# Maximizing Tissue Contrast For MRI Evaluation of Parkinson's Disease

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**Introduction:** There is a need for early diagnostic techniques for Parkinson's disease (PD) as well as a means to track its course and response to experimental therapies. Following Braak et. al's hypothesis [1], it is thought that PD pathology spreads through transmission of pathogenic forms of α-synuclein protein in a caudal-rostral manner. However, to date there is no synuclein radioligand to follow this process. In addition to abnormal synuclein aggregation (which can manifest as Lewy pathology), there is iron deposition, gliosis and neuronal loss that occurs in PD. MRI, which can image brain structures as well as brain function, could conceivably map changes in tissue composition, microstructure and functional connectivity and thereby provide a comprehensive characterization of the PD brain. In this work we employed MRI modalities that are specifically sensitive to various brain tissue properties, such as microstructural integrity, iron loads, and functional connectivity. Namely, we used diffusion tensor imaging (DTI), novel rotating frame relaxation mapping methods including adiabatic $T_{1\rho}$, $T_{2\rho}$ [2] and RAFF4 (Relaxation Along a Fictitious Field in the rotating frame of rank 4)[3], and quantitative susceptibility mapping (QSM) [4]. Finally, we acquired resting state fMRI (rsfMRI) data [5] with the goal of correlating functional with microstructural information.

**Materials and Methods:** Three mild-moderate advanced (Hoehn & Yahr Stage I-II; on medications) individuals with PD and three age matched healthy controls participated in this study and underwent MRI scanning. Scans were performed on a 3 T/ 90 cm bore, Siemens Prisma console, 64-channel receive system. Adiabatic $T_{1\rho}$, $T_{2\rho}$ and RAFF4 measurements were collected from a 30 AC-PC aligned oblique axial slices between the brainstem and basal ganglia, whereas $T_1$-weighted, $T_2$-weighted images, DTI, QSM and rsfMRI were collected throughout the brain. For $T_{1\rho}$, $T_{2\rho}$ and RAFF4 acquisitions, 30 slices in the midbrain-region were acquired with segmented GRE readout (4 segments), voxel size: 1.6 x 1.6 x 3.6 $mm^3$, GRAPPA= 3, TE=3.18 ms; TR=2s. For adiabatic relaxation measurements, Hyperbolic Secant (HS) pulses were used, with R=10, BW=1.6 kHz, pulse duration $T_p$= 6 ms, $\omega_1^{max}/(2\pi)$ = 800 Hz, 5 acquisitions with number of pulses = 0, 4, 8, 12, 16, MLEV4 phase cycling; for RAFF4, $T_p$ was 4.56 ms for one *P*-packet, number of *P*-packets 0, 4, 8, 12, 16, $\omega_1^{max}/(2\pi)$ =323 Hz. Parameters for QSM were: voxel size: 1.6 x 1.6 x 1.6 $mm^3$, 96 slices, TR=51 ms, TE=10, 19, 27, 36, 45 ms, GRAPPA 3; Flip Angle 15°; for DTI: 128 directions, with 5 additional non-diffusion weighed ($b_0$) images, b-value=1500s/$mm^2$, voxel size 1.8x1.8x1.8$mm^3$, TR=2820 ms, TE=72.6 ms; multi band (MB)=4; for rsfMRI: EPI, TR=900 ms, multi band (MB)=4; TE=30 ms; voxel size=3 x 3 x 3 $mm^3$, matrix size=64x64, 48 AC-PC aligned single oblique axial slices with interleaved slice acquisition, 502 volumes. Seed analysis from each of the defined ROIs was performed to extract functional connectivity measures. The various MRI parameters were calculated from a set of 26 brain areas relevant for PD (Fig. 1A), and compared among the subject groups.

**Results and Discussion:**

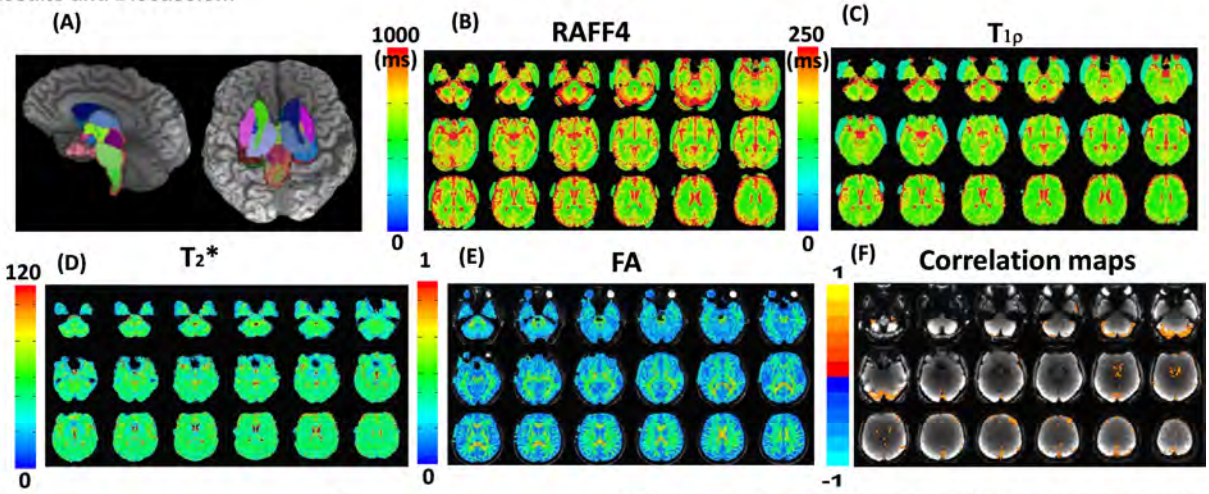


**Figure 1.** 3D rendered and multislice images with superimposed ROIs used for extracting MRI metrics from different MRI modalities (A); Relaxation time constants maps for RAFF4, $T_{1\rho}$, $T_{2\rho}$, and $T_2$* (B-D), fractional anisotropy, FA, obtained from DTI (E), and correlation maps (F) from rsfMRI.

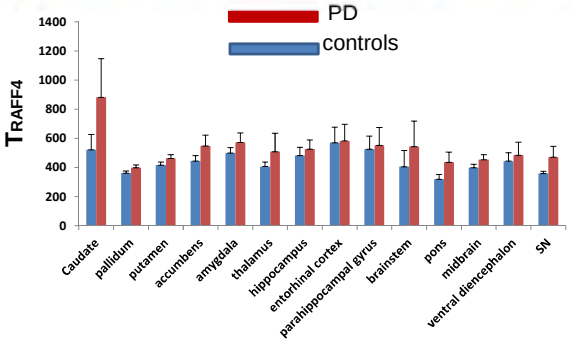


**Figure 2.** RAFF4 relaxation times measured in PD and controls in different areas of the brain. Data are mean ± SEM; left and right ROIs (where applicable) were pooled.

Representative maps from one control subject are shown in Fig. 1. RAFF4 was found to have greater sensitivity than $T_{1\rho}$, $T_{2\rho}$, $T_2$* and DTI to detect differences in several ROIs (such as caudate, thalamus and brainstem)(Fig. 2). $T_{1\rho}$ also differentiated between PD and controls in the same areas, and both RAFF4 and $T_{1\rho}$ methods exceeded other MRI techniques (e.g., FA and $T_2$*) in differentiating PD from controls. The chosen MRI methodologies provide quantitative measures of a variety of relaxation, diffusion and susceptibility parameters which allow robust characterization of the microstructural properties and iron content of the brains of our subject populations. Functional connectivity measures did not show differences between the subject groups, likely due to the limited number of subjects studied so far or related to the possibility that PD subjects were scanned while on their antiparkinsonian medications.

**Conclusion:** These results demonstrate the feasibility of adiabatic $T_{1\rho}$, $T_{2\rho}$ and RAFF4 to characterize the microstructural integrity and functional connectivity of PD subjects compared to healthy controls.

**Acknowledgments:** NIH Grants BTRC which are P41 RR008079, P41 EB015894, P30 NS057091, R01 NS061866 and Academy of Finland, Sigrid Juselius Foundation. **References:** [1] Braak H et. al, Neurobiol Aging 2003;24:197-211; [2] Michaeli S et al, Curr Anal Chem 2008;4:8-25; [3] Liimatainen Tet al. Magn Reson Med 2014:in press; [4] Shmueli K, Magn Reson Med 2009;62:1510-22; [5] Ellmore TM Sleep 2013;36:1885-92.