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Last updated by author(s): Apr 1, 2021

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	Excel Version 16.47.1
Data analysis	Prism Version 8.4.3, Excel Version 16.47.1, Magellan Version 7.2, Sequest software

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 authors declare that the data supporting the findings of this study are available within the paper and its Extended Data files.

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 all main figures a single pool of human cerebrospinal fluid or plasma was used. Therefore, the sample size is one. However, for Simoa assay validation including both spike and recovery as well as dilution linearity, each assay was run on four individual CSF and four individual plasma samples.
Data exclusions	No data was excluded
Replication	For Simoa and Elisa, two technical replicates were included within each run. Each experiment in the manuscript demonstrates a single experiment and a single pooled sample. However, these experiments have been reproduced multiple times by different operators using different biological samples and the same results were observed. Specifically, the SEC results in Figure 1 have been replicated >6 times. The density gradient experiment as well as the Western blot experiment in Figure 2 have each been replicated 2 times with similar results.
Randomization	No group comparisons were conducted and thus randomization was not relevant
Blinding	No group comparisons were conducted and thus blinding was not relevant

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 Simoa and Elisa the antibodies used are as follows:
CD9 Capture: Abcam (ab195422)
CD9 Detector: Abcam (ab58989)
CD63 Capture: R&D Systems (MAB5048)
CD63 Detector: BD Biosciences (556019)
CD81 Capture: Abcam (ab79559)
CD81 Detector: Biolegend (349502)
Albumin Capture & Detector: R&D Systems (DY1455)
L1CAM Capture: BD Biosciences (554273)
L1CAM Detector: Abcam (80832)

For western blots the antibodies used are as follows:
L1CAM external: Abcam (80832)
L1CAM internal: Abcam (24345)
CD9: Millipore Sigma MM2/57
CD63: BD Biosciences H5C6
cd81: Thermofisher Scientific M38
Anti Mouse IgG Secondary Antibody (Bethyl Labratories) polyclonal

For Immunocapture of L1CAM the antibodies used are as follows:

	L1CAM: Abcam (ab272321) MCherry Control: MCherry (ab232341)
Validation	Antibodies for Simoa were validated with spike and recovery as well as dilution linearity experiments. Data for these experiments are in the supplementary information.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	iNGN neuron cell line were developed by the Church Lab
Authentication	Authenticated as previously described: Busskamp, V., et al., Rapid neurogenesis through transcriptional activation in human stem cells. Mol Syst Biol, 2014. 10: p. 760.
Mycoplasma contamination	Negative for Mycoplasma
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study

Human research participants

Policy information about studies involving human research participants

Population characteristics	Pooled and individual human plasma and CSF from commercial sources were utilized.
Recruitment	Patient samples were from a commercial source (BIOIVT).
Ethics oversight	Since commercial samples were used without identifying information this was deemed "Not Human Subject Research" by Harvard University.

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