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

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Abstract

Background—In addition to classic midbrain pathology, Parkinson's disease (PD) is accompanied by changes in pontine and medullary brainstem structures. These additional abnormalities may underlie non-motor features as well as play a role in motor disability.

Methods—Using novel magnetic resonance imaging (MRI) methods rotating frame adiabatic $R_{1\rho}$ (i.e., measurements of longitudinal relaxation during adiabatic full passage pulses) and modified magnetization transfer (MT) MRI mapping, we sought to identify brainstem alterations in nine individuals with mild-moderate PD (off medication) and ten age-matched controls at 4 Tesla.

Results—We discovered significant differences in MRI parameters between midbrain and medullary brainstem structures in control subjects as compared to PD patients.

Conclusions—These findings support the presence of underlying functional/structural brainstem changes in mild-moderate PD.

Keywords

Parkinson's disease; medulla; MRI; magnetization transfer; $R_{1\rho}$

Introduction

Parkinson's disease (PD) is characterized by the loss of midbrain dopamine neurons as well as other brainstem neurons [1,2]. Loss of non-dopaminergic neurons may result in non-motor features of PD such as mood and sleep impairments and/or may be relevant to motor disability [3]. Presently, routine MRI methods are not sensitive to detect pontine or

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medullary changes in PD, but novel techniques have shown changes in PD and in idiopathic REM sleep disorder (iRBD) [4,5].

We have developed adiabatic MRI methods that detect midbrain changes in PD [6,7] as well as being useful in assessing the *aphakia* mouse model lacking dopaminergic neurons in substantia nigra (SN) of the brain [8]. These methods include longitudinal and transverse relaxation techniques in the rotating frame, $T_{1\rho}$ and $T_{2\rho}$, respectively. 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 a robust estimate of $R_1 (=1/T_1)$ in the presence of off-resonance saturation (R_{1sat}). This approach allows reliable quantification of the magnetization transfer (MT) effect between bulk (free) water protons and protons associated with macromolecules, often used as a marker of tissue integrity [9]. Our published data on healthy volunteers demonstrate the ability of our MT protocol to provide robust relaxation and parametric maps characterized by high tissue specificity [9]. Additionally, MT and $R_{1\rho} (=1/T_{1\rho})$ methods are sensitive to a different range of exchange rate constants: MT detects intermediate-slow exchanges, while $R_{1\rho}$ is sensitive to an intermediate-fast exchange regime. Therefore, these two techniques could provide complementary information for characterizing tissue integrity. Moreover, by adopting proper modeling of the relaxation processes, it is possible to generate parametric maps of the fundamental relaxation parameters of the tissue, e.g., rotational correlation times and exchange rate constants, k_{ex} .

In this study, we aimed at investigating the ability of adiabatic $R_{1\rho}$ and modified MT protocols to detect changes in the brainstem of PD patients as compared to age-matched control subjects.

Methods

Nine non-demented individuals with mild–moderate PD (58 ± 10 years old, mean $\pm$ SD) and ten age-matched healthy volunteers (58 ± 9 years old) consented and participated in this study which was approved by the Institutional Review Board of the University of Minnesota. Clinical assessments were made of all participants using the Mini-mental state examination (~ 29 average score for PD and controls), Montreal Cognitive Assessment (~ 27 was average score for PD and controls), Unified Parkinson Disease Rating Scale (UPDRS) and Hoehn & Yahr (H&Y) Staging. Patients with PD were off their usual antiparkinsonian medications for 12 hours prior to imaging.

This study was performed at 4-T/90-cm magnet interfaced to Varian DirectDrive™ console. A volume coil was used for signal transmission and reception from the human brain. After adjusting first order shim terms on the un-localized water signal, the RF amplitude was specifically calibrated in the brainstem region by using a localized calibration procedure. Based on our experience, the amplitude of the RF generated by the volume coil utilized in this study is highly homogenous in the brainstem region, conservatively within 5% of the calibrated value. Images were acquired using fast spin echo readout, TR = 6.5–10 s, TE = 0.073 s, matrix 256×256 , FOV = $25.6 \text{ cm} \times 25.6 \text{ cm}$, and slice-thickness = 4mm. In the adiabatic $T_{1\rho}$ configuration, a train of 0, 4, 8, 12 and 16 hyperbolic secant HS1 ($R=10$) 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. The relaxation rate constants $R_{1\rho}$ (measured in s^{-1}) were estimated by mono-exponential fitting of the signal intensity decay, on a pixel-by-pixel basis. 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 $\omega_1^{\max}/(2\pi) = 0.15$ kHz, was placed prior to the imaging readout. By progressively incrementing the duration of the off-resonance pulse, the

R_{1sat} was estimated. Differences of relaxation rate constants (i.e., $\Delta R_{1\rho}$ or ΔR_{1sat}) were calculated between various sub-regions of the brainstem in each subject, and were then compared between patients and controls. The statistical significance of these comparisons was evaluated by two-tailed un-paired student t-test, and the level of significance was set at $p=0.05$. Relaxation analyses were performed using Aedes software operating on Matlab R2009b platform.

Results

We used $R_{1\rho}$ and MT relaxations measurements in the brainstem in nine mild-moderately affected PD patients (all were H&Y Stage II, average UPDRS III off scores were 33.8, and average disease duration was 6 years) and ten age-matched control subjects. The shimming procedure resulted in a line width of the water resonance < 25 Hz in all subjects. In Figure 1 the representative $R_{1\rho}$ and R_{1sat} maps from control (top) and PD (bottom) subjects are shown. The analyzed regions of interest are indicated on the T_2 -weighted images and the results are summarized in Table 1. Statistically significant differences were observed when comparing $\Delta R_{1\rho}$ values of ROI-1 vs ROI-5 and ROI-1 vs ROI-6 between patients and control subjects ($p=0.004$ and $p=0.033$, respectively). Differences in $R_{1\rho}$ values were 6 and 8 times larger in patients than in controls when comparing ROI-1 vs ROI-5 and ROI-1 vs ROI-6, respectively (Table 1). Notably, $R_{1\rho}$ values in ROI-1 were not different between patients and controls ($p=0.25$). A trend to reach the significance level was instead observed when comparing $R_{1\rho}$ values in ROI-5 and ROI-6 between patients and controls ($p=0.062$ and $p=0.077$, respectively). Based on these observations, the changes in $\Delta R_{1\rho}$ between patients and control subjects primarily arose from the medullary nuclei rather than the 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 $R_{1\rho}$ in those regions. Together, our findings of faster $R_{1\rho}$ 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.

Discussion

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 neuronal loss in the brainstem structures such as the raphe nucleus, locus ceruleus and lateral tegmental nuclei [2, 3, 10]. Recently MRI voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) have detected brainstem changes in PD [4] and REM sleep disorder (RBD) [5]. The RBD study suggested the presence of reticular formation pathology, a potential substrate for the sleep disorder [5]. In an independent project at our institution [11], we found elevated GABA in the posterior pons in PD as compared to controls using 7 T 1H -MR magnetic resonance spectroscopy (MRS). Taken together, these findings support the possibility that MRI may be useful to detect pathological and/or functional changes in the brainstem in PD. The present study reinforces this notion. Our imaging focused on a 4mm paramedian slice that likely encompasses the reticular formation and/or several raphe nuclei and less likely more lateral structures such as the locus ceruleus, pedunculo pontine nucleus or other nuclei (Figure 1). It is known that serotonin dysregulation and dopaminergic changes are relevant for a spectrum of PD symptoms. For example, raphe nuclei changes may be part of the basis for depression in PD [2] or potentially involved in dyskinesias [12]. Serotonergic nuclei in the brainstem were selected as ROIs for analysis in the experimental design of this study, and the observed $R_{1\rho}$ differences in these regions may reflect functional/structural changes in the serotonergic nuclei [10] of the medulla.

Although at the current stage of investigation a correlation with specific pathology and clinical features is not established, we hypothesize the loss of regional heterogeneity reflect neurodegenerative changes of PD. Further animal studies using our approach may help define α -synuclein related brainstem changes related to premotor features. This study enrolled a relatively small number of patients such that we were not able to determine if imaging findings correlated with disease severity or a clinical feature such as depression or RBD. An evaluation of a larger population of patients would be helpful. Nevertheless, this present evidence shows MRI changes in PD which may be due to brainstem pathology in mild-moderately affected individuals, and are consistent with both clinical and pathological features of disease.

In conclusion, our findings may be relevant to disease pathology and/or relate to functional changes of the disease. We plan to extend our relaxation mapping methods from a single-slice approach into 3-dimensions which will help determine if it is possible to detect changes in PD in areas that are not possible with routine MRI methods. Ultimately improved clinico-radiological correlations will help relate to pathological and/or pathophysiological underpinnings in PD. Although the proposed methods provide high tissue specificity, at this stage of research it is premature to use these techniques in classifying patients in clinical practice.

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Figure 1.

Rotating frame $R_{1\rho}$ maps (middle column), MT rate maps (R_{1sat}) (right column), with relative T_2 -weighted (T_2w) images (left column) from representative control subject (top row) and PD patient (bottom row). Regions of interest (ROIs) – as depicted on T_2w images – 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.

Table 1

Differences of $R_{1\rho}$ and R_{1sat} ($\Delta R_{1\rho}$ and ΔR_{1sat} , respectively, expressed in s^{-1}) between various ROI-s in PD patients and healthy controls. For example, $\Delta R_{1\rho}$ of ROI-1 vs ROI-2 is calculated as $R_{1\rho}$ in ROI-1 minus $R_{1\rho}$ in ROI-2. Data are expressed as mean $\pm$ SD. P-values refer to un-paired t-test of $\Delta R_{1\rho}$ and R_{1sat} values between PD patients and healthy controls.

	$\Delta R_{1\rho}$ (s^{-1})		p-value
	Control	Parkinson	
ROI-1 vs ROI-2	-0.718 $\pm$ 0.876	-1.155 $\pm$ 1.051	0.337
ROI-1 vs ROI-3	-1.555 $\pm$ 0.880	1.479 $\pm$ 0.613	0.831
ROI-1 vs ROI-4	-0.734 $\pm$ 0.844	1.082 $\pm$ 0.721	0.351
ROI-1 vs ROI-5	-0.138 $\pm$ 0.412	-0.818 $\pm$ 0.486	*0.004
ROI-1 vs ROI-6	-0.133 $\pm$ 0.716	-1.158 $\pm$ 1.181	*0.033
ROI-2 vs ROI-3	-0.837 $\pm$ 0.819	0.324 $\pm$ 1.348	0.324
ROI-2 vs ROI-4	-0.016 $\pm$ 0.582	-0.073 $\pm$ 1.278	0.844
ROI-2 vs ROI-5	0.580 $\pm$ 0.729	0.337 $\pm$ 1.176	0.591
ROI-2 vs ROI-6	0.585 $\pm$ 0.979	-0.003 $\pm$ 1.203	0.256
ROI-3 vs ROI-4	0.821 $\pm$ 0.610	0.397 $\pm$ 0.810	0.212
ROI-3 vs ROI-5	1.417 $\pm$ 0.843	0.662 $\pm$ 0.881	0.073
ROI-3 vs ROI-6	1.422 $\pm$ 1.183	0.321 $\pm$ 1.467	0.088
ROI-4 vs ROI-5	0.597 $\pm$ 0.642	0.265 $\pm$ 0.766	0.319
ROI-4 vs ROI-6	0.602 $\pm$ 1.002	-0.076 $\pm$ 1.214	0.200
ROI-5 vs ROI-6	0.005 $\pm$ 0.560	-0.341 $\pm$ 0.875	0.314
	ΔR_{1sat} (s^{-1})		p-value
	Control	Parkinson	
ROI-1 vs ROI-2	-0.045 $\pm$ 0.150	-0.029 $\pm$ 0.057	0.797
ROI-1 vs ROI-3	-0.343 $\pm$ 0.157	0.322 $\pm$ 0.111	0.750
ROI-1 vs ROI-4	-0.071 $\pm$ 0.173	0.117 $\pm$ 0.128	0.521
ROI-1 vs ROI-5	0.032 $\pm$ 0.138	-0.027 $\pm$ 0.069	0.258
ROI-1 vs ROI-6	0.081 $\pm$ 0.190	0.027 $\pm$ 0.061	0.423
ROI-2 vs ROI-3	-0.298 $\pm$ 0.106	0.293 $\pm$ 0.133	0.935
ROI-2 vs ROI-4	-0.026 $\pm$ 0.136	0.088 $\pm$ 0.162	0.376
ROI-2 vs ROI-5	0.077 $\pm$ 0.131	0.002 $\pm$ 0.096	0.174
ROI-2 vs ROI-6	0.126 $\pm$ 0.167	0.056 $\pm$ 0.091	0.278
ROI-3 vs ROI-4	0.272 $\pm$ 0.098	0.205 $\pm$ 0.175	0.313
ROI-3 vs ROI-5	0.375 $\pm$ 0.132	0.295 $\pm$ 0.143	0.221
ROI-3 vs ROI-6	0.424 $\pm$ 0.168	0.349 $\pm$ 0.119	0.283
ROI-4 vs ROI-5	0.103 $\pm$ 0.133	0.090 $\pm$ 0.087	0.801
ROI-4 vs ROI-6	0.152 $\pm$ 0.121	0.144 $\pm$ 0.092	0.871
ROI-5 vs ROI-6	0.049 $\pm$ 0.083	0.054 $\pm$ 0.027	0.861