Diffusion Changes in the Medulla Oblongata in Parkinson Disease

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Target audience: Scientists and clinicians who are working in the field of neurodegenerative diseases or diffusion imaging

Introduction: Parkinson's disease (PD) is a progressive neurodegenerative illness of the nervous system characterized by extensive damage to substantia nigra pars compacta dopaminergic neurons[1]. However the nigral damage is accompanied by extensive extranigral pathology[2]. Braak et al. (2003)[3] proposed a staging model, based on neuropathology, which suggests that damage extends progressively from the medulla oblongata and pontine tegmentum to the midbrain and then to cortical structures. According to this model, the medulla oblongata should be affected early in the course of the disease. Diffusion Tensor Imaging (DTI) is increasingly used to measure the integrity of tissue microstructure and alterations of neuronal fiber tracts[5], with several outcome measures: mean diffusivity (MD), axial diffusivity (AD), longitudinal diffusivity (LD), fractional anisotropy (FA). Several DTI studies in PD patients and animal models have reported decreased FA and increased MD in the SN, basal ganglia and other parts of the brainstem[5-7], however no studies have investigated the medulla oblongata using DTI. The aim of the present study was thus to characterize medulla oblongata damage using DTI in PD patients as compared with healthy volunteers (HV).

Materials and Methods: **Subjects**: 44 patients with PD (age: 62.4±8.1 years, 15 males, disease duration: 8.8±3.1 years) were compared with 23 HV (age: 59.9±8.4 years, 11 males). Clinical examination included the Unified Parkinson's Disease Rating Scale (UPDRS III score, Off-score: 29.1±10.1, On-score: 17.45±8.6). **MRI data acquisition:** MRI acquisition was performed using a 3 Tesla TRIO TIM system (Siemens, Erlangen, Germany) using a 12-channel receive-only head coil. The protocol included three-dimensional (3D) T1-weighted (T1-w) images, 3D T2-weighted (T2-w) images and DTI with the following parameters: TR/TE/flip angle =14000 ms/101ms/90°, voxel size = 1.7*1.7*1.7 mm^3, b=value 1500 s/mm^2, 60 diffusion gradients directions). **Image analysis**: Image processing and analysis were performed using in-house software written in MATLAB and ROI were segmented using FMRIB Software Library (FSL) v5.0 (FMRIB Analysis Group, Oxford, UK). Quantitative measures of AD, LD, MD and FA were obtained in selected regions of interest (ROIs) obtained by manual tracing including the medulla oblongata and posterior pontine tegmentum (Fig.1). **Statistical analysis**: Statistical analysis of the diffusion metrics in the ROIs and the clinical metrics was performed using JMP 8 (SAS) using ANOVA. Values are presented as mean ± standard deviation.

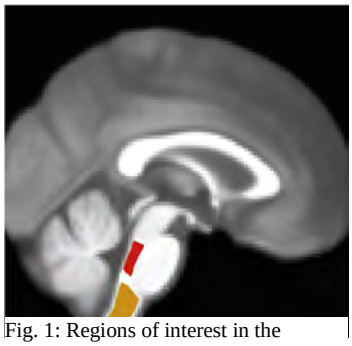

Fig. 1: Regions of interest in the medulla oblongata (yellow) and pons (red)

Results: For the **medulla oblongata**, ANOVA showed significant differences in MD (p=0.005), AD (p=0.01), and LD (p=0.003) values between groups and no significant differences in FA (p=0.37) (Table 1, Fig. 2). The same effect was observed for the **posterior pontine tegmentum** with significant differences in MD (p=0.03), AD (p=0.01), and LD (p=0.02) values between groups and no significant differences in FA (p=0.45) (Table 1, Fig. 2). **Clinical correlations**. There was no significant correlation between age, gender, disease duration, and UPDRS ON and UPDRS OFF clinical scales.

Subjects	ROI	FA	AD	LD	MD
HV	MO	0.28±0.03	0.74±0.10	0.48 ± 0.06	0.61 ± 0.05
	Pons	0.43±0.03	0.51±0.08	0.77±0.02	0.38±0.06
PD	MO	0.28 ±0.02	0.8 ± 0.07*	0.52 ±0.05**	0.56 ±0.07**
	Pons	0.43±0.04	0.55±0.06*	0.83±0.01*	0.41±0.05*

Table 1: ***Diffusion values in the medulla oblongata (MO) and posterior pons for FA, AD*** ($10^{-3}mm^2s^1$), **LD** ($10^{-3}mm^2s^1$) and **MD** ($10^{-3}mm^2s^1$), Significant differences are indicated using *(p≤0.05) and **(p≤0.005)

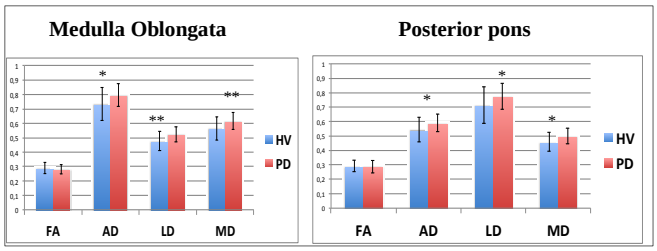

Fig. 2: ***Diffusion values in PD (red) and HV (blue)*** *for FA, AD ($10^{-3}mm^2s^1$), LD ($10^{-3}mm^2s^1$) and MD ($10^{-3}mm^2s^1$). Significant differences are indicated using asterisks (*p<0.05, **p<0.005).*

Discussion: Patients with PD showed increased MD, AD and LD values in the medulla oblongata and pontine tegmentum. Our results are in line with the medulla oblongata being affected in PD subjects[3]. In the pons, results were more variable with studies reporting diffusion changes[6,7] and others not[8]. While there was a significant difference between PD and HV for MD, AD and LD no differences were found for FA. It is possible that the increase in both AD and LD resulted in absence of changes in FA, in line with some previous studies.[8] No correlations were found with clinical variables, such as age, disease duration or UPDRS. However, clinical correlations remain to be done with specific measures of medulla oblongata functions such as autonomic dysfunction.

Conclusion: The increased MD, AD, and LD in both medulla oblongata and pontine tegmentum suggests that DTI may be an interesting biomarker of tissue microstructure and pathological alterations in this region. Progression of diffusion changes in the medulla oblongata of PD patient and correlations with measures of autonomic dysfunction are currently being investigated in a longitudinal study.

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