Investigating Parkinson's disease using rotating frame MRI

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Introduction

In our previous study performed at 4T on individuals with Parkinson's Disease (PD) and age-matched controls we have demonstrated that rotating frame relaxation methods employing so-called adiabatic HS1 pulses are capable to separate PD from control subjects based on the values of adiabatic relaxation times in the substantia nigra (SN) [1]. With the goal of investigating the physiological origin of these findings, another previous study from our group demonstrated that adiabatic $T_{1\rho}$ can ascertain cellular loss in in the substantia nigra of an animal model missing dopaminergic neurons [2]. On the other hand, the physiological basis for considering $T_{2\rho}$ as a possible biomarker of PD relies on the facts that $T_{2\rho}$ is likely sensitive to iron content, and that ferritin concentration (iron storage) is hypothesized to correlate with disease progression. Based on these observations, a methodology that could combine $T_{1\rho}$ and $T_{2\rho}$ relaxation mechanisms is anticipated to offer improved sensitivity for characterizing PD. Recently, our group has developed a novel rotating frame relaxation method which operates in sub-adiabatic regime, entitled RAFF (relaxation along a fictitious field) [3]. RAFF utilizes frequency swept pulses with *sine* and *cosine* modulation functions. When sweeping frequency sub-adiabatically, the vector sum of $d\alpha/dt$ (here α is the angle between ω_{eff} and the Z' axis of the rotating frame of reference) and ω_{eff} leads to the so-called fictitious filed, E. The angle ε between E and ω_{eff} is chosen to satisfy $\omega_{eff} = d\alpha/dt$, and thus RAFF measurements include both $T_{1\rho}$ and $T_{2\rho}$ relaxations. In the present work we employed RAFF to studying PD subjects, and compared these relaxation measurements with adiabatic $T_{1\rho}$ and $T_{2\rho}$ acquired with different modulation functions (HS1 vs HS4, which are supposed to generate MR contrast [4,5]) and conventional spin-lock (SL) $T_{1\rho}$ methods. The general goal is not only to explore the sensitivity of a variety of rotating frame relaxation measurements to characterize the SN of PD, but also to provide a set of measurements which can be used to extract intrinsic parameters of the tissue based on modeling of the relaxation mechanisms [4,5]. As an initial step for addressing the contribution of relevant relaxation pathways in the SN, we finally acquired adiabatic $T_{1,2\rho}$ from two samples with different concentration of ferritin.

Methods

Twenty one patients with a diagnosis of PD were investigated on a 4-T/90-cm Oxford magnet interfaced to Varian INOVA console. Images were acquired using fast spin echo readout, TR = 5 s, TE = 0.60 s, matrix 128 x 128, FOV = 20 cm x 20 cm, and slice-thickness = 3mm. In the adiabatic T1ρ configuration, a train of 4, 8, 12, or 16 HS1 or HS4 pulses was placed prior to the imaging readout, while in the adiabatic $T_{2\rho}$ configuration the train of adiabatic pulses was placed between two 4-ms adiabatic half passage pulses. RF peak power $\omega^1_{max}/(2\pi)$ of the adiabatic pulses was 0.88 kHz and 0.625 kHz for HS1 and HS4 pulses. Pulse length was 0.006 s, and the inversion bandwidth was ~1.6 kHz for both HS1 and HS4. For conventional spin-lock $T_{1\rho}$ experiment the locking field of $\omega^1_{max}/(2\pi)$ = 625 Hz was utilized using hard pulses. Same peak power was used for RAFF measurements [5]. Human liver ferritin was purchased from Lee Biosolutions, Inc (St. Louis, MO); samples at the concentrations of 0.25 mg/ml and 1.1 mg/ml were prepared.

Results and discussion

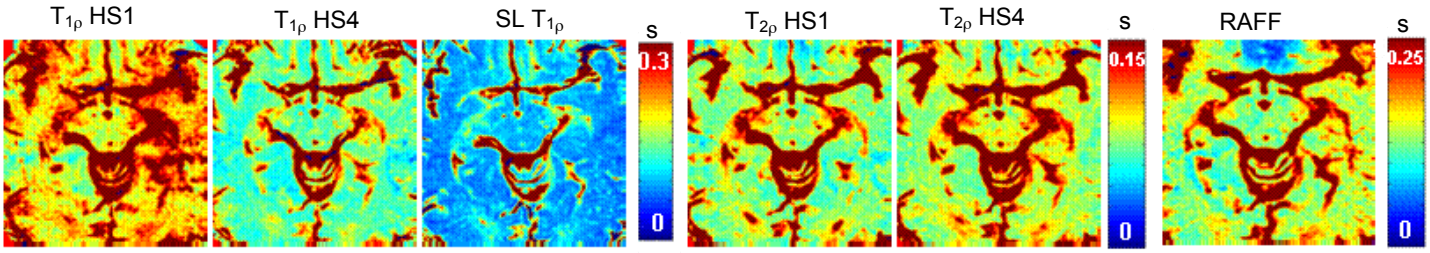

Figure 1. Rotating frame relaxation maps of representative PD patient at 4T

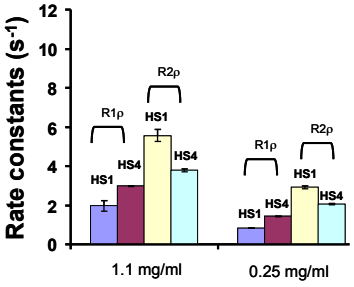

Figure 2. Adiabatic rotating frame relaxation rate constant ($1/T_{1,2\rho}$) of ferritin at 4T

As shown in Figure 1, adiabatic $T_{1,2\rho}$ and RAFF relaxation times were generally longer than SL $T_{1\rho}$; as predicted, different modulation functions of adiabatic pulses (HS1 vs HS4) affected relaxation in SN, with the difference being larger for $T_{1\rho}$ compared to $T_{2\rho}$ (~35% vs <10%). Interestingly, even if the average RAFF values were close to adiabatic $T_{2\rho}$, the RAFF maps showed a greater heterogeneity in SN compared to $T_{2\rho}$, and also compared to the other rotating frame relaxation maps. Specifically, SL $T_{1\rho}$ and $T_{1,2\rho}$ HS1 maps did not exhibit difference between substantia nigra reticulata (SNr) and compacta (SNc), and $T_{1,2\rho}$ HS4 maps showed ~5% difference between the two sub-regions ($p < 0.001$). Differences in RAFF relaxations between SNr and SNc were instead >10% ($p<0.0001$). These findings are consistent with our initial hypothesis of improved sensitivity of RAFF to characterize the SN of PD. Results from the ferritin samples (Figure 2) showed a correlation of $T_{1,2\rho}$ with ferritin concentration, and exhibited a modulation of $T_{1,2\rho}$ induced by HS1 vs HS4 pulses. Importantly, the HS1 vs HS4 $T_{1\rho}$ contrast was similar to what observed *in vivo*, as opposite to $T_{2\rho}$, thus implying that other relaxation channels (other than ferritin) are dominant in generating $T_{2\rho}$ relaxation in SN.

Conclusion

Results demonstrate that different RF pulses significantly modulate the rotating frame relaxations in the SN, providing the opportunity to extract fundamental parameters of the system based on theoretical modeling of the relaxation channels. The greatest sensitivity to identify sub-regions of the SN was achieved by RAFF, which combines $T_{1\rho}$ and $T_{2\rho}$ relaxation mechanisms.

References: [1] Michaeli et al., Movement Dis 2007; 22:334; [2] Michaeli et al, Journal of Neurosci Methods 2009;177:160. [3] Liimatainen et al. Proc. Int. Soc. Magn. Reson. Hawaii, 2008 [4] Michaeli et al. Curr Anal Chem 2008; 4:8 [5] Mangia et al Magn Reson Imaging 2009;27:1074
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