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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 Authors & Referees 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	FACS Diva (BD),ZEN Black (Zeiss), Imaris (Bitplane), Incucyte S3 (Essen), ImageStudio (LI-COR)
Data analysis	FlowJo (Treestar), Prism 7 (GraphPad), R (DESeq2, ggplot2, tidyverse), ImageJ, GSEA v3 (Broad), Enrichr, Panther, casTLE

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. 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

Raw sequencing data will be deposited in NCBI GEO. Raw CRISPR screen count data (Supp Table 1), analyzed CRISPR hits (Supp Table 2), RNA-seq (Supp Table 3 and 4) are provided.

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

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No power analyses were used to predetermine sample sizes. However, sample sizes were chosen based on prior literature using similar experimental paradigms.
Data exclusions	For long-term osmotic pump infusions, 4 mice were excluded and euthanized prior to experiment endpoint due to post-operative wound dehiscence. These exclusion criteria were predetermined as per relevant animal protocols.
Replication	For in vitro experiments, technical triplicates as well as independent experiments on separate days were performed to ensure reproducibility. For in vivo experiments, biological replicates as well as independent cohorts of mice were used. CRISPR screen data, RNA-seq data, and aged CD22-/- behavioral data were not replicated in independent experiments due to resource restrictions. All other data were replicated in at least two independent experiments as stated in figure legends.
Randomization	For long-term osmotic pump infusions, mice were randomized into 2 groups using a random list generator (random.org).
Blinding	All immunohistochemical and behavioral analyses were performed by a blinded observer.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	Flow cytometry: CD11b (clone M1/70, BioLegend, cat. no. 101205, 1:100), CD45 (clone 30-F11, Biolegend, cat. no. 147708, 1:100), Siglec-1 (clone REA197, Miltenyi Biotec, cat. no. 130-105-004, 1:10), CD22 (clone OX-97, Biolegend, cat. no. 126112, 1:100), Siglec-E (clone M1304A01, Biolegend, cat. no. 677106, 1:100), Siglec-F (clone ES22-10D8, Miltenyi Biotec, cat. no. 130-102-241, 1:10), Siglec-G (clone SH1, BD Biosciences, cat. no. 563336, 1:100), Siglec-H (clone 551, Biolegend, cat. no. 129612, 1:100), CD33 (clone 9A11, eBioscience, cat. no. 17-0331-82, 1:100) IHC: goat anti-Iba1 (1:500, ab5076, Abcam), goat anti-Prox1 (1:500, AF2727, R&D), rabbit anti-c-Fos (1:400, 9F6, Cell Signaling), rabbit anti-amyloid beta (1:200, D54D2, Cell Signaling), rabbit anti-alpha-synuclein (1:200, MJFR1, Abcam), rabbit anti-p-CREB (1:500, 06-519, Millipore), rabbit anti-synaptophysin (1:500, D8F6H, Cell Signaling), rabbit anti-PSD95 (1:500, D27E11, Cell Signaling), rabbit anti-C1q (1:1200, ab182451, Abcam), goat anti-doublecortin (1:500, SC8066, Santa Cruz Biotech), anti-Tmem119 (1:200, 28-3, Abcam) WB: mouse anti-a-tubulin (1:10,000, T9026, Sigma), rabbit anti-pSHP-1 (1:5,000, D11G5, Cell Signaling), anti-SHP-1 (1:10,000, C14H6, Cell Signaling), anti-Sall1 (1:1000, ab31526, Abcam) In vivo: mouse IgG1 isotype control antibody (MOPC21, BioXCell, cat. no. BE0083, 1mg/mL) or anti-CD22 (Cy34, BioXCell, cat. no. BE0011, 1mg/mL)
Validation	All antibodies were validated for the indicated applications by the manufacturer. For the anti-CD22 flow cytometry antibody (Ox97), we confirmed specificity using a KO control. For the anti-CD22 therapeutic antibody (Cy34) used in vivo, we confirmed function-blocking activity in ligand binding, signaling, and internalization assays.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	BV2 cells (E. Blasi), HEK293T (ATCC)
Authentication	Cell line authentication was performed by the supplier, but not independently authenticated in our lab.

Mycoplasma contamination	Cell lines were tested for mycoplasma bi-annually
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used.

Animals and other organisms

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

Laboratory animals	Mus musculus, male, C57Bl/6, aged (18-24 months from NIA rodent colony), young (2-4 months from Charles River or Jax), CD22-/- from Scripps Research Institute (J. Paulson)
Wild animals	This study did not involve wild animals.
Field-collected samples	This study did not involve field-collected samples.
Ethics oversight	Institutional Animal Care and Use Committee at Stanford University

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 on ice in PBS supplemented with 0.5% bovine serum albumin.
Instrument	FACS: BD FACSAria III Analysis: BD LSRFortessa, LSRII, Accuri C6
Software	BD FACS Diva, FlowJo
Cell population abundance	For immunophenotyping, at least 5,000 cells of the population of interest were analyzed. For sorting for RNA-seq, at least 10,000 microglia were collected.
Gating strategy	Positive and negative gates were set using 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.