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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	Lesion network maps was constructed using in-house scripts in combination with public human connectome data, as described in our prior work (MD Fox, NEJM 2018).
Data analysis	Except as otherwise specified, statistical analyses were conducted using in-house MATLAB scripts as described in the manuscript. Code for spatial permutation testing is available at our lab website, http://siddiqi.bwh.harvard.edu/data-code

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

This paper used de-identified data from multiple different datasets collected by different teams of investigators at various institutions, including the US Department of Veterans Affairs. Each dataset is available upon reasonable request from each respective team of investigators. Data sharing will be subject to the policies and

procedures of the institution where each dataset was collected. The final PTSD network map will be made available on NeuroVault and on our website (http://siddiqi.bwh.harvard.edu/data-code) as soon as it has passed peer review.

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	Because this was a study primarily of PTSD in military Veterans, the population was predominantly male. The gender distribution is noted in tables S1 and S2.
Reporting on race, ethnicity, or other socially relevant groupings	This manuscript was based on reanalysis of data that has been collected over the last 40 years, so most of the data did not include this information.
Population characteristics	Population characteristics are summarized in Tables S1 and S2.
Recruitment	We included all relevant datasets that we were able to access. Each dataset had different recruitment parameters and biases depending on the study type. Please see associated cited papers for further details.
Ethics oversight	The study was approved by the IRB at Brigham and Women's Hospital (Boston, MA) and by the individual IRBs at each individual data collection site.

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	There is no standard method for estimating sample size for this type of study, therefore we sought to include as many participants as possible. To our knowledge, this is the largest study to integrate lesion and correlative neuroimaging in PTSD.
Data exclusions	All participants with complete imaging and behavioral data were included.
Replication	As outlined in the manuscript, we replicated our results using cross-validation and tested generalizability across three different approaches.
Randomization	Rather than prospective randomization, this study capitalized on incidental variability of lesions, TMS sites, and DBS sites (as described in the manuscript). This incidental variability was presumed to be random, making it an instrumental variable.
Blinding	Blinding was not relevant because this was a secondary analysis of existing datasets. We mitigated the risk of observer bias by using several control and validation analyses.

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

Plants

Seed stocks: NA

Novel plant genotypes: NA

Authentication: NA

Magnetic resonance imaging

Experimental design

Design type: Individualized structural MRI and/or head CT combined with normative resting-state fMRI; two datasets included individualized resting-state fMRI

Design specifications: Structural MRI or CT scans were used to localize lesions. Normative resting-state fMRI data from a large connectome database (n=1000) was used to estimate connectivity of each lesion. In separate cohorts, individualized resting-state functional connectivity was used to compute within-network connectivity associated with PTSD.

Behavioral performance measures: In dataset 1, the SCID-IV (structured clinical interview for DSM-IV) was used to assess PTSD. In dataset 2, the SCID-5 was used. In dataset 3, the PTSD Checklist for DSM-5 was used.

Acquisition

Imaging type(s): functional, structural

Field strength: 3T

Sequence & imaging parameters: Dataset 1: Normative resting-state fMRI acquisition parameters: repetition time (TR) = 3,000 ms, 3 × 3 × 3-mm voxels, field of view (FOV) = 216, with 6.2 min per run (124 time points). One or two runs were acquired per subject (average of 1.7 runs).

Dataset 2: All patients completed a resting-state blood oxygen level dependent (BOLD) scan using a GE 750 scanner (3.75mm x 3.75mm x 3.75mm resolution, 6-minute duration).

Dataset 3: All patients completed a resting-state BOLD scan (3 x 3 x 3 mm resolution, 8-minute duration).

Case report: baseline resting-state fMRI scan with three 6.5 minute runs (total 22-minute acquisition), 3.4 x 3.4 x 4 mm spatial resolution, and 2.15-sec TR.

Area of acquisition: Whole-brain

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software: Normative connectome: previously developed by an outside group using FreeSurfer + in-house preprocessing scripts, as in the GSP1000 dataset (details in Yeo et al, J Neurophysiol 2011)
Individualized connectivity: CONN Toolbox

Normalization: Nonlinear volume-based registration as in Friston et al, 1995

Normalization template: MNI ICBM152

Noise and artifact removal: ART based outlier detection, bandpass filtering .008-.09 Hz, and white matter, ventricular, and grey matter signal regression

Volume censoring: Motion regression and ART based censoring

Statistical modeling & inference

Model type and settings: Lesion network mapping with voxel-wise correlation model, validated using permutation testing and cross-validation.

Effect(s) tested

Primary: Correlation between lesion connectivity and behavioral items, spatial correspondence between split-half subgroup maps, split-half prediction of PTSD status.

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

Statistic type for inference

Voxel-wise

(See Eklund et al. 2016)

Correction

Primary analyses were based on whole-brain spatial correlations with permutation testing - there were no multiple comparisons because the spatial correlation yields only a single value, which was the primary metric.
As a secondary analysis, we also used voxel-wise Westfall-Young correction as per Winkler et al. 2014.

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

Mean Pearson correlation across the normative dataset (n=1000) for each lesion to derive the network. Resting-state functional connectivity within that network in validation analyses.