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Supplementary Information for

A key requirement for synaptic Reelin signaling in ketamine-mediated behavioral and synaptic action

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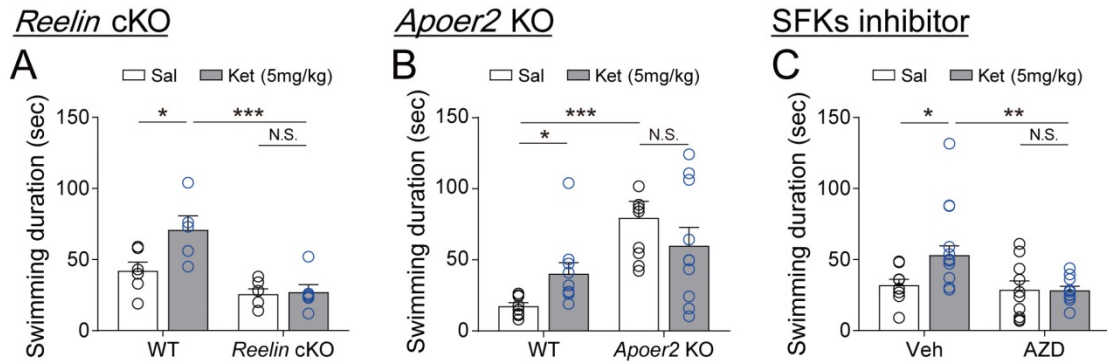> Fig. S1 - S5.
> Supplementary Table

Fig. S1. The cumulative duration of swimming in the FST. (A - C) Cumulative swimming duration was measured in the FST with *Reelin* cKO (Fig. 1), *Apoer2* KO (Fig. 2), and AZD0530-treated mice (Fig. 3). (A) Ketamine significant increased swimming duration in the *Reelin* WT mice but not in cKO mice. Ketamine-mediated increment of swimming duration was significantly attenuated in *Reelin* cKO mice [Two-way ANOVA with Tukey's multiple comparison, Genotype x Ketamine : $F_{(1, 19)}$ = 4.565, P = 0.0459, Genotype factor: $F_{(1, 19)}$ = 21.88, P = 0.0002, Ketamine factor: $F_{(1, 19)}$ = 5.494, P = 0.0301, n = 5 – 6]. (B) Ketamine significant increased swimming duration in the *Apoer2* WT mice. Saline -treated *Apoer2* KO mice showed a significant increase in swimming duration compared to saline-treated WT mice. Ketamine did not further increase swimming duration in *Apoer2* KO mice [Data were transformed with the Box-Cox transformation for parametric statistical analysis. Two-way ANOVA with Tukey's multiple comparison, Genotype x Ketamine : $F_{(1, 33)}$ = 10.97, P = 0.0023, Genotype factor: $F_{(1, 33)}$ = 21.06, P < 0.0001, Ketamine factor: $F_{(1, 33)}$ = 0.7188, P = 0.4026, n = 8 – 10]. (C) Ketamine treatment resulted in a significant increment of swimming duration in vehicle-pretreated mice. The ketamine effects were significantly attenuated by AZD pretreatment [Two-way ANOVA with Tukey's multiple comparison, Genotype x Ketamine : $F_{(1, 35)}$ = 4.199, P = 0.0480, AZD factor: $F_{(1, 35)}$ = 7.171, P = 0.0112, Ketamine factor: $F_{(1, 35)}$ = 3.918, P = 0.0557, n = 9 – 10]. All data represented as mean ± S.E.M. Veh: 1% DMSO in saline, AZD: AZD0530, Src family kinase inhibitor.
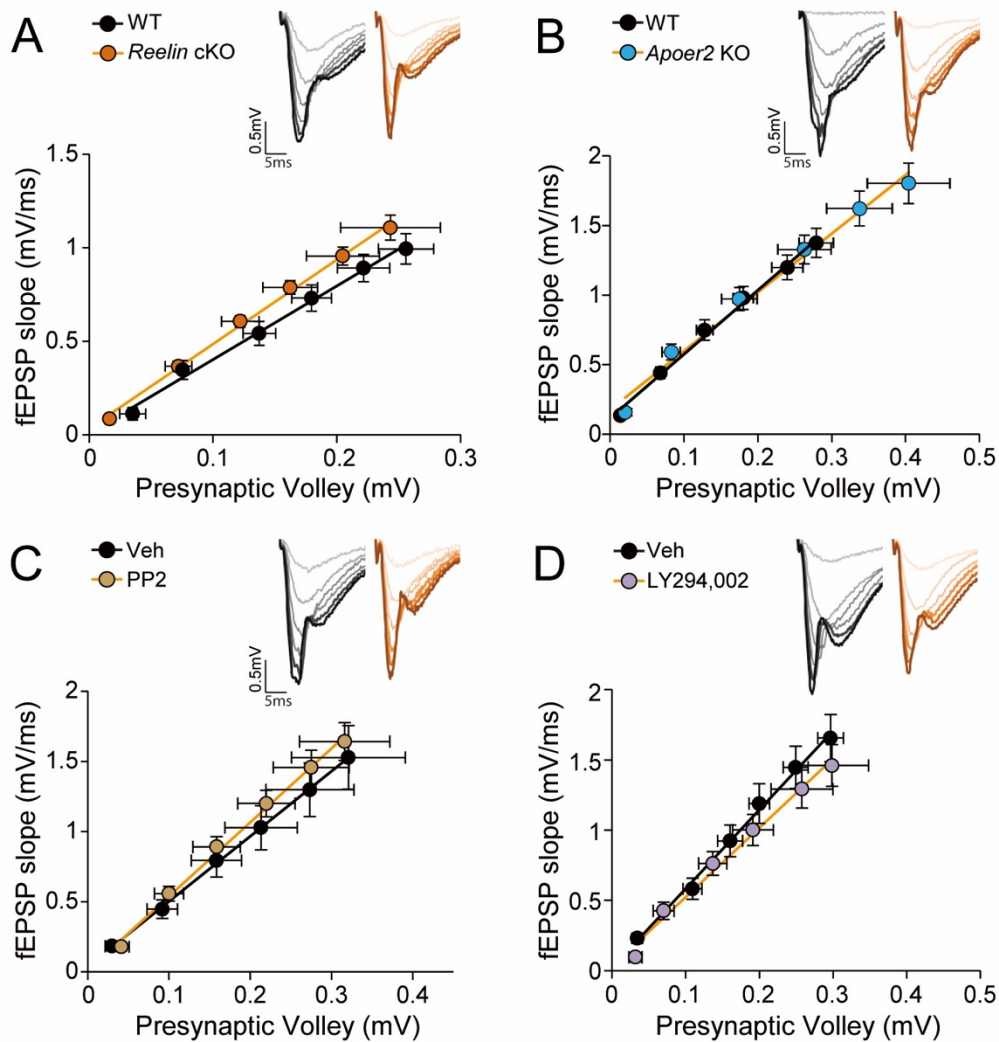
Fig. S2. Disruption of Reelin-dependent pathway does not affect the basal neurotransmission. (A - D) I-O curves were measured during baseline recording in the respective experimental conditions; Fig. S1A is from Fig. 1D and E. Fig. S1B is from Fig. 2F and G. Fig. S1C is from Fig. 3E and F. Fig. S1D is from Fig. 4C and D. Initial slopes of field potentials versus presynaptic volley values are plotted at 4, 8, 12, 16, 20, and 24 µA stimulation intensity. Any significant changes in slopes were not observed in any tested datasets, as assessed by unpaired t-test (all P-values > 0.05). All data represented as mean ± S.E.M.
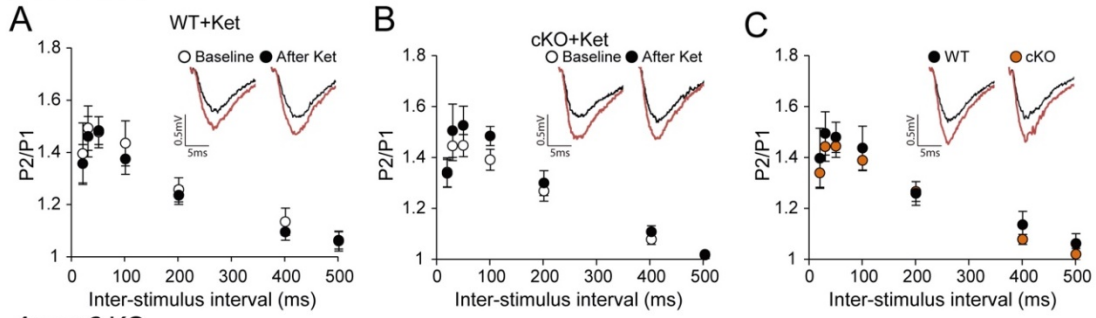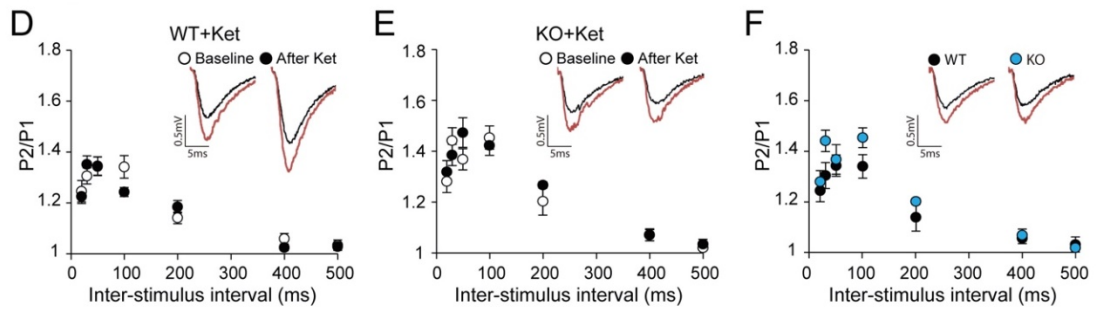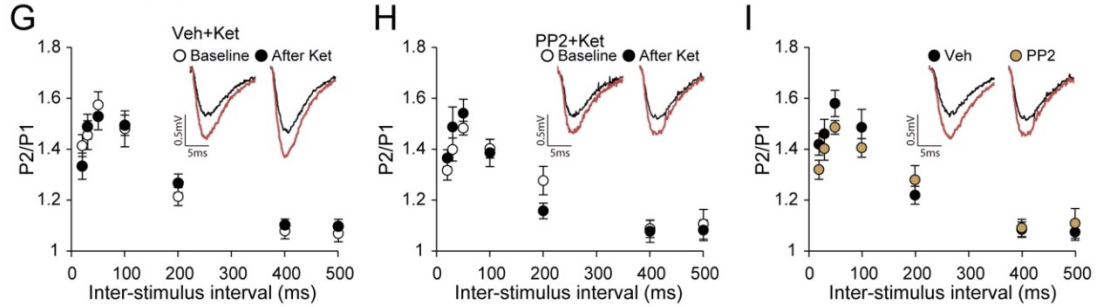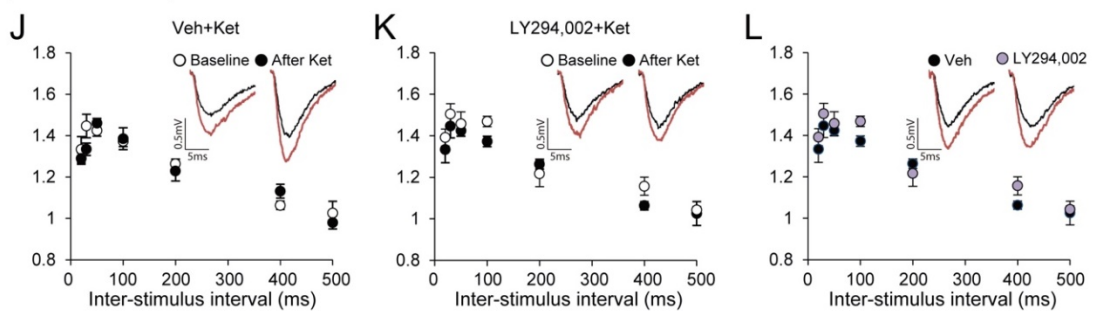
Fig. S3. Comparison of paired-pulse ratio changes due to ketamine treatment, genotypes, or pharmacological treatments. Paired-pulse ratios were measured with interstimulus intervals of 20, 30, 50, 100, 200, 400, and 500 ms before and after ketamine treatment. (A-C) and (D-F) were from CA1 hippocampal slices of *Reelin* cKO mice (Fig. 1B) and Apoer2 KO mice (Fig. 2D), respectively. (G - I) and (J - L) were from hippocampal slices treated with PP2 (SFKs inhibitor, Fig. 3C) and LY294,002 (PI3K inhibitor, Fig. 4A), respectively. In the respective datasets, there

were no significant changes (Paired t-test or Wilcoxon matched-pairs signed rank test for comparisons between baseline and after ketamine group at respective inter-stimulus interval conditions in A, B, D, E, G, H, J, and K. Unpaired t-test, or Man Whitney test, for comparisons between two groups at respective inter-stimulus interval conditions in C, F, I and L. All P-values > 0.05 in all comparisons). All data represented as mean ± S.E.M.
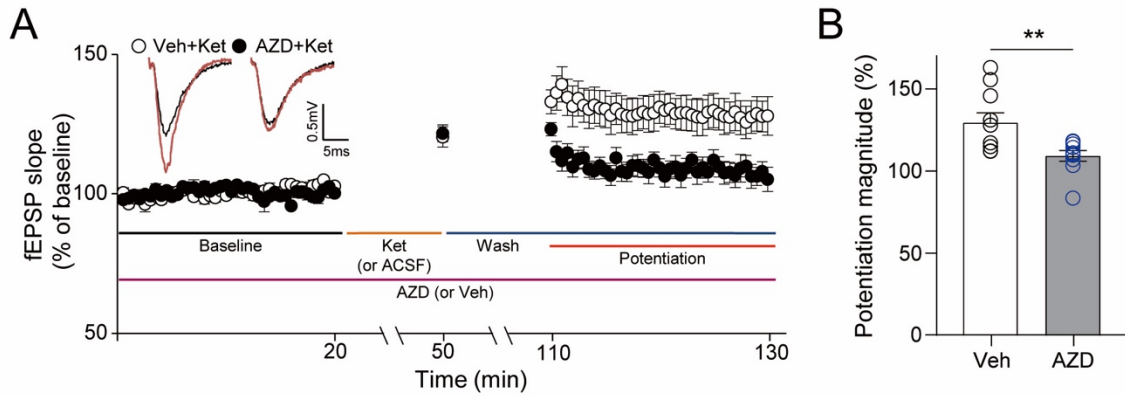
Fig. S4. AZD0530 treatment attenuates ketamine-mediated synaptic potentiation. AZD0530 was applied during the entire recording. fEPSPs were measured following 20 min of baseline recordings, 30 min of ketamine perfusion, and a 1 hr of washout period of the hippocampal CA1 region. All responses were normalized to respective baselines. Inset: representative waveforms during baseline (black) or ketamine-potentiation (red) measurement. (B) A bar graph summarizes the respective magnitudes of ketamine-potentiation in (A). AZD0530 attenuated ketamine-potentiation (Mann-Whitney test, $P = 0.0089$, n = 10 per group).
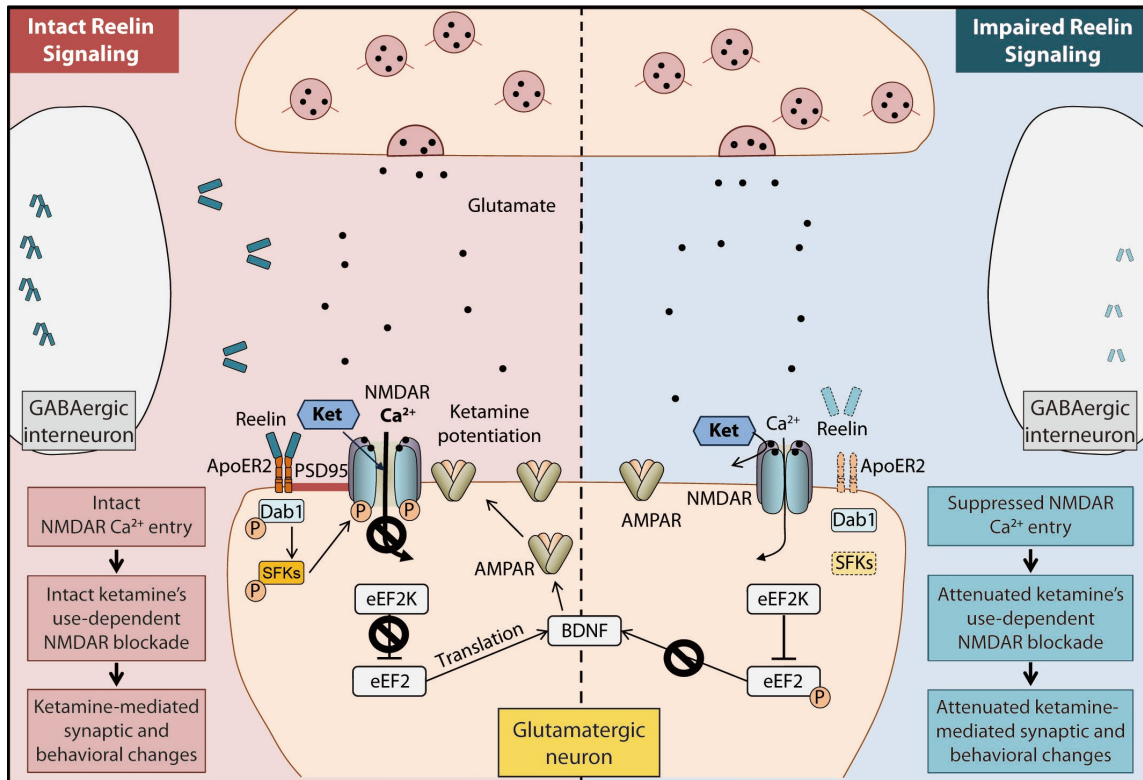
Fig. S5. The role of Reelin in regulating basal NMDA receptor function and ketamine-mediated synaptic/behavioral changes. Reelin is detected in GABAergic neurons within the forebrain region. Disruption of Reelin, ApoER2, or SFKs signaling (right side, weakly colored proteins with dashed outline) impairs basal NMDA receptor function, and thereby, prevents ketamine from binding to the NMDA receptor. Ketamine's diminished ability to signal via NMDAR block occludes downstream synaptic and behavioral changes.

Supplementary Table.

Figure 1A

Group	N number	Mean ±S.E.M	Shapiro-Wilk (p-value)	Statistics	Interaction	Genotype factor	Drug factor	Tukey's multiple comparisons P-value / Significance	
WT-Sal	6	186.7 ± 3.921	$P = 0.788$					WT-Sal vs WT-Ket	$P = 0.0054$ / **
WT-Ket	5	155.8 ± 12.32	$P = 0.689$	Two-way ANOVA	$F_{(1, 19)} = 4.815$ $P = 0.0408$	$F_{(1, 19)} = 15.68$ $P = 0.0008$	$F_{(1, 19)} = 11.47$ $P = 0.0031$	WT-Ket vs cKO-Ket	$P = 0.0022$ / **
cKO-Sal	6	202.3 ± 7.126	$P = 0.1949$					cKO-Sal vs cKO-Ket	$P = 0.8231$ / N.S.
cKO-Ket	6	194 ± 6.202	$P = 0.0617$						

Figure 1C

Group	N number	Mean ±S.E.M	Shapiro-Wilk or D'Agostino & Pearson test (p-value)	Statistics	Interaction	Genotype factor	Drug factor	Tukey's multiple comparisons P-value / Significance	
WT-ACSF	5	89.02 ± 3.487	$P = 0.1538$					WT-ACSF vs WT-Ket	$P < 0.0001$ / ***
WT-Ket	6	121.3 ± 2.128	$P = 0.2943$	Two-way ANOVA	$F_{(1, 21)} = 37.82$ $P < 0.0001$	$F_{(1, 21)} = 5.226$ $P = 0.0327$	$F_{(1, 21)} = 20.50$ $P = 0.0002$	WT-Ket vs cKO-Ket	$P < 0.0001$ / ***
cKO-ACSF	6	100.7 ± 2.773	$P = 0.4945$					cKO-Sal vs cKO-Ket	$P = 0.6225$ / N.S.
cKO-Ket	8	95.79 ± 3.146	$P = 0.4024$						

Figure 1D-E

Group	Timepoint	N number	Mean ±S.E.M	Shapiro-Wilk or D'Agostino & Pearson test (p-value)	Statistics	P-value /Significance
WT	Before	6	4.205 ± 0.6093	$P = 0.1383$	paired t-test	$t_{(5)} = 3.671$ $P = 0.0144$ / *
	After	6	5.573 ± 0.4762	$P = 0.4382$		
cKO	Before	8	5.68 ± 0.9979	$P = 0.5188$	paired t-test	$t_{(7)} = 1.129$ $P = 0.2961$ / N.S.
	After	8	6.204 ± 1.277	$P = 0.2697$		

Figure 2A

Group	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Statistics	Interaction	Genotype factor	Drug factor	P-value (Tukey's multiple comparisons) /Significance	
WT-Sal	9	210.2 ± 4.304	$P = 0.3501$					WT-Sal vs WT-Ket	$P = 0.0464$ / *
WT-Ket	10	147 ± 15.69	$P = 0.2087$	Two-way ANOVA	$F_{(1,35)} = 7.535$ $P = 0.0095$	$F_{(1,35)} = 11.36$ $P = 0.0018$	$F_{(1,35)} = 1.362$ $P = 0.2511$	WT-Sal vs KO-Sal	$P = 0.0008$ / ***
KO-Sal	10	111.4 ± 19.06	$P = 0.4481$					KO-Sal vs KO-Ket	$P = 0.6731$ / N.S.
KO-Ket	10	136.9 ± 19.07	$P = 0.6124$						

Figure 2B

Group	N number	Mean ±S.E.M	Shapiro-Wilk or D'Agostino & Pearson test (p-value)	Statistics	Interaction	Genotype factor	Drug factor	P-value (Tukey's multiple comparisons) /Significance	
WT-Sal	7	90.86 ± 8.247	$P = 0.1445$					WT-Sal vs WT-Ket	$P = 0.0325$ / *
WT-Ket	6	43.50 ± 6.238	$P = 0.1389$	Two-way ANOVA	$F_{(1,27)} = 8.509$ $P = 0.0070$	$F_{(1,27)} = 3.194$ $P = 0.0851$	$F_{(1,27)} = 2.413$ $P = 0.1319$	WT-Ket vs KO-Ket	$P = 0.0152$ / *
KO-Sal	9	78.89 ± 9.536	$P = 0.9455$					KO-Sal vs KO-Ket	$P = 0.7193$ / N.S.
KO-Ket	9	93.33 ± 13.03	$P = 0.3954$						

Figure 2C

Group	N number	Mean ±S.E.M	Shapiro-Wilk or D'Agostino & Pearson test (p-value)	Statistics	Interaction	Genotype factor	Drug factor	P-value (Tukey's multiple comparisons) /Significance	
WT-Sal	7	0.3360 ± 0.0170	$P = 0.7101$					WT-Sal vs WT-Ket	$P = 0.4308$ / N.S.
WT-Ket	6	0.3917 ± 0.0256	$P = 0.0716$	Two-way ANOVA	$F_{(1,27)} = 0.803$ $P = 0.3782$	$F_{(1,27)} = 1.352$ $P = 0.2551$	$F_{(1,27)} = 2.087$ $P = 0.1591$		
KO-Sal	9	0.3297 ± 0.0263	$P = 0.2564$					KO-Sal vs KO-Ket	$P = 0.9733$ / N.S.
KO-Ket	9	0.3428 ± 0.0214	$P = 0.7569$						

Figure 2E

Group	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Statistics	Interaction	Genotype factor	Drug factor	P-value (Tukey's multiple comparisons) /Significance	
WT-ACSF	8	96.93 ± 4.119	$P = 0.6951$					WT-ACSF vs WT-Ket	$P = 0.0001$ / ***
WT-Ket	12	124 ± 3.631	$P = 0.8297$	Two-way ANOVA	$F_{(1, 36)} = 5.181$ $P = 0.0289$	$F_{(1, 36)} = 8.669$ $P = 0.0056$	$F_{(1, 36)} = 21.62$ $P < 0.0001$	WT-Ket vs KO-Ket	$P = 0.0011$ / **
KO-ACSF	8	94.32 ± 4.057	$P = 0.5805$					KO-ACSF vs KO-Ket	$P = 0.3496$ / N.S.
KO-Ket	12	103.6 ± 3.555	$P = 0.1109$						

Figure 2F-G

Group	Timepoint	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Statistics	P-value /Significance
WT	Before	10	4.83 ± 0.4855	$P = 0.8535$	paired t-test	$t_{(9)} = 3.334$ $P = 0.0087$ / **
WT	After	10	8.917 ± 0.1.445	$P = 0.8662$		
KO	Before	11	5.8 ± 0.9422	$P = 0.2961$	paired t-test	$t_{(10)} = 3.709$ $P = 0.0040$ / **
KO	After	11	7.162 ± 1.201	$P = 0.0651$		

Figure 3A

Target protein	Group	N number	Mean ±S.E.M	Shapiro-Wilk (p-value)	Statistics	P-value /Significance
pGluN2A/GluN2A	Veh	7	1 ± 0.0800	$P = 0.5696$	unpaired t-test	$t_{(12)} = 2.423$ $P = 0.0322$ / *
pGluN2A/GluN2A	AZD	7	0.6706 ± 0.1099	$P = 0.8908$		
pGluN2B/GluN2B	Veh	6	1 ± 0.0774	$P = 0.896$	unpaired t-test	$t_{(11)} = 1.459$ $P = 0.1727$ / N.S.
pGluN2B/GluN2B	AZD	7	0.8302 ± 0.0848	$P = 0.9424$		

Figure 3B

Group	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Statistics	Interaction	AZD factor	Ketamine factor	P-value (Tukey's multiple comparisons) /Significance	
Veh-Sal	9	182.2 ± 2.803	$P = 0.6655$	Two-way ANOVA	$F_{(1, 35)} = 5.285$ $P = 0.0276$	$F_{(1, 35)} = 3.740$ $P = 0.0613$	$F_{(1, 35)} = 2.514$ $P = 0.1218$	Veh-Sal vs Veh-Ket	$P = 0.0485$ / *
Veh-Ket	10	149.0 ± 10.4	$P = 0.1454$					Veh-Ket vs AZD-Ket	$P = 0.0224$ / *
AZD-Veh	10	179.1 ± 11.46	$P = 0.1584$					AZD-Veh vs AZD-Ket	$P = 0.9559$ / N.S.
AZD-Ket	10	185.2 ± 5.571	$P = 0.6276$						

Figure 3D

Group	N number	Mean ±S.E.M	Shapiro-Wilk or D'Agostino & Pearson test (p-value)	Statistics	Interaction	PP2 factor	Ketamine factor	P-value (Tukey's multiple comparisons) /Significance	
Veh-ACSF	7	97.62 ± 2.81	$P = 0.6275$	Two-way ANOVA	$F_{(1, 28)} = 1.706$ $P = 0.2021$	$F_{(1, 28)} = 5.095$ $P = 0.0320$	$F_{(1, 28)} = 18.51$ $P = 0.0002$	Veh-ACSF vs Veh-Ket	$P = 0.0022$ / **
Veh-Ket	9	119 ± 2.58	$P = 0.3234$					Veh-Ket vs PP2-Ket	$P = 0.0430$ / *
PP2-ACSF	6	93.99 ± 5.22	$P = 0.4248$					PP2-ACSF vs PP2-Ket	$P = 0.1801$ / N.S.
PP2-Ket	10	105.4 ± 4.08	$P = 0.4484$						

Figure 3E-F

Group	Timepoint	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Statistics	P-value /Significance
Veh-Ket	Before	9	5.038 ± 0.4876	$P = 0.0349$	Wilcoxon matched-pairs signed rank test	$P = 0.0039$ / **
	After	9	8.367 ± 1.416	$P = 0.2193$		
PP2-Ket	Before	9	5.487 ± 0.5279	$P = 0.0002$	Wilcoxon matched-pairs signed rank test	$P = 0.0117$ / **
	After	9	6.325 ± 0.567	$P = 0.0007$		

Figure 3G

Protein	Group	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Statistics	Interaction	Ketamine factor	PP2 factor	P-value (Tukey's multiple comparisons) /Significance	
pGluN2A/ GluN2A	Veh-ACSF	9	1 ± 0.1822	$P = 0.9567$	Two-way ANOVA	$F_{(1, 30)} = 1.373$ $P = 0.2505$	$F_{(1, 30)} = 1.452$ $P = 0.2376$	$F_{(1, 30)} = 30.32$ $P < 0.0001$	Veh-ACSF vs PP2-ACSF	$P = 0.0225$ / *
	PP2-ACSF	8	0.1167 ± 0.0550	$P = 0.3418$						
	Veh-Ket	9	1.484 ± 0.3316	$P = 0.5592$					Veh-Ket vs PP2-Ket	$P = 0.0003$ / ***
	PP2-Ket	8	0.1235 ± 0.0379	$P = 0.1076$						
pGluN2B/ GluN2B	Veh-ACSF	9	1 ± 0.0997	$P = 0.9257$	Two-way ANOVA	$F_{(1, 32)} = 0.0051$ $P = 0.9431$	$F_{(1, 32)} = 0.4409$ $P = 0.5114$	$F_{(1, 32)} = 43.67$ $P < 0.0001$	Veh-ACSF vs PP2-ACSF	$P = 0.0002$ / ***
	PP2-ACSF	9	0.3878 ± 0.0690	$P = 0.1729$						
	Veh-Ket	9	1.054 ± 0.106	$P = 0.5246$					Veh-Ket vs PP2-Ket	$P = 0.0003$ / ***
	PP2-Ket	9	0.4553 ± 0.0874	$P = 0.4185$						

Figure 4B

Group	N number	Mean ±S.E.M	Shapiro-Wilk or D'Agostino & Pearson test (p-value)	Statistics	Interaction	LY294,002 factor	Ketamine factor	P-value (Tukey's multiple comparisons) /Significance	
Veh-ACSF	7	100.6 ± 1.534	$P = 0.9884$	Two-way ANOVA	$F_{(1, 25)} = 0.3351$ $P = 0.5678$	$F_{(1, 25)} = 0.661$ $P = 0.4239$	$F_{(1, 25)} = 27.23$ $P < 0.0001$	Veh-ACSF vs Veh-Ket	$P = 0.0024$ / **
Veh-Ket	7	122.2 ± 6.489	$P = 0.3527$					Veh-Ket vs LY-Ket	$P = 0.8187$ / N.S.
LY-ACSF	8	97.27 ± 3.573	$P = 0.9545$					LY-ACSF vs LY-Ket	$P = 0.0133$ / *
LY-Ket	7	117.5 ± 0.5029	$P = 0.9134$						

Figure 4C-D

Group	Timepoint	N number	Mean ±S.E.M	Shapiro-Wilk (p-value)	Statistics	P-value /Significance
Veh-Ket	Before	7	6.207 ± 0.8157	$P = 0.9804$	paired t-test	$t_{(6)} = 3.737$ $P = 0.0097$ / **
	After	7	10.24 ± 1.411	$P = 0.5596$		
LY-Ket	Before	7	5.140 ± 0.5879	$P = 0.6968$	paired t-test	$t_{(6)} = 4.528$ $P = 0.0040$ / **
	After	7	8.257 ± 0.8264	$P = 0.5476$		

Figure 4E

Protein	Group	N number	Mean ±S.E.M	Shapiro-Wilk or D'Agostino & Pearson test (p-value)	Statistics	Interaction	Ketamine factor	LY294,002 factor	P-value (Tukey's multiple comparisons) /Significance	
pAKT/AKT	Veh-ACSF	7	1 ± 0.1868	$P = 0.6718$	Two-way ANOVA	$F_{(1, 25)} = 0.7331$ $P = 0.4000$	$F_{(1, 25)} = 0.0690$ $P = 0.795$	$F_{(1, 25)} = 26.89$ $P < 0.0001$	Veh-ACSF vs LY-ACSF	$P = 0.0011$ / **
	LY-ACSF	8	0.1802 ± 0.0603	$P = 0.2859$						
	Veh-Ket	7	0.9195 ± 0.1895	$P = 0.3956$					Veh-Ket vs LY-Ket	$P = 0.0280$ / *
	LY-Ket	7	0.332 ± 0.0596	$P = 0.7827$						

Figure 5B

Protein	Time	N number	Mean ±S.E.M	Shapiro-Wilk or D'Agostino & Pearson test (p-value)	Statistics	P-value /Significance
Reelin/GAPDH	10 min	10	1 ± 0.1145	$P = 0.9857$	unpaired t-test	$t_{(18)} = 0.0266$ $P = 0.9791$ / N.S.
		10	0.9945 ± 0.1727	$P = 0.9664$		
	30 min	7	1 ± 0.1659	$P = 0.1861$		$t_{(12)} = 0.3503$ $P = 0.7322$ / N.S.
		7	1.079 ± 0.1523	$P = 0.892$		
pGluN2A/GluN2A	10 min	10	1 ± 0.1009	$P = 0.9762$	unpaired t-test	$t_{(18)} = 2.133$ $P = 0.047$ / *
		10	1.473 ± 0.1977	$P = 0.7931$		
	30 min	8	1 ± 0.1064	$P = 0.7136$		$t_{(14)} = 1.292$ $P = 0.2173$ / N.S.
		8	1.24 ± 0.1523	$P = 0.8386$		
pGluN2B/GluN2B	10 min	10	1 ± 0.1138	$P = 0.3091$	unpaired t-test	$t_{(18)} = 0.2721$ $P = 0.7887$ / N.S.
		10	0.9539 ± 0.1257	$P = 0.3913$		
	30 min	8	1 ± 0.1777	$P = 0.2934$		$t_{(14)} = 0.6826$ $P = 0.5060$ / N.S.
		8	0.8487 ± 0.1325	$P = 0.5695$		
pAKT/AKT	10 min	10	1 ± 0.0289	$P = 0.3323$	unpaired t-test	$t_{(18)} = 0.8431$ $P = 0.4103$ / N.S.
		10	1.038 ± 0.0346	$P = 0.3439$		
	30 min	8	1 ± 0.0674	$P = 0.6518$		$t_{(14)} = 0.7883$ $P = 0.4436$ / N.S.
		8	0.9148 ± 0.0845	$P = 0.3947$		

Figure 5C

Protein	Time	N number	Mean ±S.E.M	Shapiro-Wilk (p-value)	Statistics	P-value /Significance
pTyr-DAB1/DAB1	10 min	4	1 ± 0.0452	$P = 0.3648$	unpaired t-test	$t_{(7)} = 0.2300$
		5	0.9868 ± 0.0367	$P = 0.6141$		$P = 0.8246$ / N.S.

Figure 5D

Group	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Statistics	P-value /Significance
WT	11	0.8791 ± 0.0768	$P = 0.676$	unpaired t-test	$t_{(22)} = 2.652$
ApoER2 KO	13	0.6375 ± 0.0531	$P = 0.9352$		$P = 0.0146$ / *

Figure 5E

Group	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Statistics	P-value /Significance
Veh	10	1.224 ± 0.1533	$P = 0.349$	unpaired t-test	$t_{(22)} = 2.430$
PP2	14	0.8581 ± 0.0663	$P = 0.4869$		$P = 0.0237$ / *

Supplementary Figure 1A

Group	N number	Mean ±S.E.M	Shapiro-Wilk (p-value)	Statistics	Interaction	Genotype factor	Drug factor	P-value (Tukey's multiple comparisons) /Significance	
WT-Sal	6	34.5 ± 4.015	$P = 0.1727$					WT-Sal vs WT-Ket	$P = 0.0279$ / *
WT-Ket	5	62.4 ± 9.432	$P = 0.932$	Two-way ANOVA	$F_{(1, 19)} = 4.565$ $P = 0.0459$	$F_{(1, 19)} = 21.88$ $P = 0.0002$	$F_{(1, 19)} = 5.494$ $P = 0.0301$	WT-Ket vs cKO-Ket	$P = 0.0006$ / ***
cKO-Sal	6	24.0 ± 4.058	$P = 0.3465$					cKO-Sal vs cKO-Ket	$P = 0.9987$ / N.S.
cKO-Ket	6	25.33 ± 4.256	$P = 0.2721$						

Supplementary Figure 1B

Group	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Box-cox transformation [D'Agostino & Pearson test (p-value)]	Statistics	Interaction	Genotype factor	Drug factor	P-value (Tukey's multiple comparisons) /Significance	
WT-Sal	8	17.19 ± 2.506	$P = 0.3003$	$P = 0.6241$					WT-Sal vs WT-Ket	$P = 0.0322$ / *
WT-Ket	10	40.01 ± 7.765	$P = 0.0002$	$P = 0.0858$	Two-way ANOVA	$F_{(1, 33)} = 10.97$ $P = 0.0023$	$F_{(1, 33)} = 21.06$ $P < 0.0001$	$F_{(1, 33)} = 0.7188$ $P = 0.4026$	WT-Sal vs KO-Sal	$P < 0.0001$ / ***
KO-Sal	9	79.32 ± 11.66	$P = 0.1288$	$P = 0.8881$					KO-Sal vs KO-Ket	$P = 0.3052$ / N.S.
KO-Ket	10	59.68 ± 12.94	$P = 0.4611$	$P = 0.6489$						

Supplementary Figure 1C

Group	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Statistics	Interaction	AZD factor	Ketamine factor	P-value (Tukey's multiple comparisons) /Significance	
Veh-Sal	9	31.97 ± 4.074	$P = 0.7536$					Veh-Sal vs Veh-Ket	$P = 0.0384$ / *
Veh-Ket	10	53.11 ± 6.565	$P = 0.4648$	Two-way ANOVA	$F_{(1, 35)} = 4.199$ $P = 0.0480$	$F_{(1, 35)} = 7.171$ $P = 0.0112$	$F_{(1, 35)} = 3.918$ $P = 0.0557$	AZD-Sal vs AZD-Ket	$P > 0.9999$ / N.S.
AZD-Sal	10	28.67 ± 6.264	$P = 0.5008$					Veh-Ket vs AZD-Ket	$P = 0.0091$ / **
AZD-Ket	10	28.30 ± 2.939	$P = 0.9369$						

Supplementary Figure 2

Figure number	Group	N number	Mean ±S.E.M	Shapiro-Wilk or D'Agostino & Pearson test (p-value)	Statistics	P-value /Significance
A	WT	6	4.172 ± 0.6237	$P = 0.2383$	unapired t-test	$t_{(12)} = 1.178$ $P = 0.2616$ / N.S.
	Reelin cKO	8	5.68 ± 0.9979	$P = 0.2678$		
B	WT	10	4.83 ± 0.4855	$P = 0.8535$	unpaired t-test	$t_{(19)} = 0.3410$ $P = 0.7368$ / N.S.
	Apoer2 KO	11	5.165 ± 0.8245	$P = 0.2961$		
C	Veh	9	5.038 ± 0.4876	$P = 0.186$	unpaired t-test	$t_{(16)} = 0.6248$ $P = 0.5409$ / N.S.
	PP2	9	5.487 ± 0.5279	$P = 0.2088$		
D	Veh	7	6.207 ± 0.8157	$P = 0.9604$	unpaired t-test	$t_{(12)} = 1.209$ $P = 0.2498$ / N.S.
	LY294,002	7	4.979 ± 0.6038	$P = 0.6244$		

Supplementary Figure 3A

Group	Interstimulus interval	Group	Number	Shapiro-Wilk (p-value)	statistics	Mean ±S.E.M	P-value /Significance
Reelin WT before vs after	20	Before	6	$P = 0.8771$	paired t-test	1.399 ± 0.1183	$t(5) = 0.3573$
		after	6	$P = 0.1648$		1.361 ± 0.0733	$P = 0.7355$ / N.S.
	30	Before	6	$P = 0.9382$	paired t-test	1.497 ± 0.0847	$t(5) = 0.7335$
		after	6	$P = 0.615$		1.465 ± 0.0772	$P = 0.4962$ / N.S.
	50	Before	6	$P = 0.6013$	paired t-test	1.482 ± 0.0595	$t(5) = 1.691$
		after	6	$P = 0.3286$		1.487 ± 0.0534	$P = 0.9448$ / N.S.
	100	Before	6	$P = 0.9059$	paired t-test	1.439 ± 0.0863	$t(5) = 1.491$
		after	6	$P = 0.9492$		1.379 ± 0.0585	$P = 0.1961$ / N.S.
	200	Before	6	$P = 0.9532$	paired t-test	1.261 ± 0.0464	$t(5) = 0.8270$
		after	6	$P = 0.6698$		1.24 ± 0.0348	$P = 0.4459$ / N.S.
	400	Before	6	$P = 0.9836$	Wilcoxon matched-pairs signed rank test	1.138 ± 0.0520	$P = 0.5288$ / N.S.
		after	6	$P = 0.003$		1.099 ± 0.0311	
	500	Before	6	$P = 0.7594$	paired t-test	1.064 ± 0.0382	$t(5) = 1.355$
		after	6	$P = 0.2666$		1.067 ± 0.0328	$P = 0.2333$ / N.S.

Supplementary Figure 3B

Group	Interstimulus interval	Group	Number	D'Agostino & Pearson test (p-value)	statistics	Mean ±S.E.M	P-value /Significance
Reelin cKO before vs after	20	Before	8	$P = 0.7198$	paired t-test	1.342 ± 0.0672	$t_{(7)} = 0.1206$ $P = 0.9074$ / N.S.
		after	8	$P = 0.816$		1.338 ± 0.0645	
	30	Before	8	$P = 0.4328$	Wilcoxon matched-pairs signed rank test	1.445 ± 0.0679	$P = 0.4609$ / N.S.
		after	8	$P = 0.0011$		1.503 ± 0.1239	
	50	Before	8	$P = 0.0581$	Wilcoxon matched-pairs signed rank test	1.446 ± 0.0516	$P = 0.1953$ / N.S.
		after	8	$P = 0.0267$		1.524 ± 0.09	
	100	Before	8	$P = 0.9157$	paired t-test	1.391 ± 0.0490	$t_{(7)} = 1.741$ $P = 0.1253$ / N.S.
		after	8	$P = 0.2421$		1.483 ± 0.0449	
	200	Before	8	$P = 0.5991$	paired t-test	1.268 ± 0.0462	$t_{(7)} = 0.6486$ $P = 0.5373$ / N.S.
		after	8	$P = 0.3373$		1.3 ± 0.0579	
	400	Before	8	$P = 0.6636$	paired t-test	1.08 ± 0.0234	$t_{(7)} = 0.6918$ $P = 0.5114$ / N.S.
		after	8	$P = 0.7229$		1.11 ± 0.0286	
	500	Before	8	$P = 0.9321$	paired t-test	1.022 ± 0.0269	$t_{(7)} = 0.0604$ $P = 0.9535$ / N.S.
		after	8	$P = 0.3875$		1.019 ± 0.0165	

Supplementary Figure 3C

Group	Interstimulus interval	Group	Number	Shapiro-Wilk or D'Agostino & Pearson test (p-value)	statistics	Mean ±S.E.M	P-value /Significance
Reelin WT vs cKO	20	WT	6	$P = 0.8771$	unpaired t-test	1.399 ± 0.1183	$t_{(14)} = 0.0331$ $P = 0.6624$ / N.S.
		cKO	8	$P = 0.7198$		1.342 ± 0.0672	
	30	WT	6	$P = 0.9382$	unpaired t-test	1.497 ± 0.0847	$t_{(14)} = 0.1522$ $P = 0.6346$ / N.S.
		cKO	8	$P = 0.4328$		1.445 ± 0.0679	
	50	WT	6	$P = 0.6013$	unpaired t-test	1.482 ± 0.0595	$t_{(14)} = 0.3346$ $P = 0.6853$ / N.S.
		cKO	8	$P = 0.0581$		1.446 ± 0.0516	
	100	WT	6	$P = 0.9059$	unpaired t-test	1.439 ± 0.0863	$t_{(14)} = 0.2722$ $P = 0.6152$ / N.S.
		cKO	8	$P = 0.9157$		1.391 ± 0.0490	
	200	WT	6	$P = 0.9532$	unpaired t-test	1.261 ± 0.0464	$t_{(14)} = 0.5261$ $P = 0.9130$ / N.S.
		cKO	8	$P = 0.5991$		1.268 ± 0.0462	
	400	WT	6	$P = 0.9836$	unpaired t-test	1.138 ± 0.0520	$t_{(14)} = 0.4437$ $P = 0.2877$ / N.S.
		cKO	8	$P = 0.6636$		1.08 ± 0.0234	
	500	WT	6	$P = 0.7594$	unpaired t-test	1.064 ± 0.0382	$t_{(14)} = 0.2749$ $P = 0.3669$ / N.S.
		cKO	8	$P = 0.9321$		1.022 ± 0.0269	

Supplementary Figure 3D

Group	Interstimulus interval	Group	Number	D'Agostino & Pearson test (p-value)	statistics	Mean ±S.E.M	P-value /Significance
Apoer2 WT before vs after	20	Before	10	$P = 0.0734$	paired t-test	1.244 ± 0.0458	$t_{(9)} = 0.4563$ $P = 0.6590$ / N.S.
		after	10	$P = 0.929$		1.224 ± 0.0309	
	30	Before	10	$P = 0.0824$	paired t-test	1.304 ± 0.0345	$t_{(9)} = 1.142$ $P = 0.2828$ / N.S.
		after	10	$P = 0.1665$		1.35 ± 0.0368	
	50	Before	10	$P = 0.7491$	paired t-test	1.343 ± 0.0397	$t_{(9)} = 0.0468$ $P = 0.9637$ / N.S.
		after	10	$P = 0.9538$		1.342 ± 0.0400	
	100	Before	10	$P = 0.5476$	paired t-test	1.337 ± 0.0268	$t_{(9)} = 0.1054$ $P = 0.1054$ / N.S.
		after	10	$P = 0.5005$		1.282 ± 0.0269	
	200	Before	10	$P = 0.8752$	paired t-test	1.139 ± 0.0252	$t_{(9)} = 1.010$ $P = 0.3389$ / N.S.
		after	10	$P = 0.1437$		1.183 ± 0.0265	
	400	Before	10	$P = 0.0675$	paired t-test	1.057 ± 0.0225	$t_{(9)} = 1.303$ $P = 0.2249$ / N.S.
		after	10	$P = 0.577$		1.023 ± 0.0141	
	500	Before	10	$P = 0.0544$	paired t-test	1.032 ± 0.0227	$t_{(9)} = 0.194$ $P = 0.8505$ / N.S.
		after	10	$P = 0.7463$		1.027 ± 0.0165	

Supplementary Figure 3E

Group	Interstimulus interval	Group	Number	D'Agostino & Pearson test (p-value)	statistics	Mean ±S.E.M	P-value /Significance
Apoer2 KO before vs after	20	Before	11	$P = 0.824$	paired t-test	1.28 ± 0.0473	$t_{(10)} = 1.280$ $P = 0.2294$ / N.S.
		after	11	$P = 0.6983$		1.318 ± 0.0480	
	30	Before	11	$P = 0.1009$	paired t-test	1.441 ± 0.0556	$t_{(10)} = 1.290$ $P = 0.2261$ / N.S.
		after	11	$P = 0.9879$		1.385 ± 0.0455	
	50	Before	11	$P = 0.8258$	paired t-test	1.367 ± 0.0457	$t_{(10)} = 1.838$ $P = 0.0959$ / N.S.
		after	11	$P = 0.7372$		1.473 ± 0.0633	
	100	Before	11	$P = 0.2092$	paired t-test	1.453 ± 0.0501	$t_{(10)} = 0.5680$ $P = 0.5826$ / N.S.
		after	11	$P = 0.8359$		1.422 ± 0.0426	
	200	Before	11	$P = 0.0053$	Wilcoxon matched-pairs signed rank test	1.202 ± 0.0593	$P = 0.2061$ / N.S.
		after	11	$P = 0.8991$		1.266 ± 0.0135	
	400	Before	11	$P = 0.7766$	paired t-test	1.069 ± 0.0233	$t_{(10)} = 0.0538$ $P = 0.9581$ / N.S.
		after	11	$P = 0.2795$		1.071 ± 0.0258	
	500	Before	11	$P = 0.007$	Wilcoxon matched-pairs signed rank test	1.019 ± 0.0324	$P = 0.3652$ / N.S.
		after	11	$P = 0.5377$		1.034 ± 0.0205	

Supplementary Figure 3F

Group	Interstimulus interval	Group	Number	D'Agostino & Pearson test (p-value)	statistics	Mean ±S.E.M	P-value /Significance
Apoer2 WT vs cKO	20	WT	10	$P = 0.0734$	unpaired t-test	1.244 ± 0.0458	$t_{(19)} = 0.5380$
		cKO	11	$P = 0.824$		1.28 ± 0.0473	$P = 0.5968$ / N.S.
	30	WT	10	$P = 0.0824$	unpaired t-test	1.304 ± 0.0345	$t_{(19)} = 2.038$
		cKO	11	$P = 0.1009$		1.441 ± 0.0556	$P = 0.0557$ / N.S.
	50	WT	10	$P = 0.7491$	unpaired t-test	1.343 ± 0.0397	$t_{(19)} = 0.3905$
		cKO	11	$P = 0.8258$		1.367 ± 0.0457	$P = 0.7005$ / N.S.
	100	WT	10	$P = 0.5476$	unpaired t-test	1.337 ± 0.0268	$t_{(19)} = 1.978$
		cKO	11	$P = 0.2092$		1.453 ± 0.0501	$P = 0.0627$ / N.S.
	200	WT	10	$P = 0.8752$	Mann Whitney test	1.139 ± 0.0252	$P = 0.5116$ / N.S.
		cKO	11	$P = 0.0053$		1.202 ± 0.0593	
	400	WT	10	$P = 0.0675$	unpaired t-test	1.057 ± 0.2247	$t_{(19)} = 0.3619$
		cKO	11	$P = 0.7766$		1.069 ± 0.0233	$P = 0.7214$ / N.S.
	500	WT	10	$P = 0.0544$	Mann Whitney test	1.032 ± 0.0227	$P = 0.4679$ / N.S.
		cKO	11	$P = 0.007$		1.019 ± 0.0324	

Supplementary Figure 3G

Group	Interstimulus interval	Group	Number	D'Agostino & Pearson test (p-value)	statistics	Mean ±S.E.M	P-value /Significance
Veh before vs after	20	Before	9	$P = 0.8364$	paired t-test	1.374 ± 0.0474	$t_{(8)} = 1.245$
		after	9	$P = 0.8843$		1.327 ± 0.0542	$P = 0.2485$ / N.S.
	30	Before	9	$P = 0.3648$	paired t-test	1.477 ± 0.0661	$t_{(8)} = 1.102$
		after	9	$P = 0.1224$		1.425 ± 0.0586	$P = 0.3023$ / N.S.
	50	Before	9	$P = 0.5254$	paired t-test	1.526 ± 0.0692	$t_{(8)} = 0.1199$
		after	9	$P = 0.0980$		1.522 ± 0.0825	$P = 0.9075$ / N.S.
	100	Before	9	$P = 0.2827$	paired t-test	1.463 ± 0.0757	$t_{(8)} = 0.1089$
		after	9	$P = 0.3510$		1.457 ± 0.0557	$P = 0.9610$ / N.S.
	200	Before	9	$P = 0.8726$	paired t-test	1.201 ± 0.0463	$t_{(8)} = 0.7661$
		after	9	$P = 0.7627$		1.230 ± 0.0452	$P = 0.4656$ / N.S.
	400	Before	9	$P = 0.5238$	paired t-test	1.108 ± 0.0287	$t_{(8)} = 0.3182$
		after	9	$P = 0.8935$		1.121 ± 0.0395	$P = 0.7585$ / N.S.
	500	Before	9	$P = 0.7273$	paired t-test	1.068 ± 0.0415	$t_{(8)} = 0.3414$
		after	9	$P = 0.4159$		1.090 ± 0.0333	$P = 0.7416$ / N.S.

Supplementary Figure 3H

Group	Interstimulus interval	Group	Number	D'Agostino & Pearson test (p-value)	statistics	Mean ±S.E.M	P-value /Significance
PP2 before vs after	20	Before	10	$P = 0.6898$	paired t-test	1.316 ± 0.0371	$t_{(9)} = 0.8655$
		after	10	$P = 0.4578$		1.365 ± 0.0335	$P = 0.4092$ / N.S.
	30	Before	10	$P = 0.1444$	paired t-test	1.399 ± 0.0452	$t_{(9)} = 1.197$
		after	10	$P = 0.5749$		1.487 ± 0.0790	$P = 0.2619$ / N.S.
	50	Before	10	$P = 0.472$	paired t-test	1.483 ± 0.0367	$t_{(9)} = 1.097$
		after	10	$P = 0.5099$		1.541 ± 0.0554	$P = 0.3011$ / N.S.
	100	Before	10	$P = 0.0219$	Wilcoxon matched-pairs signed rank test	1.402 ± 0.0367	$P = 0.8457$ / N.S.
		after	10	$P = 0.4623$		1.386 ± 0.0539	
	200	Before	10	$P = 0.9028$	paired t-test	1.277 ± 0.0560	$t_{(9)} = 2.002$
		after	10	$P = 0.4046$		1.158 ± 0.0303	$P = 0.0763$ / N.S.
	400	Before	10	$P = 0.1271$	paired t-test	1.088 ± 0.0343	$t_{(9)} = 0.1962$
		after	10	$P = 0.6994$		1.078 ± 0.0430	$P = 0.8488$ / N.S.
	500	Before	10	$P = 0.001$	Wilcoxon matched-pairs signed rank test	1.106 ± 0.0587	$P = 0.6953$ / N.S.
		after	10	$P = 0.3228$		1.082 ± 0.0411	

Supplementary Figure 3I

Group	Interstimulus interval	Group	Number	D'Agostino & Pearson test (p-value)	statistics	Mean ±S.E.M	P-value /Significance
Veh vs PP2	20	Veh	9	$P = 0.8364$	unpaired t-test	1.417 ± 0.0454	$t_{(17)} = 1.722$
		PP2	10	$P = 0.6898$		1.316 ± 0.0371	$P = 0.1400$ / N.S.
	30	Veh	9	$P = 0.3648$	unpaired t-test	1.458 ± 0.0595	$t_{(17)} = 0.7909$
		PP2	10	$P = 0.1444$		1.399 ± 0.0452	$P = 0.2715$ / N.S.
	50	Veh	9	$P = 0.5254$	unpaired t-test	1.577 ± 0.0545	$t_{(17)} = 1.598$
		PP2	10	$P = 0.472$		1.483 ± 0.0367	$P = 0.0637$ / N.S.
	100	Veh	9	$P = 0.2827$	Mann Whitney test	1.483 ± 0.0742	$P = 0.8244$ / N.S.
		PP2	10	$P = 0.0219$		1.402 ± 0.0367	
	200	Veh	9	$P = 0.8726$	unpaired t-test	1.216 ± 0.0373	$t_{(17)} = 0.8794$
		PP2	10	$P = 0.9028$		1.277 ± 0.0560	$P = 0.6610$ / N.S.
	400	Veh	9	$P = 0.5238$	unpaired t-test	1.081 ± 0.0317	$t_{(17)} = 0.1425$
		PP2	10	$P = 0.1271$		1.088 ± 0.0343	$P = 0.8461$ / N.S.
	500	Veh	9	$P = 0.7273$	Mann Whitney test	1.071 ± 0.0338	$P = 0.9514$ / N.S.
		PP2	10	$P = 0.001$		1.106 ± 0.0587	

Supplementary Figure 3J

Group	Interstimulus interval	Group	Number	Shapiro-Wilk (p-value)	statistics	Mean ±S.E.M	P-value /Significance
Veh before vs after	20	Before	7	$P = 0.1851$	paired t-test	1.333 ± 0.0927	$t_{(6)} = 0.7683$
		after	7	$P = 0.5558$		1.29 ± 0.0277	$P = 0.4714$ / N.S.
	30	Before	7	$P = 0.7915$	paired t-test	1.447 ± 0.0564	$t_{(6)} = 2.337$
		after	7	$P = 0.118$		1.334 ± 0.0299	$P = 0.0581$ / N.S.
	50	Before	7	$P = 0.3773$	paired t-test	1.424 ± 0.0267	$t_{(6)} = 1.701$
		after	7	$P = 0.3384$		1.461 ± 0.0229	$P = 0.1399$ / N.S.
	100	Before	7	$P = 0.7307$	paired t-test	1.373 ± 0.0254	$t_{(6)} = 0.2453$
		after	7	$P = 0.3604$		1.386 ± 0.0524	$P = 0.8144$ / N.S.
	200	Before	7	$P = 0.2479$	Wilcoxon matched-pairs signed rank test	1.263 ± 0.0231	$P = 0.4688$ / N.S.
		after	7	$P = 0.0268$		1.228 ± 0.0467	
	400	Before	7	$P = 0.8958$	paired t-test	1.063 ± 0.0198	$t_{(6)} = 2.057$
		after	7	$P = 0.9418$		1.132 ± 0.0337	$P = 0.0854$ / N.S.
	500	Before	7	$P = 0.0086$	Wilcoxon matched-pairs signed rank test	1.026 ± 0.0572	$P = 0.2188$ / N.S.
		after	7	$P = 0.4309$		0.98 ± 0.0315	

Supplementary Figure 3K

Group	Interstimulus interval	Group	Number	Shapiro-Wilk (p-value)	statistics	Mean ±S.E.M	P-value /Significance
LY293,002 before vs after	20	Before	7	$P = 0.0156$	Wilcoxon matched-pairs signed rank test	1.357 ± 0.0299	$P = 0.8125$ / N.S.
		after	7	$P = 0.3524$		1.364 ± 0.0484	
	30	Before	7	$P = 0.0925$	paired t-test	1.449 ± 0.0423	$t_{(6)} = 0.3122$
		after	7	$P = 0.4323$		1.464 ± 0.0324	$P = 0.7655$ / N.S.
	50	Before	7	$P = 0.7928$	paired t-test	1.453 ± 0.0691	$t_{(6)} = 1.646$
		after	7	$P = 0.5773$		1.531 ± 0.0761	$P = 0.1509$ / N.S.
	100	Before	7	$P = 0.4242$	Wilcoxon matched-pairs signed rank test	1.442 ± 0.0294	$P = 0.9375$ / N.S.
		after	7	$P = 0.0028$		1.420 ± 0.0355	
	200	Before	7	$P = 0.9707$	paired t-test	1.206 ± 0.0741	$t_{(6)} = 0.0780$
		after	7	$P = 0.5693$		1.204 ± 0.0679	$P = 0.9404$ / N.S.
	400	Before	7	$P = 0.0530$	paired t-test	1.125 ± 0.0473	$t_{(6)} = 2.193$
		after	7	$P = 0.9204$		1.043 ± 0.0500	$P = 0.0708$ / N.S.
	500	Before	7	$P = 0.7137$	Wilcoxon matched-pairs signed rank test	1.045 ± 0.0225	$P > 0.9999$ / N.S.
		after	7	$P = 0.0372$		1.048 ± 0.0439	

Supplementary Figure 3L

Group	Interstimulus interval	Group	Number	Shapiro-Wilk (p-value)	statistics	Mean ±S.E.M	P-value /Significance
Veh vs LY293,002	20	Veh	7	$P = 0.1851$	Mann Whitney test	1.333 ± 0.0627	$P = 0.2593$ / N.S.
		LY293,002	7	$P = 0.0156$		1.357 ± 0.0299	
	30	Veh	7	$P = 0.7915$	unpaired t-test	1.447 ± 0.0564	$t_{(12)} = 0.0362$ $P = 0.9717$ / N.S.
		LY293,002	7	$P = 0.0925$		1.449 ± 0.0423	
	50	Veh	7	$P = 0.3773$	unpaired t-test	1.424 ± 0.0267	$t_{(12)} = 0.3965$ $P = 0.6987$ / N.S.
		LY293,002	7	$P = 0.7928$		1.453 ± 0.0691	
	100	Veh	7	$P = 0.7307$	unpaired t-test	1.373 ± 0.0254	$t_{(12)} = 1.777$ $P = 0.1010$ / N.S.
		LY293,002	7	$P = 0.4242$		1.442 ± 0.0294	
	200	Veh	7	$P = 0.2479$	unpaired t-test	1.263 ± 0.0231	$t_{(12)} = 0.7361$ $P = 0.4758$ / N.S.
		LY293,002	7	$P = 0.9707$		1.206 ± 0.0741	
	400	Veh	7	$P = 0.8958$	unpaired t-test	1.063 ± 0.0198	$t_{(12)} = 1.196$ $P = 0.2548$ / N.S.
		LY293,002	7	$P = 0.0530$		1.125 ± 0.0473	
	500	Veh	7	$P = 0.0086$	Mann Whitney test	1.026 ± 0.0572	$p = 0.9015$ / N.S.
		LY293,002	7	$P = 0.7137$		1.045 ± 0.0225	

Supplementary Figure 4B

Group	N number	Mean ±S.E.M	D'Agostino & Pearson test (p-value)	Statistics	P-value /Significance
Veh-Ket	10	129.5 ± 6.012	$P = 0.3928$	Mann-Whitney test	$P = 0.0089$ / **
AZD-Ket	10	109.3 ± 3.228	$P = 0.0012$		