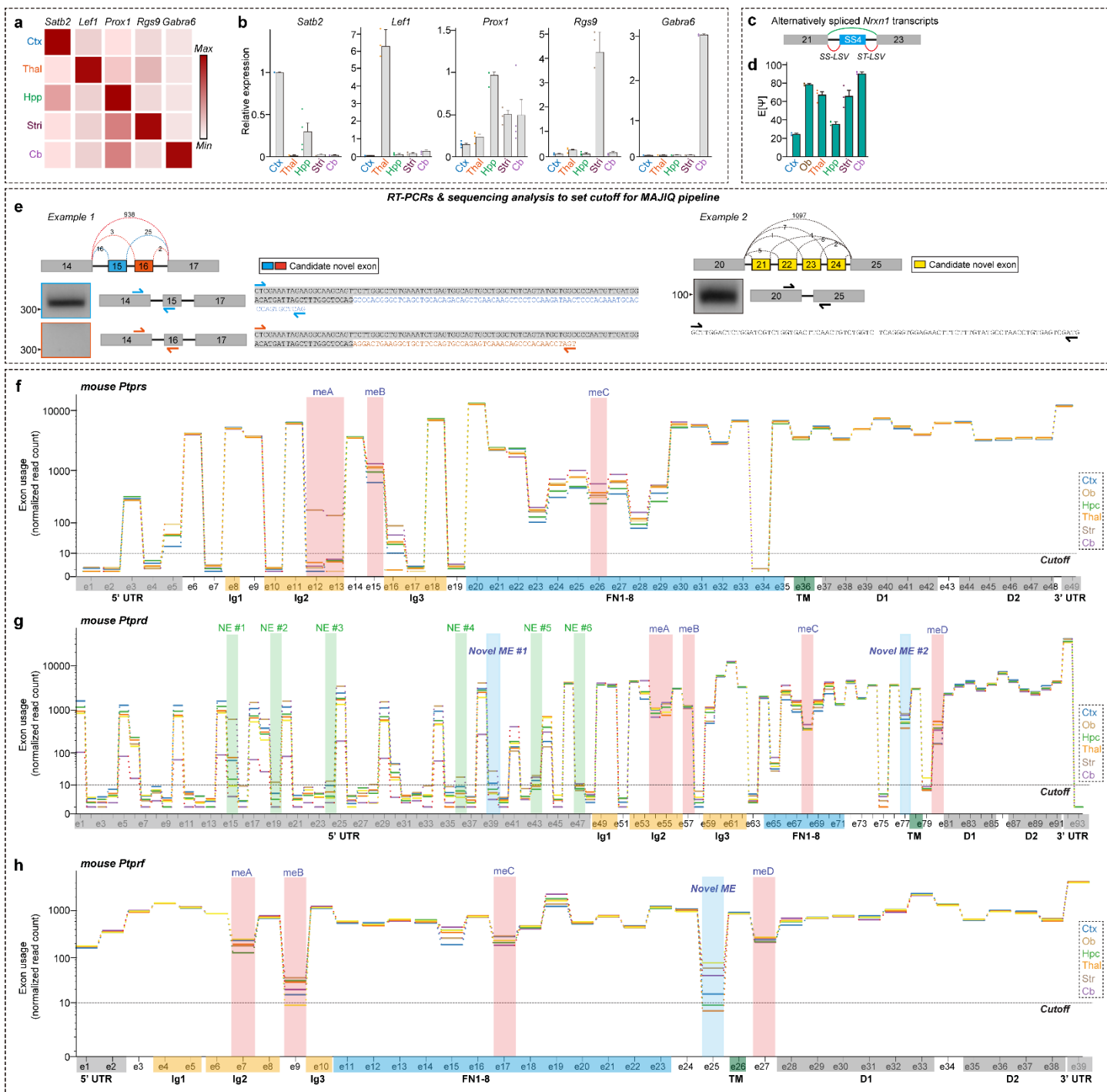


Supplementary Information

Specification of neural circuit architecture shaped by context-dependent patterned LAR-RPTP microexons

Kyung Ah Han, Taek-Han Yoon *et al.*



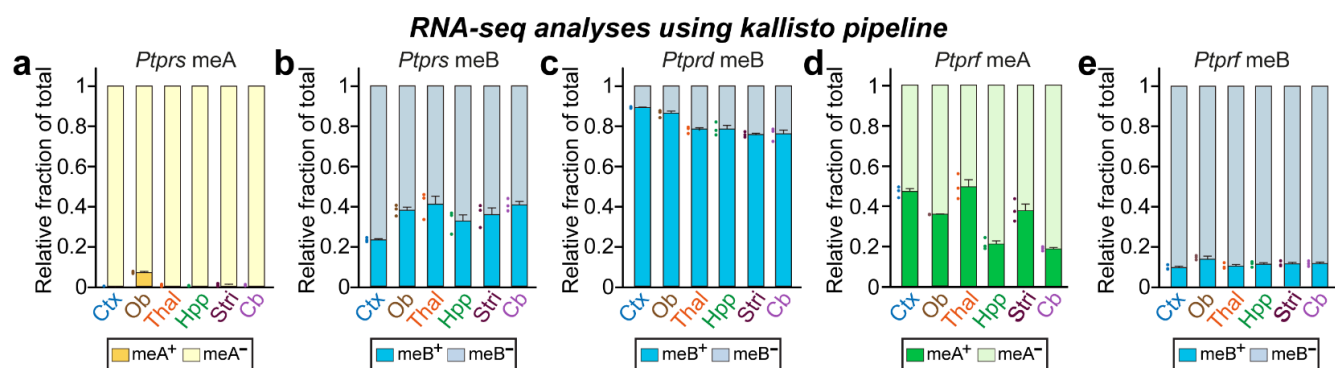
Supplementary Figure 1. Determination of the cutoff for MAJIQ-based alternative splicing analysis, analyses of brain region-specific *Nrxn1* splicing at SS#4, and alternative splicing landscapes of LAR-RPTP mRNAs

a, b Validation of each brain subregion used for RNA-seq. Summary heatmap (**a**) and summary graphs of quantitative RT-PCR analyses using tissue-specific probes (**b**). The following tissue-specific probes were used: *Satb2* (for cortex), *Lef1* (for thalamus), *Prox1* (for hippocampus), *Rgs9* (for striatum), and *Gabra6* (for cerebellum). Data are presented as means $\pm$ SEMs (n = 3 mice for all experimental groups; except for *Satb2* and *Prox1*, n = 4 mice).

c, d Schematic illustration (**c**) of *Nrxn1* SS#4-associated LSVs, and summary data (**d**) showing quantification of SS#4 (e22) across six brain regions. The bars indicate the standard error across triplicates for each region (n = 3 biological replicates). Abbreviations: Cb, cerebellum; Ctx, cortex; Hpp, hippocampus; Ob, olfactory bulb; Stri, striatum; Thal, thalamus.

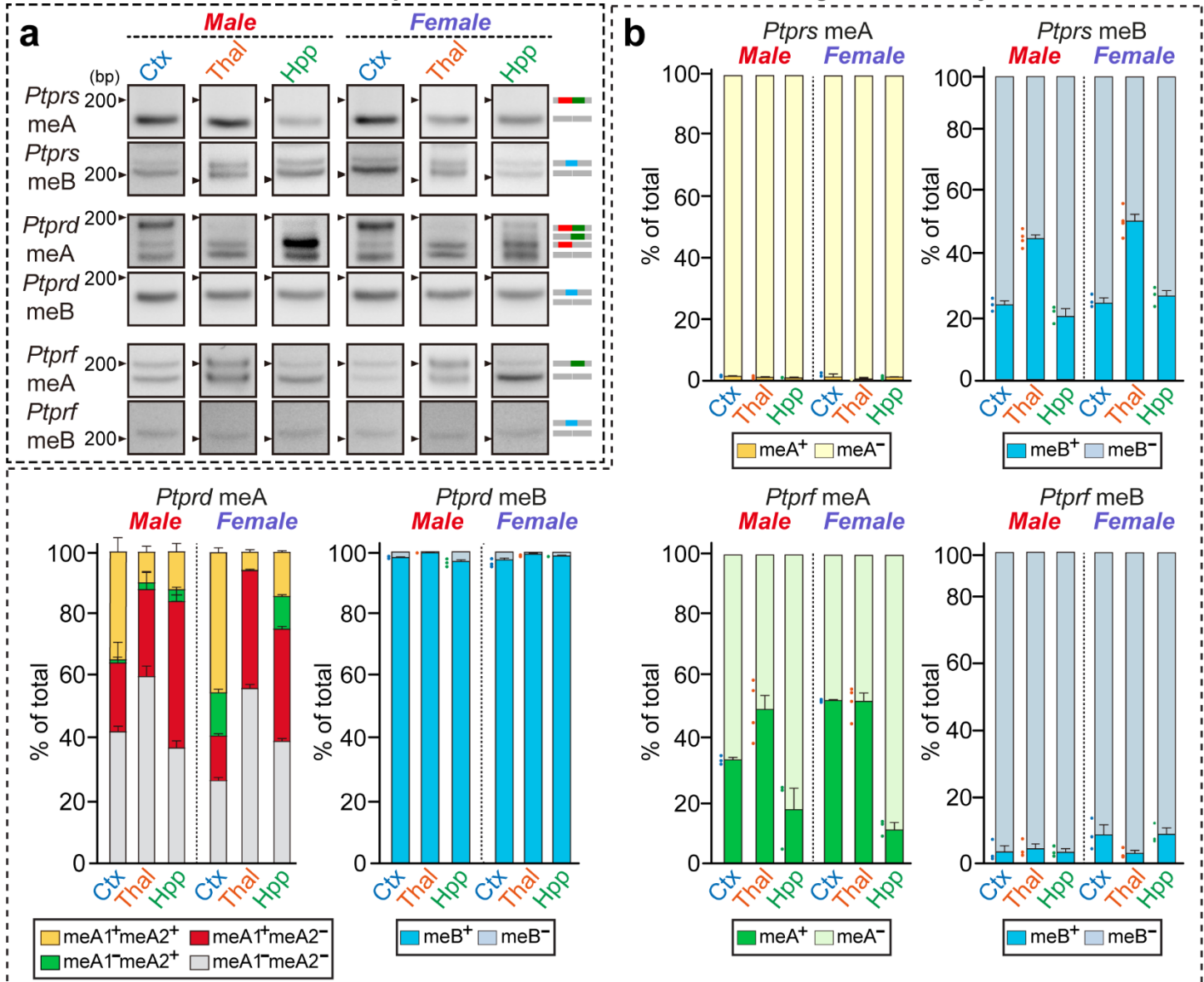
e Confirmation of the arbitrarily determined cutoff value (10) by RT-PCR analysis. Exemplary representative gel images obtained using probes targeting the indicated flanking exons are shown. Note that only exon 15 (value 15), but not exon 16 (value 2), exon 21 (value 4), exon 22 (value 4), exon 23 (value 1), or exon 24 (value 7), was robustly amplified, consistent with MAJIQ-based bioinformatics analysis.

f–h Visualization of the alternative splicing repertoire of mouse LAR-RPTP coding genes (*Ptprs*, *Ptprd*, and *Ptprf*) across six different brain areas using *DEXSeq*. Abbreviations: me, microexon; NE, novel exon; Novel ME, novel microexon; D1 and D2, phosphatase domains; FN, fibronectin type III repeat; Ig, immunoglobulin domain; TM, transmembrane domain; UTR, untranslated region. Source data are provided as a Source Data File.



Supplementary Figure 2. Isoform abundance of LAR-RPTP mRNAs, as assessed using kallisto
 Percentage of total isoforms with and without microexons across LAR-RPTP genes (*Ptprs* meA, **a**; *Ptprs* meB, **b**; *Ptprd* meB, **c**; *Ptprf* meA, **d**; *Ptprf* meB, **e**). Values are expressed as means $\pm$ SEMs (n = 3 mice for all experimental groups). Source data are provided as a Source Data File.

LAR-RPTP meA/meB profiles of male and female mice using RT-PCR analyses

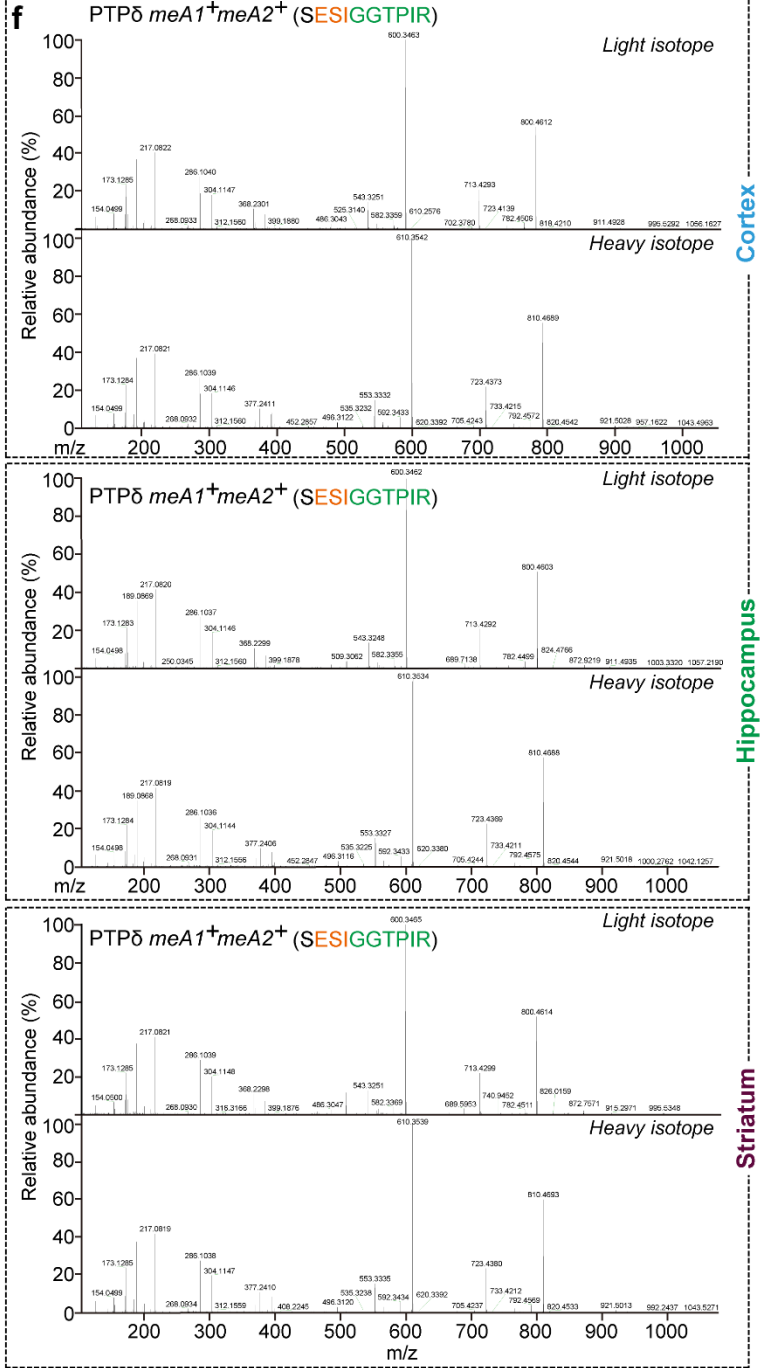
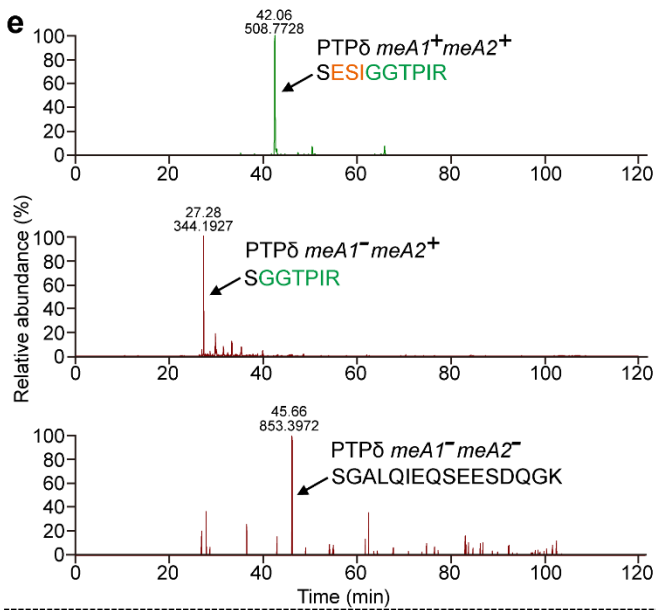
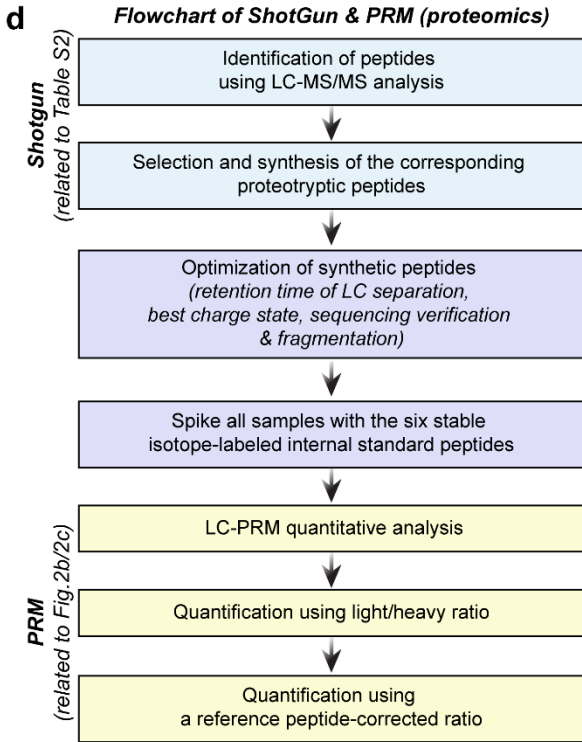
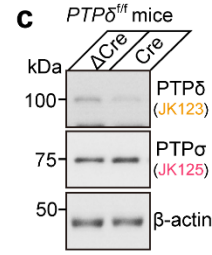
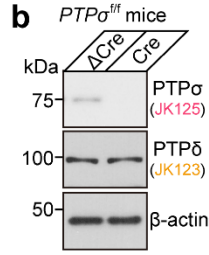


Supplementary Figure 3. Expression profiles of mouse LAR-RPTP microexons in male and female brains

a Representative DNA-PAGE gel images of LAR-RPTP microexon expression analyses in the cortex (Ctx), thalamus (Thal), and hippocampus (Hpp) of adult male and female mice.

b Summary data showing quantification of LAR-RPTP meA and meB microexons in the indicated brain areas. Data are presented as means $\pm$ SEMs ($n = 3$ mice for all experimental groups; except for *Ptprs* meA [male: Thal, female: Thal], *Ptprd* meA [male: Ctx and Hpp, female: Ctx and Hpp] and *Ptprf* meA [male: Thal, female: Thal], $n = 4$ mice). Abbreviations: Ctx, cortex; Hpp, hippocampus; Thal, thalamus. Source data are provided as a Source Data File.

Validation of PTPδ & PTPσ antibodies



Supplementary Figure 4. Authenticity testing of anti-PTP σ and anti-PTP δ antibodies, LC-MS/MS spectra of various PTP δ -derived peptides expressed in the cortex of adult mice by Shotgun mass spectrometry analysis, and spectra of PTP δ meA1⁺ meA2⁺ peptides expressed in the cortex, hippocampus and striatum of adult mice by PRM analysis

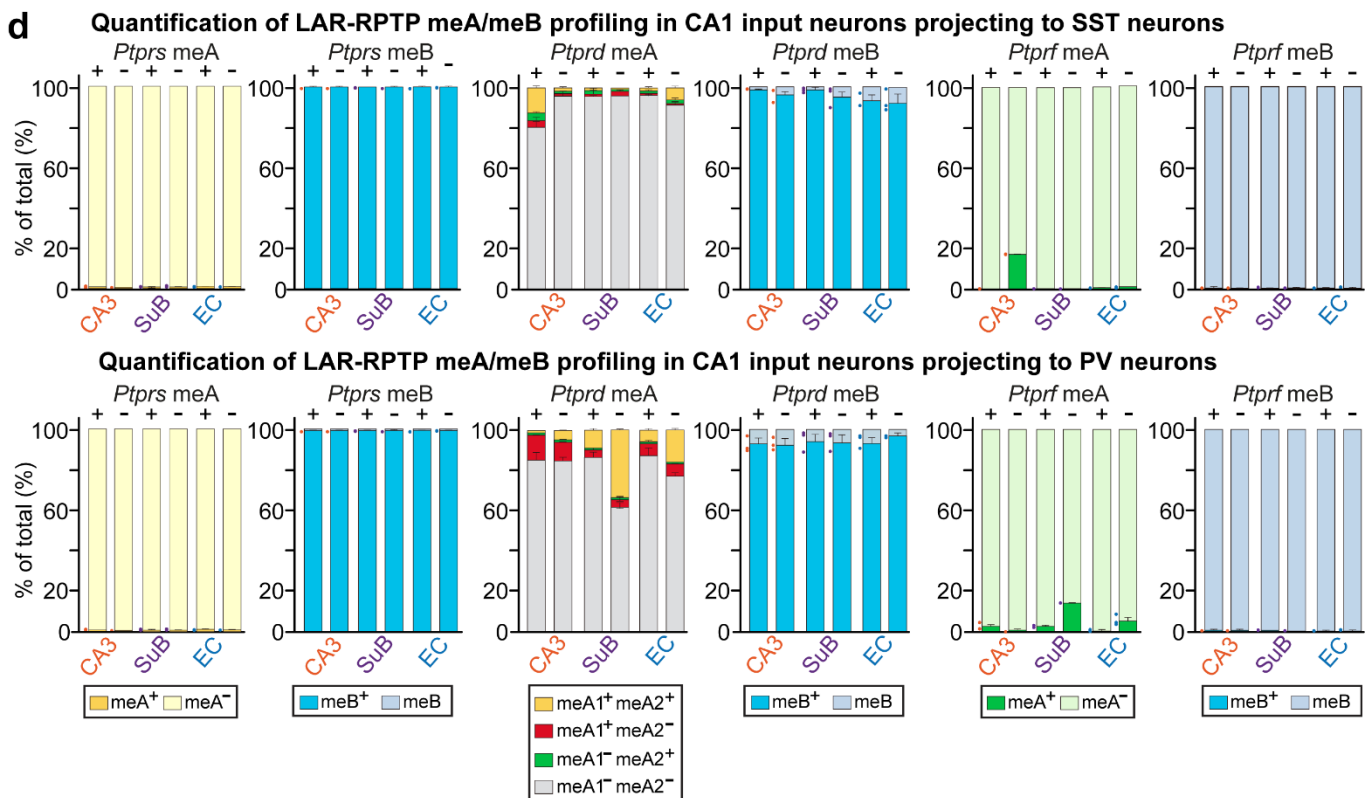
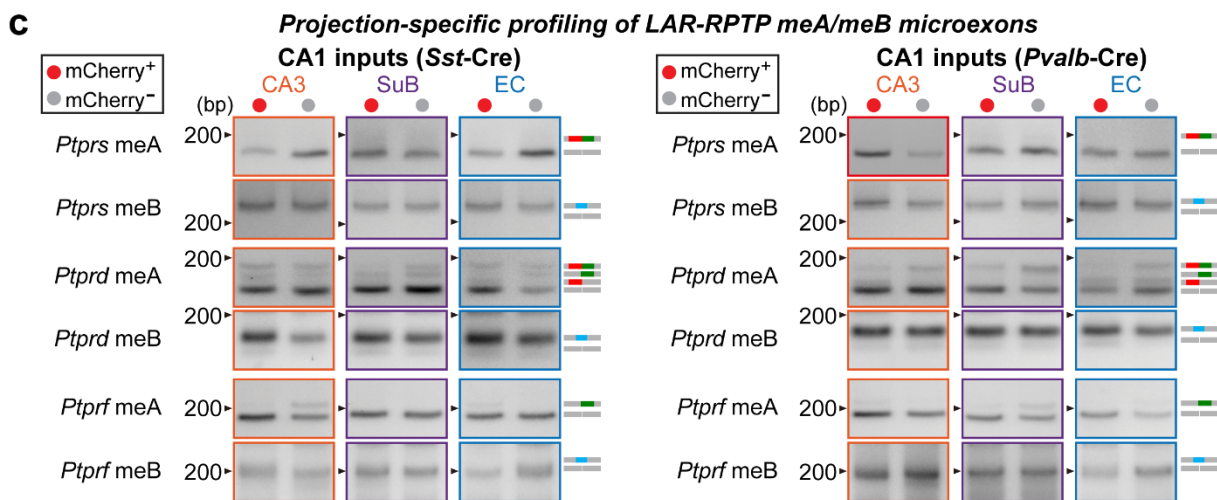
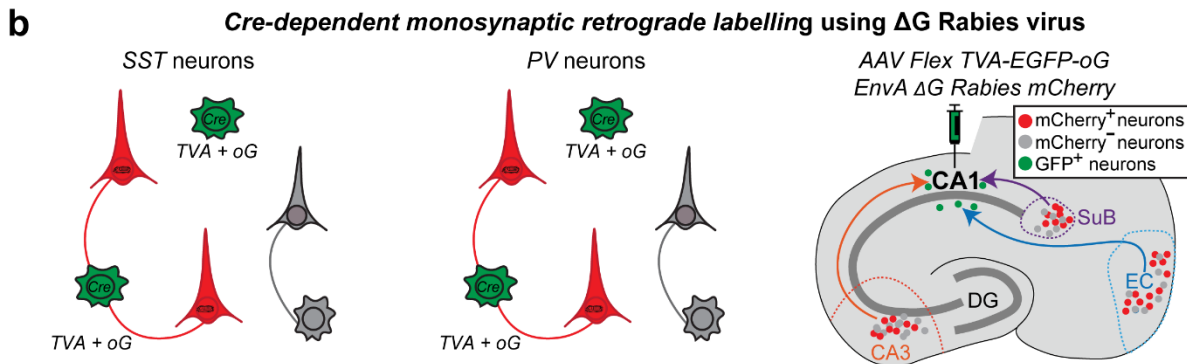
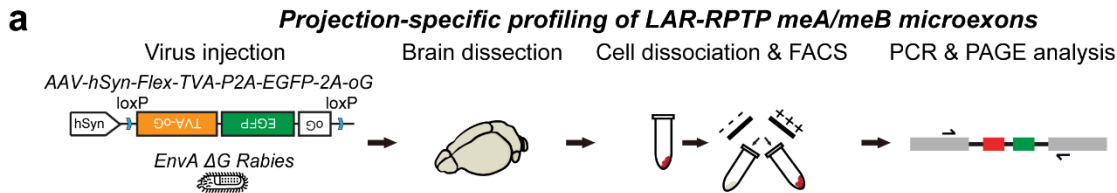
a Schematic of epitopes of anti-PTP σ and anti-PTP δ antibodies (JK125 and JK123, respectively) used in the current study. Abbreviations: D1 and D2, phosphatase domains; FN, fibronectin type III repeat; Ig, immunoglobulin domain; N, N-terminus; C, C-terminus.

b, c Representative immunoblots of the anti-PTP σ and anti-PTP δ antibodies used in this study. Adeno-associated viruses (AAVs) expressing active Cre recombinase or inactive Cre (Δ Cre) recombinase were injected into the CA1 region of adult PTP σ ^{fl/fl} (**b**) or PTP δ ^{fl/fl} (**c**) mice and the infected lysates were probed with the indicated antibodies. β -actin antibodies were used as a normalization control.

d Workflow of proteomics approaches (shotgun and PRM analyses) employed in the current study. Abbreviations: LC-MS/MS, liquid chromatography with tandem mass spectrometry; PRM, parallel reaction monitoring.

e Total ion chromatogram of tryptic digests of PTP δ -bound eluates separated by liquid chromatography (LC) and extracted ion chromatograms of m/z 508.7728 (SESIGGTPIR, 2+), 344.1927 (SGGTPIR, 2+), and 853.3972 (SGALQIEQSEESDQ GK, 2+) ions generated from mouse PTP δ meA variants using shotgun analyses.

f Representative MS/MS spectra of LC-PRM for detection of peptides encoding PTP δ meA1⁺A2⁺ from the cortex, hippocampus, and striatum of adult mice.

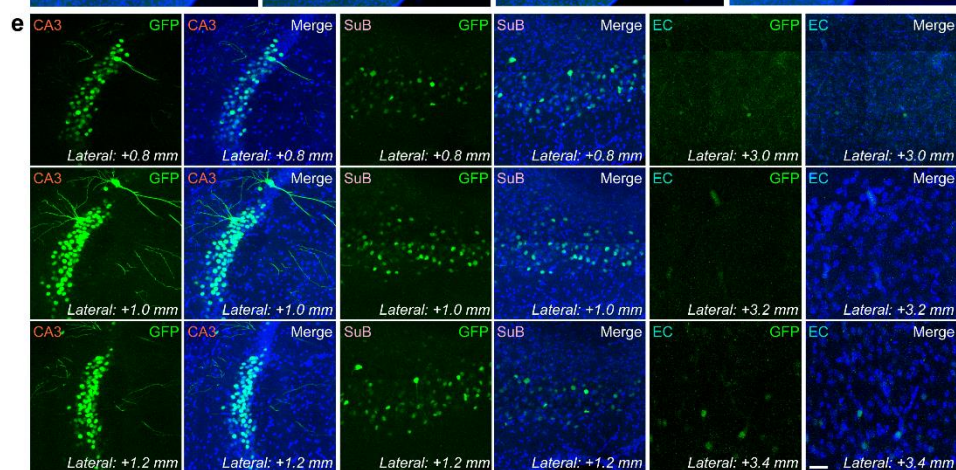
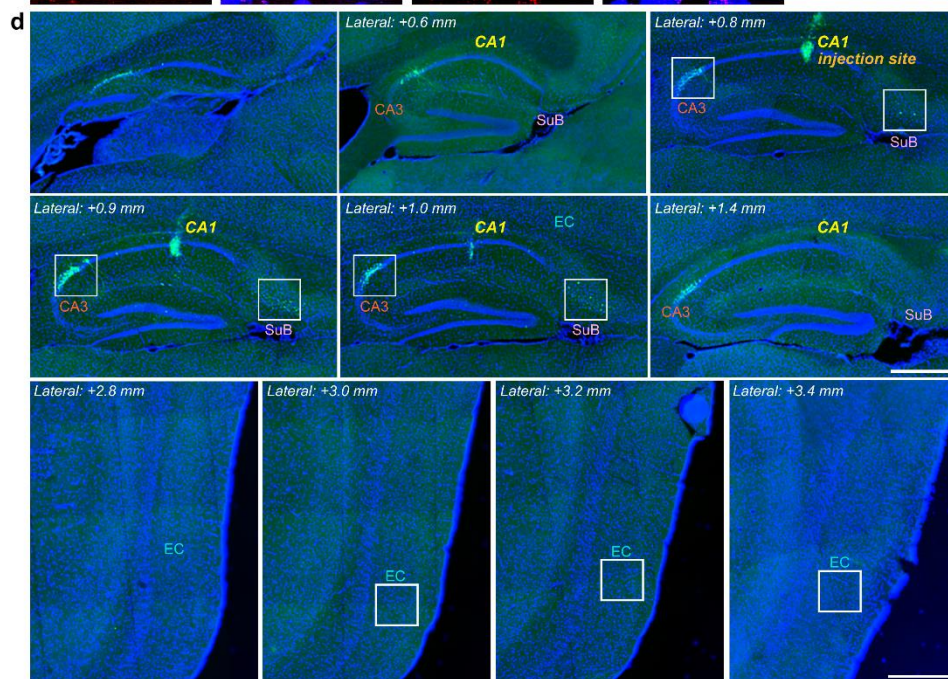
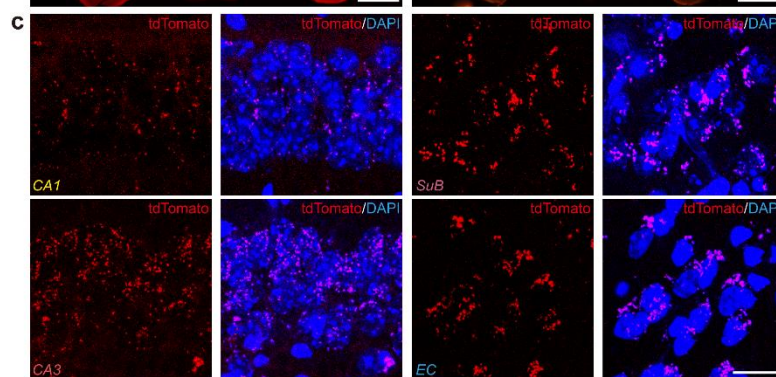
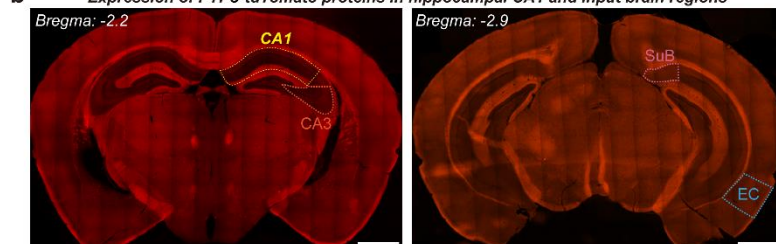


Supplementary Figure 5. Profiling of mouse LAR-RPTP microexon profiles in distinct hippocampal CA1 GABAergic interneurons

- a** Schematic showing the experimental procedure for LAR-RPTPs microexon profiling in hippocampal CA1 GABAergic (SST⁺ or PV⁺) interneurons.
- b** Cre-dependent TVA and oG expressing system for cell-type-specific retrograde labeling. TVA and oG are expressed only in Cre-expressing CA1 interneurons, and EnvA ΔG rabies is complemented in Cre-expressing cells and activated for mono-*trans*-synaptic retrograde tracing. Abbreviations: EnvA, envelop protein from avian ASLV type A; PV, parvalbumin; SST, somatostatin; TVA, EnvA receptor.
- c** Representative DNA-PAGE of LAR-RPTPs meA and meB microexons in CA3, subicular, and EC neurons that project to hippocampal CA1 GABAergic (SST⁺ or PV⁺) interneurons.
- d** Quantitative analyses of LAR-RPTPs meA and meB microexon expression repertoires in (c). Values are expressed as means ± SEMs (n = 3 mice). Abbreviations: EC, entorhinal cortex; SuB, subiculum. Source data are provided as a Source Data File.



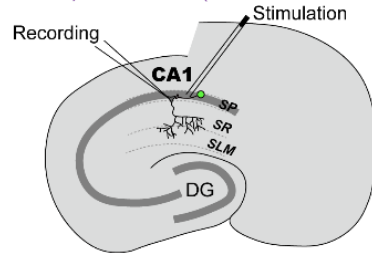
b Expression of PTPδ-tdTomato proteins in hippocampal CA1 and input brain regions



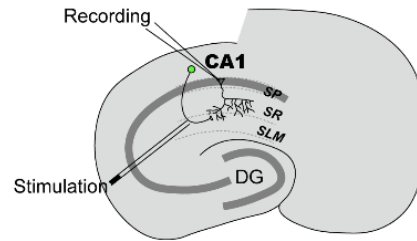
Supplementary Figure 6. Validation of the loss of *Ptprd* variants containing meA in cortical cells of PTP δ meA floxed mice expressing Cre recombinase, expression of PTP δ protein in three brain regions that innervate hippocampal CA1 neurons, and distribution of retrogradely labeled input neurons in the CA3, SuB or EC that project to dCA1 neurons

- a** Validation of *Ptprd*-meA transgenic mouse lines lacking meA conditionally, as assessed by DNA-PAGE analyses. Note that cortical cells from *Ptprd* meA-cKO mice specifically lack *Ptprd* variants containing meA.
- b** Low-resolution images of coronal brain sections from PTP δ -tdTomato reporter mice, showing the expression of tdTomato fluorescence across the hippocampal dCA1, CA3, subiculum (SuB), and entorhinal cortex (EC). Scale bar = 1 mm.
- c** Representative images of brain sections from PTP δ -tdTomato reporter mice, showing the expression of tdTomato fluorescence in the hippocampal dCA1, CA3, SuB, and EC. Scale bar = 20 μ m.
- d** Representative images of sagittal brain sections injected with rAAV2-retro. rAAV2-retro-mediated labeling of dCA1 input neurons was detected in the CA3, SuB or EC along the sagittal axis using Axioscan. Scale bar, 500 μ m. Abbreviations: EC, entorhinal cortex; GFP, green fluorescent protein; SuB, subiculum.
- e** Expanded views of the boxed area in panel A. Scale bar, 50 μ m.

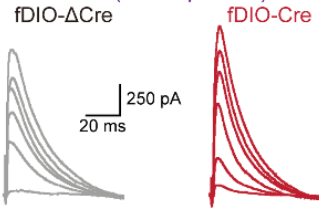
a *Parv-Flp-PTPδ* mice (**somatic inhibition**)



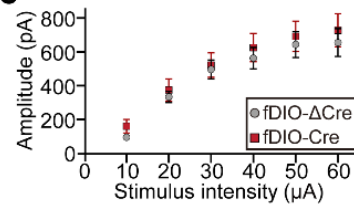
SST-Flp-PTPδ mice (**dendritic inhibition**)



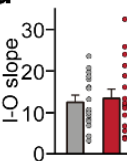
b *IPSCs (Parv-Flp-PTPδ)*



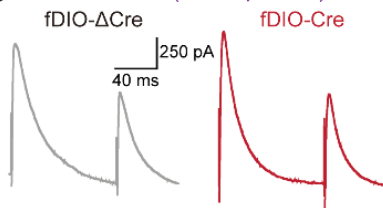
c *IPSC I-O curves (Parv-Flp-PTPδ)*



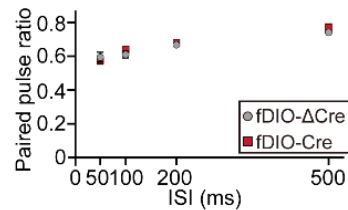
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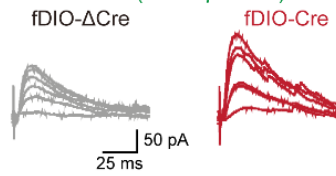
e *IPSC-PPRs (Parv-Flp-PTPδ)*



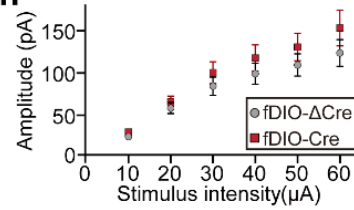
f *IPSC-PPRs (Parv-Flp-PTPδ)*



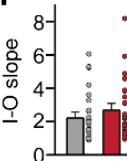
g *IPSCs (SST-Flp-PTPδ)*



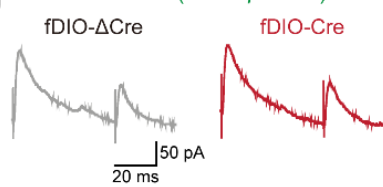
h *IPSC I-O curves (SST-Flp-PTPδ)*



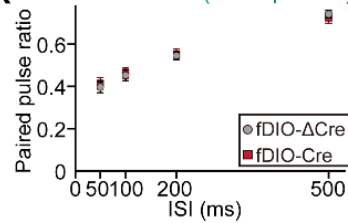
i



j *IPSC-PPRs (SST-Flp-PTPδ)*



k *IPSC-PPRs (SST-Flp-PTPδ)*



Supplementary Figure 7. Analysis of PTP δ function in regulating specific GABAergic neural circuits in the mouse hippocampal CA1

a Schematic of electrophysical recordings showing stimulation and recording sites in the hippocampal CA1. For recording input from PV⁺ interneurons of *Parv-Flp-PTP δ* mice, the stimulation electrode was positioned on the SP layer (**left**). For recording input from SST⁺ interneurons of *SST-Flp-PTP δ* mice, axon fibers on the SLM layer were electrically stimulated (**right**). Abbreviations: DG, dentate gyrus, Parv, parvalbumin; SST, somatostatin

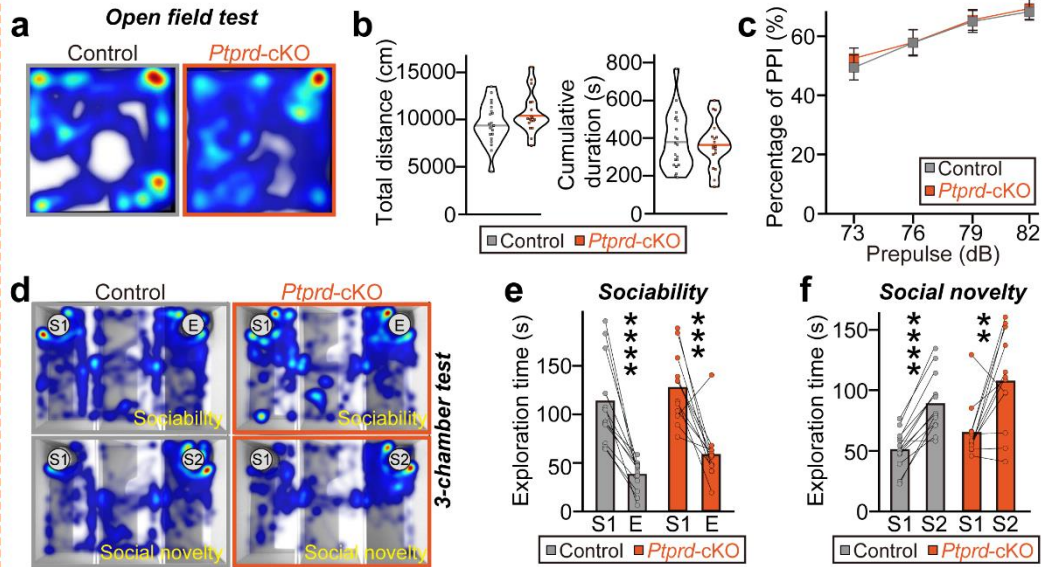
b–d Measurement of somatic-evoked IPSCs (eIPSCs). Representative somatic eIPSC traces (**b**), average eIPSC input-output (I-O) curve (**c**), and average eIPSC I-O slope (**d**) for hippocampal CA1 pyramidal neurons from *Parv-Flp-PTP δ* mice expressing fDIO- Δ Cre (black) or fDIO-Cre (red). Data are presented as means $\pm$ SEMs ('n' denotes number of cells/mice; fDIO- Δ Cre, n = 17/5; fDIO-Cre, n = 18/5; two-tailed non-parametric Mann-Whitney *U* test).

e, f Release probability of PV⁺ interneurons, measured by recording IPSC-PPRs. Representative traces of IPSC-PPRs at an interstimulus interval of 100 ms (**e**) and average of IPSC-PPRs (**f**). Data are presented as means $\pm$ SEMs ('n' denotes number of cells/mice; fDIO- Δ Cre, n = 17/5; fDIO-Cre, n = 18/5; two-tailed non-parametric Mann-Whitney *U* test).

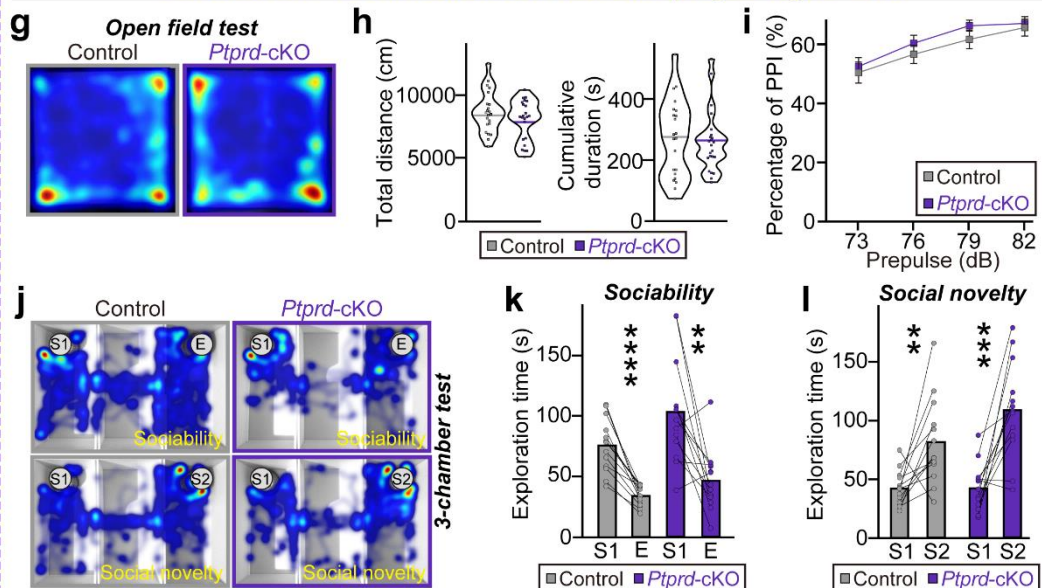
g–i Measurement of dendritic eIPSCs. Representative dendritic eIPSC traces (**g**), average eIPSC I-O curve (**h**), and average eIPSC I-O slope (**i**) for hippocampal CA1 pyramidal neurons from *SST-Flp-PTP δ* mice expressing fDIO- Δ Cre (black) or fDIO-Cre (red). Data are presented as means $\pm$ SEMs ('n' denotes number of cells/mice; fDIO- Δ Cre, n = 27/7; fDIO-Cre, n = 26/7; two-tailed non-parametric Mann-Whitney *U* test).

j, k Release probability of SST⁺ interneurons, measured by recording IPSC-PPRs. Representative traces of IPSC-PPRs at an interstimulus interval of 100 ms (**j**) and average of IPSC-PPRs (**k**). Data are presented as means $\pm$ SEMs ('n' denotes number of cells/mice; fDIO- Δ Cre, n = 27/7; fDIO-Cre, n = 26/7; two-tailed non-parametric Mann-Whitney *U* test). Source data are provided as a Source Data File.

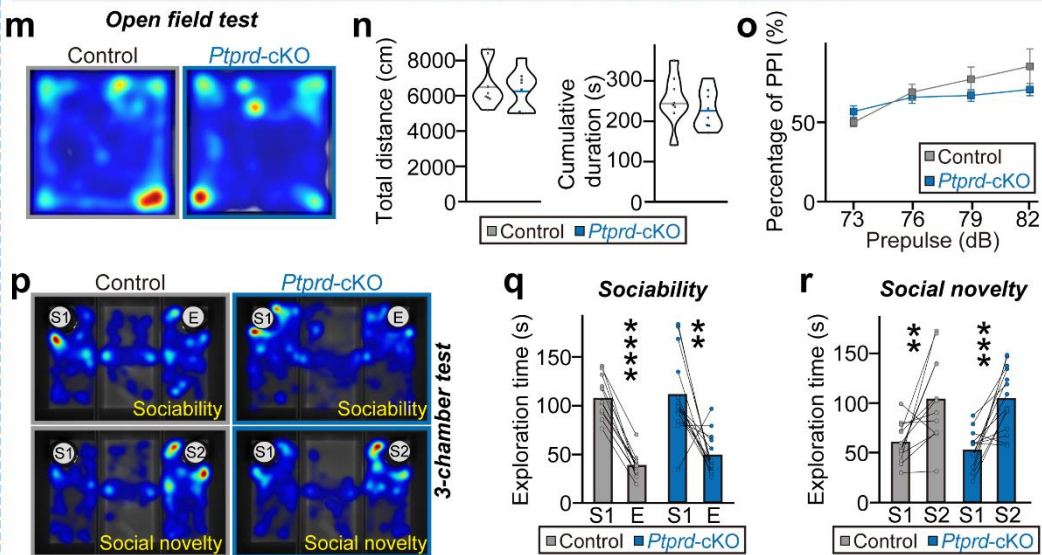
Deletion of PTPδ in CA3 neurons projecting to CA1



Deletion of PTPδ in subicular neurons projecting to CA1



Deletion of PTPδ in EC neurons projecting to CA1



Supplementary Figure 8. Behavioral analyses of hippocampal circuit-specific *Ptprd*-cKO mice

a, b Analysis of locomotor activity by open-field test in CA3→dCA1 circuit-specific *PTPδ*-cKO mice. (a) Representative heat maps of mouse movement in the open chamber. (b) Analyses of total distance moved and time spent in the center zone. Data are presented as means ± SEMs ('n' denotes number of mice; Control, n = 21; *Ptprd*-cKO, n = 18; two-tailed non-parametric Mann Whitney *U*-test).

c Analysis of acoustic startle response to a sudden intense stimulus in Control and CA3→dCA1 circuit-specific *PTPδ*-cKO mice. Data are presented as means ± SEMs ('n' denotes number of mice; Control, n = 20; *Ptprd*-cKO, n = 18; two-way ANOVA with Sidak's multiple comparisons test).

d–f Analysis of behavior in a 3-chamber test using CA3→dCA1 circuit-specific *Ptprd*-cKO mice. Representative heat maps (d) of sociability and social novelty and summary graphs of sociability (e) and novel social recognition memory (f). Data are presented as means ± SEMs ('n' denotes number of mice; Control, n = 13; *Ptprd*-cKO, n = 12; ***p* < 0.01, ****p* < 0.001, *****p* < 0.0001; two-tailed paired *t* test).

g, h Analysis of locomotor activity by open-field test in SuB→dCA1 circuit-specific *Ptprd*-cKO mice. Representative heat maps (g) of mouse movement in the open chamber and summary graphs (h). Data are presented as means ± SEMs (Control, n = 22; *Ptprd*-cKO, n = 23; two-tailed non-parametric Mann Whitney *U*-test).

i Analysis of acoustic startle response to a sudden intense stimulus in Control and SuB→dCA1 circuit-specific *Ptprd*-cKO mice. Data are presented as means ± SEMs ('n' denotes number of mice; Control, n = 22; *Ptprd*-cKO, n = 23; two-way ANOVA with Sidak's multiple comparisons test).

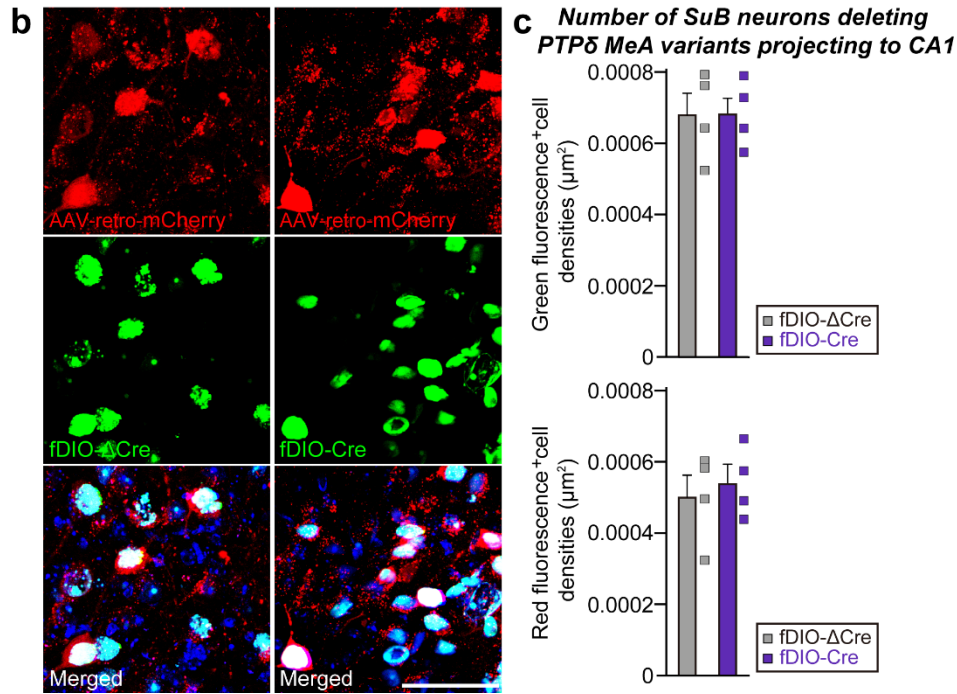
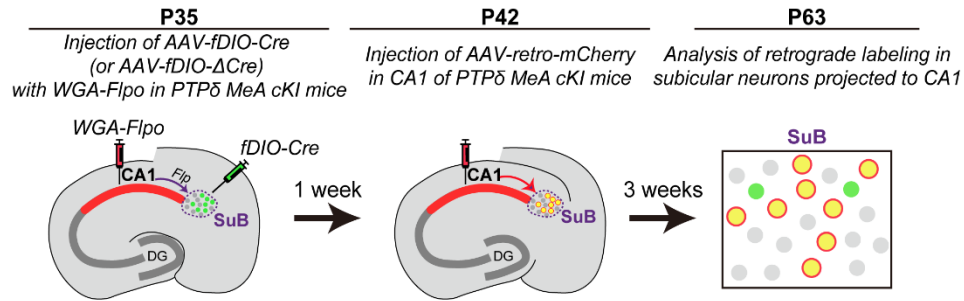
j–l Analysis of behavior in a 3-chamber test in SuB→dCA1 circuit-specific *Ptprd*-cKO mice. Representative heat maps (j) of sociability and social novelty and summary graphs of sociability (k) and novel social-recognition memory (l). Data are presented as means ± SEMs ('n' denotes number of mice; Control, n = 13; *Ptprd*-cKO, n = 13; ***p* < 0.01, ****p* < 0.001, *****p* < 0.0001; two-tailed paired *t* test).

m, n Analysis of locomotor activity by open-field test in EC→dCA1 circuit-specific *Ptprd*-cKO mice. Representative heat maps (m) of mouse movement in the open chamber and summary graphs (n). Data are presented as means ± SEMs ('n' denotes number of mice; Control, n = 8; *Ptprd*-cKO, n = 8; two-tailed non-parametric Mann Whitney *U*-test).

o Analysis of acoustic startle response to a sudden intense stimulus in Control and EC→dCA1 circuit-specific *Ptprd*-cKO mice. Data are presented as means ± SEMs ('n' denotes number of mice; Control, n = 19; *Ptprd*-cKO, n = 21; two-way ANOVA with Sidak's multiple comparisons test).

p–r Analysis of behavior in a 3-chamber test in EC→dCA1 circuit-specific *Ptprd*-cKO mice. Representative heat maps (p) of sociability and social novelty, and summary graphs of sociability (q) and novel social-recognition memory (r). Data are presented as means ± SEMs ('n' denotes number of mice; Control, n = 12; *Ptprd*-cKO, n = 14; ***p* < 0.01, ****p* < 0.001, *****p* < 0.0001; two-tailed paired *t* test). Source data are provided as a Source Data File.

a Experimental strategy to measure connectivity between SuB and hippocampal CA1



Supplementary Figure 9. Viral tracing reveals that presynaptic elimination of PTPδ meA⁺ variants in the SuB→dCA1 circuit does not affect the projection of SuB neurons onto dCA1 neurons

a Schematic showing the experimental strategy for measuring the connectivity between SuB and CA1 upon the deletion of PTPδ meA⁺ variants from SuB neurons. Abbreviations: DG, dentate gyrus; SuB, subiculum.

b Representative immunofluorescence images showing expression of fDIO-ΔCre or fDIO-Cre (green), together with expression of retrograde AAVs (red), in SuB neurons. Scale bar = 50 μm.

c Quantitative analyses of fDIO-ΔCre- or fDIO-Cre/retrograde AAV-expressing neurons, presented in (b). Data are presented as means ± SEMs (n = 4 mice for all experimental groups). Source data are provided as a Source Data File.

Supplementary Table 1. Prior studies investigating microexons of *neurexin* and LAR-RPTP mRNAs

RNA-seq methods	Read counts	<i>Nrxn</i> microexon detection	LAR- RPTPs microexon detection	Reference
PacBio long-read sequencing	A total of 23,943 full-length mRNA reads	O	×	1
Target-enrichment SMART sequencing	150-bp long and >10 million paired-end reads/cell	O	×	2
Patch single cell qRT profiling	N.D.	O	×	3
Single-cell RNA-seq	N.D.	N.D.	N.D.	4
<i>In situ</i> sequencing	N.D.	×	×	5
Ribotag immunoprecipitation sequencing	>100 million reads per biological replicate	×	×	6
Single-cell RNA-seq	10 million/cell	O	×	7
Bulk RNA-seq	N.D.	×	×	8
Single-cell RNA-seq	60,000 reads/cell; the actual median achieved was 59,728 reads/cell across 175 libraries	×	×	9
Single-cell RNA-seq	New pipeline	O	O	10

Abbreviations: N.D., not determined; RNA-seq, RNA sequencing

Supplementary Table 2. Cross-correlation score (X_{corr}) of chemically synthesized peptides used in this study

Name	Peptide	Cortex			Hippocampus		
		X_{corr}	Number of identified peptide spectral matches	Peptide sequence coverage (%)	X_{corr}	Number of identified peptide spectral matches	Peptide sequence coverage (%)
PTP δ meA1-A2-	SGALQIEQSE ESDQGK	2.992	1	50.0	4.6273	1	87.5
PTP δ meA1-A2+	SGGTPIR	1.7892	1	100.0	N.A.	N.D.	N.A.
PTP δ meA1+A2-	SESIGALQIEQ SEESDQGK	N.A.	N.D.	N.A.	N.A.	N.D.	N.A.
PTP δ meA1+A2+	SESIGGTPIR	2.366	7	90.0	2.2187	3	90.0
PTP δ exon 60	NVLELNDVR	2.3847	3	88.9	2.3675	1	88.9
PTP δ exon 61	VVAVNNIGR	2.1059	2	100.0	2.0791	2	100.0

Abbreviations: N.A., not applicable; N.D., not detected. Peptide sequence coverage (%) was calculated as [(number of matched fragment ions from LC-MS/MS analysis)/(number of amino acids in each peptide)] x 100

Supplementary Table 3. Oligonucleotide sequences for genotyping and RT-PCR experiments described in this study

Genotyping	Forward	Reverse
<i>Ptprd</i> -cKO	5'-AATTGGGACTGTGCTCCACAACCTCT -3'	5'-ATGTAAGGGCCTCCTTGAAGACAGC-3'
<i>Ptprs</i> -cKO	5'-CACATACTCCTTCCTCTCCAAACGG-3'	5'-AGACACACTCTGAGCCCTCTGAGC-3'
<i>Ptprd</i> -meA cKI (WT)	5'-TGTCTTAAAAGTCAAAGAATGACTCCCC-3'	5'-ATCACTGCTCGAGGACCTCTGGATA-3'
<i>Ptprd</i> -meA cKI (KO)	5'-TGTCTTAAAAGTCAAAGAATGACTCCCC-3'	5'-GGCCACACAGTAGCTGTGGCAATA-3'
<i>Emx1</i> -Cre	WT: 5'-AAGGTGTGGTTCCAGAATCG-3' Mut: 5'-GCGGTCTGGCAGTAAAAACTATC-3'	WT: 5'-CTCTCCACCAGAAGGCTGAG-3' Mut: 5'-GTGAAACAGCATTGCTGTCTAC TT-3'
<i>Poarb</i> -Cre	WT: 5'-CAGAGCAGGCATGGTGACTA-3' Mut: 5'-GCGGTCTGGCAGTAAAAACTATC-3'	WT: 5'-AGTACCAAGCAGGCAGGAGA-3' Mut: 5'-TGAAACAGCATTGCTGTCACTT-3'
<i>Sst</i> -Cre	WT: 5'-TCTGAAAGACTTGC GTTTGG-3' Mut: 5'-TGGTTTGTCCAAACTCATCAA-3'	5'-GGGCCAGGAGTTAAGGAAGA-3'
<i>Drd1</i> -Cre	5'-GCTATGGAGATGCTCCTGATGGAA-3'	5'-CGGCAAACGGACAGAAGCATT-3'
<i>Drd2</i> -Cre	5'-GTGCGTCAGCATTTGGAGCAA-3'	5'-CGGCAAACGGACAGAAGCATT-3'
qPCR	Forward	Reverse
<i>Satb2</i>	5'-CAGAGGTACCACGTGAAGCA-3'	5'-GCCTGCGGAGTTCACATTAT-3'
<i>Prox1</i>	5'-TTGCAACGCTCTTTTGAATG-3'	5'-CCCCTTGTGATGAAGGAAAA-3'
<i>Rgs9</i>	5'-AGAAATGCTGGCCAAAGCTA-3'	5'-GCAGCTCCTTTTTGAGTTGG-3'
<i>Lef1</i>	5'-CGGTTGTTTCGGAAAAAGAA-3'	5'-GGTCTGCTGGCTTTCTAGTTG-3'
<i>Gabra6</i>	5'-AGGAGTCAGTCCCAGCAAGA-3'	5'-GTTGACAGCTGCGAATTCAA-3'
<i>Gapdh</i>	5'-ACATGGTCTACATGTTCCAG-3'	5'-TCGCTCCTGGAAGATGGTGAT-3'
RT-PCR	Forward	Reverse
<i>Ptprs</i> meA	5'-GAGGTTGGCAGGTGATGAGT-3'	5'-TAAGGACTTCCTGCCTGTGG-3'
<i>Ptprs</i> meB	5'-TGAGTCCTTGACATCCGTGA-3'	5'-ACTCATCACCTGCCAACCTC-3'
<i>Ptprd</i> meA	5'-TGGTGGCAACACACTCGTAT-3'	5'-CGGATCCAGAAATCACTTGG-3'
<i>Ptprd</i> meB	5'-TACACTTCCACCTGGCATGA-3'	5'-CCGACCAAGGAAAATACGAG-3'
<i>Ptprf</i> meA	5'-TCGCTGCTCTCTATCTGCAA-3'	5'-CGACTATCGACATGGGACCT-3'
<i>Ptprf</i> meB	5'-GCCCATCATCCATTTACAT-3'	5'-AGAGAGCAGCGAGGAGTCTG-3'
<i>Nrxn1</i> SS#4	5'-CTGGCCAGTTATCGAACGCT-3'	5'-GCGATGTTGGCATCGTTCTC-3'
<i>Ptprd</i> e14	5'-CTCGAAATAGAAGGCAAGCA-3'	–
<i>Ptprd</i> e15	–	5'-CTGAGCACTGGGTGCATTT-3'
<i>Ptprd</i> e16	–	5'-ACTAGGTTGTGGGCTGTT-3'
<i>Ptprd</i> e20	–	5'-GCTTGGACTCTGGATCGT-3'
<i>Ptprd</i> e25	5'-CATCGACTCACAGGTTAGG-3'	–
<i>Ptprd</i> e60	5'-ACCCACTAATCATGAAATCA-3'	5'-CGTCGACATAGCAACA-3'
<i>Ptprd</i> e61	5'-CATCGACTCACAGGTTAGG-3'	5'-CTCTATACCCTTGGATCTG-3'

Supplementary Table 4. Information on peptides used for LC-PRM analyses

Peptide	Light (L) or heavy (H)	Peptide sequence	Monoisotopic mass	m/z Value for LC-PRM analysis (charge)	Fragment ions for quantification
PTP δ meA1 ⁺ A2 ⁻	L	SGALQIEQSEESDQ GK	1705.7875	853.3974 (2+)	y ⁸ , y ¹⁰ , y ¹¹
	H	SGALQIEQSEESDQ GK [Label: 13C(6)15N(2)]	1713.8017	857.4045 (2+)	
PTP δ meA1 ⁺ A2 ⁺	L	SESIGGTPIR	1016.5371	508.7722 (2+)	y ⁶ , y ⁷ , y ⁸
	H	SESIGGTPIR [Label: 13C(6)15N(4)]	1026.5454	513.7762 (2+)	
PTP δ meA1 ⁺ A2 ⁺	L	SGGTPIR	687.3784	334.1928 (2+)	y ³ , y ⁵ , y ⁶
	H	SGGTPIR [Label: 13C(6)15N(4)]	697.3867	349.1970 (2+)	
PTP δ meA1 ⁺ A2 ⁻	L	SESIGALQIEQSEESDQ GK	2034.9462	1017.9767 (2+)	y ¹⁰ , y ¹¹ , y ¹²
	H	SESIGALQIEQSEESDQ GK [Label: 13C(6)15N(2)]	2042.9604	1021.9838 (2+)	
PTP δ exon 60	L	NVLELNDVR	1071.5793	536.2936 (2+)	y ⁵ , y ⁶ , y ⁷
	H	NVLELNDVR [Label: 13C(6)15N(4)]	1081.5876	541.2977 (2+)	
PTP δ exon 61	L	VVAVNNIGR	941.5527	471.2803 (2+)	y ⁵ , y ⁶ , y ⁷
	H	VVAVNNIGR [Label: 13C(6)15N(4)]	951.5610	476.2844 (2+)	

Supplementary Table 5. Summary of the LAR-RPTP microexon profiles identified in the current study

Region	LAR-RPTP microexons					
	<i>Ptprs</i> meA	<i>Ptprs</i> meB	<i>Ptprd</i> meA	<i>Ptprd</i> meB	<i>Ptprf</i> meA	<i>Ptprf</i> meB
Cortex	98.9	75.0	54.5	3.3	50.7	85.2
Olfactory bulb	92.5	79.1	54.5	3.6	59.3	74.0
Thalamus	98.2	53.4	45.2	14.5	47.2	95.9
Hippocampus	98.4	77.3	42.1	13.4	72.5	79.5
Striatum	97.8	62.5	47.5	18.2	58.1	89.3
Cerebellum	98.7	66.5	60.9	15.3	68.3	90.7

Region	Cell type	LAR-RPTP microexons					
		<i>Ptprs</i> meA	<i>Ptprs</i> meB	<i>Ptprd</i> meA	<i>Ptprd</i> meB	<i>Ptprf</i> meA	<i>Ptprf</i> meB
Cortex	Excitatory neuron	95.7	42.8	49.9	2.0	34.5	91.9
	SST ⁺ interneuron	89.9	92.1	17.1	31.6	0.6	92.6
	PV ⁺ interneuron	80.0	5.6	13.1	18.9	1.0	91.9
Olfactory bulb	Excitatory neuron	94.1	88.4	43.9	14.2	46.5	92.3
	SST ⁺ interneuron	96.6	4.9	48.2	27.3	23.0	2.2
	PV ⁺ interneuron	92.7	7.8	71.9	34.7	90.2	1.4
Thalamus	Excitatory neuron	90.8	0.2	63.5	17.6	74.1	98.8
	SST ⁺ interneuron	99.2	11.1	44.0	11.1	98.4	95.0
	PV ⁺ interneuron	98.2	50.9	9.2	17.6	99.8	0.4
Hippocampus	Excitatory neuron	95.9	28.0	39.9	9.9	34.5	7.2

	SST ⁺ interneuron	90.7	12.7	22.8	11.4	59.1	0.4
	PV ⁺ interneuron	87.4	13.5	36.03	11.6	29.3	91.1
Striatum	SST ⁺ interneuron	75.5	29.0	16.1	25.1	98.9	38.6
	PV ⁺ interneuron	88.2	93.8	29.8	15.8	86.5	5.5
	Drd1 ⁺ dopaminergic neuron	89.3	30.2	45.9	17.4	97.2	92.9
	Drd2 ⁺ dopaminergic neuron	97.5	22.5	2.1	42.8	97.8	39.7

Projection from the indicated input regions		LAR-RPTP microexons					
Target region	Input neuron region	<i>Ptprs</i> meA	<i>Ptprs</i> meB	<i>Ptprd</i> meA	<i>Ptprd</i> meB	<i>Ptprf</i> meA	<i>Ptprf</i> meB
Medial prefrontal cortex	Cortex	1.1	33.3	10.6	3.7	89.7	85.1
	Thalamus	92.8	86.3	13.3	34.9	78.8	92.2
	Hippocampus	0.4	82.1	36.7	3.8	90.7	92.0
	Striatum	1.0	24.7	38.0	0.8	92.3	89.7
Hippocampal CA1	CA3	98.0	1.0	39.5	32.3	99.0	2.5
	Subiculum	99.4	92.9	44.2	16.4	98.9	2.3
	Entorhinal cortex	99.0	2.4	53.3	45.2	98.9	76.9

Supplementary references

1. Treutlein, B., Gokce, O., Quake, S.R. & Südhof, T.C. Cartography of neurexin alternative splicing mapped by single-molecule long-read mRNA sequencing. *Proc Natl Acad Sci U S A* **111**, E1291-1299 (2014).
2. Schreiner, D., *et al.* Targeted combinatorial alternative splicing generates brain region-specific repertoires of neurexins. *Neuron* **84**, 386-398 (2014).
3. Fuccillo, M.V., *et al.* Single-Cell mRNA Profiling Reveals Cell-Type-Specific Expression of Neurexin Isoforms. *Neuron* **87**, 326-340 (2015).
4. Földy, C., *et al.* Single-cell RNAseq reveals cell adhesion molecule profiles in electrophysiologically defined neurons. *Proc Natl Acad Sci U S A* **113**, E5222-5231 (2016).
5. Wang, X., *et al.* Three-dimensional intact-tissue sequencing of single-cell transcriptional states. *Science* **361**, eaat5691 (2018).
6. Furlanis, E., Traunmuller, L., Fucile, G. & Scheiffele, P. Landscape of ribosome-engaged transcript isoforms reveals extensive neuronal-cell-class-specific alternative splicing programs. *Nat Neurosci* **22**, 1709-1717 (2019).
7. Lukacsovich, D., *et al.* Single-Cell RNA-Seq Reveals Developmental Origins and Ontogenetic Stability of Neurexin Alternative Splicing Profiles. *Cell Rep* **27**, 3752-3759 (2019).
8. Attilio, P.J., *et al.* Transcriptomic Analysis of Mouse Brain After Traumatic Brain Injury Reveals That the Angiotensin Receptor Blocker Candesartan Acts Through Novel Pathways. *Front Neurosci* **15**, 636259 (2021).
9. Yao, Z., *et al.* A transcriptomic and epigenomic cell atlas of the mouse primary motor cortex. *Nature* **598**, 103-110 (2021).
10. Parada, G.E., *et al.* MicroExonator enables systematic discovery and quantification of microexons across mouse embryonic development. *Genome Biol* **22**, 43 (2021).

Uncropped scans of all DNA-PAGE and immunoblot gel images

Fig. 1 Profiling of LAR-RTP microexon expression repertoires by targeted deep RNA sequencing

Figure 1f

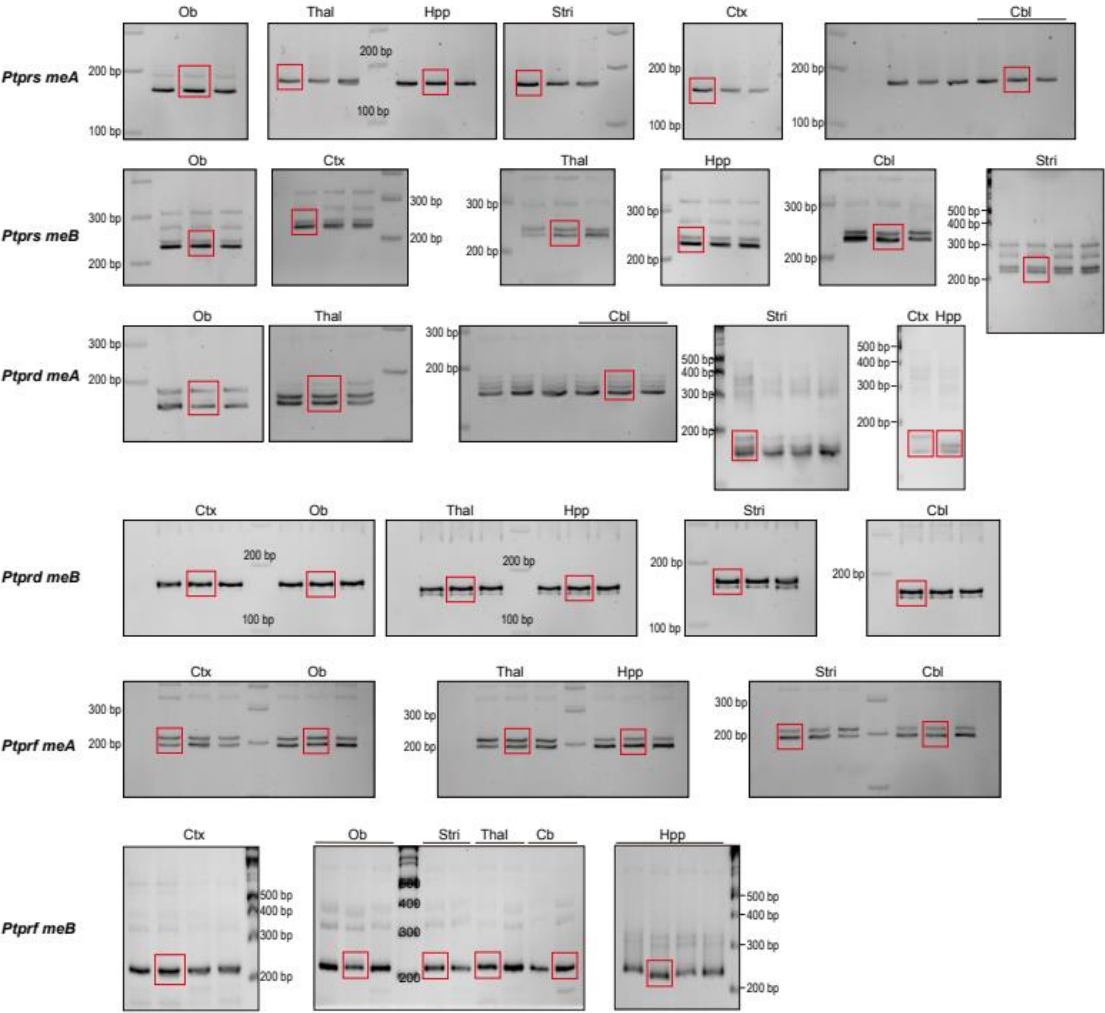


Fig. 2 Profiling the PTPδ meA+ proteoform by targeted proteomics

Figure 2e

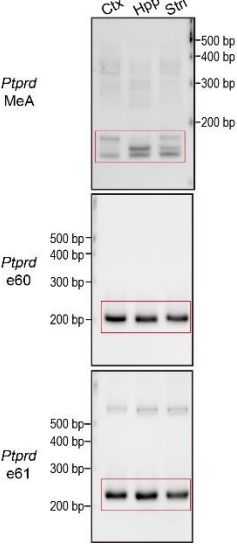


Fig. 3 Profiling of cell-type-specific LAR-RTP microexon expression repertoires

Figure 3c

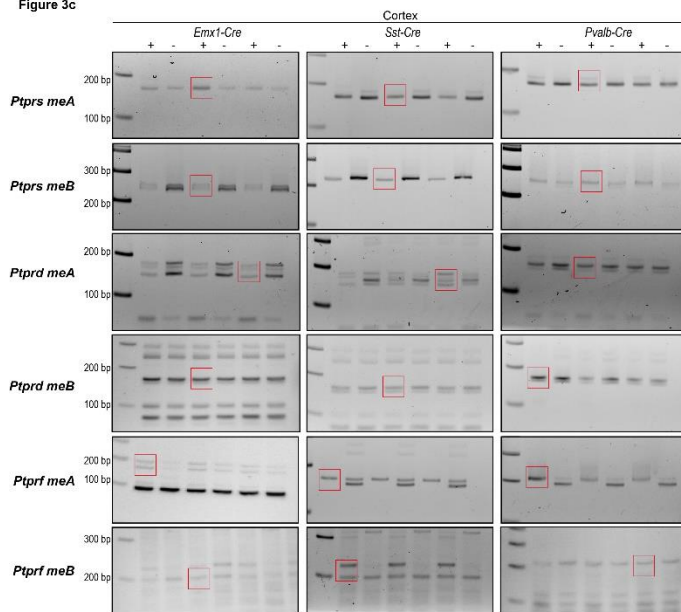


Figure 3c

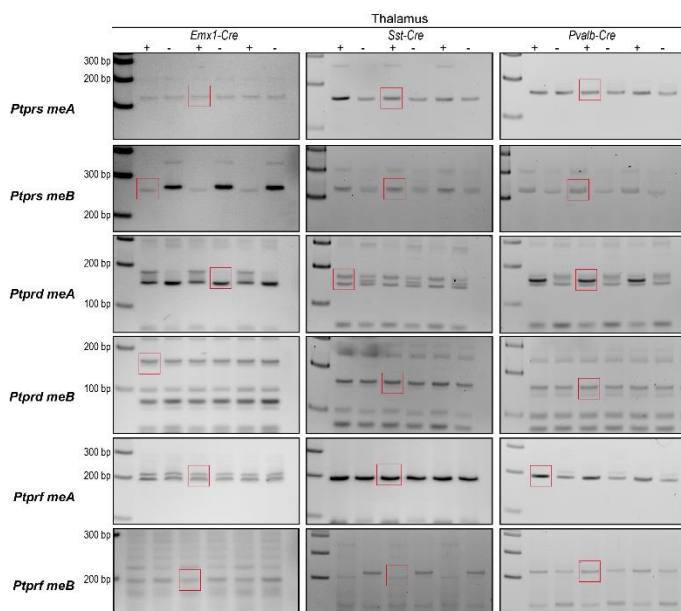
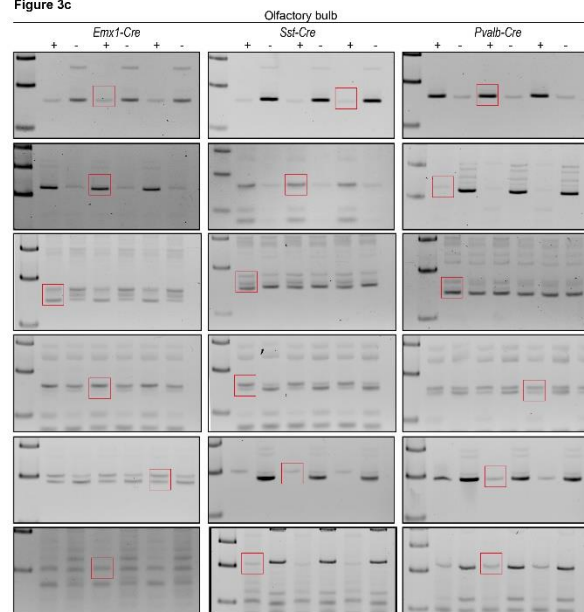


Figure 3c

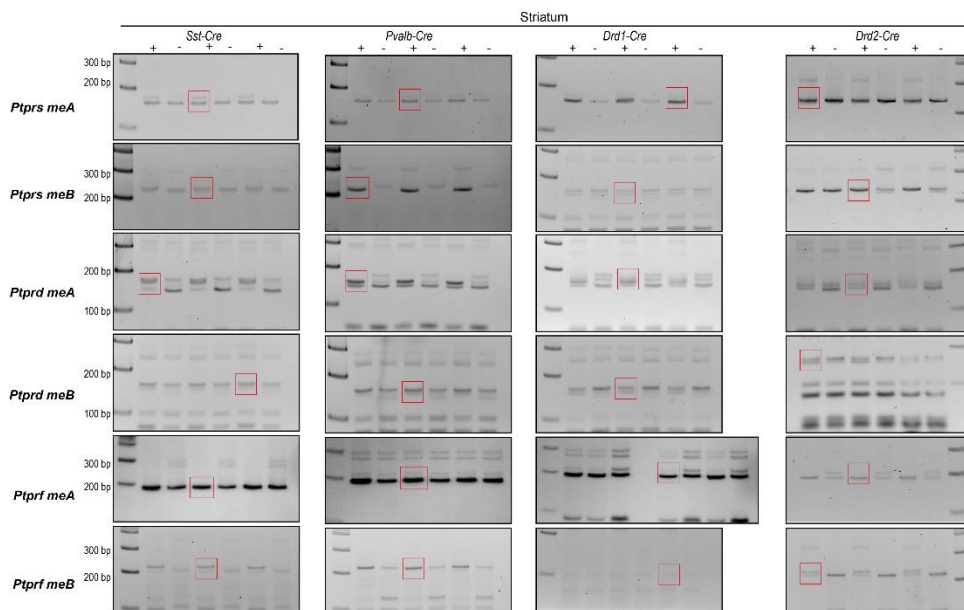
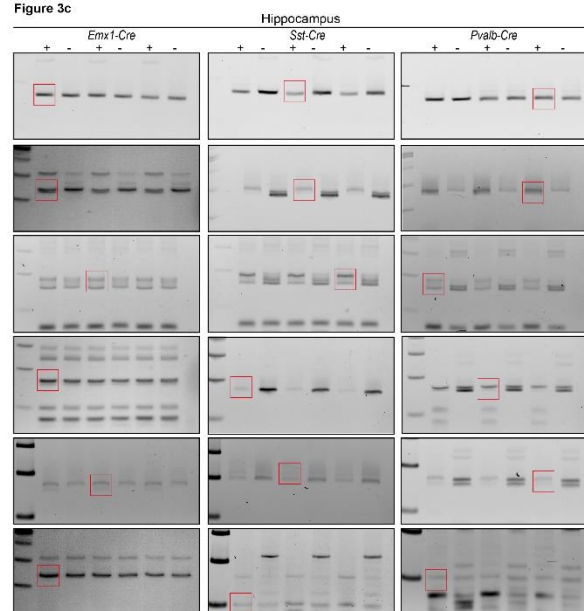


Fig. 4 Profiling of circuit-type-specific LAR-RTP microexon expression repertoires

Figure 4e

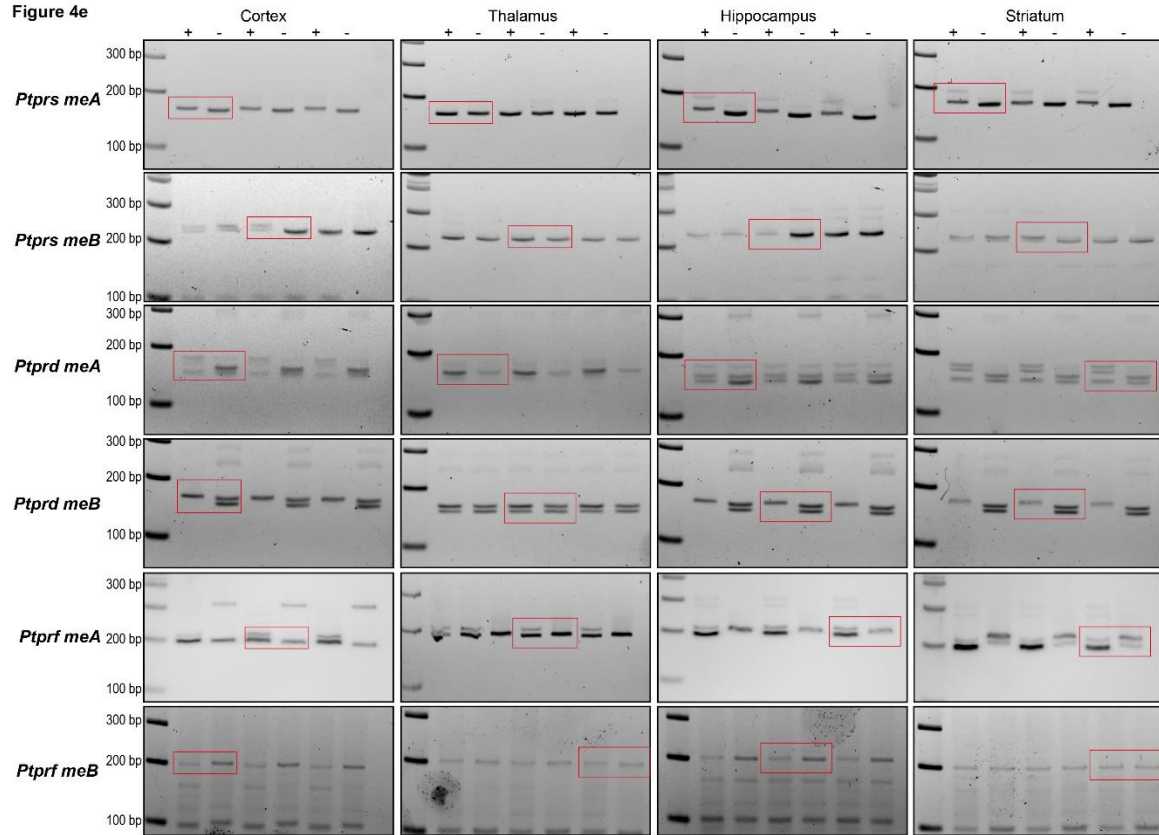


Figure 4f

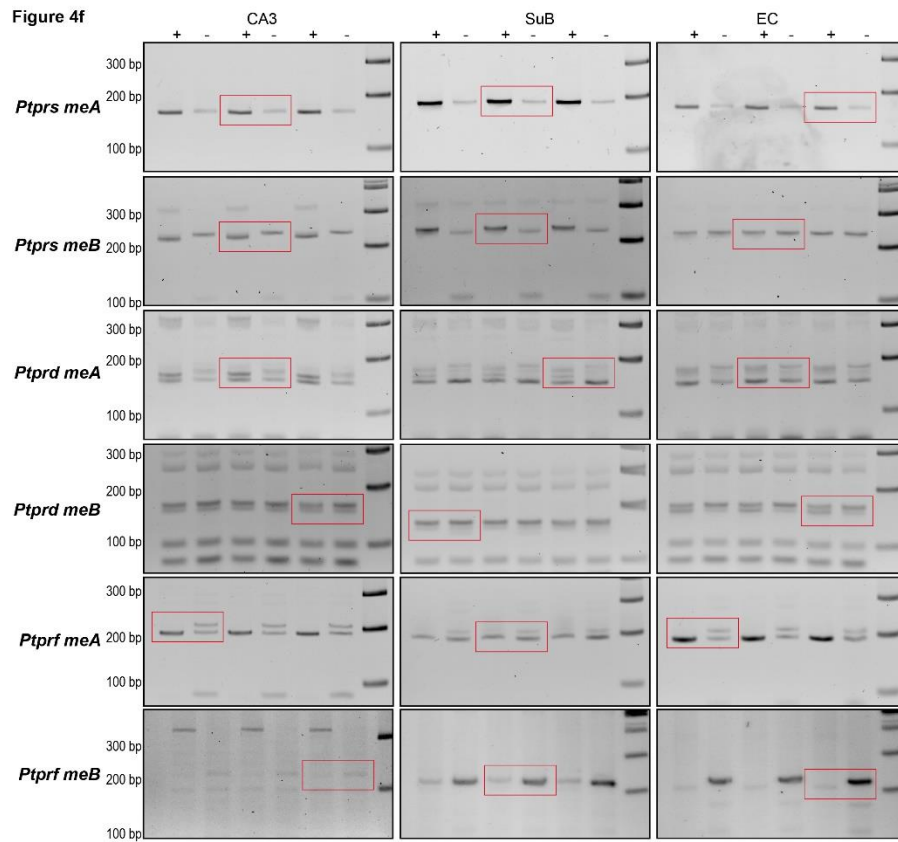


Fig. 5 Increased *Ptprd* meA microexon inclusion in fear memory engrams of the adult mouse DG

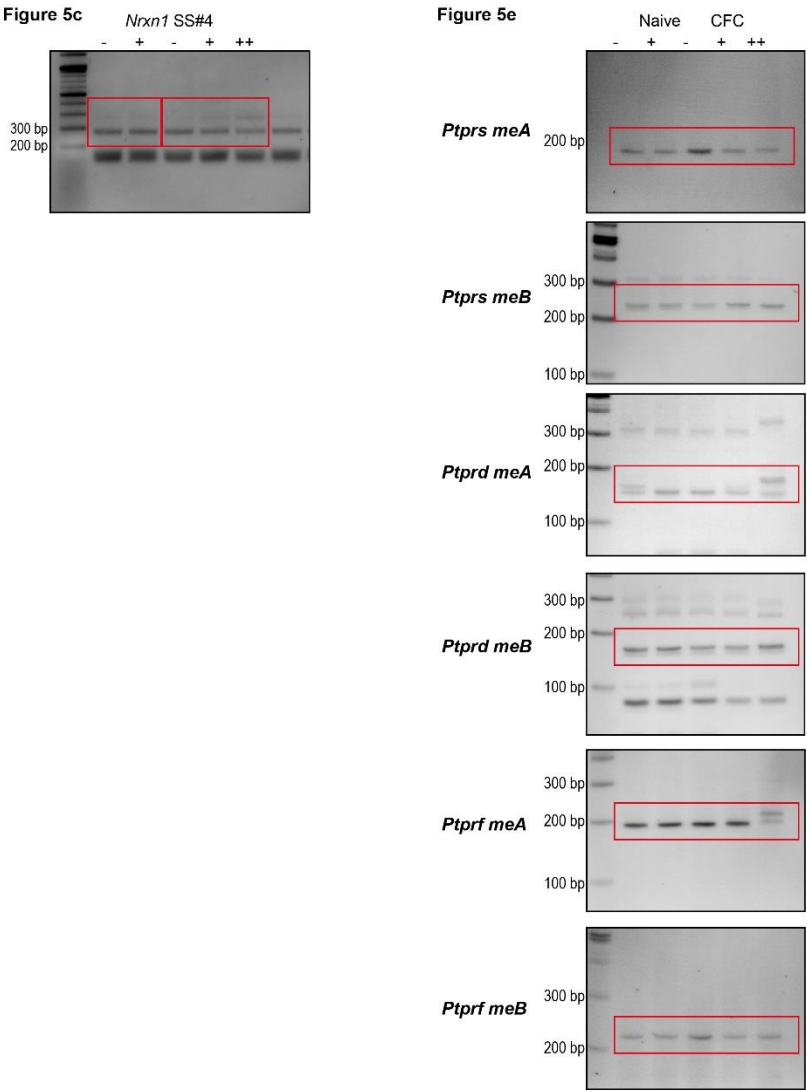


Fig. 6 Effects of neural circuit-specific deletion of PTPδ on the specific glutamatergic synaptic properties of hippocampal CA1 pyramidal neurons

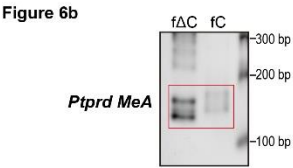


Fig. 7 Presynaptic PTPδ employs meA Microexon inclusion for differential regulation of distinct excitatory synaptic transmission in hippocampal CA1 neural circuits

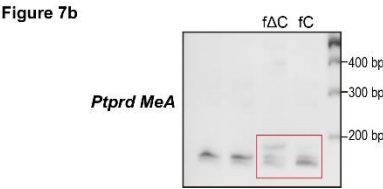
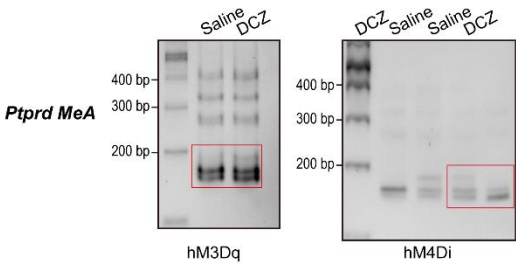


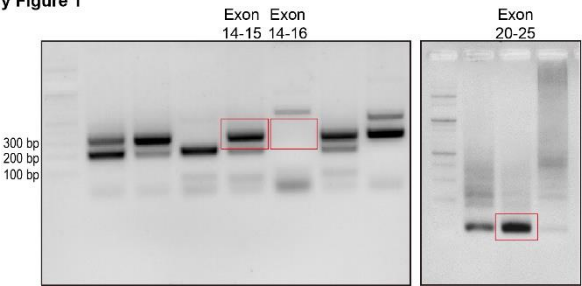
Fig. 9 Activity-triggered SuB-CA1 circuit-specific changes of PTPδ meA insertion modulates NMDA receptor-mediated responses and object-location memory in mice

Figure 9d



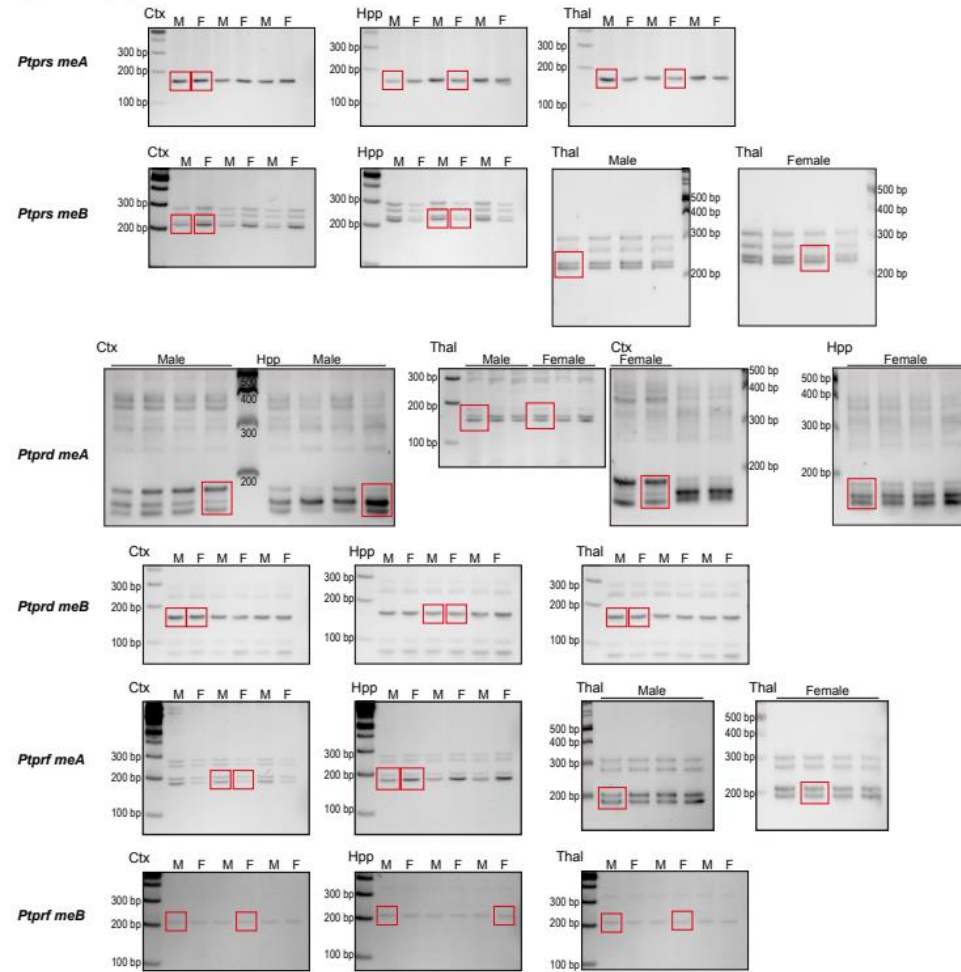
Supplementary Figure 1. Determination of the cutoff for MAJIQ-based alternative splicing analysis, analyses of brain region-specific Nrnx1 splicing at SS#4, and alternative splicing landscapes of LAR-RTP mRNAs

Supplementary Figure 1



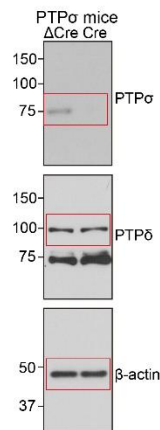
Supplementary Figure 3. Expression profiles of mouse LAR-RTP microexons in male and female brains

Supplementary Figure 3a

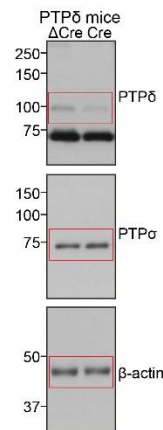


Supplementary Figure 4. Authenticity testing of anti-PTP δ and anti-PTP σ antibodies, LC-MS/MS spectra of various PTP δ -derived peptides expressed in the cortex of adult mice by Shotgun mass spectrometry analysis, and spectra of PTP δ meA1+ meA2+ peptides expressed in the cortex, hippocampus and striatum of adult mice by PRM analysis

Supplementary Figure 4b

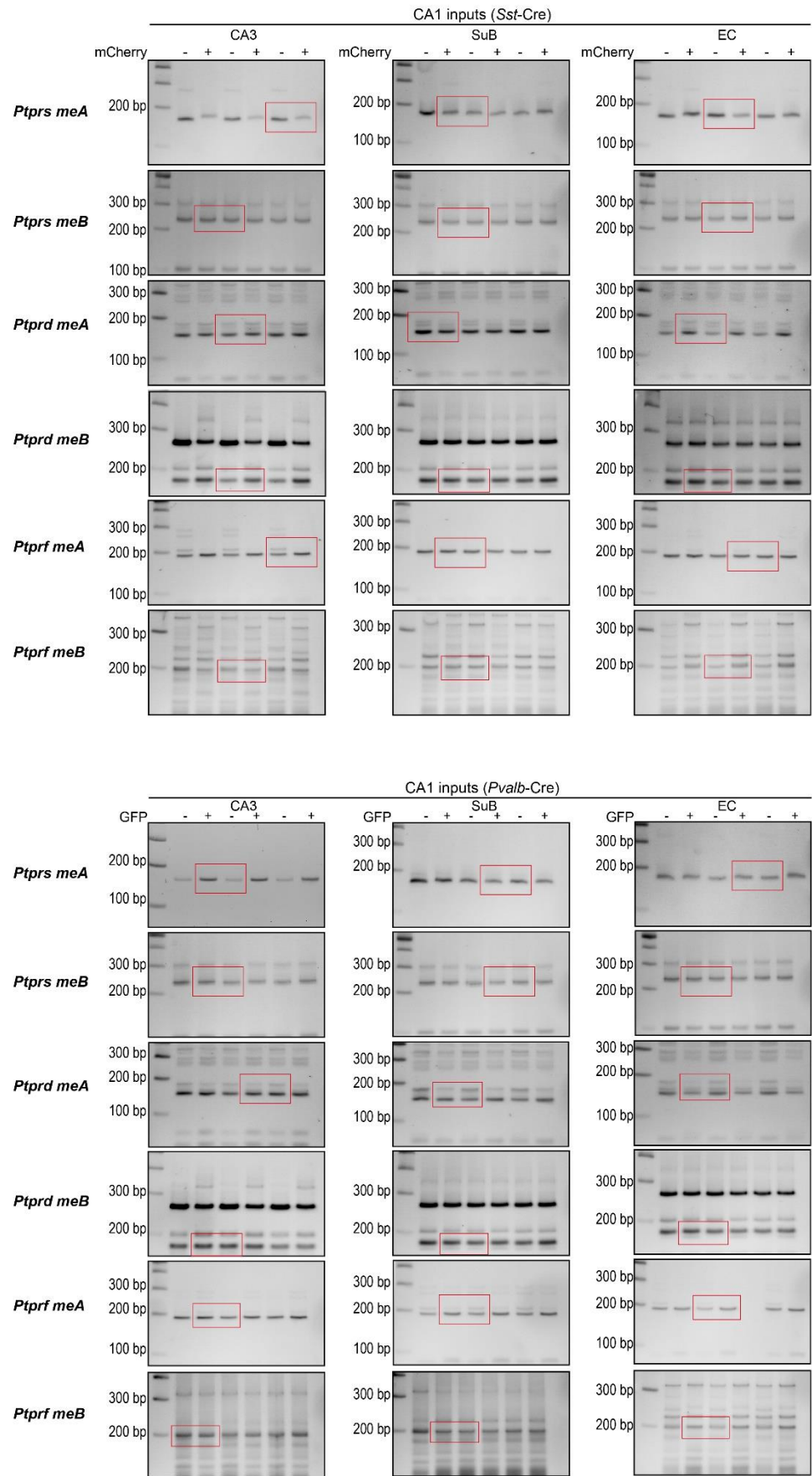


Supplementary Figure 4c



Supplementary Figure 5. Profiling of mouse LAR-RPTP microexon profiles in distinct hippocampal CA1 GABAergic interneurons

Supplementary Figure 5c



Supplementary Figure 6. Validation of the loss of *Ptprd* variants containing *meA* in cortical cells of *PTPδ meA* floxed mice expressing Cre recombinase, expression of *PTPδ* protein in three brain regions that innervate hippocampal CA1 neurons, and distribution of retrogradely labeled input neurons in the CA3, SuB or EC that project to dCA1 neurons

Supplementary Figure 6a

