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Unveiling the biological and physical origins of the neuromelanin-sensitive MRI contrast in rat model and early patients of Parkinson's disease

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Purpose:
Neuromelanin MRI (NM-MRI) is a promising biomarker of dopaminergic neuron loss in the substantia nigra (SN) in Parkinson's disease (PD). The biological and physical origins of NM-MRI contrast are debated. We quantitatively described the origin of NM signal and longitudinal changes *in vivo* using multiparametric MRI with histological confirmation in a recent AAV-hTyr rat model of PD with accumulation of NM in the SN. We hypothesized that intracellular NM levels may be associated with degeneration in dopaminergic neurons, establishing a threshold for the initiation of PD. Longitudinal NM-MRI in early and prodromal patients of PD is consistent with this hypothesis.

Methods:
Preclinical imaging: Forty rats injected in the right SN with adeno-associated viral vector expressing human tyrosinase (AAV-hTyr) were imaged at 11.7T (Bruker) at 0-, 1-, 2-, 4-, and 8-month post injection (mpi) with acquisition of NM-MRI, quantitative R_1, R_2, R_2*, Quantitative Susceptibility Mapping (QSM), and MPF^8. Eight rats were euthanized following each imaging session for histological analysis.

Clinical imaging: Healthy volunteers (HV), PD patients, and prodromal PD patients (iRBD) were included from the ICEBERG cohort. Participants were followed longitudinally up to 5 years with 2 to 3 imaging sessions, including NM-MRI of the substantia nigra.

Results:
AAV-hTyr rats: Following injection, intracellular and extracellular NM accumulated in the ipsilateral SN. This resulted in increased contrast at 1mpi. Subsequently, intracellular NM continued to increase, extracellular NM reached a plateau, and the number of dopaminergic neurons decreased in the ipsilateral SN (-60% at 4mpi, $p<0.001$). This resulted in exponential decrease of NM-MRI contrast between 1 and 8mpi.
R_1 showed a similar curve to that of NM-MRI, with initial increase (+15% at 1mpi, $p<0.001$) followed with decrease. Magnetic susceptibility showed continuous increase ($p<0.001$ after 2mpi). MPF, R_2, and R_2* did not show significant differences.

Patients: PD patients showed reduced NM-MRI SNR in the SN compared with HV and accelerated decrease with time. At the time of onset, 60.9 years old on average, PD patients showed 1.2% reduction of NSI compared to the average NSI in HV. iRBD patients showed a similar curve delayed in time.

Discussion
The results show that increase in the NM-MRI signal is due to the increase in intra and extracellular NM up to a certain threshold beyond which the NM signal drops due to neurodegeneration of melanized neurons. According to our results, the NM signal is due to a paramagnetic effect of NM-iron complexes which significantly reduce T_1 and increase susceptibility.

Our results show that PD patients present accelerated and early decrease of the signal that suggests neuronal loss. iRBD patients showed a similar decrease delayed in time, which could explain the late onset of PD in these patients. These results are consistent with our hypothesis of a pathogenic threshold of intracellular neuromelanin concentration.

Perspectives
The role of neuromelanin accumulation and its interaction with iron in the degenerative process in PD needs further investigation. NM-MRI could enable better stratification and may be used as a biomarker for therapeutic evaluation.