Magnetization transfer and adiabatic $R_{1\rho}$ MRI in the brainstem of Parkinson disease

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Introduction

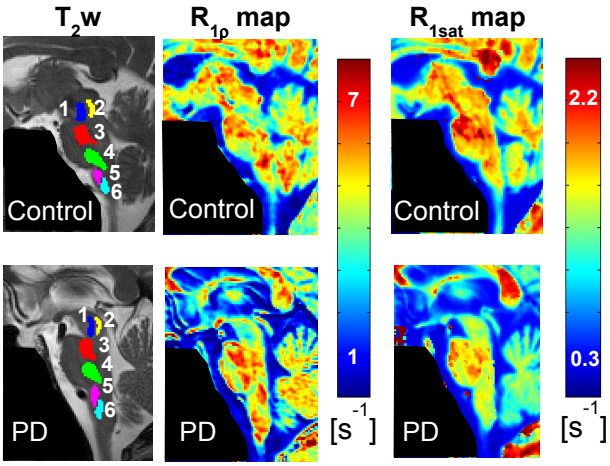
Parkinson disease (PD) is characterized by the loss of midbrain dopaminergic neurons as well as other brainstem neurons [1, 2]. Loss of pontine neurons may result in non-motor features of PD such as mood and sleep impairments and/or may be relevant to motor disability [3]. Routine MRI methods were shown to be insensitive to detect pontine changes in PD, but MRI voxel-based morphometry and diffusion tensor imaging have recently detected brainstem changes in PD [4] and REM sleep disorder (RBD) [5]. We have developed adiabatic MRI methods ($R_{1\rho}$ and $R_{2\rho}$) that detect midbrain changes in PD [6,7] and are useful in assessing the *aphakia* mouse model lacking dopaminergic neurons in substantia nigra of the brain [8]. Another method that we have recently developed attempts to address poor MRI sensitivity that has been observed using qualitative magnetization transfer ratios (MTRs). Our modified acquisition and data analysis protocols provide robust estimate of R_1 in the presence of off-resonance saturation (R_{1sat}). This approach allows reliable quantification of the magnetization transfer (MT) effect [9], often used as a maker of tissue integrity. In this study, we aimed at investigating the ability of adiabatic $R_{1\rho}$ and R_{1sat} to detect changes in the brainstem of PD patients as compared to age-matched control subjects.

Methods

The brains of nine non-demented individuals with mild–moderate PD (59 ± 9 years old, mean ± SD) and ten age-matched healthy volunteers (57 ± 9 years old) were imaged at 4T. Patients with PD were off their usual antiparkinsonian medications for 12 hours prior to imaging. Images were acquired using fast spin echo readout, TR = 6.5-10 s, TE = 0.073 s, matrix 256 x 256, FOV = 25.6 cm x 25.6 cm, and slice-thickness = 4mm. In the adiabatic $R_{1\rho}$ configuration, a train of 0, 4, 8, 12 and 16 hyperbolic secant pulses was placed prior to the imaging readout. RF peak amplitude $\omega_1^{max}/(2\pi)$ of the adiabatic pulses was 0.88 kHz, pulse duration was 0.006 s, and the inversion bandwidth was ~1.6 kHz. For the MT experiment, a 6 kHz off-resonance continuous-wave pulse, with incremental duration (0, 0.2, 0.5, 0.8, 1.0, 1.2 s) and pulse amplitude of $\omega_1^{max}/(2\pi)$ = 0.15 kHz, was placed prior to the imaging readout with or without initial global inversion [9]. Differences of relaxation rates ($\Delta R_{1\rho}$ and ΔR_{1sat}) were calculated between various sub-regions of the brainstem in each subject, and were then compared between patients and controls with two-tailed unpaired student t-test.

Results and Discussion

Representative $R_{1\rho}$ and R_{1sat} maps from control (top) and PD (bottom) subjects are shown in figure. The analyzed regions of interest are indicated on the T_2-weighted images. Statistically significant different $\Delta R_{1\rho}$ were observed when comparing ROI-1 vs ROI-5 and ROI-1 vs ROI-6 between patients and control subjects (p=0.004 and p=0.033, respectively). $\Delta R_{1\rho}$ were 6 and 8 times larger in patients than in controls for ROI-1 vs ROI-5 and ROI-1 vs ROI-6, respectively. Notably, $R_{1\rho}$ values in ROI-1 were not different between patients and controls (p=0.25), whereas faster $R_{1\rho}$ values were observed in ROI-5 and ROI-6 of PD as compared to controls, with p-values close to significance level (p=0.062 and p=0.077, respectively). Based on these observations, the changes in $R_{1\rho}$ between PD and controls primarily arose from the medullary nuclei rather than the more rostral regions. Finally, no statistical differences were observed between patients and controls when considering R_{1sat}, indicating no changes in tissue integrity. This is again supported by the absence of slower $R_{1\rho}$ values in those regions. Together, our findings of faster $R_{1\rho}$ values and no R_{1sat} changes in the medullary nuclei might indicate changes in the macromolecular composition which occur prior to neuronal death within the same structures.



Regions of interest (ROIs) were obtained in maps from six areas: (1) medial raphe nucleus; (2) dorsal raphe nucleus; (3) nucleus raphe pontis; (4) nucleus raphe magnus; (5) nucleus raphe pallidus; (6) nucleus raphe obscuris.

Braak et al. have emphasized medullary and pontine pathology in addition to classic midbrain involvement in PD [1], hypothesizing that the disease progresses from caudal to more rostral brain regions. Medullary and pontine pathology includes formation of Lewy bodies and neurites, and subsequent neuronal loss in the brainstem structures such as the raphe nucleus, locus ceruleus and lateral tegmental nuclei [2, 3, 10]. Our imaging study showed differences in MR parameters in the medullary regions of the brainstem of mild-moderately affected individuals that may be due to structural changes from the disease. Since a relatively small number of patients were enrolled, we were not able to determine if imaging findings correlated with disease severity or a clinical feature such as depression or RBD. Nevertheless, the results showed MRI changes in PD which are consistent with both clinical and pathological understating of the disease.

References: [1] Braak et al. Neurobiol Aging 2003;24:197 [2] Halliday et al. Brain Res 1990;510:104 [3] Dickson et al. Park Rel Disord 2009;15:1 [4] Jubault et al. PLoS One 2009;4:e8247. [5] Scherfler et al. Ann Neurol 2011;69:400 [6] Michaeli et al. Mov Disord 2007;22:334 [7] Nestrasil I et al. Journal of neurology 2010;257:964 [8] Michaeli et al. J Neurosci Methods 2009;177:160 [9] Mangia MRI 2011; Epub May 19. [10] Kish SJ. Adv Neurol 2003;91:39. **Acknowledgments:** Minnesota Medical Foundation, NIH grants BTRR-P41RR008079, R01NS061866, R21NS059813, P30 NS057091, S10 RR023730, S10 RR027290.