Multimodal characterisation of substantia nigra pathology in Parkinson disease brains: A pilot MRI study at 3 and 7 Tesla.

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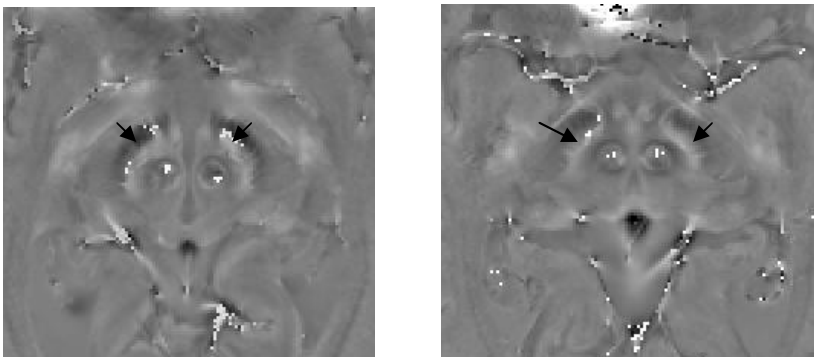
Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting about 1% of people older than 70 years. The pathologic hallmarks are loss of dopaminergic neurons in the substantia nigra (SN) and Lewy bodies consisting of ubiquinated intracytoplasmatic protein deposits. Diagnosis is made clinically, and up to 25% of clinically diagnosed cases are pathologically not confirmed. This highlights the need for improved diagnostic tests, in particular in the early or even presymptomatic stage of the disease. About 80% of nigral dopaminergic cells will have died before symptoms emerge opening a potential diagnostic window of opportunity.
Neuropathologic findings of elevated iron content in PD brains triggered a number of studies over the past two decades to use iron sensitive MRI techniques to characterise PD pathology. Controversial qualitative and quantitative nigral T2 signal changes (increase, no change or signal decrease) have been described indicating that refined techniques and higher magnetic field strength may be required to detect locally increased iron levels against a background of increased water and susceptibility artefacts[1]. Moreover, neuromelanin loss underlies the pathologic hallmark of depigmenteded SN, resulting in reduced paramagnetism in SN. Based on the expected complexity of signal changes and the clinical need to develop a sensitive test, we aimed to characterise the SN changes in early PD using a multiparametric approach deploying both 3 and 7 Tesla.

Material and methods: 7 patients with clinically idiopathic PD (52-77 years, mean 62.8 with 1-7 years duration, and 7 controls (53-77 years, mean 65.3) were included in the study after giving informed consent. The study was approved by the local research Ethics Committee. MR examinations were performed at 3T and 7T (Philips, Best, Netherlands) using standard imaging and a 3D inversion recovery T1 mapping technique and a multi-echo FSE T2 mapping technique at 3T. At 7T T2* mapping and high resolution 3D gradient echo imaging was performed to assess local phase shifts. T1 maps and unwrapped phase maps were generated using in-house software.
Bilateral ROI of the substantia nigra were manually defined at the level of the red nucleus on proton density images known to allow a better definition of SN compared with T2 images.

Results: Averaged left and right T1 relaxtion times in SN were significantly reduced in PD patients (n; mean [SD] 6; 983 [44]ms vs. 4; 1046 [7.5]ms, $p<0.05$, t-test). Focusing on patients with still asymmetric disease, the difference was more marked in the predominantly affected hemisphere (n=5; 1050 vs. 965ms, $p<0.05$, t-test), but non significant for the less affected hemisphere (1042 vs. 997ms). T1 values were slightly, but consistently smaller in the more affected hemisphere ($p<0.1$). There were non significant reductions in nigral T2 at 3T, and no consistent change in T2* at 7T (n=4). Phase images suggested reduced phase shifts between red nucleus and corticofugal cerebral peduncles in PD patients possibly reflecting SN cell and neuromelanin loss (Fig).



Control PD patient

Fig. Note the smaller area of phase shifts (arrows) in the PD brain

Discussion: This pilot study suggests that T1 relaxometry may allow more reliable assessment of paramagnetic changes in the SN in PD patients compared with T2 and T2* even at very high field strenghth. This is further supported by the observed asymmetry of T1 shortening. Moreover, preliminary analysis of phase images suggest a reduction in nigral phase shift in PD that may allow to depict the SN volume loss, the key pathologic feature in PD. Both quantiative T1 and phase maps are promising new approaches to characterise SN pathology in PD brains. Further investigations are required to research the underlying mechanisms in particular the interplay between neuromelanin loss and iron increase and its respective subcellular compartmentalisation.

[1] Haacke EM, et al. Imaging iron stores in the brain using magnetic resonance imaging. MRI 23 (2005) 1-25.