nature portfolio

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Last updated by author(s): 10-3-2023

Reporting Summary

Nature Portfolio 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 Portfolio 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
☐	☒ 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	EGI software for EEG data acquisition used in collection of evoked potentials (NetStation Review (Electrical Geodesics, Inc.).
Data analysis	THOMAS automated thalamic segmentation algorithm applied to white matter null MRI sequence data, using version v0 of this tool (https://github.com/sujason/thomas); DWI data was processed using DSI Studio (https://dsi-studio.labsolver.org/); synthetic MRI atlas created using Advanced Normalization Tools software (ANTs, http://stnava.github.io/ANTs/), /); predictive models of axonal activation created in SCIRun (https://sci.utah.edu/software/scirun.html); EEG evoked potential plotting functions EGI, Matlab EEGLAB v2021.1 software (https://sccn.ucsd.edu/eeglab/index.php) run on MATLAB R2021a, The Mathworks, Inc.; EEG-Clean-Tools toolbox (PREP pipeline) v0.56.0 (http://vislab.github.io/EEG-Clean-Tools); Independent components were identified using AMICA v1.5 (https://sccn.ucsd.edu/~jason/amica_web.html) and labeled as brain signal, muscle artifact, eye movement, heart artifact, line noise, channel noise, or other using ICLabel v1.3 (https://github.com/sccn/ICLabel); REDCAP database tools for computation of behavioral test results, Matlab functions and Excel programs for behavioral data analysis, SAS version 9.4 (SAS Institute, Inc., Cary, NC) for statistical analysis.

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

A minimum dataset extracted from the REDCAP database has been made available on Dryad: https://datadryad.org/stash/share/qJ1U_HqZYVgzadpn9vxF2CE6hhvGEQYHjARtQ3zs6uU

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	We sought to recruit participants representative of the general population of those with msTBI in terms of sex which is anticipated to yield a 2:1 Male:Female ratio.We enrolled 4 men and 2 women based on self-report. We did not collect disaggregated sex and gender information. Given the small N of the study and the reporting of sex only, we do not report any sex and gender-based analyses.
Reporting on race, ethnicity, or other socially relevant groupings	We enrolled 4 men (white) and 2 women (white).
Population characteristics	1. History of moderate to severe TBI based on estimated GCS score within first 48 hours of injury (acceptable GCS range = 3-12); 2. Age 22-60; 3. At least 24 months from date of onset; 4. Fluent in English and able to independently provide consent; 5. Rating of lower moderate disability to lower good recovery on the Glasgow Outcome Scale-Extended (GOSE) at time of enrollment (acceptable GOSE range 5-7); 7. Failure to return to pre-injury level of vocational or educational function.
Recruitment	Participant recruitment Participants were recruited through a variety of channels, including self-referral and provision of IRB-approved recruitment materials to academic research partners and consumer advocacy organizations serving patients with TBI. To accelerate enrollment, we also received IRB approval to subcontract with PatientWing (Philadelphia, PA), a digital media marketing firm specializing in clinical trial recruitment. PatientWing identified potential study candidates using key-word searches on several online platforms including Google and various social media channels. To ensure equal access to our trial, PatientWing also launched a print campaign during the heavy holiday travel season in several Greyhound bus stations throughout California, targeting individuals without access to the internet. Candidates initially underwent telephone screening, which included administration of the Glasgow Outcome Scale-Extended (GOS-E) Structured Interview to ensure that the candidate had not returned to pre-injury level of vocational or educational function (GOS-E rating no higher than 5). Through these efforts, 419 inquiries were received and 15 individuals were consented for further assessment to confirm eligibility. Of these, 9 candidates were excluded and 6 met all eligibility criteria and were randomized (See CONSORT Diagram). All recruited patients responded to advertised information about the study potentially biasing the sample recruited to those able to search for information or looking for clinical studies.
Ethics oversight	All sites designated to the single Stanford University IRB which maintained oversight of this study.

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	6 participants; FDA feasibility study under IDE; population size determined in conjunction with the FDA. 6 participants considered sufficient for establishing safety testing at the level of early feasibility trial.
Data exclusions	One secondary measure, Ruff 2&7 test, was excluded for participant P1 due to a test administration error detected by quality assurance procedures as reported in the manuscript.
Replication	Replication was tested by applying the same test batteries and measurement procedures across the study population. Replication was tested

Replication	in 5 sets of individual participant data obtained at pre-surgical and treatment end time points for all measures with the noted exception above of the secondary Ruff 2& 7 test which was excluded from this replication for one participant, P1, due to a test administration error on the first (pre-surgical) administration of the test.
Randomization	Participants were randomized into three cohorts that varied the time after implantation surgery prior to initial titration of stimulation and to conditions of a washout phase following treatment end phase. Procedures are described in the manuscript.
Blinding	Group membership was blinded to study investigators and unblinding of conditions occurred only after closure of the REDCAP database.

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	NCT02881151
Study protocol	FDA IDE #G160019
Data collection	All primary data obtained at Stanford University Medical Center beginning August 2018 and ending
Outcomes	Primary outcome measure, a >10% improvement on Trial Making Test Part B, TMT-B, was decided in conjunction with NINDS program staff and formed the basis of GO-NO GO milestones for the continuation of the study. Both requirements for a positive signal (at least one participant meeting this level among the first four participants to continue study to completion) and stopping criteria (no more than two participants showing a worsening of similar magnitude across the first four participants) were pre-specified. For secondary measures a >10% improvement for success was pre-defined.

Magnetic resonance imaging

Experimental design

Design type	Anatomical imaging with white matter null and diffusion weighted magnetic resonance imaging sequences
Design specifications	N/A
Behavioral performance measures	N/A

Acquisition

Imaging type(s)	WMn-MPRAGE protocol (WMn) protocol and a diffusion tensor imaging (DTI) protocol,
Field strength	3T GE MR750 scanner using a 32-channel head coil.
Sequence & imaging parameters	WMn image volumes were acquired using the following parameters: 3D MPRAGE sequence, coronal orientation, TE 4.7ms, TR 11.1ms, TI 500ms, TS 5000ms, views per segment 240, FA: 8°, RBW +/-11.9kHz, spatial resolution 1mm isotropic, 220 slices per volume k-space ordering; 2D radial fanbeam, ARC parallel imaging acceleration: 1.5x1.5, scan time 8 min. DTI image volumes were acquired using the following parameters: 2D diffusion-weighted single-shot spin-echo echo planar imaging (EPI) sequence, axial orientation, TE 74ms, TR 8000ms, RBW +/-250kHz, diffusion directions: 60, diffusion weighting (b-value): 2500 s/mm^2, spatial resolution 2mm isotropic, 70 slices per volume, parallel imaging

acceleration: 2, scan time 11min.

Area of acquisition: Whole brain

Diffusion MRI ☒ Used ☐ Not used

Parameters: 2D diffusion-weighted single-shot spin-echo echo planar imaging (EPI) sequence, axial orientation, TE 74ms, TR 8000ms, RBW

Preprocessing

Preprocessing software: Whole-brain WMn volumes were processed with the THOMAS thalamic segmentation tool with no preprocessing. The THOMAS algorithm applied to WMn images has been validated against manual segmentation35. Using version v0 of this tool (https://github.com/sujason/thomas), we segmented and extracted the volumes of 12 lateralized structures in each hemisphere of the brain

Normalization: Each individual patient data used in subsequent pipeline; in addition a synthetic atlas used for group comparisons.

Normalization template: For the group analyses a synthetic atlas was developed to organize all participant electrode placements within a single common brain space (see Methods). The atlas was created by warping all individual image volumes to a common template using Advanced Normalization Tools software (ANTs, http://stnava.github.io/ANTs/), followed by averaging the warped volumes together. More specifically, white matter-nulled MRI image volumes from each of the five participants were combined using nonlinear registration to produce a template or synthetic atlas volume, representative of all participants

Noise and artifact removal: WMnMPRAGE and DTI image volumes were visually inspected to ensure that scans were of sufficient quality for analysis and were not corrupted by motion artifact.

Volume censoring: N/A

Statistical modeling & inference

Model type and settings: N/A

Effect(s) tested: N/A

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

Statistic type for inference: *Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.*

(See Eklund et al. 2016)

Correction: *Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).*

Models & analysis

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