Figure S1. Related to Figure 1.

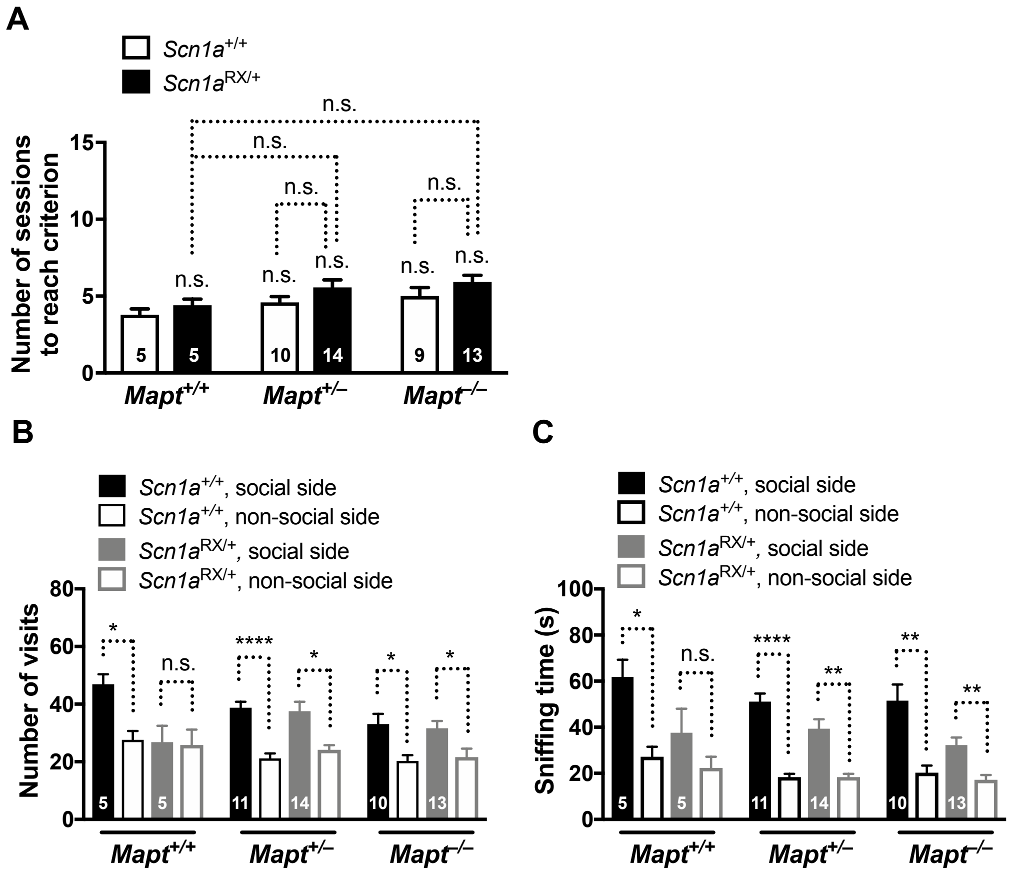

Figure S1 | Tau Reduction Prevents Autism-like Behaviors in *Scn1a*$^{RX/+}$ Mice. Related to Figure 1.

Male *Scn1a*$^{+/+}$ and *Scn1a*$^{RX/+}$ mice with the indicated *Mapt* genotypes were assessed for autism-like behaviors at 4–7 months of age. (**A**) Initial learning in water T-maze relearning test. The number of training sessions mice required to learn the initial location of the submerged escape platform was counted. (**B–C**) Three-chamber social interaction test. The number of visits (**B**) and total time mice spent (**C**) interacting with an enclosure containing a live mouse on the "social" side or an empty enclosure in the "nonsocial" side were recorded for 10 minutes. Numbers in bars indicate numbers of mice per genotype. ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001 vs. *Scn1a*$^{+/+}$*Mapt*$^{+/+}$ mice or as indicated by brackets, determined by Kruskal-Wallis test with Dunn correction (**A**) or two-tailed paired *t* tests with Holm-Sidak correction (**B, C**). n.s., not significant. Values are mean ± SEM.

Figure S2. Related to Figure 1.

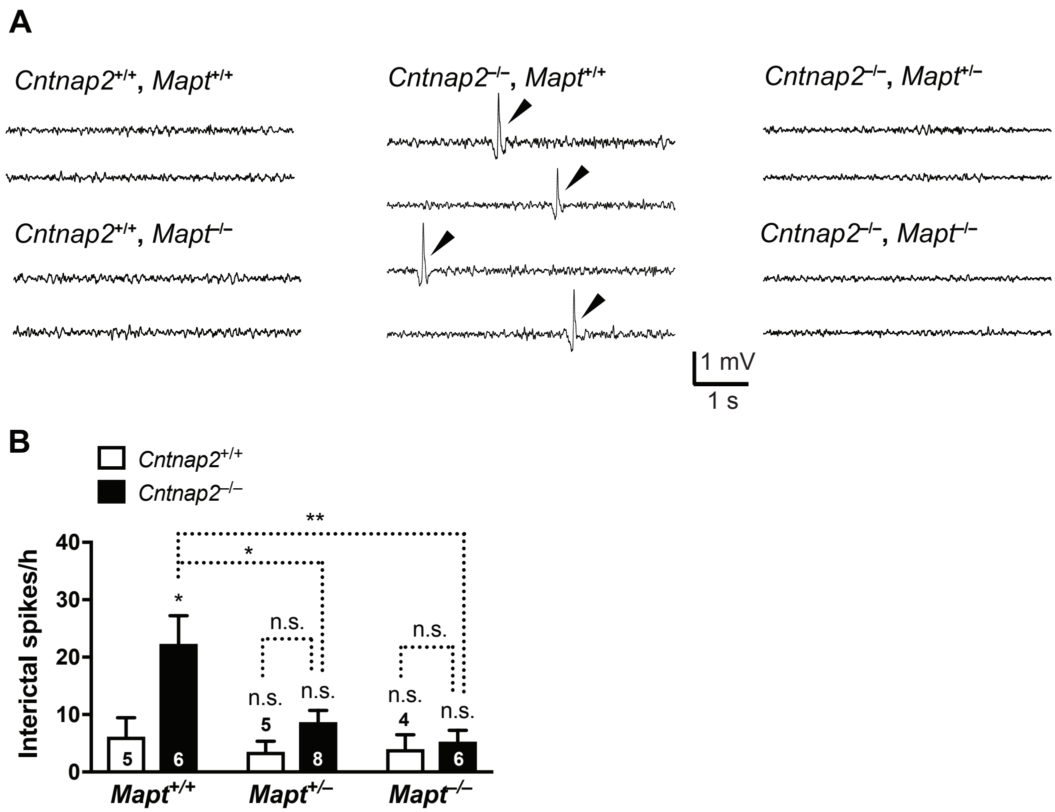

Figure S2 | Tau Reduction Reduces Epileptic Interictal Spikes in *Cntnap2*$^{–/–}$ Mice. Related to Figure 1.

Cntnap2$^{+/+}$ and *Cntnap2*$^{–/–}$ mice with 2, 1, or 0 *Mapt* alleles were compared at 7–11 months of age. Epileptic interictal spike frequency was determined by subdural EEG recordings in resting mice. (**A**) Representative EEG traces. Note the epileptic spikes (arrowheads) in *Cntnap2*$^{–/–}$*Mapt*$^{+/+}$ mice. (**B**) Quantitation of interictal spikes during a 24-hour recording session. Numbers in bars indicate numbers of mice per genotype. *$P < 0.05$, **$P < 0.01$ vs. *Cntnap2*$^{+/+}$*Mapt*$^{+/+}$ mice or as indicated by brackets, determined by two-way ANOVA with Holm-Sidak test. Interaction between *Scn1a* and *Mapt* genotypes by two-way ANOVA: $P = 0.063$, $F_{2, 28} = 3.05$. n.s., not significant. Values are mean ± SEM.

Figure S3. Related to Figure 2.

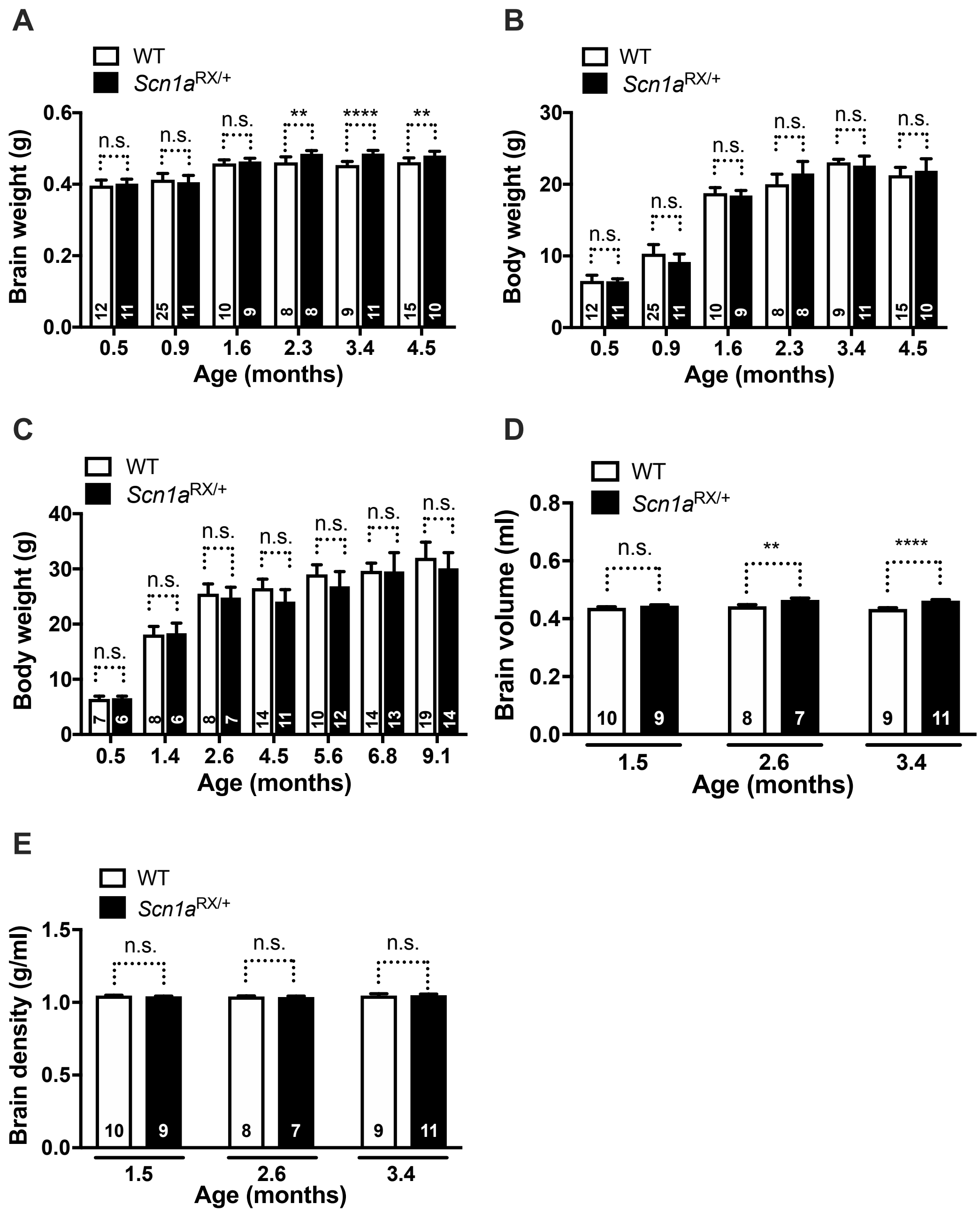

Figure S3 | *Scn1a*$^{RX/+}$ Mice Have Increased Brain Weight and Volume but Normal Brain Density and Body Weight. Related to Figure 2.

Different groups of *Scn1a*$^{+/+}$ (WT) and *Scn1a*$^{RX/+}$ mice on the *Mapt*$^{+/+}$ background were compared at different ages. (**A, B**) Brain (**A**) and body (**B**) weights of female mice. (**C**) Body weights of the male mice shown in Figure 2A. (**D, E**) Brain volumes (**D**) and densities (**E**) were determined in a subset of female (ages: 1.5 and 3.4 months) and male (age: 2.6 months) mice. **$P < 0.01$, ****$P < 0.0001$ vs. age-matched WT mice or as indicated by brackets, determined by two-way ANOVA with Holm-Sidak test (**A, D**), Kruskal-Wallis test with Dunn's test (**E**), or multiple Welch's *t* tests with Holm-Sidak correction (**B**, **C**). Interaction between age and brain weight by two-way ANOVA: (**A**) $P < 0.0001$, $F_{5, 127} = 6.52$; and between age and brain volume: (**D**) $P = 0.021$, $F_{2, 48} = 4.19$. n.s., not significant. Values are means ± SEM.

Figure S4. Related to Figures 2 and 4.

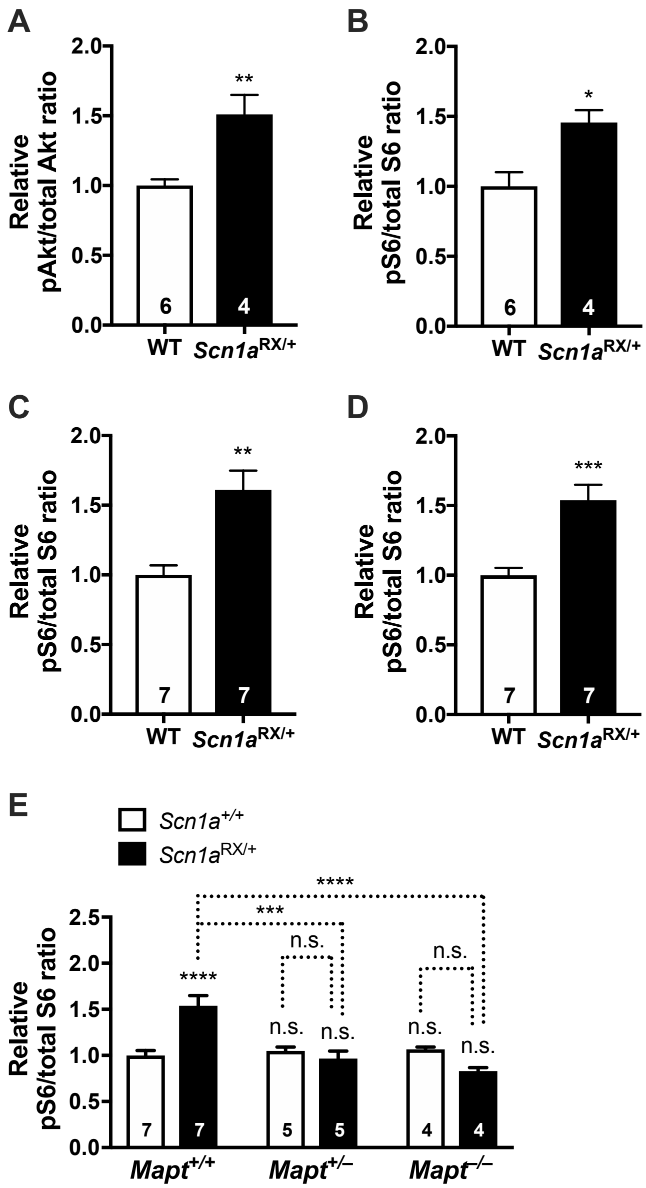

Figure S4 | Overactivation of PI3K/Akt/mTOR Signaling in *Scn1a*$^{RX/+}$ Mice and Prevention by Tau Reduction. Related to Figures 2 and 4.

(**A–B**) Relative hippocampal signal ratios for pAkt/total Akt (**A**) and pS6 (Ser235/236)/total S6 (**B**) in WT and *Scn1a*$^{RX/+}$ mice were determined by western blot analysis at 9–10 months of age. Measurements in these and the other panels of this figure were normalized to the mean ratios in WT mice (defined as 1.0). (**C–D**) Relative hippocampal signal ratios for pS6 (Ser235/236)/total S6 (**C**) and pS6 (Ser240/244)/total S6 (**D**) in WT and *Scn1a*$^{RX/+}$ mice were determined by western blot analysis at 2–3 months of age. (**E**) Relative hippocampal pS6 (Ser240/244)/total S6 ratios were compared in *Scn1a*$^{+/+}$ and *Scn1a*$^{RX/+}$ mice that had 2, 1, or 0 *Mapt* alleles. Numbers in bars indicate numbers of mice per genotype. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$ vs. WT mice or as indicated by brackets, determined by unpaired, two-tailed Student's *t* test (**A**–**D**), or two-way ANOVA with Holm-Sidak test (**E**). Interaction between *Scn1a* and *Mapt* genotypes by two-way ANOVA (**E**): $P < 0.0001$, $F_{2, 26} = 14.86$. n.s., not significant. Values are means ± SEM.

Figure S5. Related to Figure 5 and STAR Methods.

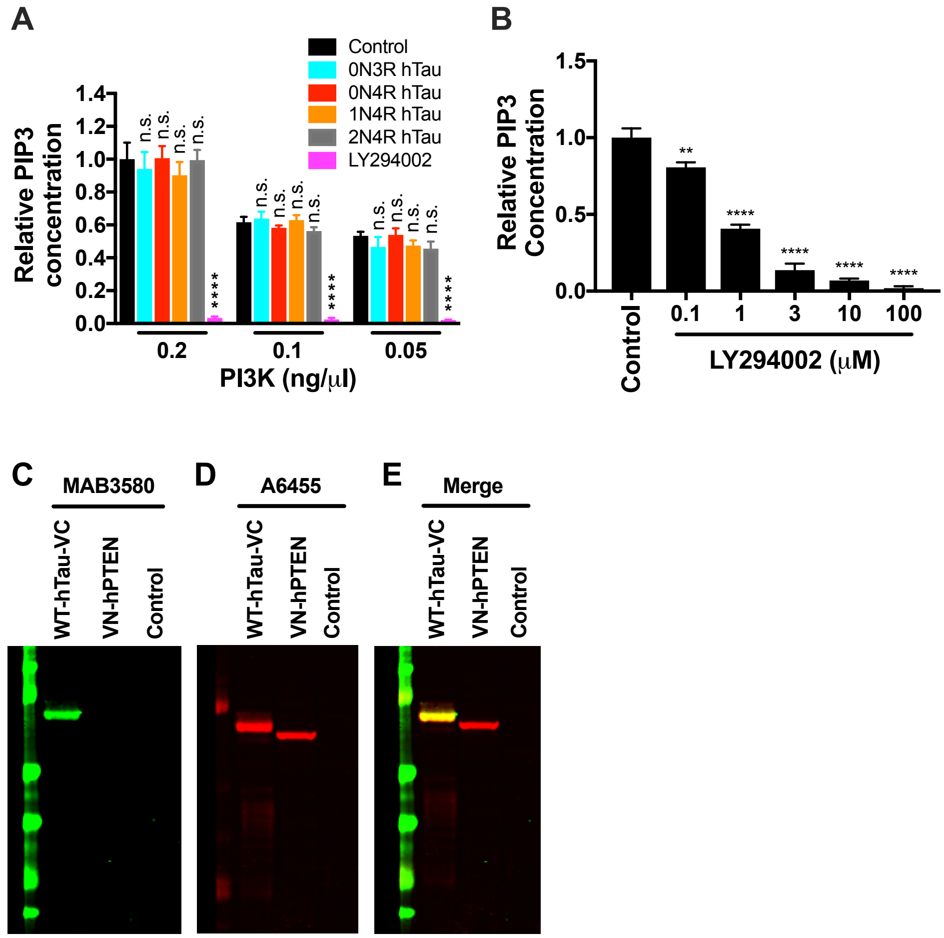

Figure S5 | Tau Does Not Affect the Lipid Kinase Activity of PI3K; MAB3580 Recognizes VC-tagged but not VN-tagged Proteins. Related to Figure 5 and STAR Methods.

(**A**) The lipid kinase activity of PI3K was measured under cell-free conditions in the presence of different recombinant human tau species. Albumin was used as the negative control (Control). $n = 4$ independent experiments, each including two replicates per condition. LY294002 (10 μM) was used as a positive control. To combine data from independent experiments, measurements were normalized to the mean PIP3 concentration at 0.2 ng/µl PI3K with albumin (defined as 1.0). (**B**) LY294002 inhibits PI3K's lipid kinase activity in a dose-dependent manner. $n = 3$ independent experiments. PIP3 concentrations in the absence of LY294002 were defined as 1.0. (**C–E**) Representative western blots of HEK-293 cells that were transfected with hTau-WT-VC or VN-hPTEN or were untransfected (control). Blots were probed with (**C**) MAB3580, a monoclonal mouse antibody that specifically recognizes VC, or (**D**) A6455, a rabbit polyclonal antibody that cross-reacts with VC and VN. A merged image is shown in (**E**). $^{**}P < 0.01$, $^{****}P < 0.0001$ vs. PI3K concentration-matched control (**A**) or the left most bar (**B**), determined by two-way ANOVA with Holm-Sidak test (**A**) or one-way ANOVA with Holm-Sidak test (**B**). Interaction between PI3K concentration and tau species by two-way ANOVA (without LY294002 bars): (**A**) $P = 0.8635$, $F_{8, 45} = 0.48$. n.s., not significant. Values are means ± SEM.

Figure S6. Related to Figure 6.

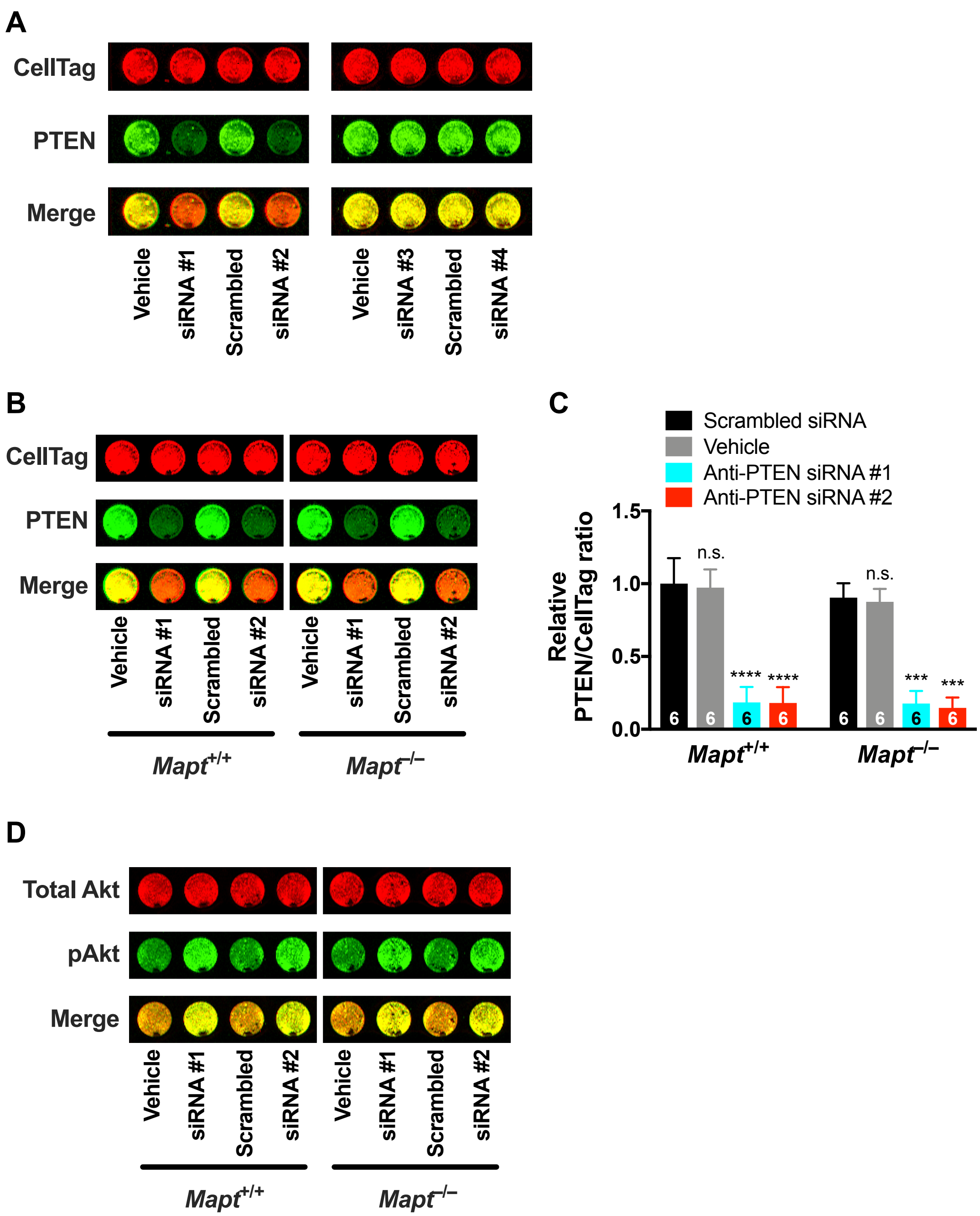

Figure S6 | Li-COR In-Cell Western Blots Demonstrating Reduced PTEN Protein Levels and Increased PI3K Signaling in *Mapt*$^{+/+}$ and *Mapt*$^{-/-}$ Neurons Treated with Anti-PTEN siRNAs. Related to Figure 6.

(A) Representative CellTag 700 and PTEN signals in wells of DIV 11 *Mapt*$^{+/+}$ mouse neurons after treatment with scrambled siRNA, anti-PTEN siRNAs #1 to #4, or vehicle (1x siRNA buffer, 1:100) on DIV 7. Blots were probed with an antibody against PTEN and with CellTag 700, a reagent used to control for well-to-well variation in cell numbers. For quantitative analyses, see Figure 6A. **(B–C)** CellTag 700 and PTEN signals in DIV 11 *Mapt*$^{+/+}$ and *Mapt*$^{-/-}$ mouse neurons after treatment with scrambled siRNA, anti-PTEN siRNAs #1 or #2, or vehicle (1x siRNA buffer, 1:100) on DIV 7. Representative In-Cell blots are shown in (**B**) and relative PTEN/CellTag signal ratios in **(C)**. Measurements were normalized to the mean of *Mapt*$^{+/+}$ samples treated with scrambled siRNA on the same 96-well plate (defined as 1.0). Numbers in bars indicate biological replicates (independent cultures from individual mouse pups). **(D)** Representative Akt and pAkt signals in DIV 11 *Mapt*$^{+/+}$ and *Mapt*$^{-/-}$ neurons after treatment with scrambled siRNA, anti-PTEN siRNAs #1 or #2, or vehicle (1x siRNA buffer, 1:100) on DIV 7. For quantitative analyses, see Figure 6B. $^{***}P < 0.001$, $^{****}P < 0.0001$ vs. the leftmost bar in each genotype, determined by two-way ANOVA and Holm-Sidak test (**C**). By two-way ANOVA, interaction between genotype and siRNA (**C**): $P = 0.97$, $F_{3, 40} = 0.08$. n.s., not significant. Values are means ± SEM.

Figure S7. Related to Figure 7.

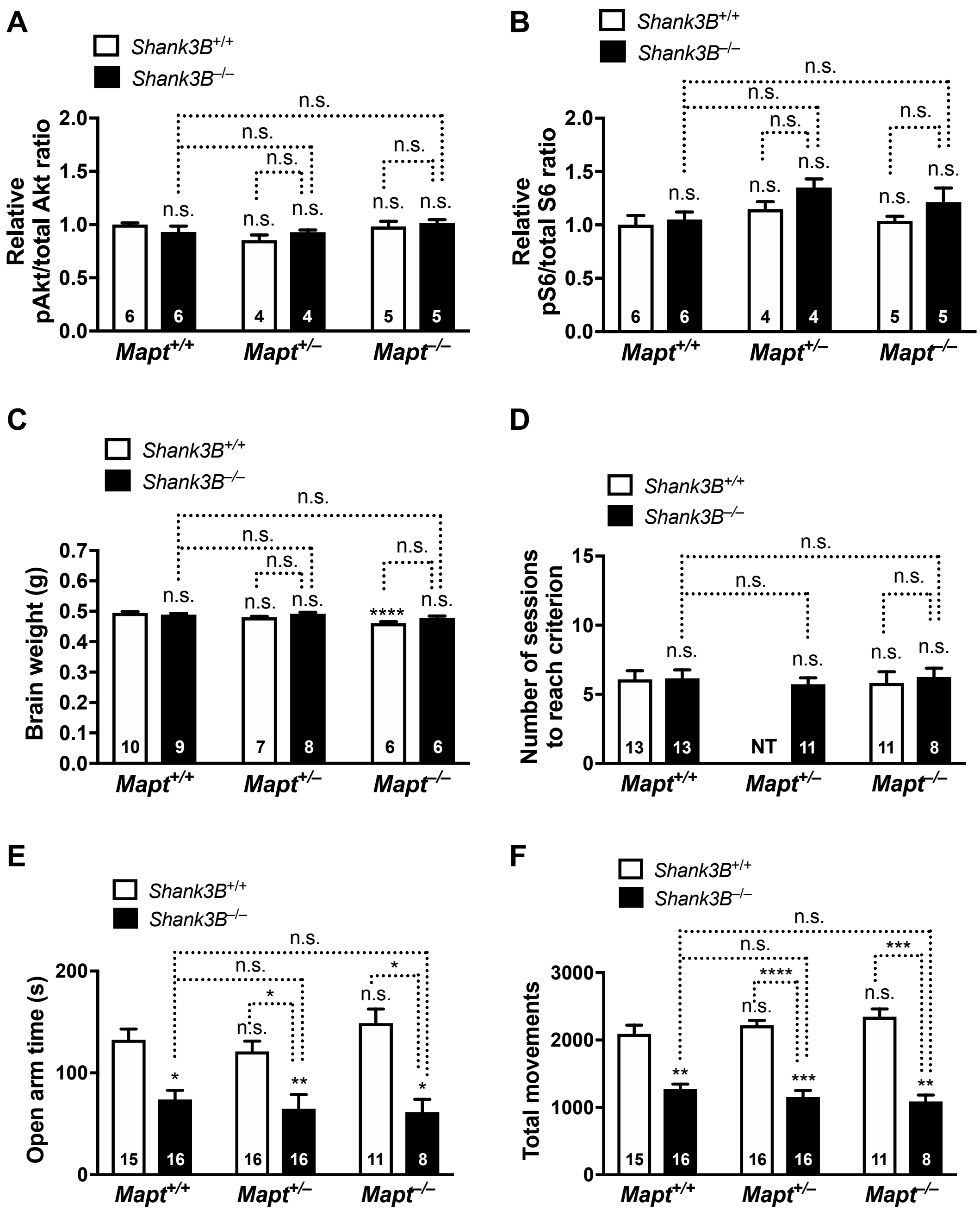

Figure S7 | Tau Reduction Does Not Affect pAkt and pS6 Activity, Brain Weight or Autism-like Behaviors in *Shank3B*$^{-/-}$ Mice. Related to Figure 7.

(**A–C**) *Shank3B*$^{+/+}$ and *Shank3B*$^{-/-}$mice with 2, 1, or 0 *Mapt* alleles were assessed at 4–6 months of age. (**A–B**) Relative hippocampal signal ratios for pAkt/total Akt (**A**) and pS6/total S6 (**B**) were determined by western blot analysis. Measurements were normalized to the average of *Shank3B*$^{+/+}$*Mapt*$^{+/+}$ samples on the same gel (defined as 1.0). (**C**) Brain weights. (**D–F**) Male *Shank3B*$^{+/+}$ and *Shank3B*$^{-/-}$ mice with 2, 1, or 0 *Mapt* alleles were assessed for autism-like behaviors at 8–11 months of age. (**D**) Initial learning in the water T-maze test. The number of training sessions mice required to learn the initial location of the submerged escape platform was counted. *Shank3B*$^{+/+}$*Mapt*$^{+/-}$ mice were not tested (NT) in this paradigm. (**E**) Elevated plus maze. The time mice spent in the open arms of the maze was recorded for 10 minutes. (**F**) Open-field test. Total movements were recorded for 15 minutes. Numbers in bars indicate numbers of mice per genotype. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$ vs. *Shank3B*$^{+/+}$*Mapt*$^{+/+}$ mice, determined by two-way ANOVA with Holm-Sidak test (**A, B, C**), one-way ANOVA with Holm-Sidak test (**D**) or Kruskal-Wallis test with Dunn's test (**E, F**). Interaction between *Shank3B* and *Mapt* genotypes by two-way ANOVA: (**A**) $P = 0.19$, $F_{2, 24} = 1.77$; (**B**) $P = 0.62$, $F_{2, 24} = 0.48$; (**C**) $P = 0.028$, $F_{2, 40} = 3.94$. n.s., not significant. Values are means ± SEM.

Table S1 | Tau Dependence of Behavioral Abnormalities in *Scn1a*$^{RX/+}$, *Cntnap2*$^{-/-}$ and *Shank3B*$^{-/-}$ Mice. **Related to Figures 1, 2, 7, S1 and S8.**

ASD Domain	Behavioral Paradigm	*Scn1a*$^{RX/+}$		*Cntnap2*$^{-/-}$		*Shank3B*$^{-/-}$	
		Abnormal	Tau Dependent	Abnormal	Tau Dependent	Abnormal	Tau Dependent
Repetitive behavior	Self-grooming	Yes	Yes	Yes	Yes	Yes	No
	Water T-maze	Yes	Yes	No*	N/A	Yes	No
Communication deficit	Olfactory exploration	Yes	Yes	Yes	Yes	Yes	No
	Ultrasonic vocalizations	N/T	N/T	Yes	Yes	N/T	N/T
Social deficit	Social preference test	Yes	Yes	No*	N/A	Yes	No
	Reciprocal social interaction test	Yes	Yes	No*	N/A	No*	N/A
Anxiety and hyperactivity	Elevated plus maze	Yes*	Yes*	No*	N/A	Yes	No
	Open-field test	Yes	Yes*	No*	N/A	Yes	No
Multiple	Nesting	Yes*	Yes*	Yes	Yes	No*	N/A

*data not shown; N/A, not applicable; N/T, not tested.

Table S2: Summary of data and statistical analyses. **Related to STAR Methods.**

Figure	Panel	Gaussian distribution	Equal variance	Analysis method	Multiple comparisons	Biological N
Figure 1	1A	Yes	Yes	Two-way ANOVA	Holm-Sidak	9–14
	1B	Yes	Yes	Two-way ANOVA	Holm-Sidak	5-14
	1C	Yes	Yes	Two-way ANOVA	Holm-Sidak	6–12
	1D	No	No	GEE framework	Holm-Sidak	10–13
	1E	Yes	Yes	Two-way ANOVA	Holm-Sidak	10–13
	1F	Yes	Yes	Two-way ANOVA	Holm-Sidak	6–23
	1G	Yes	No	Multiple Welch's t-tests	Holm-Sidak	6–15
	1H	No	No	GEE framework	Holm-Sidak	9–17
	1I	Yes	Yes	Two-way ANOVA	Holm-Sidak	9–17
	1J	Yes	Yes	Two-way ANOVA	Holm-Sidak	12–24
Figure 2	2A	Yes	Yes	Two-way ANOVA	Holm-Sidak	6–19
	2B	Yes	Yes	Two-way ANOVA	Holm-Sidak	7–17
	2C	No	Yes	Kruskal-Wallis test	Dunn	12–16
	2D	Yes	Yes	Paired t-tests	Holm-Sidak	5–16
	2F	Yes	Yes	Student's t-test	N/A	5–6
	2G	Yes	Yes	Student's t-test	N/A	5–6
	2I	Yes	Yes	Two-way ANOVA	Holm-Sidak	4–9
	2J	Yes	Yes	Two-way ANOVA	Holm-Sidak	4–9
Figure 4	4A	Yes	Yes	Two-way ANOVA	Holm-Sidak	15–23
	4B	Yes	Yes	Two-way ANOVA	Holm-Sidak	4–6
	4C	Yes	Yes	Two-way ANOVA	Holm-Sidak	4–6
	4D	Yes	Yes	Two-way ANOVA	Holm-Sidak	5–9
	4E	Yes	Yes	Two-way ANOVA	Holm-Sidak	5–9
	4F	Yes	Yes	Two-way ANOVA	Holm-Sidak	10–12
	4G	Yes	Yes	One-way ANOVA	Holm-Sidak	4–5
	4H	Yes	Yes	One-way ANOVA	Holm-Sidak	4–5
Figure 5	5C	Yes	No	Multiple Welch's t-tests	Holm-Sidak	3
	5H	Yes	Yes	One-way ANOVA	Holm-Sidak	3
Figure 6	6A	Yes	Yes	One-way ANOVA	Holm-Sidak	4-7
	6B	Yes	Yes	Two-way ANOVA	Holm-Sidak	9
	6C	Yes	Yes	Two-way ANOVA	Holm-Sidak	9
	6D	Yes	Yes	Two-way ANOVA	Holm-Sidak	9
	6E	Yes	Yes	Two-way ANOVA	Holm-Sidak	9
	6F	Yes	Yes	Two-way ANOVA	Holm-Sidak	9
Figure 7	7A	Yes	Yes	Two-way ANOVA	Holm-Sidak	5–6
	7B	Yes	Yes	Two-way ANOVA	Holm-Sidak	5–6
	7C	No	Yes	Kruskal-Wallis test	Dunn	7–10
	7D	Yes	Yes	Two-way ANOVA	Holm-Sidak	5–12
	7E	Yes	No	Multiple Welch's t-tests	Holm-Sidak	10–20
	7F	Yes	Yes	One-way ANOVA	Holm-Sidak	8–13
	7G	Yes	No	Paired t-tests	Holm-Sidak	8–16
	7H	No	No	GEE framework	Holm-Sidak	8–15
	7I	Yes	Yes	One-way ANOVA	Holm-Sidak	8–15
Figure S1	S1A	No	Yes	Kruskal-Wallis test	Dunn	5–14
	S1B	Yes	Yes	Paired t-tests	Holm-Sidak	5–14
	S1C	Yes	Yes	Paired t-tests	Holm-Sidak	5–14
Figure S2	S2	Yes	Yes	Two-way ANOVA	Holm-Sidak	4–8
Figure S3	S3A	Yes	Yes	Two-way ANOVA	Holm-Sidak	8–25

	S3B	Yes	No	Multiple Welch’s t-tests	Holm-Sidak	8–25
	S3C	Yes	No	Multiple Welch’s t-tests	Holm-Sidak	6–19
	S3D	Yes	Yes	Two-way ANOVA	Holm-Sidak	7–11
	S3E	No	Yes	Kruskal-Wallis test	Dunn	7–11
Figure S4	S4A	Yes	Yes	Student's t-test	N/A	4–6
	S4B	Yes	Yes	Student's t-test	N/A	4–6
	S4C	Yes	Yes	Student's t-test	N/A	7
	S4D	Yes	Yes	Student's t-test	N/A	7
	S4E	Yes	Yes	Two-way ANOVA	Holm-Sidak	4–7
Figure S5	S5A	Yes	Yes	Two-way ANOVA	Holm-Sidak	4
	S5B	Yes	Yes	One-way ANOVA	Holm-Sidak	3
Figure S6	S6C	Yes	Yes	Two-way ANOVA	Holm-Sidak	6
Figure S7	S7A	Yes	Yes	Two-way ANOVA	Holm-Sidak	4–6
	S7B	Yes	Yes	Two-way ANOVA	Holm-Sidak	4–6
	S7C	Yes	Yes	Two-way ANOVA	Holm-Sidak	6–10
	S7D	Yes	Yes	One-way ANOVA	Holm-Sidak	8–13
	S7E	No	Yes	Kruskal-Wallis test	Dunn	8–16
	S7F	No	Yes	Kruskal-Wallis test	Dunn	8–16

GEE, Generalized Estimating Equations