Subregional Nigral Neurodegeneration in Parkinson's Disease Using Multisite Longitudinal MRI

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Introduction:

Parkinson's disease (PD) is characterized by progressive loss of neuromelanin (NM)-containing dopaminergic neurons in substantia nigra pars compacta (SNc). Although NM-MRI technique has been useful in tracking nigral NM progression, changes over years using multiple scanners in multisite studies are not well known.[1,2,3,4] We quantified nigral NM changes in the whole as well as the sensorimotor, associative and limbic subregions of the SN in a large multisite cohort of PD patients and healthy volunteers (HVs).

Methods:

PD patients and HVs were prospectively assessed for demographical, clinical and brain volumetric characteristics at baseline (V1) and after a 1-year follow-up (V2) as a part of MPI-R2* study (ClinicalTrials.gov: NCT02816645). They were scanned at 13 centers using 3T MRI obtained from different vendors (Philips, Siemens and General Electric). The MRI protocol included two T1-weighted acquisitions dedicated to spatial normalization and NM evaluation in SN.
Whole SNc: Using MRtrix3 viewer (v3.0), the SNc was manually segmented twice by a rater blind to the clinical status of the participant (DICE=0.82). SNc volumes (Vol); corrected volume (Cvol=Vol/total intracranial volume) to normalize for the head size; normalized signal to noise ratio (NSI) and contrast to noise ratio (CNR) using a background region was obtained.
Subregional SNc: NM images were aligned to an average brain template obtained using a balanced representation of HVs from our previous study. NSI was computed for each participant using an SNc mask subdivided into posterolateral sensorimotor, anteromedial associative and posteromedial limbic territories and a background region in the template space.[5,6,7]
To investigate the scanner effect in HVs at V1, one-way ANOVA with scanner as a between-group effect was performed for whole SNc measures. Further, we used linear mixed-effects modeling (LMM) to investigate the changes in the groups, visits, SNc (whole and subregional) measurements, and interactions between them along with random effects of subjects nested within scanners. Based on the fitted LMM, significance of the main factors and interactions was tested using type II Wald Chi2 tests followed by pairwise comparisons with Tukey's tests in emmeans using FDR correction for multiple comparisons. Age and sex were included as covariates.

Results:

We analyzed 142 PD patients (MDS-UPDRS III OFF score: 30.9±18.3, disease duration: 4.0±2.9 years) and 76 HVs at V1. Among them, 96 PD patients and 49 HVs were followed up after a year (V2). There were no significant differences in age or sex between the groups. There was a significant scanner effect in NSI ($p<0.001$) but not in Vol ($p=0.85$), Cvol ($p=0.31$) and CNR ($p=0.99$).

Whole SNc: At V1, values were significantly lower in PD than HV. At V2, Vol and Cvol decreased significantly in PD but not in HV. Overall, we observed a significant group effect for all measurements and visit effect for Vol and Cvol along with a group visit interaction trend in Vol ($p=0.09$) and Cvol ($p=0.07$), no interaction in NSI ($p=0.3$) and a significant interaction in CNR ($p=0.04$).

Subregional SNc: We found an interaction effect of group and subregions on NSI ($p=0.04$) without a visit effect ($p=0.18$). In both HV and PD, pairwise comparison showed higher NSI in associative with respect to limbic and sensorimotor (all $p<0.01$). Also, we observed higher NSI in limbic than sensorimotor in PD ($p<0.0001$) but not in HV ($p=0.93$).

Overall, lower NSI values in all three subregions were observed in PD compared to HV. Moreover, the NSI diminution in PD patients was more significant in the sensorimotor (-4.14) as compared to the limbic territory (-2.79).

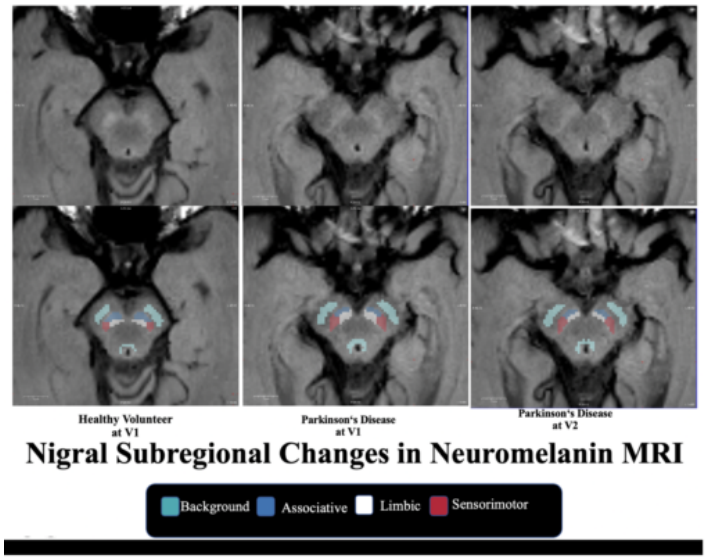

Figure 1 (a): Nigral subregional changes in Neuromelanin MRI

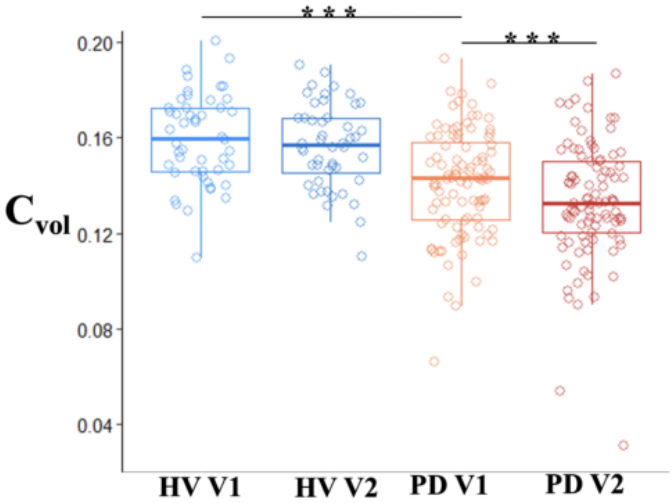

Figure 1 (b): Box plot of whole nigral corrected volume changes over one year.

All significant differences are represented with four asterisks (adjusted $p < 0.0001$).

·Figure 1: Whole and subregional nigral neuromelanin MRI changes

	HV at V1	HV at V2	% Change	PD at V1	PD at V2	% Change
Volume (mm^3)	228.6 ± 29.2	224.0 ± 22.8	-2.0%	207.9 ± 29.5	197.4 ± 34.9**	-5.1%
C_{vol}	0.159 ± 0.02	0.156 ± 0.02	-1.9%	0.142 ± 0.02	0.134 ± 0.03*	-5.6%
NSI	112.3 ± 2.1	112.1 ± 1.96	-1.5%	108.6 ± 2.2	108.7 ± 1.9	+0.8%
CNR	1.77 ± 0.39	1.69 ± 0.39	-4.1%	1.16 ± 0.35	1.21 ± 0.31	+3.8%
Limbic subregion	108.3 ± 2.4	108.2 ± 2.8	-1.65%	105.8 ± 2.8	105.0 ± 3.9	14.03%
Associative subregion	110.3 ± 3.0	109.6 ± 2.8*	-6.87%	106.4 ± 2.9	106.4 ± 0.1	-0.57%
Sensorimotor subregion	108.03 ± 3.4	108.20 ± 2.6	-2.21%	104.1 ± 3.2	103.6 ± 4.9	-11.73%
* = p <0.05 ** = p <0.01						

Table 1: Whole and subregional nigral neuromelanin measurements

·Table 1: Whole and subregional nigral neuromelanin MRI measurements

Conclusions:

We demonstrated a predominant NM signal loss in sensorimotor subregion of PD patients. These results suggest that NM-MRI can provide sensitive biomarkers for clinical trials in PD, that can track melanized neuronal loss in multisite settings.

Disorders of the Nervous System:

Neurodegenerative/ Late Life (eg. Parkinson's, Alzheimer's) [1]

Lifespan Development:

Aging

Modeling and Analysis Methods:

Image Registration and Computational Anatomy
Other Methods

Novel Imaging Acquisition Methods:

Anatomical MRI [2]

Keywords:

Brainstem
Degenerative Disease
Movement Disorder
MRI
Neurological
STRUCTURAL MRI

Other - Neuromelanin

[1|2]Indicates the priority used for review

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No

Please indicate below if your study was a "resting state" or "task-activation" study.

Other

Healthy subjects only or patients (note that patient studies may also involve healthy subjects):

Patients

Was any human subjects research approved by the relevant Institutional Review Board or ethics panel? NOTE: Any human subjects studies without IRB approval will be automatically rejected.

Yes

Was any animal research approved by the relevant IACUC or other animal research panel? NOTE: Any animal studies without IACUC approval will be automatically rejected.

Not applicable

Please indicate which methods were used in your research:

Structural MRI

For human MRI, what field strength scanner do you use?

3.0T

Which processing packages did you use for your study?

SPM
Free Surfer
Other, Please list - MRtrix3

Provide references using author date format

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