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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 *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	Sudan black for volumetric analysis and AT8 for imunohistochemisty were scanned using a Hamamatsu NanoZoomer microscope at 20x magnification. Plasma NFL concentration was measured with a Samoa HD analyzer (Quanterix). Immunoflorencent stains were scanned using Zeiss LSM 880 Confocal. Flow data were recorded by BD Symphony A3 or collected by FACSAria II. Single cell immune sequencing libraries were generated by 10X Genomics Chromium platform and sequencing was done by Illumina NovaSeq6000.
Data analysis	Imaging were analyzed and quantified using ImageJ and Imaris 9.7.0 software. Flow data were analyzed by flowJo V10. Statistical analyses for imaging, flow and behavior were done using GraphPad Prism7.0. Single Cell-deq data alignment, barcode assignment, and UMI counting with Cell Ranger (v6.1.1) were used for preparation of count matrices for gene expression library. For alignment, a custom mouse genome (GRCm38) containing human sequences for APOE, PSEN1, APP, MAPT genes was used as a reference. Barcodes in all samples that were considered to represent noise and low-quality cells were filtered out using knee-inflection strategy available in default Cell Ranger (v6.1.1) from 10x genomics. For downstream analysis, Seurat package (v4.0.4) was used, genes which express in less than three cells were additionally filtered from expression matrices. The mitochondrial gene fraction was calculated for every cell, and cells with a mitochondrial fraction more than highest confidence interval for scaled mitochondrial percentage were filtered out which results in removal of the cells with mitochondrial percentage more than 20%. Additionally, cut off with log10 (number of unique expressed genes) as 2.5 was used for removing the cells from both CD45-high and CD45-total parenchymal cells, and 2 was used as a threshold for the cells from meninges. Doublets have been excluded based on the co-expression of the canonical cell-type specific genes. Each sample was normalized using SCTransform function with mitochondrial content as a variable to regress out in a second non-regularized

linear regression. For integration aims, variable genes across the samples were identified by SelectIntegrationFeatures function with the number of features equal to 2000. Then the object was prepared for integration (PrepSCTIntegration function), the anchors were found (FindIntegrationAnchors function) and the samples were integrated into the whole object (IntegrateData function).

The principal component analysis was used for dimensionality reduction, and the first 20 principal components (PCs) were used further to generate uniform manifold approximation and projection (UMAP) dimensionality reduction by RunUMAP function. Clustering procedure was performed by FindNeighbors and FindClusters with a range of resolutions (from 0.2 to 1.0 with 0.2 as a step) and the first 20 PCs as input.

The object covering all cells has been subsetted into T-cell, microglia and myeloid specific sub-objects based on expression of canonical gene markers. Additionally, the T-cells object was split into CD4+ and CD8+ cells. Then, all objects passed through the iterative process of quality control with doublets removal and exclusion of the clusters which have no relevant markers and contained high mitochondrial content as well as poor coverage (all filters are object-specific).

Cell Ranger's vdj workflow (v6.1.1) was used for TCR data analysis. Non-canonical T cells (such as gamma-delta T cells and natural killer T cells) as well as T cells with inappropriate combinations of alpha/beta chains were removed. Then, all barcodes were assigned to two populations based on CD4 and CD8 gene expression. The Gini coefficient was calculated using the immunarch package (v0.6.6) in order to estimate the clonal diversity among samples.

Trajectory analysis was done using a slingshot container available at dynverse package (https://github.com/dynverse/dyno) with normalized count matrices with barcodes assigned to microglia as input data as well as cells assigned to CD8+ T cells.

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

Single cell immune sequencing sample and data information (Extended data table 1 and 3) and List of brain sample from AD patients information (Extended data table 2) can be found in the supplemental data. All source data, including sequencing reads and single-cell expression matrices and TCR sequencing data are available from the Gene Expression Omnibus (GEO) under accession code GSE221856. Code for preprocessing of single-cell RNA-sequencing and TCR bioinformatic analysis are available from the authors on request.

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	For tau-pathology related brain volume, imaging, behavioral experiments, n>10 mice per group were used (Figure legends). For amyloid-pathology related volume and imaging experiments, n>5 mice per group were used (Figure legends). For Single cell RNA sequencing, 2 biological replicates per group with 5-10 mice pooled per sample were used (Extended Data Table 1).
Data exclusions	In single cell immune RNA-seq analysis, barcodes in all samples that were considered to represent noise and low-quality cells were filtered out using knee-inflection strategy available in default CellRanger analysis. Genes which express in less than three cells were additionally filtered from expression matrices. The mitochondrial genes fraction was calculated for every cell, and cells with a mitochondrial fraction more than highest confidence interval for scaled mitochondrial percentage were filtered out which results in removal of the cells with mitochondrial percentage more than 20%. Additionally, cut off with log10 (number of unique expressed genes) as 2.5 was used for removing the cells from both CD45-high and CD45-total parenchymal cells, and 2 was used as a threshold for the cells from meninges. Doublets have been excluded based on the co-expression of the canonical cell-type specific genes. In expression of cytokines, chemokines, growth factors and soluble receptors in brain lysates analysis, with Q=0.1% identify outlier function, n=1 E4 and n=1 TEKO samples for IFN-gamma measurements were removed; n=1 E4 sample for IL-1β measurements was removed.
Replication	Biological replicates were performed for all experiments and reported in the figure legends.
Randomization	All mice were allocated into sex-matched, littermate-matched and age-matched experimental groups.
Blinding	Brain volume analysis, histological quantification, and behavioral experiments were performed by investigators who were blinded to sample IDs.

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

For immunofluorescent staining, primary antibodies were as follows: CD3 (Novus, NB600-1441, 1:200), CD8 (Invitrogen, MA1-145, 1:100), Iba1(Wako, 019-19741, 1:2000; Abcam, ab5076, 1:500), AT8 (Invitrogen, MN1020B, 1:500), Aβ (Homemade, HJ3.4B, 1:1000), P2ry12 (Gift from Butovsky lab, 1:2000), NeuN (Abcam, ab177487, 1:1000), MBP (Abcam, ab7349, 1:500), MHCII (Biolgend, 107650, 1:200), X34 (Sigma, 1954-25MG, 10mM in DMSO stock, 1:5000), CD206 (Bio-Rad, MCA2235, 1:300), Hoechst (sigma, 94403, 1:5000). Secondary antibodies were as follows: Donkey anti-Rat 488 (Invitrogen, A21208, 1:500), Donkey anti-Rabbit 405 (Invitrogen, A48258, 1:500), Donkey anti-Rabbit 568 (Invitrogen, A10042, 1:500), Streptavidin 568 (Invitrogen, S11226, 1:500), Donkey anti-Goat 647 (Invitrogen, A21447, 1:500).

For T cell depletion, anti-CD4 (BioXCell, BP0003-1), anti-CD8 antibody (BioXCell, BP0061) and IgG (BioXCell, BP0090) were used.

For PD1 signaling blocking, anti-PD-1 antibody (BioXCell, BP0146) and IgG (BioXCell, BP0089) were used.

For IFN-γ signaling blocking, anti-mouse IFN-γ (Leinco, clone H22, I-1190) and IgG (Leinco, P376)antibodies were used.

Validation

All antibodies are commercially available and have been tested in mice.
Website reference, CD3 (Novus, NB600-1441, 1:200) https://www.novusbio.com/products/cd3-antibody-sp7_nb600-1441; CD8 (Invitrogen, MA1-145, 1:100) https://www.thermofisher.com/antibody/product/CD8-Antibody-clone-2-43-Monoclonal/MA1-145; Iba1(Wako, 019-19741, 1:2000; Abcam, ab5076, 1:500) https://labchem-wako.fujifilm.com/us/product/detail/W01W0101-1974.html,https://www.abcam.com/iba1-antibody-ab5076.html; AT8 (Invitrogen, MN1020B, 1:500), https://www.thermofisher.com/antibody/product/Phospho-Tau-Ser202-Thr205-Antibody-clone-AT8-Monoclonal/MN1020B; NeuN (Abcam, ab177487, 1:1000) https://www.abcam.com/neun-antibody-epr12763-neuronal-marker-ab177487.html; MBP (Abcam, ab7349, 1:500) https://www.abcam.com/myelin-basic-protein-antibody-12-ab7349.html, MHCII (Biolgend, 107650, 1:200) https://www.biolegend.com/en-ie/products/alexa-fluor-594-anti-mouse-i-a-i-e-antibody-12448; X34 (Sigma, 1954-25MG, 10mM in DMSO stock, 1:5000) https://www.sigmaaldrich.com/US/en/product/sigma/sml1954; CD206 (Bio-Rad, MCA2235, 1:300)https://www.bio-rad-antibodies.com/monoclonal/mouse-cd206-antibody-mr5d3-mca2235.html?f=purified.

Animals and other organisms

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

Laboratory animals

Human ApoE knock-in mice, ApoE3 and ApoE4 (E3 and E4, respectively), were generated by replacing the mouse genomic sequence from the translation initiation codon in exon2 to the termination codon in exon4 with its human counterparts flanked by loxP sites (PMID: 31623648). P301S tau transgenic mice (Jax, #008169) on C57BL/6 background were crossed to human ApoE KI mice to generate P301S/E3 (TE3) and P301S/E4 (TE4) mice respectively. A/PE4 and 5XFADE4 mice have been described (PMID: 24893973 and PMID: 33597265). ApoE knockout (EKO) mice (Jax, #002052) on C57BL/6 background were crossed to P301S mice to generate P301S/EKO (TEKO). All tau transgenic mice involved in the final analysis were obtained from the same generation. Littermates of the same sex were randomly assigned to experimental groups.

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 animal experiments were performed according to protocols approved by the Animal Studies Committee of Washington University School of Medicine in accordance with the National Institutes of Health guidelines.

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

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	Mice were perfused with PBS to fully remove blood contamination. Hippocampus and cortex were dissected. Cell suspensions were then passed through Percoll density centrifugation to remove myelin and debris. The cell pellets were washed with 0.5% BSA for analysis or collection. For meninges, meninges were peeled intact from the skullcap using fine forceps and prepared for single cell analysis. All steps were performed on ice or using pre-chilled centrifuge. Single cell suspensions were incubated with anti-CD16/32 (Fc block; Bio legend) for 5 min then fluorescently conjugated antibodies were added for 20 min. After washing, samples were collected by 300g followed by a 5 min spin down and suspended in 5% BSA with PI for live/Dead selection before sorting. Cells were sorted using FACsAria II (BD Bioscience).
Instrument	FACSAria II (BD) were used for sorting
Software	Data analysis and figure generation were performed using FlowJo v10.
Cell population abundance	Cell numbers were quantified both by Countess II (Invitrogen) automatically and hemocytometer (iNCYTO) manually.
Gating strategy	FSC/SSC were used for initial gating. PI or live/die were used for live cell selection. CD45 high and CD11b low were applied to gating lymphocytes.CD3 for total T cells and CD4, CD8 antibodies were used to separate CD4+ and CD8+ T cells. Negative control and single color composition were performed.

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