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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	No software used
Data analysis	Prism 8.0 (GraphPad, Inc, San Diego CA) was used for data analysis

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

The data that support the findings of this study are available from the corresponding author upon reasonable 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	Variance is known from previously conducting similar experiments and power at 0.8-0.9 based on 30-40% differences between means
Data exclusions	For multiple-time regression analysis, the method calls for exclusion of data points that contribute to non-linearity of the curve. Outliers whose exclusion improved the r2 > 0.2 were excluded from analysis. Excluded points are noted in Figures 2 and 3 by filled circles and further explained in those figure legends. For ANOVAs and comparisons of means, the Grubbs outlier exclusion test (alpha < 0.05) was applied once to detect single outliers, and any outliers that were excluded by this method are stated in the Figure legends and their values provided.
Replication	Each figure was generated as a single experimental replicate, with the exception of iPSC studies where S1 and albumin transport were compared in three independent experiments. However, use of T-Alb as an internal control for all experiments allowed us to track consistency between experiments with different designs based on its predictable tissue/serum ratios. Further, the I-S1 tissue-serum ratios taken at the same time points from different experiments may be compared, and agree well with each other, demonstrating a reproducible observation of I-S1 transport into the brain and other tissues.
Randomization	Anesthetized mice were randomized between test groups by alternating their assignments. Transwells were assessed for TEER prior to experiments and assigned to groups in such a way that TEER values between groups had approximately equal means and variances.
Blinding	Blinding was not done for experiments or analysis because this knowledge is required to carry out experiments 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

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	GM25256 iPSC line from the Coriell Institute
Authentication	Cells are routinely verified for iPSC markers such as Oct4, Nanog, and alkaline phosphatase
Mycoplasma contamination	Cell lines were not tested for mycoplasma contamination in-house
Commonly misidentified lines (See ICLAC register)	Not applicable

Animals and other organisms

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

Laboratory animals	6-10 week-old male CD-1 mice, and 4 month old male and female APOE3 and APOE4 targeted replacement mice.

Wild animals	Wild animals were not used
Field-collected samples	Field-collected samples were not used.
Ethics oversight	Studies were approved by the institutional animal research review board and the facilities are approved by AAALAC

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