

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
<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. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P 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 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	No custom software was used in data collection.
Data analysis	All statistical analyses and raw figures were generated using R (version 4.3.1), with the following open source packages: car (version 3.1-2), dplyr (version 1.1.2), ggplot2 (version 3.5.1), mediation (version 4.5.0), nlme (version 3.1-162), ppcor (version 1.1), sjPlot (version 2.8.15). No custom code or packages were used in the statistical analyses.

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](#)

Deidentified data from HABS can be requested online (<https://habs.mgh.harvard.edu/researchers/request-data/>). Details of the request process have been published previously (Dagley et al., Neuroimage 2017) and include the completion of an online data request form and acceptance of the terms of a data use

agreement. The approval process is primarily designed to ensure that the proposed purpose of the data request is consistent with the data use agreement and would not pose a risk to the HABS participants. The most important restriction of use is to not attempt to re-identify the participants in any way. Other requirements include agreement to abide by human subject research policies, only using the data for the project detailed in the data request (separate requests can be made for additional projects), no commercialization of the data, and no marketing or fundraising with the data.

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	Harvard Aging Brain Study (HABS) aimed to have a balanced representation of both biological sex (self-report). In the aging population, the proportion of women compared to men is increased. The recruited cohort is comprised of 59% female participants. Sex was adjusted for in all statistical models. Baseline participant characteristic by sex were summarized in Extended Data Table 4. Sex-based analysis will be pursued in a future project.
Reporting on race, ethnicity, or other socially relevant groupings	HABS cohort consists of highly educated and predominantly (83%) non-Hispanic white individuals. We acknowledged in the manuscript and that future studies in more diverse cohorts (including race/ethnicity and education) are needed to improve generalizability of our findings.
Population characteristics	HABS is a community cohort of individuals aged 50 to 90 who were cognitively unimpaired at baseline and followed longitudinally. At study entry, all participants had a global Clinical Dementia Rating (CDR) of 0, education-adjusted Mini-Mental State Examination (MMSE) score of 27 or greater, and Logical Memory IIa Delayed Recall performance within the normal range. Exclusion criteria included a modified Hachinski ischemic score greater than 4, and a history of stroke with persistent neurological deficits.
Recruitment	Participants were recruited from several sources in order to maximize the ethnic, socio-economical and educational diversity of our cohort: 1. Advertisements posted in local community senior centers. 2. The Harvard Cooperative Program on Aging Newsletter, which is distributed to 8,000 older individuals of diverse ethnic backgrounds and the Harvard Medical School Division on Aging Volunteer Roster, which has over 1,500 local older individuals who are interested in participating in research. 3. Print advertisements in "Over Fifty" a local newspaper for older individuals, which highlights research opportunities, and the "Banner", a local newspaper that is focused on the African American population in the suburbs of Boston. 4. The Massachusetts Alzheimer's Disease Research Center (MADRC) database includes a large number of older subjects who have previously participated in cognitive studies and who have indicated the desire to be contacted for future studies. 5. The Alzheimer's Association's TrialMatch Website and Massachusetts Alzheimer's Association's Support Group Network for Research Opportunities.
Ethics oversight	The Mass General Brigham Institutional Review Board (IRB) approved HABS protocol and procedures, and all participants signed a written informed consent prior to the completion of any study procedures. Participants received compensation of between \$50 to \$200 per study visit, commensurate to the time and potential risks/discomfort involved, as approved by the IRB.

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	We included all participants (N=296) with baseline physical activity measurement, amyloid PET imaging, and at least 2 longitudinal cognitive assessments. Extended Data Figure 5 illustrates that out of 348 eligible HABS participants at baseline, 50 were excluded from the current study due to missing data. Importantly, the included group did not differ in demographics or baseline cognition (Extended Data Table 3). Subsets of participants were used in the longitudinal amyloid PET (N=241) and tau PET (N=172) analyses. Data collected from April 2010 through February 2025 were included in the analyses.
Data exclusions	For pedometer data, we used previously published cutoffs for pedometer data quality, and excluded days that registered less than 100 or greater than 30000 steps. We included participants with at least 4 days of recorded activity within these cutoffs to calculate mean steps per day as the primary measure of physical activity.
Replication	We conducted sensitivity analyses to examine the robustness of our primary findings, as described in the manuscript. Direct replication was not pursued as we are not aware of other available data in cognitively unimpaired older adults that included pedometer-measured physical activity and longitudinal amyloid/tau PET imaging and cognitive assessments.
Randomization	Participants were not randomized due to the nature of HABS as an observational cohort study. In our statistical models, we adjusted for age,

Randomization	sex, education, and (in longitudinal amyloid models only) APOE ε4 carrier status. There were no significant APOE ε4 effects on longitudinal tau or cognition; therefore, APOE was removed from these models to include 3 participants with missing genotype data.
Blinding	Study investigators were blinded to the Alzheimer's disease biomarkers, genotype and cognitive status of participants during data collection.

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	<i>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.</i>
Novel plant genotypes	<i>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.</i>
Authentication	<i>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.</i>

Magnetic resonance imaging

Experimental design

Design type	Structural T1 MRI was used in this study primarily for the purpose of processing and analysis of amyloid and tau PET data. Baseline total cortical grey matter volume and intracranial volume-adjusted hippocampal volume were included in Extended Data Table 2 to illustrate that there were no significant differences across physical activity groups.
Design specifications	<i>Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.</i>
Behavioral performance measures	<i>State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).</i>

Acquisition

Imaging type(s)	Structural T1 MRI
Field strength	3T
Sequence & imaging parameters	Structural T1-weighted volumetric magnetization-prepared, rapid acquisition gradient echo (MPRAGE) scans were collected using the following parameters: repetition time = 2300ms, echo time = 2.98ms, inversion time = 900ms, flip angle = 9°, 1x1x1.2mm resolution, 0 acceleration
Area of acquisition	Whole brain
Diffusion MRI	☐ Used ☒ Not used

Preprocessing

Preprocessing software	To use the structural T1 MRI for PET data processing, region of interest (ROI) labeling was implemented using FreeSurfer v6.0 (http://surfer.nmr.mgh.harvard.edu/). Cortical region of interest measurements were made using the Desikan-Killiany atlas (https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation). Subcortical region of interest measurements were made using the Freesurfer aseg atlas (https://surfer.nmr.mgh.harvard.edu/ftp/articles/fischl02-labeling.pdf)
Normalization	If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.
Normalization template	Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.
Noise and artifact removal	Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).
Volume censoring	Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings	Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).
Effect(s) tested	Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.
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	Involvement in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis
Functional and/or effective connectivity	Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).
Graph analysis	Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).
Multivariate modeling and predictive analysis	Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.