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Reporting Summary

Nature Portfolio 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 Portfolio 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	All softwares for data collection are detailed in the manuscript. Images were captured by following software, fluorescent microscope: Metamorph Basic software, Olympus; confocal microscope: Olympus LS, Olympus. EEG/EMG data were captured by Sirenia Acquisition, Pinnacle Technology or Clampex, Molecular Devices .
Data analysis	All softwares for data analysis are detailed in the manuscript. EEG spectrum was analyzed by Chronux toolbox (http://chronux.org/) script in MatLab (Mathworks). Image registration was analyzed by Advanced Normalization Tools (ANTs, https://github.com/ANTsX/ANTsPy) script in Python 3.6. Images were analyzed in ImageJ. Data were analyzed using Graphpad Prism Software 7.

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 Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

All data are available in the main text and extended data set. Source data is provided as supplementary materials.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	NA
Reporting on race, ethnicity, or other socially relevant groupings	NA
Population characteristics	NA
Recruitment	NA
Ethics oversight	NA

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

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	Sample sizes were based on accepted standards in the field. These are sufficient to generate meaningful conclusions given biologically relevant effect sizes and typical data variance for the measures used. Sample sizes used were comparable to previous studies that used similar techniques and designs (Hussain, et al. Nature, 2024. https://doi.org/10.1038/s41586-023-06737-7; Monai, et al. PNAS, 2019 https://doi.org/10.1073/pnas.1817347116)
Data exclusions	Mice died during the development of epilepsy were not included in the analysis.
Replication	Experiments were replicated at least 3 times where applicable (e.g. immunohistochemistry, Open field and Rota-rod test). The effect of PPA on chronic epilepsy was evaluated at three conditions - 1. PPA applied 5 minutes after KA with EEG at 3-4 weeks. 2. PPA applied 30 hours after KA with EEG at 3-4 weeks. 3. PPA applied 30 hours after KA with EEG at 2 months. The main effect (seizure numbers) showed same tendency. Replication was successful.
Randomization	Wild-type animals were randomly distributed to different experimental groups. For transgenic mice, their litter mates were used as control.
Blinding	Group identities were blinded to experimenters as far as possible (e.g. EEG/EMG recording, Open field test, Rota-rod test, immunohistochemistry and imaging). While comparing wild-type and epilepsy mice, the group identity could be inferred by gross behavioral deficits as a result of epilepsy.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Antibodies

Antibodies used: mouse anti-GFAP (1:500, Chemicon, MAB360), mouse anti-NeuN (1:500, Chemicon, MAB377), rat anti-CD68 (1:500, Serotec, MCA1957), and rabbit anti-AQP4 (1:500, Chemicon, AB3594), Cy2 donkey anti-rabbit (1:500; A-21206, ThermoFisher Scientific), Cy2 donkey anti-mouse (1:500; A-21202, ThermoFisher Scientific), Cy3 donkey anti-mouse (1:500; A10036, ThermoFisher Scientific), and Cy3 donkey anti-rat (1:500; A10040, ThermoFisher Scientific).

Validation: All the antibodies used in this study were commercially available and have been validated by the manufacturer. The details can be accessed at their website (antibody references/catalogue numbers are provided above).

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals: Wild type FVB/2J male mice, aged 8-12 weeks were purchased from Taconic Biosciences (Germantown, NY, USA). AQP4 knockout mice on a C57BL/6 background were the generous gift of Dr. Ming Xiao (Nanjing Medical University, China) . All mice were housed under standard laboratory conditions with ad libitum access to food and water.

Wild animals: NA

Reporting on sex: Only male mice were used in this study. This is a limitation of this study.

Field-collected samples: NA

Ethics oversight: The committees on animal experimentation at the Universities of Rochester and Fudan separately approved all experiments (Protocol No. 2011-022 and 2011-023). The animal studies were performed in accordance with guidelines of the National Institutes of Health and Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) standards, and according to the Animal Experiment and Use Committee at the Shanghai Medical School of Fudan University (20200306-051).

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

Plants

Seed stocks: NA

Novel plant genotypes: NA

Authentication: NA