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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

Describe how sample size was determined.

The number of experiments were based on previous publications (in our labs as well as from other labs working on these topics) on LTP/LTD, immunostaining on cultured neurons and behavioral tests

2. Data exclusions

Describe any data exclusions.

In water maze tests, if the mouse floats in water for more than 20 s, then mouse is excluded from analysis.

3. Replication

Describe whether the experimental findings were reliably reproduced.

Yes, all the reported data were reliably reproduced.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

WT and mutant littermates were grouped, coded and then experiments performed blindly.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

Yes, in all experiments.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ A statement indicating how many times each experiment was replicated
☐	☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	PClamp, WinLTP, Mini Analysis, Zen2010 (Zeiss), AimImage Browser (Zeiss), ImageJ (NIH), AlphaEaseFC, ANYmaze, FreezeFrame, SPSS statistics.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	The newly generated mouse strains, GluA1C1KI and GluA2C1KI, are available upon request. All requests should be directed to the corresponding author Zhengping Jia at zhengping.jia@sickkids.ca. A material transfer agreement with the Hospital for Sick Children (Toronto, Canada) is required for using the mice.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Primary and secondary antibodies include: Rabbit polyclonal anti-GluA1-CTD (Millipore, Cat#MAB2263), Rabbit polyclonal anti-GluA1-NTD (Cell signaling technology, Cat#T8850), Mouse monoclonal anti-GluA2-NTD (Millipore,Cat#MAB397), Rabbit polyclonal anti-GluA3 (Cell signaling technology, Cat#4676), Rabbit polyclonal anti-GluA4 (Cell signaling technology, Cat#T8030), Rabbit polyclonal anti-p-GluA1-831 (Santa Cruz, Cat#sc-16313), Rabbit polyclonal anti-p-GluA1-845 (Cell signaling technology, Cat#8084), Rabbit polyclonal anti-p-GluA2-Tyr (869/873/876) (Cell signaling technology, Cat#3921). Mouse monoclonal anti-MAP2 (Millipore, Cat#MAB3418), Rabbit polyclonal anti-NR1 (Millipore, Cat#AB9864), Rabbit polyclonal anti-NSF (Cell signaling technology, Cat#3924), Rabbit polyclonal anti-Pan-cadherin (Cell signaling technology, Cat#4068), Mouse monoclonal anti-PSD95 (Millipore, Cat#MABN68), Rabbit polyclonal anti-SAP97 (Abcam, Cat#ab134156), Rabbit polyclonal anti-Synapsin1 (Bioworld, Cat#BS4116), Rabbit polyclonal anti-Synaptophysin (Cell signaling technology, Cat#D35E4), Mouse monoclonal anti-Tubulin (Sigma-Aldrich, Cat#T9026), Goat anti-rabbit (Genscript, Cat#A00098), Goat anti-mouse (Genscript, Cat#A00160), Alexa Fluor 488 donkey anti-mouse IgG (Thermo-Fisher, Cat#R37114), Alexa Fluor 555 goat anti-mouse IgG (Thermo-Fisher, Cat#A-21422), Alexa Fluor 555 donkey anti-rabbit IgG (Thermo-Fisher, Cat#A-31570), Alexa Fluor 633 goat anti-mouse IgG (Thermo-Fisher, Cat#A-21050). Anti-rabbit GluA2-CTD antibody was a gift from YT Wang (UBC, Canada) and was validated using GluA2 KO and GluA2C1KI mice (Page 34-35).

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	N/A
b. Describe the method of cell line authentication used.	N/A
c. Report whether the cell lines were tested for mycoplasma contamination.	N/A
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	N/A

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

wild type (C57BL/6J) and three new knock in strains (derived from ES cells of c57BL/6J) were used. The details of these mice were described in the Methods section. The age of mice was 13-15 days for LFS-LTD and non-SFA experiments and 3-4 weeks for PP-LFS-LTD, DHPG-LTD and all other LTP and western blot experiments. Behavioral tests were done at the age of 3 ± 0.5 months. The sex (male and female) of the mice was balanced.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

N/A