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Structural and metabolic correlates of neuropsychological profiles in multiple system atrophy and Parkinson's disease

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ABSTRACT

Background: Despite increased recognition of cognitive impairment in Multiple System Atrophy (MSA), its neuroanatomical correlates are not well defined. We aimed to explore cognitive profiles in MSA with predominant parkinsonism (MSA-P) and Parkinson's disease (PD) and their relationship to frontostriatal structural and metabolic changes.

Methods: Detailed clinical and neuropsychological evaluation was performed together with diffusion tensor imaging (DTI) and [^{18}F]-fluoro-deoxyglucose positron emission tomography ([^{18}F]-FDG-PET) in patients with MSA-P (n = 11) and PD (n = 11). We compared clinical and neuropsychological data to healthy controls (n = 9) and correlated neuropsychological data with imaging findings in MSA-P and PD.

Results: Patients with MSA-P showed deficits in executive function (Trail Making Test B-A) and scored higher in measures of depression and anxiety compared to those with PD and healthy controls. Widespread frontostriatal white matter tract reduction in fractional anisotropy was seen in MSA-P and PD compared to an imaging control group. Stroop Test interference performance correlated with [^{18}F]-FDG uptake in the bilateral dorsolateral prefrontal cortex (DLPFC) and with white matter integrity between the striatum and left inferior frontal gyrus (IFG) in PD. Trail Making Test performance correlated with corticostriatal white matter integrity along tracts from the bilateral IFG in MSA-P and from the right DLPFC in both groups.

Conclusion: Executive dysfunction was more prominent in patients with MSA-P compared to PD. DLPFC metabolism and frontostriatal white matter integrity seem to be a driver of executive function in PD, whereas alterations in corticostriatal white matter integrity may contribute more to executive dysfunction in MSA-P.

1. Introduction

Multiple system atrophy (MSA) is a neurodegenerative disorder clinically characterized by autonomic failure in combination with parkinsonism and cerebellar ataxia [1]. Compared to the other principal degenerative α-synucleinopathy, Parkinson's disease (PD), MSA shows faster disease progression and a poorer prognosis. However, the differences in cognitive profile between these conditions are not as well defined. Whereas the profile of mild cognitive impairment (PD-MCI) and dementia (PD-D) in PD are well known, dementia is an exclusion criterion for a diagnosis of MSA according to the current consensus criteria [1]. Nevertheless, cognitive impairment in MSA is increasingly recognized [2]. For example, Brown and colleagues reported impairment in a single cognitive domain in 29% of patients with MSA, particularly

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deficits in initiation, perseveration and memory [3].

The neuroanatomical substrates of cognitive impairment in MSA and their differences in comparison to PD, however, have only been explored to a limited extent. A comparative study by Siri and colleagues showed no significant cognitive differences between PD and MSA patients of similar disease duration but confirmed that frontal lobe dysfunction was more prevalent in patients with MSA [4]. Given this frontal predominance of cognitive deficits in MSA, the involvement of frontosubcortical pathways is a probable underlying substrate. Evaluation of grey and white matter structure and function is therefore important to understand mechanisms of cognitive impairment in parkinsonism.

[^{18}F]-fluoro-deoxyglucose positron emission tomography ([^{18}F]-FDG PET) is a well-established tool to demonstrate changes in brain metabolism in neurodegenerative disorders. In PD patients, hypermetabolism in the putamen, pallidum and thalamus and hypometabolism in the frontal, inferior parietal and parietooccipital cortices has been described, whereas hypometabolism in the striatum, cerebellum and frontal cortex is reported in MSA [5]. A cognitive-related pattern of [^{18}F]-FDG PET hypometabolism in PD-MCI has been reported in prefrontal and parietal association areas [6]. The role of frontal dysfunction in cognitive impairment in MSA with predominant parkinsonism (MSA-P) is supported by the correlation between executive dysfunction and medial frontal and right dorsolateral prefrontal cortex hypoperfusion measured by SPECT [7]. Frontostriatal deafferentation in MSA-P has been suggested due to a correlation between frontal and striatal hypometabolism, but no relationship was seen with global measures of cognition [8].

Alterations in white matter integrity as measured using magnetic resonance diffusion tensor imaging (DTI) have been reported in striatal and extrastriatal regions in MSA [9]. Changes in white matter integrity in areas including the frontal and parietal lobe and corticostriatal tracts have been linked to cognitive impairment in PD [10,11]. Frontostriatal white matter changes in MSA have not been linked to cognitive function using DTI, although atrophy of the DLPFC was identified in MSA patients with cognitive deficits [12]. However, widespread white matter atrophy was seen in all patients, thus supporting a link between cognitive dysfunction in MSA and focal frontostriatal degeneration [12].

As demonstrated by these studies, the anatomical and functional substrates of cognitive dysfunction in parkinsonian syndromes, especially in MSA-P, are only partially understood. To date, there have been no approaches linking white matter integrity (DTI), metabolic ([^{18}F]-FDG PET) and neuropsychological changes in patients with parkinsonian syndromes. In our study, by combining these complementary imaging modalities with the assessment of cognitive function in patients with MSA-P and PD, we aimed to achieve a better understanding of the substrates of cognitive dysfunction in these α-synucleinopathies. In particular, we were interested in distinct combinations of structural and metabolic changes in MSA-P and PD associated with deficits in different cognitive domains.

2. Methods

2.1. Study participants

We recruited 11 patients without a clinical diagnosis of dementia fulfilling the consensus criteria for probable or possible MSA-P [1] and 11 patients meeting brain bank criteria for idiopathic PD [13]. Patients were recruited from a tertiary movement disorder service, Salford Royal NHS Foundation Trust. Healthy control participants without a history of significant neurological or systemic disease and with mini-mental state examination (MMSE) scores $\geq$28 (n = 9) performed detailed neuropsychology. [^{18}F]-FDG PET and DTI imaging changes in PD and MSA-P participants were compared to data from a previously published healthy control cohort (n = 10, mean age 68.8 ± 5.4, 8 females, mean MMSE 29.6 ± 0.5) [14]. Exclusion criteria for patients as well as imaging controls were confounding neurological or general medical comorbidity, significant psychiatric disease within the last two years and substance abuse, as well as contraindications to MR or PET scanning.

All procedures were conducted according to the Declaration of Helsinki and ethical approval and permission for all study procedures were given by North West 6 Research Ethics Committee (REC reference no: 10/H1003/76). ARSAC approval number was 595/3586/26570. Participants gave written informed consent prior to enrolment in the study.

The data supporting the findings of this study are available within the article and its supplementary material. Further data are available on reasonable request from the corresponding author.

2.2. Clinical assessments

Demographic information on age, sex, disease duration and medication was recorded in participants with PD and MSA-P and Levodopa equivalent daily dose (LEDD) was calculated. Motor assessments, performed in the "on" state, comprised the Unified Parkinson's Disease Rating Scale (UPDRS-III) and the Unified Multiple System Atrophy Rating Scale (UMSARS II – MSA-P only) motor scores. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) [15]. Overall cognitive performance was evaluated using the Montreal Cognitive Assessment [16] and Mini-Mental State Examination (MMSE). Premorbid intelligence was assessed by means of the National Adult Reading Test (NART) [20].

2.3. Neuropsychological evaluation

Patients and controls underwent a detailed standardized neuropsychological assessment consisting of five pencil-and-paper tasks. All tests were conducted by an experienced psychologist while patients were on medication. The Hopkins Verbal Learning Test-Revised (HVLT-R) was used to assess verbal learning and memory [17]. Lexical fluency was assessed by asking participants to name as many words as possible beginning with the letters F, A and S, whereas semantic fluency was evaluated by participants naming as many animals as possible in 1 min [22]. Digit span score forwards and backwards were tested to evaluate verbal working memory. Attention and executive function were assessed using the Stroop Test (3 colours, horizontal form version, number of correct items in 45 s) [23] and Trail Making Test (TMT) [18].

2.4. MRI - data acquisition and processing

MR imaging was performed on a 3.0 T Philips Achieva scanner (Philips Medical Systems, Best, Netherlands) using an 8-element SENSE head coil. T1-weighted 3D acquisition fast field echo images were acquired with a 256 × 256 matrix, SENSE acceleration factor = 2, slice thickness 1 mm, 150 contiguous slices, reconstructed voxel size 1 × 1 × 1 mm, TR = 8.4 ms, TE = 3.8 ms, TI = 1150 ms. Diffusion weighted imaging was performed using a PGSE EPI sequence with TE = 54 ms, TR = 11884 ms, G = 62 mTm^{-1}, half scan factor = 0.679, 112 × 112 image matrix reconstructed to 128 × 128 using zero padding, reconstructed resolution 1.875 × 1.875 mm, slice thickness 2.1 mm, 60 contiguous slices, 43 non-collinear diffusion sensitization directions at b = 1200 smm^{-2} (Δ, δ = 29.8, 13.1 ms), 1 at b = 0, SENSE acceleration factor = 2.5. For each diffusion gradient direction, two separate volumes were obtained with opposite polarity and hence reversed phase and frequency encode direction. This was done so that an algorithm for correcting susceptibility and eddy current induced artifacts could be applied [19]. Cardiac gating was used to reduce artifacts caused by pulsatile brain motion.

DTI data was analyzed with the open-source software DSI Studio. The b-table was checked by automatic quality control [20]. The restricted diffusion was quantified using restricted diffusion imaging [21]. The diffusion data were reconstructed using generalized q-sampling imaging [22] with a diffusion sampling length ratio of 1.25. A

deterministic fiber tracking algorithm was used with augmented tracking strategies [23] to improve reproducibility. Four regions of interest (ROIs) expected to be involved in executive functions were selected for further analysis: The anterior and posterior cingulate as well as the middle (including the dorsolateral prefrontal cortex) and inferior frontal gyrus (including the ventrolateral prefrontal cortex). For ROI-based analysis in individual MR space, seeding regions were placed at the ROIs and ending regions were placed at the ipsilateral striatum (caudate nucleus and putamen). A region of avoidance (ROA) was placed at the midline in order to exclude false positive crossing tracts.

In order to examine anatomical tracts, autotractography in MNI space was conducted. A population-averaged high-resolution tractography atlas [24] was used to map the bihemispherical anterior and superior corticostriatal tracts with a distance tolerance of 16 mm. Seeding regions were placed at each of these tracts and ROAs were placed at track tolerance regions. Topology-informed pruning [25] was applied to the tractography with 16 iterations to remove false connections.

For both approaches, the anisotropy threshold was randomly selected. The change threshold was 20%. The angular threshold was randomly selected from 15° to 90°. The step size was randomly selected from 0.5 voxel to 1.5 voxels. Tracks with length shorter than 28.125 or longer than 281.25 mm were discarded. A total of 100000 seeds were placed. Mean fractional anisotropy (FA), a measure of coherence in the main diffusion direction for each voxel and mean diffusivity (MD), a measure of increased free diffusion for each voxel were extracted from the tracts between seed and end regions or within anatomical tracts were extracted.

3. Methods: [^{18}F] -FDG PET - data acquisition and processing

[^{18}F]-FDG PET imaging was performed on the high-resolution research tomograph (HRRT; CTI/Siemens) at Wolfson Molecular Imaging Centre, University of Manchester. Participants fasted for a minimum of 6 h prior to PET imaging in order to ensure stable blood glucose levels; those with a fasting blood glucose of >8 mmol/l at baseline were excluded from scanning. Participants were comfortably positioned within the scanner with gentle restriction of head movement by tape. PET imaging was carried out in standardized quiet conditions, with low light, eyes closed and ears unplugged. A slow bolus intravenous injection of 10 ml (target dose 370 MBq, mean 363.2 ± 13.0 MBq) [^{18}F]-FDG was given over 20 s 7 min subsequent to the start of the emission scan, followed by a slow bolus saline flush. PET emission data were acquired for a total of 60 min post-injection in list mode, and image reconstruction was performed using HRRT community software's implementation of 3D iterative ordinary Poisson ordered subset expectation maximization (OP-OSEM) with resolution modelling using 12 iterations and 16 subsets with images returned consisting of 256 × 256 x 207 voxels each of 1.22 mm^3 [26]. Correction for head movement was applied as previously described [27].

Summed static PET images from 20 to 60 min post injection and smoothed at 2 mm full width at half maximum were co-registered to the T1-weighted MR scans in SPM8. ROI analysis was performed first by unified segmentation of structural T1-weighted MR images in SPM8 (2011, http://www.fil.ion.ucl.ac.uk/spm/), following which we spatially normalized a probabilistic anatomical brain atlas [28] to individual MR space. A grey matter object map was created by multiplying the normalized anatomical atlas with a grey matter binary mask. [^{18}F]-FDG uptake values, normalized to the mean whole brain grey matter uptake to produce standardized uptake value ratios, were extracted in ANALYZE 10.0 (Mayo Clinic Software).

Supplementary Fig. 1: Visualization of imaging data acquisition (A) and processing as well as correlation with neuropsychology. A1, B1, C1 and E2 describe specific PET methodology and A2, B2, C2 and E2 describe the DTI pipeline. Steps D, F and G are the same for both imaging techniques.

3.1. Statistical Analysis

Statistical analysis was conducted with SPSS Statistics 27. Normality of distribution of data from clinical scales, imaging and neuropsychology was determined according to the Kolmorogov-Smirnov test. Group comparisons between PD and MSA-P groups were performed with Mann-Whitney *U* test and comparisons between three groups using Kruskal-Wallis tests. Differences were considered statistically significant if the p-value from after Bonferroni-correction for multiple comparisons was $p \leq 0.05$. Correlational analysis across MSA-P and PD patients was performed between neuropsychological scores and FDG-PET and DTI data in the pre-specified regions detailed above. Correction for multiple comparisons was insured using Monte-Carlo permutations (1000x). The procedure entails random resampling of the data iteratively. For each iteration, a calculation of probability to test whether the statistical inference is or is not based on chance is estimated. This method is safe against violation of statistical distribution in small sample sizes [29] Scatterplots were visualized with 95% confidence interval using the gramm Matlab toolbox [30].

4. Results

Demographic data and clinical scores of the four groups are summarized in Table 1a. Age, global cognitive screening tests MMSE and MoCA or premorbid intelligence as measured by NART did not differ

Table 1a
Demographic data and clinical scores: Values are given as mean ± standard deviation (minimum - maximum). MSA-P: multiple system atrophy-parkinsonism, PD: Parkinson's disease, LEDD: Levodopa equivalent daily dose, DA: medication includes dopamine agonist, UPDRS III: Unified Parkinson's Disease Rating Scale motor examination, UMSARS II: Unified Multiple System Atrophy Rating Scale motor examination, HADS: Hospital Anxiety and Depression Scale, n.d.: not done, MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, NART: National Adult Reading Test. N.S, not significant; *p < 0.05, **p < 0.01 after post hoc testing.

	MSA-P (n = 11)	PD (n = 11)	Controls (n = 9)	Test statistic, P value
Age (years)	61.4 ± 8.2 (47–72)	66.2 ± 7.0 (54–75)	60.0 ± 5.8 (52–69)	H = 9.79, *P* = 0.02 N.S.
Sex (female/male)	7/4	5/6	4/5	X^2 = 3.528 *P* = 0.317
Age at disease onset (years)	57.6 ± 7.8 (44–69)	59.4 ± 9.5 (45–70)	–	U = 47.0, *P* = 0.375
Disease duration (years)	3.9 ± 2.0 (1–8)	6.5 ± 3.7 (2–14)	–	U = 32.0, *P* = 0.06
LEDD	765 ± 446 (300–1760)	722 ± 378 (300–1200)	–	U = 60.0, *P* = 0.974
UPDRS III	37.6 ± 11.6 (21–60)	26.4 ± 6.7 (18–36)	–	U = 24.5, *P* = 0.02
UMSARS II	22.6 ± 7.0 (15–35)	–	–	
HADS anxiety	10.1 ± 4.9 (4–20)	5.0 ± 2.2 (2–9)	5.1 ± 2.7 (2–11)	H = 9.57, *P* = 0.008 * MSA-P vs control, * MSA-P vs PD
HADS depression	10.0 ± 3.7 (4–15)	4.6 ± 2.2 (1–8)	2.7 ± 3.5 (0–9)	H = 13.4, *P* = 0.001 ** MSA vs control
MMSE	28.5 ± 1.7 (26–30)	28.9 ± 0.8 (28–30)	29.7 ± 0.7 (28–30)	H = 4.41, *P* = 0.110
MoCA	25.6 ± 2.7 (21–29)	26.0 ± 2.9 (21–29)	28.3 ± 1.4 (25–30)	H = 3.49, *P* = 0.175
NART	35.2 ± 8.5 (23–46)	39.0 ± 8.2 (23–50)	41.7 ± 9.2 (24–49)	H = 5.52, *P* = 0.063

between groups. Regarding affective symptoms, MSA-P patients scored higher in the HADS anxiety score (p = 0.049) than PD patients, indicating higher levels of affective disturbance. Compared to the control group, MSA-P patients showed higher HADS anxiety (p = 0.046) and HADS depression scores (p = 0.002). There were no significant differences in HADS scores between the PD and control group. Disease duration was not statistically different between MSA-P and PD, although there was a trend to significance. Motor severity as measured by the UPDRS-III was higher in the MSA-P compared to PD group. All PD patients and ten MSA-P patients were taking levodopa, and total dopaminergic medication dose as measured by LEDD was similar between groups.

The main results of the neuropsychological test set are listed in Table 1b. MSA-P patients showed deficits in the TMT B-A score (p = 0.039) compared to PD patients. Compared to controls, MSA-P patients performed worse in the Digit span total backwards score (p = 0.044) and TMT B-A score (p = 0.011). There were no group differences between PD patients and controls and no group differences in the remaining tests (lexical or semantic verbal fluency, HVLT-R or Stroop).

The main results of DTI data from the ROI-based approach and from corticostriatal tractography can be found in Supplementary Table 1. No group differences between patients with MSA-P and PD were detected. Compared to controls, patients with MSA-P showed lower FA along tracts from the left anterior (p = 0.041) and left posterior cingulate gyrus (p = 0.036) to the striatum and lower FA along the right anterior (p < 0.001) and left superior (p = 0.003) corticostriatal tracts. Patients with PD showed lower FA along tracts to the striatum from the bilateral anterior cingulate gyrus (left p = 0.007, right p = 0.016), left posterior cingulate gyrus (p = 0.024), bilateral middle frontal gyrus (left p = 0.002, right p = 0.022), bilateral inferior frontal gyrus (left p = 0.004, right p = 0.010) and lower FA in the left superior corticostriatal tract (p = 0.015) compared to controls. There were no differences between groups concerning MD along tracts.

Comparing regional glucose uptake ratios of MSA-P with PD patients (Supplementary Table 2 and Supplementary Fig. 2), uptake was relatively reduced in the bilateral striatum (left p = 0.013, right p = 0.015) and relatively increased activity in the bilateral occipital lobe (left p = 0.004, right p = 0.001) and cuneus (left p = 0.026, right p = 0.043), left posterior temporal lobe (p = 0.002), bilateral parietal lobe (left p < 0.001, right p = 0.009) and bilateral superior parietal gyrus (left p = 0.015, right p = 0.002).

Compared to controls, MSA-P patients showed reduced uptake in the left pallidum (p = 0.037) and increased uptake in the left postcentral gyrus (p = 0.014).

Compared to controls, PD patients showed reduced FDG uptake in the bilateral occipital lobe (left p = 0.029, right p = 0.006), right lingual gyrus (p = 0.001) and bilateral cuneus (left p = 0.016, right p = 0.027) and left posterior temporal lobe (p = 0.012) and relatively increased uptake in the right superior temporal gyrus (p = 0.033), right anterior gyrus cinguli (p = 0.015), left middle frontal gyrus (p = 0.019), bilateral precentral gyrus (right p = 0.001, left p = 0.008), left anterior orbital gyrus (p = 0.035), and left postcentral gyrus (p = 0.006).

We identified several correlations between metabolic and structural measures in the pre-defined ROIs and neuropsychological performance. Performance in the interference condition of the Stroop test was correlated with [^{18}F]-FDG uptake ratio in the left (r = 0.44, p = 0.019) and right (r = 0.56, p = 0.007) middle frontal gyrus. When looking at MSA-P and PD patients separately, these correlations were driven by the PD group (Fig. 1).

Time to perform Trail Making Test-B was correlated with MD along the tracts from the right middle frontal gyrus to the striatum (r = 0.55, p = 0.001). This correlation was also significant when analyzing MSA-P and PD patients separately (Fig. 2a).

Additionally, performance in the interference condition of the Stroop Test correlated negatively with MD along tracts from the left inferior frontal gyrus to the striatum (r = −0.53, p = 0.004). When looking at MSA-P and PD patients separately, this correlation is driven by the PD group (Fig. 2b).

Performance on Trail Making Test-B was correlated with MD along tracts from the left inferior frontal gyrus to the striatum (r = 0.52, p = 0.014) and MD along tracts from the right inferior frontal gyrus to the striatum (r = 0.43, p = 0.029). These correlations are mainly driven by the MSA-P group (Fig. 3).

Table 1b
Results from neuropsychology: Values are given as mean ± standard deviation (minimum - maximum). MSA-P: multiple system atrophy-parkinsonism, PD: Parkinson's disease. HVLT-R: Hopkins Verbal Learning Test revised, TMT: Trail Making Test. N.S. not significant; *p < 0.05, **p < 0.01 after post hoc testing.

	MSA-P (n = 11)	PD (n = 11)	Controls (n = 9)	Test statistic, *P* value
HVLT-R total recall score	20.1 ± 6.9 (7–30)	20.3 ± 4.1 (13–27)	24.1 ± 3.4 (17–28)	H = 4.40, *P* = 0.11
HVLT-R delayed recall score	7.2 ± 3.0 (3–12)	6.4 ± 2.9 (0–10)	8.7 ± 2.4 (4–12)	H = 5.28, *P* = 0.07
HVLT-R recognition discrimination index	9.8 ± 1.3 (8–12)	8.6 ± 2.5 (3–12)	10.6 ± 1.4 (8–12)	H = 4.57, *P* = 0.10
Verbal fluency lexical	31.7 ± 12.3 (6–53)	36.8 ± 12.1 (13–56)	40.0 ± 10.9 (24–59)	H = 2.59, *P* = 0.28
Verbal fluency semantic	16.1 ± 3.9 (12–24)	18.1 ± 7.1 (6–30)	21.2 ± 3.6 (14–26)	H = 5.55, *P* = 0.06
Digit span total forwards score	7.7 ± 2.6 (5–13)	9.0 ± 1.8 (6–12)	9.4 ± 2.5 (6–12)	H = 3.52, *P* = 0.17
Digit span total backwards score	5.4 ± 1.4 (3–8)	6.5 ± 1.4 (4–8)	8.1 ± 2.5 (5–12)	H = 7.29, *P* = 0.02 * MSA-P vs control
Stroop colour naming correct	60.4 ± 12.9 (36–87)	67.3 ± 13.6 (43–92)	74.2 ± 12.4 (58–97)	H = 5.71 *P* = 0.058
Stroop interference correct	34.2 ± 12.5 (13–52)	35.3 ± 9.8 (19–53)	45.2 ± 12.3 (30–72)	H = 3.68. *P* = 0.16
Stroop colour minus interference score	26.2 ± 11.5 (9–52)	32.0 ± 8.7 (20–52)	29.0 ± 11.3 (10–46)	H = 2.30, *P* = 0.32
TMT A (sec)	44.9 ± 11.5 (36–75)	41.3 ± 18.9 (25–85)	31.8 ± 11.6 (18–47)	H = 4.78, *P* = 0.09
TMT B (sec)	92.5 ± 29.5 (33–145)	82.4 ± 52.9 (37–220)	57.6 ± 11.5 (42–74)	H = 6.09, *P* = 0.048 N.S.
TMT B-A score	53.4 ± 18.3 (23–79)	33.1 ± 18.1 (8–54)	25.8 ± 7.8 (15–44)	H = 11.77, *P* = 0.003 * MSA-P vs PD, ** MSA-P vs control

5. Discussion

In this multimodal imaging study, we were able to identify distinct patterns of cognitive dysfunction in MSA-P and PD, as well as relate these to changes in frontostriatal metabolic and white matter changes.

We showed poorer performance of patients with MSA-P on tests of executive function and higher indices of anxiety compared to patients with PD. Compared to controls, patients with MSA-P showed deficits in attention and executive function and also impaired working memory, as well as higher levels of anxiety and depression. Similar performances on tests of executive function were seen in a study which matched MSA and PD patients for overall cognitive performance, albeit the MoCA scores were numerically lower in both groups compared to our findings [31]. Fiorenzato and colleagues, however, did not identify any differences in executive function measured by Trail Making or Stroop Test in 30 patients with mixed subtype MSA compared to 65 with PD [32]. In

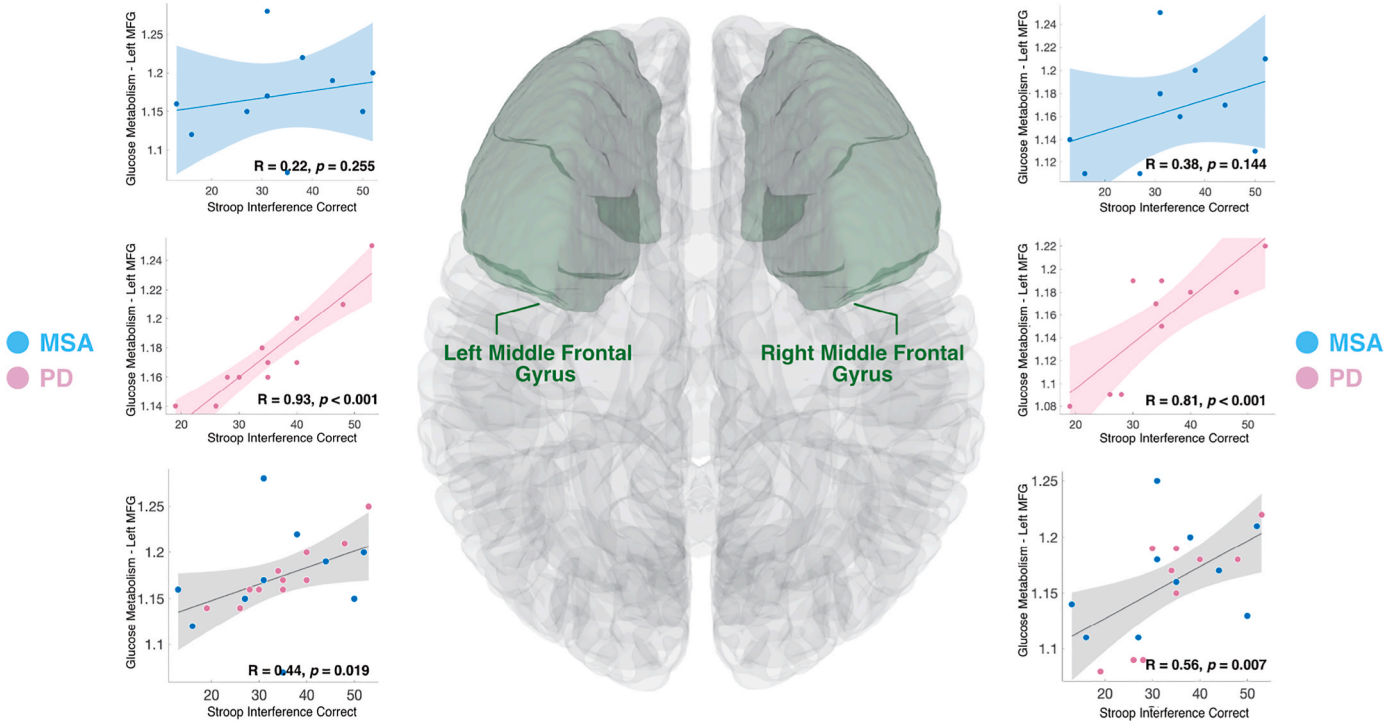

Fig. 1. Correlations between the number of correct responses in the interference condition of the Stroop test with FDG uptake ratio in the left and right middle frontal gyrus (MFG, green ROIs) shown for both patient groups together and PD (red scatterplot) and MSA-P (blue scatterplot) separately. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

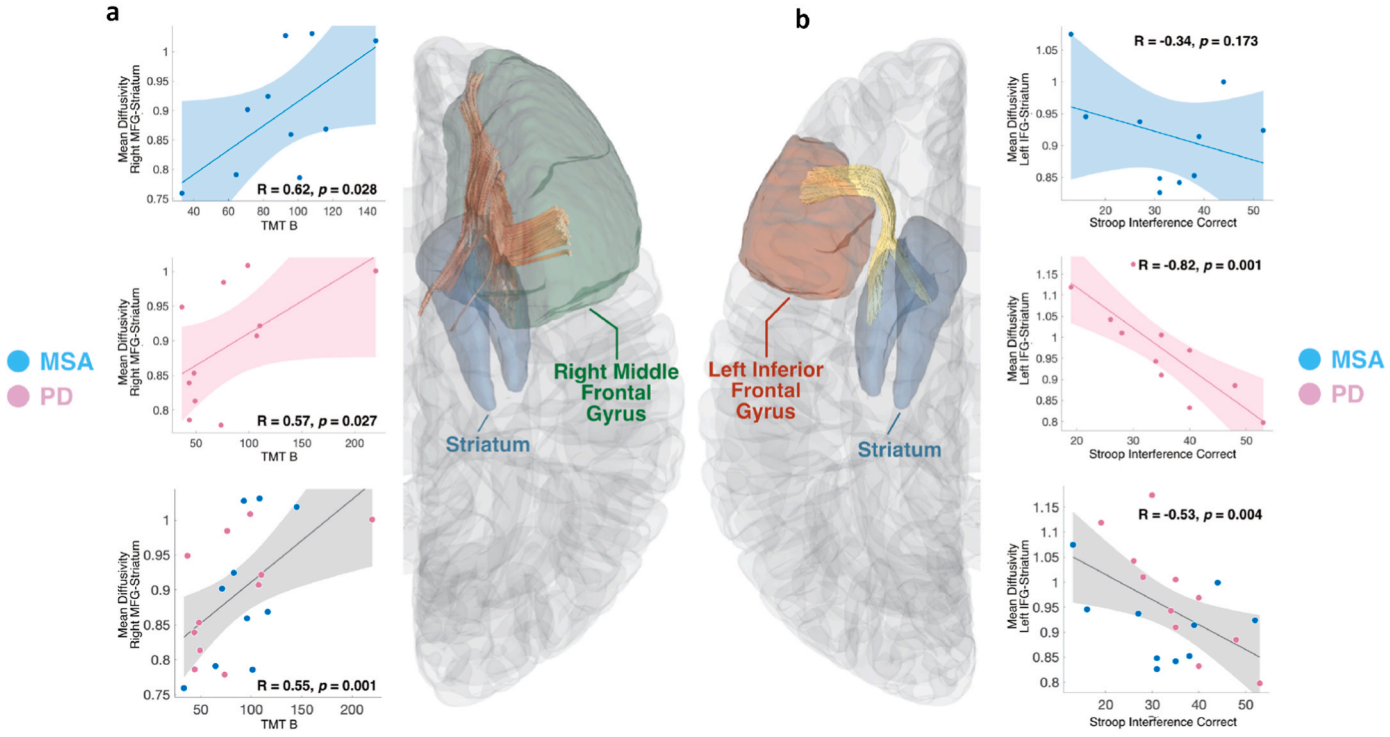

Fig. 2a. Correlation between the time needed for part B of the Trail Making Test with MD along tracts from the right middle frontal gyrus (MFG, green ROI) to the striatum (blue ROI) shown for both patient groups together and PD (red scatterplot) and MSA-P (blue scatterplot) separately, **2b:** Correlation between the number of correct responses in the interference condition of the Stroop test with MD along tracts from the left inferior frontal gyrus (IFG, orange ROI) to the striatum (blue ROI) shown for both patient groups together and PD (red scatterplot) and MSA-P (blue scatterplot) separately. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

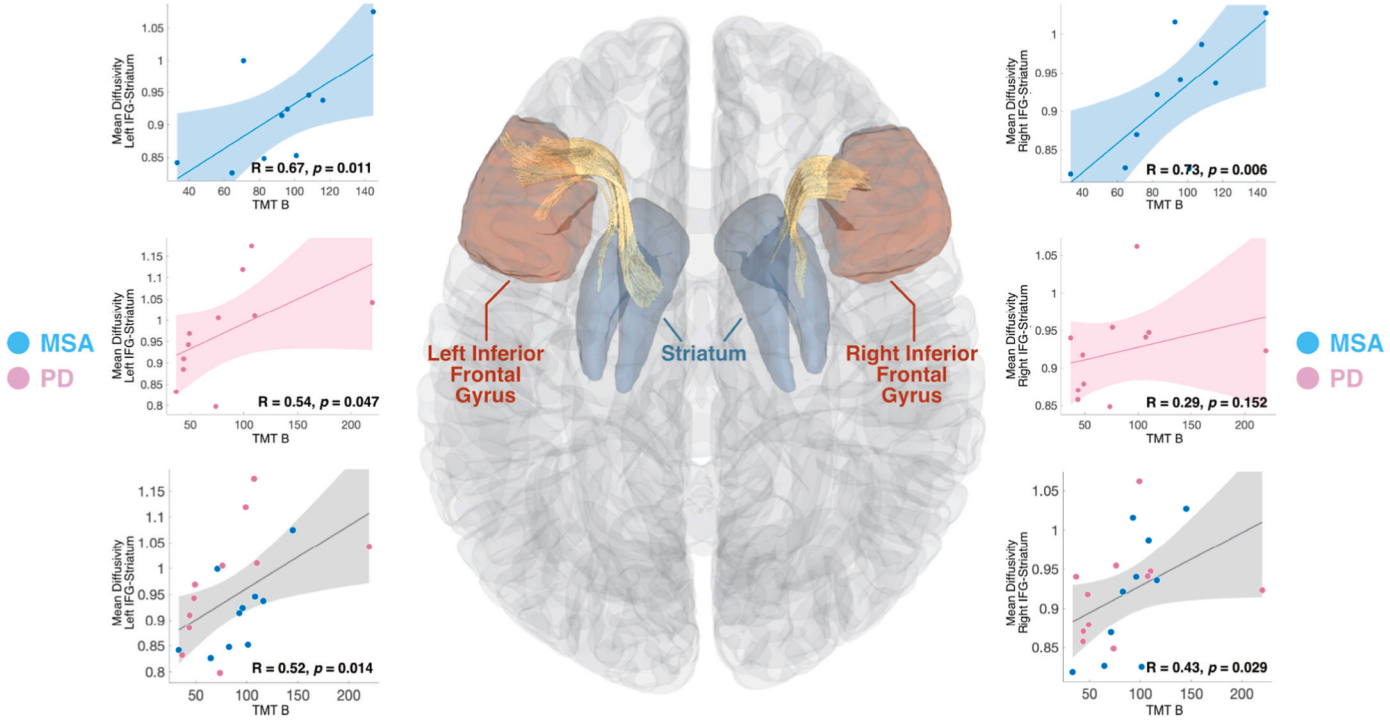

Fig. 3. Correlations between the time needed for part B of the Trail Making Test with MD along tracts from the left and right inferior frontal gyrus (IFG, orange ROIs) to the striatum (blue ROI) shown for both patient groups together and PD (red scatterplot) and MSA-P (blue scatterplot) separately. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

particular, PD patients of a similar disease duration to this report showed normal baseline executive function. The finding of participants with MSA-P endorsing more affective disturbance and specifically anxiety compared to both PD patients and controls is consistent with previous studies examining mood and cognitive function in MSA [7]. Our study was not powered to assess the impact of affective disturbance on cognitive dysfunction. However, previous work in a more advanced population of MSA-P patients indicated an impact of mood on episodic memory and delayed recall, neuropsychological measures which were not impaired in our analysis [33]. The possibility that depression and anxiety could impact on cognitive test performance remains and further studies specifically examining this relationship in larger cohorts at an earlier disease stage would be of value.

Our main focus was to relate neuropsychological deficits to putative underlying functional and structural correlates. Performance in the Stroop interference condition, which measures response inhibition, was correlated with [^{18}F]-FDG uptake in the bilateral middle frontal gyrus including the DLPFC in the PD group. A similar association between executive function and (right) DLPFC and medial frontal metabolism has been reported in a SPECT study of patients with MSA-P [7]. Our data, however, suggest a greater contribution of DLPFC function to executive performance in PD than in MSA-P. Stroop interference test performance was also correlated with white matter integrity along tracts between the striatum and the left inferior frontal gyrus in PD, but not MSA-P. Interestingly, in a recent PET study in PD patients by Han and colleagues, executive function was found to correlate with metabolism in the inferior frontal gyrus and additionally in the putamen and insula [34].

Processing speed, attention and mental flexibility as assessed by part B of the Trail Making Test correlated with corticostriatal white matter integrity along tracts from the bilateral inferior frontal gyrus in MSA-P and from the right middle frontal gyrus in both MSA-P and PD patients. Deficits in attention correlate with white matter changes of the cingulate gyrus in PD patients [10] It has been suggested that fronto-subcortical white matter change relates to executive dysfunction in MSA [12]. Our study supports this hypothesis by showing the association between bilateral frontostriatal white matter changes in MSA-P and executive dysfunction.

Koga and colleagues examined differences in clinicopathological disease burden in 33 of 102 MSA patients with cognitive impairment [35]. Whereas they found no correlation between frontal pathological changes and cognitive impairment, greater pathological change was seen in the dentate gyrus in MSA patients with cognitive impairment compared those without. In contrast to this retrospective study, our data suggest that changes in frontostriatal white matter integrity are an important driver of cognitive dysfunction in relatively early MSA-P. These changes, however, may not correlate directly with pathological change as seen post mortem in advanced cases.

Measures of frontostriatal white matter tract integrity did not differ between patients with MSA-P and PD. However, compared to a control imaging group, both patient groups showed widespread white matter damage as indicated by decreased FA. A recent study identified significant change in fibre density and other DTI metrics in frontostriatal motor and cognitive fibres in PD compared to healthy controls [11]; our findings indicate similar changes occurring in MSA-P. Taken together, both patient groups suffer from disruption of frontostriatal connectivity associated with cognitive decline. Regarding the results from [^{18}F]-FDG PET, the distribution of metabolic changes seen in MSA-P and PD was similar to previous reports albeit using a different method [5,36]. Cerebellar metabolic deficits were prominent even in our patients with MSA-P, whereas posterior changes were apparent in PD. Compared to controls, reduced glucose uptake in the basal ganglia in MSA-P was shown as well, although we did not find putaminal hypermetabolism in PD vs controls which has been reported previously.

We acknowledge limitations of our study. The relatively small sample size may restrict the generalizability of our conclusions, as may the relatively short disease duration of patients with MSA-P compared to those with PD. The short disease duration may limit diagnostic accuracy in MSA-P, although all participants met published diagnostic criteria. However, early participation for people with MSA is important, due to

the increasing disability and faster disease course limiting the opportunity for assessment as symptoms accrue. Assessments encompassing the course of cognitive impairment longitudinally might give a different picture of the evolution of the underlying structural and functional substrates. Although we have compared cognitive performance in PD and MSA-P to a healthy control group, those controls did not undergo imaging so direct correlation between cognitive and imaging measures in healthy subjects was not possible. In addition, the relatively small numbers of the healthy control group also represent a potential limitation. The potential impact of motor disability on performance on cognitive testing is also a possible limitation, given the greater motor impairment in participants with MSA-P than PD. However, the most robust differences were seen in non-motor tasks like digit span, or those which intrinsically correct for motor dysfunction like Trail making B-A. Other factors such as medication could also impact on cognitive performance; however, there was no difference in dopaminergic medication intake between groups. Whereas patients met current diagnostic criteria for MSA-P and PD, pathological verification was not available in most cases. Strengths of the study include multimodal imaging techniques used, and detailed characterization using validated neuropsychological assessments.

In conclusion, patients with MSA-P show severity of executive dysfunction not seen in comparable patients with PD. [^{18}F]-FDG uptake in DLPFC is associated with executive function in PD, whereas reduced white matter integrity in inferior frontostriatal tracts may be more important to executive function in MSA-P. Our study is novel in that it explores both structural and metabolic changes in frontostriatal pathways and their relationship to cognitive dysfunction. These findings add to our understanding of the substrates of cognitive dysfunction in MSA-P and PD, and suggest a bigger role for white matter pathology in MSA-P, whereas frontal hypometabolism may relatively predominate in PD. Given the early executive dysfunction seen, our study supports the cognitive evaluation of patients with MSA in clinical practice. The long-term goal should be to develop comprehensive therapeutic strategies that take into account these important non-motor symptoms in MSA, including disease-modifying strategies to reduce white matter damage in this condition.

Authors' roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.

D Kübler: 1B–C, 2A-C, 3A
C Kobylecki: 1A-C, 2B–C, 3A
KR McDonald: 1A-C, 3B
J Anton-Rodriguez: 1C, 3B
K Herholz: 1A, 3B
SF Carter: 1C, 3B
R Hinz: 1C, 3B
JC Thompson: 1A, 1C, 3B
B Al-Fatly: 2 A-C, 3B
A Gerhard: 1A-B, 2B, 3B

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Declaration of competing interest

No conflicts of interest are reported.

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Appendix A. Supplementary data

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