our ability to evaluate how well the measures actually differentiate parkinsonian syndromes. Thus, the results of the analyses without healthy controls are more likely to be up to the task of being applied to clinical diagnosis. Then, unfortunately, the widely accepted cutoff values for the midbrain diameter (9.35 mm), M/P diameter (0.52) and MRPI (13.55) did not yield perfect sensitivity (100%) and specificity (100%) in our study as has been reported in the literature[14, 15]. Actually, the relatively moderate sensitivity and specificity levels for differentiating PSP have been previously reported [25-27]. A similar situation also occurred with the upgraded measurements (MRPI 2.0 and P/M area 2.0). The newly set cutoff values suitable for the patient cohort in this study differed from those in previous studies. This inconsistency may be more likely to reflect the application of these manual measurements in real clinical situations. However, despite the inconsistency, the manual parameters were still better suited to identify and differentiate (higher AUC) PSP from the other two parkinsonian groups compared with the automated volumetric analysis. The modified biomarkers, including MRPI 2.0 and P/M area 2.0, all showed a better diagnostic performance in comparison with their original biomarkers (MRPI and M/P area) in differentiating PSP from MSA-P, PD. This finding was consistent with previous literature[17]. Among these measures, the P/M area 2.0 displayed the highest performance for PSP differentiation, and also had the highest accuracy. Furthermore, a combined indicator, the P/M area 2.0 in addition to the other 2 manual parameters

(MRPI and M/P diameter) and volumetric quantitative MR markers (relative volume of the midbrain), helped increase diagnostic accuracy in discriminating PSP-RS from MSA-P, and PD to the greatest extent (from an AUC of 0.801 to 0.870). This result demonstrated that the comprehensive evaluation of these radiological markers for disease differentiation in the clinical settings is necessary.

Subcortical volume atrophy was found in the putamen and caudate in the MSA-P group compared with the PSP and PD groups. Volume atrophy in the putamen was most distinguishable and showed the best diagnostic performance in differentiating MSA-P from PSP and PD with moderate accuracy (AUC 0.844). Subcortical volume atrophy in the cerebellum, pons and pallidum were also identified in the MSA-P when compared with the PD and healthy controls. The higher degree of basal ganglia and cerebellar atrophy has been largely confirmed in the previous results and is in accordance with the evidence of MSA being a more aggressive and widespread disorder than PD[28]. The pons volumetric change can also explain the reduced values of the two manual biomarkers, including pons diameter and its area, but these two manual biomarkers did not result in good performance for MSA-P differentiation. Similarly, the combined marker, volumetric changes in the putamen and caudate in combination with a manual index (M/P diameter), improved the diagnostic accuracy to the greatest extent when discriminating MSA-P from PSP and PD (AUC>0.9). It has been reported that the volumes of the putamen and caudate were decreased in PD brains compared with control brains[29, 30]. However, the volumetric difference of these two regions in PD was conflict with previous studies. The relative volume of the putamen and caudate was found to be lager in the PD patients compared with controls, which is opposite to the result in the previous literature. This contradictory result may indicate that the volume changes of the putamen in PD patients are not stable. Atrophy was also observed in

cortical areas; including the temporal and parietal lobes, compared with the controls, which was in line with the findings reported in the early literature[31-34].

There were several limitations in this study. First, we used clinical criteria as an inclusion standard for PSP, MSA-P and PD patients, but pathological confirmation was not achieved in our patients. Thus, it is possible that in some patients, the clinical diagnosis could have been erroneous. However, it is difficult to select data for only pathologically confirmed patients. Furthermore, the diagnoses in this study were clinically evaluated by two of the authors (X.D. and W.H.) with more than 10 years of experience in movement disorders together according to the consensus criteria. Second, we did not specify clinical variants of PSP. This could have narrowed the differences found between the groups and therefore reduced the diagnostic performance of certain brain volumetric changes. However, in actual clinical scenarios, it is always more important and meaningful to differentiate the APS from PD than differentiate among the variants of APS. Additionally, this study discussed only a limited number of brain regions. Other brain structural changes that may be characteristic of certain diseases and helpful in disease differentiation were not included. A more comprehensive morphological imaging analysis is still needed in future studies.

In conclusion, the manual measurements and automated volumetry can identify different brain atrophy patterns among PSP, MSA-P, and PD patients and controls. The combination of radiological quantitative differences is helpful in the differential diagnosis of disease, although there is a current lack of agreement across studies on which specific regions should be used, and further validation of these results in independent cohorts is necessary. Whether disease-specific patterns of atrophy can be reliably detected in very early disease stages when the need for a correct diagnosis is most urgent remains to be proven.

## **Abbreviations**

PSP Progressive supranuclear palsy

MSA-P Multiple system atrophy with the parkinsonian variant

PD Parkinson's disease

ICV Intracranial volume

APS Atypical parkinsonism syndromes

HC Healthy controls

MRI Magnetic resonance imaging

SCP Superior cerebellar peduncles

MCP Middle cerebellar peduncles

MRPI MR parkinsonism index

3<sup>rd</sup>V third ventricle

FH frontal horns

P pons

M midbrain

TFE-CS Turbo field echo compressed SENSE

T1W T1-weighted

TE Echo time

TR Repetition time

FOV Field of view

ANOVA Analysis of variance

LSD Post-hoc least significant difference

ROC Receiver-operating characteristic curve

AUC Area under the curve

## **Declarations**

### **- Ethics approval and consent to participate**

The retrospective study was approved by the Institutional Ethics Committee of Peking Union Medical College Hospital. Written informed consent was obtained from all individual participants included in the study.

### **- Consent to publish**

All patients agreed to participate in this study and provided written informed consent.

### **- Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

### **- Competing interests**

L.S. is the director of BrainNow Medical Technology Limited. Y.L. is employee of BrainNow Medical Technology Limited. All other authors report no financial relationships with commercial interests.

### **- Funding**

Not applicable

### **- Authors' contribution**

Study design: HW and FF; Data collection: YZ, DX, BH, TL; Volumetric Data analysis: LS and YL; Manual morphometric analysis: HY and YZ, Manuscript preparation: YZ and FF. The authors read and approved the manuscript.

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Not applicable

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	MSA-P(n=32)	PSP (n=95)	PD (n=136)	HC (n=100)	P value	
Sex(M/F)	18/14	48/47	72/64	50/50	0.916 <sup>a</sup>	
Age at examination, ys <sup>b</sup>	63.0±7.0	67.9±7.6	66.6±7.8	66.2±3.2	0.005 <sup>c</sup>	
Age at disease onset, ys <sup>b</sup>	60.1±7.4	64.0±8.5	61.7±8.6	/	0.01 <sup>c</sup>	
Disease duration, ys <sup>b</sup>	2.8±1.6	3.8±3.5	4.8±3.9	/	0.036 <sup>c</sup>	
Hoehn-Yahr's modified scale Stage <sup>e</sup>	1	12.5%	1.1%	22.8%	/	<0.001 <sup>d</sup>
	1.5	0%	0%	0.7%	/	
	2	21.875%	12.6%	42.6%	/	
	2.5	12.5%	31.6%	13.2%	/	
	3	31.25%	34.7%	17.7%	/	
	4	18.75%	13.7%	1.5%	/	
	5	3.125%	6.3%	1.5%	/	

Table 1. Demographic and clinical data of patients. a. Chi-square test. b. Data are expressed as the mean ± standard deviation. c. ANOVA. d. Kruskal-Wallis test. e. Data are expressed as the percentage frequency.

MR parameters <sup>a</sup>	MSA-P	PSP	PD	HC	P value <sup>b</sup>
Manual measurements (mm/m <sup>2</sup> )					
Midbrain diameter	9.8±0.8	8.8±1.2	9.9±1.0	10.6±0.8	<0.001
Pons diameter	16.0±1.7	16.9±1.3	17.0±1.4	16.7±1.2	0.001
3rdV width	7.4±1.8	8.7±2.2	7.0±2.2	6.4±1.4	<0.001
FH width	34.4±3.6	36.5±4.4	34.7±4.2	35.1±3.6	0.008
3rdV-FH ratio	0.21±0.04	0.24±0.05	0.20±0.05	0.18±0.03	<0.001
M/P diameter	0.61±0.06	0.52±0.07	0.58±0.06	0.64±0.05	<0.001
Midbrain area	111.61±18.41	92.34±24.36	114.66±20.42	130.17±14.30	<0.001
Pons area	446.93±81.34	482.49±53.56	495.60±52.66	501.28±52.89	<0.001
M/P area	0.26±0.05	0.19±0.05	0.23±0.04	0.26±0.03	<0.001
P/M area 2.0	0.87±0.31	1.29±0.34	0.92±0.38	0.71±0.19	<0.001
MRPI	8.93±2.26	13.52±4.25	10.43±2.51	8.63±1.38	<0.001
MRPI 2.0	1.93±0.71	3.17±1.18	2.15±0.95	1.58±0.45	<0.001
Automated volumetric analysis (%) <sup>c</sup>					
Midbrain	0.38±0.03	0.36±0.04	0.39±0.03	0.39±0.03	<0.001
Pons	0.86±0.17	0.92±0.11	0.97±0.11	0.96±0.10	<0.001
Cerebellum	8.76±0.74	9.07±0.67	9.11±0.58	9.11±0.67	0.034
Putamen	0.56±0.09	0.66±0.07	0.69±0.07	0.66±0.07	<0.001
Pallidum	0.17±0.03	0.17±0.03	0.20±0.03	0.20±0.02	<0.001
Caudate	0.42±0.04	0.46±0.06	0.46±0.05	0.43±0.05	<0.001
Brain parenchyma	76.09±2.26	74.77±2.47	76.03±2.33	75.74±1.88	<0.001
Frontal lobe <sup>d</sup>	10.63±0.87	10.07±0.73	10.42±0.75	10.66±0.54	<0.001
Occipital lobe <sup>d</sup>	4.73±0.39	4.63±0.40	4.60±0.42	4.60±0.38	0.334
Temporal lobe <sup>d</sup>	7.22±0.59	6.80±0.58	6.93±0.53	7.39±0.43	<0.001
Parietal lobe <sup>d</sup>	5.67±0.53	5.34±0.46	5.39±0.52	5.61±0.38	0.004
Insula <sup>d</sup>	0.93±0.10	0.90±0.12	0.95±0.09	0.92±0.07	0.007

Table 2. The analysis of manual and volumetric parameters on a group level. a. Data are expressed as the mean  $\pm$  standard deviation. b. ANOVA. c. Relative brain volume adjusted for ICV. d. Grey matter of the brain lobe.

P value <sup>a</sup>		Midbrain	Pons	Cerebellum	Putamen	Pallidum	Caudate
PSP	MSA-P	PSP<MSA-P (0.001)	0.018	0.016	MSA-P<PSP (<0.001)	0.892	MSA-P<PSP (<0.001)
	PD	PSP<PD (<0.001)	PSP<PD (<0.001)	0.621	PSP<PD (0.001)	PSP<PD (<0.001)	0.925
	HC	PSP<HC (<0.001)	PSP<HC (<0.001)	0.704	0.979	PSP<HC (<0.001)	PSP<HC (<0.001)
MSA-P	PD	0.062	MSA-P<PD (<0.001)	MSA-P<PD (0.004)	MSA-P<PD (<0.001)	MSA-P<PD (<0.001)	MSA-P<PD (<0.001)
	HC	0.023	MSA-P<HC (<0.001)	MSA-P<HC (0.007)	MSA-P<HC (<0.001)	MSA-P<HC (<0.001)	0.389
PD	HC	0.464	0.582	0.93	HC<PD (0.001)	0.81	HC<PD (<0.001)

(A)

P value <sup>a</sup>		Brain parenchyma	Frontal lobe	Occipital lobe	Temporal lobe	Parietal lobe	Insula
PSP	MSA-P	PSP<MSA-P (0.004)	PSP<MSA-P (<0.001)	0.208	PSP<MSA-P (<0.001)	PSP<MSA-P (0.001)	0.228
	PD	PSP<PD (<0.001)	PSP<PD (<0.001)	0.496	0.055	0.431	PSP<PD (0.001)
	HC	PSP<HC (0.003)	PSP<HC (<0.001)	0.619	PSP<HC (<0.001)	PSP<HC (<0.001)	0.164
MSA-P	PD	0.882	0.129	0.077	PD<MSA-P (0.006)	PD<MSA-P (0.003)	0.272
	HC	0.442	0.814	0.106	0.088	0.550	0.816
PD	HC	0.335	0.009	0.880	PD<HC (<0.001)	PD<HC (0.001)	0.046

(B)

Table 3. (A) The comparison of groups in infra-tentorial and subcortical regions; (B) The comparison of groups in brain parenchyma and the grey matter of different brain lobes. a. ANOVA followed by post-hoc least significant difference (LSD) test with Bonferroni-corrected significance level  $P = 0.05/6 = 0.0083$ .

	MR Parameter	AUC (AUC>0.7)	sensitivity	specificity	PPV	NPV	accuracy	cutoff
PSP vs MSA-P, PD	Manual measurements (mm/m <sup>2</sup> )							
	<b>P/M area 2.0</b>	<b>0.801 (0.747-0.855)</b>	<b>69.50%</b>	<b>82.10%</b>	<b>68.75%</b>	<b>82.6%</b>	<b>77.55%</b>	<b>≥1.156</b>
	MRPI 2.0	0.798 (0.745-0.852)	80%	67.30%	68.50%	85.60%	71.89%	≥2.37
	M/P (area)	0.781 (0.721-0.841)	71.60%	76.20%	63%	82.6%	74.54%	≤0.21
	MRPI	0.777 (0.717-0.837)	75.80%	67.90%	57.10%	83.20%	70.75%	≥10.84
	Midbrain area	0.773 (0.711-0.835)	58.90%	88.10%	73.70%	79.10%	77.55%	≤94.35
	M/P (diameter)	0.768 (0.708-0.828)	67.40%	75%	60.40%	80.30%	72.25%	≤0.55
	Midbrain diameter	0.762 (0.701-0.822)	62.10%	81.50%	65.60%	79.20%	74.49%	≤9.15
	Automated Volumetric analysis (%)							
	Midbrain	0.749 (0.687-0.812)	69.50%	82.10%	68.80%	82.60%	77.55%	≤1.15
	Pallidum	0.704 (0.637-0.770)	64.20%	68.50%	53.50%	77.20%	66.95%	≤0.18
MSA-P vs PSP, PD	Manual measurements (mm/m <sup>2</sup> )							
	M/P (diameter)	0.739 (0.653-0.825)	65.60%	78.80%	30.00%	94.30%	77.19%	≥0.61
	MRPI	0.734 (0.656-0.829)	87.50%	51.50%	20.00%	96.75%	55.88%	≤10.88
	M/P (area)	0.712 (0.617-0.807)	56.30%	77.50%	25.74%	92.75%	74.92%	≥0.25
	Volumetry (%)							
<b>Putamen</b>	<b>0.844 (0.767-0.921)</b>	<b>81.30%</b>	<b>75.30%</b>	<b>31.32%</b>	<b>96.67%</b>	<b>76.03%</b>	<b>≤0.633</b>	
Caudate	0.712 (0.621-0.802)	62.50%	72.30%	23.81%	93.30%	71.11%	≤0.43	
PSP vs MSA-P	Manual measurements (mm/m <sup>2</sup> )							
	<b>MRPI</b>	<b>0.857 (0.788-0.925)</b>	<b>87.50%</b>	<b>74.40%</b>	<b>91.03%</b>	<b>66.72%</b>	<b>84.20%</b>	<b>≥10.88</b>
	<b>M/P (diameter)</b>	<b>0.854 (0.779-0.929)</b>	<b>84.40%</b>	<b>76.80%</b>	<b>91.53%</b>	<b>62.38%</b>	<b>82.49%</b>	<b>≤0.57</b>
	<b>MRPI2.0</b>	<b>0.841 (0.763-0.920)</b>	<b>81.30%</b>	<b>80%</b>	<b>92.35%</b>	<b>59.03%</b>	<b>80.97%</b>	<b>≥2.37</b>
	<b>M/P (area)</b>	<b>0.835 (0.758-0.911)</b>	<b>84.40%</b>	<b>71.60%</b>	<b>89.82%</b>	<b>60.72%</b>	<b>81.17%</b>	<b>≤0.21</b>
	<b>P/M area 2.0</b>	<b>0.817 (0.726-0.909)</b>	<b>84.40%</b>	<b>76.80%</b>	<b>91.53%</b>	<b>62.38%</b>	<b>82.49%</b>	<b>≥1.07</b>
	Midbrain area	0.755 (0.666-0.845)	60%	87.50%	93.44%	42.42%	66.93%	≤95.75
	Midbrain diameter	0.751 (0.660-0.842)	62.10%	84.40%	92.20%	42.86%	67.72%	≤9.15
	Automated Volumetric analysis (%)							
	<b>Putamen</b>	<b>0.807 (0.715-0.898)</b>	<b>68.80%</b>	<b>83.20%</b>	<b>92.40%</b>	<b>47.32%</b>	<b>72.43%</b>	<b>≥0.61</b>
	Caudate	0.712 (0.621-0.802)	62.50%	72.30%	23.81%	93.30%	71.11%	≤0.43
PSP vs PD	Manual measurements (mm/m <sup>2</sup> )							
	P/M area 2.0	0.797 (0.740-0.855)	69.50%	80.90%	71.77%	79.15%	76.21%	≥1.157
	MRPI2.0	0.788 (0.730-0.846)	89.50%	56.60%	59.03%	88.53%	70.13%	≥2.08
	Midbrain area	0.777 (0.714-0.840)	58.90%	88.20%	77.71%	75.44%	76.15%	≤94.35
	M/P (area)	0.768 (0.705-0.832)	71.60%	74.30%	66.06%	78.93%	73.19%	≤0.21
	Midbrain diameter	0.764 (0.702-0.826)	62.10%	80.90%	69.43%	75.34%	73.17%	≤9.15
	MRPI	0.758 (0.694-0.822)	58.90%	82.40%	70.04%	74.16%	72.74%	≥12.08
	M/P (diameter)	0.748 (0.683-0.813)	67.40%	72.10%	62.79%	76.00%	70.17%	≤0.55
	3rdV width	0.707 (0.639-0.774)	77.90%	54.40%	54.41%	77.90%	64.06%	≥6.99
	Automated Volumetric analysis (%)							
	Midbrain	0.765 (0.702-0.828)	58.90%	83.10%	70.88%	74.32%	73.15%	≤0.36
Pallidum	0.752 (0.687-0.818)	64.20%	77.20%	66.29%	75.53%	71.85%	≤0.1835	
MSA-P vs PD	Automated Volumetric analysis (%)							
	<b>Putamen</b>	<b>0.870 (0.796-0.943)</b>	<b>81.30%</b>	<b>83.10%</b>	<b>53.09%</b>	<b>94.97%</b>	<b>82.76%</b>	<b>≤0.633</b>
	Pallidum	0.791 (0.704-0.879)	81.30%	69.90%	38.86%	94.08%	72.07%	≤0.1885
	Caudate	0.726 (0.629-0.823)	62.50%	75%	37.04%	89.47%	72.62%	≤0.4345
	Pons	0.717 (0.615-0.820)	46.90%	88.20%	48.33%	87.59%	80.33%	≤0.8585

Table 4. The diagnostic performance of manual and volumetric parameters with AUC > 0.7 among the MSA-P, PSP and PD groups, arranged in decreasing order of AUC within each domain. Parameters with an AUC ≥ 0.8 are marked in boldface.

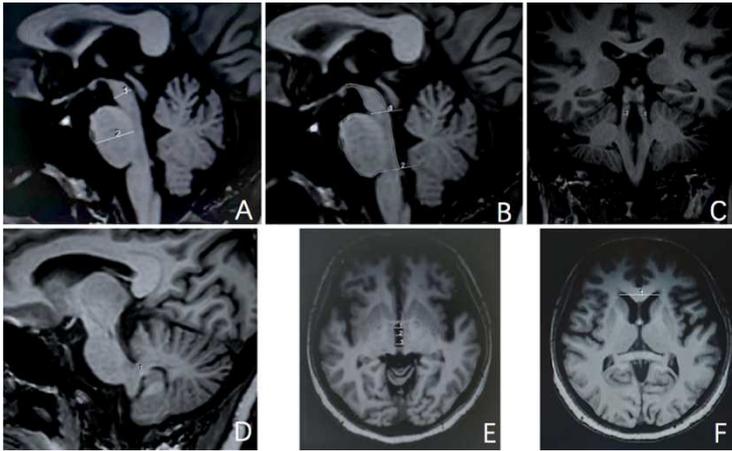


Figure 1. A). Example of diameter of the pons and midbrain; B). Example of area of pons and midbrain; C). Example of the superior cerebellar peduncles (SCP); D). Example of the middle cerebellar peduncle (MCP); E). Third ventricle (3rdV) at the level of the anterior and posterior commissures. Measurements were performed at the level of the anterior (1), middle (2), and posterior (3) sections of the 3rdV; F). Frontal horns (FH) of the lateral ventricles showing their maximal dilatation, in which their largest left-to-right width was measured.

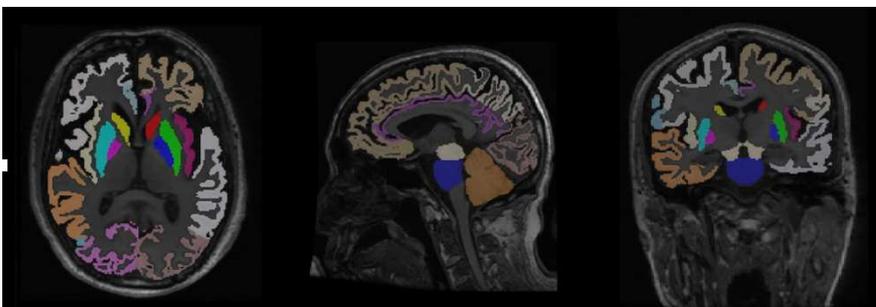


Figure 2: Examples of the intracranial segmentation by AccuBrain.

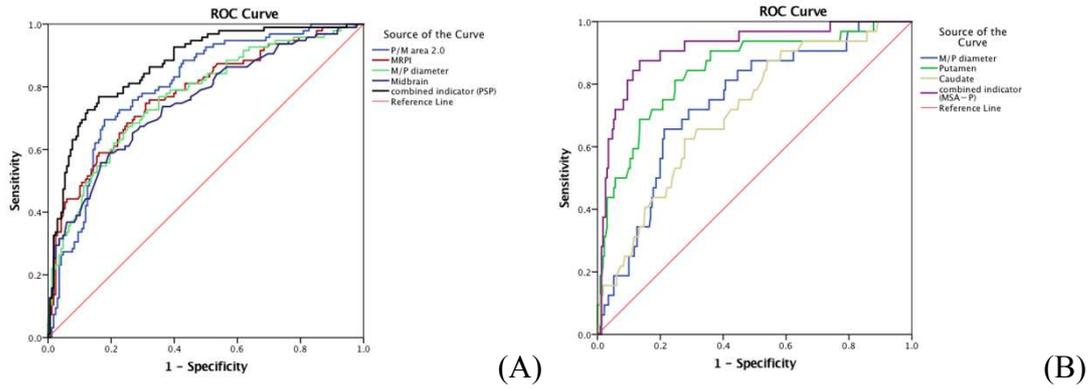
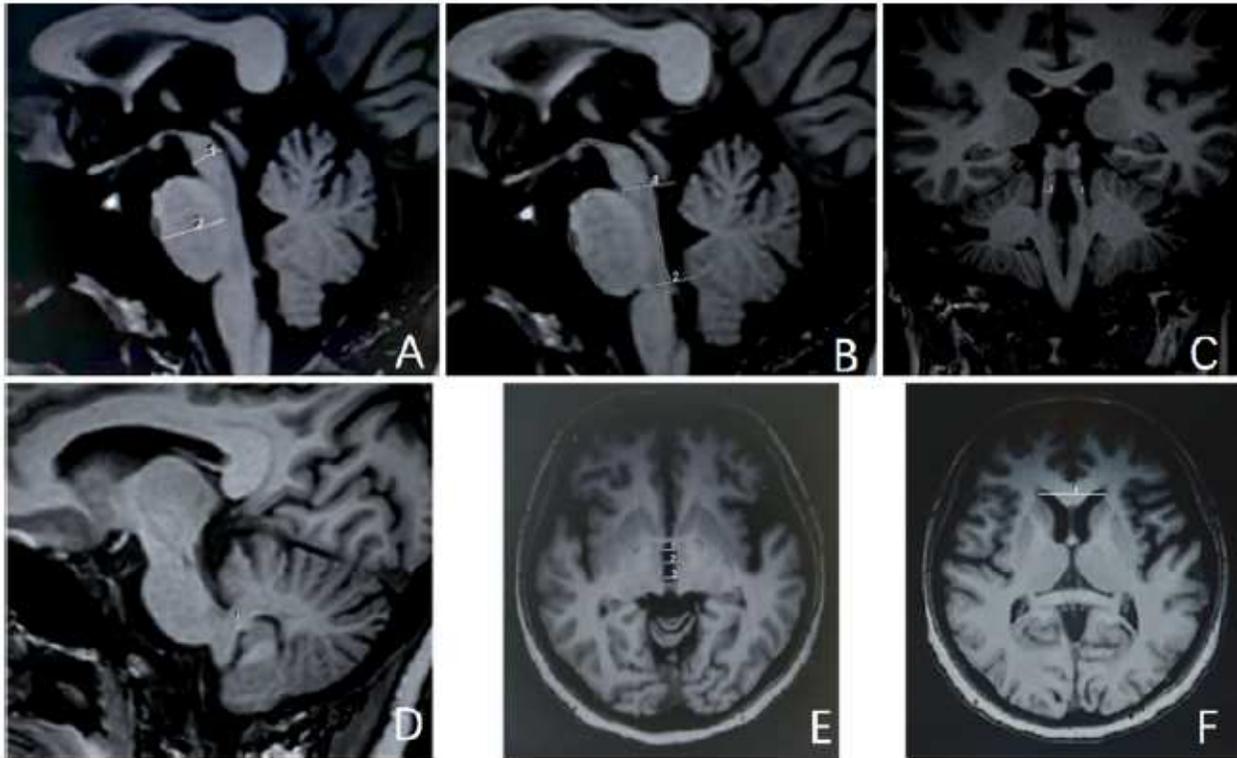


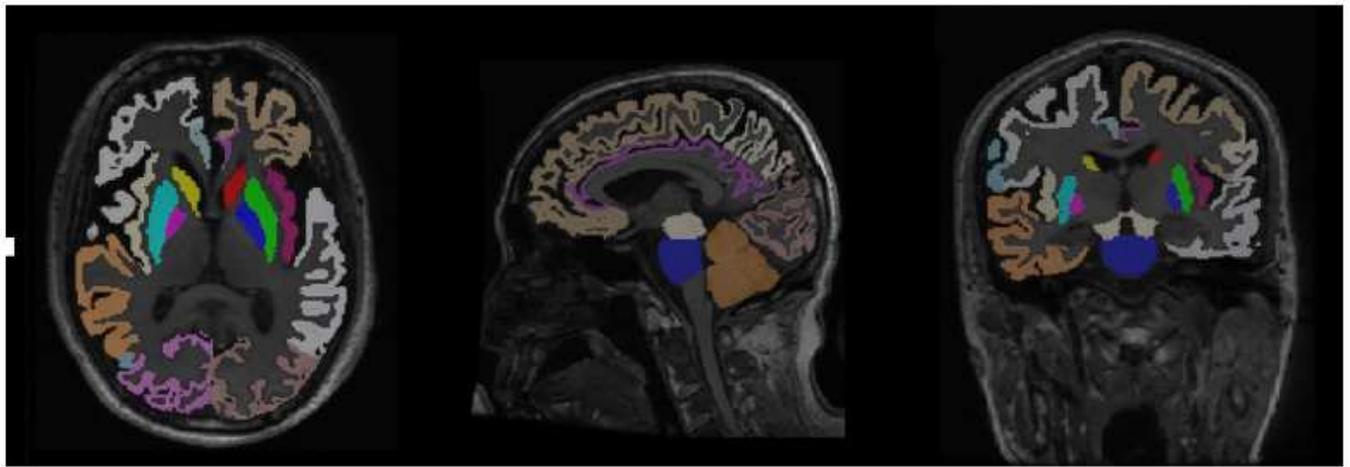
Figure 3. (A). The ROCs of manual (P/M area 2.0, MRPI, M/P diameter) and volumetric parameters (midbrain) and the combined indicator of there 4 parameters in differentiating PSP from MSA-P and PD. (B). The ROCs of manual (M/P diameter) and volumetric parameters (putamen and caudate) and the combined indicator of these 3 parameters in differentiating MSA-P from PSP and PD.

# Figures



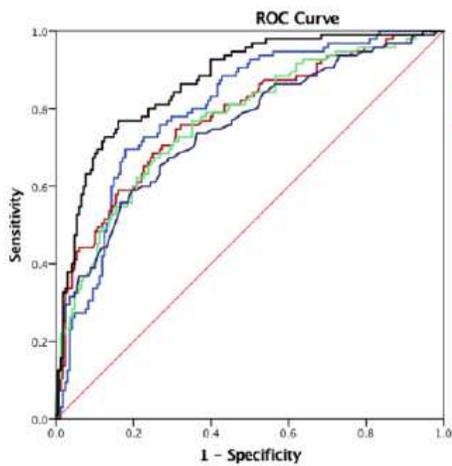
**Figure 1**

A). Example of diameter of the pons and midbrain; B). Example of area of pons and midbrain; C). Example of the superior cerebellar peduncles (SCP); D). Example of the middle cerebellar peduncle (MCP); E). Third ventricle (3rdV) at the level of the anterior and posterior commissures. Measurements were performed at the level of the anterior (1), middle (2), and posterior (3) sections of the 3rdV; F). Frontal horns (FH) of the lateral ventricles showing their maximal dilatation, in which their largest left-to-right width was measured.

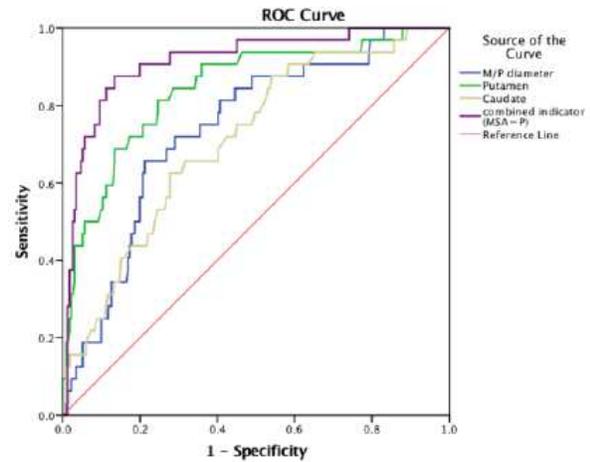


**Figure 2**

Examples of the intracranial segmentation by AccuBrain.



(A)



(B)

**Figure 3**

(A). The ROCs of manual (P/M area 2.0, MRPI, M/P diameter) and volumetric parameters (midbrain) and the combined indicator of there 4 parameters in differentiating PSP from MSA-P and PD. (B). The ROCs of manual (M/P diameter) and volumetric parameters (putamen and caudate) and the combined indicator of these 3 parameters in differentiating MSA-P from PSP and PD.