Nigrostriatal pathway evaluation with diffusion MRI and three-dimensional histological analysis in a monkey model of Parkinson′s disease

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Introduction

Movement dysfunction in Parkinson's disease (PD) is caused by the degeneration of dopaminergic (DA) neurons in the nigrostriatal pathway. A diffusion tensor imaging (DTI) study showed that fractional anisotropy in brain regions between the substantia nigra pars compacta (SNc) and the striatum was lower in PD patients than in healthy controls [1]. However, the nigrostriatal pathway has not been visualized by diffusion tensor tractography (DTT) because of the sparsity of fibers. The purpose of this study was to visualize the nigrostriatal pathway in the marmoset monkey brain using microscopic DTT technique with three-dimensional (3D) histological analysis, and to assess DA degeneration in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated animals, a model of PD. Moreover, as a preclinical imaging tool to assess the severity of neuronal degeneration in PD, we performed longitudinal voxel-based analysis (VBA) of T1-weighted images (T1WI) and DTI in the marmoset brain and statistically evaluated the distribution of degenerated DA neurons.

Methods

Common marmosets (n = 6) received MPTP on three consecutive days at a daily dose of 2, 2, and 1 mg/kg s.c. on day 1, 2, and 3, respectively. These marmosets showed long lasting and stable parkinsonism symptoms such as movement tremor and immobility (measured objectively as decreased locomotion count). Before and 3 month after MPTP administration, 3D T1WI with an isotropic resolution of 0.2 mm and two-dimensional DTI with an in-plane resolution of 0.38 mm and a slice thickness of 1 mm were performed. After the acquisition of longitudinal MRI, ex vivo microscopic DTI with an isotropic resolution of 60 µm and histological examination with Kluver-Barrera and tyrosine hydroxylase staining were performed on fixed brains. DTT and VBA were analyzed using TrackVis [2] and SPM software, respectively.
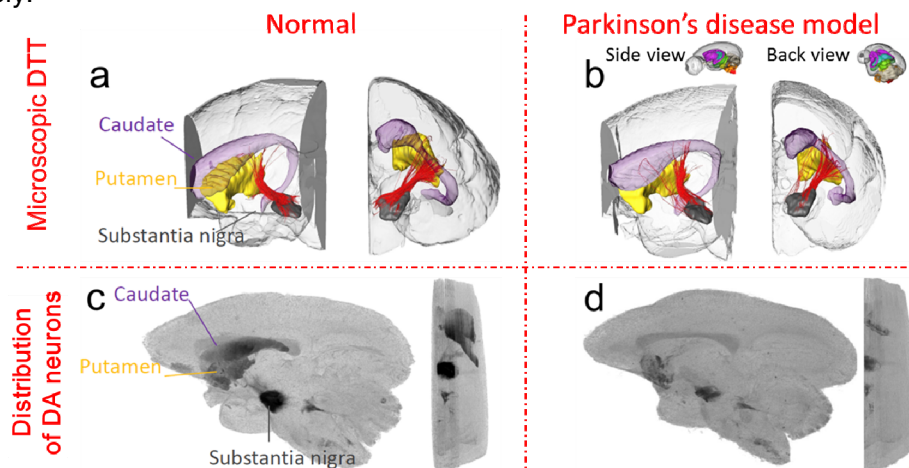

Figure 1. Microscopic DTT (a, b) and distribution of DA neurons (c, d) in intact (left) and PD (right) marmoset model.

Results and Discussion

Microscopic DTT clearly depicted the fiber structure between the substantia nigra (SN) and the putamen (red in Figure 1a) in normal brain, and the regions were consistent with the distribution of DA neurons identified by histological analysis (Figure 1c). Nigrostriatal fibers are selectively destroyed by administration of MPTP, and there was a drastic reduction of DA neurons identified by 3D histological analysis (Figure 1c and d). DTT results revealed that the number of tracking structures between the SN and the putamen in the MPTP-treated brain was nearly half that in the intact brain (Figure 1a and b). In longitudinal VBA, volume decreases in bilateral SNc were observed by longitudinal T1WI in regions that were consistent with the distribution of DA neurodegeneration, and a bilateral increase in radial diffusivity was observed by longitudinal DTI in the regions of the nigrostriatal pathway.

Conclusion

Our microscopic DTT technique visualized the nigrostriatal pathway of the marmoset monkey and concurred with the results of 3D histological analysis. Longitudinal VBA evaluated volume loss in the SNc and axonal disruption of nigrostriatal fibers. We are currently using these MR neuroimaging techniques to detect the onset of PD in a transgenic marmoset model. These techniques may be useful for understanding the mechanisms of PD.

References: [1] Yoshikawa et al., J Neurol Neurosurg Psychiatry, 2004, [2] Wang et al., Proc ISMRM, 2007