SUPPLEMENTARY FILES

Convergent therapeutic networks across neuromodulation in obsessive-compulsive disorder reveal a multiscale biological architecture

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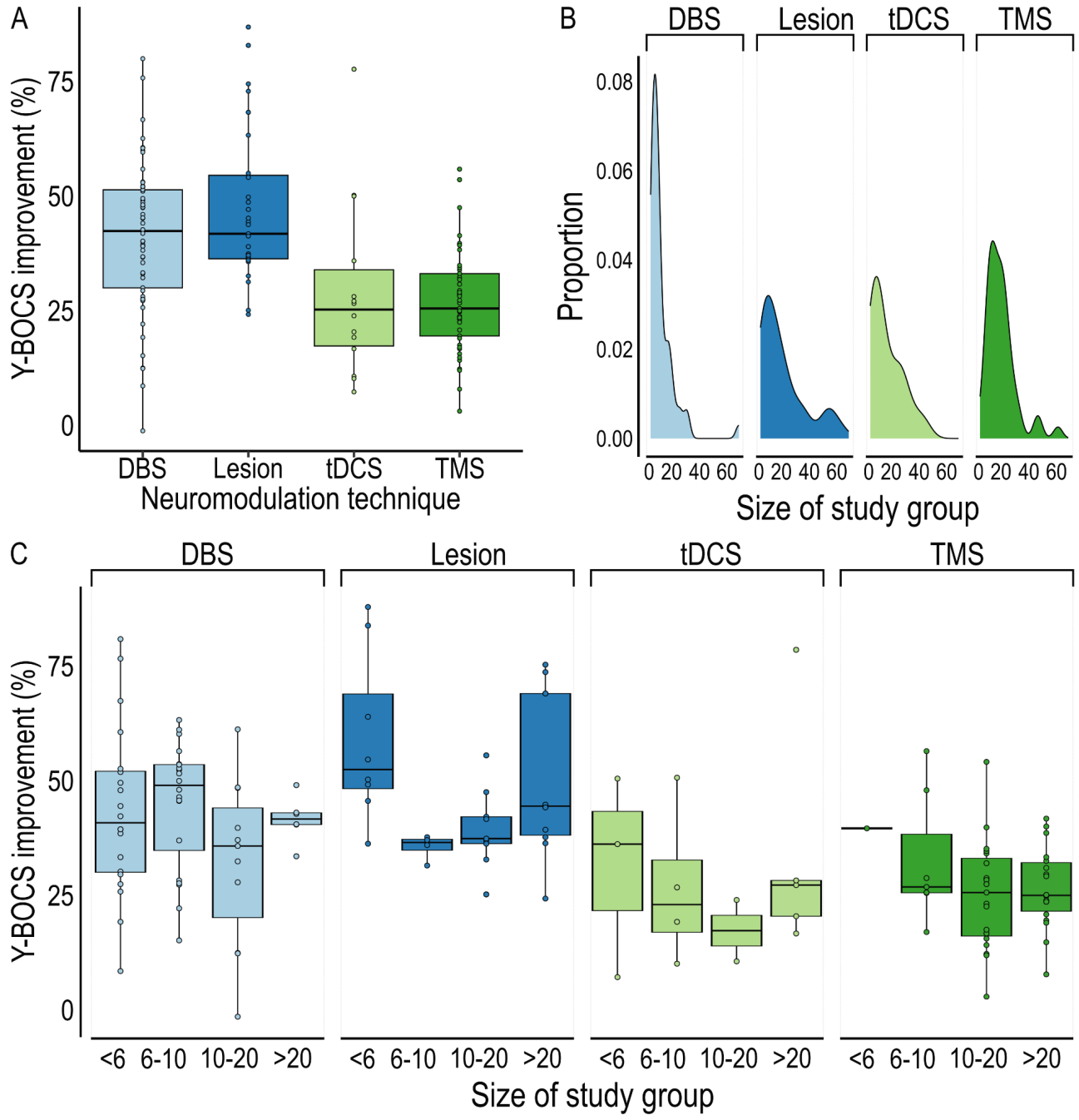
SUPPLEMENTARY TABLE 1

Supplementary Table 1. Targets utilized in neuromodulation therapies and associated improvement.

Neuromodulation modality	Brain target	Number of studies	Number of individuals included	Average YBOC improvement (%)	Weighted average YBOCS improvement (%)
DBS	ALIC	11	197	32.9	34.8
	BNST	4	32	45.3	46.0
	CN	2	11	31.4	24.0
	ITP	3	16	50.6	50.6
	MFB	1	2	30.0	30.0
	NAcc	7	58	37.1	37.1
	STN	6	64	45.1	35.5
	VC/VS	13	107	46.9	46.3
	Multiple	9	83	42.6	42.9
Lesion-based	ACC	5	120	36.2	35.5
	ALIC	21	396	47.2	50.2
	NAcc	1	2	63.3	63.3
	Multiple	1	7	37.4	37.4
TMS	DLPFC	14	201	25.3	23.9
	DMPFC	1	20	39.7	39.7
	OFC	5	113	17.3	18.5
	pre-SMA	2	45	31.1	31.3
	SMA	16	314	28.1	27.0
	multiple	7	126	17.5	29.8
tDCS	FronTemp	1	7	50.2	50.2
	OFC	2	30	18.6	23.7
	pre-SMA	1	26	20.4	20.4
	SMA	6	47	25.5	20.1
	multiple	4	90	35.8	49.2

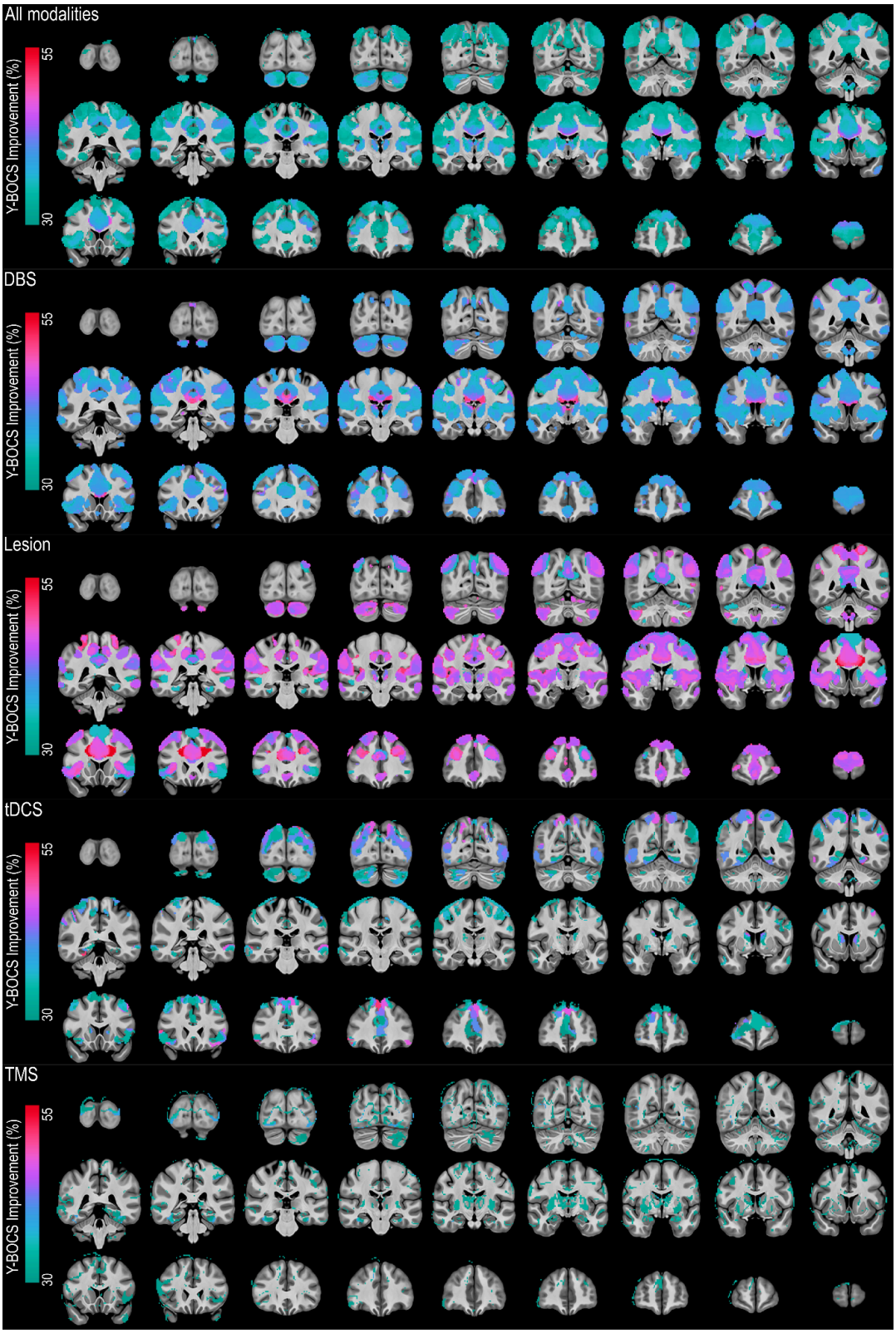
Abbreviations: ACC: Anterior cingulate cortex; ALIC: Anterior limb of the internal capsule; BNST: Bed nucleus of the stria terminalis; CN: Caudate nucleus; DBS: Deep brain stimulation; DLPFC: Dorsolateral prefrontal cortex; DMPFC: Dorsomedial prefrontal cortex; FronTemp: Frontotemporal area; ITP: Inferior thalamic peduncle; MFB: Medial forebrain bundle; NAcc: Nucleus accumbens: OFC: Orbitofrontal cortex; pre-SMA: Pre supplementary motor area; SMA: Supplementary motor area; STN: Subthalamic nucleus; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation; VC/VS: Ventral capsule/ventral striatum; YBOCS: Yale-Brown Obsessive Compulsive Scale.

SUPPLEMENTARY FIGURE 1



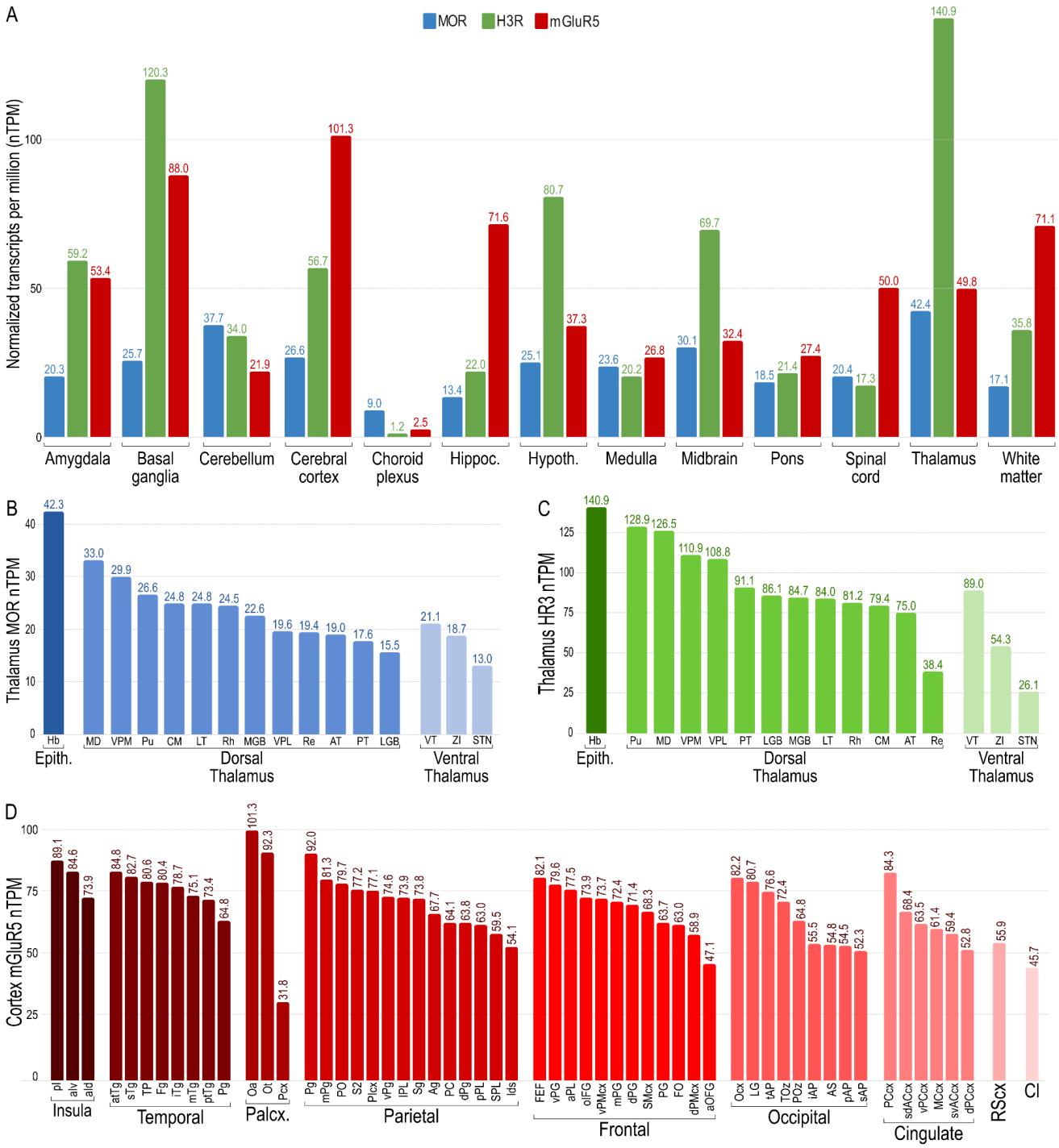
Supplementary Figure 1. Study-level characteristics across neuromodulation modalities. A) Distribution of study-level Y-BOCS percentage improvement stratified by neuromodulation modality (DBS, lesion, tDCS, TMS). Boxplots display median, interquartile range, and individual study values. B) Distribution of study sample sizes by modality, shown as density plots illustrating the proportion of studies across increasing cohort sizes. C) Y-BOCS percentage improvement stratified jointly by neuromodulation modality and study sample size category (<6, 6–10, 10–20, >20 participants), demonstrating the relationship between reported efficacy and cohort size. Abbreviations: DBS, deep brain stimulation; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; Y-BOCS, Yale–Brown Obsessive Compulsive Scale.

SUPPLEMENTARY FIGURE 2



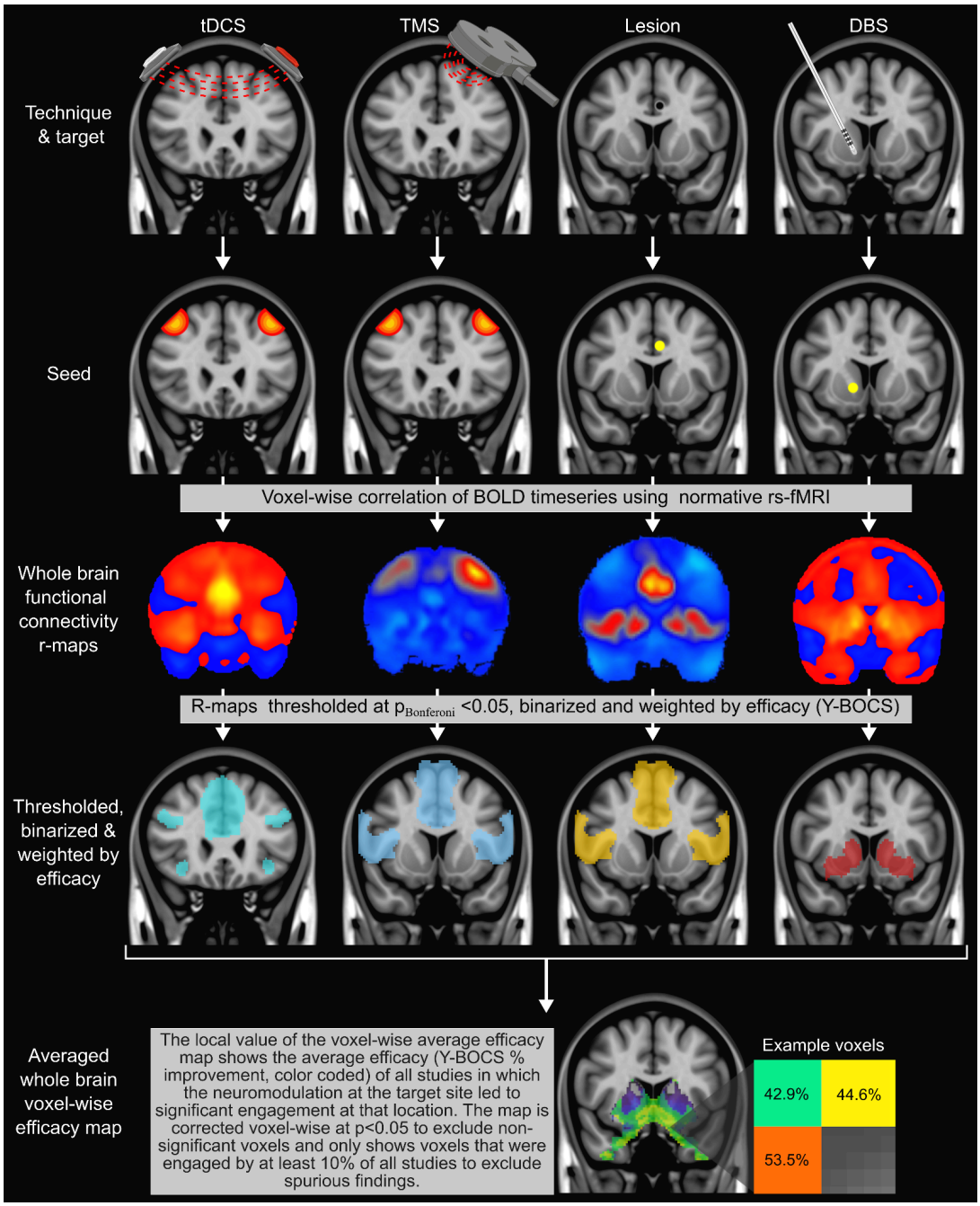
Supplementary Figure 2. Full coronal representation of pan-modality and modality-specific efficacy-weighted connectivity maps (see Figure 1). Voxels reflect normative functional connectivity to stimulation/lesion targets that scaled with study-level Y-BOCS improvement.

SUPPLEMENTARY FIGURE 3



Supplementary Figure 3. Regional transcriptomic distribution of MOR, H3R, and mGluR5 from the Human Protein Atlas. (A) Normalized transcript per million (nTPM) expression values across major brain regions for the mu-opioid receptor (MOR), histamine H3 receptor (H3R), and metabotropic glutamate receptor 5 (mGluR5). (B) Subregional distribution of MOR expression across thalamic nuclei, including epithalamus (habenula) and dorsal and ventral thalamic subdivisions. (C) Subregional distribution of H3R expression across thalamic nuclei. (D) Cortical regional distribution of mGluR5 expression across insular, temporal, parietal, frontal, occipital, and cingulate cortices. Expression values are derived from the Human Protein Atlas (brain tissue RNA-seq; nTPM).

SUPPLEMENTARY FIGURE 4



Supplementary Figure 4. Normative connectomic pipeline for generating efficacy-weighted connectivity maps. Target coordinates were extracted from each included study and used to generate study-specific ROIs in MNI standard space representing the stimulated or lesioned region. Each ROI served as a seed for whole-brain functional connectivity mapping using a normative 1000-subject resting-state fMRI connectome. This produced a voxel-wise r-map for each study reflecting normative connectivity to the target. Connectivity maps were thresholded (Bonferroni-corrected $p < 0.05$), binarized, and weighted by the study's mean Y-BOCS percentage improvement. Weighted maps were then averaged voxel-wise to generate pan-modality and modality-specific efficacy-weighted maps. Final maps were frequency-masked (≥10% study contribution) and statistically thresholded (voxel-wise $p < 0.05$) to retain voxels consistently associated with clinical improvement. Abbreviations: MNI, Montreal Neurological Institute; ROI, region of interest; rs-fMRI, resting-state functional magnetic resonance imaging; Y-BOCS, Yale–Brown Obsessive Compulsive Scale.