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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Our GUI code (https://github.com/petmri/ROCKETSHIP) running with Matlab R2013a was used for DCE-MRI analyses. We also used FreeSurfer (v5.3.0) software package for regional brain volume analyses.
Data analysis	Statistical analyses were conducted with a commercial statistical software package -- SPSS (IBM). No custom software was used.

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/reviewers upon request. 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

A full data availability statement is included in the manuscript. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences

Study design

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

Sample size	We expected a sample size of n>150 to be sufficient to detect significant blood-brain barrier marker effects on cognitive status based on observed effect sizes reported in prior studies (see Montagne et al., Neuron). Consistent with previous studies, we observed large effect sizes for our primary analyses in the present study (up to $\eta 2 > .32$, indicating >99% power to detect significant differences, $\lambda = 47.04$, for an $\alpha = .05$ in a post-hoc power analysis). On the lowest end, we observed a smallest effect size of $\eta 2 = .07$, indicating 90% power, $\lambda = 10.53$. For DCE-MRI ktrans markers of blood-brain barrier breakdown, we observed similar effect sizes, indicating >99% power ($\lambda = 22.89$) to detect significant differences for large effects $\eta 2 > .32$ with 73 participants, and ~70% power ($\lambda = 6.57$) for smaller effect sizes, $\eta 2 = .09$. Post-hoc power analyses were conducted using G*Power.
Data exclusions	All continuous variables were screened for outliers (+/- 3 SDs from mean were removed based on pre-established criteria) and evaluated for departures from normality through quantitative examination of skewness and kurtosis, as well as visual inspection of frequency distributions. Further, as stated in our Inclusion / Exclusion critera (see Online Methods), we excluded participants with any history of psychiatric or neurological disease, or taking any medications, that might better account for observed cognitive impairment. The text from Online Methods is provided below: Included participants (≥45 years of age) with neuropsychologically-confirmed no cognitive dysfunction and/or early cognitive dysfunction had no current or prior history of any neurological or psychiatric conditions that might better account for any observed cognitive impairment, including organ failure, brain tumors, epilepsy, hydrocephalus, schizophrenia, major depression. Participants were stratified based on CSF analysis as either Aβ-positive (Aβ+, <190 pg/mL) or Aβ-negative (Aβ-, >190 pg/mL), or pTau-positive (pTau+, >78 pg/mL) or pTau-negative (pTau-, <78 pg/mL), using the accepted cutoff values. Participants were excluded if they were diagnosed with vascular cognitive impairment or vascular dementia. These clinical diagnoses were conducted by neurologists and the criteria whether the patient 1) had a known vascular brain injury and 2) the clinician judged that the vascular brain injury played a role in their cognitive impairment, and/or pattern and course of symptoms. In addition to clinical diagnosis, presence of vascular lesions was confirmed by moderate-to-severe white matter changes and lacunar infarcts by fluid-attenuated inversion recovery (FLAIR) MRI and/or subcortical microbleeds by T2*-weighted MRI. Participants were also excluded if they were diagnosed with Parkinson's disease, Lewy body dementia or frontotemporal dementia. History of a single stroke or transient ischemic attack was not an exclusion unless it was related to symptomatic onset of cognitive impairment. Participants also did not have current contraindications to MRI and were not currently using medications that might better account for any observed cognitive impairment.
Replication	All study findings regarding CSF biomarkers analyses were replicated in two independent samples, as shown in the supplemental figures. The DCE-MRI findings were conducted only at one site due to limited availability of this method at the time of the current study--future studies will examine DCE-MRI across sites.
Randomization	We did not randomize since this was not an experimental design.
Blinding	All CSF assays and DCE-MRI scans were conducted by investigators who were blinded to participant clinical diagnostic status.

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☒	☐ Unique materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Research animals
☐	☒ Human research participants

Antibodies

Antibodies used	For quantitative western blot assay, the following primary antibody was used: PDGFRbeta polyclonal goat IgG antibody (R&D Systems Catalog #AF1042, Lot #GOV0418041). Membranes were incubated with 1 ug/mL of antibody overnight at room temperature, then incubated with donkey anti-goat IgG secondary antibody (Invitrogen, Cat #A15999, Lot #44-33-100114,

1:5000 dilution) for 1 hour at room temperature.

Validation

Recombinant human PDGFRbeta protein (R&D Systems Catalog #385-PR/CF, Lot #AMO0714072) was used as a positive control in validating the antibodies. Consistently, the manufacture's website specifies this antibody exhibits approximately 35% cross-reactivity with recombinant human PDGFRbeta.

Human research participants

Policy information about studies involving human research participants

Population characteristics

We studied 161 participants with clinical dementia ratings of 0 (n=82), 0.5 (n=63), or 1 (n=16), who exhibited no cognitive domain impairment (n=83), one impaired domain (n=39) or two or more impaired domains (n=39). Relevant covariates (means +/- standard deviations) included age (72.3 +/- 9.6 years), sex (51.6% male), education (15.5 +/- 9.6 years) and APOE4 carrier status (44.5%).

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ Magnetic resonance imaging

Magnetic resonance imaging

Experimental design

Design type	Resting state
Design specifications	N/A
Behavioral performance measures	N/A

Acquisition

Imaging type(s)	Dynamic Contrast-Enhanced (DCE)-MRI
Field strength	3T
Sequence & imaging parameters	From Online Methods: Anatomical coronal spin echo T2-weighted scans were first obtained through the hippocampi (TR/TE 1550/97.15 ms, NEX = 1, slice thickness 5 mm with no gap, FOV = 188 x 180 mm, matrix size = 384 x 384). Baseline coronal T1-weighted maps were then acquired using a T1-weighted 3D spoiled gradient echo (SPGR) pulse sequence and variable flip angle method using flip angles of 2°, 5° and 10°. Coronal dynamic contrast-enhanced (DCE)-MRI covering the hippocampi and temporal lobes were acquired using a T1-weighted 3D SPGR pulse sequence (FA = 15°, TR/TE = 8.29/3.09 ms, NEX = 1, slice thickness 5 mm with no gap, FOV 188 x 180 mm, matrix size 160 x 160, voxel size was 0.625 x 0.625 x 5 mm3). This sequence was repeated for a total of 16 min with an approximate time resolution of 15.4 s. Gadolinium-based CA, Gadobenate dimeglumine (MultiHance®, Bracco, Princeton, New Jersey) or Gadoterate meglumine (Dotarem®, Guerbet, France) (0.05 mmol/kg) was administered intravenously into the antecubital vein using a power injector, at a rate of 3 mL/s followed by a 25 mL saline flush, 30 s into the DCE scan.
Area of acquisition	Scan was coronal with slices covering hippocampi, temporal lobes and other in plane regions. These regions were chosen due to their importance in aging, cognitive decline, Alzheimer's disease, and prior studies of blood-brain barrier dysfunction in older adults.

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software

From Online Methods:
- Blood-brain barrier permeability: Post-processing analysis was performed using Rocketship71 running with Matlab. The arterial input function (AIF), which was extracted from a region-of-interest (ROI) positioned at the internal carotid artery, was fitted with a bi-exponential function prior to fitting with Patlak model72. The Patlak linearized regression mathematical analysis was used to generate the BBB permeability Ktrans maps8,71,72 with high spatial and temporal resolutions allowing not only simultaneous measurements of the regional BBB permeability in different white (WM) and gray matter (GM) regions, but also accurate calculations of the Ktrans values in anatomical regions as small as the subdivisions of the hippocampus. We determined in each individual AIF from the internal carotid artery.
- Volumetric analysis: Hippocampus (HC) and parahippocampus (PHC) morphometry were performed using the FreeSurfer (v5.3.0) software package73, which is documented and freely available online (http://surfer.nmr.mgh.harvard.edu/). In brief, HC and PHC gyri were segmented using the included FreeSurfer Desikan-Killiany and subcortical atlases74,75. Then, regional volumes (mm3) were derived accordingly. The technical details of this procedure are described in previous publications76–79. Data processing was performed using the Laboratory of Neuro Imaging (LONI) pipeline system (http://pipeline.loni.usc.edu)80–84.

Normalization	N/A
Normalization template	N/A
Noise and artifact removal	Motion correction (for DCE-MRI) was applied using ImageJ's Stack Reg - Rigid Body plugin.
Volume censoring	N/A

Statistical modeling & inference

Model type and settings	N/A
Effect(s) tested	N/A

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

Anatomical location(s)	The regional BBB Ktrans permeability were measured in 13 different GM ROIs including the hippocampi [HC] and their subfields (i.e., CA1, CA3, and dentate gyrus [DG]), parahippocampus [PHC], caudate nucleus [Caud], superior frontal cortical gyri [SFG Cx], inferior temporal cortical gyri [ITG Cx], thalamus [Thal], and striatum [Str] and WM ROIs including subcortical frontal white matter fibers [SubP WM fibers], corpus callosum (CC), and internal capsule (IC). Regions were chosen to cover a variety of brain regions and tissue compartments (e.g., cortical white matter, subcortical white matter, cortical grey matter, subcortical grey matter, and limbic areas of special focus--in this case the hippocampus and medial temporal lobes). The regional brain volumes were measured in HC and PHC gyri.
Statistic type for inference (See Eklund et al. 2016)	We did not conduct a voxel-level analysis.
Correction	We did not conduct a voxel-level analysis.

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis