Brain Iron and Neuronal Integrity in Patients with Parkinson's Disease Probed by Novel MRI Contrasts

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Introduction To date, the exact causes of substantia nigra (SN) neuronal loss in Parkinson's disease (PD) remain elusive. However, the generation of reactive oxygen species, possibly facilitated by iron, may play a role in causing cellular damage and subsequent cell death. Supportive of this theory is postmortem evidence of increased iron stores in the SN of Parkinsonian brains.[(1),(2)] Others have suggested that iron levels increase with disease progression.[(3)] To date, however, MRI has failed to show significant *in vivo* differences in (SN) iron levels in subjects with PD versus control subjects. This may be due to the limitations in tissue contrasts achievable with conventional T_1 and T_2 weighted MRI sequences that have been employed. With the recent development of novel rotating frame transverse ($T_{2\rho}$) and longitudinal ($T_{1\rho}$) relaxation MRI methods that appear to be sensitive to iron and neuronal loss, respectively, we embarked on a study of eight individuals with PD (Hoehn & Yahr, Stage II) and eight age-matched control subjects. Employing these techniques using a 4T MRI magnet, we assessed iron deposits and neuronal integrity in the SN. We show here that sub-millimeter resolution $T_{1\rho}$ and $T_{2\rho}$ MRI relaxation methods can provide a *non-invasive measure* of iron content as well as evidence of neuronal loss in the midbrain of patients with PD.

Methods MR imaging was performed with 4T magnet. An efficient TEM volume coil was used for RF transmission and signal reception.[(4)] After the subject was positioned in the magnet, transverse multislice images were obtained with a rapid relaxation enhancement (RARE) sequence. For the relaxation measurements, the TurboFLASH imaging readout [4 segments] was used.[(5)] Images were measured using $(0.70\ mm)^2$ in-plane resolution, FOV = $(20\ cm)^2$, 256^2 matrix, and slice thickness = 3 mm, TR=4.5 s Thus, the digital pixel area was 0.49 mm^2 and voxel volume was 1.5 μL. The $T_{1\rho}$ and $T_{2\rho}$ measurements were performed as described in prior work[(6),(7)] using variable numbers (*m*) of hyperbolic secant (HS1) adiabatic full passage (AFP) pulses.[(8)] For $T_{2\rho}$ measurements, the AFP pulse train was placed after the coherence excitation by an adiabatic half passage (AHP) pulse and the magnetization was returned back to the longitudinal (Z') axis using another AHP pulse placed prior to the TurboFLASH imaging readout. For $T_{1\rho}$ measurements, the AFP pulse train was placed prior to the imaging readout. T_2 measurements were performed using a double-spin echo (DSE) pulse sequence[(7)].

Results and Discussion

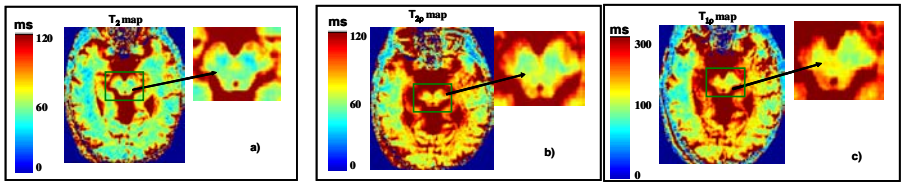

Figure 1. T_2 (a), $T_{2\rho}$ (b) and $T_{1\rho}$ (c) maps generated from a transverse slice in one patient with PD.

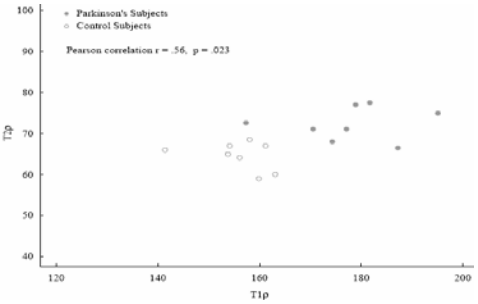

Figure 2. Correlation analysis between $T_{2\rho}$ and $T_{1\rho}$

Table 1. Averaged calculated $T_{2\rho}$, $T_{1\rho}$ and T_2 time constants (in ms) in the PD patients and controls (MEAN ± SD)

Time constants (ms)			
Controls	**72.3 ± 3.9** [a]	**59.4 ± 4.3** [b]	**156 ± 6.7** [c]
PD	**64.6 ± 3.4** [a]	**57.1 ± 4.2** [b]	**178 ± 11.6** [c]

[a] Significant difference between PD and controls (P<0.01, two-tailed).

[b] No significant difference between PD and controls (P = 0.32, two-tailed).

[c] Significant difference between PD and controls (P = 0.036, two-tailed).

$T_{2\rho}$ MRI, which is reflective of iron-related dynamic dephasing mechanisms (e.g., chemical exchange and diffusion in the locally different magnetic susceptibilities), demonstrated a statistically significant difference between the PD and control group, while routine T_2 MRI did not. $T_{1\rho}$ measurements, which appear to reflect upon neuronal count, indicated neuronal loss in the SN in PD. Representative ^1H_2O $T_{2\rho}$ and T_2 relaxation maps from one PD patient are shown in Figures 1a and 1b. Inspection of these figures reveal that tissue $T_{2\rho}$ values are longer than the corresponding T_2 values and the differences between $T_{2\rho}$ and T_2 maps provide a unique type of MRI contrast.[(7)] In Figure 1c, the $T_{1\rho}$ map generated from the same brain slice is displayed. Based on the multi-subject $T_{2\rho}$, $T_{1\rho}$ and T_2 relaxograms obtained from the SN area of healthy volunteers and PD patients, a significant difference between $T_{2\rho}$ and $T_{1\rho}$ values in the SN area was obtained in P D *versus* controls (Table 1). Here, T_2 MRI was unable to demonstrate a significant difference between PD and controls (P=0.32, two tailed). It can be seen that both $T_{2\rho}$ and $T_{1\rho}$ maps exhibit better spatial specificity of the distribution of relaxation time constants as compared to conventional T_2 maps. *In a blinded analysis, $T_{2\rho}$ and $T_{1\rho}$ maps revealed asymmetry in the SNc of 5 of 8 PD patients. Asymmetry was not observed in controls.* Person correlation analysis indicated that, although neither the Parkinson's patients nor controls have a significant correlation separately, the $T_{1\rho}$ and $T_{2\rho}$ are correlated within the combined group of PD and controls (Figure 2, r=0.56,p=0.023). Our future work is focused on determining the degree of this asymmetry and if iron accumulation and cellular loss continue to be more prominent in the SNc contralateral to the more severely clinically affected side over time. An investigation of the later stage PD patients (Hoehn & Yahr, Stage III and IV) is underway in our laboratory. To conclude, the novel adiabatic $T_{2\rho}$ and $T_{1\rho}$ MRI relaxation methods utilized here for the measurement of the load and distribution of iron and neuronal loss may provide unique information on the pathogenesis of PD.

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