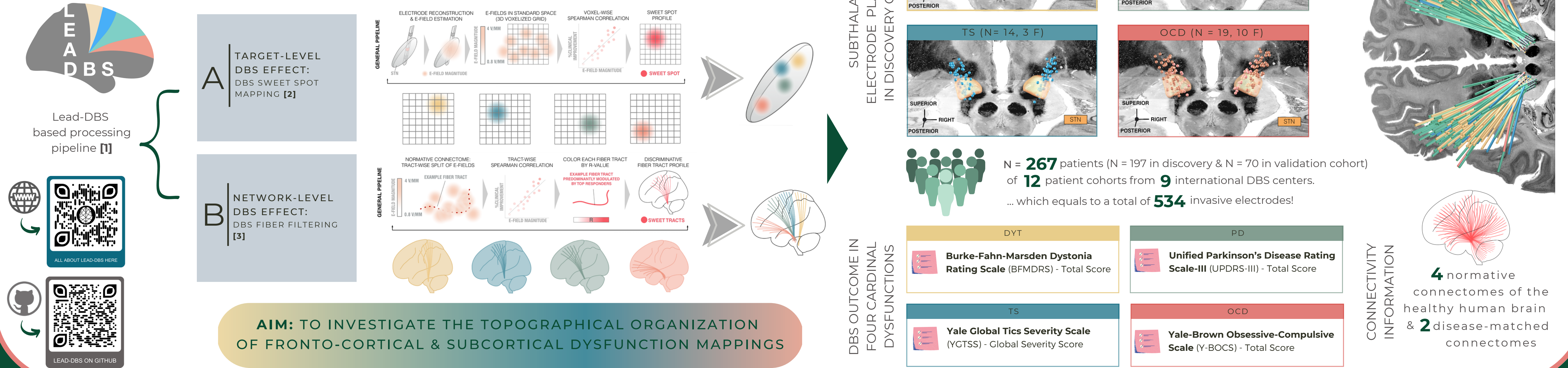# MAPPING DYSFUNCTIONAL CIRCUITS IN THE FRONTAL CORTEX USING DEEP BRAIN STIMULATION

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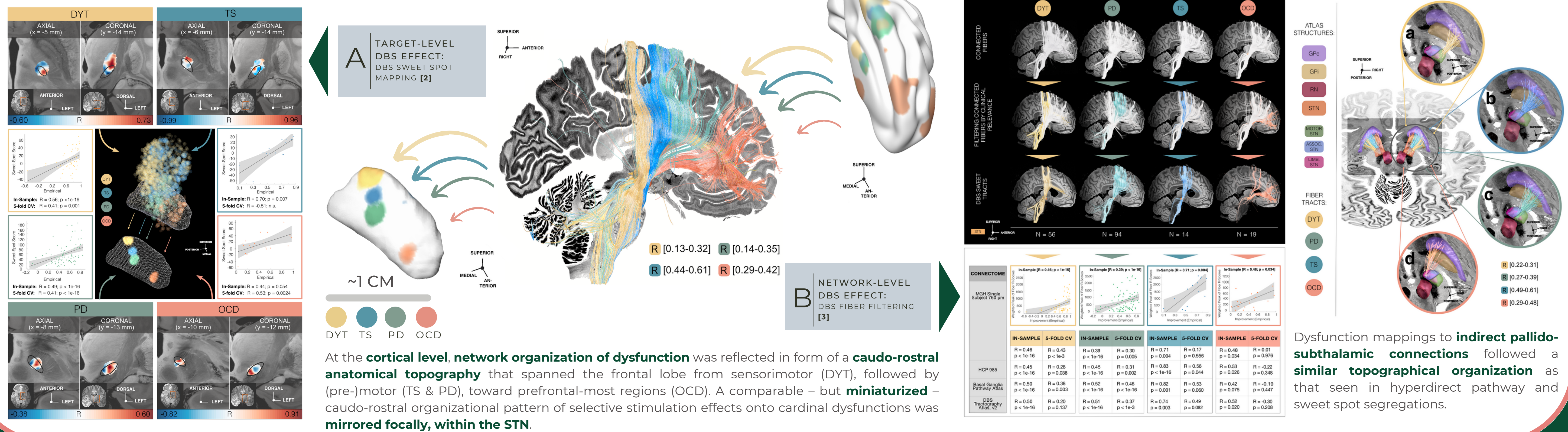
* equal contributions as shared last authors

How is it that **deep brain stimulation** (DBS) to one and the same, merely centimeter-long subcortical brain structure – the **subthalamic nucleus** (STN) – can be effective in treating **cardinal dysfunctions** in disorders as **heterogeneous** as dystonia (DYT), **Parkinson's disease** (PD), **Tourette's syndrome** (TS), & **obsessive-compulsive disorder** (OCD)?
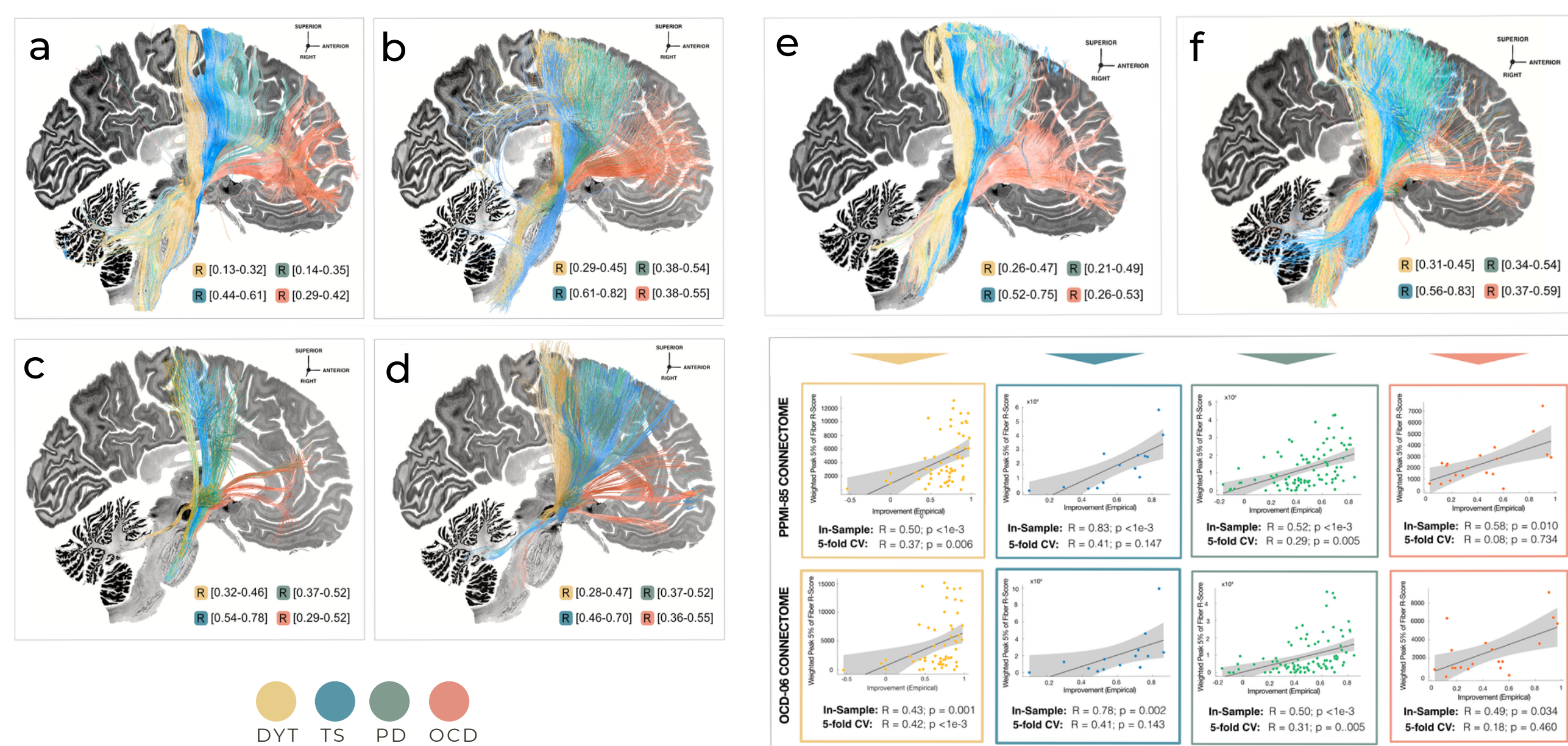
METHODS & COHORTS

Lead-DBS based processing pipeline [1]

A TARGET-LEVEL DBS EFFECT: DBS SWEET SPOT MAPPING [2]

B NETWORK-LEVEL DBS EFFECT: DBS FIBER FILTERING [3]

AIM: TO INVESTIGATE THE TOPOGRAPHICAL ORGANIZATION OF FRONTO-CORTICAL & SUBCORTICAL DYSFUNCTION MAPPINGS

SUBTHALAMIC ELECTRODE PLACEMENT IN DISCOVERY COHORTS

- DYT (N = 70, 38 F)
- PD (N = 95, 30 F)
- TS (N = 14, 3 F)
- OCD (N = 19, 10 F)

N = **267** patients (N = 197 in discovery & N = 70 in validation cohort) of **12** patient cohorts from **9** international DBS centers. ... which equals to a total of **534** invasive electrodes!

DBS OUTCOME IN FOUR CARDINAL DYSFUNCTIONS

- **DYT** — Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) - Total Score
- **PD** — Unified Parkinson's Disease Rating Scale-III (UPDRS-III) - Total Score
- **TS** — Yale Global Tics Severity Scale (YGTSS) - Global Severity Score
- **OCD** — Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) - Total Score

CONNECTIVITY INFORMATION

4 normative connectomes of the healthy human brain & **2** disease-matched connectomes

RESULTS (DISCOVERY COHORTS)

A TARGET-LEVEL DBS EFFECT: DBS SWEET SPOT MAPPING [2]

B NETWORK-LEVEL DBS EFFECT: DBS FIBER FILTERING [3]

~1 CM

R [0.13-0.32] R [0.14-0.35]
R [0.44-0.61] R [0.29-0.42]

DYT TS PD OCD

At the **cortical level, network organization of dysfunction** was reflected in form of a **caudo-rostral anatomical topography** that spanned the frontal lobe from sensorimotor (DYT), followed by (pre-)motor (TS & PD), toward prefrontal-most regions (OCD). A comparable – but **miniaturized** – caudo-rostral organizational pattern of selective stimulation effects onto cardinal dysfunctions was **mirrored focally, within the STN**.

CONNECTED FIBERS / FILTERING CONNECTED FIBERS BY STRENGTH OF CLINICAL RELEVANCE / DBS SWEET TRACTS

N = 56   N = 94   N = 14   N = 19

ATLAS STRUCTURES: GPe, GPi, STN, RN, VTA, STR

FIBER TRACTS: DYT, PD, TS, OCD

R [0.22-0.31]
R [0.27-0.39]
R [0.49-0.61]
R [0.29-0.48]

Dysfunction mappings to **indirect pallido-subthalamic connections** followed a **similar topographical organization** as that seen in hyperdirect pathway and sweet spot segregations.

CONNECTOME	In-Sample (R = 0.59, p < 1e-16) S-FOLD CV		In-Sample (R = 0.71, p < 0.001) S-FOLD CV		In-Sample (R = 0.48, p < 0.01) S-FOLD CV		In-Sample (R = 0.66, p < 0.05) S-FOLD CV	
	IN-SAMPLE	S-FOLD CV	IN-SAMPLE	S-FOLD CV	IN-SAMPLE	S-FOLD CV	IN-SAMPLE	S-FOLD CV
MGH Source Subject 760 µm	R = 0.59 p < 1e-16	R = 0.58 p < 1e-16	R = 0.45 p = 0.038	R = 0.43 p = 0.1e-16	R = 0.51 p = 0.034	R = 0.48 p = 0.035	R = 0.61 p = 0.001	
HCP 985	R = 0.46 p < 1e-16	R = 0.28 p = 1e-16	R = 0.45 p = 0.038	R = 0.41 p = 0.008	R = 0.54 p = 0.004	R = 0.48 p = 0.054	R = 0.66 p = 0.001	
Basal Ganglia Pathway Atlas	R = 0.50 p < 1e-16	R = 0.36 p = 0.003	R = 0.52 p = 1e-3	R = 0.46 p = 0.003	R = 0.82 p = 0.003	R = 0.53 p = 0.075	R = 0.81 p = 0.447	
DBS Tractography Atlas, v2	R = 0.50 p < 1e-16	R = 0.44 p = 0.107	R = 0.71 p = 1e3	R = 0.57 p = 0.071	R = 0.57 p = 0.082	R = 0.75 p = 0.088	R = 0.68 p = 0.208	

MODEL VALIDATION RESULTS

a. R [0.13-0.32] R [0.14-0.35] R [0.44-0.61] R [0.29-0.42]
b. R [0.29-0.45] R [0.38-0.54] R [0.61-0.82] R [0.38-0.55]
c. R [0.32-0.46] R [0.37-0.52] R [0.54-0.78] R [0.39-0.52]
d. R [0.28-0.47] R [0.37-0.52] R [0.46-0.70] R [0.36-0.55]
e. R [0.26-0.47] R [0.21-0.49] R [0.52-0.75] R [0.26-0.53]
f. R [0.31-0.45] R [0.34-0.54] R [0.56-0.83] R [0.37-0.59]

DYT TS PD OCD
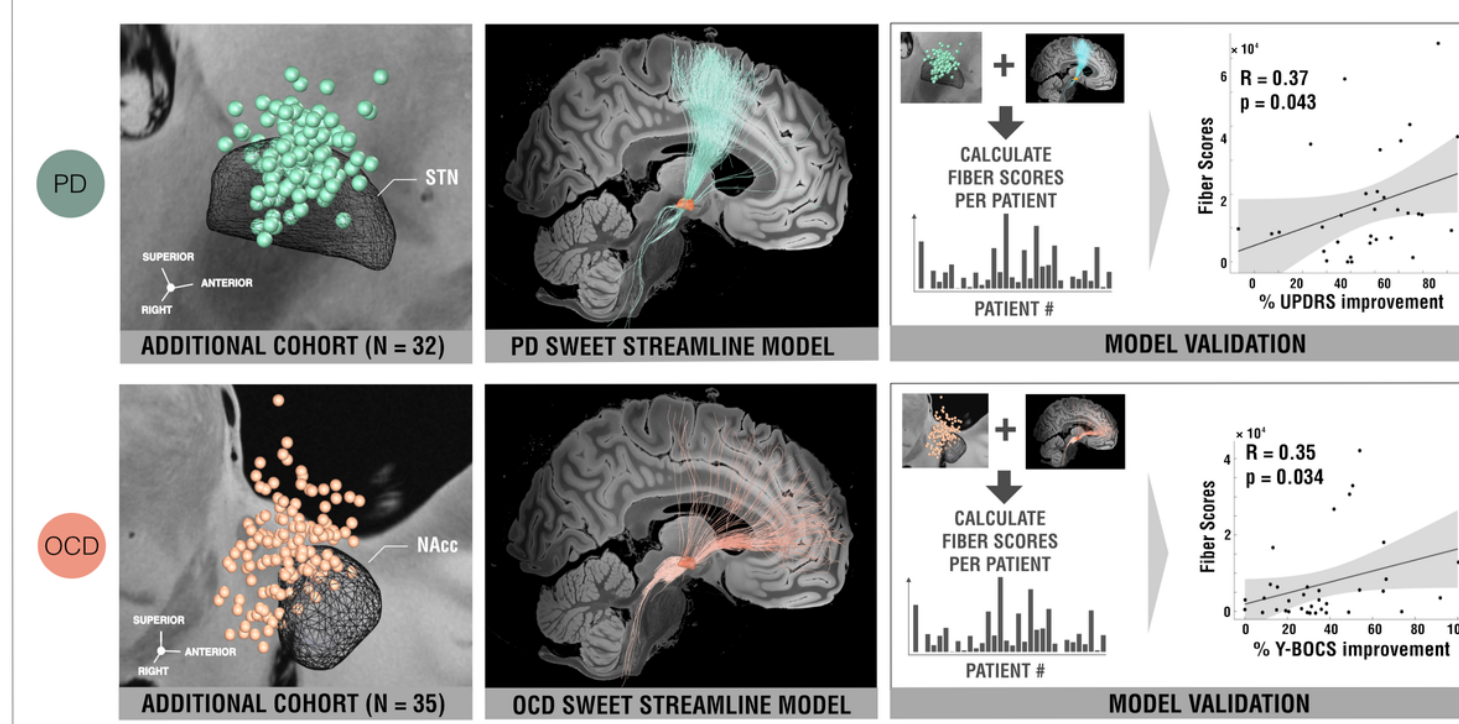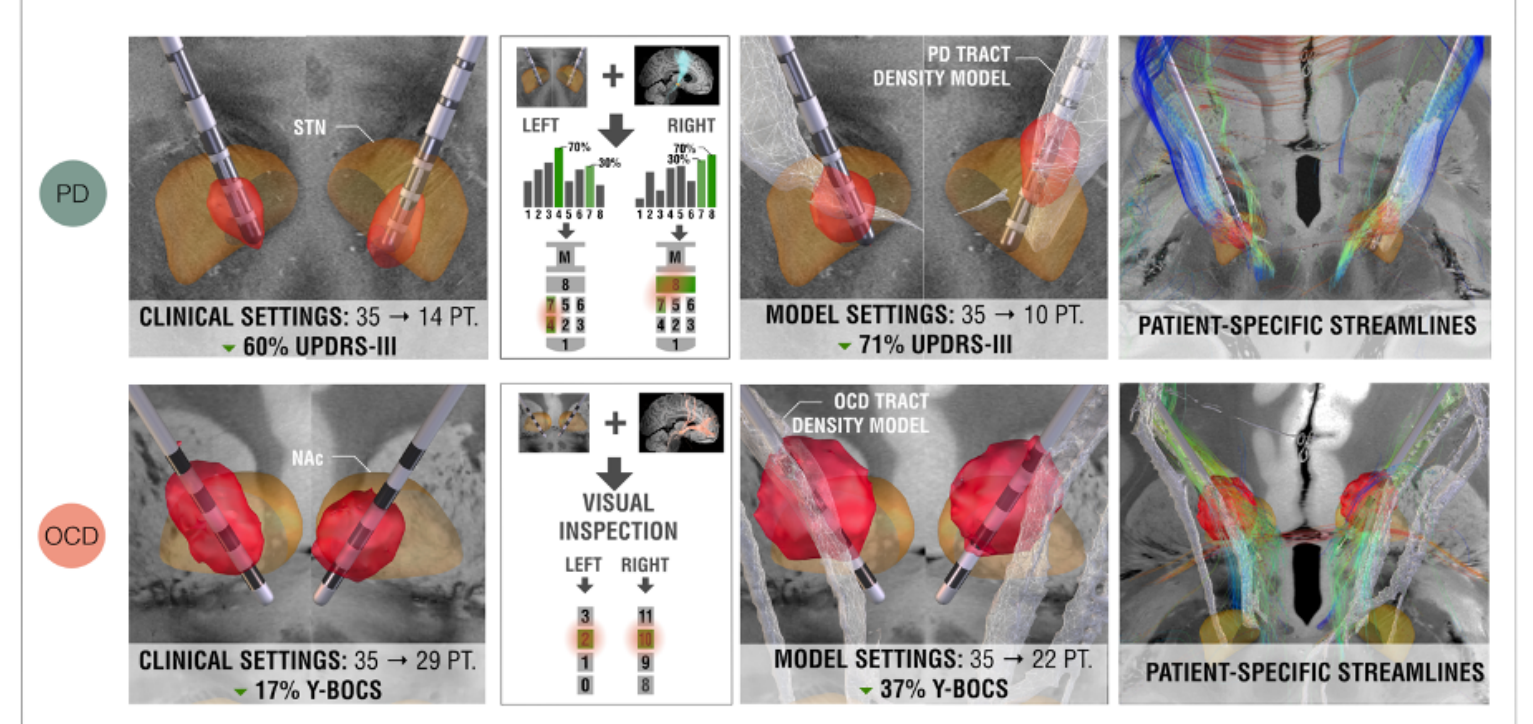
The same order of dysfunction mappings (motor disorders in sensorimotor and premotor cortices toward associative-limbic OCD connections) emerged for clinically beneficial sets of streamlines filtered from the **Massachusetts General Hospital Single Subject 760 µm Connectome** (a) [4], the **Human Connectome Project 985 Connectome** (b) [5,6], the **Basal Ganglia Pathway Atlas** (c) [7], the **DBS Tractography Atlas, v2** (d), as well as an **OCD-** (e) and a **PD-matched connectome** (f) [8].

RETROSPECTIVE VALIDATION: ESTIMATING UNSEEN OUTCOMES

ADDITIONAL COHORT (N = 32) / PD SWEET STREAMLINE MODEL / CALCULATE FIBER SCORES PER PATIENT / MODEL VALIDATION — R = 0.37, p = 0.043, % UPDRS improvement

ADDITIONAL COHORT (N = 35) / OCD SWEET STREAMLINE MODEL / CALCULATE FIBER SCORES PER PATIENT / MODEL VALIDATION — R = 0.35, p = 0.034, % Y-BOCS improvement

PROSPECTIVE VALIDATION: REPROGRAMMING

PD: CLINICAL SETTINGS: 35 → 14 PT = 60% UPDRS-III / MODEL SETTINGS: 35 → 10 PT = 71% UPDRS-III / PATIENT-SPECIFIC STREAMLINES

OCD: CLINICAL SETTINGS: 35 → 29 PT = 17% Y-BOCS / MODEL SETTINGS: 35 → 22 PT = 37% Y-BOCS / PATIENT-SPECIFIC STREAMLINES

PROSPECTIVE VALIDATION: SURGICAL PLANNING & PROGRAMMING

OCD: SURGICAL PLANNING PRE-OP Y-BOCS: 25 PT / MODEL SETTINGS: 26 → 6 PT = 77% Y-BOCS / PATIENT-SPECIFIC STREAMLINES
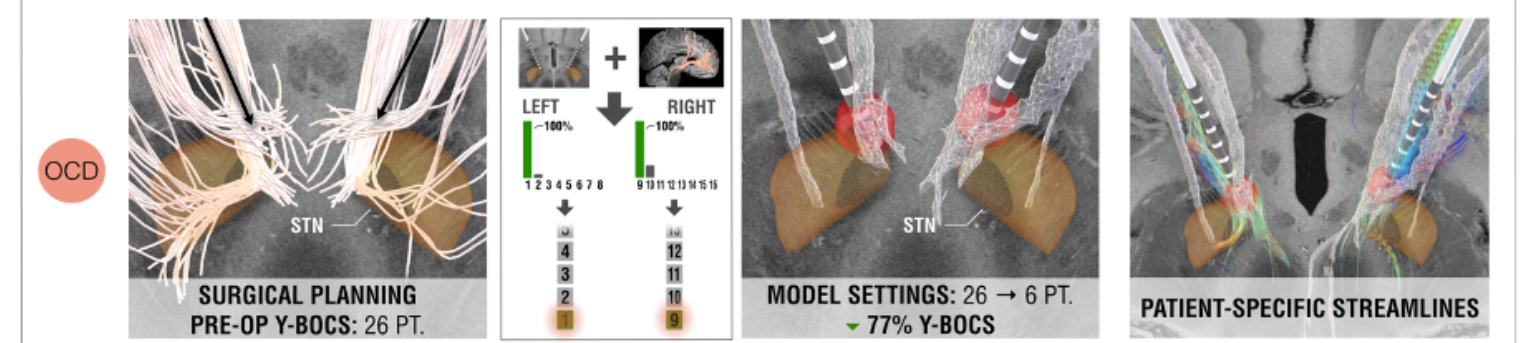
Therapeutic potential of PD and OCD streamlines was demonstrated by estimating clinical outcomes in **two entirely independent retrospective patient cohorts** as a function of the degree of overlap of their stimulation volumes with the corresponding streamline model (informed on the discovery cohort). Further, **two prospective patient cases** (OCD & PD) underwent **streamline-based optimization of stimulation parameters**, and **one OCD patient** was **implanted and programmed** with the aim of maximizing stimulation impact onto the OCD streamline model.
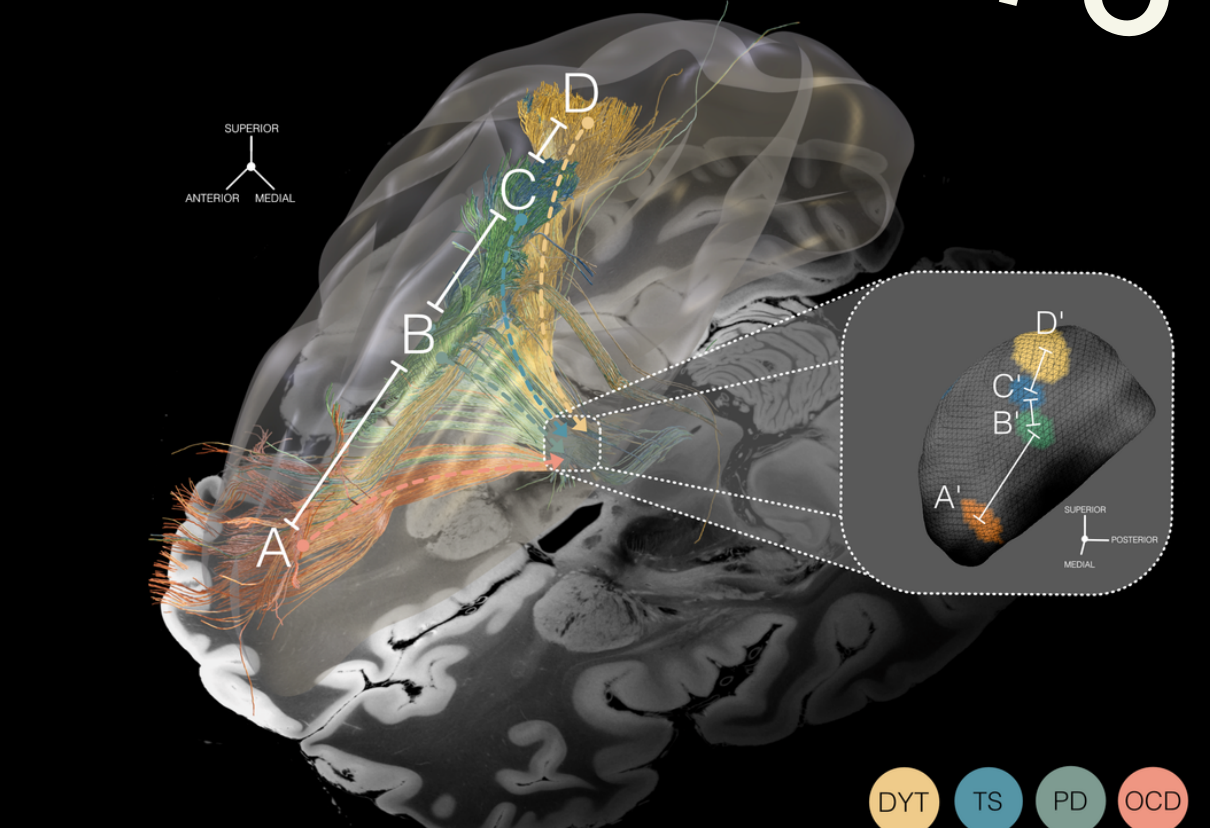
CONCLUSIONS

CONNEC-TOMIC DBS

OPENS A WINDOW INTO NEUROANATOMY-DYSFUNCTION-MAPPINGS WITHIN THE HUMAN BRAIN

The **miniaturized anatomical representation of dysfunction within the subcortex** relative to the cortex may explain why DBS to the STN can be used as an effective treatment for a variety of brain disorders of heterogeneous phenomenology.

ALL ABOUT LEAD-DBS HERE / LEAD-DBS ON GITHUB / FIND THE PREPRINT HERE / DOWNLOAD THE POSTER HERE

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