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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	Paravision 6.0 software; PMOD, version 3.908, PMOD Technologies LLC, Zürich, Switzerland; SPM version 12, http://www.fil.ion.ucl.ac.uk/spm software package; MATLAB version 7.4 (R2021a) signal analyzer toolbox and functions; ZEN Blue 2.1 image acquisition software (Carl Zeiss); Photoshop (Adobe, 2020, 23.0.2 release); ImageJ software (Image J 1.52i); IBM SPSS Statistics, Version 26; Waxholm rat brain atlas package (Version 2); Amira Software (version 6.5.0); QuickBundle algorithm (Python 3.7.3); VisIt (3.0.2).
Data analysis	Code availability: The rOMT code used for analysis of the DCE-MRI data is available https://zenodo.org/record/5809635#.YczwqS2ZNBw. Custom codes used for pre-processing of the DCE-MRI data sets for glymphatic analysis are available at https://zenodo.org/record/5809482#.YczwgC2ZNBw.

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

Statistical source data files depicting the quantification values mentioned in the text or plotted in graphs shown in Figs. 1, 2 and Extended Data Figs. 3, 5 and 6 are available in the online version of this paper. The rOMT processed speed maps and Péclet maps datasets generated from WT and rTg-DI and analyzed in the current study are available at https://zenodo.org/record/5809664#.Yczwyy2ZNBw.

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

Sample sizes were chosen on the basis of previously published brain morphometry experiments in rTg-DI and WT rats (Lee et al., J Cereb Blood Flow Metab. 2021 41:1103) and rodent MRI based glymphatic experiments (Nygaard Mortensen et al., J Neuroscience 39:6365; Xue et al., 2020 Sci Rep 10: 14592). Neither a priori nor a post hoc power analysis was conducted to formally determine or justify sample size due to the unknown effect size of the impact of evolving cerebral amyloid angiopathy pathology of the different age cohorts when planning the current study. After all the modelings, the least square (marginal) mean difference (and 95% CI) of the outcomes was calculated as the effect size estimate, which would be informative in the design of a future study in which the sample size needs to be directly calculated based on a target statistical power (e.g., 80%) and significance level (e.g., 0.05) to detect a prespecified effect size

Data exclusions

All the statistical analyses were 'complete data analysis'. No data were excluded.

Replication

Number of reliable reproductions of each experimental finding is stated in each Figure legend. Unless stated otherwise, main experimental findings were replicated at least once.

Randomization

Reported in Method section. No randomization was performed. Covariates (strain type, animal age) were adjusted in the regression models.

Blinding

Reported in the Method section. Experimenters were blinded to the identity of experimental groups from the time of euthanasia until the end of data collection and analysis for all the independent experiments.

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
☒	☐	Human research participants
☒	☐	Clinical data
☒	☐	Dual use research of concern

Methods

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

Antibodies

Antibodies used

Rabbit polyclonal antibody to collagen IV to detect cerebral blood vessels (1:250, SD2365885, Invitrogen, Carlsbad, CA), goat polyclonal antibody to glial fibrillary acidic protein (GFAP, 1:250, ab53554, Abcam, Cambridge, MA) to detect astrocytes, goat antibody to ionized calcium-binding adapter molecule 1 (Iba-1, 1:250, NB100-1028, Novus Biologicals, Centennial, CO) to detect microglia or rabbit polyclonal antibody to AQP4 (1:250, Novus Biologicals Catalog # NBP1-87679, Novus Biologicals, LLC 10730E, Briarwood Avenue, Building IV, Centennial CO 80112). Alexa Fluor 488 donkey anti-rabbit IgG(H+L) (1:1000), Donkey polyclonal secondary antibody, Catalog # A21206, Invitrogen. Alexa Fluor 594 donkey anti-rabbit IgG(H+L) (1:1000), Donkey polyclonal secondary antibody, Catalog # A21207, Invitrogen.

Validation

Each antibody was validated for the rat tissue and immunohistochemistry, by the correspondent manufacturer. The usage was described in full detail the methods section of the manuscript.
Immunohistochemistry:
Antigen retrieval was performed by incubation with proteinase K (0.2 mg/ml) for 5 min at 22o C. The treated tissue sections were then blocked in Superblock blocking buffer (cat. #37518, ThermoFisher, Bedford, MA) containing 0.3% Triton X-100 at room temperature for 30 min and incubated with individual primary antibodies at the following dilutions overnight: rabbit polyclonal antibody to collagen IV to detect cerebral blood vessels (1:250, SD2365885, Invitrogen, Carlsbad, CA), goat polyclonal antibody to glial fibrillary acidic protein (GFAP, 1:250, ab53554, Abcam, Cambridge, MA) to detect astrocytes, goat antibody to ionized calcium-binding adapter molecule 1 (Iba-1, 1:250, NB100-1028, Novus Biologicals, Centennial, CO) to detect microglia or rabbit polyclonal

antibody to AQP4 (1:250, Novus Biologicals). Primary antibodies were detected with Alexa Fluorescent 594- or 488-conjugated secondary antibodies (1:1000). Deposited fibrillar amyloid was detected with Amylo-Glo (TR-300-AG, Biosensis Inc., Thebarton, South Australia), as described by the manufacturer. Primary antibodies were detected with Alexa Fluorescent 594- or 488-conjugated secondary antibodies (1:1000). Deposited fibrillar amyloid was detected with Amylo-Glo (TR-300-AG, Biosensis Inc., Thebarton, South Australia), as described by the manufacturer.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Female hemizygous rTg-DI CAA type 1 rat line (Sprague Dawley (SD) background), which expresses human Swedish/Dutch/Iowa vasculotropic mutant amyloid-beta precursor protein (AβPP) under control of the neuronal Thy1.2 promoter and produces chimeric Dutch/Iowa CAA mutant Aβ peptides in brain. Separate cohorts of in-house bred female rTg-DI rats and non-transgenic female littermates (serving as WT controls) were used at 3-months (M), 6M and 12M of age. A separate series of 4-month-old female SD rats were purchased from Charles River (Charles River Laboratories International, Inc., NC, USA) and used for the lymph node studies.
Wild animals	No wild animals were used in the study.
Field-collected samples	No field collected samples were used in the study.
Ethics oversight	All the animal work was approved by the local institutional animal care and use committees at University of Rhode Island, USA and Yale University, New Haven, USA.

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	Observational, cross-sectional design.
Design specifications	N/A
Behavioral performance measures	N/A

Acquisition

Imaging type(s)	Structural and contrast enhanced dynamic sequences
Field strength	9.4T
Sequence & imaging parameters	Whole brain imaging: A single flip angle spoiled gradient echo (SPGR) sequence was used to acquire 3D PDW MRIs: (repetition time (TR) = 50ms, echo time (TE) = 4ms, flip angle (FA) = 7°, Average = 1, field of view (FOV) = 30x30x15mm, spatial resolution = 0.234x0.234x0.234mm, scan time = 6mins50s. DCE-MRI images were acquired using a single flip angle spoiled gradient echo (SPGR) sequence: TR=15ms, TE=4ms, FA=15°, Average = 2, FOV = 32x30x30mm, the spatial resolution= 0.302x0.300x0.300mm, acquisition time/scan = 5mins). Lymph nodes on the neck: A set of 3D T1 weighted scans were acquired dynamically before and after contrast administration using a single flip angle spoiled gradient echo (SPGR) sequence: TR=15ms, TE=4ms, FA=15°, Average = 1, FOV = 30x30x30mm, Matrix = 150x150x150 the spatial resolution= 0.200x0.200x0.200mm, acquisition time/scan = 5mins 38s.
Area of acquisition	For whole brain data the whole head of the rat was in the field-of-view. For the lymph node data part of the brain, spine was in the field of view including the superficial and deep cervical lymph nodes.

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	Custom codes used for pre-processing of the DCE-MRI data sets for glymphatic analysis are available at https://zenodo.org/record/5809482#.YczwgC2ZNBw.
Normalization	For the lymph node analysis the parametric DCE-MRI data acquired (%signal from baseline) was normalized to the signal in the cerebrospinal fluid compartment outlined manually using PMOD software.
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	The time-signal curves extracted from DCE-MRI data acquired on the neck (the cervical lymph nodes) underwent noise cancellation using a 2-time step moving average procedure.
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)	Hippocampus and Cerebellum were selected based 1) on known information on regional amyloid beta deposition in the CAA rTg-DI rat and 2) regions in which glymphatic transport can be assessed based on the dynamic contrast enhanced MRI method.
Statistic type for inference (See Eklund et al. 2016)	N/A
Correction	N/A

Models & analysis

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