The brain in Parkinson's Disease: Structural connectivity analysis in Freezing of Gait patients

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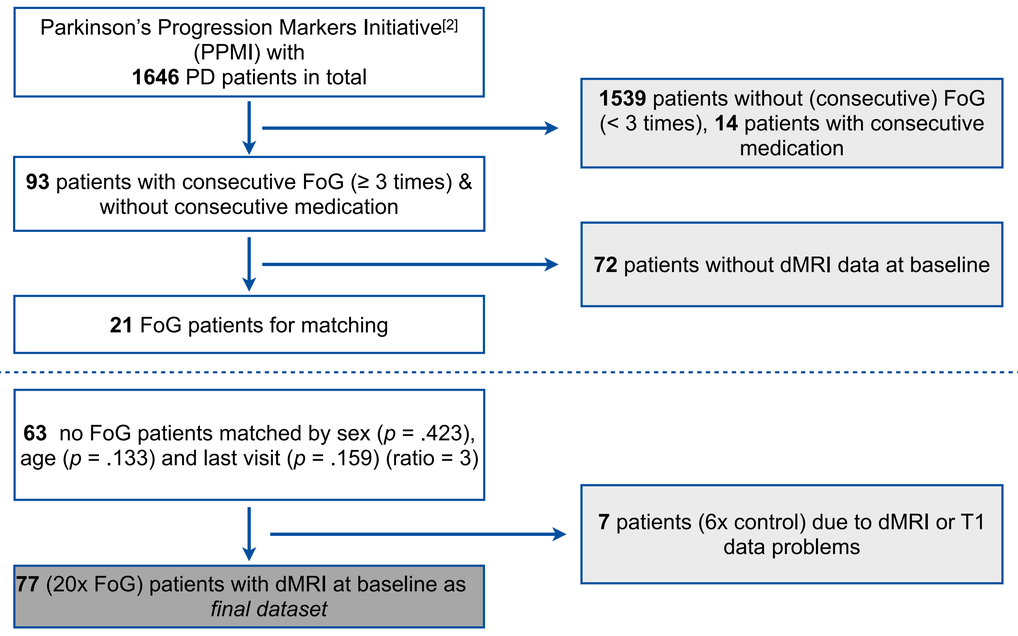
Introduction

- Parkinson's Diseases (PD) as second most common neurodegenerative disorder
- specific motor impairment: Freezing of Gait (FoG)
  - various subtypes, complete akinesia most severe[4, 6]
  - dangerous falls & injuries possible[3]
- in literature no homogenous picture of origin & treatment of FoG
  - e.g. FoG responsive <u>or</u> resistant to L-Dopa (most common PD medication)[4]
- objective: analysis of structural connectivity differences between supplementary motor area (SMA) & thalamus in no FoG and FoG PD patients using diffusion MRI (dMRI) data
- expected: right hemisphere increased structural connectivity (SMA & thalamus) in FoG patients at baseline[1]

Dataset



Methods

Data processing

Following the B.A.T.M.A.N. tutorial[5]:

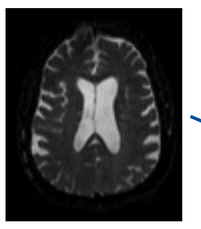


Figure 1: raw dMRI data

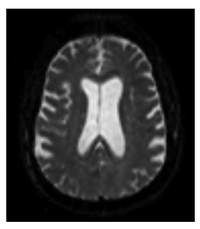


Figure 2: preprocessed dMRI data

1) Preprocessing of dMRI data

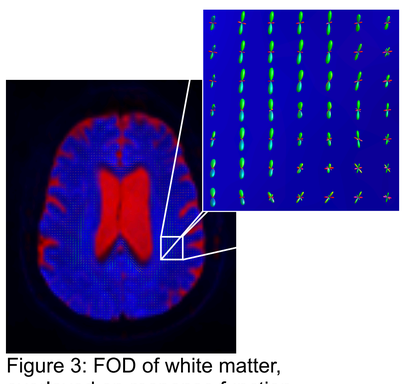


Figure 3: FOD of white matter, overlayed on response function

2) Estimation of Fiber Orientation Distribution (FOD)

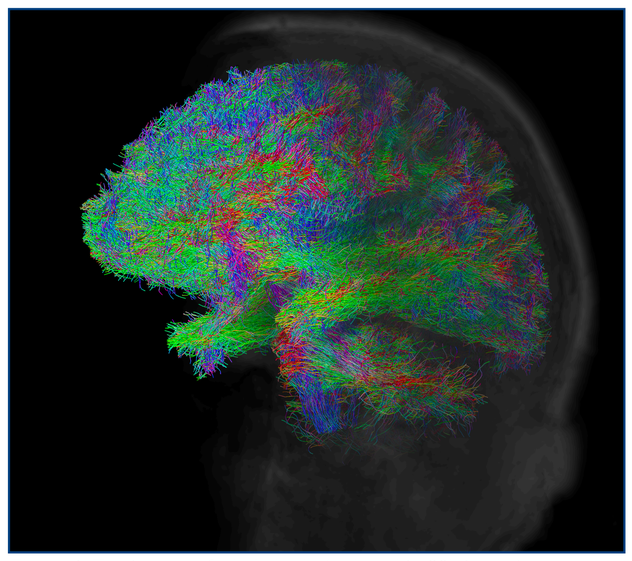


Figure 4: Tractogram of whole brain (reduced to 20k tracks)

3) Creation of Anatomically Constrained Tractography of whole brain

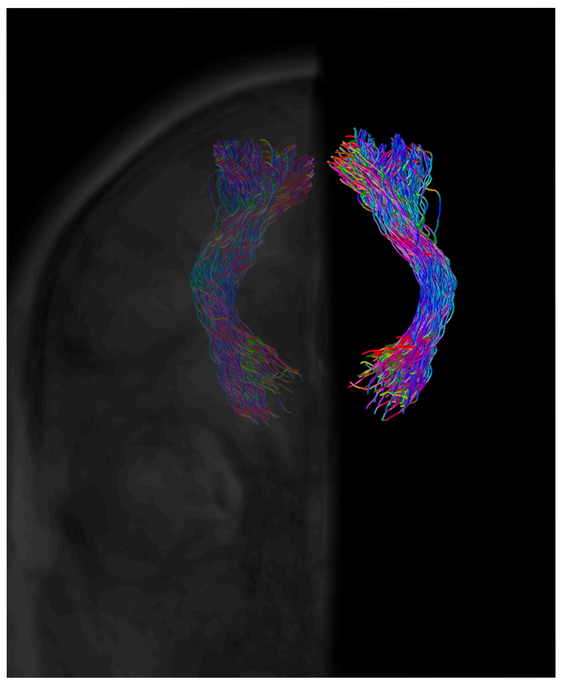


Figure 5: Tractogram of ROI connection (SMA & thalamus)

4) Creation of Region Of Interest (ROI) connection tractogram

Analysis

Statistical comparison of structural connectivity of FoG patients and PD control

- calculation of absolute streams between SMA and thalamus
- normalisation of amount for inter-patient comparison
- calculation of multiple regression for each hemisphere including possible covariates (sex & age)

Results

Structural connectivity comparison of SMA and thalamus in FoG vs. no FoG patients:

Multiple regression in **left hemisphere**
($F(3, 73) = 3.41$, $p = .022$, *adj.* $R^2 = .087$)

- significant higher structural connectivity ($p = .010$) in male patients
- no significant group differences in FoG vs. no FoG

Multiple regression in **right hemisphere**
($F(3, 73) = 4.40$, $p = .007$, *adj.* $R^2 = .118$)

- significant group differences ($p = .019$) in structural connectivity in FoG vs. no FoG patients

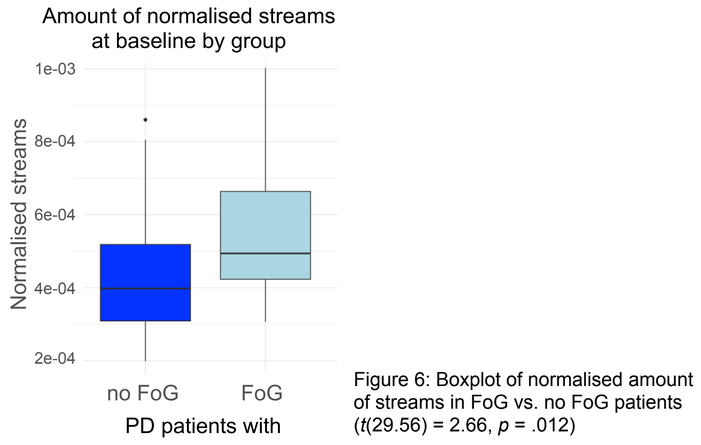


Figure 6: Boxplot of normalised amount of streams in FoG vs. no FoG patients ($t(29.56) = 2.66$, $p = .012$)

Discussion

- amount of normalised streams in FoG vs. no FoG patients increased
- RH structural connectivity higher in FoG patients at baseline:
  - might result from compensatory mechanism in PD brain[1]
  - might be predictive marker for future FoG

Follow-up studies should evaluate, if:

- FoG vs. no FoG structural connection still alters with longer duration of disease.
- the structural connectivity can be used as more reliable predictor for FoG than the Unified Parkinson's Disease Rating Scale.

Literature

[1] Fling, B. W., Cohen, R. G., Mancini, M., Carpenter, S. D., Fair, D. A., Nutt, J. G. & Horak, F. B. (2014). Functional Reorganization of the Locomotor Network in Parkinson Patients with Freezing of Gait. *PLoS ONE*, *9*(6).
[2] Marek, K., Jennings, D., Lasch, S., Siderowf, A., Tanner, C., Simuni, T., Coffey, C., Kieburtz, K., Flagg, E., Chowdhury, S., Poewe, W., Mollenhauer, B., Paracelsus-Elena Klinik, Sherer, T., Frasier, M., Meunier, C., Rudolph, A., Casaceli, C., Seibyl, J., …, & Taylor, P. (2011). The Parkinson Progression Marker Initiative (PPMI). *Progress in Neurobiology*, *95*(4), 629–635.
[3] Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., Schrag, A. E. & Lang, A. E. (2017). Parkinson disease. *Nature reviews. Disease primers*, *3*, 17013.
[4] Snijders, A. H., Takakusaki, K., Debu, B., Lozano, A. M., Krishna, V., Fasano, A., Aziz, T. Z., Papa, S. M., Factor, S. A. & Hallett, M. (2016). Physiology of freezing of gait. *Annals of neurology*, *80*(5), 644–659.
[5] Tahedl, M. (2020). B.A.T.M.A.N.: Basic and Advanced Tractography with MRtrix for All Neurophiles.
[6] Weiss, D., Schoellmann, A., Fox, M. D., Bohnen, N. I., Factor, S. A., Nieuwboer, A., Hallett, M. & Lewis, S. J. G. (2020). Freezing of gait: understanding the complexity of an enigmatic phenomenon. *Brain : a journal of neurology*, *143*(1), 14–30.