श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Final Report of Completed Project, Submitted to the Department of Biotechnology, Government of India

A. Summary

1. Project Title: **Quantitative estimation of regional brain iron deposition – a potential biomarker for Parkinson's Disease and other neurodegenerative conditions causing atypical Parkinsonism. (Ref: BT/PR19115/MED/122/11/2016)**
2. Date of Start of the project (as per sanction order): 25 July, 2017
3. Completion Report Duration: 25 July, 2017 to 24 November 2020.
4. Extension duration and revised completion date: 4 months of extension; total duration- 3 years and 4 months. Revised completion date: 24th November 2020
5. Total cost of the project (including revision): Rs. 20.1172 Lakhs, as per revised order dated 09/07/2019
6. Coordinator's detail: Dr Rajneesh K Gaur, Scientist E, Department of Biotechnology
7. Sanctioned objectives and objectives achieved (Tabular format):

Sanctioned Objectives	Objectives achieved
Quantitative estimation of regional iron content in the deep grey matter structures of the brain in patients with clinical diagnosis of Parkinson's Disease (PD) and Atypical Parkinsonism in whom clinical diagnosis has been made as per standard diagnostic criteria), using Susceptibility-Weighted Magnetic Resonance Imaging techniques	Achieved
Quantitative estimation of regional iron content in the same structures, in age matched healthy control subjects and comparison with the patient groups.	Achieved

Comparison of the regional iron content among the three study subject groups for significant differences	Achieved

8. Reason for non-achievement of objectives (Bullet points only): The objectives were achieved. In the original proposal, it was planned to include two different types of atypical Parkinsonisms – Progressive Supranuclear Palsy (PSP) and Multiple System atrophy (MSA). MSA is a much rarer disease compared to PSP and we did not get sufficient number of subjects during the study period, satisfying the clinical diagnostic criteria of MSA and able to / consenting to undergo the imaging protocols of the study. Therefore, the final analysis included only one type of atypical Parkinsonism (PSP), Parkinson's disease and healthy volunteers. This does not compromise the objectives of the study.
9. Infrastructure established (as per sanction order): No specific budget was requested for or sanctioned for establishing the infrastructure, as we already had the necessary infrastructure for the study, in our Institute
10. Manpower trained (as per sanction order, please include the break up with figures only e.g., number of M.Sc. Students/JRF/SRF/RA and Assistant Professor, etc.): Two JRFs (Both with post-graduate degree- M Tech – in Engineering) were trained in the specialized techniques involved in this study. In addition, six post-doctoral fellows in Movement disorders (Who were undergoing advanced training in the sub-specialty of Movement Disorders, after completing their DM in Neurology) who were involved in the project activities, also got trained in the clinical assessments and imaging protocols done as part of the study.
11. Number of SC/ST/OBC category people trained (Plz provide figures separately for each category): SC/ST: Nil OBC: Nil
12. Research outcome:
    - Publications: One publication being prepared, expected to be published by the end of 2021
    - Two presentations in an international conference
    - Patents: Nil (Not applicable)
    - Technology developed, transferred or commercialized: Nil (Not applicable)
    - Status of commercialized technology: Nil (Not applicable)
13. Summary (in two hundred words only): Parkinsonism is a clinical syndrome characterized by the presence of rigidity of muscles, bradykinesia (slowness of activities), rest tremor and postural instability. Parkinsonism is a manifestation of many neurodegenerative diseases including Parkinson's disease (PD) and the conditions labelled as "Atypical Parkinsonisms" which include many entities like Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA) and Corticobasal Degeneration (CBD). The diagnosis of all these conditions is clinical, as there are no

accurate radiological, blood or other body fluid biomarkers for these conditions. Differentiating Parkinson's disease from other Atypical Parkinsonisms is important as it has a different natural history, neuropathology and treatment strategy. Mineralization/ iron deposition of the deep gray nuclei undergoing neurodegeneration is a feature of the neurodegenerative diseases presenting with Parkinsonism. In this study, we explored whether the patterns of abnormal mineralization can be detected in live subjects using susceptibility-weighted magnetic resonance imaging (MRI) techniques and whether such patterns differentiate PD from healthy volunteers and atypical Parkinsonian disorders (Represented by the commonest sub-type- PSP). We found that mineralization of substantia nigra was more in PD compared to healthy volunteers and showed a modest degree of correlation with disease severity. Similarly, the mineralization of several of the deep gray structures was more in PSP compared to PD and healthy subjects and the increased mineralization correlated well with severity of clinical manifestations as assessed by the PSP-Rating Scale (PSP RS)

14. Grant remaining unspent along with justification: Rs 22747/-. Some of the participating subjects did not need travel allowance (E.g.: Patients admitted in our hospital for evaluation / management). Cost of MR imaging for some of the PD / Healthy volunteer subjects was lesser than estimated earlier as they consented and underwent MR imaging for other ongoing studies also, MR protocols were clubbed and cost was shared between the projects. Cheque for this amount is being submitted along with this report.
15. Justification for non-submission of yearly financial documents: All the financial documents have been submitted on time and the final financial documents are being submitted along with this report.

B. Progress in details (not more than 8 pages)

Parkinsonism is a clinical syndrome characterized by the presence of rigidity of muscles, bradykinesia (slowness of activities), rest tremor and postural instability. Parkinsonism is a manifestation of many neurodegenerative diseases including Parkinson's disease (PD) and the conditions labelled as "Atypical Parkinsonisms" which include many entities like Progressive Supranuclear Palsy (PSP), Multiple System Atrophy and Corticobasal Degeneration. PSP is the second-most common neuro-degenerative Parkinsonian disorder and is the commonest atypical Parkinsonian disorder. (1) It is a disabling and fatal disease with a median survival of around 7 years. (2) PSP is a 4R tauopathy. The current treatment of PSP is symptomatic and supportive; disease-modifying therapies including tau-focused ones may become available in future. (3) Though radiological features reflecting midbrain atrophy could support the diagnosis, the disease lacks a validated biomarker and the diagnosis is currently made on clinical grounds. (1,4,5) The core clinical features helping the diagnosis include supranuclear gaze

abnormalities, early axial motor dysfunction and postural instability. However, it has been identified that PSP has wide phenotypic variability with clinical features overlapping with those of Parkinson's disease (PD), Corticobasal Degeneration (CBD) and Frontotemporal Dementia (FTD). (3,5) Around a third of patients may have a phenotype resembling PD. (2) Differentiation from PD is likely to become all the more important in future, if tau-specific disease modifying therapies emerge.

Mineralization of brain parenchyma occurs in neurodegenerative diseases. Deposition of iron is of particular interest, though it is debatable whether iron accumulation is the cause or consequence of neurodegeneration; it could probably be both. (6,7) Susceptibility weighted magnetic resonance (MR) imaging techniques can be used to evaluate the mineralization of deep gray matter (8) and visual inspection of topographic differences in mineralization could differentiate various neurodegenerative Parkinsonian disorders. (9) Quantitative Susceptibility Mapping (QSM) is a recently evolved technique and is found useful in *in vivo* quantification of iron content. (10,11) Strong correlation of bulk magnetic susceptibility detected by QSM, with tissue iron content from deep gray matter structures has been demonstrated by post mortem studies. (12) The technique has been applied in neurodegenerative conditions including motor neuron disease and degenerative Parkinsonism to quantify mineralization in various brain regions and significant quantitative differences have been demonstrated between various neurodegenerative Parkinsonian disorders. (13–15)

Ageing could affect mineralization and magnetic susceptibility of deep gray matter. (16) In this study, we examined whether magnetic susceptibility estimates from deep gray matter structures differ between those with neurodegenerative Parkinsonisms and age-matched healthy volunteers, and between PSP and PD which is the most frequent and closest clinical mimic of PSP. We also explored whether quantitative susceptibility estimates correlated with disease severity assessed using disease-specific rating scales in PSP and PD.

Methods:

Consecutive patients with PSP attending the Movement Disorders clinic of our University Hospital were recruited for the study. The clinical diagnosis in all the patients was confirmed independently by two movement disorder specialists. The clinical criteria published by the International Parkinson and Movement Disorder Society (MDS) (2017) was used for diagnostic categorization. (5) As our patients had no neuropathological confirmation of diagnosis, we included only patients with the highest level ("probable" PSP) of clinical diagnostic certainty.(3) Patients with PD who were recruited for the study were age- and duration-matched to PSP patients. Diagnosis of PD was made based on the United Kingdom Parkinson's disease Society Brain Bank criteria. (17) As PD patients were matched with PSP patients for duration of Parkinsonism, majority belonged to "early PD" category. Therefore, to

maximize diagnostic accuracy in the group, MDS clinical diagnostic criteria for PD was also applied and only those patients who fulfilled the criteria for the highest degree of diagnostic certainty (clinically established PD) were finally selected. (18,19) Age-matched healthy volunteer subjects were selected from those who responded to the call notification regarding the study, family friends of patients and visitors to the hospital. Subjects with poorly controlled vascular risk factors and other medical comorbidities were excluded.

All subjects underwent detailed clinical evaluation. Disease-specific rating scales were administered by the movement disorder specialists to assess severity of neurological deficits in the two patient groups. PSP rating Scale (PSPRS) (20) and Unified Parkinson's Disease Rating Scale (UPDRS), parts II and III (21) respectively were used for PSP and PD patients. The UPDRS assessment was done after overnight withdrawal of medications in the practically defined OFF state in PD. (22) For post-hoc analysis of correlation of SN susceptibility with the severity of contralateral signs of PD, the TRIB (tremor, rigidity and bradykinesia) scores were calculated for each side of the body separately as previously described. (23)

MR Imaging, Image Processing and Analysis:

All the subjects underwent MR imaging using 3T MR System (Discovery MR 750w, GE Healthcare, USA) with 24 channel neurovascular phased array head coil. The scanning protocol included acquisition of T2* weighted image using 3D multi-echo gradient-echo sequence for SWAN (Susceptibility Weighted Angiography) (Five equally spaced echoes with TE ranging from 5.7 to 29.5 ms, TR=62.2 ms, flip angle = 15^{o}, slice thickness = 2mm, voxel size = 512 x 512 x 2 mm^{3}). Structural T1 weighted MRI scans were acquired for each subject using a 3D FSPGR sequence for anatomic identification and image normalization. In addition to the above sequences, a multiple dynamic multiple echo (MDME) sequence was carried out (TR= 4000 ms, number of TE = 2, TE = 21.84 and 87.36, ETL=12, Matrix=320x288, Bandwidth=22.73, Slice thickness=5mm, spacing=1mm, NEX=1, FOV=22cm, acquisition time = 6.08 minutes) to measure T1 and T2 relaxation rates in structural regions of interest. The guidelines provided by the institution were followed during the scanning procedure. The run-time for the protocol was approximately 25 minutes.

The axial SWAN images acquired using the flow compensated 3D GRE sequence with multiple echoes were subjected to several post-processing stages using Morphology Enabled Dipole Inversion (MEDI) approach to generate QSM. (24) The input stage utilised real and imaginary data of 3D gradient echo images. The reconstruction process involved acquisition of magnitude and phase data from the real and imaginary data. Binary masks of tissue were created from the magnitude data. Brain Extraction Tool (BET) of FSL software was utilised for generation of brain masks. (25) The raw phase images were unwrapped using Laplacian based unwrapping algorithm and background field removal

was performed on the unwrapped phase data to eliminate the background fields generated by sources external to the volume of interest. This stage was followed by generation of a local field map that preserved relevant tissue information. After the background field removal stage, solving an ill-posed inverse problem (dipole inversion) with the help of MEDI method gave the QSM maps.

Region-of-Interest (ROI)-based quantitative analysis of magnetic susceptibility was done with the help of ITK-snap (Version 3.6) a public domain software. (26) Substantia nigra (SN), red nucleus (RN), head of caudate nucleus (CN), putamen and globus pallidus (GP) were identified a priori as the areas of interest and were segmented out and analyzed (9,15,27) Figure 1 shows the segmentation images from a healthy subject. The segmentations were saved in NIfTI format (single file, compressed format). Left and right counterparts of the regions of interest (ROI) were colored and labelled differently. For each ROI, the susceptibility values were quantified in parts per billion (ppb). For each patient, the mean value of the two sides was calculated for each ROI, for between-group comparisons and correlation with clinical rating scales. Figure 2 shows the steps involved in Quantitative Susceptibility Mapping.

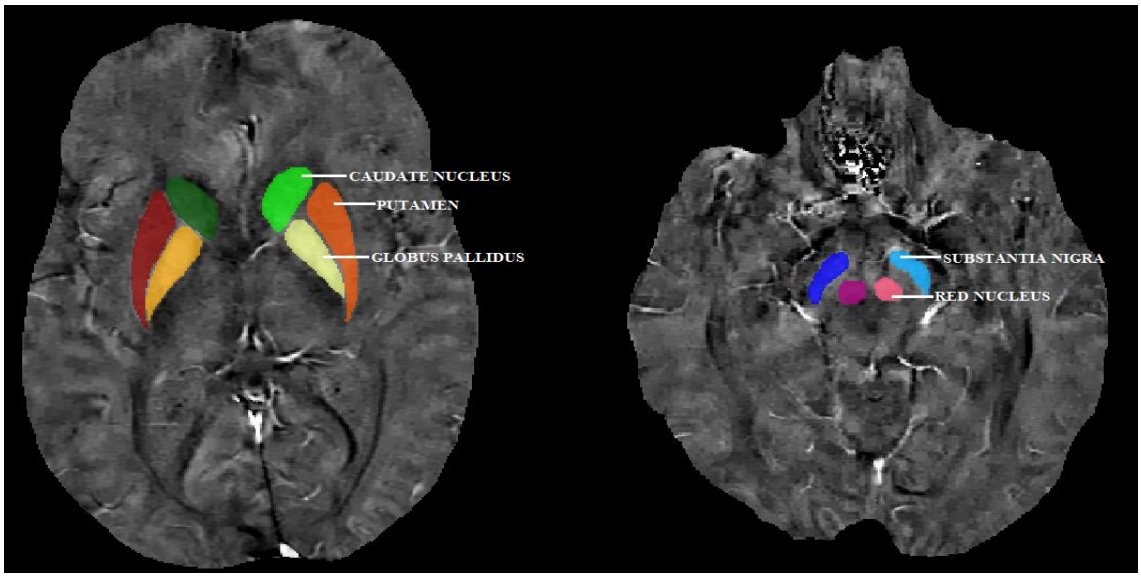

Figure 1: Segmentation images from a healthy subject showing the regions of interest (ROIs)

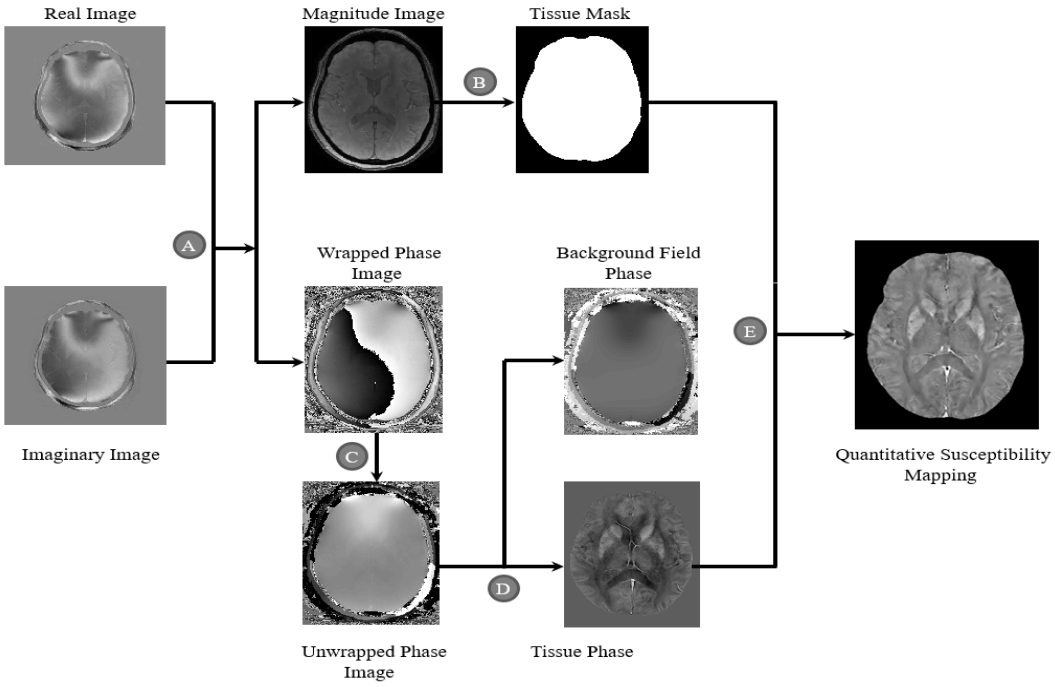

Figure 2: Steps involved in Quantitative Susceptibility Mapping

Statistical Analysis: Data in tables is presented as means ± standard deviation. Categorical variables were analyzed using Chi square test. For continuous variables, Bartlett's test for equal variances was used to assess variability. One-way ANOVA was used when the variability was not significant and the non-parametric Kruskal Wallis test was used otherwise. Post-hoc comparisons were done using Bonferroni test or Dunn's pairwise comparisons when significant differences were detected respectively in ANOVA or Kruskal Wallis test. Pearson correlation coefficient was used to assess the strength of correlation between magnetic susceptibility of grey matter structures and clinical variables. P value less than 0.05 was considered statistically significant for. The data was analyzed using medical statistics software (IBM SPSS Statistics 21).

The study protocol was reviewed and approved by the Technical Advisory Committee and Institutional Ethics Committee and all participants gave written informed consent.

Results:

We recruited 30 patients with PSP, 30 patients with PD and 30 healthy volunteers for the study. The scans from 27 patients with PSP and 26 patients each in the PD and healthy volunteer groups were available for final analysis. The remaining scans were excluded because of movement related artefacts (scans from 6 subjects), presence of significant white matter abnormalities indicating co-existent microvascular disease (2 subjects) and technical issues in the acquired imaging files (3 subjects)

Table 1 shows the demographic and clinical features of the study participants, including the scores of the disease-specific rating scales used. The proportion of women in the healthy volunteer group was significantly higher (P=0.006) compared to the patient groups. The three groups had similar age (P=0.07) and no significant difference was noted among the PD and PSP groups with regard to duration of motor symptoms at the time of recruitment to the study.

Table 2 shows the magnetic susceptibility from the various ROIs in parts per billion and the respective P values. Patients with PD showed significantly higher mineralization in the substantia nigra while it was similar to healthy volunteers in all other ROIs. The mineralization in all the ROIs, including substantia nigra, was significantly higher in PSP patients when compared to healthy volunteers or PD patients. Figures 3 and 4 show representative images from healthy volunteer, patient with PD and patient with PSP.

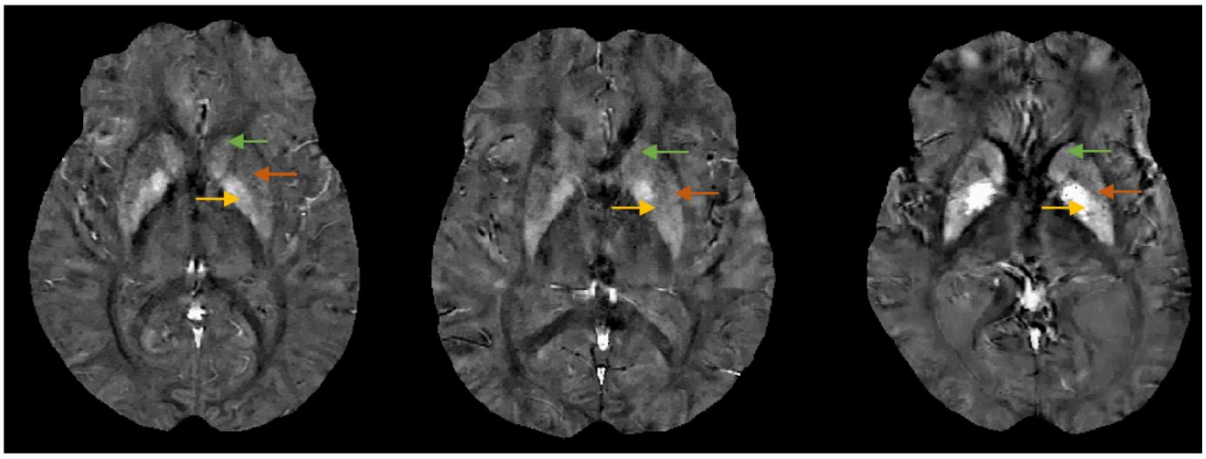

Figure 3: SWAN images showing the magnetic susceptibility in the caudate nucleus, putamen and globus pallidus , in a healthy volunteer (first image), patient with PD (second image) and patient with PSP (third image). Brighter signals indicate higher magnetic susceptibility

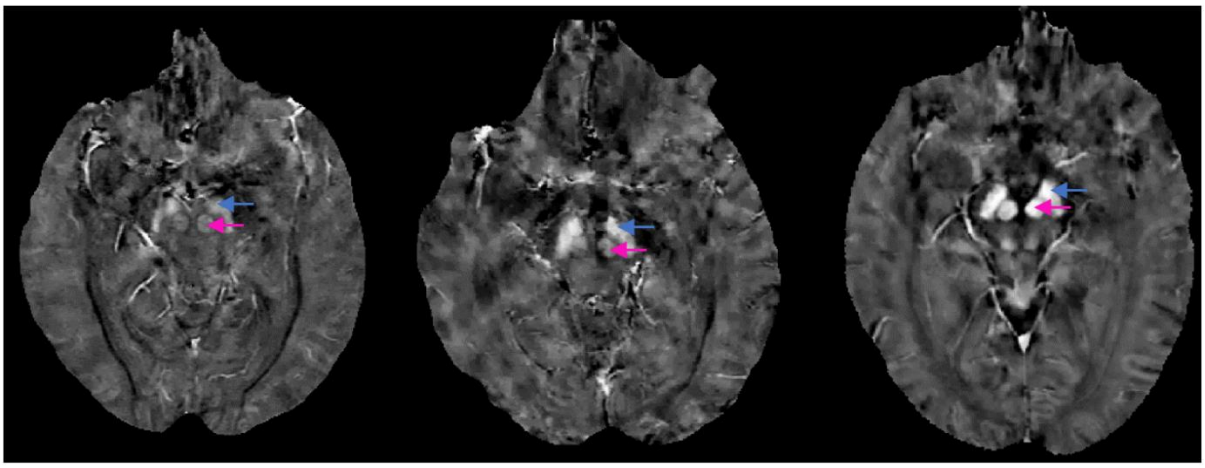

Figure 4: SWAN images showing the magnetic susceptibility in the substantia nigra and red nucleus , in a healthy volunteer (first image), patient with PD (second image) and patient with PSP (third image). Brighter signals indicate higher magnetic susceptibility

We examined whether age correlates with mineralization in any of the ROIs in our healthy volunteer group. None of the ROIs (Caudate nucleus- R <0.01 P=0.98; Putamen- R=0.17, P=0.42; Globus Pallidus- R=-0.09, P=0.67; Substantia nigra- R=0.11, P=0.59; Red Nucleus- R=0.12, P=0.54) showed any significant correlation with age.

The correlation of mineralization in the ROIs, with age, duration of disease and disease-specific rating scales in the two patient groups are shown in table 3. The mineralization of the substantia nigra showed a moderate degree of correlation with the duration of PD and the Unified Parkinson's disease rating scale motor scores. In patients with PSP, the mineralization of the deep gray nuclei correlated with the PSP-RS scores; the correlation was strongest for the mineralization of the red nucleus.

Table 1. Demographic and clinical features of study participants (Mean ± SD)

	Healthy Volunteers	Patients with PD	Patients with PSP
Gender (Male: Female)	10:16	20:6	20:7
Age (Years)	59.5 ±3.6	60.3 ±7.0	62.6 ±5.5
Duration of motor symptoms (Months)	NA	28.2 ± 14.4	26.4 ±7.3
UPDRS, part II	NA	13.5 ± 3.6	NA
UPDRS, part III	NA	25.4 ± 7.0	NA
UPDRS, part III, axial score	NA	5.4 ± 2.5	NA
UPDRS, part III, TRIB score	NA	20.0 ± 4.8	NA
PSPRS, History	NA	NA	13.5 ± 4.0
PSPRS, Mentation	NA	NA	5.3 ± 1.6
PSPRS, Bulbar	NA	NA	3.2 ± 1.6
PSPRS, Ocular Motor	NA	NA	7.6 ± 2.8
PSPRS, Limb Motor	NA	NA	6.5 ± 2.6
PSPRS, Gait and Midline	NA	NA	12.9 ± 4.1
PSPRS, Total	NA	NA	49.0 ± 13.4

NA- Not Applicable PD- Parkinson's disease; PSP- Progressive Supranuclear Palsy; PSPRS- Progressive Supranuclear Palsy Rating Scale.

Table 2. Magnetic susceptibility values from the ROIs from the three groups of study participants.

	HV	Patients with PD	Patients with PSP	P value
Caudate nucleus	40.8 ±8.3	42.0 ± 9.7	56.9 ± 12.1	<0.0001* HV Vs PD 0.9** HV Vs PSP <0.001** PD Vs PSP<0.001**
Putamen	40.1±11.8	40.4 ±11.1	64.1±18.6	<0.0001* HV Vs PD =0.9** HV Vs PSP <0.001** PD Vs PSP <0.001**
Globus Pallidus	105.8 ± 11.6	107.5 ± 21.0	135.0 ± 32.1	0.0001* HV Vs PD=0.9** HV Vs PSP =0.004** PD Vs PSP=0.004**
Substantia Nigra	85.2 ± 14.9	110.8 ± 20.5	144.3 ± 30.1	0.0001* HV Vs PD=0.007** HV Vs PSP <0.001** PD Vs PSP =0.005**
Red nucleus	80.9 ± 20.7	80.3 ± 25.8	127.3 ± 35.1	0.0001* HV Vs PD=0.9** HV Vs PSP <0.001** PD Vs PSP<0.001**

HV- Healthy volunteers; PD- Parkinson's disease; PSP- Progressive supranuclear palsy

*P value in ANOVA / Kruskal Wallis test; ** P value in post-hoc Bonferroni test/ Dunn's pairwise comparison.

Table 3: Correlation of mineralization with demographic features and disease specific rating scales in patients.

	Caudate Nucleus	Putamen	Globus Pallidus	Substantia Nigra	Red nucleus
PD					
Age (Years)	R=0.27 P=0.18	R=0.35 P=0.07	R=-0.12 P=0.55	R=0.12 P=0.57	R=-0.20 P=0.32
Duration of motor symptoms (Months)	R=-0.09 P=0.67	R=0.01 P=0.96	R=0.39 P=0.06	R=0.50 P=0.01	R=-0.08 P=0.71
UPDRS, part II	R=-0.03 P=0.90	R=0.09 P=0.68	R=0.19 P=0.35	R=0.39 P=0.05	R=-0.21 P=0.30
UPDRS, part III	R=-0.04 P=0.84	R=0.06 P=0.78	R=0.22 P=0.27	R=0.43 P=0.03	R=-0.14 P=0.51
UPDRS, part III, axial score	R=-0.25 P=0.22	R=-0.13 P=0.54	R=0.25 P=0.22	R=0.27 P=0.19	R=-0.19 P=0.34
PSP					
Age (Years)	R=-0.02 P=0.90	R=-0.02 P=0.92	R=0.16 P=0.44	R=-0.02 P=0.92	R=0.24 P=0.22
Duration of motor symptoms (Months)	R=0.06 P=0.76	R=0.32 P=0.10	R=0.14 P=0.50	R=0.37 P=0.05	R=0.64 P<0.001
PSPRS, History	R=0.05 P=0.79	R=0.42 P=0.03	R=0.29 P=0.15	R=0.41 P=0.04	R=0.81 P<0.001

PSPRS, Mentation	R=0.07 P=0.71	R=0.28 P=0.16	R=-0.05 P=0.81	R=-0.11 P=0.57	R=0.25 P=0.20
PSPRS, Bulbar	R=-0.08 P=0.69	R=0.46 P=0.02	R=0.41 P=0.03	R=0.33 P=0.09	R=0.83 P<0.001
PSPRS, Ocular Motor	R=-0.09 P=0.67	R=0.08 P=0.66	R=0.13 P=0.5	R=0.31 P=0.12	R=0.50 P=0.008
PSPRS, Limb Motor	R=0.02 P=0.92	R=0.24 P=0.22	R=0.16 P=0.42	R=0.76 P<0.001	R=0.62 P<0.001
PSPRS, Gait and Midline	R=0.02 P=0.93	R=0.40 P=0.04	R=0.35 P=0.08	R=0.44 P=0.02	R=0.85 P<0.001
PSPRS, Total	R=0.007 P=0.97	R=0.40 P=0.03	R=0.29 P=0.13	R=0.49 P=0.009	R=0.85 P<0.001

Key observations and Conclusions:

We found that the mineralization (as indicated by magnetic susceptibility values in QSM) of the substantia nigra differs significantly between those with neurodegenerative Parkinsonian disorders and healthy volunteers, with higher degree of mineralization in those with Parkinsonism. Among those with Parkinsonism, the mineralization of substantia nigra was more in those with PSP, compared to PD. The mineralization values in other deep gray nuclei (Caudate nucleus, Putamen, Globus Pallidus and Red Nucleus) were similar between healthy volunteers and PD, while it was significantly more in PSP in all these ROIs, compared to the other two groups. The mineralization of the substantia nigra showed a moderate degree of correlation with the duration of PD and the Unified Parkinson's disease rating scale motor scores. In patients with PSP, the mineralization of the deep gray nuclei correlated well with the clinical severity as assessed by PSP-RS scores; the correlation was strongest for the mineralization of the red nucleus. Our findings suggest that quantitative susceptibility mapping techniques could be used for differentiating PD from PSP and could also monitor progression of these conditions.

References

1. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology. 1996 Jul;47(1):1–9.

2. Golbe LI. Progressive supranuclear palsy. Semin Neurol. 2014 Apr;34(2):151–9.

3. Armstrong MJ. Progressive Supranuclear Palsy: an Update. Curr Neurol Neurosci Rep. 2018 Feb 17;18(3):12.

4. Giagkou N, Höglinger GU, Stamelou M. Progressive supranuclear palsy. Int Rev Neurobiol. 2019;149:49–86.

5. Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord. 2017;32(6):853–64.

6. Ward RJ, Zucca FA, Duyn JH, Crichton RR, Zecca L. The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurol. 2014 Oct;13(10):1045–60.

7. Dexter DT, Carayon A, Javoy-Agid F, Agid Y, Wells FR, Daniel SE, et al. Alterations in the levels of iron, ferritin and other trace metals in Parkinson's disease and other neurodegenerative diseases affecting the basal ganglia. Brain. 1991 Aug 1;114(4):1953–75.

8. Sehgal V, Delproposto Z, Haacke EM, Tong KA, Wycliffe N, Kido DK, et al. Clinical applications of neuroimaging with susceptibility-weighted imaging. J Magn Reson Imaging JMRI. 2005 Oct;22(4):439–50.

9. Gupta D, Saini J, Kesavadas C, Sarma PS, Kishore A. Utility of susceptibility-weighted MRI in differentiating Parkinson's disease and atypical parkinsonism. Neuroradiology. 2010 Dec;52(12):1087–94.

10. Haacke EM, Liu S, Buch S, Zheng W, Wu D, Ye Y. Quantitative susceptibility mapping: current status and future directions. Magn Reson Imaging. 2015 Jan;33(1):1–25.

11. Eskreis-Winkler S, Zhang Y, Zhang J, Liu Z, Dimov A, Gupta A, et al. The clinical utility of QSM: disease diagnosis, medical management, and surgical planning. NMR Biomed. 2017 Apr;30(4).

12. Langkammer C, Schweser F, Krebs N, Deistung A, Goessler W, Scheurer E, et al. Quantitative susceptibility mapping (QSM) as a means to measure brain iron? A post mortem validation study. NeuroImage. 2012 Sep;62(3):1593–9.

13. Sheelakumari R, Madhusoodanan M, Radhakrishnan A, Ranjith G, Thomas B. A Potential Biomarker in Amyotrophic Lateral Sclerosis: Can Assessment of Brain Iron Deposition with SWI and Corticospinal Tract Degeneration with DTI Help? AJNR Am J Neuroradiol. 2016 Feb;37(2):252–8.

14. Sjöström H, Granberg T, Westman E, Svenningsson P. Quantitative susceptibility mapping differentiates between parkinsonian disorders. Parkinsonism Relat Disord. 2017 Nov;44:51–7.

15. Mazzucchi S, Frosini D, Costagli M, Del Prete E, Donatelli G, Cecchi P, et al. Quantitative susceptibility mapping in atypical Parkinsonisms. NeuroImage Clin. 2019;24:101999.

16. Harder SL, Hopp KM, Ward H, Neglio H, Gitlin J, Kido D. Mineralization of the deep gray matter with age: a retrospective review with susceptibility-weighted MR imaging. AJNR Am J Neuroradiol. 2008 Jan;29(1):176–83.

17. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992 Mar;55(3):181–4.

18. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30(12):1591–601.

19. Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B. Clinical characteristics in early Parkinson's disease in a central California population-based study. Mov Disord Off J Mov Disord Soc. 2005 Sep;20(9):1133–42.

20. Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain J Neurol. 2007 Jun;130(Pt 6):1552–65.

21. Martínez-Martín P, Gil-Nagel A, Gracia LM, Gómez JB, Martínez-Sarriés J, Bermejo F. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. Mov Disord Off J Mov Disord Soc. 1994 Jan;9(1):76–83.

22. Langston JW, Widner H, Goetz CG, Brooks D, Fahn S, Freeman T, et al. Core assessment program for intracerebral transplantations (CAPIT). Mov Disord Off J Mov Disord Soc. 1992;7(1):2–13.

23. Krishnan S, Prasad S, Pisharady KK, Sarma G, Sarma SP, Kishore A. The decade after subthalamic stimulation in advanced Parkinson's disease: A balancing act. Neurol India. 2016 Feb;64(1):81–9.

24. Vinayagamani S, Sheelakumari R, Sabarish S, Senthilvelan S, Ros R, Thomas B, et al. Quantitative Susceptibility Mapping: Technical Considerations and Clinical Applications in Neuroimaging. J Magn Reson Imaging JMRI. 2020 Jan 17;

25. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp. 2002 Nov;17(3):143–55.

26. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. NeuroImage. 2006 Jul 1;31(3):1116–28.

27. Langkammer C, Pirpamer L, Seiler S, Deistung A, Schweser F, Franthal S, et al. Quantitative Susceptibility Mapping in Parkinson's Disease. PloS One. 2016;11(9):e0162460.

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