

Visualization and Quantification of the Striato-pallidonigral Fibers in Parkinson's Disease Using Diffusion Tensor Imaging

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(PPMI)

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Motivation

- The substantia nigra (SN) is highly vulnerable to Parkinson's Disease (PD). The most consistent pathological finding in PD is degeneration of the melanin-containing cells in the pars compacta (posterior part) of the SN.
- Melanin-containing cells synthesize dopamine. Dopamine transfers—via axoplasmic flow—to the nerve terminals in the striatum (caudate nucleus and putamen). The lack of dopamine transmitter is a hallmark of PD.
- Some diffusion tensor imaging (DTI) studies but not all found abnormalities locally in the SN.
- Diffusion tensor tractography assessment of the fiber tracts linking the SN and the striatum may help characterizing PD.

Anatomy

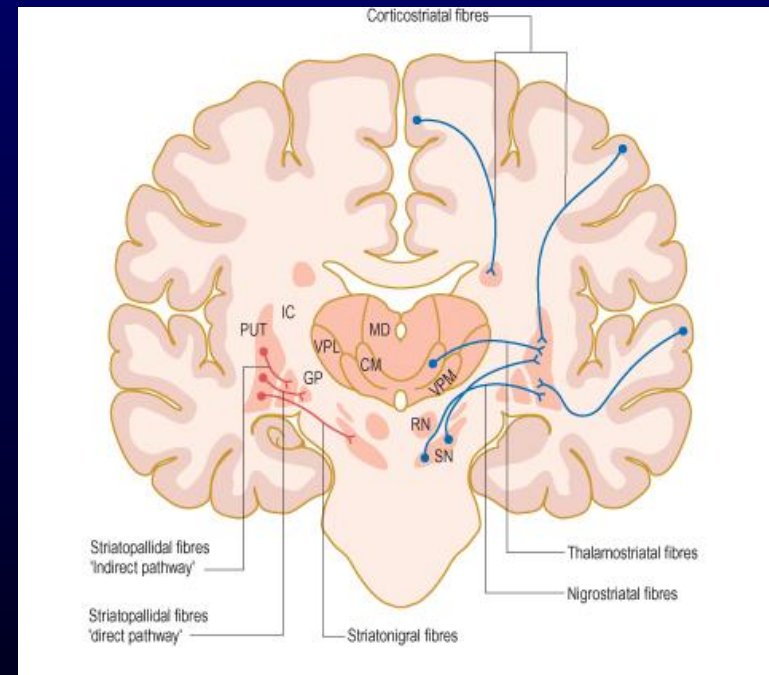
Axonal pathways connect to the SN:

Afferents reaching mostly the **pars reticulata (SNr)**:

- Striato-nigral pathway:
Striatum → globus pallidus (GP)
→ SNr
- Thalamo-nigral pathway:
less numerous

Efferents arising mostly from the **pars compacta (SNc)**:

- **Nigro-pallidal pathway:**
SNc → over subthalamic nucleus (STN) → traverse globus pallidus (GP) → terminate in putamen (Put).
[dopaminergic]
- Nigro-thalamic pathway:
SNc → terminate in thalamus
[GABAergic]



Aims

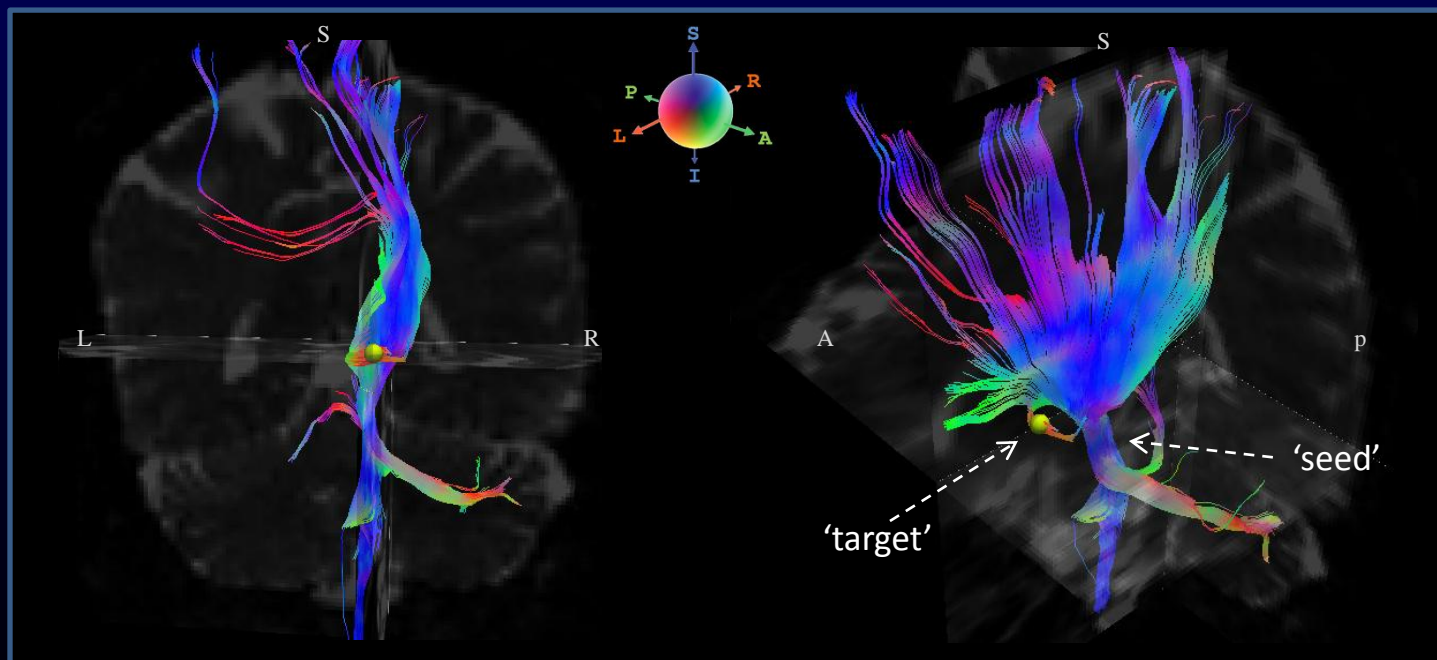
- Visualization of the nigro-pallidal tract in DTI
- Determination of measurement reliability
- Quantification of DTI profiles along the tract
- Hypothesis tests:
 - DTI along the nigro-pallidal tract is abnormal in PD
 - DTI alterations in PD correlate with disease severity, e.g. DAT score, UPDRS III scores

Methods

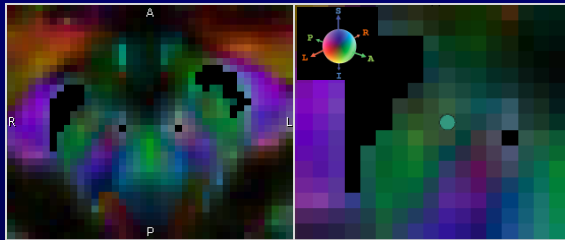
- DTI data collected from the Parkinson's Progression Marker Initiative (PPMI)
- Baseline study of de-novo PD and control subjects
- Multicenter DTI study, involving 10 international sites
- DTI scan protocol:
 - TR/TE = 900/88 ms
 - GRAPPA: 2-fold acceleration
 - b=0, b=1000 s/mm²
 - 64 sensitization directions
 - 72 contiguous slices
 - 2×2×2 mm³ resolution
 - scan time: ~11 minutes
 - Cardiac triggered

Initial Step For Visualization Of The Nigro-Pallidal Tract

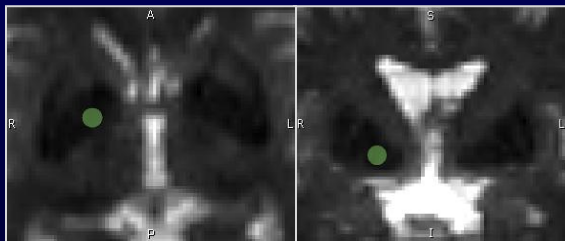
- Fiber tracking using TrackVis (URL: <http://trackvis.org>)
- 'Seed' location (ROI) placed in the SN
- 'Target' location (ball) in the Put/GP.
- Fiber tracking is performed at 1 mm³ high resolution.



Final Step For Visualization Of The Nigro-Pallidal Tract

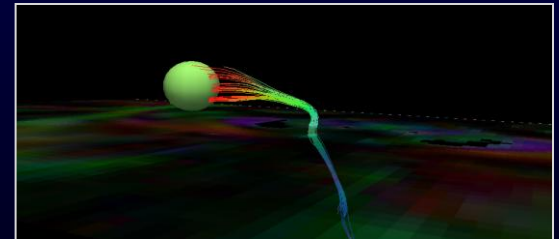


1. The SN is identified on the DTI directional map. The 'seed' ROI (1 mm disk) is placed in the SN. The disk angle is adjusted perpendicular to the tract orientation.

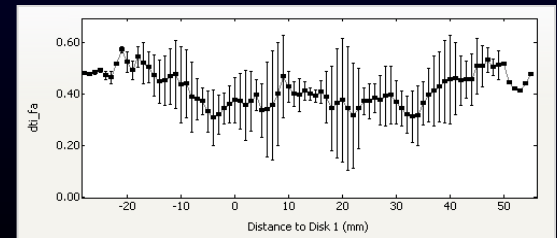


2. The 'target' (2 mm ball) is placed in the medial-inferior part of Put/GP

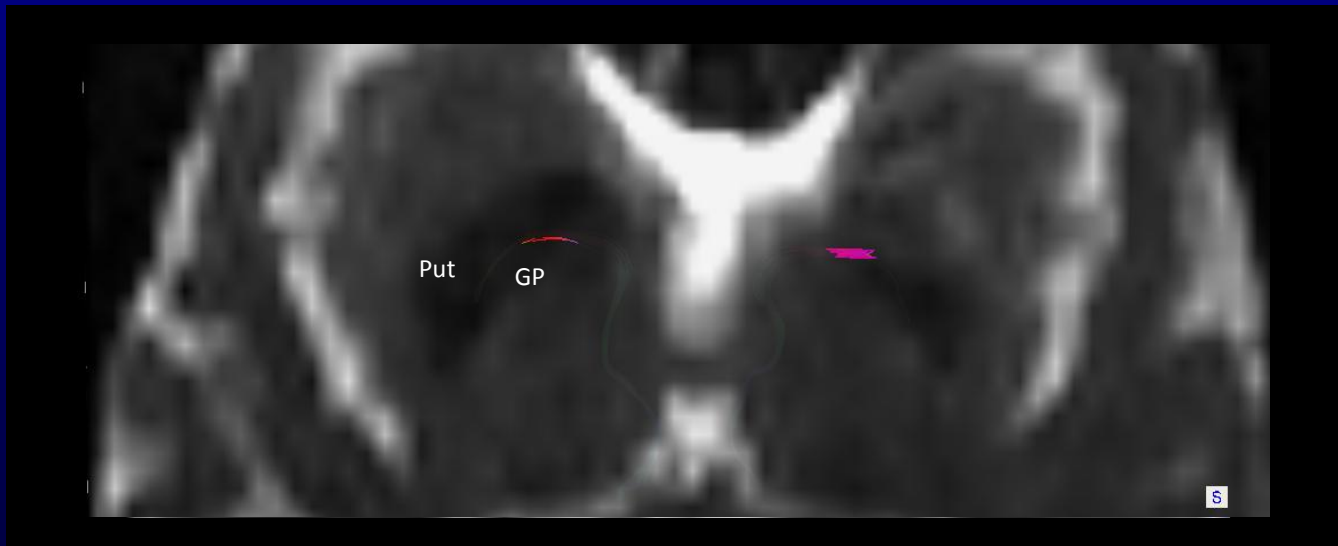
3. The 'seed' ROI within the SN is moved around until tracts reach the 'target' ball



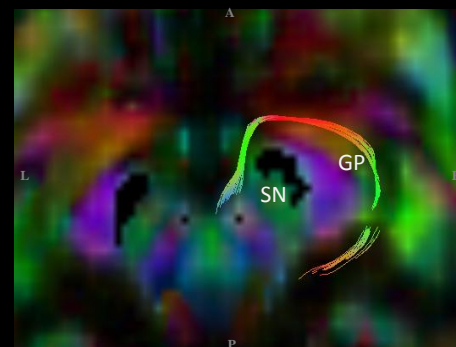
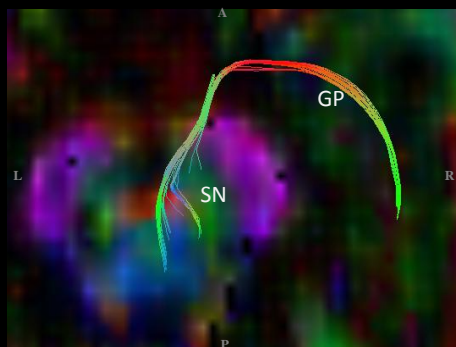
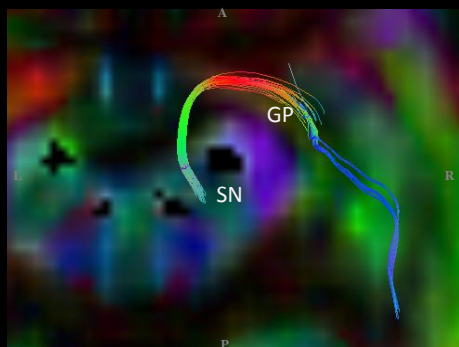
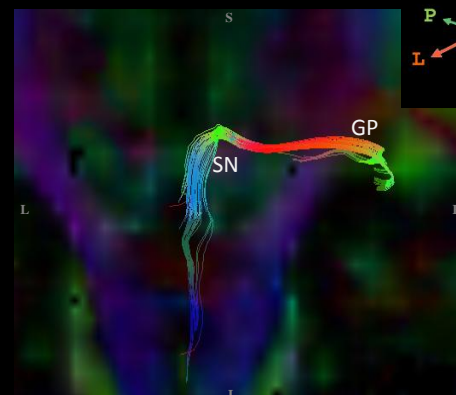
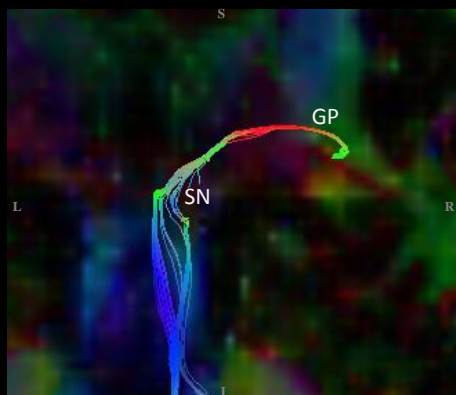
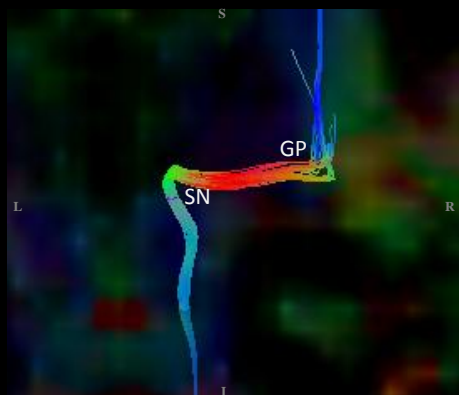
4. The DTI profile point-by-point along the tract is obtained



Tract Anatomy



Consistency And Variation



Example-1

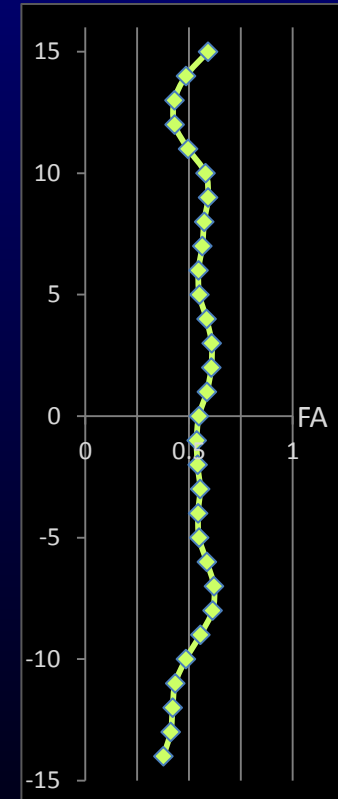
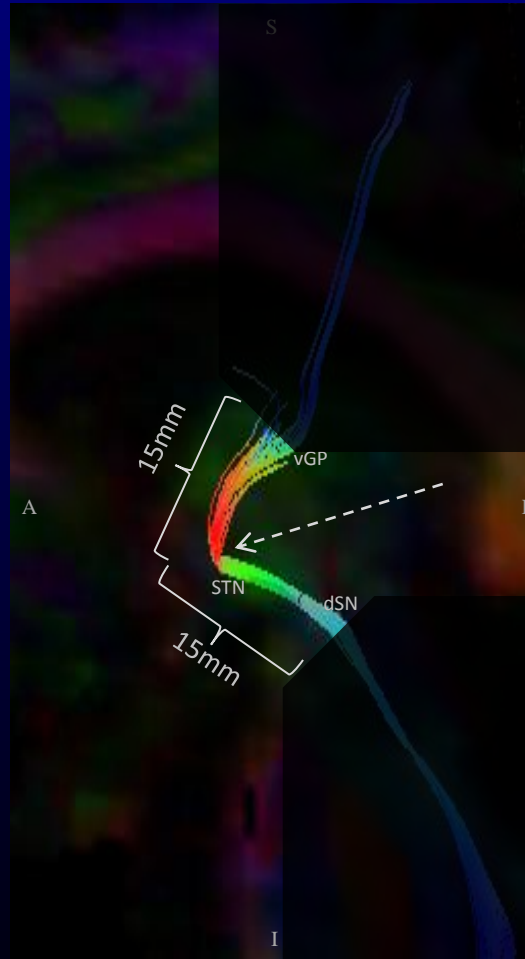
Example-2

Example-3

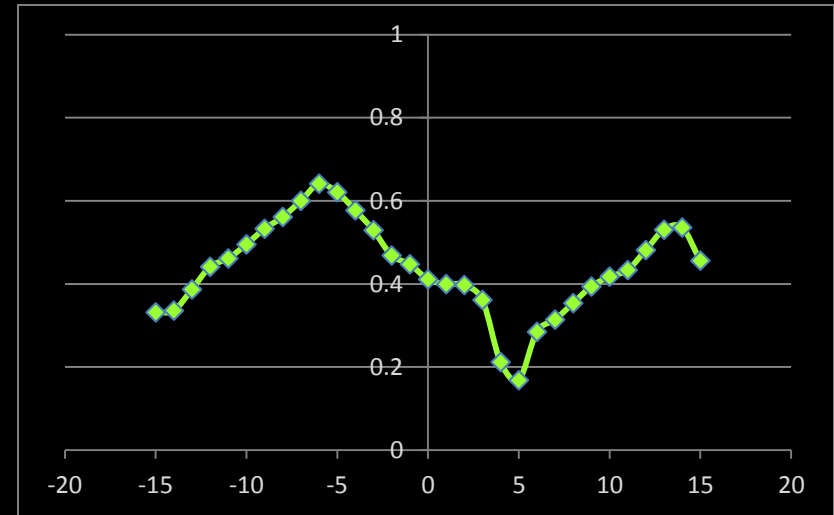
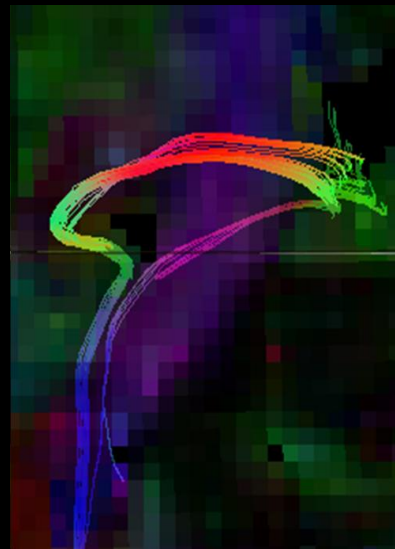
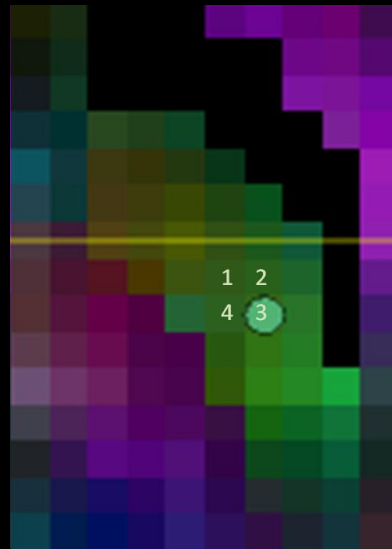
Most consistent part: Between dorsal SN (green: A-P) and ventral GP (red: L-R)
 Variable part: lower level of SN (blue: S-I) and higher level of Put/GP (green/blue)

Tract Quantification

- DTI profiles are measured in the consistent part of the tract
- A center point is determined where the tract direction changes from green to red
- DTI profiles are obtained from 15 mm sections on each side of the center
- DTI indices (eigenvalues, FA, MD, fiber counts) are recorded point-by-point along the sections



Fiber Tracking Reliability



Intraclass Correlation Coefficient (ICC)
of 12 random selected subjects

| Intra-Rater Reliability | | Repeated Scan Reliability | |
|-------------------------|-------|---------------------------|-------|
| Left | Right | Left | Right |
| 0.912 | 0.947 | 0.727 | 0.801 |

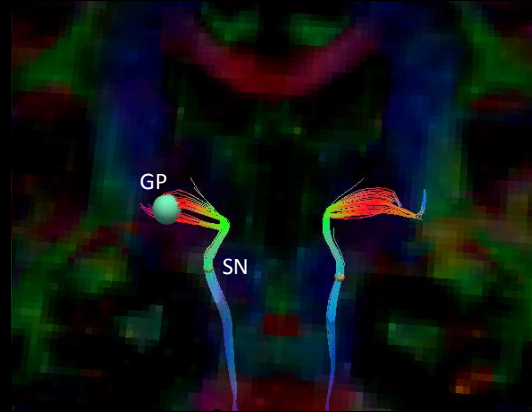
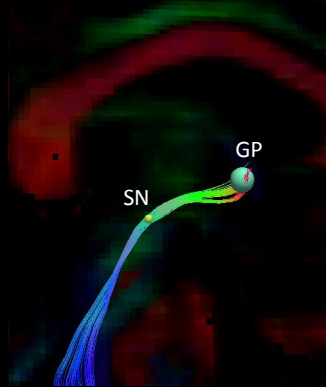
Demographics

| | Control | PD |
|------------------------------|----------------|-----------------|
| Number of selected subjects | 18 | 19 |
| Number of successful cases | 15 | 18 |
| Age (range) [years] | 60 (45~75) | 61.2 (50~73) |
| Sex | 12M : 3F | 9M : 9F |
| Total UPDRS III | 6.1 \pm 2.4 | 43.5 \pm 16.2 |
| Tremor Subscore* | 0.03 \pm 0.1 | 0.44 \pm 0.3 |
| Akinetic-Rigid (AR) Subscore | 0.03 \pm 0.1 | 1.17 \pm 0.5 |
| L/R averaged putaminal DAT | 1.3 \pm 0.3 | 0.7 \pm 0.2 |

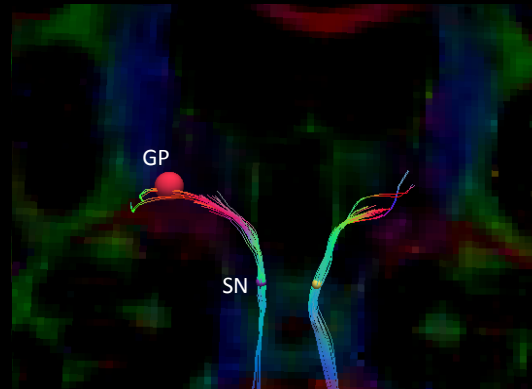
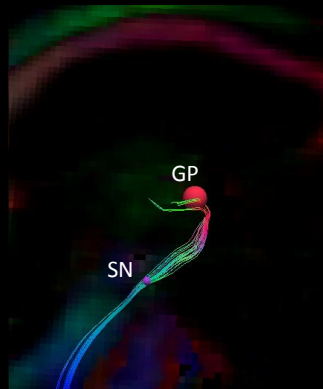
- Tremor score: ratio of Tremor items relative to total UPDRS III
- AR Score: ratio of AR items relative to total UPDRS III

Representative Tract Maps

Control

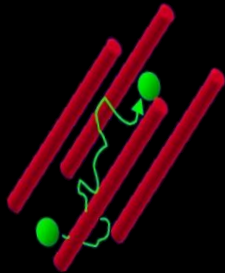


PD

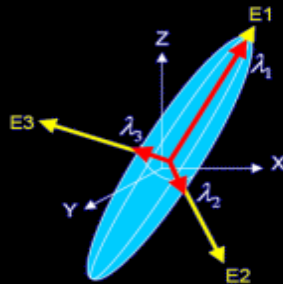


Quantitative DTI measures

Molecular base



Tensor model



$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

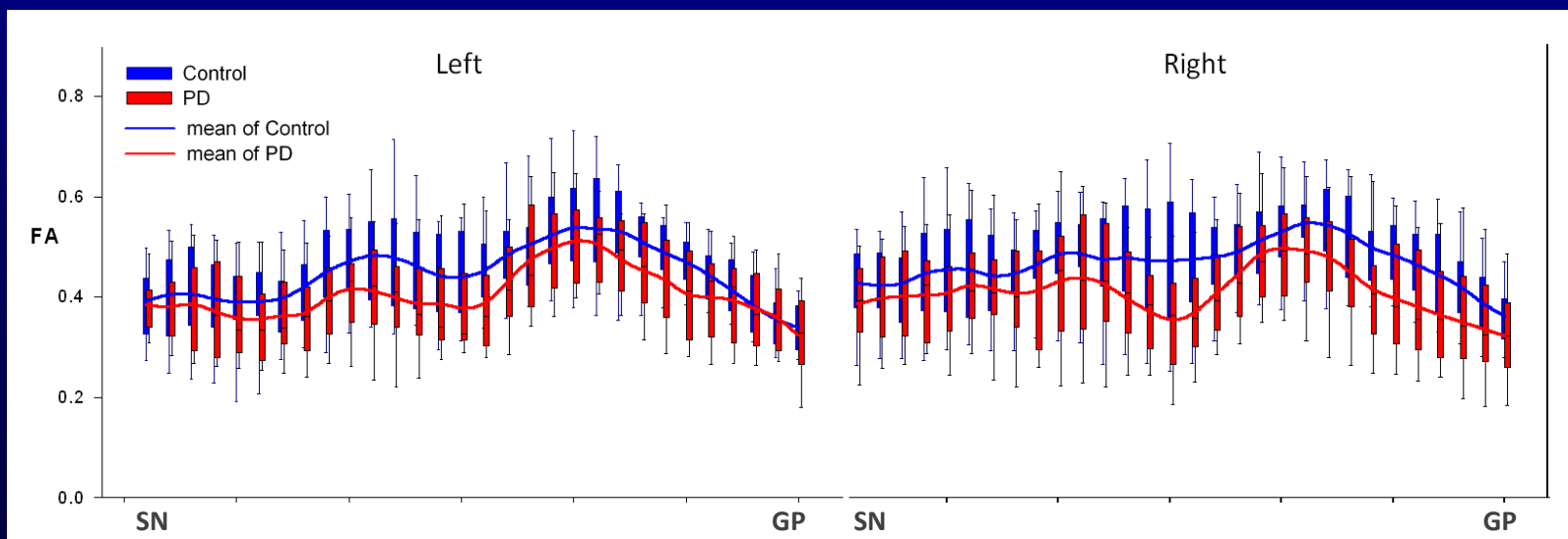
$$DA = \lambda_1$$

$$DR = (\lambda_2 + \lambda_3) / 2$$

$$MD = (\lambda_1 + \lambda_2 + \lambda_3) / 3$$

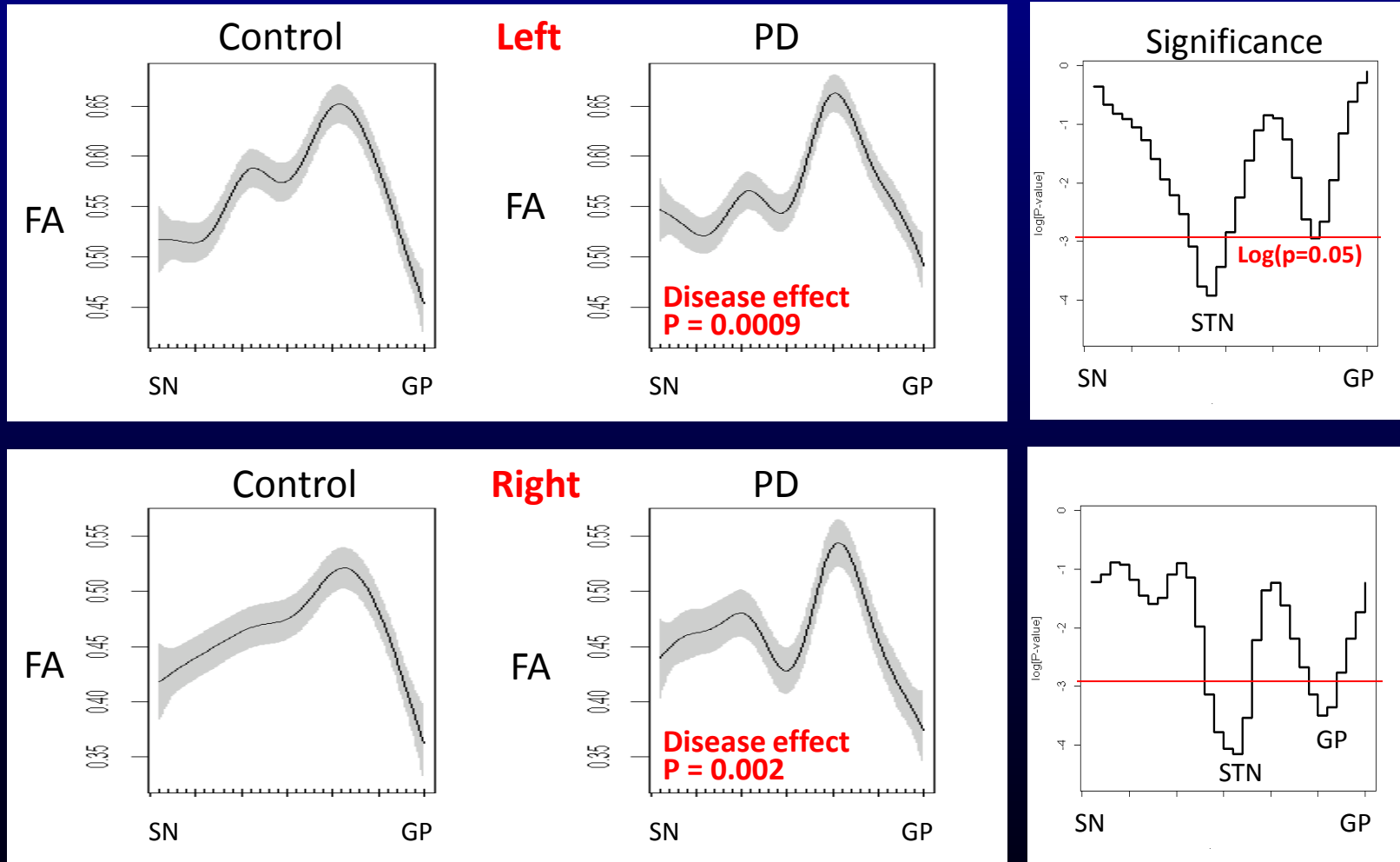
| Indices | Abbr. | Description | Possible Interpretation |
|---|-----------|-----------------------------------|---|
| Fractional Anisotropy | FA | Directionally dependent diffusion | Decrease with fiber loss and demyelination |
| Axial Diffusivity [10 ⁻³ mm ² /s] | DA | Main direction of diffusion | Increases with axonal loss |
| Radial Diffusivity [10 ⁻³ mm ² /s] | DR | Perpendicular diffusion | Increases with demyelination |
| Mean diffusivity [10 ⁻³ mm ² /s] | MD | Average diffusion | Increase with axonal loss and demyelization, etc. |
| Fiber Density | | Mathematical construct | Unclear |
| Fiber Count | | Mathematical construct | Correlates with FA |

Group Averaged DTI Profile Point-by-Point



| | Control | PD | <i>p</i> value |
|--|-------------|-------------|----------------|
| Fractional Anisotropy | 0.46 ± 0.03 | 0.41 ± 0.04 | 0.001 |
| Axial Diffusivity [10 ⁻³ mm ² /s] | 1.21 ± 0.08 | 1.27 ± 0.18 | n.s. |
| Radial Diffusivity [10 ⁻³ mm ² /s] | 0.57 ± 0.07 | 0.69 ± 0.13 | 0.006 |
| Mean diffusivity [10 ⁻³ mm ² /s] | 0.78 ± 0.07 | 0.88 ± 0.14 | 0.02 |
| Fiber Density | 55.6 ± 12.0 | 52.2 ± 12.3 | n.s. |
| Fiber Count | 47.7 ± 18.9 | 34.1 ± 17.7 | 0.04 |

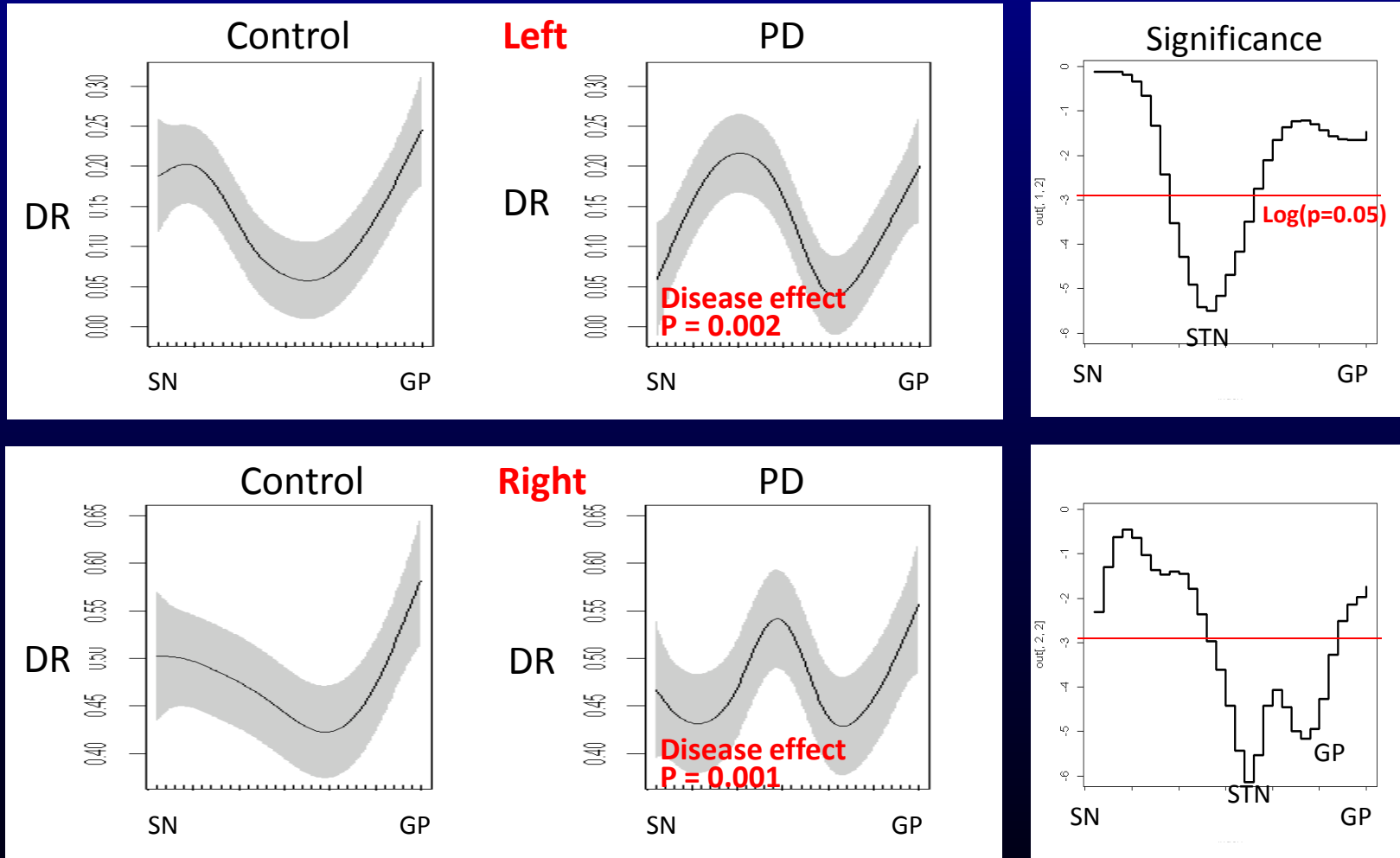
Model-Based* Smoothed FA Estimation



* Using mixed effects generalized additive regressions with smoothed FA as fixed effect and subject variation as random effect

- Mean and SE (shaded) are shown

Model-Based* Smoothed DR Estimation

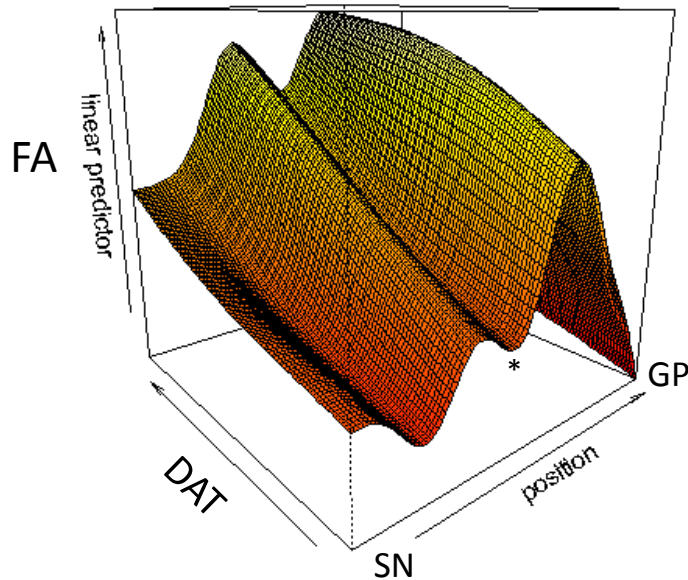


* Using mixed effects generalized additive regressions with smoothed DR as fixed effect and subject variation as random effect

- Mean and SE (shaded) are shown

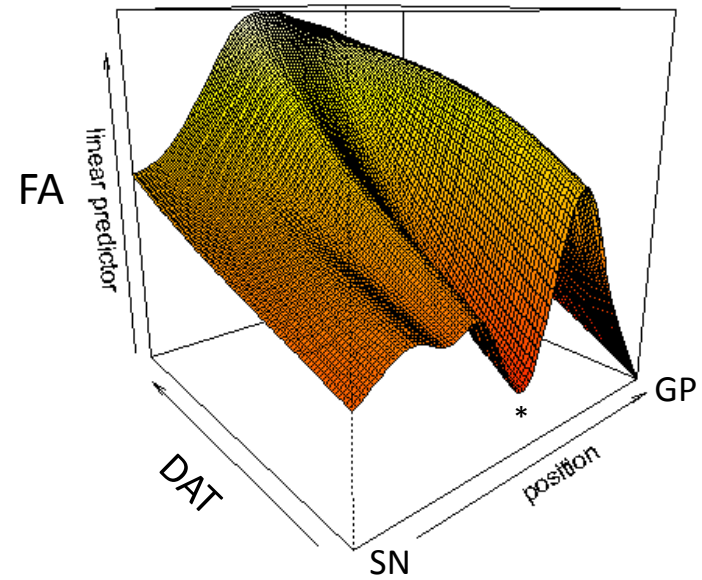
DAT Dependent Variations In FA Profiles

Left



~ 4% FA decrease per unit DAT decrease, $t = 2.46$

Right

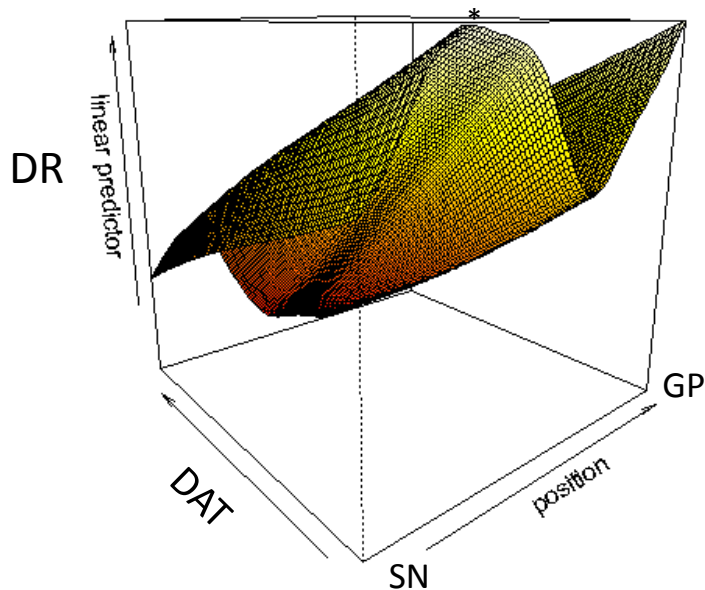


~ 6% FA decrease per unit DAT decrease, $t = 2.76$

- Using mixed effects generalized additive regressions with smoothed FA as fixed effect and subject variation as random effect
- Includes entire subjects (PD + Control)

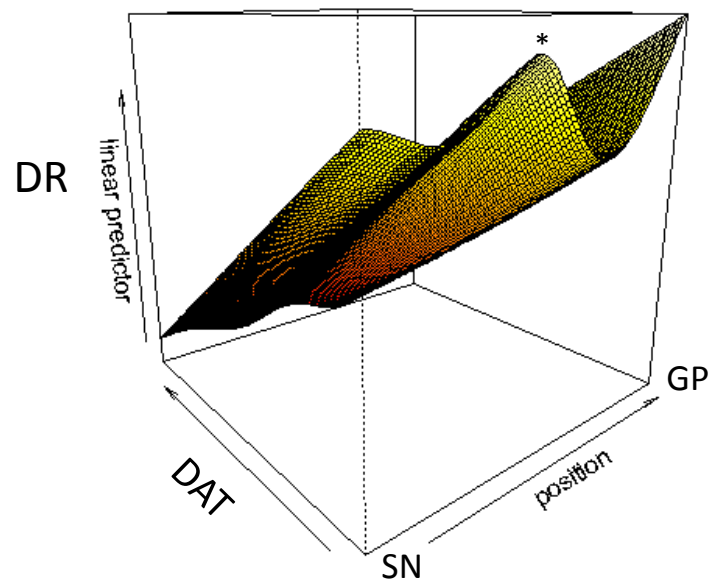
DAT Dependent Variations In DR Profiles

Left



~ 8% DR increase per unit DAT decrease, $t = -2.51$

Right

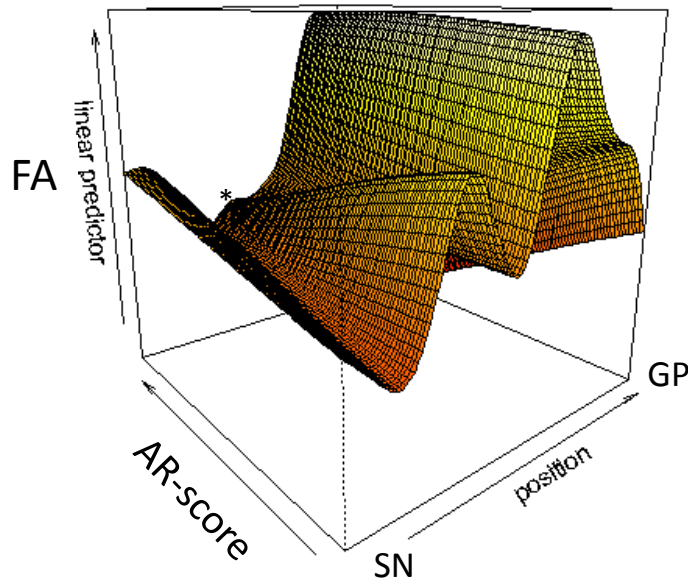


~ 11% DR increase per unit DAT decrease, $t = -3.2$

- Using mixed effects generalized additive regressions with smoothed FA as fixed effect and subject variation as random effect
- Includes entire subjects (PD + Control)

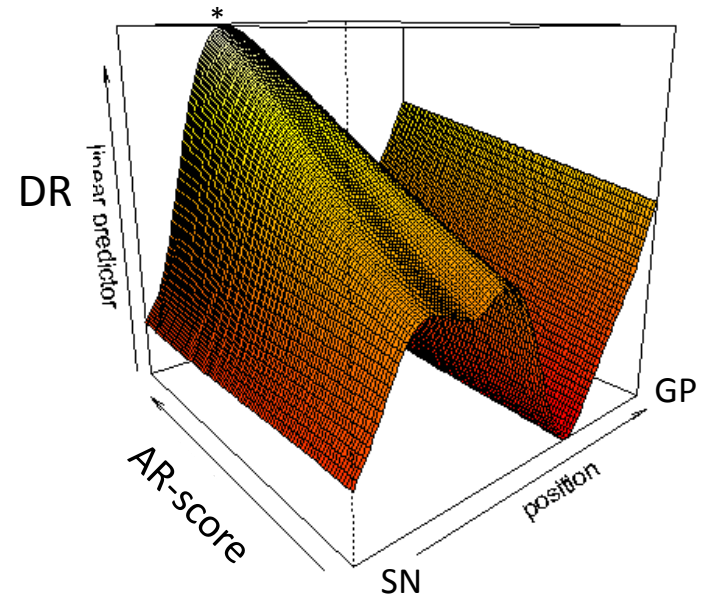
AR-Score Dependent Variations In FA and DR Profiles

Left



~ 10% FA decrease per AR increase, $t = -2.1$

Left



~ 12% DR increase per AR unit, $t = 2.0$

- Using mixed effects generalized additive regressions with smoothed FA as fixed effect and subject variation as random effect
- Includes patients only
- Not Significant on Right

Conclusion

1. Reliable visualization and quantification of the nigral–pallidal tract is feasible, even in a multicenter DTI study
2. PD diagnosis and dopamine deficiency are associated with an abnormal DTI profile, mainly due to the increased radial diffusivity, which is consistent with the view of diminished fiber myelination
3. DTI assessment of the nigral–pallidal tract is potentially useful for characterizing PD

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