nature portfolio

Corresponding author(s): Prof. Tony Wyss-Coray

Last updated by author(s): Sep 26, 2021

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	Zeiss 710 Confocal Laser Scanning Microscope (Carl Zeiss MicroImaging), Open Field Activity Arena (Med Associates Inc., St. Albans, VT. Model ENV-515) with a sound attenuating chamber (Med Associates Inc., St. Albans, VT. MED-017M-027). Ethovision XT (Noldus Information Technology, Wageningen, the Netherlands), chambers equipped with steel shocking floor (Coulbourn Instruments, Whitehall, PA), SmartCage (AfaSci, SmartCage system). Illumina Novaseq 6000, Novaseq S4 flow cell, Orbitrap Fusion Lumos Mass Spectrometer (ThermoFisher), SOMAscan V3 assay (SomaLogic Inc), ARIA 3.3 (BD Biosciences).
Data analysis	Prism 7 (GraphPad), R Studio v1.2.5033 and 3.6, DESeq v1.32, ImageJ (NIH) 1.51h, STAR v2.5.3, SeqMonk v1.48.0, TopGO v2.36 and 2.44, CageScore software (AfaSci), Ethovision XT, FreezeFrame and FreezeView software (Actimetrics, Evanston, IL), Proteome Discoverer v2.2.0.388 (ThermoScientific), Proteome Discoverer v2.4.0.305 (ThermoScientific), Cellranger 10X genomics (version 3.1.0) and FACSDiva software (BD Biosciences), Med Associates Open Field Activity.

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

The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE(reference 67) partner repository with the dataset identifier PXD022262 and PXD027406 for male and female plasma proteins respectively.
Single cell data and bulk RNAseq data sets have been deposited to GEO (Gene Expression Omnibus) and can be access under the accession number GSE164401

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	We used published data (Van Praag, H. et al. 1999, Fabel, K et al., 2003 and Villeda, S.A. et al., 2011) to determine an optimal n for our studies on the RP effects on neuroplasticity and behavior. We also performed preliminary studies that were not included in the manuscript. For the single cell sequencing studies we used previous studies (Chen, M.B. et al., 2020 and Yang, A. C. et al.,2020) and performed preliminary studies to confirm that we will obtain enough BECs for statistical analysis, not included in the manuscript.
Data exclusions	Animals were excluded from the experiments when showing an apparent state of disease, or died before the experiment finished. Samples were excluded if there was not enough processing material (e.g. plasma).
Replication	For in vivo studies we used biological replicates as well as independent cohorts of mice. In addition, experiments showing effects of RP on stem cell activity were replicated in Extended data 2f; experiments showing effects of RP on the hippocampus of LPS inoculated mice via RNAseq, shown in FIg 2, was replicated in with qPCR in Extended data 3b;, Mass Spectrometry plasma data shown in Fig. 3, were replicated using TMT (Extended data fig. 5a). Single cell sequencing data was performed once and validated with two different neuroinflammatory models (acute and chronic) and in two different brain areas (hippocampus and cortex).
Randomization	In this study all samples were randomly assigned to experimental or control groups, and treatments were administered in a sequential alternating manner.
Blinding	In this study investigators were blinded to the treatments.

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	Inmmunostaining primary antibodies: rat anti- BrdU (1:2500, ab6326, Abcam), mouse anti GFAP (1: 1:1000, MAB360, Millipore), goal

Antibodies used	anti-sox2 (1:1000, sc-365823, Santa Cruz Biotechnology), mouse anti-NeuN (1:400, MAB377, Millipore), goat anti-DCX (1:500, sc-8066, Santa Cruz Biotechnology), Mouse anti-SMA (1:100, F377, Sigma Aldrich), rat anti-tfrc (1:200, NB100-64979, Novus Biologicals), lectin tomato (1:200, FL-1171-1, Vector Laboratories), rabbit anti-CLU (20ug antibody/mL of plasma, ab184100, Abcam), goat anti-PEDF(20ug antibody/mL of plasma, AF1149, R&D Systems), sheep anti-FactorH (20ug antibody/mL of plasma, ab8842, Abcam), rabbit anti-LIFR (20ug antibody/mL of plasma, 22779-1-AP, Proteintech) Immunostaining secondary antibodies: the Click-iT Plus EdU AlexaFluor® 555 Imaging Kit (ThermoFisher, Cat# C10638). Alexafluor® 488, 555, or 647 antibodies (Invitrogen) raised in donkey against the appropriate target animal. All fluorescent secondary antibodies were diluted at a concentration of 1:200. Nuclei were fluorescently labeled with Hoechst 33342 (1:2000, Sigma) Flow cytometry: rat anti-CD31-PE/CF594 (1:75, BD, cat. No. 563616), rat anti-CD45-PE/Cy7 (1:200, BD, cat. no. 103114), and anti-Cd11b-FITC (1:100, BD 101206), and anti-Cd11b-FITC (1:100, BD 101206), SYTOX™ Blue Dead Cell Stain (1:2000, Thermo S34857)
Validation	All antibodies were validated for the indicated species and applications by the manufacturer.

Animals and other organisms

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

Laboratory animals	C57BL/6 male mice, 3 to 15 month of age and APP mice mThy-1-hAPP751V171I, KM670/671NL; T41 line, the line was maintained on a C57BL/6 genetic background. C57BL/6 female mice, 3 to 4 months of age.All mice were housed at the Palo Alto VA animal facility under a 12hr:12hr light:dark cycle with dark hours between 6:30PM – 6:30AM. Housed at 68-73 F and 40 - 60% humidity.
Wild animals	The study did not involve wild animals
Field-collected samples	The study did not involve samples collected from the field
Ethics oversight	All animal procedures were conducted with the approval of the animal care and use committees of the Veterans Administration Palo Alto Health Care System

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Please see Supplementary Information table 20
Recruitment	Participant were recruited through a multi-pronged approach that included community-based recruitment as well as recruitment through primary care clinics and specialty care outpatient clinics at the VA to minimize recruitment biases.
Ethics oversight	The study was approved by Stanford University Institutional Review Board

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	For immunostaining, cells were passed through a 100 micron strainer, blocked for 10 minutes on ice with mouse Fc-blocking reagent (BD), and stained for 30 minutes in PBS supplemented with 1% bovine serum albumin.
Instrument	FACS ARIA 3.3. (BD Biosciences)
Software	FACSDiva software (BD Biosciences)
Cell population abundance	For analysis of the effects of rCLU on LPS inoculated mice analyzed n = 5,403 cells in the saline group, n = 3,289 cells in the LPS group and n = 4723 cells in the LPS+rCLU group. For the analysis of the effects of rCLU on APP mice we analyzed, n =

3685 cells in the WT group, n = 2275 cells in the APP group, n = 1624 cells in the APP+Sal group and n = 2144 cells in the APP +rCLU group.

Gating strategy

Positive and negative gates were set using unstained and fluorescence minus one (FMO) background intensity controls. Fluorophores were chosen to minimize spectral overlap.

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