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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data was sourced from Data was sourced from Tiantan Hospital, Beijing; Peking Union Medical College Hospital, Beijing; and Qilu Hospital, Jinan, China., as explained in the manuscript and in the Data section below. MRI data was collected from MRI scanners, no software or code was used.
Data analysis	All fMRI data were preprocessed using a cloud medical image data processing software, pBFS cloud, at https://app.neuralgalaxy.cn/research/. Code specific to analyses can be found at https://github.com/pBFSLab/open-DBS. The bCompCor code can be found in the Github repository and has also been directly implemented in DeepPrep, available at https://deepprep.readthedocs.io/en/latest/. Software packages incorporated into the above code for data analysis include: Python v3.7, https://www.python.org; Matlab R2020b, https://www.mathworks.com/; R v4.3.1, https://www.r-project.org; Connectome Workbench v1.5, http://www.humanconnectome.org/software/connectome-workbench.html; Freesurfer v6.0.0, https://surfer.nmr. mgh.harvard.edu/; FSL v6.0, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki; ANTs v0.3.8 https://github.com/ANTsX/ANTs; LeadDBS v2.0, https://www.lead-dbs.org/.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Anonymous individual patient data, including all brain imaging modalities—sMRI, rsfMRI, bdfMRI, DTI, and CT—demographic data, and neurological assessments are available in the Science Data Bank repository: https://doi.org/10.57760/sciencedb.26302. The preprocessed imaging data will also be available on the repository.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Findings apply to all studied individuals and groups, regardless of sex. PD Patients: 14 (5F, 9M) Healthy controls: 28 (14F, 14M)
Reporting on race, ethnicity, or other socially relevant groupings	No socially constructed or socially relevant categorization variables were used or are relevant for our manuscript.
Population characteristics	Findings apply to all studied individuals and groups, regardless of age. Age ranges: PD patients: mean age = 54.9, standard deviation = 7.7 years Healthy controls: mean age = 55.9, standard deviation = 6.6 years
Recruitment	Patients with the akinetic-rigid dominant form of idiopathic PD were recruited from Tiantan Hospital, Beijing; Peking Union Medical College Hospital, Beijing; and Qilu Hospital, Jinan, China. Healthy control participants who were age-matched to the patient group were recruited.
Ethics oversight	The ethics approval for this project was granted by the ethics committees of Tiantan Hospital (QX2016-009-02, 21 July, 2016), Peking Union Medical College Hospital (HS2016094, 21 September, 2016), and Qilu Hospital (2016008, 28 August, 2016).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We leveraged recent advancements in 3T MRI-compatible DBS and precision imaging to collect extensive data from 14 PD patients who received DBS. Across five timepoints spanning one year, each patient underwent 11.7-hour fMRI under seven stimulation conditions (30-172 minutes/session), 2.2-hour structural MRI (26 min/session), 1.3-hour diffusion-weighted MRI (16 min/session), and neurological assessments. Imaging data were also collected from 27 healthy participants.
Data exclusions	One healthy participant was excluded due to discomfort in the MRI scanner.
Replication	The main experimental findings (Fig. 2, Fig.6, Fig.7) were replicated in all individuals and group-averaged dataset.
Randomization	N/A: There were no separate experimental groups.
Blinding	N/A: There were no separate experimental groups.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT02937727
Study protocol	Study overview is available online (NCT02937727: https://clinicaltrials.gov/study/NCT02937727?term=NCT02937727;&rank=1#study-overview;)
Data collection	Data was collected at Tiantan Hospital, Beijing; Peking Union Medical College Hospital, Beijing; and Qilu Hospital, Jinan, China.
Outcomes	The primary outcome is change in UPDRS part III [Time Frame: 1 month,3 months, 6 months and 12months] and change in Local Field Potential Recordings using G106R [Time Frame: 1 month,3 months, 6 months and 12months]. Secondary outcome is change in UPDRS part III [Time Frame: 1, 3 months of stimulation], UPDRS part II [Time Frame: 1, 3 months stimulation], Levodopa Equivalent Dose [Time Frame: 1, 3 months stimulation], Drug Therapy are definied as levodopa equivalent dose,which is devodopa containing or dopamine agonist containing medications and Local Field Potential Recordings using G106R [Time Frame: 1 month, 3 months].

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

Magnetic resonance imaging

Experimental design

Design type	Resting-state fMRI; Task-state fMRI
Design specifications	We acquired BOLD fMRI and UPDRS-III data under several DBS frequencies: low frequency (60 Hz), high frequency (130 Hz), and variable frequency (alternating between 60 and 130 Hz). A washout period of over one hour was implemented between each condition. The order of conditions was pseudorandomized. The conditions are described in more detail below. Condition 1 (C1): Acquisition without STN stimulation, i.e. presurgical status or postsurgical DBS OFF status. Condition 2 (C2): Acquisition with continuous 60 Hz stimulation to the STN. Condition 3 (C3): Acquisition with continuous 130 Hz stimulation to the STN. Condition 4 (C4): Acquisition with continuous, variable frequency stimulation to the STN, i.e. stimulation frequency was periodically alternated between 60 Hz and 130 Hz every 2 seconds. Condition 5 (C5): Block-design acquisition using 60 Hz stimulation to the STN, i.e. 36 seconds of 60 Hz stimulation interleaved with 24 seconds of DBS OFF status. Condition 6 (C6): Block-design acquisition using 130 Hz stimulation to the STN, i.e. 36 seconds of 130 Hz stimulation interleaved with 24 seconds of DBS OFF status. Condition 7 (C7): Block-design acquisition using variable frequency stimulation to the STN, i.e. 36 seconds of variable

frequency stimulation (stimulation frequency was periodically alternated between 60 Hz and 130 Hz every 2 seconds) interleaved with 24 seconds of DBS OFF status.
Conditions 2-4 mimicked conventional therapeutic strategies with different stimulation frequencies, which are critical for revealing frequency-related modulation effects. Conditions 5-7 employed block designs to investigate the immediate modulatory effects of different stimulation frequencies. The motor symptoms were assessed using the UPDRS-III at least one hour after each stimulation condition switch to washout the immediate after-effects of stimulation. Because UPDRS-III measurement during block-design stimulation (conditions 5-7) is difficult to be interpreted, only DBS-OFF state (condition 1) and continuous stimulation with different frequencies (conditions 1-4) were accompanied by UPDRS-III assessments.

Behavioral performance measures

We acquired UPDRS-III data under several DBS frequencies: low frequency (60 Hz), high frequency (130 Hz), and variable frequency (alternating between 60 and 130 Hz). A neurologist optimized the DBS settings with regards to contacts selection, stimulation amplitude, and pulse width. A total of seven different stimulation conditions were investigated during postsurgical fMRI scanning and four of them were included in postsurgical UPDRS-III assessment. The conditions are described in above.

Acquisition

Imaging type(s)

structural; functional; diffusion-weighted

Field strength

3T

Sequence & imaging parameters

Seven different MRI sequences, five for structural imaging (MPRAGE, FLAIR, TSE, QSM, and SNAP), one for functional imaging (BOLD), and one for diffusion-weighted imaging (NODDI), were employed in the study.
MPRAGE: T1-weighted sagittal images were acquired for 4 min 14 sec using a magnetization-prepared rapid gradient echo (MPRAGE) sequence, FOV=256×256, pixel spacing=1 mm×1 mm, 180 slices, slice thickness=2 mm, spacing between slices=1 mm, TR=7.52 ms, TE=3.70 ms, flip angle=8°.
FLAIR: T2-weighted sagittal images were acquired for 6 min 30 sec using a fluid-attenuated inversion recovery (FLAIR) sequence, FOV=384×384, pixel spacing=0.602 mm×0.602 mm, 120 slices, slice thickness=1.5 mm, spacing between slices=1.5 mm, TR=5000 ms, TE=340.29 ms, TI=1650 ms, flip angle=90°.
TSE: T2-weighted images were acquired with a 2 min 56 sec turbo spin-echo (TSE) sequence, with FOV=512×512, pixel spacing=0.391 mm×0.391 mm, 45 slices, slice thickness=2 mm, spacing between slices=2 mm, TR=2595 ms, TE=90 ms, flip angle=90°. One transversal TSE imaging and one coronal TSE imaging were performed and the center plane was set to cover the subthalamic nuclei completely.
QSM: Magnetic susceptibility images were acquired with a 3 min 55 sec transversal quantitative susceptibility mapping (QSM) sequence, with FOV=512×512, pixel spacing=0.449 mm×0.449 mm, 173 slices, slice thickness=1.5 mm, spacing between slices=0.75 mm, TR=30.253 ms, flip angle=12°.
MRA: Magnetic resonance angiography (MRA) images were acquired with a 5 min 8 sec transversal simultaneous non-contrast angiography and intra-plaque hemorrhage (SNAP) sequence, with FOV=400×400, pixel spacing=0.602 mm×0.602 mm, 150 slices, slice thickness=0.8 mm, spacing between slices=0.4 mm, TR=10.025 ms, TE=5.64 ms, flip angle=11°.
BOLD: Functional images were acquired with a 6 min 14 sec transversal gradient-echo echo-planar imaging (GE-EPI) sequence, with FOV=80×80, pixel spacing=2.875 mm×2.875 mm, 37 slices, slice thickness=3.5 mm, spacing between slices=4 mm, TR=2000 ms, TE=30 ms, flip angle=90°, 184 frames.

Area of acquisition

Head/Brain

Diffusion MRI ☒ Used ☐ Not used

Parameters

NODDI: Diffusion-weighted images were acquired with a 7 min 47 sec transversal neurite orientation and dispersion density imaging (NODDI) sequence, with FOV=128×128, pixel spacing=1.75 mm×1.75 mm, 50 slices, slice thickness=2.8 mm, spacing between slices=2.8 mm, TR=5499.745ms, TE=85.069 ms, flip angle=90°, 81 images with three b values (1 image with b=0, 40 images with b=1000, and 40 images with b=2000).

Preprocessing

Preprocessing software

The processing of both rs-fMRI and structural data was conducted using the personalized Brain Functional Sectors (pBFS) Cloud v1.0.7 (Neural Galaxy Inc., Beijing). Resting-state fMRI, i.e. BOLD fMRI data acquired under conditions 1-4, were preprocessed using a previously published pipeline, which includes: 1) slice-timing correction (SPM12; Wellcome Department of Cognitive Neurology, London, UK); 2) rigid-body correction for head motion (FSL6.0; FMRIB, Oxford, UK); 3) linear detrending and band-pass filtering (0.01-0.08 Hz); 4) regressing nuisance variables including the global signal, the six parameters obtained through rigid-body head motion correction, their first temporal derivatives, as well as the component-based confounds (see the next section for a detailed description).
T1w images were preprocessed to reconstruct individual cortical surface using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) version 6.0.0. The reconstructed cortical surfaces were registered to the FreeSurfer cortical surface template (fsaverage6). The individual anatomical images were also nonlinearly aligned to the MNI152 template. The anatomical and functional images were affinely aligned using boundary-based registration from the FsFast software package (http://surfer.nmr.mgh.harvard.edu/fswiki/FsFast). The preprocessed functional images were projected to the surface and volumetric template. A 6-mm full-width half- maximum (FWHM) smoothing kernel was then applied to the fMRI data in both the surface and volumetric space.

Normalization

For the surface preprocessing pipeline, the functional images were aligned with the FreeSurfer cortical surface template (fsaverage6, 40,962 vertices per hemisphere).

For the volumetric preprocessing pipeline, the preprocessed functional images in native space were normalized to a 2-mm spatial resolution volumetric template (the FSL-version of the MNI ICBM152 nonlinear template) using a co-registration matrix and volumetric nonlinear registration with ANTs.

Normalization template

Surface: fsaverage6, 40,962 vertices per hemisphere
volumetric : FSL-version of the MNI ICBM152 nonlinear template

Noise and artifact removal

Additional confound analyses: regression to account for nuisance variables, which encompassed the six motion parameters, white matter signal, ventricular signal, global signal, and their first-order temporal derivatives.

Volume censoring

N/A

Statistical modeling & inference

Model type and settings

We used linear mixed effects (LME) models to analyze the therapeutic effects of DBS, with changes in motor symptoms, as assessed by UPDRS-III total scores, as the dependent variable. The independent variables included stimulation conditions (OFF, HFS, VFS, LFS), follow-up visits (1 month, 3 months, 6 months, 12 months), and their interactions, with random intercepts for individual subjects. To analyze the time effects on therapeutic effects, one-way repeated measures ANOVA was performed. To analyze the time effects on therapeutic effects, one-way repeated measures ANOVA was performed.

To evaluate the reliability of neurological assessments, we compared the UPDRS-III total scores and 5 sub-scores assessed by two neurologists, using two metrics: the intraclass correlation coefficient (ICC) and the repeated measures correlation coefficient (rmcorr).

The DBS's modulatory effect size of these identified edges was estimated using Cohen's d, based on the contrast between DBS-ON and presurgical conditions (C2–C4 vs. C1).

DBS-induced responses were estimated using a general linear model (GLM) and restricted maximum likelihood approach (REML), in which the noise term was prewhitened by an autoregression with an optimized autocorrelation parameter set. To examine functional activation at the individual level, [illegible]-contrast maps from each condition and each follow-up visit were analyzed using a fixed-effects GLM model for each patient. Moreover, to examine functional activation at the group level, [illegible]-contrast maps from the same condition and/or the same follow-up visit were analyzed using a random-effects model across patients.

Spin-based permutation tests, also termed spin tests, were used to assess the statistical significance of the similarity between two STN (VTA)-cortical RSFC maps (Fig. 4b & Extended Data Fig. 3 & Supplementary Fig. 8) while accounting for spatial autocorrelation110-112. The null distribution was generated by 10,000 random surface-based rotations of one of the RSFC maps for comparisons.

Effect(s) tested

see above

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☒ Both

Anatomical location(s)

Each patient's cerebral cortex was individually parcellated into 152 regions (76 regions for the left and right hemisphere, respectively) based on their rsfMRI data, using an iterative clustering approach similar to that described in our previous studies(Wang, D. et al., Nature Neuroscience, 2015).
In addition, we assigned the 152 regions to one of 18 large-scale functional networks, which include 17 canonical networks and the somato-cognitive action network (SCAN), according to the overlapping surface area of each region with each network.
The HybraPD atlas is available at https://www.lead-dbs.org/helpsupport/knowledge-base/atlasesresources/atlases-2/

Statistic type for inference

No cluster wise inferences were made.

(See Eklund et al. 2016)

Correction

Multiple comparisons were controlled using FDR correction.

Models & analysis

n/a	Involved in the study
☐	☒ Functional and/or effective connectivity
☒	☐ Graph analysis
☐	☒ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Resting-state functional connectivity was estimated by Pearson's correlation coefficient of BOLD-fMRI signals

Multivariate modeling and predictive analysis

In Fig4 ,the resulting masked map was deemed the ideal STN (VTA) or target connectivity profile, designed to guide motor symptom prediction in the leave-one-subject-out cross-validation (LOSOCV) analysis.

For the prediction of clinical outcomes at baseline (1 month before surgery) (Extended Data Fig. 2), presurgical patient-specific and normative STN (VTA) connectivity maps were used. LOSOCV was applied:

connectivity maps from 13 patients' STN (VTA)s were used to generate the ideal target-cortical connectivity map, which was then employed to predict the clinical outcome for the remaining patient. Clinical outcome estimates were derived from the similarity, measured by Pearson correlation, between the ideal map and the STN (VTA) connectivity map of the remaining patient. This procedure was repeated 14 times to estimate clinical outcomes for all patients, and Spearman's correlation was performed between observed and predicted outcomes. For postsurgical clinical outcome prediction (Fig. 4e), a similar approach was used, but each patient's STN (VTA) corresponded to the patient-specific data across all stimulation conditions and follow-up visits. To prevent information leakage, all data from the patient whose outcomes were being predicted, across all stimulation conditions and follow-up visits, were excluded when generating the ideal map. A LME model was used to test the association between observed and predicted clinical outcomes. The dependent variable was the observed clinical outcomes and the independent variable was the predicted scores of different timepoints and stimulation conditions, with random intercepts for individual patients.