Structural white matter alterations in the DRTT of Parkinson's disease motor phenotypes

Bethany Facer[1,2], Corey Ratcliffe[1,3,4], Antonella Macerollo[1,2] & Simon Keller[1,2]

1. University of Liverpool, Institute of Systems, Molecular and Integrative Biology; 2. The Walton Centre NHS Foundation Trust, Liverpool, UK; 3. CNNP Lab, School of Computing, Newcastle University; 4. Department of Neuroimaging and Interventional Radiology, NIMHANS, Bangalore, India.

We report that newly diagnosed patients with tremor-dominant Parkinson's disease (TD-PD) show a trending increase in DRTT fibre density and cross-section (FDC) compared to controls. Higher baseline DRTT FDC was associated with greater tremor severity, and greater longitudinal reductions in DRTT FDC were linked to attenuated progression of tremor symptoms, suggesting early compensatory or adaptive mechanisms within tremor-related white matter pathways.

Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by motor dysfunction and considerable patient heterogeneity, including tremor-dominant (TD-PD) and postural instability gait difficulty (PIGD-PD) motor phenotypes[1,2]. Advances in fixel-based analysis (FBA) enable fibre-specific investigation of white matter pathways[3]. The dentato-rubro-thalamic tract (DRTT) is clinically significant and often targeted with deep brain stimulation for tremor relief[4]. This study investigates DRTT structural differences across newly diagnosed TD-PD and PIGD-PD phenotypes, examines associations with baseline tremor severity, and explores how DRTT integrity changes over a four-year period in relation to tremor.

Conclusion

TD-PD patients showed a trending increase in DRTT FDC compared to controls, suggesting early fibre-specific alterations, similar to previously reported findings in the motor pathways[7]. Higher DRTT FDC at baseline was associated with worse tremor severity, indicating that increased structural integrity may not always reflect preserved function. Longitudinally, greater FDC reductions were linked to smaller deterioration in tremor, suggesting possible compensatory changes or dynamic reorganisation within motor pathways. Alternatively, stable or increased FDC could represent maladaptive plasticity contributing to symptom progression. These findings highlight the complex role of white matter changes in early PD and support further fibre-specific investigations.

Methods

Participants included individuals with de novo PD and age-matched healthy controls from the Parkinson's Progression Markers Initiative. All participants were over 45 years of age, had a Hoehn & Yahr (H&Y) stage under 3, and completed the MDS-UPDRS Part III motor examination. PD patients were stratified into TD-PD and PIGD-PD subtypes[2].

Diffusion-weighted images (DWI) were pre-processed and then using the MRtrix3 fixel-based analysis (FBA) pipeline the fibre orientation distributions (FODs) were estimated using constrained spherical deconvolution[5]. From this, the fibre density cross-section (FDC) metric was computed to capture both microstructural and macrostructural white matter properties[3].

The DRTT was delineated on a population FOD template using anatomically guided regions of interest[6]. Inclusion masks were placed on the superior cerebellar peduncle, red nucleus, and primary motor cortex. An exclusion mask was applied to the corpus callosum to minimise false positives FDC values were extracted from fixels within the DRTT for each subject.

Statistical analyses were performed using fixelcfestats with 1000 permutations, correcting for family-wise error. Analyses included: ANCOVA to assess group differences (TD-PD, PIGD-PD, controls), correlation of ipsilateral DRTT FDC with side-specific baseline tremor scores, and associations between longitudinal change in FDC and tremor severity over a four-year follow-up.

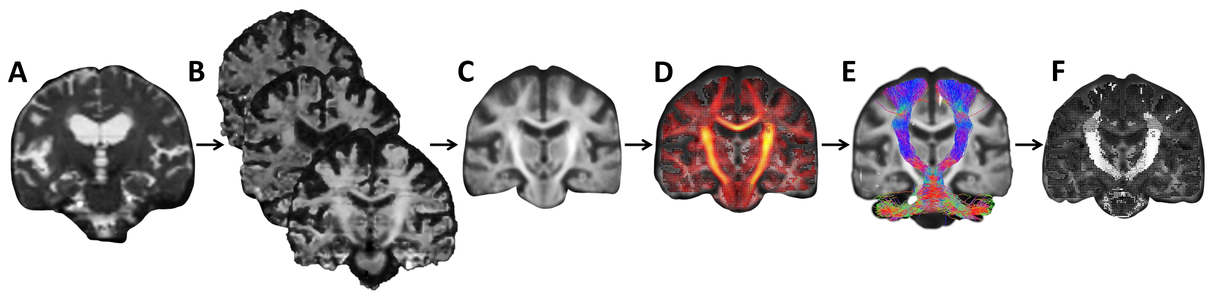

Figure 1) Fixel-based analysis pipeline. (**A**) Pre-processed diffusion-weighted images following eddy current correction; (**B**) Estimation of white matter fibre orientation distributions (FODs) using constrained spherical deconvolution; **(C**) Generation of a population-specific FOD template to enable inter-subject alignment; (**D**) Extraction of FDC (fibre density and cross-section) fixel maps from the FOD template for statistical analysis; (**E**) Isolation of the dentato-rubro-thalamic tract (DRTT) using anatomically defined inclusion and exclusion masks; (**F**) Binarisation of the DRTT fixel mask to extract tract-specific FDC values for group comparisons and symptom correlation analysis.

Results

99 TD-PD, 30 PIGD-PD, and 55 healthy controls were included in the analysis. The PD and control groups were matched for age and sex. TD-PD and PIGD-PD groups were matched for sex, UPDRS-III, Hoehn & Yahr stage, and disease duration; however, PIGD-PD patients were significantly older than TD-PD patients (**Table 1**). A subset of 51 PD participants underwent longitudinal imaging and OFF-medication UPDRS-III assessment over a four-year follow-up period.

For the motor phenotype baseline comparison, TD-PD exhibited significantly larger FDC in the DRTT compared to healthy controls (p = 0.1 , ES = 0.67). No other significant group differences were found. At baseline, a trending association was observed between left DRTT FDC and left-sided tremor severity at baseline (p = 0.06, effect size = 0.35), with greater tremor severity associated with higher FDC **(Figure 2**).

	TD	PIGD	HC	P value
N	99	30	55	
Age	61.43 +/- 8.48	64.97 +/- 7.87	63.09 +/- 7.77	TD-HC: .23 PIGD-HC: .29 TD-PIGD: .05
Sex	36F/ 63M	9F/21M	22F/33M	TD-HC: .79 PIGD-HC: .50 TD-PIGD: .67
UPDRS-III	21.25 +/- 9.23	22.13 +/- 6.92	0.62 +/- 1.41	TD-HC: <.001 PIGD-HC: <.001 TD-PIGD: .63
Hoehn and Yahr Scale	1.53 +/- 0.5	1.7 +/- 0.47	0	TD-HC: <.001 PIGD-HC: <.001 TD-PIGD: .09
Disease Duration	14.76 +/- 7.18	16.9 +/- 7.73	N/A	TD-PIGD: .41

Table 1) Clinical demographics

.

No significant correlation was found between right DRTT FDC and right-side tremor. Longitudinally, FDC was calculated by subtracting Year 4 FDC from baseline FDC, and tremor was calculated by subtracting Year 4 tremor scores from baseline scores. A significant positive correlation was found between right DRTT FDC and right-sided tremor change over four years ($p < 0.01$, ES = 0.76), indicating that greater FDC reduction was associated with smaller increases in tremor severity. No significant correlation was observed between left DRTT FDC and left-side tremor change.

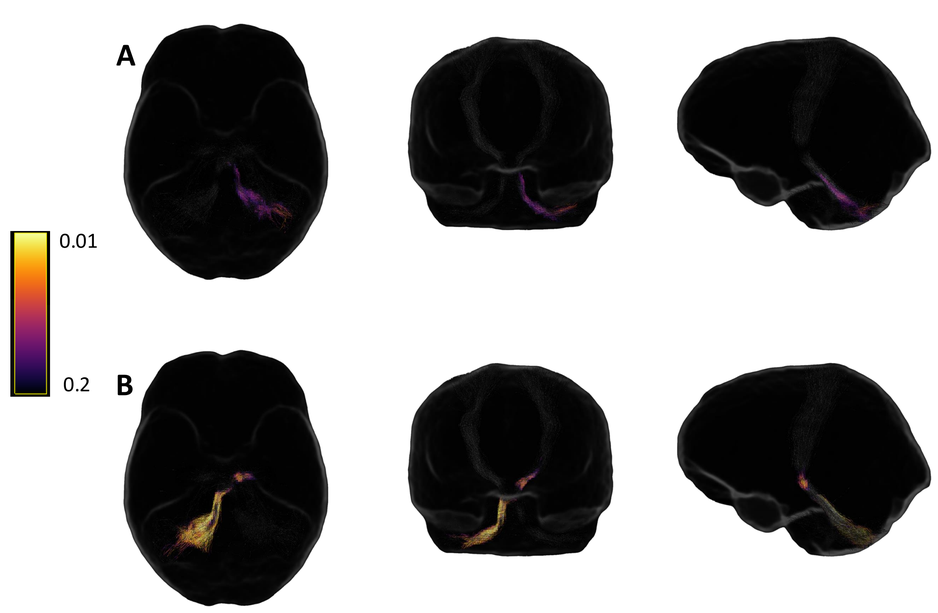

Figure 2) Significant fixel-wise results mapped onto the DRTT.
(**A**) Significant findings from the baseline association between left DRTT FDC and left-sided tremor severity, and from the **(B)** longitudinal association between right DRTT FDC and right-sided tremor change, are shown. Fixels were thresholded at p < 0.2 for visualisation purposes and coloured by p-value intensity. Results are overlaid on the DRTT tractogram to highlight fibre-specific effects.

Key references: [1]Jakovic., 2008, JNNP; [2]Stebbins et al., 2013, Movement Disorders; [3]Raffelt et al., 2017, NeuroImage; [4]Coenen et al, 2020, Acta Neurochir; [5]Tournier *et* al., 2019, NeuroImage. [6]Kwon *et al.*, 2011, Functional Neuroradiology; [7]Andica *et al.*, 2021, npj Parkinson's Disease.