

Reporting Summary

Nature Research 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 Research 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

Data 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 Research [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 list of figures that have associated raw data
- A description of any restrictions on data availability

Field-specific reporting

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The study included the DABNI and SPIN cohorts. The DABNI cohort was based on a population-based health plan and all available plasma samples were analyzed in this study. Sample size was calculated based on previous biomarker studies that demonstrated enough statistical power. In particular, our previous study with smaller sample size (Fortea et al, Lancet Neurol 2018) showed adequate power.
Data exclusions	In 22 cases MRI studies were excluded due to movement artifacts or segmentation errors of the Freesurfer. In 4 cases FDG-PET images were excluded due to excessive time between MRI and PET.
Replication	The measurement of p-tau concentrations was performed using a robust immunoassay. All samples were measured at the first attempt.
Randomization	Randomization was not applicable as this study did not include any intervention.
Blinding	The technicians who measured concentrations of p-tau181 in plasma were blinded to the biomarker and clinical data. Investigators who removed imaging studies due to artifacts were blinded to clinical data. Blinding was not possible when obtaining clinical data.

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	Included in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

Methods

n/a	Included in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input type="checkbox"/>	<input checked="" type="checkbox"/> MRI-based neuroimaging

Antibodies

Antibodies used	AT270 mouse monoclonal antibody (MN1050; Invitrogen, Waltham, MA, USA) as capture antibody. Anti-tau mouse monoclonal antibody Tau12 (806502; BioLegend, San Diego, CA, USA) as the detector. It is not possible to report dilutions. Full details can be found in Karikari et al. Lancet Neurol 2020; 19: 422–33
Validation	Full validation of the assay was described in Karikari et al. Lancet Neurol 2020; 19: 422–33

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	Adults with DS (age range 18-71) and euploid controls (age range 21-55). Both genders were included.
Recruitment	Adults with DS were recruited from a population-based health plan designed to screen for AD dementia, which includes yearly neurological and neuropsychological assessments. We acknowledge that this study may be biased towards subjects with DS and mild/moderate disability as subjects with profound intellectual disability have difficulties in access to research studies. Those individuals interested in research studies are included in the longitudinal cohort. We recruited the euploid controls from the Sant Pau Initiative on Neurodegeneration cohort.
Ethics oversight	The study was approved by the Sant Pau Ethics Committee, following the standards for medical research in humans recommended by the Declaration of Helsinki.

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

Magnetic resonance imaging

Experimental design

Design type	The study included structural MRI measurements.
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Design specifications

Behavioral performance measures

Acquisition

Imaging type(s)

Field strength

Sequence & imaging parameters

Area of acquisition

Diffusion MRI Used Not used

Preprocessing

Preprocessing software

Normalization

Normalization template

Noise and artifact removal

Volume censoring

Statistical modeling & inference

Model type and settings

Effect(s) tested

Specify type of analysis: Whole brain ROI-based Both

Statistic type for inference (See [Eklund et al. 2016](#))

Correction

Models & analysis

n/a | Involved in the study

Functional and/or effective connectivity

Graph analysis

Multivariate modeling or predictive analysis

Multivariate modeling and predictive analysis