Non-invasive imaging markers of iron accumulation in Multiple System Atrophy

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OBJECTIVE

- To define the localization and extent of iron accumulation in patients with early multiple system atrophy (MSA).

BACKGROUND

- Early diagnosis of MSA is vital for maximizing neuronal preservation with disease modifying therapies.
- Iron dyshomeostasis is critical in MSA pathogenesis due its ability to promote α-synuclein aggregation and oxidative stress in key regions of pathology.[1]
- We used quantitative susceptibility mapping (QSM) to evaluate iron accumulation[2] in early MSA patients from the Biomarkers of progression in Multiple Systems Atrophy (bioMUSE) study, Parkinson's disease (PD), and healthy controls (HC).

METHODS

- All participants completed a neurologic examination and underwent 3T brain MRI.
- 9 MSA patients 30-75 years old, were included, and all had evidence of parkinsonism, autonomic dysfunction, pyramidal, and/or ataxic findings on exam. All 17 PD participants met UK Brain health criteria for diagnosis and were of similar age to MSA and HC cohorts (Table 1).
- QSM data were acquired using a 3D multi-echo gradient echo sequence (acquisition time=7 min). QSM reconstruction was performed using the MEDI toolbox.[3]
- QSM images were coregistered to the PD25 MNI template[4] and voxel-wise analyses were performed to assess differences in iron accumulation between groups.
- Mean susceptibility values in the regions-of-interest (ROI) in the putamen (PT), caudate (CN), globus pallidus internus and externus (GPi/GPe), substantia nigra (SN), red nucleus (RN) and dentate nucleus (DN) (Fig. 3) were obtained, and Wilcoxon tests were used to compared results between groups.

Table 1. Demographic and clinical data

Variables	MSA	PD	HC
N	9	17	18
Sex (M/F)	3/6	12/5	8/10
Age (years)	63.1 ± 9.1	63.2 ± 6.1	65.6 ± 6.9
UMSARS Total	34.0 ± 10.4	-	-
MDS-UPDRS Part III (OFF)	-	26.9 ± 10.1	-

RESULTS

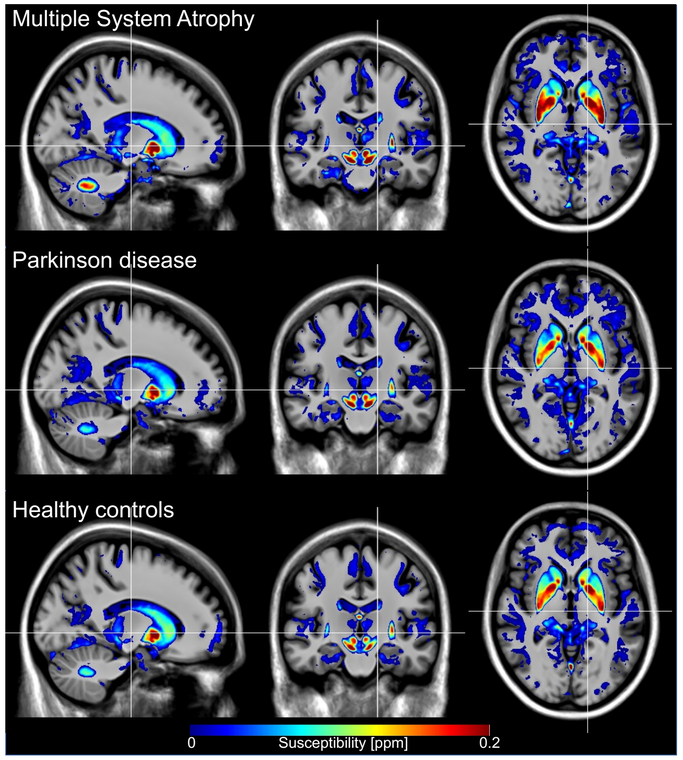

Fig. 1. Mean QSM for the MSA, PD and HC groups overlaid on the PD25 T1w template

- Voxel-wise evaluations revealed higher iron accumulation in MSA patients compared to both PD and HC in clusters located in the PT, GPi, GPe, and thalamus. A cluster in the SN and RN was also observed when compared to HC (Fig. 2)

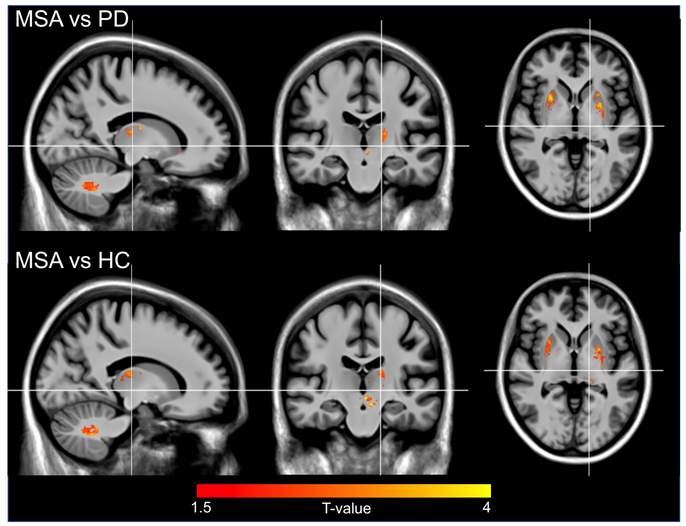

Fig.2. Voxel-wise results. Map of clusters (p<0.05, cluster size>10 voxels) where iron accumulation was increased in MSA vs. PD and HC. Clusters localized to areas including the PT, GPe, SN, RN, DN and thalamus.

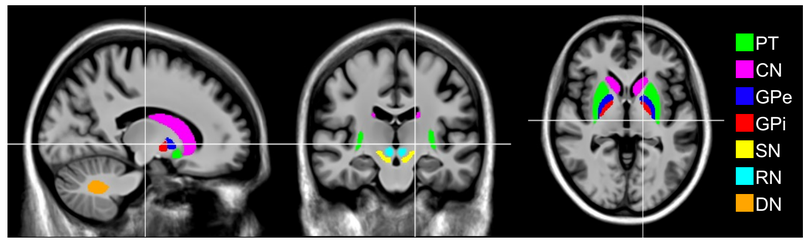

Fig. 3. Illustration of the location of the ROIs

- The ROI analysis showed increased iron concentration in MSA patients compared to PD and HC in the PT and GPe (Table 2).
- Significant differences were also observed in the DN when compared to HC.

Table 2. Region-of-interest QSM results

ROI	MSA	PD	HC	MSA vs PD†	MSA vs HC†
PT	0.11 ± 0.04	0.08 ± 0.03	0.09 ± 0.03	**0.03***	**0.04***
CN	0.07 ± 0.02	0.08 ± 0.03	0.08 ± 0.02	0.90	0.72
GPe	0.18 ± 0.03	0.15 ± 0.03	0.16 ± 0.02	**0.04***	**0.04***
GPi	0.13 ± 0.02	0.12 ± 0.03	0.11 ± 0.02	0.18	0.06
SN	0.16 ± 0.04	0.16 ± 0.04	0.14 ± 0.03	0.94	0.22
RN	0.14 ± 0.03	0.13 ± 0.04	0.12 ± 0.03	0.17	0.16
DN	0.10 ± 0.07	0.07 ± 0.03	0.06 ± 0.02	0.11	**0.04***

Mean ± standard deviation
† Wilcoxon Rank Sum Test p-value
* p-value<0.05

CONCLUSIONS

- Advanced quantitative MRI methods demonstrated pathological iron accumulation in the nigrostriatal, pallidal, thalamic, and dentate nucleus of the cerebellum in patients with early MSA.
- Iron concentration over time is a novel biomarker of disease progression.
- QSM methods may improve patient selection in clinical trials of disease modifying therapy in early MSA and has potential for assessing treatment induced changes.

REFERENCES

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