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Combining quantitative susceptibility mapping to the morphometric index in differentiating between progressive supranuclear palsy and Parkinson's disease

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ABSTRACT

Purpose: To determine whether the susceptibility value in the deep gray matter obtained by quantitative susceptibility mapping (QSM) provides additive value to the morphometric index for differentiating progressive supranuclear palsy (PSP) from Parkinson's disease (PD).

Materials and methods: PSP- (n = 8) and PD patients (n = 18) and 18 age-matched healthy controls who underwent QSM and 3D magnetization-prepared rapid gradient echo (MPRAGE) sequences. The mean susceptibility values (MSVs) of the deep gray matter structures on QSM- and areas of the midbrain (morphometric index, MI) on 3D MPRAGE images were measured by two neuroradiologists. Analysis of variance, the Scheffe test and receiver operating characteristic (ROC) analysis were conducted to assess differences and discriminate among PSP, PD and controls by the MSVs and the MI. Using the MSV of a structure with the best area under the curve (AUC) and the MI, we created a decision tree to differentiate between PSP and PD.

Results: The MSVs of the globus pallidus (GP) and substantia nigra (SN) were significantly higher in PSP than PD and the controls ($p < .05$). By ROC analysis (PSP vs PD), AUC was greatest (0.903) for the GP. The MI was significantly smaller in PSP than PD and the controls ($p < .05$); AUC (PSP vs PD) was 0.917. The decision tree using cutoff values of 244 parts per billion for MSV of the GP and 74.0 mm^2 for MI served to completely differentiate between PSP and PD.

Conclusion: The MSV in the GP on QSM images adds value to the MI for differentiating PSP from PD.

1. Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative tauopathy that may result in Parkinsonism. Despite diagnostic consensus criteria it can be difficult to clinically differentiate PSP from Parkinson's disease (PD) [1]. The morphology and signal- and diffusion changes of brain structures have been studied on conventional magnetic resonance images (MRI) to discriminate PSP from healthy controls and from Parkinsonism due to other etiologies [2]. Oba et al. [3] showed that information on the area of the midbrain on mid-sagittal MRI can differentiate PSP from PD, from multiple-system atrophy of the Parkinson type (MSA-P), and from normal aging. Although the sensitivity and specificity of MRI findings are relatively high [2,3], the diagnosis of- and the differentiation between PSP and PD on conventional MRI scans remains difficult [2].

Pathologically, PSP patients manifest increased iron concentrations in the substantia nigra (SN) and globus pallidus (GP). In PD patients, the iron concentration is increased in the SN and decreased in the GP [4,5]. Quantitative susceptibility mapping (QSM) facilitates the calculation of the bulk magnetic susceptibility of tissue in vivo; it eliminates blooming artifacts by deconvolving the susceptibility-generated field [6–8]. Post-mortem brain studies revealed a strong correlation between the iron concentration and the QSM-measured bulk susceptibility in the deep gray matter [7–9]. The diagnostic accuracy of QSM exceeded that

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Table 1
Demographics of the study population.

	PSP patients	PD patients	Healthy controls
No. (female, male)	8 (3, 5)[a]	18 (10, 8)[b]	18 (8, 10)
Age (mean ± SD)	69.5 ± 7.7	69.6 ± 6.2	69.1 ± 7.0
Disease duration (month, mean ± SD)	40.5 ± 40.3	74.6 ± 54.0	–

Abbreviations: PSP = progressive supranuclear palsy, PD = Parkinson's disease, HC = healthy controls, SD = standard deviation, n.s. = not significant.
[a] Scheffe test.
[b] Independent *t*-test.

of R2* mapping in PD patients [10,11]. Sjöström et al. [12] showed that QSM yields a promising biomarker for the differentiation of parkinsonian disorders. Consequently, we hypothesized that the combination of a morphometric index (MI) on conventional MRI and QSM data may help to discriminate between PSP and PD.

We assessed whether the susceptibility value in the deep gray matter on QSM adds value to the MI on conventional MRI for the differentiation of PSP from PD.

2. Materials and methods

2.1. Subjects

Our institutional ethics committee approved this study; prior consent from participants was waived. This study includes part of a clinicoradiologic cohort study described previously [13]; it was comprised of 44 subjects, i.e. 8 PSP patients (3 women, 5 men; age range 54–81 years; mean 69.5 years), 18 PD patients (10 women, 8 men; age range 56–82 years; mean 69.6 years), and 18 healthy controls (8 women, 10 men; age range 62–81 years; mean 69.1 years) (Table 1). The patients were recruited consecutively at Kumamoto University Hospital between April 2013 and November 2014. Their clinical diagnoses were established in accordance with the consensus criteria for PSP and PD by a board-certified neurologist (S.Y), a psychiatrist (M.H.), and a neurosurgeon (K.Y.) who specialize in movement disorders. The diagnosis of PSP and PD was based on criteria of the National Institute for Neurological Disorders and the Society for PSP (NINDS-SPSP) and of the UK Parkinson's Disease Society Brain Bank, respectively [1,14]. We included 4 probable- and 4 possible PSP patients. The disease duration was 9–120 months in PSP- and 12–200 months in PD patients.

The healthy controls were 18 age- and sex-matched members of Kumamoto University Hospital and members of the local community; none manifested brain abnormalities on MRI scans or had a history of cardiovascular-, metabolic-, neurologic-, or psychiatric disorders.

2.2. MRI

Brain MRI scans were performed on a 3 T MR system (Magnetom Trio; Siemens, Erlangen, Germany) using a 12-channel head coil. All were axial scans parallel to the anterior-posterior commissure line. We acquired three dimensional (3D) multi-echo gradient echo (GRE) sequences; the parameters were: TE = 6.2/12.4/18.6/24.8/31.0/37.2/43.4/49.6 ms; field of view = 24 cm; matrix = 256 × 256 mm^2; flip angle = 15°; voxel size = 0.9 × 0.9 × 2.0 mm^3; scan time = 5 min 35 s. 3D multi-echo GRE data were used for generating images; QSM was calculated using a morphology-enabled dipole inversion method [15]. The MRI protocol also included 3D T1W magnetization-prepared rapid GRE (MPRAGE) sequences; the parameters were: TR/TE = 2000/2.29 ms; field of view = 24 cm; matrix = 256 × 256 mm^2; flip angle = 8°; voxel size = 0.94 × 0.94 × 0.95 mm^3; scan time = 5 min 20 s.

2.3. Image analysis

The susceptibility values of the deep gray matter structures were measured by using ImageJ (National Institutes of Health, Bethesda, MD). For major deep gray matter structures except the SN, the mean susceptibility value (MSV) of the bilateral GP, the red nucleus (RN), putamen (PT) and caudate nucleus (CN) was obtained on axial QSM images. Two neuroradiologists (M.A. and Y.I. with 8 and 11 years of MRI experience, respectively), blinded to clinical and neurologic findings, independently placed a region of interest (ROI) on the largest area of each structure. Bilateral susceptibility values in each structure were acquired from segmented ROIs; they were averaged over the left and right brain hemisphere. The unit of susceptibility values measured on QSM was expressed as parts per billion (ppb).

To measure the susceptibility value of the SN, we used coronal multiplanar reconstruction (MPR) images and placed a maximal ROI in the SN with reference to the Schaltenbrand and Wahren atlas [16]. Details on the measurement of the susceptibility value of the structures can be found elsewhere [13]. To measure the susceptibility value in the bilateral anterior, middle, and posterior part of the SN (aSN, mSN, and pSN), coronal axial MPR images were selected at three planes, the anterior edge and the middle- and the posterior edge level of the RN. To avoid contamination of the subthalamic nuclei, an ROI was placed on the aSN, mSN, and pSN below the caudal edge of the RN on coronal images. The susceptibility values were averaged over the left and right brain hemisphere for each gray matter structure. The MSV of the SN recorded by the two neuroradiologists was also averaged for further statistical analysis. The averaged value of the three parts of the SN was defined as the value of the whole SN.

Using workstation display tools, the area of the midbrain including the tegmentum but not the tectum was independently measured by two neuroradiologists (M.A. and Y.I.) on mid-sagittal 3D MRI scans. Measurement details are presented elsewhere [3]. The readers were blinded to clinical and neurologic findings.

2.4. Statistical analysis

We used analysis of variance (ANOVA) and the Scheffe test to assess differences in the mean age among the three groups (PSP- and PD patients and controls). Differences in the mean disease duration of PSP and PD were assessed with the independent *t*-test. Interobserver agreement with respect to the recorded measurements of the susceptibility value in each structure and the area of the midbrain tegmentum was determined with the intraclass correlation coefficient (ICC); < 0.40 was considered poor-, 0.40–0.59 fair-, 0.60–0.74 good-, and > 0.74 excellent agreement [17]. For further statistical analyses, the observers' measurements were averaged for each structure. ANOVA and the Scheffe test were used to evaluate differences in the susceptibility values of the SN, GP, PT, RN, and CN and in the areas of the midbrain tegmentum among the PSP- and PD patients and controls. To assess the sensitivity, specificity and area under the curve (AUC) of the QSM and MI for discriminating PSP from PD and the controls, we performed receiver operating characteristic (ROC) analysis. Data were analyzed with the MedCalc software package for Windows. Differences of $p < .05$ were considered statistically significant.

We used Python programming software (version 3.5; https://www.python.org/) and the susceptibility value of a structure with the best AUC and the area of the midbrain tegmentum to create a decision tree to differentiate between PSP and PD. The diagnostic performance of the decision tree, the susceptibility value of a structure with the best AUC and the MI was compared with the Delong test.

Table 2
Summary of the mean susceptibility values in patients with progressive supranuclear palsy (PSP) or Parkinson's disease (PD) and in the healthy controls.

Structure	Mean susceptibility value[a]			*P* value		
	PSP	PD	HC	PSP vs PD	PSP vs HC	PD vs HC
GP	284.8 ± 82.5	160.2 ± 34.5	183.6 ± 58.9	< 0.001[b]	< 0.001[b]	NS
PT	115.3 ± 25.9	87.1 ± 25.9	96.7 ± 17.1	NS	NS	NS
CN	92.3 ± 51.6	73.2 ± 25.7	72.2 ± 15.0	NS	NS	NS
RN	178.0 ± 88.2	132.9 ± 41.7	109.2 ± 20.5	NS	< 0.001[b]	NS
aSN	250.8 ± 66.7	185.0 ± 52.2	146.8 ± 43.2	< 0.05[b]	< 0.001[b]	NS
mSN	242.3 ± 70.0	157.8 ± 50.6	108.9 ± 30.4	< 0.001[b]	< 0.001[b]	< 0.05[b]
pSN	162.7 ± 56.7	111.5 ± 36.3	69.9 ± 27.9	< 0.05[b]	< 0.001[b]	< 0.01[b]
whole SN	218.6 ± 62.2	151.4 ± 44.2	108.6 ± 32.0	< 0.005[b]	< 0.001[b]	< 0.05[b]

NS, not significant.
[a] Data are the mean. The unit of the mean susceptibility value is expressed as parts per billion.
[b] Significant.

3. Results

3.1. The ICC of the observers' measurements

As shown in Table 1, there was no significant difference in the mean age among the 44 study participants; the mean disease duration was shorter in PSP- than PD patients but not statistically different. The ICC of the observers' measurements for the susceptibility values ranged from 0.7329–0.9607 for PSP, from 0.7147–0.9462 for PD, and from 0.7090–0.9608 for the controls; all values were in good or excellent agreement. The ICC [95% confidence interval (CI)] for interobserver agreement of measurements of the midbrain tegmentum area was excellent; it was 0.9670 (95% CI, 0.8617–0.9925) for PSP, 0.9589 (0.8938–0.9844) for PD, and 0.9183 (0.7749–0.9718) for the controls.

3.2. The difference of the susceptibility values of the deep gray matter

As shown in Table 2, the MSV of the GP, whole SN, aSN, mSN, and pSN was significantly higher in PSP than PD and the controls (Figs. 1 and 2); the MSV of the whole SN, the aSN, mSN, and pSN was significantly higher in PD than the controls. Although there was no significant difference in the MSV of the PT among the three groups, it was highest in PSP and lowest in PD. There was no statistically significant difference in the MSV of the CN among the three groups.

3.3. The difference of the mean area of the midbrain tegmentum

The mean area of the midbrain tegmentum was 71.3 ± 20.6 mm^2 for PSP, 113.6 ± 15.9 mm^2 for PD, and 122.4 ± 14.1 mm^2 for HC (Figs. 1 and 2). The area of the midbrain tegmentum was lowest in PSP and the difference among the three groups was statistically significant ($p < .05$).

3.4. ROC analysis

ROC analysis (PSP vs PD) showed that the AUC was highest (0.903) for the MSV of the GP; at a cutoff value of 221 ppb, sensitivity and specificity were 75% and 100%, respectively (Table 3). The second-highest AUC (0.883) was for the MSV of the mSN; at a cutoff value of 208.3 ppb, sensitivity and specificity were 75% and 94.44%, respectively. By ROC analysis (PSP vs controls), the AUC was highest (0.958) for the MSV of the mSN; the mean AUC for the pSN and the whole SN was high (0.944 and 0.944, respectively). The AUC for the area of the midbrain tegmentum (PSP vs PD) was 0.917; at a cutoff value of 66 mm^2, sensitivity and specificity were 75% and 100%, respectively. The AUC (PSP vs HC) was 0.967; at a cutoff value of 94 mm^2, sensitivity and specificity were 87.5% and 100%, respectively.

3.5. Decision tree to differentiate PSP from PD

Using the susceptibility value of the GP and the area of the midbrain tegmentum, we developed a decision tree to differentiate PSP from PD (Fig. 3). As shown in Fig. 4, at our cutoff values (susceptibility value of the GP = 244.0 ppb, area of the midbrain tegmentum = 74.0 mm^2), PSP and PD were clearly differentiated. The diagnostic performance of the decision tree (AUC = 1.00) was higher than of the susceptibility

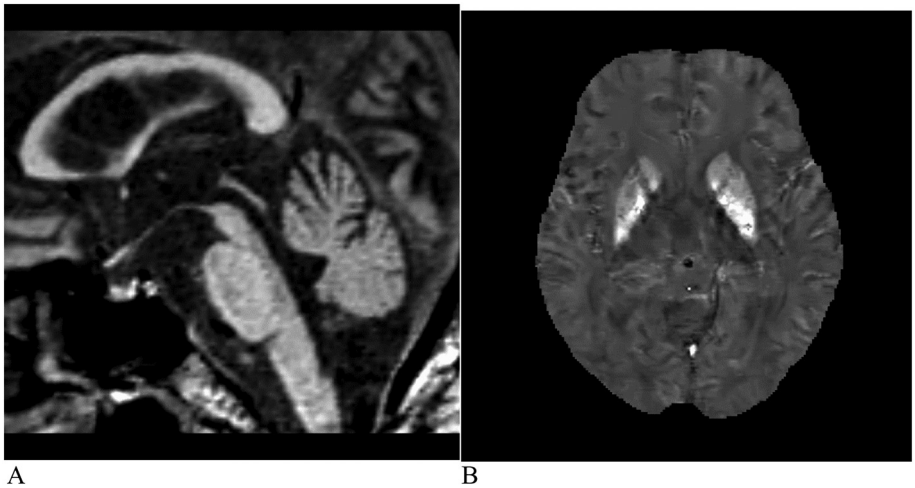

Fig. 1. A 75-year-old male with progressive supranuclear palsy. In 3D T1 MPRAGE image, the area of the midbrain including the tegmentum but not the tectum was 59.5 mm^2 (A). The mean susceptibility value of the GP on QSM image was 276.8 parts per billion (B).

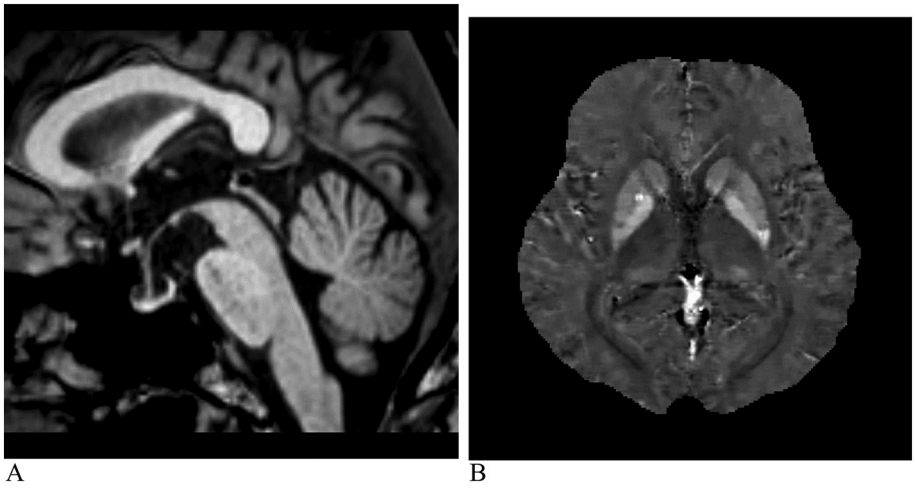

Fig. 2. A 56-year-old male with Parkinson's disease. In 3D T1 MPRAGE image, the area of the midbrain including the tegmentum but not the tectum was 135mm^2 (A). The mean susceptibility value of the GP on QSM image was 126.0 parts per billion (B).

Table 3
Area under the curve and sensitivity and specificity of QSM for discriminating between PSP- and PD patients and between PSP patients and the healthy controls (HC)

(a) PSP versus PD

	AUC	Cutoff value (ppb)	Sensitivity (%)	Specificity (%)
GP	0.903	221.0	75.00	100.00
PT	0.653	123.4	37.50	100.00
CN	0.611	69.8	75.00	61.11
RN	0.674	168.5	50.00	88.89
aSN	0.778	237.8	62.50	94.44
mSN	0.883	208.3	75.00	94.44
pSN	0.785	112.6	87.50	66.67
whole SN	0.806	171.8	75.00	77.78

(b) PSP versus HC

	AUC	Cutoff value (ppb)	Sensitivity (%)	Specificity (%)
GP	0.854	249.3	75.00	94.44
PT	0.576	120.8	37.50	94.44
CN	0.635	97.3	37.50	100.00
RN	0.840	134.5	75.00	100.00
aSN	0.896	205.5	75.00	88.89
mSN	0.958	169.0	87.50	100.00
pSN	0.944	90.3	100.00	77.78
whole SN	0.944	157.2	87.50	94.44

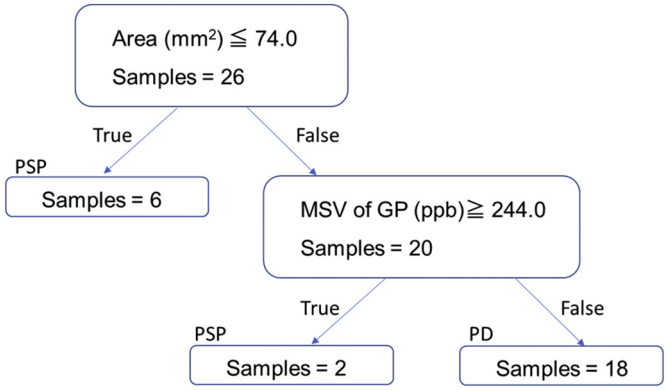

Fig. 3. Decision tree differentiating PSP from PD by using the mean susceptibility value of the GP and the area of the midbrain tegmentum.

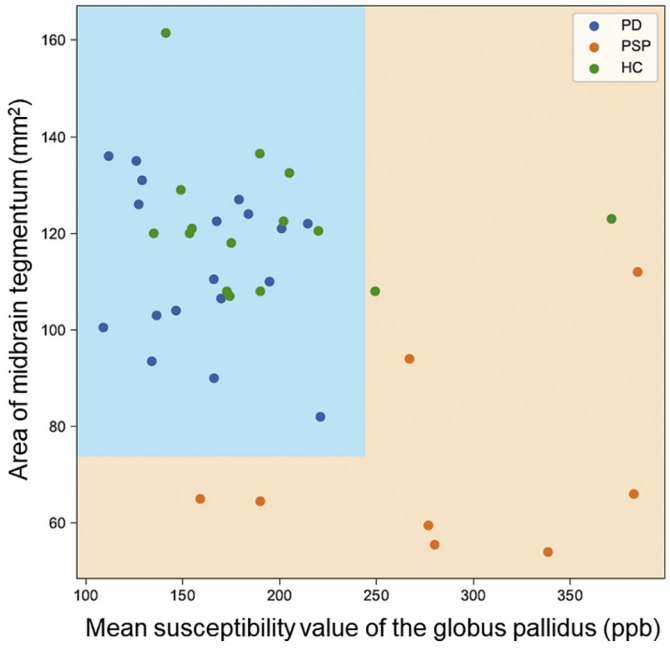

Fig. 4. Graph of disease differentiation based on the two-parameter decision tree obtained by combining the susceptibility value of the globus pallidus and the area of the midbrain tegmentum (26 patients and 18 healthy controls).
PD, Parkinson's disease; PSP, progressive supranuclear palsy; HC, healthy controls.
PSP is clearly differentiated from PD.

value of the GP (AUC = 0.90) and of the area of the midbrain tegmentum (AUC = 0.92), although there were no significant differences between the three indexes (Fig. 5).

4. Discussion

In our series, the GP showed the highest diagnostic performance for differentiating PSP from PD. Pathologically, the iron concentration was increased in the GP and SN of PSP- and in the SN of PD patients [4,5]. The diffuse accumulation of Tau has been shown to be co-localized with ferritin in the basal ganglia of PSP patients [18]. We found a diffuse increase in the susceptibility value of the basal ganglia (i.e., GP, PT, RN, CN), an observation consistent with the pathologically documented increase in the iron concentration related to ferritin deposits. Based on

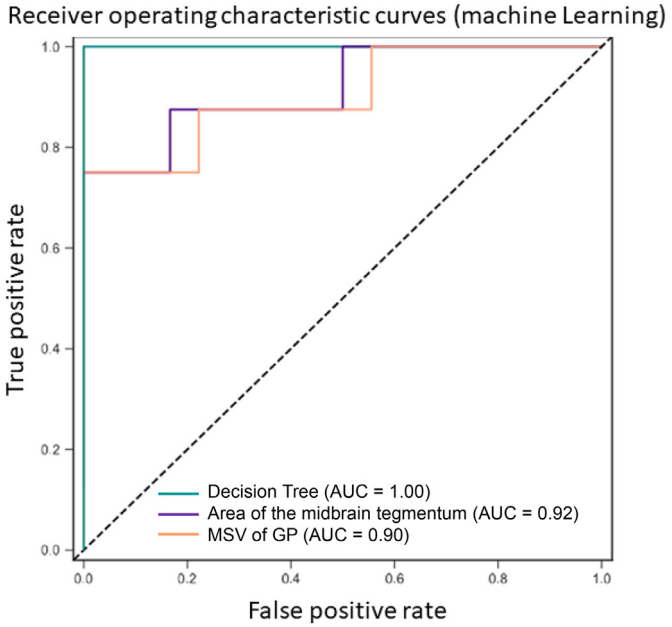

Fig. 5. Comparison of three receiver operating characteristic curves by machine learning.
The diagnostic performance of the decision tree (AUC = 1.00) was higher than of the susceptibility value of the GP (AUC = 0.90) and of the area of the midbrain tegmentum (AUC = 0.92). However, there were no significant differences between the three indexes.

the functional neuroanatomy model of the basal ganglia, the activity of the GABAergic pathway from the PT to the GP is increased in PD patients [19]. Experimental evidence that the utilization of GABA leads to a reduction in the iron concentration [20] suggests that the lower iron concentration in the GP of the PD brain may be attributable to an alteration in the GABA metabolism [21]. Therefore, the MSV in the GP on QSM images may help to differentiate PSP from PD.

According to Han et al. [22], the iron-related R2* value of the GP was higher in their patients with PSP than in patients with PD or a parkinsonian variant of multiple system atrophy (MSA-p), or in healthy controls and the R2* values were negatively correlated with the GP volume. As the increased iron concentration was related to GP atrophy, this suggests a degenerative process epiphenomenon. A susceptibility-weighted imaging (SWI) study [23] showed that the phase-shift value of the GP was significantly higher in patients with PSP than in PD- and MSA-p patients and in healthy controls. These earlier findings using the R2* value or SWI are consistent with ours. However, as QSM reduces blooming artifacts and facilitates quantitative assessments, it may more accurately reflect iron deposition in the basal ganglia of PSP patients.

The QSM study of Ito et al. [24] showed that the AUC values of the GP and PT that distinguish between PD and PSP were 0.85 and 0.80, respectively. However, they evaluated only the susceptibility value of the GP and PT and did not assess other deep gray matter structures. We, on the other hand, studied the susceptibility value on QSM images of 5 deep gray matter structures (SN, GP, RN, PT, CN) and identified the GP as having the best AUC value (0.90), followed by the mSN (0.88), for distinguishing between PD and PSP. The AUC value of the PT was 0.65 in our study and a little different from theirs. Sjöström et al. [12] reported that the AUC value distinguishing between PD and PSP was lower for the GP (0.75) than the RN (0.97). Our MSV was higher for the GP than the RN; the AUC value of the RN distinguishing between PD and PSP was 0.67. Their results differed from ours and other radiological studies [24,25]. Further investigations using QSM are needed to clarify whether the GP is the best site for distinguishing between PD and PSP.

In the differentiation between PSP and PD, assessment of the midbrain tegmentum area yielded almost the same high diagnostic performance as the susceptibility value of the GP. In fact, the combined assessment of the susceptibility value of the GP and of the area of the midbrain tegmentum clearly distinguished between PSP and PD. Oba et al. [3] who used a cutoff of 70 mm^2 for the area of the midbrain tegmentum reported that diagnostic sensitivity and specificity were 100% and 91.3%, respectively. On the other hand, according to Boxer et al. [25], sensitivity of the area of the midbrain tegmentum for discriminating between PSP from PD may be low. As midbrain atrophy may not be PSP-specific, the combined assessment of the susceptibility value of the GP by QSM and of the area of the midbrain tegmentum may prove more highly informative.

With respect to the differentiation between PSP patients and our controls, the highest AUC values were recorded for the mSN. Although the MSV of the aSN, mSN, pSN, and whole SN was significantly higher in the PSP- and PD patients than the controls, the increase was significantly higher in PSP- than PD brains. These results indicate that the MSV of the SN is also useful for differentiating PSP from PD. As the prognosis and appropriate treatment of PSP- and PD patients are different, QSM may play a role in differentiating between the two entities.

Our study has some limitations. Our study population was relatively small and we did not consider the relationship between susceptibility values and the progression of PSP and PD. Further QSM studies are needed to understand the role of longitudinal changes in the susceptibility difference in the deep gray matter of PSP- and PD patients.

5. Conclusion

The diagnostic performance of the susceptibility value of the GP and of the area of the midbrain tegmentum was equivalently high. The combined assessment of both clearly differentiated PSP from PD.

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Declaration of Competing Interest

None

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