

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 (<i>n</i>) 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 <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☐	☒ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ 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 <i>d</i> , Pearson's <i>r</i>), 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	We utilize the resting-state (RS) fMRI scans, the fMRI scans during the n-back tasks, the performance of the n-back tasks and the diffusion tensor imaging (DTI) scans from the Human Connectome Project (HCP) S1200 release. For analyzing the activation, functional connectivity and structural connections, we select 737 right-handed subjects (age: 22-36 years old, 413 female/324 male) from the data release based on the selection criteria. For fitting the EI-MFM model, we consider the resting-state (RS) data of 1052 participants from the HCP S1200 release. Details of the data collection can be found in the overview.
Data analysis	Data analysis was performed using MATLAB, Python, and standard neuroimaging/statistical toolboxes. The EI-MFM simulations and perturbation analyses were performed using MATLAB/Python scripts. Functional connectivity, dynamic functional connectivity, ALFF/fALFF, and statistical analyses were performed using MATLAB/Python scripts and relevant open-source scientific computing packages. Molecular-enriched network analyses were performed using the REACT toolbox. Figure preparation and visualization were performed using MATLAB and Python.

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](#)

The HCP data is publicly available (<https://www.humanconnectome.org/>). The PET images used to perform the analyses are also public available (https://github.com/netneurolab/hansen_receptors).

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	This study used publicly available human neuroimaging data from the Human Connectome Project (413 female/324 male). Gender identity was not analyzed separately because it was not relevant to the primary research question and was not available as a separate variable for the present analyses. No sex- or gender-based subgroup analyses were performed.
Reporting on race, ethnicity, or other socially relevant groupings	Race, ethnicity, and other socially relevant groupings were not analyzed in the present study because they were not part of the primary research question. The analyses focused on neuroimaging-derived functional, structural, and receptor-enriched measures. No race- or ethnicity-based subgroup analyses were performed.
Population characteristics	The study included healthy adult participants from the Human Connectome Project. The analyses used de-identified resting-state fMRI, working-memory task fMRI, diffusion MRI, and associated demographic information where applicable. The model-fitting analyses used resting-state fMRI data from 1,052 participants, and the empirical fMRI/DTI analyses used data from 737 right-handed participants. Full sample information is provided in the Methods section.
Recruitment	No new participants were recruited for this study. Participant recruitment and data collection were performed by the original Human Connectome Project investigators according to their approved study protocols.
Ethics oversight	No new data were collected for this study. The original Human Connectome Project data collection procedures were approved by the relevant institutional review boards, and written informed consent was obtained from all participants by the original data-collecting institutions.

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	No a priori sample-size calculation was performed. Sample sizes were determined by the availability of eligible Human Connectome Project data after applying the inclusion criteria described in the Methods. The EI-MFM fitting analysis used resting-state fMRI data from 1,052 participants, which were divided into training, validation, and test sets. The empirical fMRI/DTI analyses of working-memory-related functional and structural connectivity used 737 right-handed participants with available resting-state fMRI, working-memory task fMRI, and diffusion MRI data.
Data exclusions	Participants were excluded from a given analysis if the required imaging modality or task data were unavailable, incomplete, or did not meet the preprocessing and quality-control requirements described in the Methods. For the empirical fMRI/DTI analyses, participants were further restricted to right-handed individuals to reduce potential variability related to hemispheric lateralization. No participants or data points were excluded based on the statistical results.
Replication	This study did not involve independent experimental replication. Reproducibility and robustness were assessed through validation using independent model test data, sensitivity analyses across model configurations and brain parcellations, and additional control analyses. These analyses are reported in the Results and Supplementary Information.
Randomization	Random allocation to experimental groups was not applicable because this study used existing observational neuroimaging data and did not involve experimental treatment groups. Where applicable, analyses were performed using predefined datasets, model configurations, and

brain parcellations.

Blinding

Blinding was not applicable because this study involved secondary analysis of de-identified neuroimaging data and computational modeling rather than experimental group assignment or intervention. The analyses were based on predefined computational and statistical procedures.

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

Methods

- 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

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

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, mosaicism, off-target gene editing) were examined.

Magnetic resonance imaging

Experimental design

Design type

The study used resting-state fMRI and task fMRI from the Human Connectome Project. The working-memory fMRI task used a block-design N-back paradigm including 0-back and 2-back conditions. Diffusion MRI data were used to estimate structural connectivity.

Design specifications

For the HCP working-memory task, participants completed two task runs. Each run included blocks of 0-back and 2-back trials with different stimulus categories, following the standard HCP N-back task design. Resting-state fMRI data were acquired during eyes-open rest. Full task and acquisition details followed the Human Connectome Project protocol.

Behavioral performance measures

Behavioral performance during the working-memory task was assessed using task accuracy and/or response measures provided by the Human Connectome Project. These measures were used to evaluate working-memory performance where applicable. Details of the behavioral variables used in the analyses are provided in the Methods section.

Acquisition

Imaging type(s)

Functional MRI, diffusion MRI, and structural MRI data from the Human Connectome Project were used. Resting-state fMRI and working-memory task fMRI were used for functional analyses, and diffusion MRI was used for structural connectivity estimation.

Field strength

All MRI data used in this study were acquired on the Human Connectome Project 3T MRI scanner.

Sequence & imaging parameters

Functional MRI data were acquired using multiband gradient-echo echo-planar imaging with 2-mm isotropic resolution, TR = 720 ms, TE = 33.1 ms, and flip angle = 52°, following the standard Human Connectome Project protocol. Diffusion MRI data were acquired using the HCP multishell diffusion protocol with 1.25-mm isotropic resolution.

Area of acquisition

Whole-brain MRI data were used. Functional and diffusion MRI analyses were performed on cortical brain regions defined by the parcellation schemes used in the study.

Diffusion MRI ☒ Used ☐ Not usedParameters HCP multishell diffusion MRI; (b=1000), (2000), and (3000, mm^2), approximately 90 directions per shell, 1.25-mm isotropic resolution.

Preprocessing

Preprocessing software	The study used Human Connectome Project minimally preprocessed MRI data. HCP preprocessing includes correction for spatial distortions and head motion, registration to structural images and standard space, surface reconstruction, and denoising procedures according to the HCP minimal preprocessing pipelines. Additional functional connectivity, dynamic functional connectivity, ALFF/fALFF, structural connectivity, and model-based analyses were performed using custom MATLAB/Python scripts.
Normalization	The analyses used HCP minimally preprocessed data normalized according to the standard HCP preprocessing pipelines. Functional data were aligned to standard cortical surface and/or volumetric spaces as provided in the HCP release and were subsequently summarized within the brain parcellations used in this study.
Normalization template	Data were used in the standard HCP normalized space, including fs_LR surface space and standard volumetric space as provided by the HCP minimally preprocessed release. Regional analyses were performed after mapping data to the corresponding cortical parcellations
Noise and artifact removal	The study used HCP minimally preprocessed and denoised fMRI data. Standard HCP preprocessing includes correction for motion and spatial distortions, alignment across modalities, and removal of structured noise components according to the HCP preprocessing procedures. Additional nuisance handling and quality-control procedures, where applicable, are described in the Methods section.
Volume censoring	No additional volume censoring was applied beyond the preprocessing and quality-control procedures of the Human Connectome Project data release, unless otherwise specified in the Methods section.

Statistical modeling & inference

Model type and settings	Statistical analyses included correlation analyses, regression analyses, paired or one-sample tests where applicable, permutation tests, and Bonferroni correction for multiple comparisons. Model-based analyses were performed using the EI-MFM fitted to resting-state FC and FCD, followed by in silico perturbation and sensitivity analyses.
Effect(s) tested	The main effects tested were differences between resting-state and working-memory functional patterns, perturbation-related changes in simulated FC similarity to empirical resting-state and working-memory FC, associations between DLPFC functional measures and FP/DM network measures, and receptor-enriched functional differences between resting state and working memory.
Specify type of analysis: ☐ Whole brain ☐ ROI-based ☒ Both	
Anatomical location(s)	Whole-brain and ROI-level analyses were performed using DK68, Schaefer100, and Glasser parcellations where applicable, with ROI analyses focused on bilateral DLPFC and FP/DM network regions.
Statistic type for inference (See Eklund et al. 2016)	Inference was based on Pearson correlation, regression coefficients, test statistics from paired or one-sample tests where applicable, Cohen's (d_z) for perturbation-related effect sizes, and permutation-derived statistics. Exact statistical tests are described in the Methods and figure legends.
Correction	Multiple comparisons were corrected using Bonferroni correction where applicable. Permutation-based procedures were used for selected model-comparison, perturbation, and spatial specificity analyses as described in the Methods and Supplementary Information.

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	Functional connectivity was calculated using Pearson correlation between regional fMRI time series. Dynamic functional connectivity was estimated from time-resolved functional connectivity patterns and compared between empirical and simulated data. Structural connectivity from diffusion MRI was used to constrain the EI-MFM and to assess DLPFC-network structural associations. No effective connectivity analysis was performed.
Multivariate modeling and predictive analysis	EI-MFM simulations were fitted to empirical resting-state FC and FCD and evaluated using FC disagreement ($(1-r)$), FCD KS distance, and total cost. Perturbation analyses tested changes in simulated FC similarity to empirical resting-state and working-memory FC. REACT two-step multivariate regression was used for receptor-enriched functional analyses.