

## Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

### 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

- |                                     |                                     |  |
|-------------------------------------|-------------------------------------|--|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | A description of all covariates tested   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/>            | For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes   |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> | 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 analysis https://github.com/netstim/leaddbs, <https://osf.io/bckuf/>, <https://github.com/netstim/SlicerNetstim>  
3D Slicer Version 5.0.3  
Mango Version 4.1  
Neurosynth decoder: <https://github.com/neurosynth/neurosynth>"/>

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 Research [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 list of figures that have associated raw data
- A description of any restrictions on data availability

Anonymized derivatives of stimulation data used for the described analyses are openly available on OSF (<https://osf.io/bckuf/>). The resulting tract atlas, sweet spot and fMRI network pattern are openly available within Lead-DBS software ([www.lead-dbs.org](http://www.lead-dbs.org)).

## Normative data:

Structural connectome: <https://datadryad.org/stash/dataset/doi:10.5061/dryad.nzs7h44q2>, Functional connectome: <http://neuroinformatics.harvard.edu/gsp/>  
 Neurosynth database: <https://github.com/neurosynth/neurosynth-data>

## 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](https://www.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	46 subjects. The sample size was determined according to data availability from a phase I (NCT00658125) and a phase II (NCT01608061) clinical trials to evaluate the safety of fornix-Deep Brain Stimulation. A post-hoc power calculation for achieved power was performed with an effect size $f^2$ of 0.15 (moderate effect), power (1 - Beta error prob) of 0.73.
Data exclusions	2 subjects from NCT01608061 were excluded due to unavailability of imaging data.
Replication	Cross-Prediction across 2 subcohorts, Leave-one-out and K-fold cross validation
Randomization	Training and hold-out cohorts were determined in a randomized way.
Blinding	We estimated relationships between electrode placements and clinical improvements, rather than evaluating whether the surgical intervention is effective or not. The authors were, however, blinded to clinical data during imaging pre-processing and manual refinements to normalization and electrode localization.

## 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	Involvement in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants
<input type="checkbox"/>	<input checked="" type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

### Methods

n/a	Involvement in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input type="checkbox"/>	<input checked="" type="checkbox"/> MRI-based neuroimaging

## Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	46 patients with mild Alzheimer's Disease (23 females, $67 \pm 7.9$ years old), diagnosed by expert clinicians with ADAS-cog 11 scores 12-24 points, and CDR of 0.5 or 1 intervened with Deep Brain Stimulation to the fornix were included.
Recruitment	Patients were retrospectively analyzed based on previously published data from clinical trials NCT00658125 and NCT01608061.
Ethics oversight	The study was approved by the ethics board of Charité – Universitaetsmedizin Berlin (master vote EA2/186/18). All procedures were carried out according to the declaration of Helsinki from 1975, participants signed an informed consent in person with the participation of a surrogate consentor.

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

## 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	Retrospective analysis of NCT00658125, NCT01608061.
Study protocol	N/A. Purely retrospective analysis of published data.
Data collection	N/A. Purely retrospective analysis of published data.
Outcomes	N/A. Purely retrospective analysis of published data.

## Magnetic resonance imaging

### Experimental design

Design type	Retrospective-Post hoc analysis
Design specifications	N/A
Behavioral performance measures	N/A

### Acquisition

Imaging type(s)	Structural
Field strength	1.5 Tesla
Sequence & imaging parameters	Pre-op T1, T2-weighted MRI, Post-op T1-weighted MRI
Area of acquisition	Whole brain
Diffusion MRI	<input type="checkbox"/> Used <input checked="" type="checkbox"/> Not used

### Preprocessing

Preprocessing software	SPM12, ANTs, Lead-DBS, MATLAB
Normalization	ANTs
Normalization template	ICBM 2009b NLIN Asymmetric non-linear 2009b MNI152
Noise and artifact removal	Biasfield correction
Volume censoring	N/A

### Statistical modeling & inference

Model type and settings	Mass univariate analysis, training -> hold-out cohort prediction, leave-one-out and k-fold cross-validations
Effect(s) tested	Cognitive improvement following DBS to the Fornix (as measured by changes on the ADAS-cog 11 scale).
Specify type of analysis:	<input checked="" type="checkbox"/> Whole brain <input type="checkbox"/> ROI-based <input type="checkbox"/> Both
Statistic type for inference (See <a href="#">Eklund et al. 2016</a> )	training -> hold-out cohort prediction, leave-one-out and k-fold crossvalidations, predictive accuracy measured by Pearson- / Spearman cross-validations
Correction	FDR for flashback data analysis

### Models & analysis

n/a	Involvement in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> Functional and/or effective connectivity
<input checked="" type="checkbox"/>	<input type="checkbox"/> Graph analysis
<input checked="" type="checkbox"/>	<input type="checkbox"/> Multivariate modeling or predictive analysis
Functional and/or effective connectivity	Spearman correlation, Pearson correlation