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Supplementary Tables: 5

Supplementary Videos:

Reporting Checklist for Nature Neuroscience

This checklist is used to ensure good reporting standards and to improve the reproducibility of published results. For more information, please read Reporting Life Sciences Research.

Please note that in the event of publication, it is mandatory that authors include all relevant methodological and statistical information in the manuscript.

Statistics reporting, by figure

- Please specify the following information for each panel reporting quantitative data, and where each item is reported (section, e.g. Results, & paragraph number).
- Each figure legend should ideally contain an exact sample size (n) for each experimental group/condition, where n is an exact number and not a range, a clear definition of how n is defined (for example x cells from x slices from x animals from x litters, collected over x days), a description of the statistical test used, the results of the tests, any descriptive statistics and clearly defined error bars if applicable.
- For any experiments using custom statistics, please indicate the test used and stats obtained for each experiment.
- Each figure legend should include a statement of how many times the experiment shown was replicated in the lab; the details of sample collection should be sufficiently clear so that the replicability of the experiment is obvious to the reader.
- For experiments reported in the text but not in the figures, please use the paragraph number instead of the figure number.

Note: Mean and standard deviation are not appropriate on small samples, and plotting independent data points is usually more informative. When technical replicates are reported, error and significance measures reflect the experimental variability and not the variability of the biological process; it is misleading not to state this clearly.

		TEST USED		n			DESCRIPTIVE STATS (AVERAGE, VARIANCE)		P VALUE		DEGREES OF FREEDOM & F/t/z/R/ETC VALUE	
	FIGURE NUMBER	WHICH TEST?	SECTION & PARAGRAPH #	EXACT VALUE	DEFINED?	SECTION & PARAGRAPH #	REPORTED?	SECTION & PARAGRAPH #	EXACT VALUE	SECTION & PARAGRAPH #	VALUE	SECTION & PARAGRAPH #
example	1a	one-way ANOVA	Fig. legend	9, 9, 10, 15	mice from at least 3 litters/group	Methods para 8	error bars are mean +/- SEM	Fig. legend	p = 0.044	Fig. legend	F(3, 36) = 2.97	Fig. legend
example	results, para 6	unpaired t-test	Results para 6	15	slices from 10 mice	Results para 6	error bars are mean +/- SEM	Results para 6	p = 0.0006	Results para 6	t(28) = 2.808	Results para 6
+ -	1b RIPA	unpaired t-test	Fig. legend	11, 12	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.002	Fig. legend	t(21) = 3.444	Fig. legend

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		TEST USED		n			DESCRIPTIVE STATS (AVERAGE, VARIANCE)		P VALUE		DEGREES OF FREEDOM & F/t/z/R/ETC VALUE	
	FIGURE NUMBER	WHICH TEST?	SECTION & PARAGRAPH #	EXACT VALUE	DEFINED?	SECTION & PARAGRAPH #	REPORTED?	SECTION & PARAGRAPH #	EXACT VALUE	SECTION & PARAGRAPH #	VALUE	SECTION & PARAGRAPH #
+ -	1b UREA	unpaired t-test	Fig. legend	11, 12	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.038	Fig. legend	t(21) = 2.205	Fig. legend
+ -	1c RIPA	unpaired t-test	Fig. legend	11, 12	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.023	Fig. legend	t(21) = 2.443	Fig. legend
+ -	1c UREA	unpaired t-test	Fig. legend	11, 12	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.005	Fig. legend	t(21) = 3.126	Fig. legend
+ -	1e	unpaired t-test	Fig. legend	12, 14	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.002	Fig. legend	t(24) = 3.447	Fig. legend
+ -	1f	unpaired t-test	Fig. legend	12, 14	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.999	Fig. legend	t(24) = 0.0001	Fig. legend
+ -	1g	unpaired t-test	Fig. legend	12, 14	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.013	Fig. legend	t(24) = 2.667	Fig. legend
+ -	2b	unpaired t-test	Fig. legend	15, 15	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.003	Fig. legend	t(28) = 3.270	Fig. legend
+ -	2d	unpaired t-test	Fig. legend	15, 15	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.013	Fig. legend	t(28) = 2.659	Fig. legend
+ -	2f	unpaired t-test	Fig. legend	15, 15	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.022	Fig. legend	t(28) = 2.437	Fig. legend
+ -	2g	unpaired t-test	Fig. legend	7, 7	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.026	Fig. legend	t(12) = 2.542	Fig. legend
+ -	2i	unpaired t-test	Fig. legend	11, 13	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.003	Fig. legend	t(22) = 3.277	Fig. legend
+ -	2k	unpaired t-test	Fig. legend	11, 13	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.030	Fig. legend	t(22) = 2.322	Fig. legend
+ -	2l CTL	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.963	Fig. legend	R(14) = 0.3288	Fig. legend
+ -	2l AD	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.980	Fig. legend	R(14) = 0.630	Fig. legend
+ -	2m	unpaired t-test	Fig. legend	15, 15	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.0001	Fig. legend	t(28) = 4.504	Fig. legend
+ -	3a	moderated t-test	Fig. legend	97, 98	number of human cases	Fig. legend	box plot	Fig. legend	p = 7.5E-11	Fig. legend and suppl. table 3	t(193) = 6.890	Fig. legend and suppl. table 3
+ -	3b	moderated t-test	Fig. legend	97, 98	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.805	Fig. legend and suppl. table 3	t(193) = -0.247	Fig. legend and suppl. table 3
+ -	3c	moderated t-test	Fig. legend	97, 98	number of human cases	Fig. legend	box plot	Fig. legend	p = 3.7E-11	Fig. legend and suppl. table 3	t(193) = 7.017	Fig. legend and suppl. table 3
+ -	3d	linear regression	Fig. legend	93	number of human cases	Fig. legend	scatter plot	Fig. legend	p = 1.1E-03	Figure	R(91) = -0.333	Figure
+ -	4a	ordinal logistical regression	Fig. legend	94	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.035	Fig. legend and suppl. table 3	t(92) = 2.107	Fig. legend and suppl. table 3

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+ -	4b	ordinal logistical regression	Fig. legend	94	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.499	Fig. legend and suppl. table 3	t(92) = 0.677	Fig. legend and suppl. table 3
+ -	4c	ordinal logistical regression	Fig. legend	94	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.013	Fig. legend and suppl. table 3	t(92) = 2.488	Fig. legend and suppl. table 3
+ -	4d	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.99	Fig. legend	R(13) = 0.605	Fig. legend
+ -	4e	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.98	Fig. legend	R(13) = 0.529	Fig. legend
+ -	4f	quantile regression	Fig. legend	62	number of human cases	Fig. legend	scatter blot	Fig. legend	multiple p values	suppl. table 4	multiple t values	suppl. table 4
+ -	4g	quantile regression	Fig. legend	62	number of human cases	Fig. legend	scatter blot	Fig. legend	multiple p values	suppl. table 4	multiple t values	suppl. table 4
+ -	4h	quantile regression	Fig. legend	62	number of human cases	Fig. legend	scatter blot	Fig. legend	multiple p values	suppl. table 4	multiple t values	suppl. table 4
+ -	4i	quantile regression	Fig. legend	62	number of human cases	Fig. legend	scatter blot	Fig. legend	multiple p values	suppl. table 4	multiple t values	suppl. table 4
+ -	6a	two-way ANOVA followed by Bonferroni post hoc	Fig. legend	14, 12, 14, 14	mice	Fig. legend	mean ± SEM	Fig. legend	interaction: p = 0.014; group: p < 0.001; days: p < 0.0001	Fig. legend	interaction: F(12,250) = 2.158; group: F(3,250) = 21.37; days: F(4,250) = 31.26	Fig. legend
+ -	6b	two-way ANOVA followed by Bonferroni post hoc	Fig. legend	14, 12, 14, 14	mice	Fig. legend	mean ± SEM	Fig. legend	interaction: p = 0.04; group: p < 0.001; days: p < 0.0001	Fig. legend	interaction: F(12,250) = 1.87; group: F(3,250) = 31.46; days: F(4,250) = 45.48	Fig. legend
+ -	6c	one-way ANOVA followed by Bonferroni post hoc	Fig. legend	14, 12, 14, 14	mice	Fig. legend	box plot	Fig. legend	p < 0.0001	Fig. legend	F(3,50) = 11.59	Fig. legend
+ -	6d	linear regression	Fig. legend	14, 12, 14, 14	mice	Fig. legend	mean ± SEM	Fig. legend	p = 0.037	Fig. legend	F(1, 38) = 4.67	Fig. legend
+ -	6e	one-way ANOVA followed by Bonferroni post hoc	Fig. legend	14, 12, 14, 14	mice	Fig. legend	box plot	Fig. legend	p = 0.333	Fig. legend	F(3,50) = 1.164	Fig. legend
+ -	6h	Mander's correlation	Fig. legend	8	mice	Fig. legend	mean ± SEM	Fig. legend	N/A	N/A	N/A	N/A
+ -	6i	Mander's correlation	Fig. legend	8	mice	Fig. legend	mean ± SEM	Fig. legend	N/A	N/A	N/A	N/A
+ -	6j	Mander's correlation	Fig. legend	8	mice	Fig. legend	mean ± SEM	Fig. legend	N/A	Fig. legend	N/A	Fig. legend
+ -	6k	one-way ANOVA followed by Bonferroni post hoc	Fig. legend	8, 8, 8	mice	Fig. legend	box plot	Fig. legend	p < 0.001	Fig. legend	F(2,23) = 70.35	Fig. legend
+ -	7b	one-way ANOVA followed by Bonferroni post hoc	Fig. legend	18	3 pictures per mouse, 6 mice/ group	Fig. legend	box plot	Fig. legend	p < 0.0001	Fig. legend	F(3,67) = 21.77	Fig. legend
+ -	7c	linear regression	Fig. legend	18	3 pictures per mouse, 6 mice/ group	Fig. legend	mean ± SEM	Fig. legend	p = 0.032	Fig. legend	F(1, 67) = 4.79	Fig. legend

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+ -	8a	two-way ANOVA followed by Bonferroni post hoc	Fig. legend	12, 36	4 wells per mouse/ treatment/time point from 3 WT and 9 APP/PS1	Fig. legend	mean ± SEM	Fig. legend	interaction: p = 0.0002; group: p = 0.0002; days: p < 0.0001	Fig. legend	interaction: F(3,184) = 7.109; group: F(3,184) = 7.109; time: F(1,184) = 76.13	Fig. legend
+ -	8b	one-way ANOVA followed by Bonferroni post hoc	Fig. legend	4, 4, 5, 5	1 well per mouse	Fig. legend	box plot	Fig. legend	p = 0.0008	Fig. legend	F(3,14) = 10.20	Fig. legend
+ -	8c	two-way ANOVA followed by Bonferroni post hoc	Fig. legend	16, 72	8 wells per mouse/ treatment/time point from 2 WT and 9 APP/PS1	Fig. legend	mean ± SEM	Fig. legend	interaction: p < 0.0001; group: p < 0.0001; days: p < 0.0001	Fig. legend	interaction: F(3,344) = 78.43; group: F(3,344) = 102.4; time: F(1,344) = 170.2	Fig. legend
+ -	8d	one-way ANOVA followed by Bonferroni post hoc	Fig. legend	4, 4, 5, 5	1 well per mouse	Fig. legend	box plot	Fig. legend	p = 0.0005	Fig. legend	F(3,14) = 11.30	Fig. legend
+ -	8f	unpaired t-test	Fig. legend	4, 5	mice	Fig. legend	box plot	Fig. legend	p = 0.0341	Fig. legend	t(7) = 2.627	Fig. legend
+ -	8g	unpaired t-test	Fig. legend	4, 4	mice	Fig. legend	box plot	Fig. legend	p = 0.0033	Fig. legend	t(6) = 4.353	Fig. legend
+ -	S1b triton	unpaired t-test	Fig. legend	11, 12	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.409	Fig. legend	t(21) = 0.840	Fig. legend
+ -	S1c TBS	unpaired t-test	Fig. legend	11, 12	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.691	Fig. legend	t(21) = 0.402	Fig. legend
+ -	S1c triton	unpaired t-test	Fig. legend	11, 12	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.724	Fig. legend	t(21) = 0.357	Fig. legend
+ -	S1d TBS	unpaired t-test	Fig. legend	11, 12	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.862	Fig. legend	t(21) = 0.176	Fig. legend
+ -	S1d triton	unpaired t-test	Fig. legend	11, 12	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.949	Fig. legend	t(21) = 0.065	Fig. legend
+ -	S3b	unpaired t-test	Fig. legend	15, 15	number of human cases	Fig. legend	box plot	Fig. legend	p < 0.0001	Fig. legend	t(28) = 4.561	Fig. legend
+ -	S3c CTL	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.96	Fig. legend	R(13) = 0.319	Fig. legend
+ -	S3c AD	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.97	Fig. legend	R(13) = 0.365	Fig. legend
+ -	S3d	unpaired t-test	Fig. legend	15, 15	number of human cases	Fig. legend	box plot	Fig. legend	p < 0.0001	Fig. legend	t(28) = 6.991	Fig. legend
+ -	S3e	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.99	Fig. legend	R(13) = 0.4155	Fig. legend
+ -	S4a CTL	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.965	Fig. legend	R(13) = 0.6159	Fig. legend
+ -	S4a AD	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.970	Fig. legend	R(13) = 0.6075	Fig. legend
+ -	S4b	unpaired t-test	Fig. legend	15, 15	number of human cases	Fig. legend	box plot	Fig. legend	p = 0.752	Fig. legend	t(28) = 0.319	Fig. legend
+ -	S5a	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.99	Fig. legend	R(13) = 0.583	Fig. legend
+ -	S5b	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.63	Fig. legend	R(13) = 0.179	Fig. legend
+ -	S5c	Mander's correlation	Fig. legend	15	number of human cases	Fig. legend	mean ± SEM	Fig. legend	Costes p = 0.96	Fig. legend	R(13) = 0.578	Fig. legend
+ -	S7b FAD	unpaired t-test	Fig. legend	7, 5	mice	Fig. legend	box plot	Fig. legend	p = 0.036	Fig. legend	t(10) = 2.423	Fig. legend
+ -	S7b APP	unpaired t-test	Fig. legend	8, 8	mice	Fig. legend	box plot	Fig. legend	p = 0.0234	Fig. legend	t(14) = 1.245	Fig. legend

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+ -	S7c FAD	unpaired t-test	Fig. legend	7,5	mice	Fig. legend	box plot	Fig. legend	p = 0.016	Fig. legend	t(10) = 2.910	Fig. legend
+ -	S7c APP	unpaired t-test	Fig. legend	8, 8	mice	Fig. legend	box plot	Fig. legend	p = 0.433	Fig. legend	t(14) = 0.807	Fig. legend
+ -	S7d FAD	unpaired t-test	Fig. legend	7, 5	mice	Fig. legend	box plot	Fig. legend	p = 0.012	Fig. legend	t(10) = 3.076	Fig. legend
+ -	S8c	unpaired t-test	Fig. legend	14	mice/group	Fig. legend	box plot	Fig. legend	p = 0.242	Fig. legend	t(26) = 1.197	Fig. legend
+ -	S8d	unpaired t-test	Fig. legend	14	mice/group	Fig. legend	box plot	Fig. legend	p = 0.655	Fig. legend	t(26) = 0.4513	Fig. legend
+ -	S8e	unpaired t-test	Fig. legend	14	mice/group	Fig. legend	box plot	Fig. legend	p = 0.520	Fig. legend	t(26) = 0.6518	Fig. legend
+ -	S8f	unpaired t-test	Fig. legend	14	mice/group	Fig. legend	box plot	Fig. legend	p = 0.415	Fig. legend	t(26) = 0.8277	Fig. legend
+ -	S8h	unpaired t-test	Fig. legend	7, 8	mice	Fig. legend	box plot	Fig. legend	p = 0.637	Fig. legend	t(13) = 0.484	Fig. legend
+ -	S8i	unpaired t-test	Fig. legend	7, 8	mice	Fig. legend	box plot	Fig. legend	p = 0.640	Fig. legend	t(13) = 0.480	Fig. legend
+ -	S8j	unpaired t-test	Fig. legend	7, 8	mice	Fig. legend	box plot	Fig. legend	p = 0.640	Fig. legend	t(13) = 0.480	Fig. legend

Representative figures

1. Are any representative images shown (including Western blots and immunohistochemistry/staining) in the paper?

   If so, what figure(s)?

Fig. 1a, d: western blots and immunofluorescent staining
Fig. 2a, c, e, g, h, j, and l: western blots and immunofluorescent staining
Fig. 4d, e: immunofluorescent staining
Fig. 6f-j: immunofluorescent staining
Fig. 7a: immunofluorescent staining
Fig. 8e: immunofluorescent staining
Suppl. Fig. 1a: western blots
Suppl. Fig. 3a, c, e: immunofluorescent staining
Suppl. Fig. 4a: immunofluorescent staining
Suppl. Fig. 5a-c: immunofluorescent staining
Suppl. Fig. 7e-f: immunofluorescent staining
Suppl. Fig. 8a-b: immunohistochemistry
Suppl. Fig. 10e-f: immunofluorescent staining

2. For each representative image, is there a clear statement of how many times this experiment was successfully repeated and a discussion of any limitations in repeatability?

   If so, where is this reported (section, paragraph #)?

While representative images are shown, the statistical analyses were performed on the entire sample as indicated in each figure legend.

We reported this statement in the Statistical Analyses section, within the Methods.

Statistics and general methods

1. Is there a justification of the sample size?

   If so, how was it justified?

   Where (section, paragraph #)?

   Even if no sample size calculation was performed, authors should report why the sample size is adequate to measure their effect size.

An a priori power analysis was not performed, our sample sizes are similar to those reported in previously published papers, in which this sample size has been demonstrated to be appropriate to detect significant effects.

We reported this statement in the Statistical Analyses section, within the Methods.

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2. Are statistical tests justified as appropriate for every figure?

   Where (section, paragraph #)?

Examination of descriptive statistics revealed no violation of any test assumptions that would warrant using statistical test other than the ones used.

This statement is reported in the Statistical Analyses section, within the Methods.

   a. If there is a section summarizing the statistical methods in the methods, is the statistical test for each experiment clearly defined?

Yes, there is a "Statistical Analyses Section" within the Methods. However, the statistical test used for each experiment is clearly defined in the figure legends.

   b. Do the data meet the assumptions of the specific statistical test you chose (e.g. normality for a parametric test)?

      Where is this described (section, paragraph #)?

Yes.

This statement is reported in the Statistical Analyses section, within the Methods.

   c. Is there any estimate of variance within each group of data?

      Is the variance similar between groups that are being statistically compared?

      Where is this described (section, paragraph #)?

The estimate of variance is reported in graphical form in each graph.

Yes, the variance is similar between groups.

This statement is reported in the Statistical Analyses section, within the Methods.

   d. Are tests specified as one- or two-sided?

The tests were two sided

   e. Are there adjustments for multiple comparisons?

Yes, there are. The results showed in Fig. 3a-c and Fig. 4f-i were corrected for multiple comparisons. The results showed in Fig. 6c, Fig. 6e, Fig. 6k, Fig. 7b, Fig. 8b, and Fig. 8d were analyzed by one-way ANOVA, followed by Bonferroni's post hoc analysis. The results showed in Fig. 6a-b, Fig. 8a, Fig. 8c were analyzed by two-way ANOVA, followed by Bonferroni's post hoc analysis.

3. To promote transparency, *Nature Neuroscience* has stopped allowing bar graphs to report statistics in the papers it publishes. If you have bar graphs in your paper, please make sure to switch them to dot-plots (with central and dispersion statistics displayed) or to box-and-whisker plots to show data distributions.

All the graphs were switched to box-and-whiskers plots or dot blots.

4. Are criteria for excluding data points reported?

   Was this criterion established prior to data collection?

   Where is this described (section, paragraph #)?

No data points were excluded. In the analyses for brain weight (Fig. 3d), Braak stage (Fig. 4a-c), and MMSE (Fig. 4d-g) the sample size was smaller than the total number of cases, due to unavailability of these variables from the Banner Sun Health Research Institute Brain and Body Donation Program.

All the sample sizes were reported in Supplementary Tables 1 and 2.

5. Define the method of randomization used to assign subjects (or samples) to the experimental groups and to collect and process data.

   If no randomization was used, state so.

   Where does this appear (section, paragraph #)?

Human cases were selected randomly among the tissue available. Mice were assigned to a specific group based on their genotype after birth and there were no other factors that determined group selection. No mice were excluded.

This statement is reported in the Human tissue and mice section, within the Methods.

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6. Is a statement of the extent to which investigator knew the group allocation during the experiment and in assessing outcome included? If no blinding was done, state so. Where (section, paragraph #)?	For the behavioral analyses shown in Fig. 6, the experimenters were blinded to genotype and treatment. No blinding was done for the other experiments. This statement is reported in the Morris water maze and Human tissue and mice sections, within the Methods.
7. For experiments in live vertebrates, is a statement of compliance with ethical guidelines/regulations included? Where (section, paragraph #)?	Yes. Human tissue and mice section within the Methods
8. Is the species of the animals used reported? Where (section, paragraph #)?	Yes. Human tissue and mice section within the Methods
9. Is the strain of the animals (including background strains of KO/ transgenic animals used) reported? Where (section, paragraph #)?	Yes. Human tissue and mice section within the Methods
10. Is the sex of the animals/subjects used reported? Where (section, paragraph #)?	Yes, the sex for animals/subject is reported. For human cases, see Supplementary Table 1. For mice, see second paragraph in the "Brains with AD-like pathology are more prone to necroptosis" section within the Results.
11. Is the age of the animals/subjects reported? Where (section, paragraph #)?	Yes, the age for animals/subject is reported. For human cases, see Supplementary Tables 1. For mice, see first and second paragraphs in the "Brains with AD-like pathology are more prone to necroptosis" section within the Results.
12. For animals housed in a vivarium, is the light/dark cycle reported? Where (section, paragraph #)?	Yes. Human tissue and mice section within the Methods.
13. For animals housed in a vivarium, is the housing group (i.e. number of animals per cage) reported? Where (section, paragraph #)?	Yes. Human tissue and mice section within the Methods.
14. For behavioral experiments, is the time of day reported (e.g. light or dark cycle)? Where (section, paragraph #)?	Yes. Morris water maze section within the Methods
15. Is the previous history of the animals/subjects (e.g. prior drug administration, surgery, behavioral testing) reported? Where (section, paragraph #)?	For human subjects, we do not have access to their previous history. For the behavioral studies in mice, we used mice that underwent stereotaxic surguries for viral injections as reported in the second and third paragraphs of the "Brains with AD-like pathology are more prone to necroptosis" section within the Results.
a. If multiple behavioral tests were conducted in the same group of animals, is this reported? Where (section, paragraph #)?	N/A

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16. If any animals/subjects were excluded from analysis, is this reported?

Where (section, paragraph #)?

No animals/subjects were excluded from the analyses.

a. How were the criteria for exclusion defined?

Where is this described (section, paragraph #)?

N/A

b. Specify reasons for any discrepancy between the number of animals at the beginning and end of the study.

Where is this described (section, paragraph #)?

N/A

Reagents

1. Have antibodies been validated for use in the system under study (assay and species)?

Yes

a. Is antibody catalog number given?

Where does this appear (section, paragraph #)?

Yes.

"Immunohistochemistry" and "Western blot and ELISA" sections within the Methods.

b. Where were the validation data reported (citation, supplementary information, Antibodypedia)?

Where does this appear (section, paragraph #)?

Supplementary Figures 10 and "Antibody Validation" section within the Methods.

2. Cell line identity

a. Are any cell lines used in this paper listed in the database of commonly misidentified cell lines maintained by ICLAC and NCBI Biosample?

Where (section, paragraph #)?

N/A

b. If yes, include in the Methods section a scientific justification of their use--indicate here in which section and paragraph the justification can be found.

N/A

c. For each cell line, include in the Methods section a statement that specifies:

- the source of the cell lines
- have the cell lines been authenticated? If so, by which method?
- have the cell lines been tested for mycoplasma contamination?

Where (section, paragraph #)?

N/A

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Data availability

Provide a Data availability statement in the Methods section under "Data availability", which should include, where applicable:

- Accession codes for deposited data
- Other unique identifiers (such as DOIs and hyperlinks for any other datasets)
- At a minimum, a statement confirming that all relevant data are available from the authors
- Formal citations of datasets that are assigned DOIs
- A statement regarding data available in the manuscript as source data
- A statement regarding data available with restrictions

See our data availability and data citations policy page for more information.

Data deposition in a public repository is mandatory for:

a. Protein, DNA and RNA sequences
b. Macromolecular structures
c. Crystallographic data for small molecules
d. Microarray data

Deposition is strongly recommended for many other datasets for which structured public repositories exist; more details on our data policy are available here. We encourage the provision of other source data in supplementary information or in unstructured repositories such as Figshare and Dryad.

We encourage publication of Data Descriptors (see Scientific Data) to maximize data reuse.

Where is the Data Availability statement provided (section, paragraph #)?

The statement ""The data that support the findings of this study are available from the corresponding author upon reasonable request" is reported in the "Data availability" section at the end of the Methods.

All the datasets used in this study, with ID and name, are reported in the "Accession codes" section. Specifically:

- The microarray data are available in the Gene Expression File 1. This sentence is reported in the "Necroptosis activation negatively correlates with brain weight and MMSE" section within the Results.

- The external dataset used for validation was already deposited in the database Gene Expression Omnibus (GEO). The ID, GSE5281, is reported in the "Necroptosis activation negatively correlates with brain weight and MMSE" section within the Results.

- The external datasets used for generating the RIPK1 causal gene regulatory network were already deposited on www.synapse.org: syn3157743: MSBB AD RNA-seq Gene Expression Data; and syn4645334: MSBB AD Whole Exome Sequencing (WES) Data. The IDs are reported in the "Construction of RIPK1 causal gene regulatory network" section within the Methods.

Computer code/software

Any custom algorithm/software that is central to the methods must be supplied by the authors in a usable and readable form for readers at the time of publication. However, referees may ask for this information at any time during the review process.

1. Identify all custom software or scripts that were required to conduct the study and where in the procedures each was used.

N/A

2. If computer code was used to generate results that are central to the paper's conclusions, include a statement in the Methods section under "**Code availability**" to indicate whether and how the code can be accessed. Include version information as necessary and any restrictions on availability.

We used functions implemented in the R packages: ggplot2, stats, car, lumi, limma, annotate, lumiHumanAll.db, lumiHumanIDMapping, AnnotationDbi, MASS, quantreg, multtest (https://cran.r-project.org; https://bioconductor.org). For the construction of the RIPK1 causal gene regulatory network, we used the Matrix eQTL software and the causal inference testing (CIT), available in Shabalin, Bioinformatics 2012, and Millstein et al., BMC Genet 2009.

Human subjects

Nature Neuroscience: doi:10.1038/nn.4608

1. Which IRB approved the protocol?

   Where is this stated (section, paragraph #)?

   Only post mortem human tissue was used and thus no IRB approval was needed

2. Is demographic information on all subjects provided?

   Where (section, paragraph #)?

   Yes, Supplementary Tables 1-2.

3. Is the number of human subjects, their age and sex clearly defined?

   Where (section, paragraph #)?

   Yes, Supplementary Table 1.

4. Are the inclusion and exclusion criteria (if any) clearly specified?

   Where (section, paragraph #)?

   N/A

5. How well were the groups matched?

   Where is this information described (section, paragraph #)?

   The groups were matched for age and sex. This information is reported in Supplementary Table 1.

6. Is a statement included confirming that informed consent was obtained from all subjects?

   Where (section, paragraph #)?

   N/A

7. For publication of patient photos, is a statement included confirming that consent to publish was obtained?

   Where (section, paragraph #)?

   N/A

fMRI studies

For papers reporting functional imaging (fMRI) results please ensure that these minimal reporting guidelines are met and that all this information is clearly provided in the methods:

1. Were any subjects scanned but then rejected for the analysis after the data was collected?

   N/A

   a. If yes, is the number rejected and reasons for rejection described?

      Where (section, paragraph #)?

      N/A

2. Is the number of blocks, trials or experimental units per session and/or subjects specified?

   Where (section, paragraph #)?

   N/A

3. Is the length of each trial and interval between trials specified?

   N/A

4. Is a blocked, event-related, or mixed design being used? If applicable, please specify the block length or how the event-related or mixed design was optimized.

   N/A

Nature Neuroscience: doi:10.1038/nn.4608

5. Is the task design clearly described? Where (section, paragraph #)?	N/A
6. How was behavioral performance measured?	N/A
7. Is an ANOVA or factorial design being used?	N/A
8. For data acquisition, is a whole brain scan used? If not, state area of acquisition.	N/A
a. How was this region determined?	N/A
9. Is the field strength (in Tesla) of the MRI system stated?	N/A
a. Is the pulse sequence type (gradient/spin echo, EPI/spiral) stated?	N/A
b. Are the field-of-view, matrix size, slice thickness, and TE/TR/ flip angle clearly stated?	N/A
10. Are the software and specific parameters (model/functions, smoothing kernel size if applicable, etc.) used for data processing and pre-processing clearly stated?	N/A
11. Is the coordinate space for the anatomical/functional imaging data clearly defined as subject/native space or standardized stereotaxic space, e.g., original Talairach, MNI305, ICBM152, etc? Where (section, paragraph #)?	N/A
12. If there was data normalization/standardization to a specific space template, are the type of transformation (linear vs. nonlinear) used and image types being transformed clearly described? Where (section, paragraph #)?	N/A
13. How were anatomical locations determined, e.g., via an automated labeling algorithm (AAL), standardized coordinate database (Talairach daemon), probabilistic atlases, etc.?	N/A
14. Were any additional regressors (behavioral covariates, motion etc) used?	N/A
15. Is the contrast construction clearly defined?	N/A
16. Is a mixed/random effects or fixed inference used?	N/A
a. If fixed effects inference used, is this justified?	N/A
17. Were repeated measures used (multiple measurements per subject)?	N/A

Nature Neuroscience: doi:10.1038/nn.4608

a. If so, are the method to account for within subject correlation and the assumptions made about variance clearly stated?	N/A
18. If the threshold used for inference and visualization in figures varies, is this clearly stated?	N/A
19. Are statistical inferences corrected for multiple comparisons?	N/A
a. If not, is this labeled as uncorrected?	N/A
20. Are the results based on an ROI (region of interest) analysis?	N/A
a. If so, is the rationale clearly described?	N/A
b. How were the ROI's defined (functional vs anatomical localization)?	N/A
21. Is there correction for multiple comparisons within each voxel?	N/A
22. For cluster-wise significance, is the cluster-defining threshold and the corrected significance level defined?	N/A

Additional comments

Additional Comments	

Nature Neuroscience: doi:10.1038/nn.4608