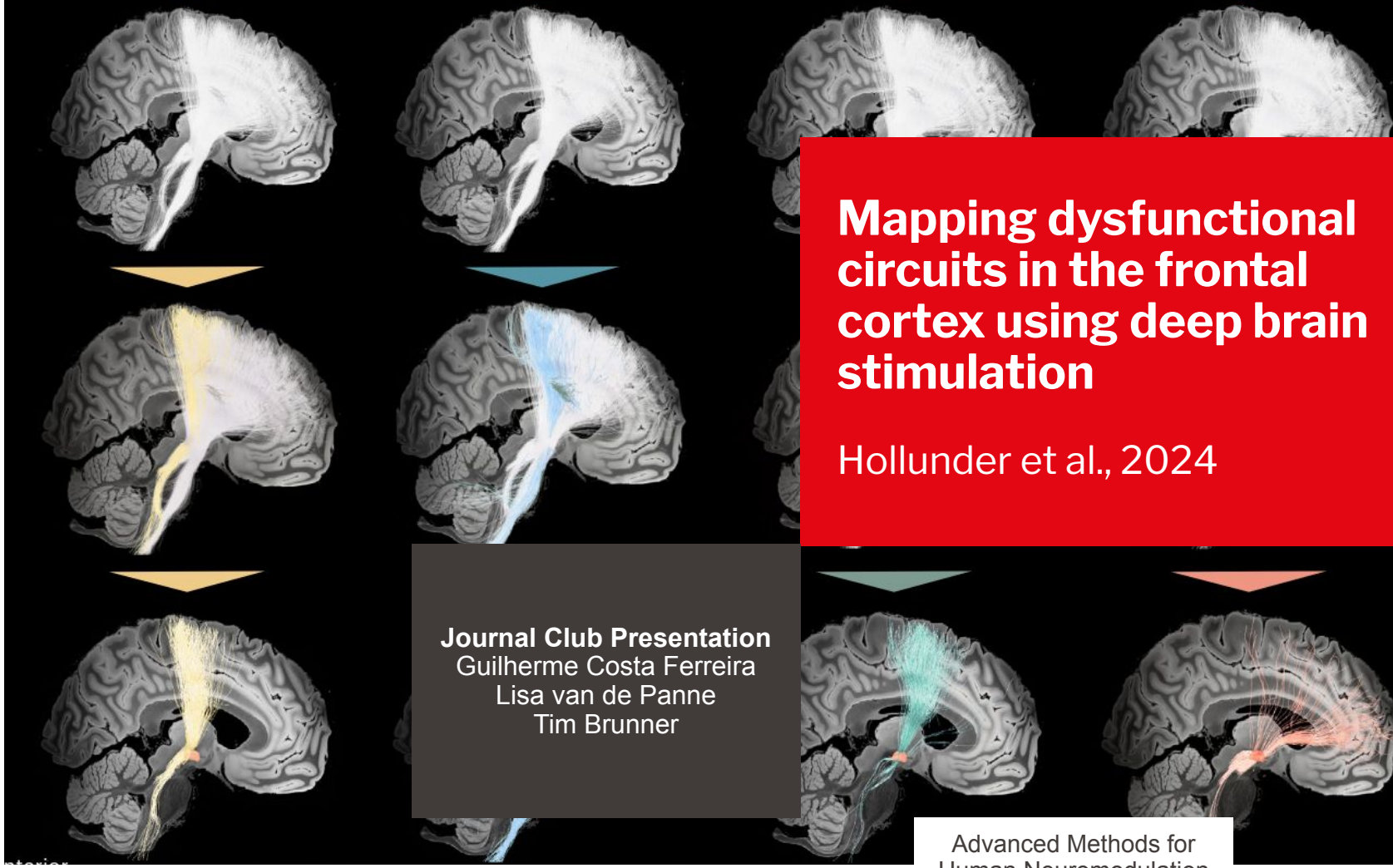

Mapping dysfunctional circuits in the frontal cortex using deep brain stimulation

Hollunder et al., 2024

Journal Club Presentation

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Lisa van de Panne
Tim Brunner

Advanced Methods for Human Neuromodulation

École polytechnique fédérale de Lausanne

Outline

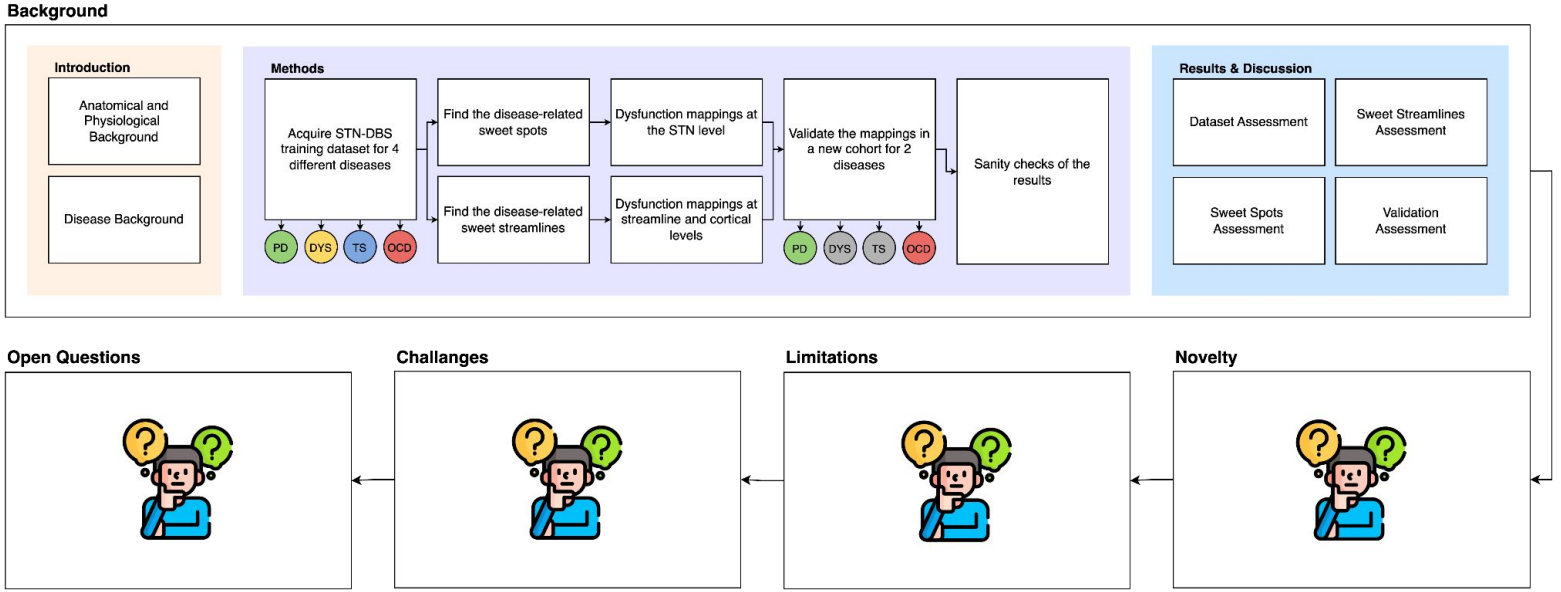


Fig 1 - Presentation outline based on the paper structure

Background - Frontal Cortex

Frontal Cortex

- Motor processing
- Cognitive processing
- Affective processing
- Unclear which dysfunctions are mediated by which frontal domains

Fig 2 - Frontal Cortex Overview

Background - Subthalamic Nucleus

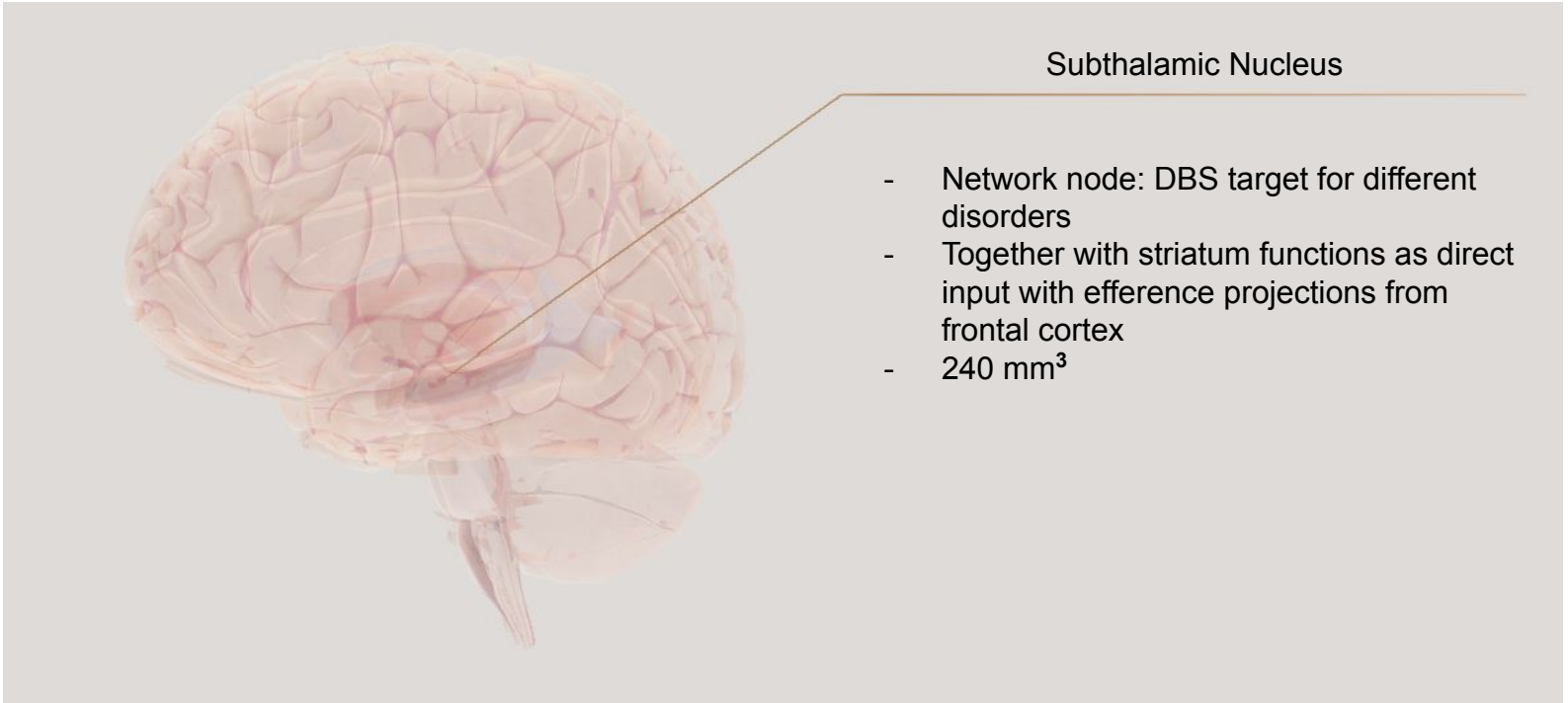
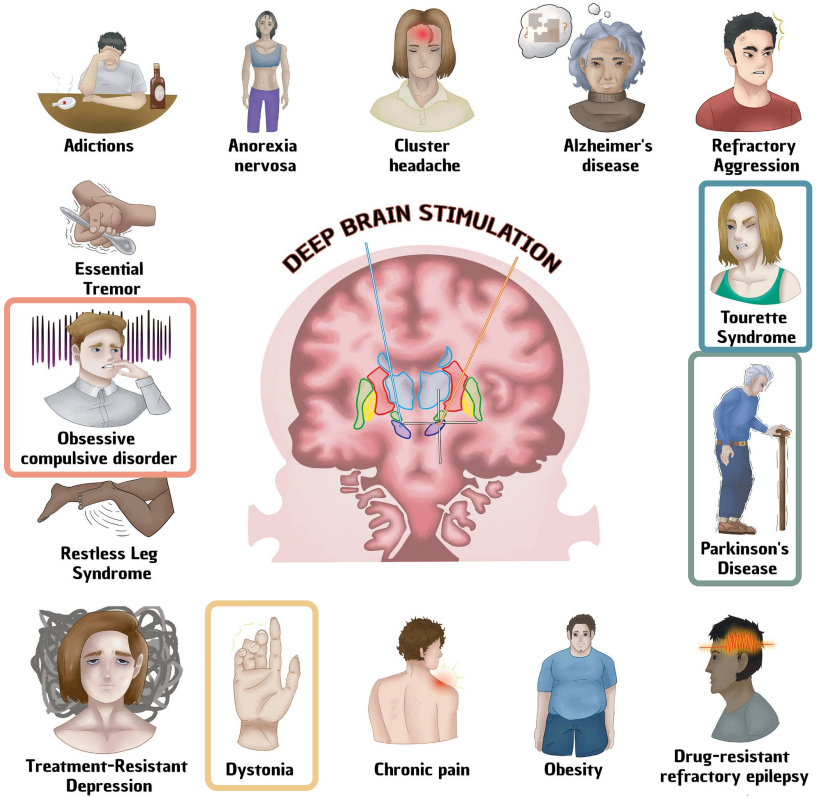


Fig 3 - Subthalamic Nucleus Overview

Background - DBS



- Electrode lead delivers electrical impulses to specific brain regions
- Allows to treat various neurological disorders, mostly related to movement
- 2002 approved for Parkinson's disease
- 2003 approved for dystonia
- 2009 approved for obsessive compulsive disorder.
- Not approved for Tourette's syndrome

- Can be used to study the connectome of the human brain

Fig 4 - DBS targets overview

Background - Analyzed Disorders

Brain connectomics analysis in four neural diseases:
Successful DBS neuromodulation therapy reveal involved circuits

Parkinson's Disease (PD)
- Primarily affecting movement
- Tremors
- Stiffness, slow movement
- Motor cortex

Dystonia (DYT)
- Movement disorder
- Involuntary muscle contractions
- Motor cortex

Obsessive Compulsive Disorder (OCD)
- Mental health condition
- Repetitive behavior (compulsions)
- Unwanted thoughts (obsessions)
- Medial frontal cortex hyperactivity

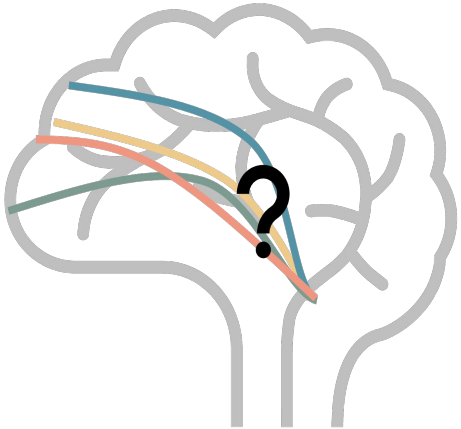
Tourette's Syndrome (TS)
- Neurological disorder
- Involuntary tics: movements and vocal
- Blinking, throat clearing
- Motor cortex

Background - Methods

Objective: Find STN stimulation sites and streamlines (“sweet spots”) that maximize positive clinical outcomes

Model Inputs
DBS Stimulation Locations

Stimulated STN sites

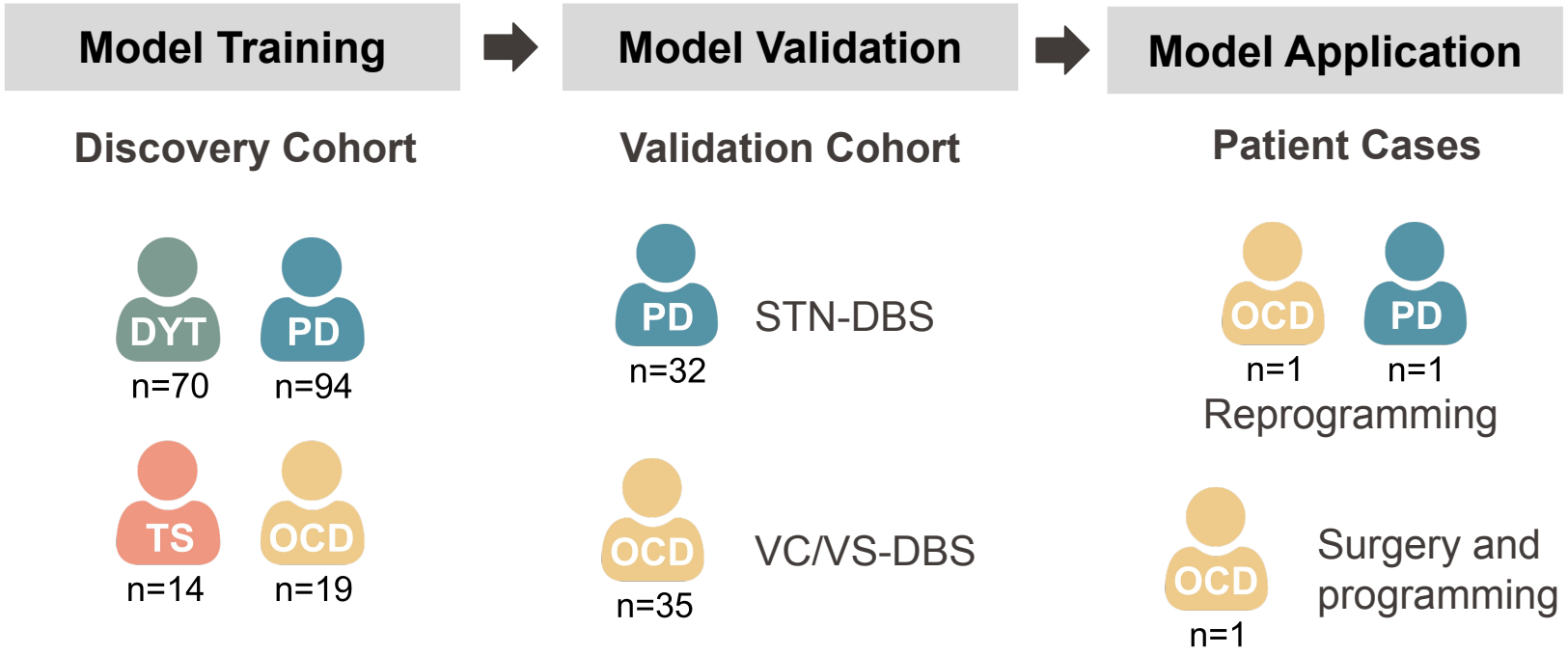


Stimulated streamlines

Model Outputs
Clinical Outcome Scores

- PD Unified Parkinson’s Disease Rating Scale-III
- Yale-Brown Obsessive-Compulsive Scale
- TS Yale Global Tics Severity Scale
- Burke-Fahn-Marsden Dystonia Rating Scale

Background - Methods



Background - Methods

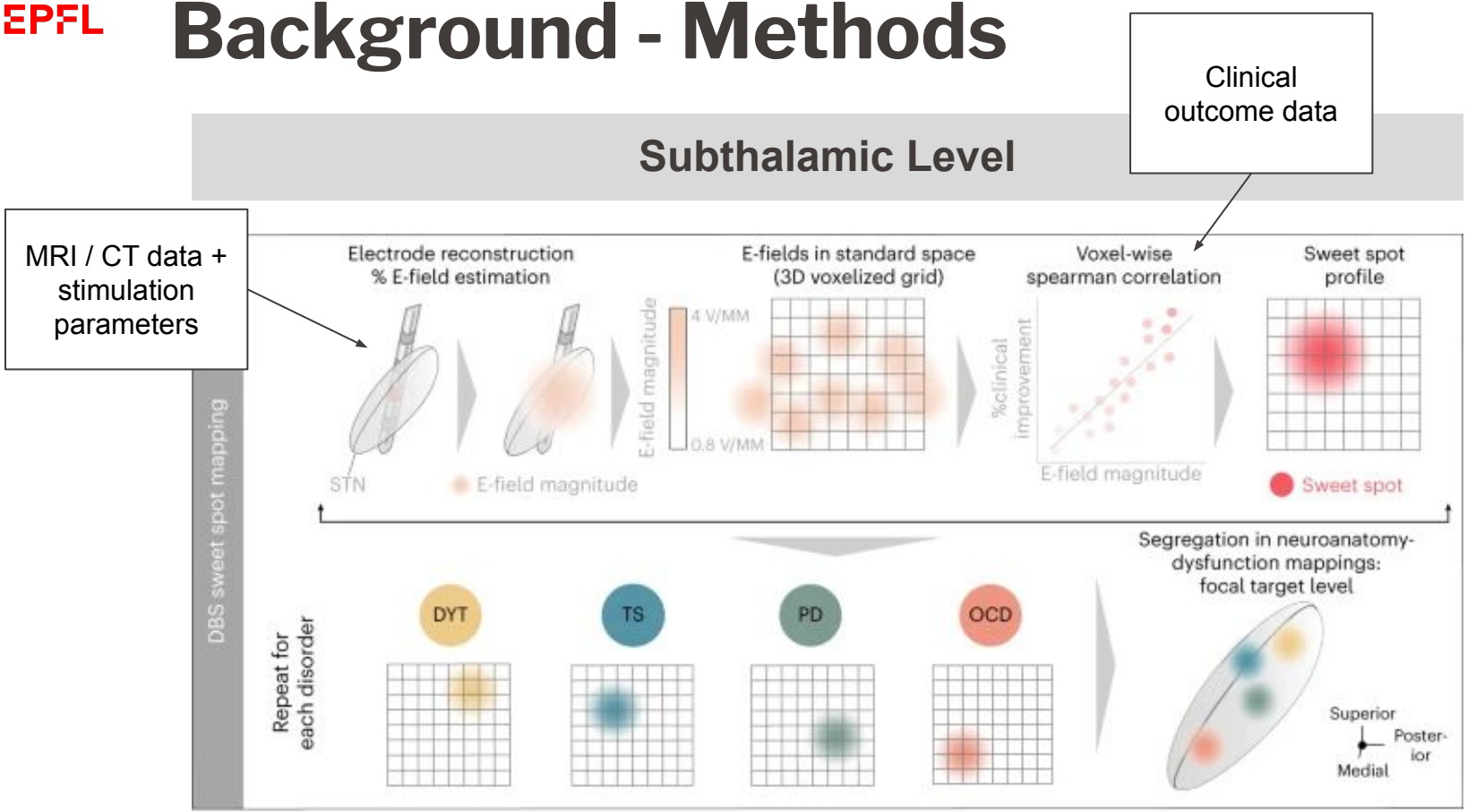


Fig 5: Process Pipeline for DBS sweet spot mapping (Hollunder et al., 2024).

Background - Methods

MRI / CT data + stimulation parameters + connectome dataset

Clinical outcome data

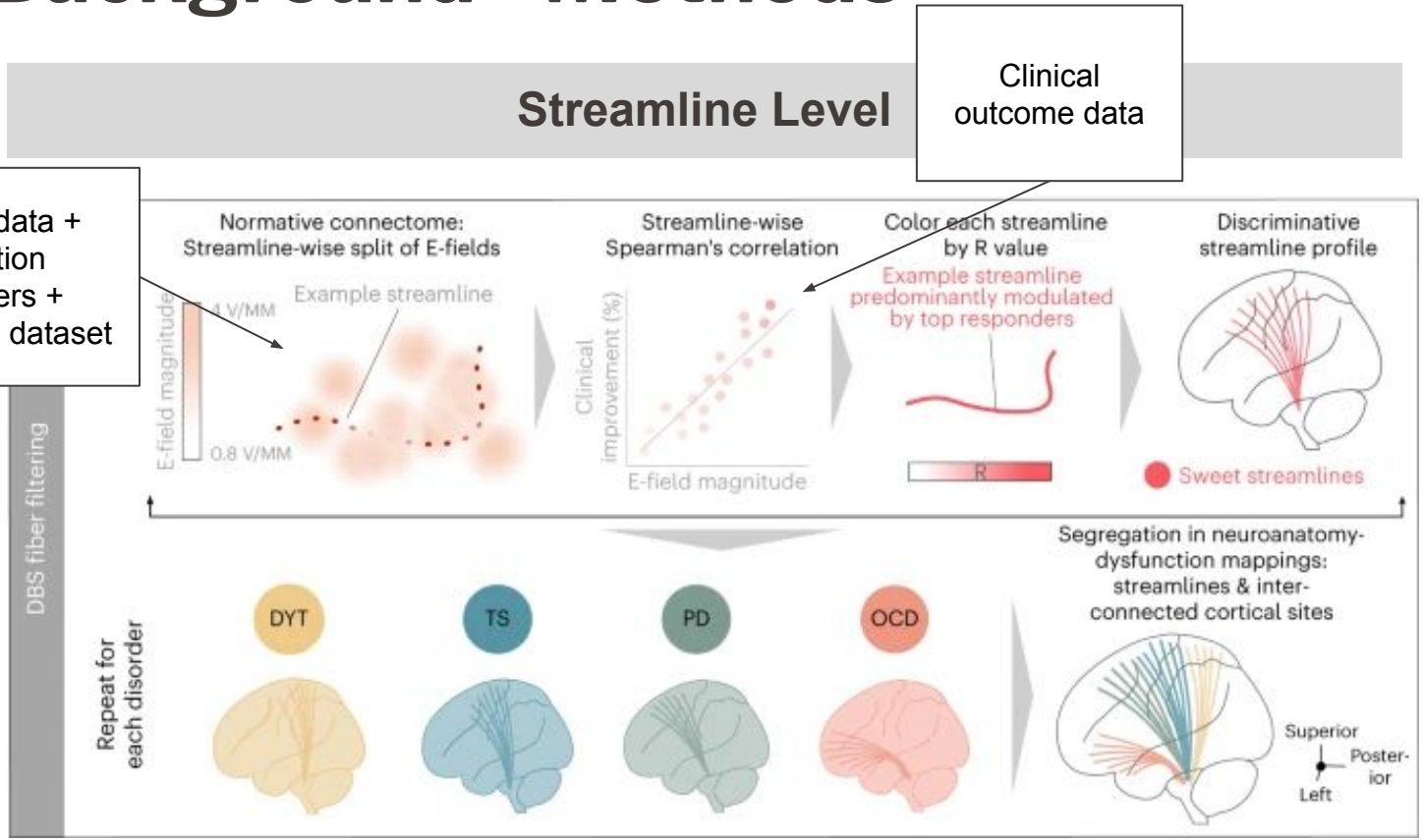


Fig 6: Process Pipeline for DBS fiber filtering (Hollunder et al., 2024).

Background - Methods

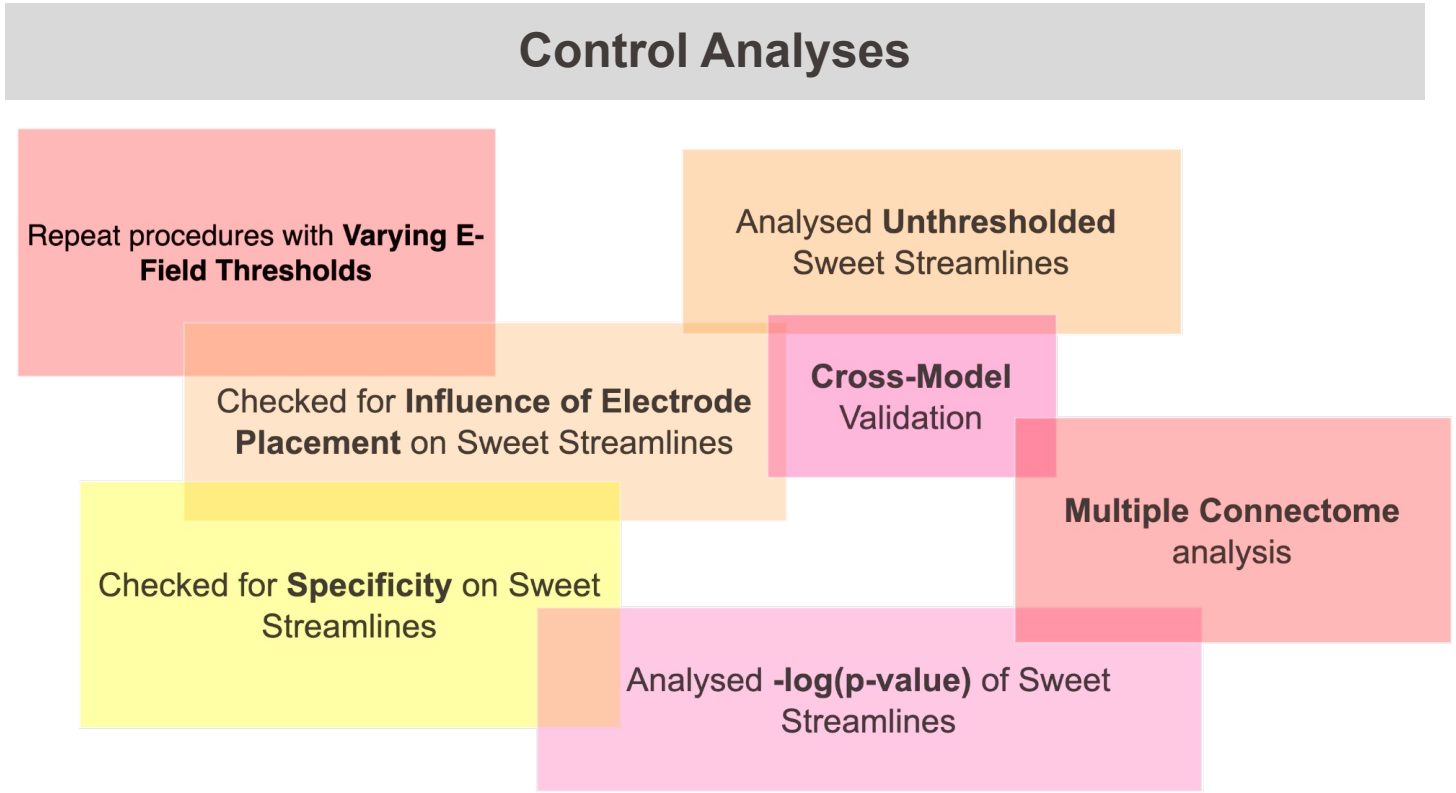


Fig 7 - Sanity checks summary

Results - Dataset

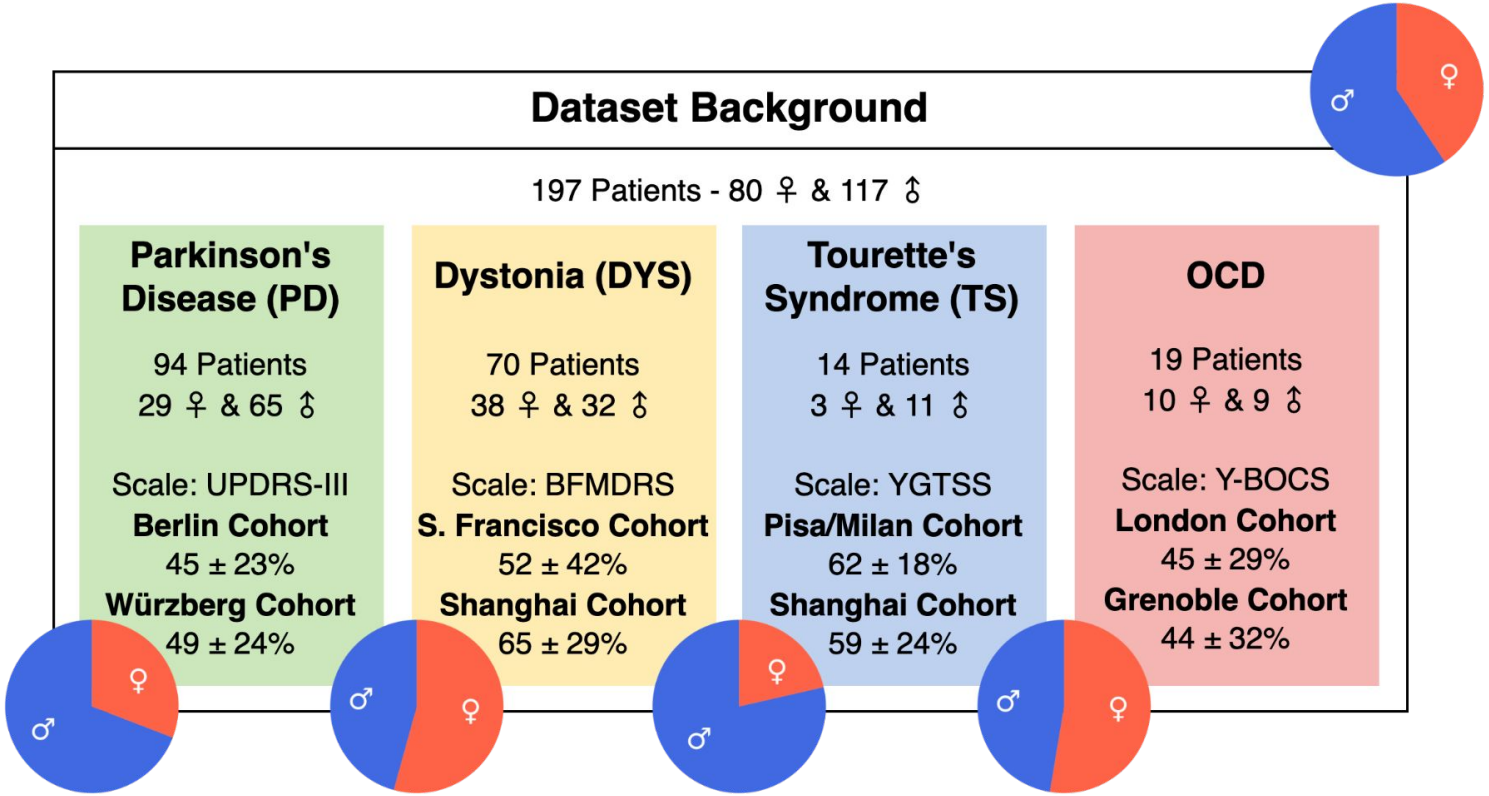


Fig 8 - Dataset analysis plot summary

Results - DBS Rods Placements

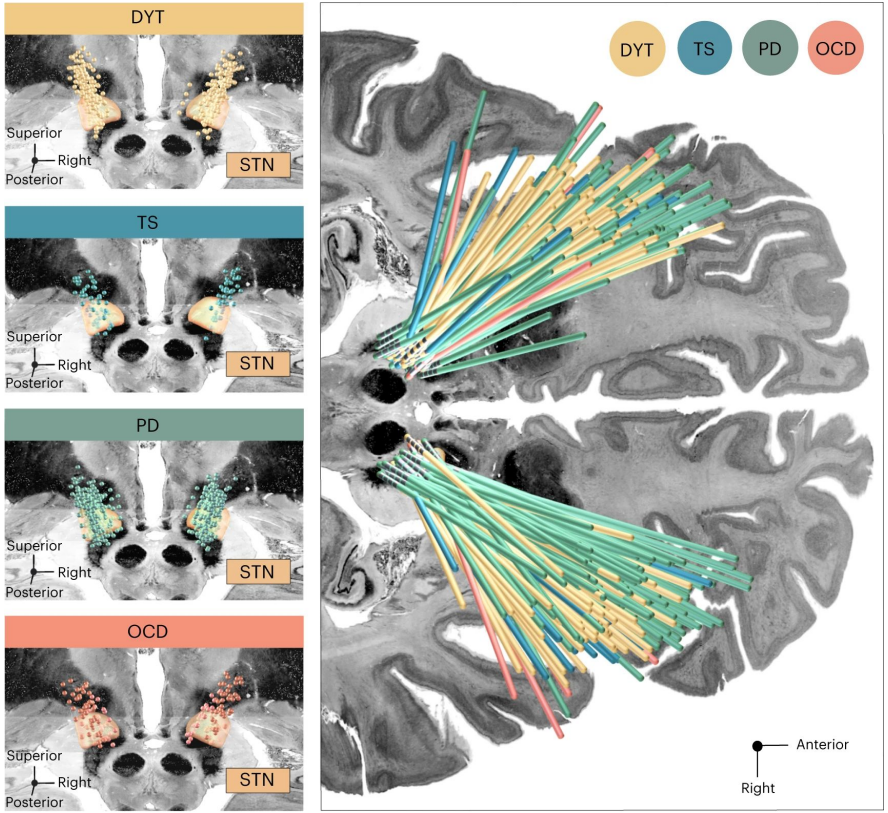
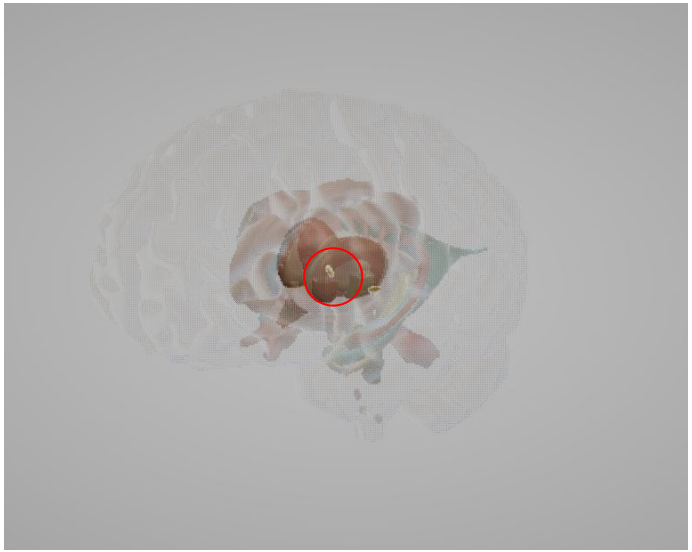
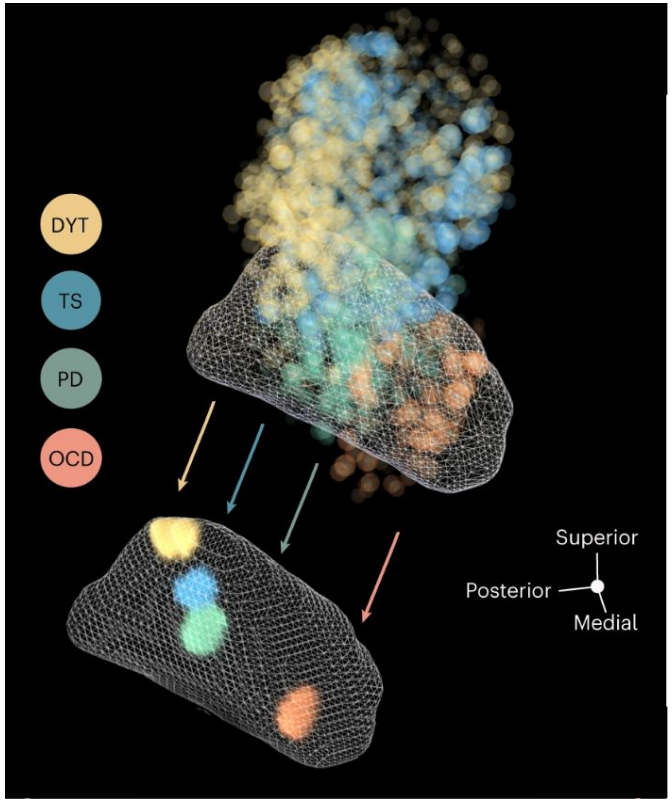


Fig XX - Left panels show DBS electrode placements as point clouds relative to the posterior STN. Right panel displays axial views of DBS leads from four discovery cohorts, color-coded by indication (Hollunder et al., 2024).

Fig XX - 3D model of the brain with Subthalamic Nucleus highlighted (Neurotorium 3D brain).



Results - Sweet Spots



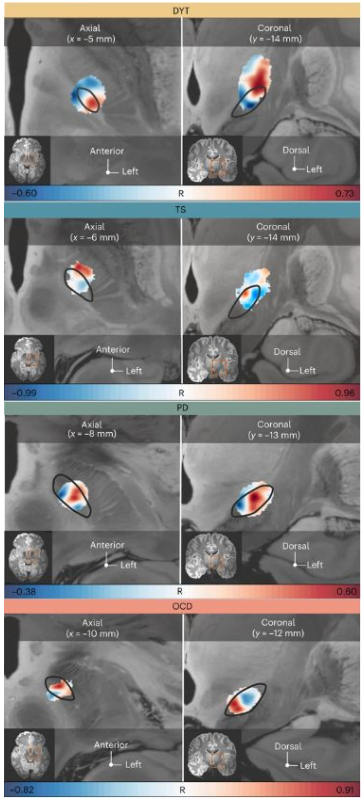
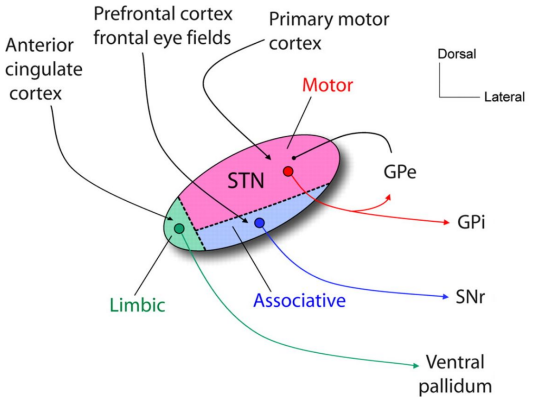


Fig 9: Topographical DBS sweet spots (left panel) shown as density clouds over the left STN, with sphere size/transparency indicating correlation strength. Right panel shows axial and coronal views of sweet and sour spots relative to the STN for each disorder (Hollunder et al., 2024).

Fig 10: The subthalamic nucleus (STN) is divided into motor, associative, and limbic territories, each with distinct cortical inputs and outputs to nuclei like GPi, GPe, SNr, and ventral pallidum (Benarroch, 2008).



Results - Sweet Streamlines

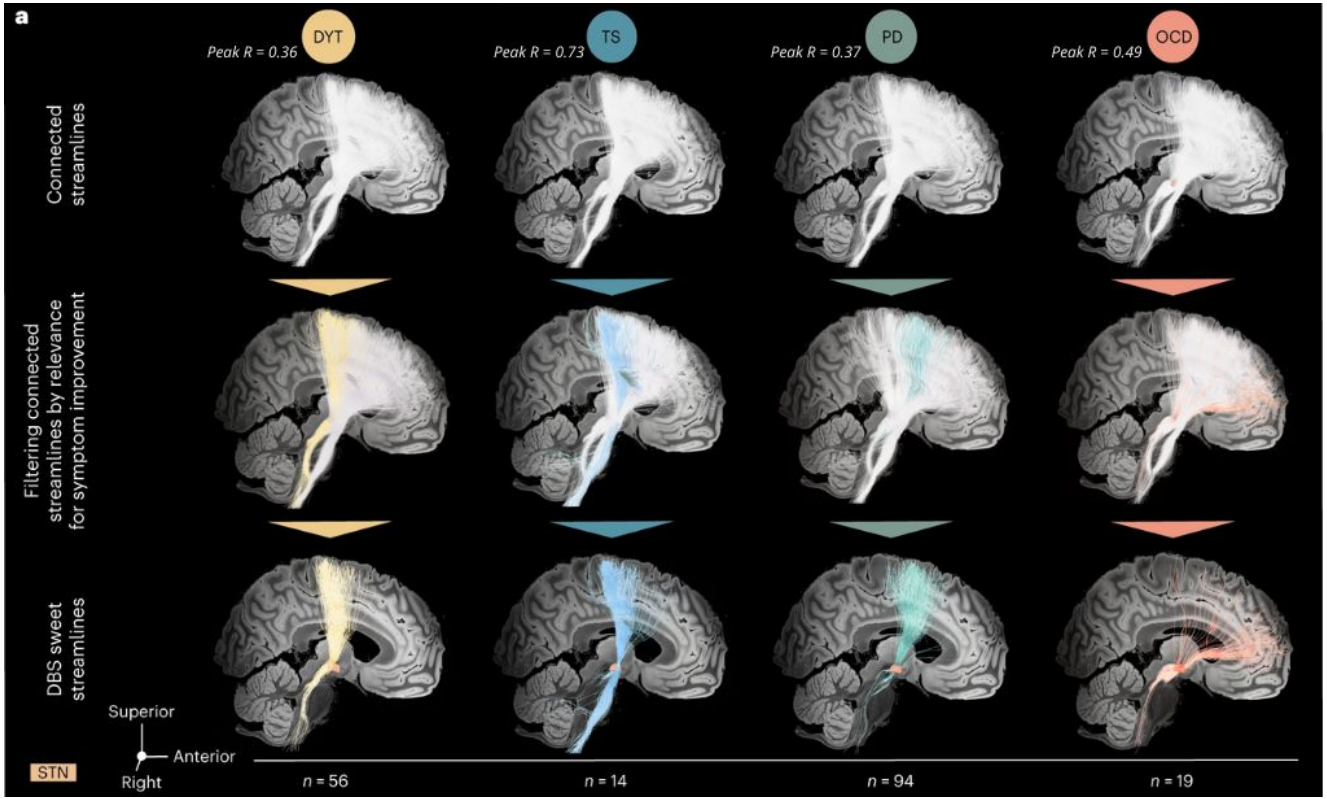
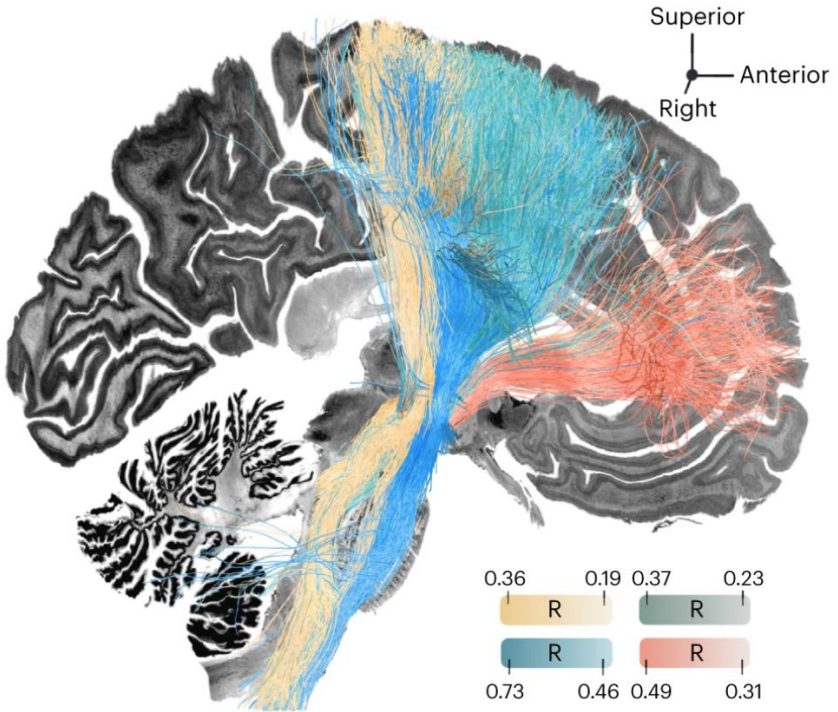


Fig 11: Streamlines of all diseases (top row) show connections from stimulation volumes across patients, filtered for clinical outcome correlations (middle row). Disease-specific streamlines (bottom row) are highlighted and thresholded (Hollunder et al., 2024).

Results - Sweet Streamlines



DYS
Somatosensory (S1)
Primary Motor (M1)

TS
Primary Motor (M1)
Supplementary Motor Areas (SMAs)

PD
Premotor Regions
Supplementary Motor Areas (SMAs)

OCD
Ventromedial Prefrontal Cortex
Dorsal Anterior Cingulate Cortex
Dorsolateral Prefrontal Cortex
Orbitofrontal Cortex

Fig 12: Therapeutic networks were identified using DBS Fiber Filtering for all diseases. Disease-specific streamlines were isolated by correlating E-field magnitudes with clinical improvements. Mappings, thresholded by R values, are shown on a sagittal brain slice, with darker colors indicating stronger correlations (Hollunder et al., 2024).

Results - Indirect Sweet Streamlines

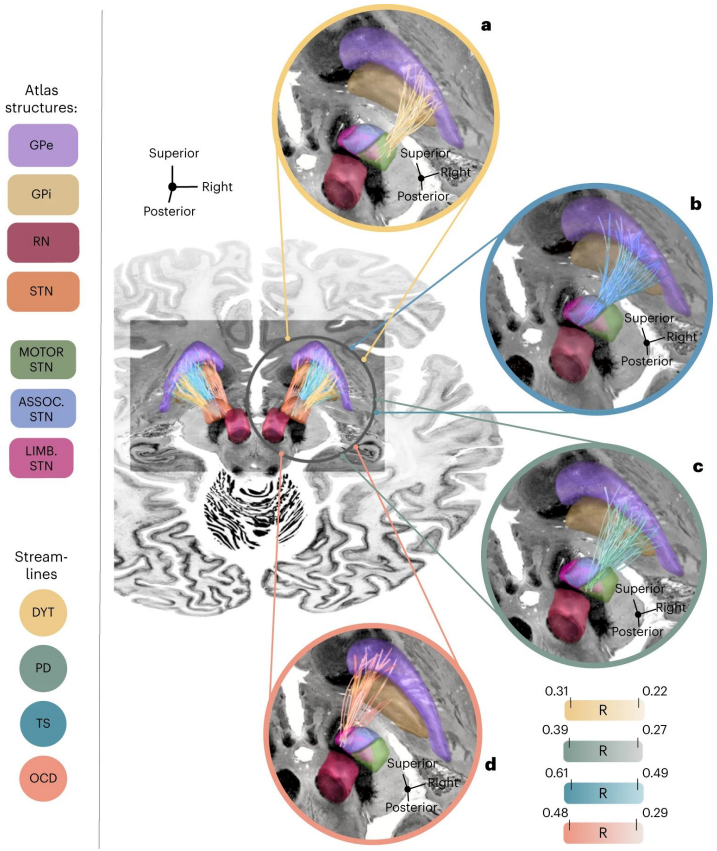


Fig 13: Disease-wise sweet streamlines retain a high degree of specificity along their indirect pathway trajectory connecting the STN with the GPi and GPe. Connectivity is modeled based on the Basal Ganglia Pathway Atlas26. Sweet streamlines associated with optimal DBS outcomes in DYT (n = 56) are interconnected with sensorimotor (Hollunder et al., 2024).

Results - Validation of Sweet Spots

PD
DYS
TS
OCD

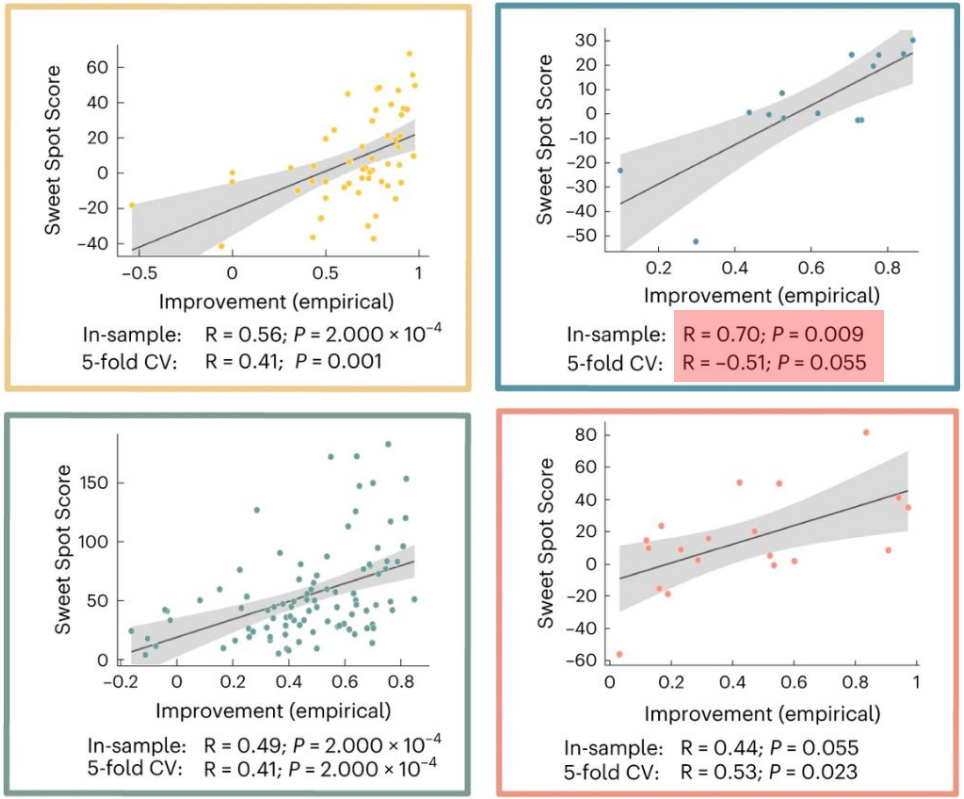
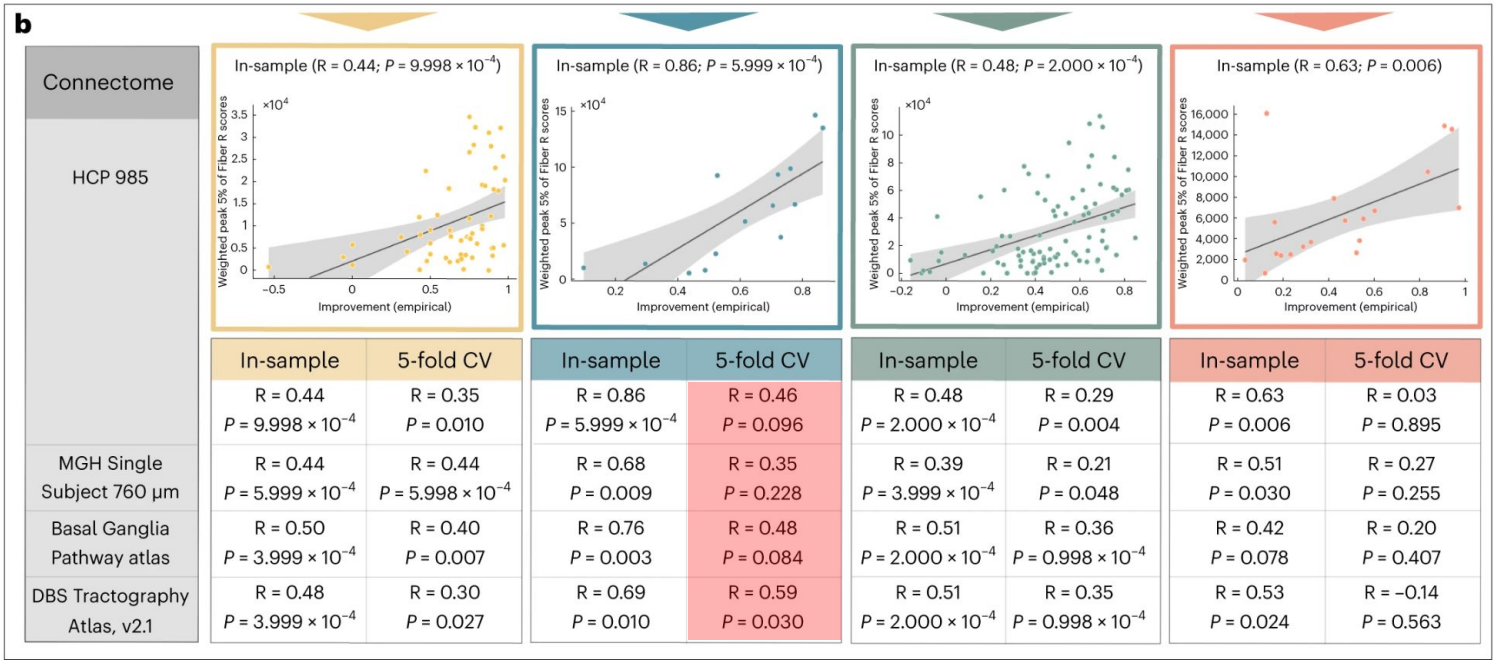


Fig 14: Spearman's correlation plots show clinical outcome variance explained by spatial similarity of E-field peaks with sweet spot models, averaged bilaterally per patient. Gray areas indicate 95% confidence intervals (Hollunder et al., 2024).

Fig XX: Spearman's Correlation equation

$$\rho = 1 - \frac{6 \sum d_i^2}{n(n^2 - 1)}$$

Results - Validation of Sweet Streamlines



Connectome	In-sample	5-fold CV	In-sample	5-fold CV	In-sample	5-fold CV	In-sample	5-fold CV
HCP 985	R = 0.44 $P = 9.998 \times 10^{-4}$	R = 0.35 $P = 0.010$	R = 0.86 $P = 5.999 \times 10^{-4}$	R = 0.46 $P = 0.096$	R = 0.48 $P = 2.000 \times 10^{-4}$	R = 0.29 $P = 0.004$	R = 0.63 $P = 0.006$	R = 0.03 $P = 0.895$
MGH Single Subject 760 µm	R = 0.44 $P = 5.999 \times 10^{-4}$	R = 0.44 $P = 5.998 \times 10^{-4}$	R = 0.68 $P = 0.009$	R = 0.35 $P = 0.228$	R = 0.39 $P = 3.999 \times 10^{-4}$	R = 0.21 $P = 0.048$	R = 0.51 $P = 0.030$	R = 0.27 $P = 0.255$
Basal Ganglia Pathway atlas	R = 0.50 $P = 3.999 \times 10^{-4}$	R = 0.40 $P = 0.007$	R = 0.76 $P = 0.003$	R = 0.48 $P = 0.084$	R = 0.51 $P = 2.000 \times 10^{-4}$	R = 0.36 $P = 0.998 \times 10^{-4}$	R = 0.42 $P = 0.078$	R = 0.20 $P = 0.407$
DBS Tractography Atlas, v2.1	R = 0.48 $P = 3.999 \times 10^{-4}$	R = 0.30 $P = 0.027$	R = 0.69 $P = 0.010$	R = 0.59 $P = 0.030$	R = 0.51 $P = 2.000 \times 10^{-4}$	R = 0.35 $P = 0.998 \times 10^{-4}$	R = 0.53 $P = 0.024$	R = −0.14 $P = 0.563$

PD
DYS
TS
OCD

Fig 15: In-sample correlations and fivefold CVs are shown for models using four normative connectomes. Top row plots show how E-field overlap with sweet streamlines explains clinical outcome variance (Spearman's correlation, two-sided). Gray areas indicate 95% confidence intervals (Hollunder et al., 2024).

Results - Validation Cohorts

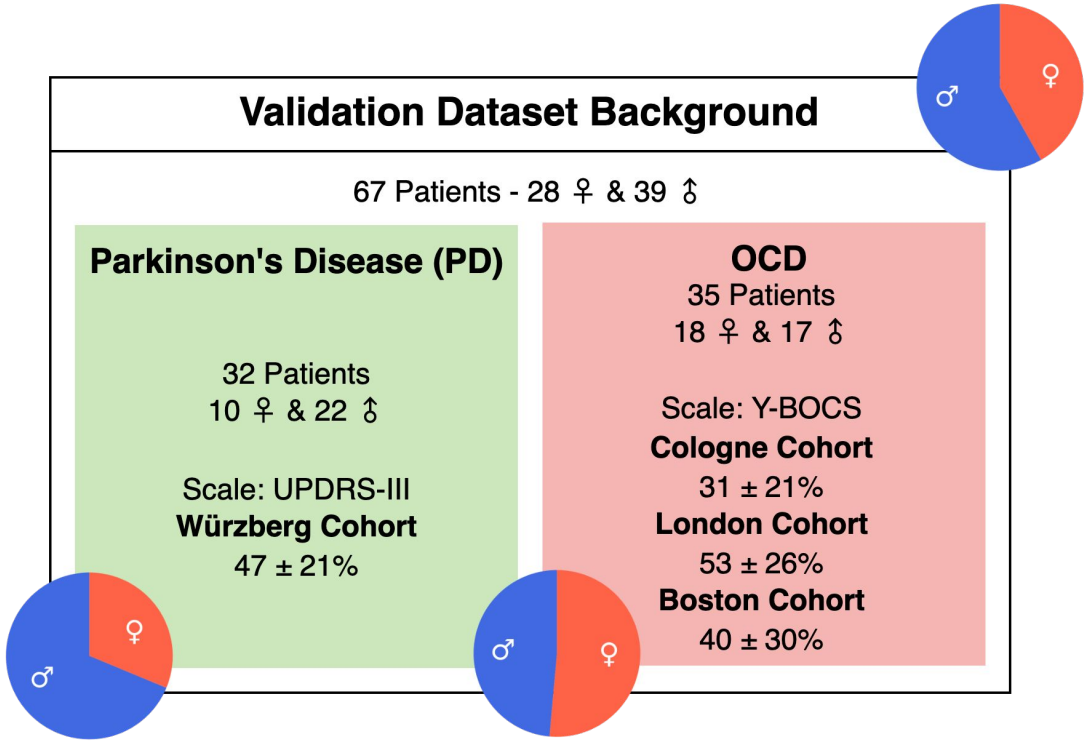


Fig 16 - Dataset analysis plot summary

Results - Retrospective Cohorts

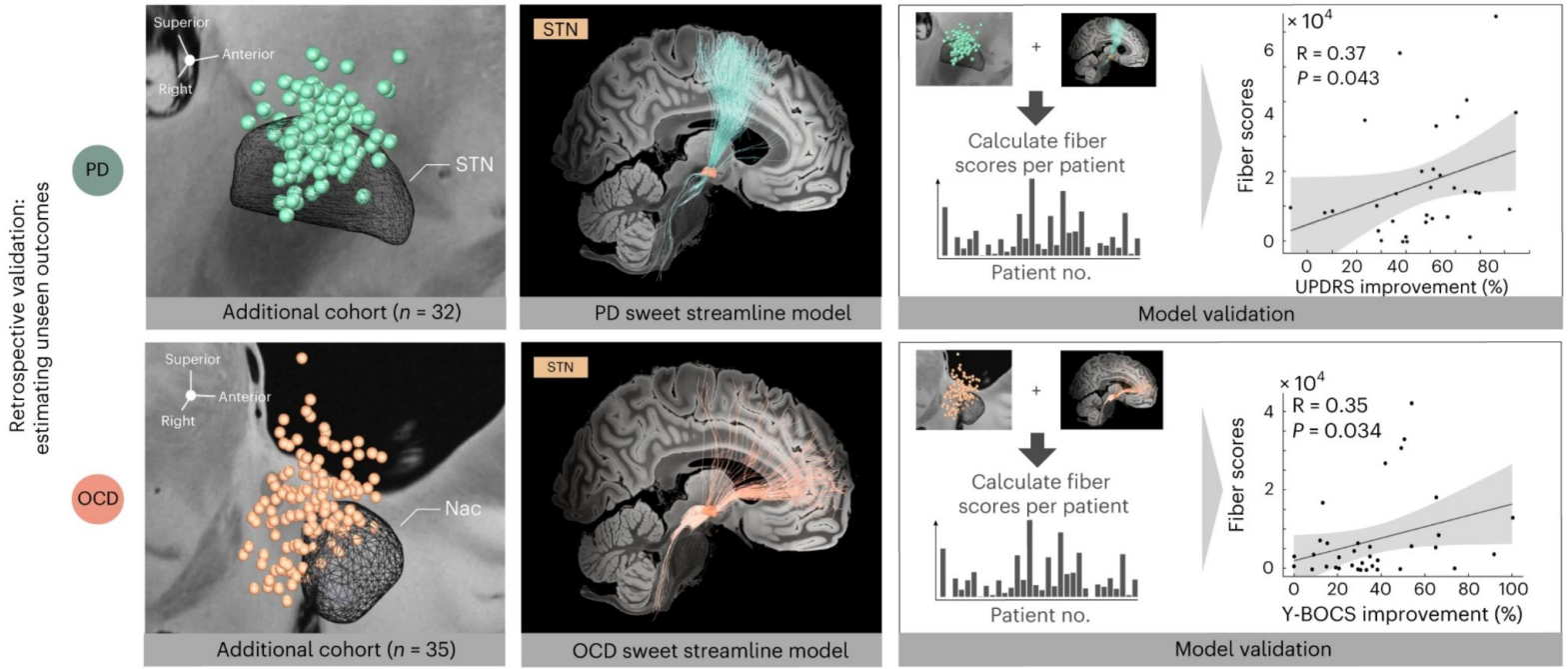


Fig 17: Empirical outcomes from independent datasets were significantly estimated by overlap of stimulation volumes with streamline models. Spearman's correlations measured model validity, with weighted peak 5% of Fiber R scores averaged bilaterally. Gray areas indicate 95% confidence intervals (Hollunder et al., 2024).

Results - Reprogrammed Patients

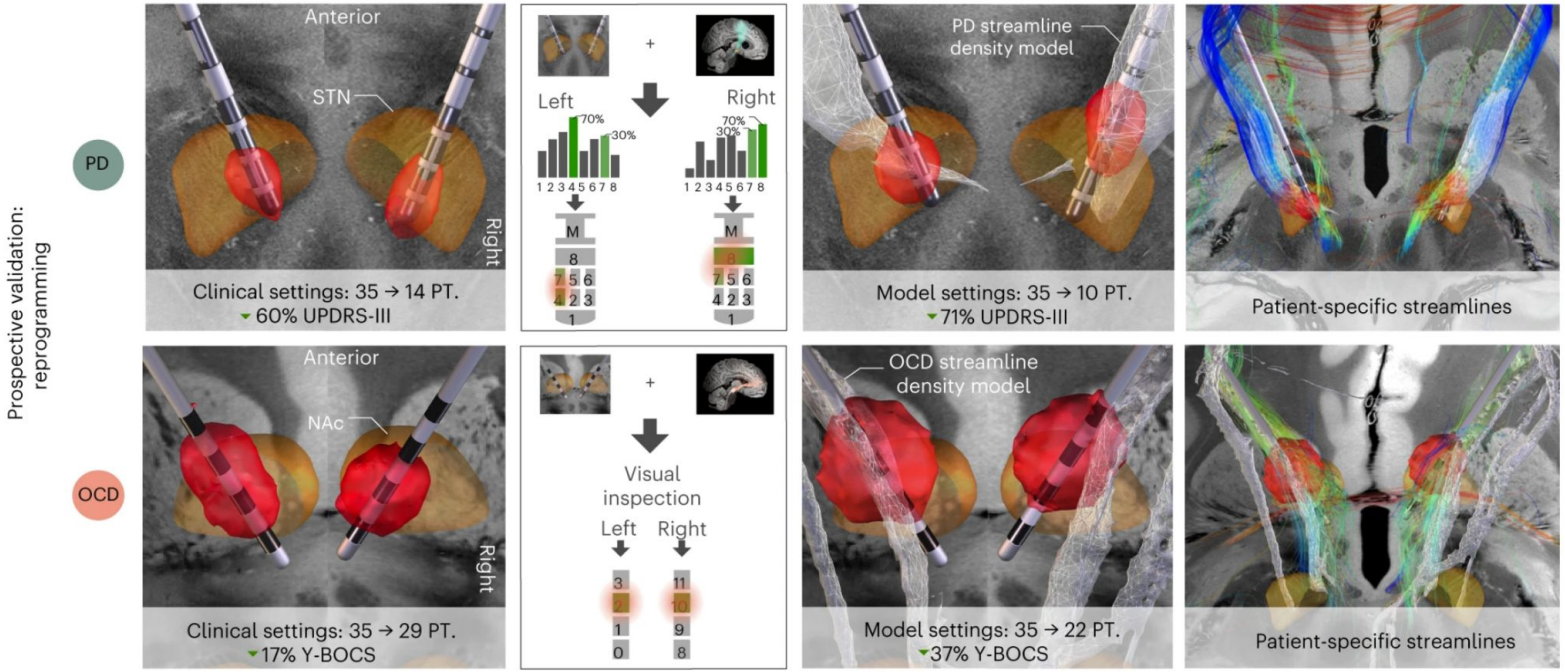


Fig 18: Prospective reprogramming improved outcomes for two patients. For PD improved symptoms by 71% (vs. the original 60%). For OCD, selecting contacts via streamline models reduced symptoms by 37% (vs. the original 17%) (Hollunder et al., 2024).

Results - Prospective Validation

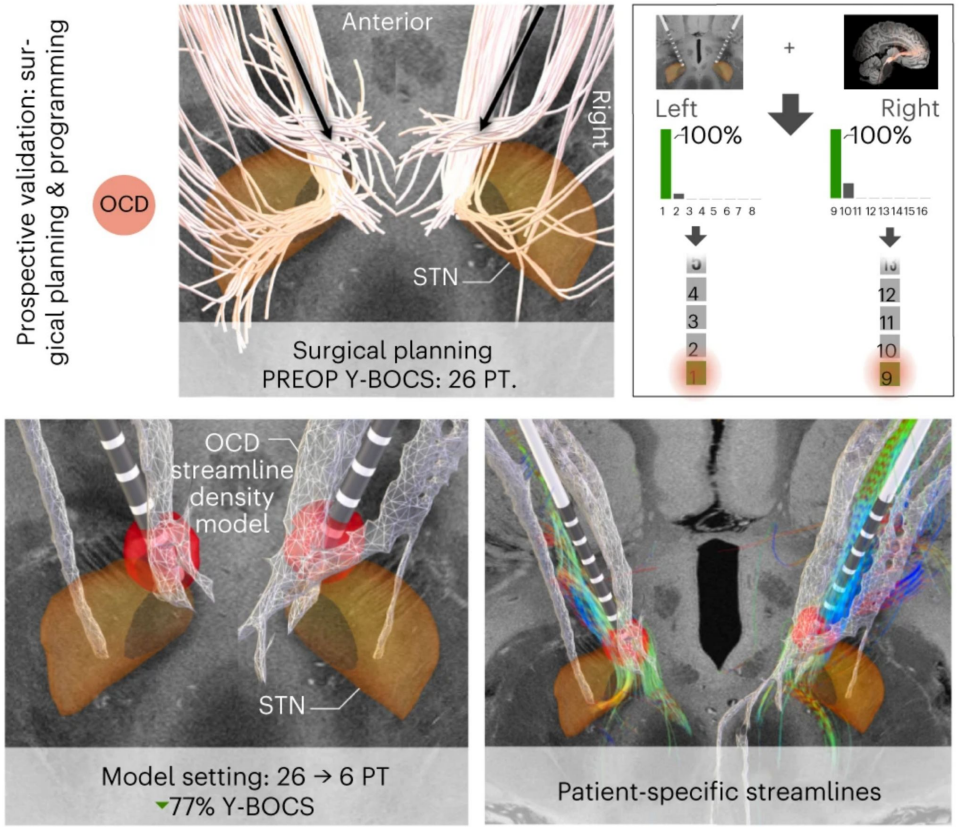


Fig 19: A prospective OCD case with streamline-guided DBS showed a 77% Y-BOCS reduction one month post-surgery. Electrodes were activated at the most ventral contacts, visualized using 3D models of the STN or nucleus accumbens (Hollunder et al., 2024).

Results - Sanity Checks

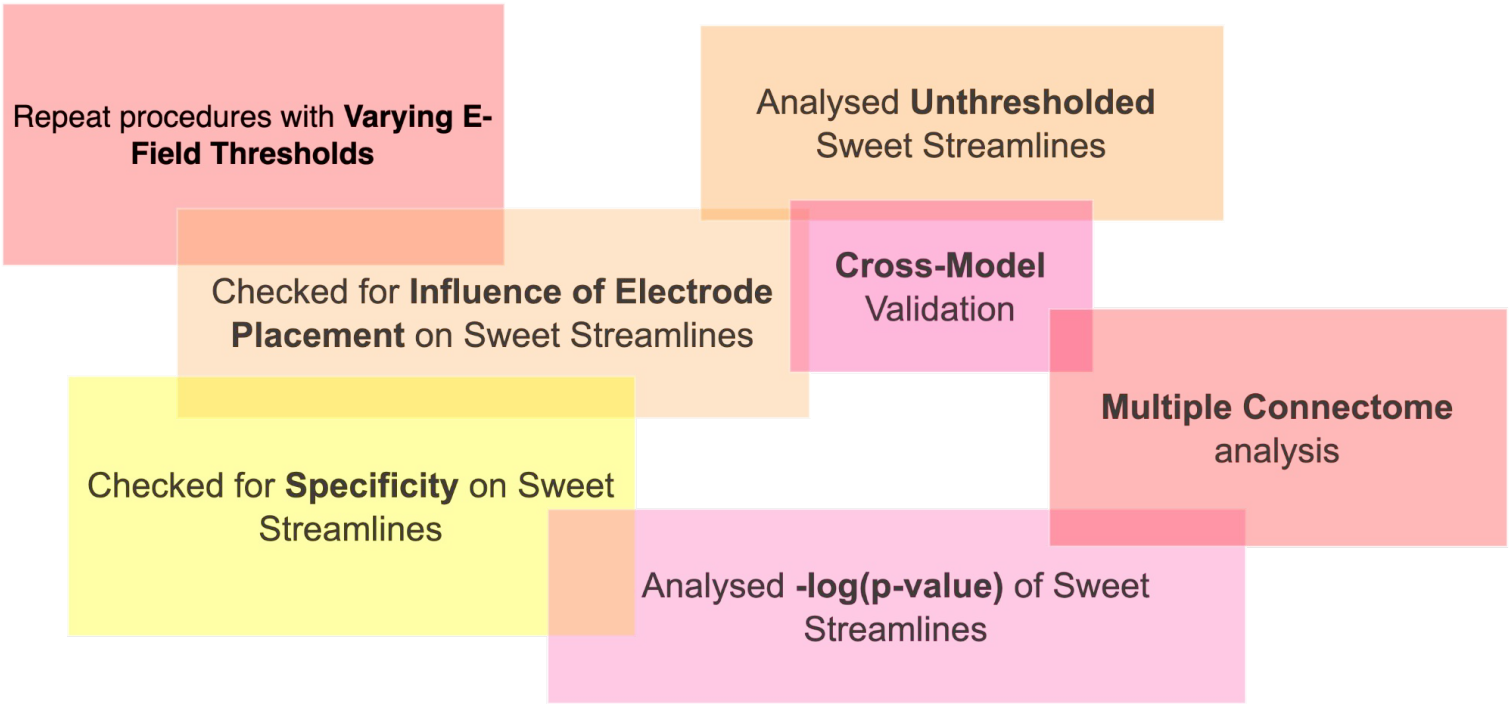


Fig 7 - Sanity checks summary

Discussion

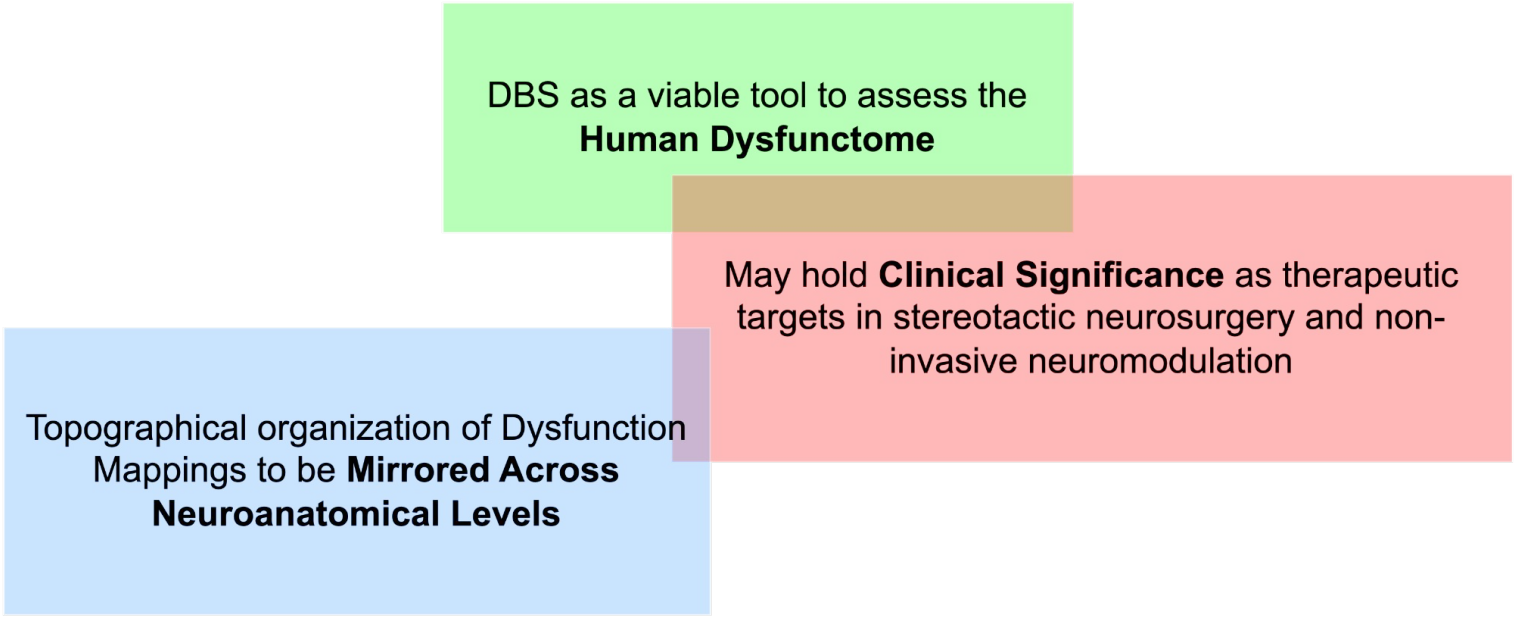


Fig 20 - Discussion points summary

Novelty

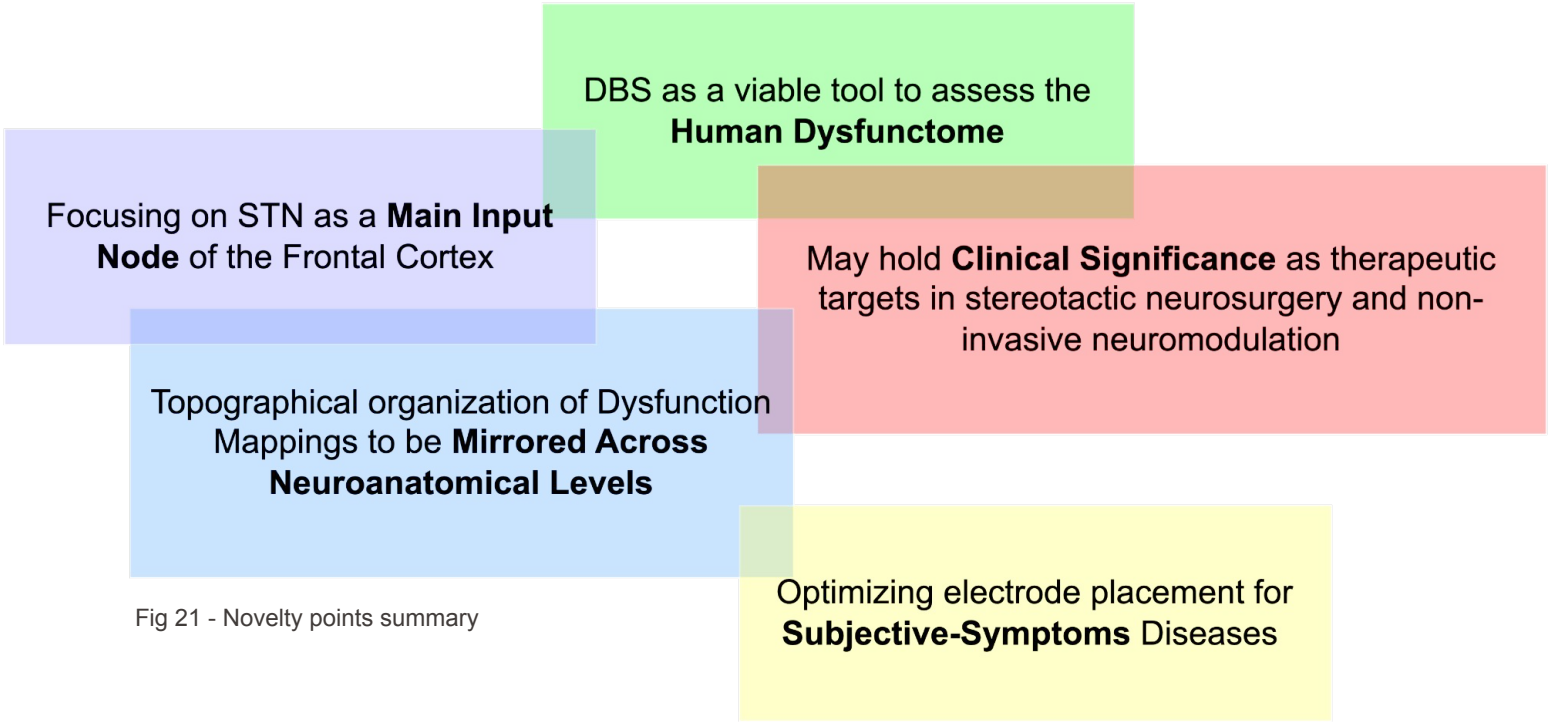


Fig 21 - Novelty points summary

Limitations

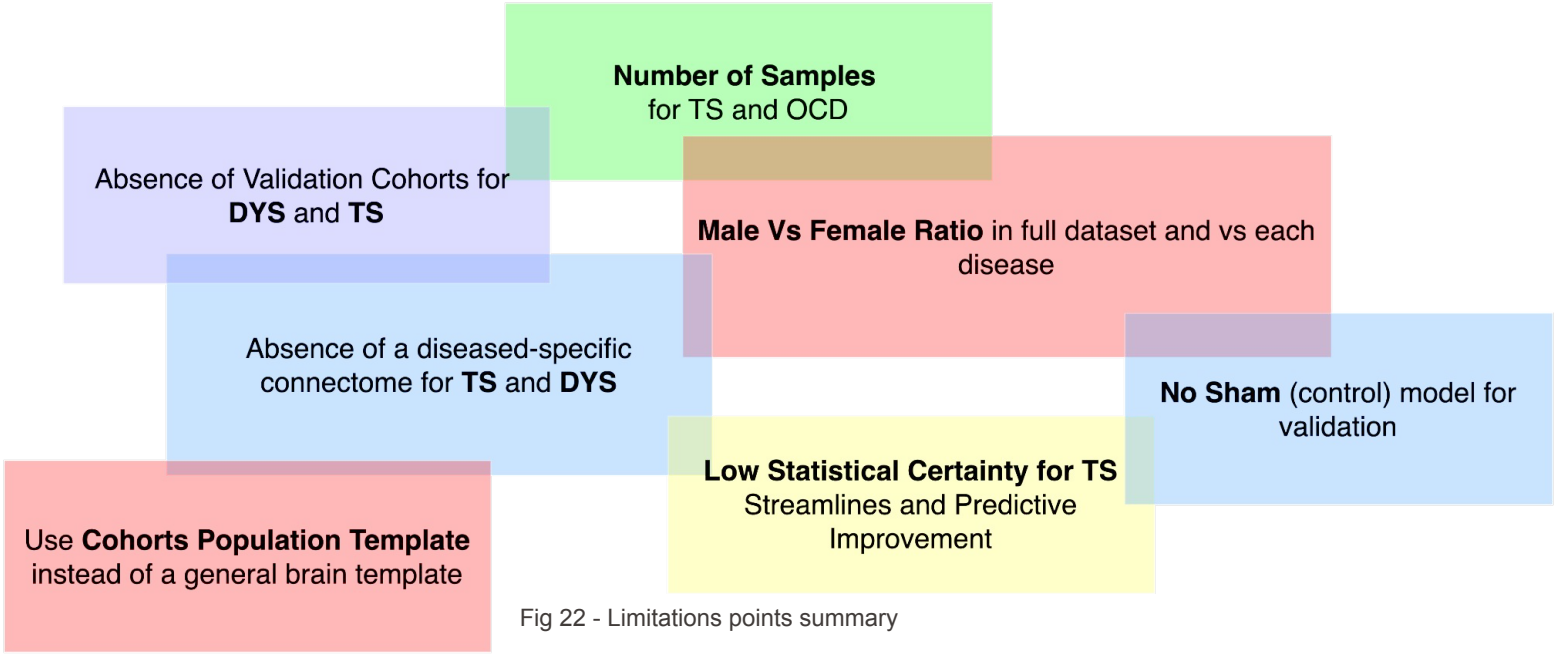


Fig 22 - Limitations points summary

Challenges

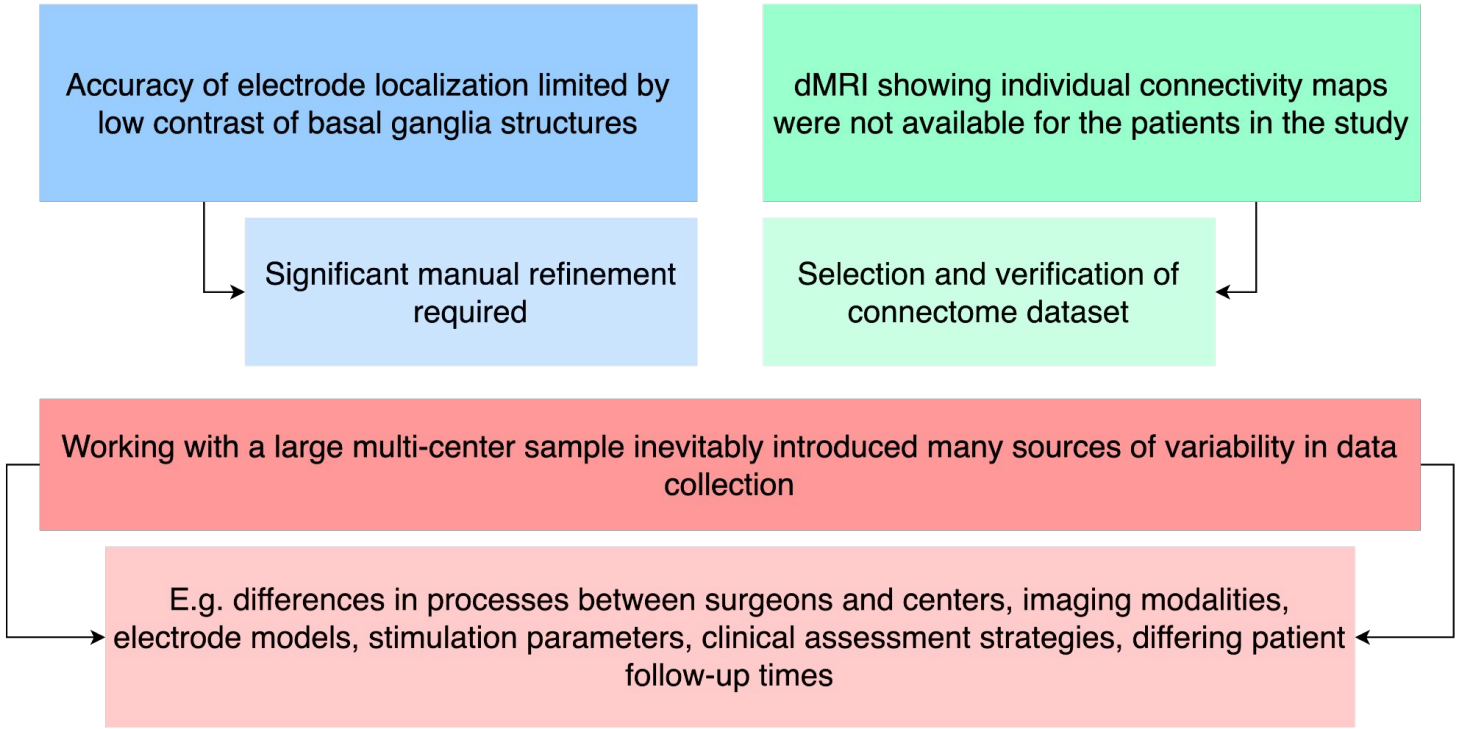


Fig 23 - Challenges points summary

Open Questions

How can stereotactic neurosurgery methods and **Non-Invasive Neuromodulation** methods take advantage of these findings?

How can we get the **Second Degree Interactions**?

How can the model be optimized to more **Accurately** represent the activated tissue in the **E-Field Simulation**?

How can we use this method to increase granularity, finding the functional connections associated with **Individual Symptoms**?

How could a similar model be used to **Optimize Stimulation Parameters** (other than location) for each disease?

How to move away from using a normative connectome model and validate streamlines in **Patient-Specific Data?**

Fig 24 - Open Questions summary

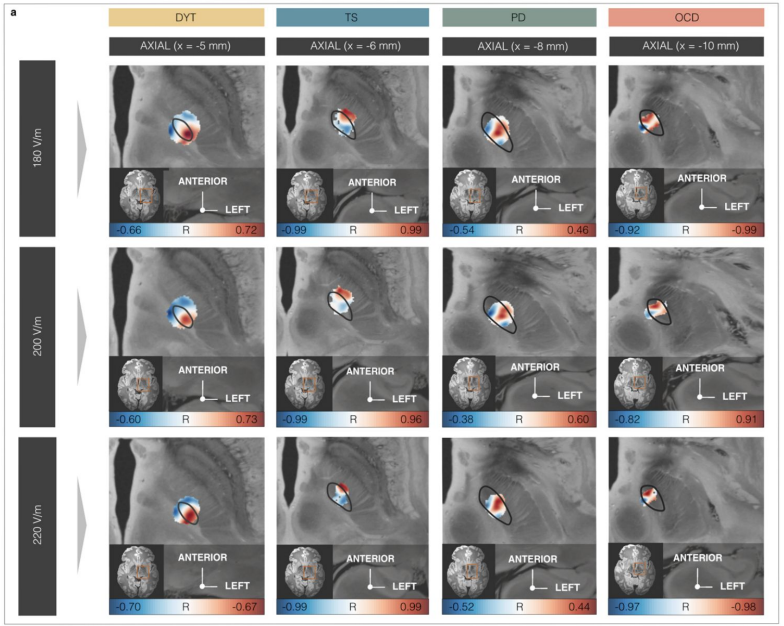
Bibliography and Sources

Main Paper: Hollunder, B., Ostrem, J. L., Sahin, I. A., Rajamani, N., Oxenford, S., Butenko, K., Neudorfer, C., Reinhardt, P., Zvarova, P., Polosan, M., Akram, H., Vissani, M., Zhang, C., Sun, B., Navratil, P., Reich, M. M., Volkmann, J., Yeh, F.-C., Baldermann, J. C., & Dembek, T. A. (2024). Mapping dysfunctional circuits in the frontal cortex using deep brain stimulation. Nature Neuroscience, 1–14. https://doi.org/10.1038/s41593-024-01570-1

Benarroch, E. E. (2008). Subthalamic nucleus and its connections: Anatomic substrate for the network effects of deep brain stimulation. Neurology, 70(21), 1991–1995. https://doi.org/10.1212/01.wnl.0000313022.39329.65

DBS Figure: G. Marín, C. Castillo-Rangel, L. Salomón-Lara, L.A. Vega-Quesada, C.J. Zarate Calderon, C.D. Borda-Low, J.E. Soto-Abraham, G.A. Coria-Avila, J. Manzo, L.I. García-Hernández(2022) Deep brain stimulation in neurological diseases and other pathologies, DOI: 10.1016/j.neurop.2022.03.001

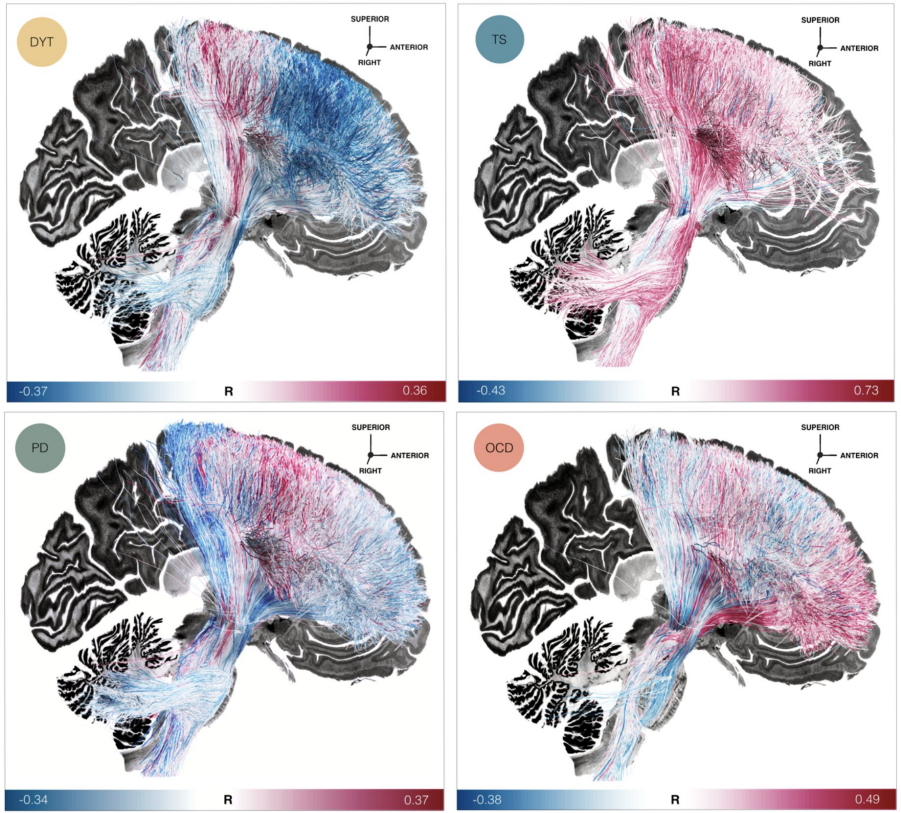
EXTRA - E-Fields Thresholding



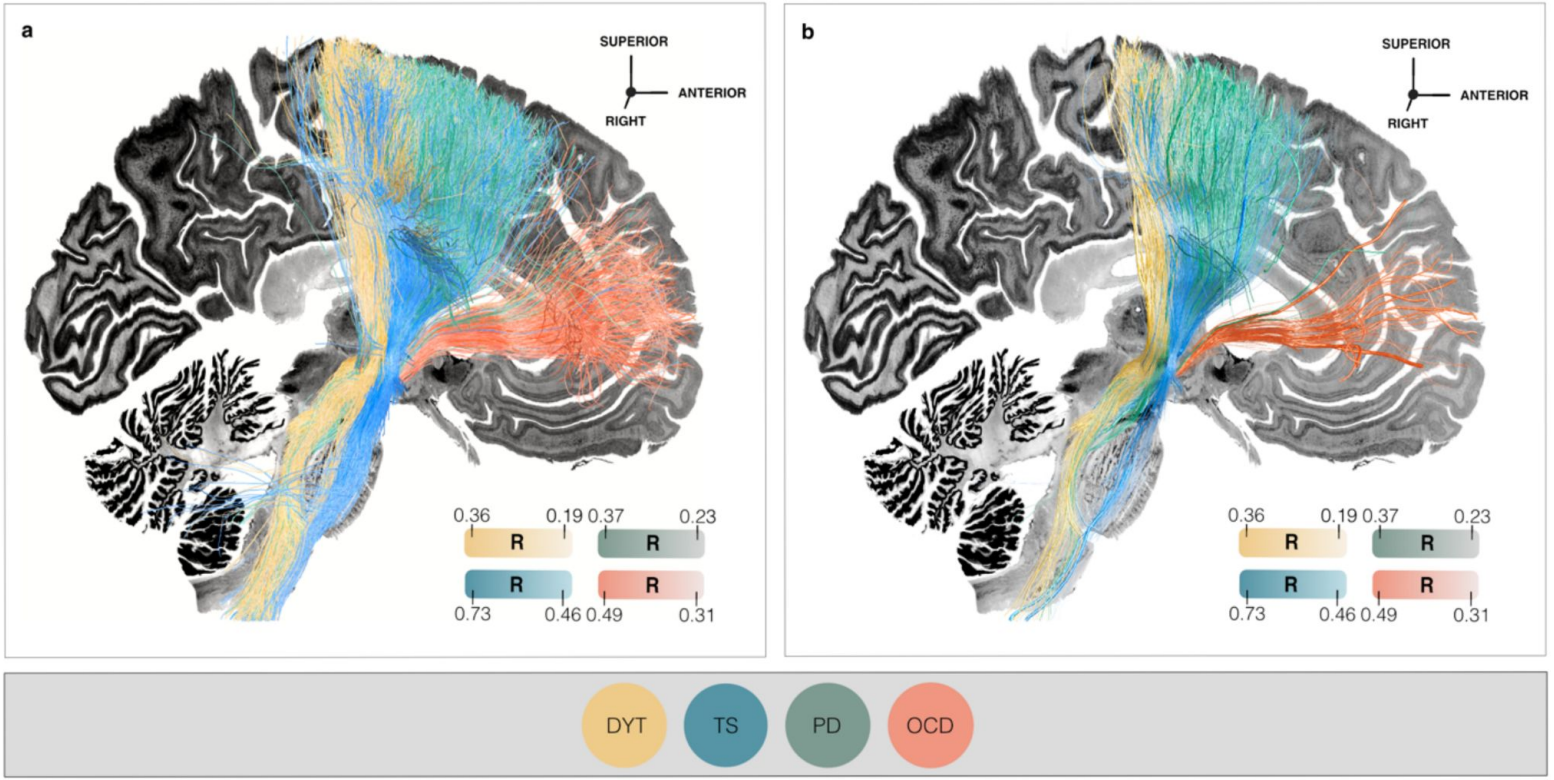
b

E-FIELD THRESHOLD	DYT IN-SAMPLE	DYT 5-FOLD CV	TS IN-SAMPLE	TS 5-FOLD CV	PD IN-SAMPLE	PD 5-FOLD CV	OCD IN-SAMPLE	OCD 5-FOLD CV
180 V/m	R = 0.57; p = 2.000e-4	R = 0.42; p = 0.002	R = 0.48; p = 2.000e-4	R = 0.38; p = 5.999e-4	R = 0.81 p = 7.998e-4	R = -0.49; p = 0.067	R = 0.52; p = 0.027	R = 0.36 p = 0.129
200 V/m	R = 0.56; p = 2.000e-4	R = 0.41; p = 0.001	R = 0.49; p = 2.000e-4	R = 0.41; p = 2.000e-4	R = 0.70; p = 0.009	R = -0.51; p = 0.055	R = 0.44; p = 0.055	R = 0.53; p = 0.023
220 V/m	R = 0.56; p = 2.000e-4	R = 0.40; p = 0.001	R = 0.49; p = 2.000e-4	R = 0.44; p = 2.000e-4	R = 0.71; p = 0.005	R = -0.50; p = 0.057	R = 0.47; p = 0.046	R = 0.52; p = 0.025

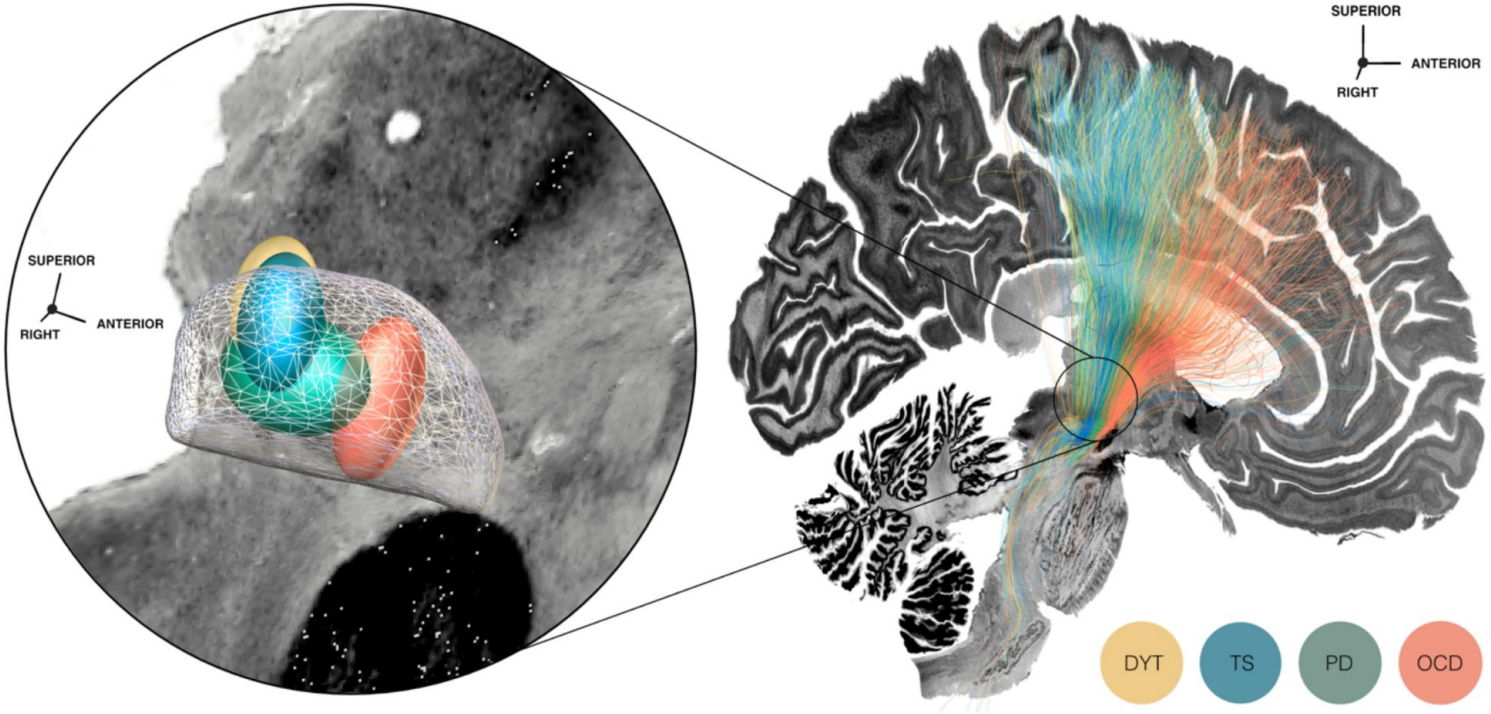
EXTRA - Unthresholded Streamlines



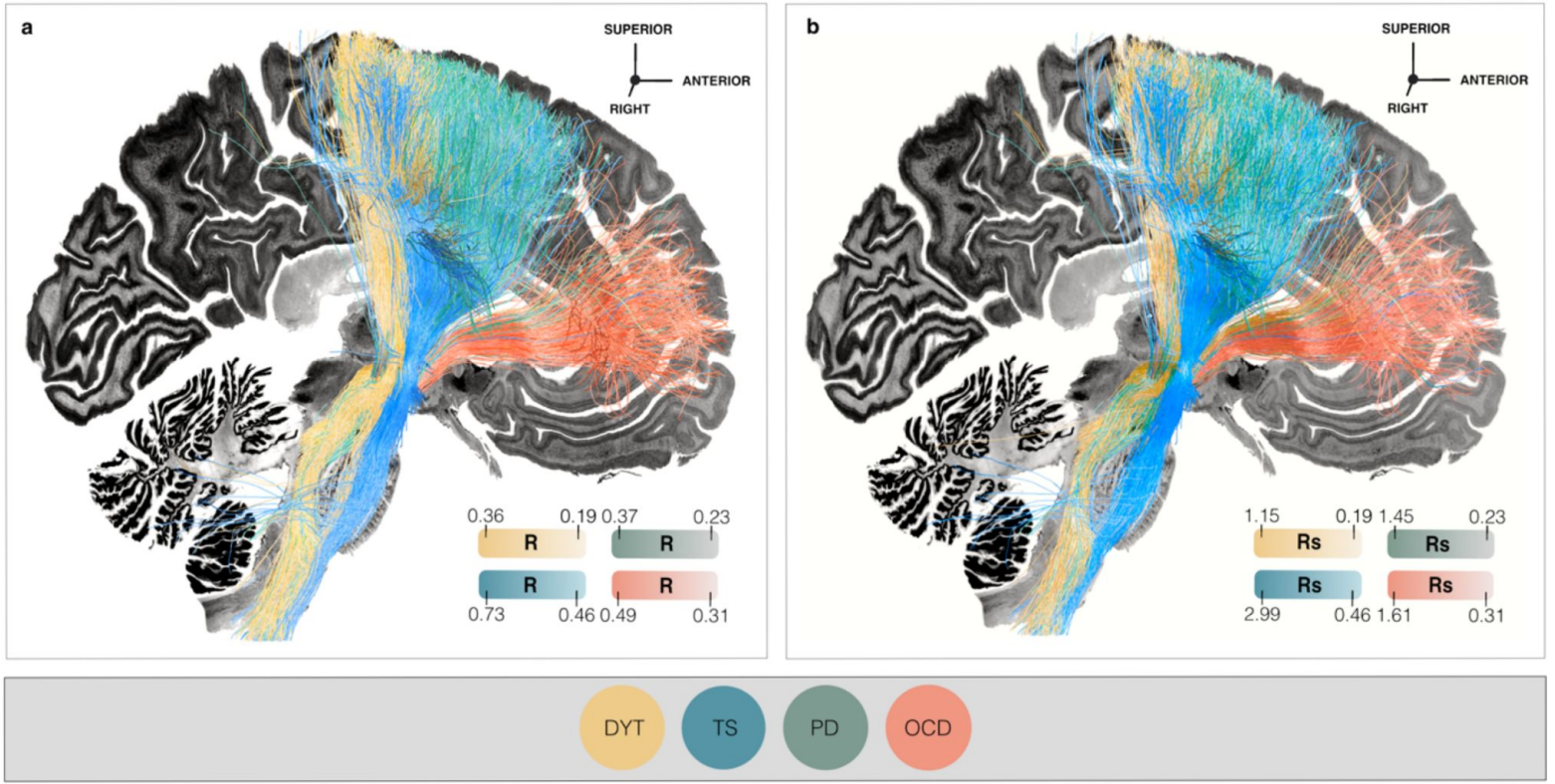
EXTRA - -log(p-value)



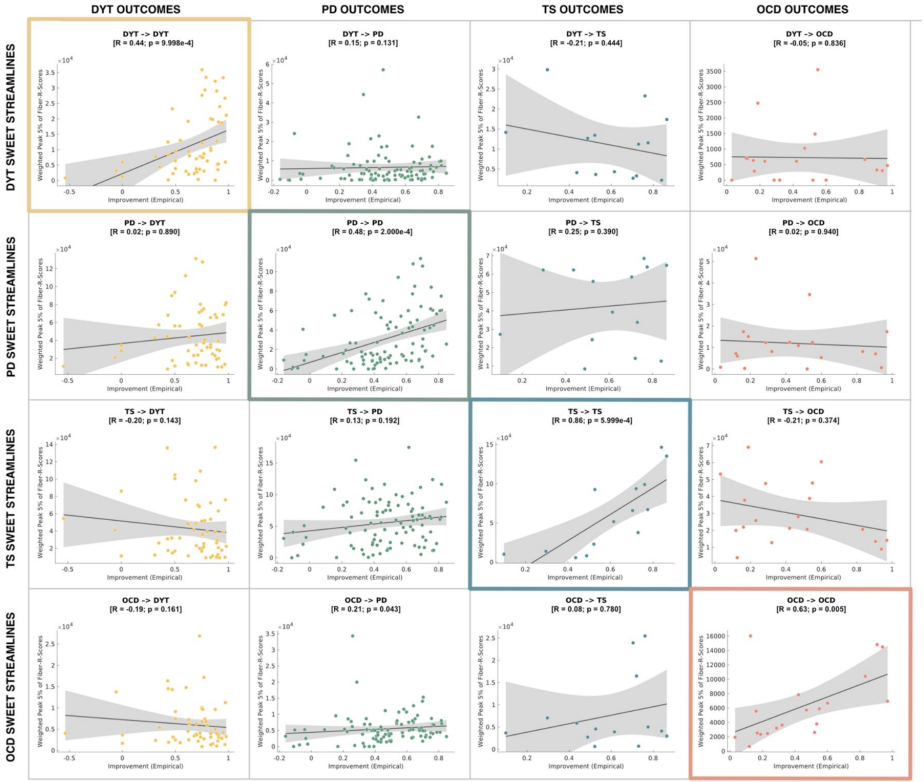
EXTRA - Electrode Placement Influence



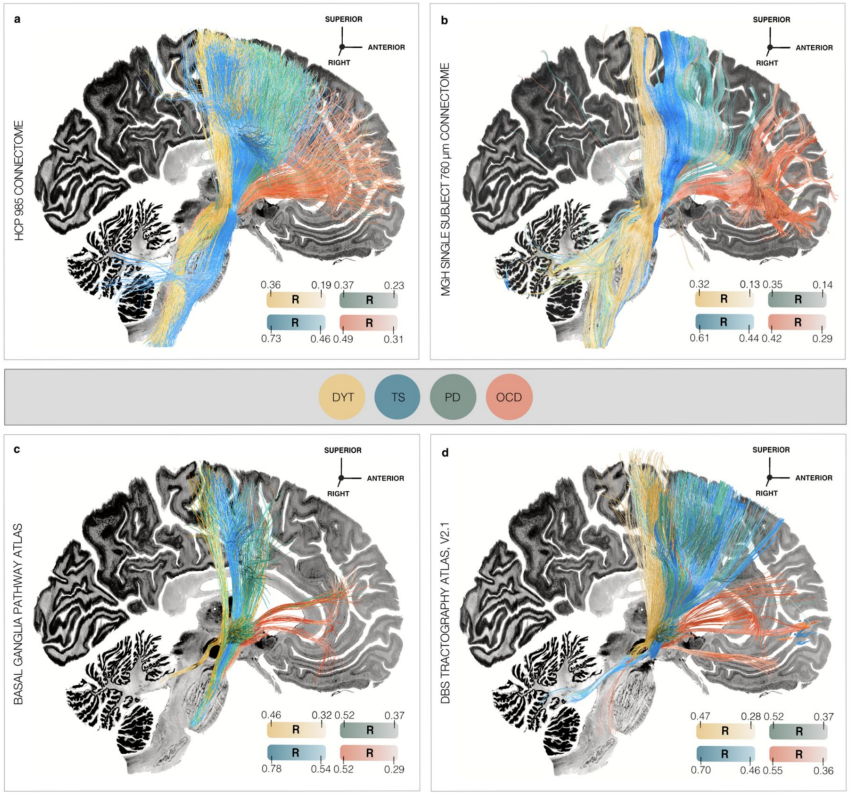
EXTRA - Streamlines Specificity



EXTRA - Cross Model Validation



EXTRA - Connectome Influence



EXTRA - Connectome Influence