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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	HCP: rsfMRI time series were derived from minimally preprocessed and ICA-FIX denoised images; dMRI tractography and streamlines were derived from minimally preprocessed structural connectomes and reconstructed using FSL (v6.0.4). Human [18F]FEOBV PET acquisition is described here: https://doi: 10.1016/j.nbas.2022.100039 Mouse [18F]FEOBV PET data were acquired as 150-minute list-mode emission scans from a Siemens Inveon microPET and reconstructed using an OSEM3D algorithm.
Data analysis	All code used to run the analyses and generate the figures can be found at https://github.com/sudesnac/HumanBF-Connectivity. Analyses were run using a virtualenv Python (v3.9.7) environment relied on the following open-source Python packages: neuromaps (v0.0.3), brainspace(v0.1.10), nibabel(v5.2.1), nilearn(v0.10.4), surfplot(v0.2.0), matplotlib(v3.9.1), numpy(1.26.4), palettable(v3.3.3), pandas(v2.2.2), scikit-learn(v1.5.1), scipy(v1.14.0), seaborn(v0.13.2), the full list is available at: https://github.com/sudesnac/HumanBF-Connectivity/blob/main/code/requirements.txt. Data was analyzed using Matlab (R2020b), FSL (v6.0.4), SPM, Connectome Workbench (v1.5.0), FreeSurfer (v7.1), ANTs (v2.3.5).

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

For origin and use of the multiple datasets described in this paper, see Table 1. The Human Connectome (HCP) project dataset is available at http://www.humanconnectomeproject.org/. The main human [18F] FEOBV PET data was derived from Kanel et al. (ref 38) the processed imaging data is available at https://github.com/sudesnac/HumanBF-Connectivity/tree/main/results/connectivity_distance, the human [18F] FEOBV PET data used in the supplemental analysis are available at neuromaps (ref 37) https://netneurolab.github.io/neuromaps/index.html. The mouse [18F] FEOBV PET data were collected by K.M.O. and the processed images can be accessed at https://doi.org/10.5281/zenodo.13750996 by contacting tschmitz@uwo.ca. The viral tracing data were derived from Li et al. (ref 2) and are available in their supplemental materials (SI Appendix Fig 7). All source data for figures are provided with this paper.

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	Structural and functional connectomes were group consensus networks generated from individual connectomes of subjects of both sexes. Human [18F]FEOBV PET were acquired from subjects of both sexes.
Reporting on race, ethnicity, or other socially relevant groupings	Information on recruitment demographics for HCP can be found here: https://www.humanconnectome.org/study/hcp-young-adult/project-protocol/recruitment. Information for human [18F]FEOBV PET acquisition is described here: https://doi: 10.1016/j.nbas.2022.100039.
Population characteristics	HCP: n=173; 69 male, 104 female 55% female); aged 22 to 35 years. Human PET: n=13; 10 male, 3 female(27% females); mean age = 24.5 years, SD = 4.9 years,
Recruitment	Only data from healthy control subjects were used in the analyses.
Ethics oversight	HCP: Informed consent was obtained for all subjects. The protocol was approved by the Washington University Institutional Review Board as part of the HCP. Ethics information for human [18F]FEOBV PET acquisition is described here: https://doi: 10.1016/j.nbas.2022.100039.

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	The justification for the sample size of each dataset is provided in the original articles (HCP) and/or derived from a priori power analyses from relevant work (mouse). Human connectomes (HCP): https://doi.org/10.1016/j.neuroimage.2013.05.041 Human PET data: https://doi.org/10.1016/j.nbas.2022.100039 Mouse positron emission tomography (PET): https://doi.org/10.1038/s41398-019-0416-7
Data exclusions	Human connectomes (HCP): All subject with complete 7T rs-fMRI and dMRI data were included. Human PET data: all data published in Kanel et al. 2022 (https://doi.org/10.1016/j.nbas.2022.100039) is presented.
Replication	Analyses presented in Figures 2 and 4 were replicated in cross-validation and replication experiments that included using split-half and leave-one-out cross validation (Figure 2, Supplemental Figures 3) and using independently acquired datasets (Figure 4, Supplemental Figure 5).
Randomization	No randomization was performed as this study does not include experimental groups.
Blinding	Blinding is not relevant to this study because it does not include 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

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Data were acquired in 11 (5 male, 6 female) control mice, either C57BL/6J or VAChTflox/fox at 6 months of age.
Wild animals	Not applicable
Reporting on sex	55% female. Sex was not predicted a priori to differentiate mean VAChT binding.
Field-collected samples	Not applicable
Ethics oversight	All small-animal imaging procedures were conducted in accordance with the Canadian Council of Animal Care's current policies and were approved by the University of Western Ontario's Animal Care Committee (Animal Use Protocols: #2016-104, #2020-163) and the Lawson Health Research Institute's Health and Safety board.

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

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

Magnetic resonance imaging

Experimental design

Design type	Structural MRI, resting-state fMRI and diffusion-weighted MRI
Design specifications	No trials
Behavioral performance measures	No behavioural measures

Acquisition

Imaging type(s): ructural MRI, resting-state fMRI and diffusion-weighted MRI

Field strength: 7T

Sequence & imaging parameters: 1.6 mm3 isotropic voxel size, TR=1000 ms, TE=22.2 ms, FOV=208 mm2, spanning 4 runs of 16-minute duration each, per subject. More information on acquisition is available at: https://www.humanconnectome.org/storage/app/media/documentation/s1200/HCP_S1200_Release_Reference_Manual.pdf

Area of acquisition: Whole brain

Diffusion MRI ☒ Used ☐ Not used

Parameters: HCP: 1.05 mm3 isotropic voxel size, TR=7000 ms, TE=71.2 ms, b-values=1000, 2000 s/mm2 , FOV=210 x 210 mm2. More information on acquisition is available at: https://www.humanconnectome.org/storage/app/media/documentation/s1200/HCP_S1200_Release_Reference_Manual.pdf

Preprocessing

Preprocessing software: HCP: More information regarding data preprocessing is available in: https://doi.org/10.1016/j.neuroimage.2020.117429

Normalization: HCP: More information regarding data preprocessing is available in: https://doi.org/10.1016/j.neuroimage.2020.117429

Normalization template: HCP: More information regarding data preprocessing is available in: https://doi.org/10.1016/j.neuroimage.2020.117429

Noise and artifact removal: HCP: More information regarding data preprocessing is available in: https://doi.org/10.1016/j.neuroimage.2020.117429

Volume censoring: HCP: More information regarding data preprocessing is available in: https://doi.org/10.1016/j.neuroimage.2020.117429

Statistical modeling & inference

Model type and settings: The structure-function tethering metric was computed with respect to the structural and functional connectomes.

Effect(s) tested: We tested whether structure-function tethering of basal forebrain connectivity was stable across participants and sample splits (split half and leav eone out cross-validation) and whether our metric of tethering was related to empirical micro-architectural attributes using spatial autocorrelation-preserving null models

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

Anatomical location(s): HCP: A priori anatomical annotations were derived from: http://doi: 10.1152/jn.00338.2011
Mouse: A priori anatomical annotations were derived from: https://doi.org/10.1016/j.cell.2020.04.007

Statistic type for inference (See Eklund et al. 2016): t-tests, permutation tests, bootstrap analysis

Correction: False Discovery Rate (Benjamini-Yekutieli procedure)

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: HCP: A group-average functional connectivity matrix was constructed by concatenating the regional fMRI BOLD time series of all four resting-state sessions from all participants and computing the zero-lag Pearson correlation coefficient between each pair of brain regions.