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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	FreezeScan tracking system (Cleversys), ZEN Black (Zeiss), Keyence microscope (BZ-X800), IncuCyte (Essen BioScience), SH800S (Sony), ImageStudio (LI-COR), Nextseq550 (Illumina), Hiseq 4000 (Illumina), LightCycler 480 (Roche).
Data analysis	Imaris 8 (Bitplane), FlowJo 10 (Treestar), Prism 8 and 9 (GraphPad), ImageJ/ Fiji (NIH), bcl2fastq v2.20.0.422, R v4 (DESeq2, ggplot2, tidyverse), STAR v2.6.1d, Nextflow v20.11.0-edge, nf-core/rnaseq pipeline v3.0, RSEM v1.3.1, Samtools v1.10, GeneTrail 3.0, SlamDunk v0.3.4, Snakemake v5.5.4. For the genome alignment reference fasta and gff files of GRCm38 (Mus musculus) and Rnor_6.0.97 (Rattus norvegicus) were downloaded from the Ensembl database. In case of aligning samples with high expected nuclear RNA content, we modified the gff files to account for intronic sequences and for determining the final read counts.

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

All data is available in the main text or the supplementary materials. Raw and processed sequencing data were deposited to NCBI's SRA and GEO databases using the accession ID GSE198008.. Summarized bulk RNA-seq (Supp Table 1,2,4,5,6) are provided and meta analysis of publicly available datasets is referenced in the methods.

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 (Villeda, S.A. et al, 2011, Castellano, J.M. et al. 2017, De Miguel, Z. et al. 2021) to determine an optimal n for our studies on the effects of young CSF on behavior. For teh bulk RNAseq of sorted oligodendrocyte nuclei we performed preliminary studies to ensure we will capture enough nuclei for downstream library prep and statistical analysis.
Data exclusions	Animals were excluded from the experiments when showing an apparent state of disease, or died before the experiment finished. Mouse CSF samples were excluded for blood contamination using a cutoff of below 0.02 AU using the UV-vis setting with a 415nm wavelength for detection of oxyhemoglobin (see Methods).
Replication	For in vivo experiments, biological replicates (individual mice) are reported. Data in figure 1b, 1e, 1i, 1k, 4l and Extended data fig. 1a-f are combined raw data from two independent cohorts of mice as stated in 'Statistics and reproducibility' method section. Data in Fig. 1l-o, 2e, 2i, 4b-c, 4f, 4h, 4j and 4s and Extended data 2b, 7a, 7b, 7d, 7e, 7f, 7h, 7i, 9a, 9b, 9d, 9e, were successfully replicated in two independent experiments as stated in 'Statistics and reproducibility' method section RNA-seq data were not replicated in independent experiments due to resource restrictions.
Randomization	Same aged mice were allocated into groups to achieve an equal average weight. All other criteria were not considered and as such, were randomized.
Blinding	All behavioral and immunohistochemical analyses were performed by a blinded observer. In general, experimenters were blinded to group allocation during data acquisition and analysis.

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	Flow cytometry: Anti-NeuN antibody-Alexa Fluor® 647 (1:100, abcam, EPR12763) and Anti-Olig2 antibody-Alexa Fluor® 488 (1:100, Millipore, MABN50A4). Immunostaining antibodies: PDGF Receptor α (D1E1E) XP® Rabbit mAb (1:500, Cell Signaling, 3174S), Rabbit-anti-MBP (1:100, MAB386, Millipore), Rat anti-BRDU antibody (1:500, ab6326, Abcam), Rabbit-anti-MBP (1:100, abcam, ab7349) and mouse anti-GFAP (1:500, Chemicon, MAB360), Rabbit anti-Fgf17 (1:500, PA5-109722, Thermo), goat anti-PROX1 (1:500, AF2727, R&D), rabbit anti-c-Fos (1:500, 9F6, Cell Signaling), Rabbit-anti-GFAP (Dako, Z0334, 1:500) RNAscope secondary antibodies: secondary Opal 690 and 520 reagents (FP1497001KT and FP1487001KT, Akoya Biosciences) were diluted at 1:1500 in TSA buffer.
Validation	All antibodies were validated for the indicated species and applications by the manufacturer.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293 (ATCC)
Authentication	Cell line was not authenticated.
Mycoplasma contamination	Cell line was not tested for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	This study did not use any commonly misidentified lines

Animals and other organisms

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

Laboratory animals	C57Bl/6 male mice, aged (18-22 months from NIA rodent colony), young (2-3 months from Charles River or Jackson Labs). Il of the mice were housed at the Palo Alto VA animal facility under a 12h–12h light–dark cycle with dark hours between 18:30–06:30, and housed at 68–73°F under 40–60% humidity.
Wild animals	This study did not involve wild animals
Field-collected samples	This study did not involve field-collected samples.
Ethics oversight	All animal care and procedures complied with the Animal Welfare Act and were in accordance with institutional guidelines and approved by the V.A. Palo Alto Committee on Animal Research and the institutional administrative panel of laboratory animal care at Stanford University.

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	CSF samples of nine young heathy individuals (ages 24-26) were obtained through a collaboration with Dr. Henrik Zetterberg, University of Gothenburg, Sweden. The study was approved by the regional ethics committee at the University of Gothenburg and informed consent was obtained from all participants (Olssom, M et al. 2018, 2019). For in vitro experiments, three pools consisting of three individuals each were made for each experiment, two pools from six male samples and one of female samples were each used in 3-4 technical triplicates. Aged human CSF from healthy individuals (ages 65-76) was obtained from the Stanford Alzheimer's Disease Research Center.
Recruitment	The samples were baseline (normal sleep) lumbar CSF samples, collected in the morning, from healthy volunteers who took part in a study on sleep restriction-induced changes of CSF composition.
Ethics oversight	University of Gothenburg, Sweden. Stanford Alzheimer's Disease Research Center (ADRC), California, USA.

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	Mouse hippocmapal nuclei were isolated using Nuclei EZ Prep Kit (Sigma-Aldrich, St. Louis, USA) and stained for 30 min on ice.
Instrument	SH800S (Sony)
Software	SH800S (Sony) and FlowJo (Treestar)

Cell population abundance	NeuN+ gate consisted of 50-60% of nuclei, Olig2-high were 5% and Olig2-low 20% of nuclei.
Gating strategy	Single nucei were gated by Hoechst staining (roughly 50% in young and 25% in aged). Olig2-high nuclei were sorted as OPCs and Olig2-low as mature oligodendrocytes. 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.