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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	All in vivo mouse data was taken with a custom built 2-photon microscope, Biospec 70/30, Bruker and custom built laser speckle setup. Histology sections have been analyzed by a Zeiss Examiner.D1 AXIO, behavioral data was collected using ViewerIII from BIOBSERVE (Germany), scanimage (Vidrio Tech.), and flow cytometry data was taken on a Guava easyCyte Flow Cytometer (EMD Millipore Corporation).
Data analysis	Data has been analyzed using MATLAB (The MathWorks, Inc), ImageJ (NIH), FlowJo (LLC), Gen5 (BioTeck), Imaris 8 (Bitplane), R 3.5.1 (The R Foundation), G*Power, and Prism7 (GraphPad).

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

The data reported in this manuscript are archived at https://doi.org/10.7298/9PR3-D773.

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 ☐ Ecological, evolutionary & environmental 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	In most cases, sample sizes for comparisons across groups were determined from power analysis calculations. The data on capillary stall incidence in Fig. 1c and d in APP/PS1 vs. wt mice is significantly overpowered, as this data includes experiments that yielded the initial discovery of elevated capillary stalling in APP/PS1 mice as well as all subsequent baseline data. For measurements of the cellular cause of capillary stalls (Fig. 2a and b), we anticipated finding ~20 stalls per mouse (~2% of 1,000 characterized capillaries). Assuming each possible stall cause was equally likely and wanting to resolve these percentages to +/-10% at a 95% confidence interval, then binomial statistics implied the need for ~100 capillary stalls, or about five mice. For 2PEF measurements of penetrating arteriole blood flow (Fig. 3b and c), ASL-MRI measurements of cortical perfusion (Fig. 3d and e), and behavioral experiments (Fig. 4) comparing APP/PS1 and wt mice before and after antibody treatment, we used a matched-pairs study design, estimates of measurement variability from published and preliminary data, and estimates of minimal biologically-relevant effect size to determine minimum group sizes using G*Power. This yielded minimum group sizes of 5 mice for 2PEF measurements of penetrating arteriole blood flow and 10 mice for ASL-MRI and behavioral experiments. In subsequent experiments with other mouse models and other treatments we continued using these group sizes.
Data exclusions	Animals were excluded from further study if the clarity of the imaging window was insufficient for 2PEF imaging. All animals included in our analysis of the frequency of capillary stalling had at least 800 capillary segments scored as flowing or stalled. Animals with fewer characterized capillaries were excluded.
Replication	Experiments to determine the fraction of capillaries stalled and the cell type responsible for stalls have been conducted by several different experimenters across different microscopes, and even different laboratories. The manual scoring of capillaries as flowing or stalled was performed with the researcher blinded to the genotype and treatment status of the animal. Blood flow experiments (line scans, ALS-MRI, and Laser Speckle Imaging) were conducted and analyzed with the experimenter blinded to the treatment and genotype of the animals. Behavior experiments in APP/PS1 mice were done twice with two independent groups with similar results. The experimenter was blinded to the treatment and animal genotype. In addition to the automatic results we obtained, a blinded experimenter independently scored mouse behavior manually. All manual and automated analysis results concurred.
Randomization	Animals were matched by age and similar numbers of male and female animals were used in nearly all comparisons. Controls were litter mates. Mice were randomly selected for treatment or control groups. All treatments were given by a different researcher where possible to ensure blinding.
Blinding	During experiments comparing the impact of treatments, the experimenter was blinded to the treatment and genotype of the mouse. All analysis was conducted with the experimenter blinded to the genotype, treatment, and time point of the data. Image processing was done also blinded to genotype and treatment, if possible (note that AD mouse models can be readily distinguished at some ages by presence of amyloid plaques).

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

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

Antibodies

Antibodies used

Antibodies:
Antibodies were validated in preliminary experiments involving serial dilutions (Ly6G). The final concentration used for each antibody is:
Ly6G (for in vivo imaging): clone 1A8, Alexa 488 labeled, Catalog No.560257, BD Biosciences
Ly6G (for in vivo blocking of adherence):clone 1A8, FITC labeled, Catalog No.551460, BD Biosciences
LFA-1: clone M17/4, CD11b, Catalog No. 550528 BD Biosciences
Iso-Ctr: clone IgG2a, k, Catalog No. 553387, BD Biosciences

in vivo imaging:
Ly6G antibodies (0.1 mg/kg), i.v. injection

Blocking adherence or causing depletion:
acute experiments: Ly6G or isotype control antibodies (4 mg/kg), i.p. injection
chronic experiments: Ly6G or isotype control antibodies (2 mg/kg), i.p. injection
LFA-1 experiments: LFA-1 or saline control injection (4 mg/kg), retro-orbital injection (blood flow expts.) or i.p. injection (behavioral expts.)

Flow cytometry:
Chronic experiments: 24h after Ly6G or control injection (4 mg/kg), i.p. injection
Neutrophil determination: anti-CD45 (Catalog No.5560695, BD Bioscience), anti-CD11b (Catalog No.561690, BD Bioscience) and anti-Ly6G (551460, BD Bioscience).

Histology:
Chronic treatment experiment: Sections have been incubated with 1% Thioflavin-S (T1892, Sigma) for 10 min at room temperature and washed twice with 80% ethanol for 2 min and counter-stained with and 1:5000 DAPI (Sigma)

Validation

Ly6G (for in vivo imaging) has been validated for example in: Journal of Experimental Medicine Apr 2012, 209 (4) 819-835; DOI: 10.1084/jem.20112322
Ly6G (for in vivo blocking of adherence):clone 1A8, FITC labeled, BD Biosciences, has been used widely for flow cytometry and in vivo imaging: Journal of Immunology Research, 2018, (1), (2018)
LFA-1: clone M17/4 has been used for in vivo studies and behavioral studies for example in Nature Medicine volume 21, pages 880–886 (2015)
CD45- widely used and validated references on the BD Biosciences web-page
CD11b widely used and validated references on the BD Biosciences web-page
Iso-Ctr: clone IgG2a, k, BD Biosciences targets an unknown sequence

Animals and other organisms

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

Laboratory animals

Heterozygous APP/PS1 mice have been used in this study (The Jackson Laboratory (Bar Harbor, ME)). These mice over express the amyloid precurser protein (APP) (Mo/HuAPP695swe) together with the human muted presenilin 1 (PS1-dE9) gene driven under the prion (PrP) promoter.
As a second mouse model we used TgCRND8 that over expresses the APP gene 695 (KM670/671NL+V717F) under the PrP promoter.
As a third mouse model we used 5xFAD mice (The Jackson Laboratory) that overexpress APP with the following mutations (Swedish (K670N, M671L), Florida (I716V), and London (V717I)) along with mutated PS1 with the following mutations (M146L and L286V), under the Thy1 promoter.
12-90 weeks old male and female (APP/PS1 n=28 and wild-type n=12) mice have been used for the analyses done in figure 1.
Antibody injected animals to determine blood flow and number of stalls after Ly6G treatment have been male and female APP/PS1 mice 3-4 month: APP/PS1, α-Ly6G n=5; APP/PS1 Iso-Ctl, n=5;and wt α-Ly6G, n=5; 11-14 month: APP/PS1, α-Ly6G n=3; and APP/PS1 Iso-Ctl, n=3)
ALS-MRI has been performed with 7-9 month old male and female APP/PS1 mice (APP/PS1, α-Ly6G n=10; APP/PS1 Iso-Ctl, n=10; and wt α-Ly6G, n=10)
Capillary stalls and flow in 5xFAD mice: 5-7 months of age, wt α-Ly6G: 3 mice; 5xFAD Iso-Ctr: 3 mice,; and 5xFAD α-Ly6G: 3 mice.
Behavior experiments used 11 month old APP/PS1 male and female animals have been used (APP/PS1, α-Ly6G n=11; APP/PS1 Iso-Ctl, n=9; wt α-Ly6G, n=10; and wt Iso-Ctl, n=10). Brains for the ELISA and histology experiments has been from the the ones

	from behavioral experiments For behavior experiments animal of both sexes got randomly distributed into experimental group, APP/PS1 mice and α-LFA-1, animals were 11-13 months of age (APP/PS1, α-LFA-1 n=10; APP/PS1 Iso-Ctl, n=10; wt α-LFA-1, n=7; and wt Iso-Ctl, n=8). For behavior experiments animal of both sexes got randomly distributed into experimental group, 5xFAD mice and α-Ly6G, animals were 5-6 months of age (5xFAD, α-Ly6G n=8; 5xFAD Iso-Ctl, n=8; and wt α-Ly6G, n=10).
Wild animals	We did not use wild animals.
Field-collected samples	We had no field collected samples.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Blood from APP/PS1 and wt mice was collected from the submandibular vein and mixed with 1x RBC lysis buffer (00-4300-54, ThermoFisher Scientific). After incubation at room temperature for 10 min, the sample was centrifuged at 500 g for 5 min and the supernatant was removed. The cell pellet was re-suspended in 500 uL of Hank's balanced salt solution (HBSS) supplemented with 1% bovine serum albumin (BSA) and centrifuged again; this washing procedure was repeated 3 times. Following isolation, neutrophils were re-suspended at a density of 107 cells per ml in HBSS supplemented with 1% BSA. The cell samples were labeled at room temperature for 45 min with the following anti-mouse antibodies: anti-CD45 (560695, BD Bioscience), anti-CD11b (557686, BD Bioscience) and anti-Ly6G (551460, BD Bioscience). After washing the samples with HBSS samples have been re-suspended in FACS buffer (1% BSA and 2mM EDTA in PBS), the remaining leukocytes were analyzed by flow cytometry
Instrument	Guava easyCyte Flow Cytometer (EMD Millipore Corporation)
Software	Data were analyzed using FlowJo software (FlowJo LLC)
Cell population abundance	In a first step dead cells that have a higher side scatter and lower forward scatter than living cells were gated based on FSC versus SSC to analyze viable cells. Then CD45 was used to gate all Leukocytes and CD11b with Ly6G to determine the neutrophils population.
Gating strategy	Relevant example is shown in Extended Data Fig. 7a

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	Arterial spin labeling and anatomical T2 imaging was used to measure blood flow and structure in APP/PS1 and wild-type mice before and 3-6 hr after Ly6G antibody or isotype control antibody treatment.
Design specifications	2 mice per day were imaged. Baseline measurements required a 40 min scan time. After about 48 h antibodies were i.p. injected and 3-6 h later animals were imaged for another 40 min. Mice age ranged from 6-9 month.
Behavioral performance measures	n/a

Acquisition

Imaging type(s)	Arterial spin labeling and T2 anatomical imaging
Field strength	7.0 Tesla
Sequence & imaging parameters	ASL imaging was based on a FAIR-RARE pulse sequence that labeled the inflowing blood by global inversion of the equilibrium magnetization. The inversion recovery data from the imaging slice are acquired after selective inversion of the slice and after inversion of both the slice and the surrounding tissue. The difference of the apparent R1 relaxation rate images then yields a measure of the CBF: Detail: Three averages of one axial slice were acquired with a field of view of 15 × 15 mm, spatial resolution of 0.23 × 0.23 × 2 mm3, echo time TE of 5.36 ms, effective TE of 26.84 ms, repeat time TR of 10 s, and a RARE factor of 36. T2 images:

Turbo-RARE anatomical images were acquired with the following parameters: 10 averages of 14 slices with the same field-of-view and orientation as the ASL images, resolution = 0.078 × 0.078 × 1 mm3, TE = 48 ms, TR = 2000 ms, and a RARE factor of 10

Area of acquisition

Anatomical localizer images were acquired to find the transversal slice at a location approximately corresponding to Bregma -0.94 mm

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software

For computation of rCBF, the Bruker ASL perfusion processing macro was used. It uses the model of Kober, et al., and includes steps to mask out the background and ventricles. The masked rCBF images were exported to Analyze format on the MRI console. Statistics has been finalized in PRISM.

F. Kober et al., High-resolution myocardial perfusion mapping in small animals in vivo by spin-labeling gradient-echo imaging. Magnetic resonance in medicine 51, 62-67 (2004).

Normalization

n/a

Normalization template

n/a

Noise and artifact removal

n/a

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

Our primary comparisons are between the baseline measurements for wild type and AD mouse models (t-test, as data were normally distributed), and a paired comparision of wt or AD mice before and after antibody treatment (paired t-test, data were normally distributed).

Effect(s) tested

Measured cerebral blood flow in the same mice before and after treatment. Secondary measure comparing blood flow in wt and AD mice.

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

Anatomical location(s)

The masked CBF images were exported to Analyze format on the MRI console. We then used the anatomical image to create a mask that outlined the entire cortical region,excluding the sinus, and averaged the CBF measurement across this region for each animal at each imaging time point. Analysis of ASL-MRI data was conducted blinded to animal genotype and treatment.

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

voxel-wise

Correction

n/a

Models & analysis

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