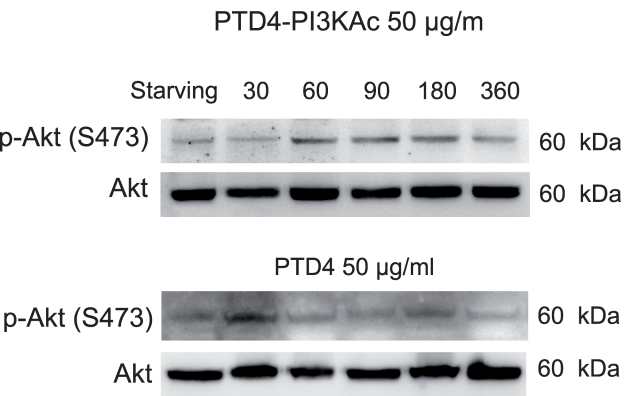
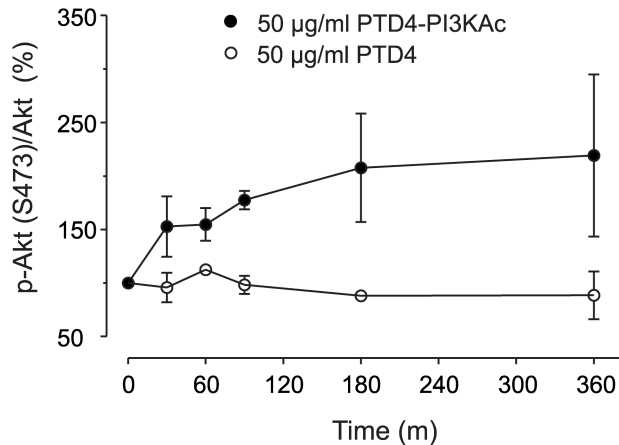
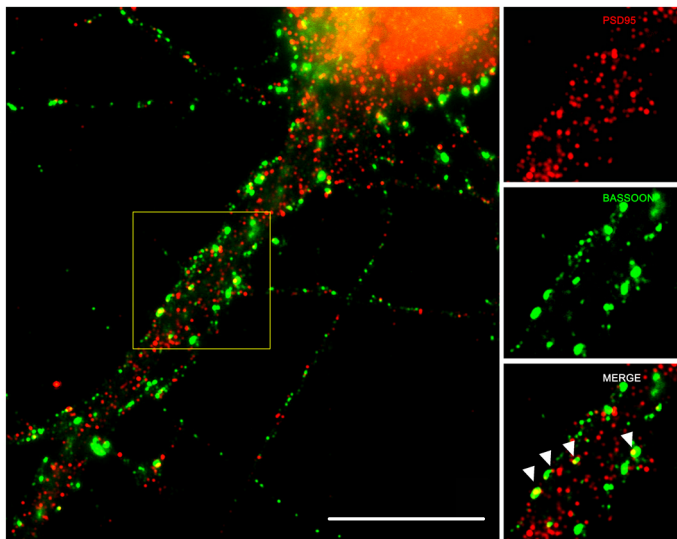
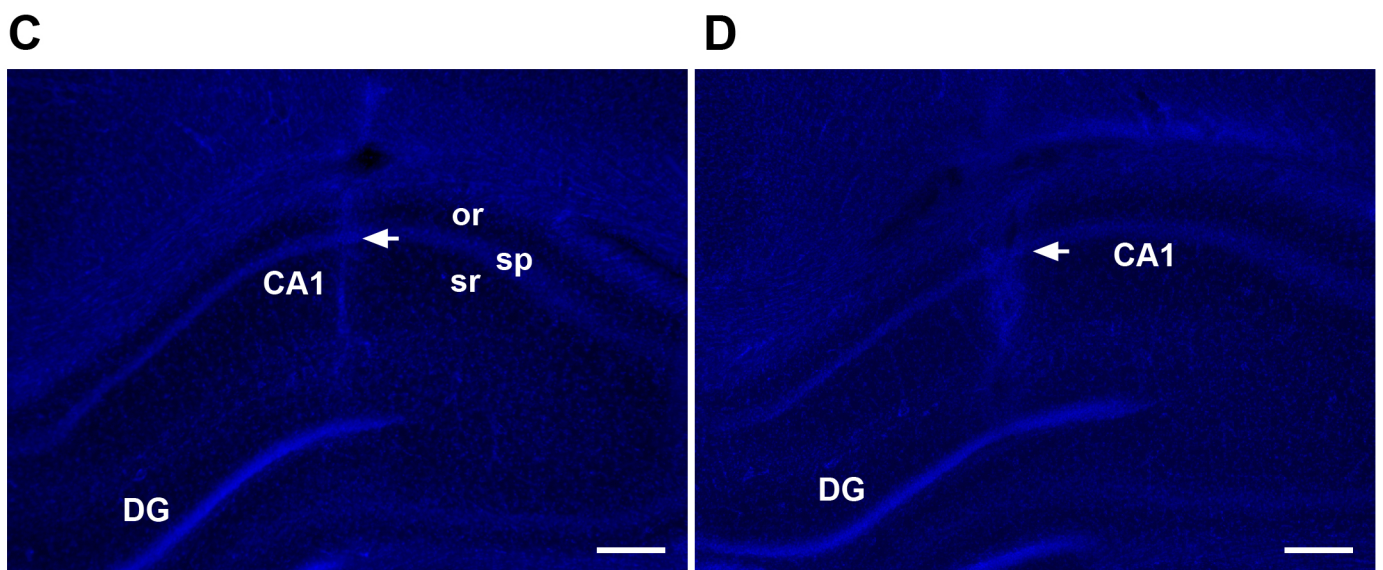
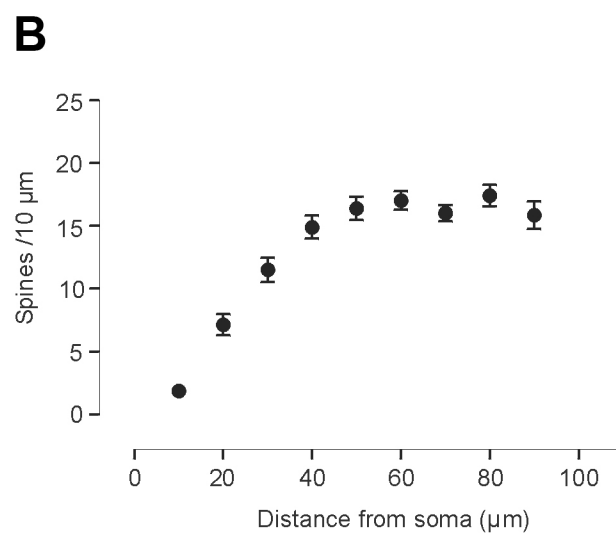
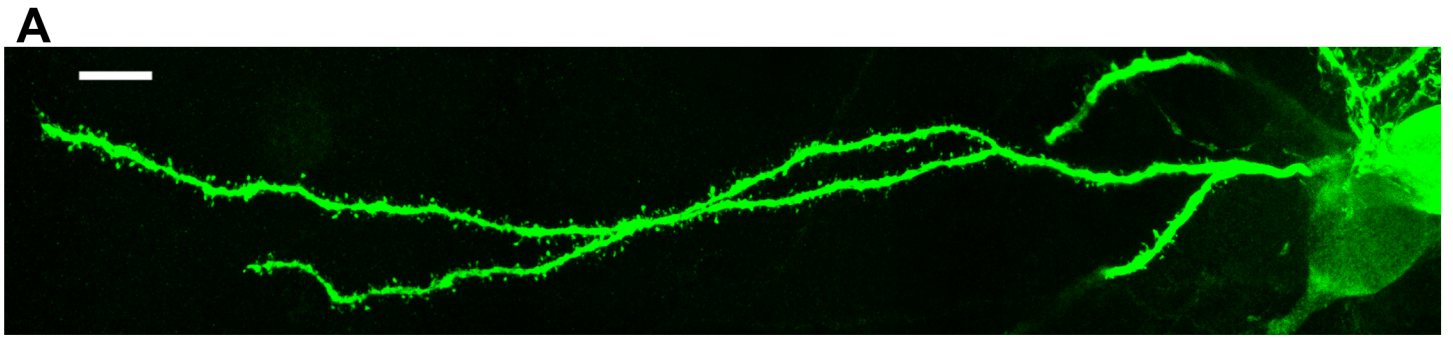
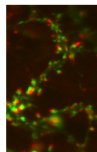
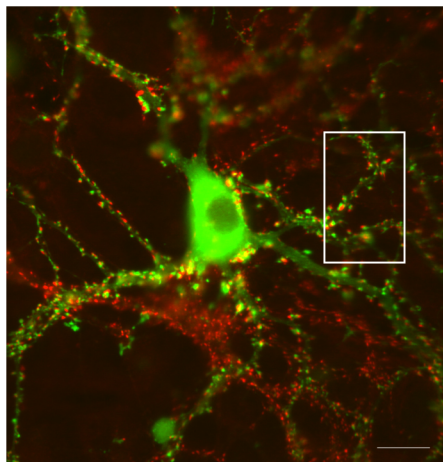


**A****B**

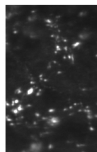


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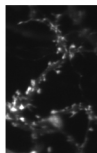




Merge

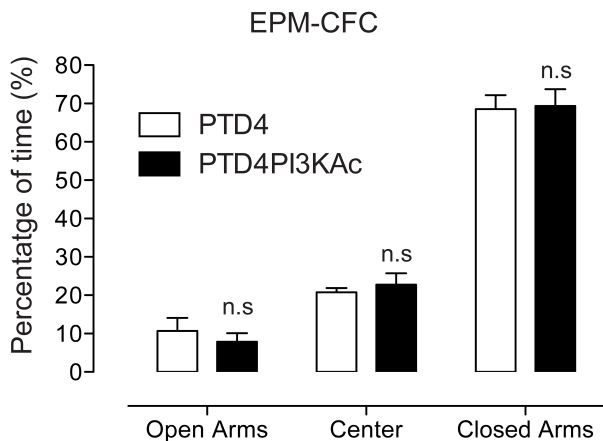
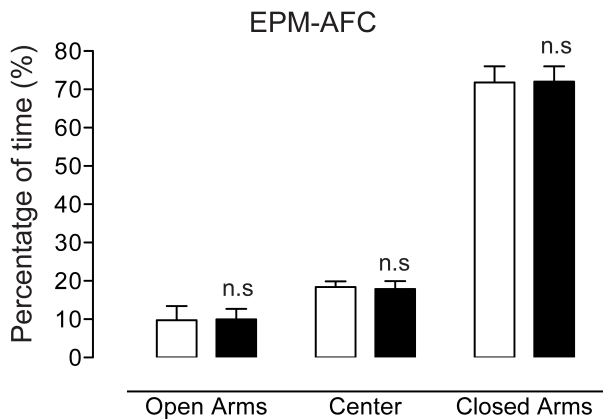


Synapsin



GFP-Actin

Cuesto et al., Fig S4

**A****B**

**A**

**Contextual**

		<b>Open</b>	<b>Center</b>	<b>Close</b>
<b>Rat</b>	<b>Group (before injection)</b>	<b>%</b>	<b>%</b>	<b>%</b>
9	PTD4-peptide	33,4	18,3	48,3
16	PTD4-peptide	21,2	24,1	54,7
8	PTD4-peptide	18,7	23,0	58,3
3	PTD4-peptide	10,9	22,5	66,7
6	PTD4-peptide	9,2	17,7	73,1
14	PTD4-peptide	6,6	19,2	74,2
18	PTD4-peptide	3,6	21,0	75,4
19	PTD4-peptide	2,1	23,2	74,7
11	PTD4-peptide	0,6	25,0	74,4
12	PTD4-peptide	0,5	13,7	85,8
	PTD4-peptide			
	<b>Mean</b>	10,7	20,8	68,6
	<b>SEM</b>	3,4	1,1	3,6

		<b>Open</b>	<b>Center</b>	<b>Close</b>
<b>Rat</b>	<b>Group (before injection)</b>	<b>%</b>	<b>%</b>	<b>%</b>
1	PTD4-PI3KAc	23,3	24,7	51,9
7	PTD4-PI3KAc	15,9	25,5	58,6
17	PTD4-PI3KAc	9,9	38,1	52,1
2	PTD4-PI3KAc	8,5	28,2	63,3
4	PTD4-PI3KAc	7,5	21,3	71,2
5	PTD4-PI3KAc	3,9	26,2	69,9
20	PTD4-PI3KAc	3,8	11,7	84,5
13	PTD4-PI3KAc	2,5	31,6	65,9
15	PTD4-PI3KAc	2,1	11,9	86,0
10	PTD4-PI3KAc	1,3	8,5	90,3
	PTD4-PI3KAc			
	<b>Mean</b>	7,9	22,8	69,4
	<b>SEM</b>	2,2	3,0	4,4

p-valor            0,497335   0,541228   0,8876

# B

## Auditory

		Open	Center	Close	Close edge
Rat	Group (before injection)	%	%	%	%
1	PTD4-peptide	9,1	28,2	62,7	7,8
2	PTD4-peptide	20,7	15,3	63,9	8,5
5	PTD4-peptide	0,9	17,1	82,1	8,1
6	PTD4-peptide	37,5	19,5	43,0	5,1
9	PTD4-peptide	6,1	17,3	76,6	16,0
10	PTD4-peptide	3,3	15,0	81,7	19,4
11	PTD4-peptide	0,7	11,6	87,6	14,3
12	PTD4-peptide	2,4	18,3	79,3	21,7
16	PTD4-peptide	0,4	25,5	74,0	14,3
17	PTD4-peptide	24,6	19,8	55,5	5,7
18	PTD4-peptide	1,3	14,8	83,9	14,2
	<b>Mean</b>	9,7	18,4	71,8	12,3
	<b>SEM</b>	3,7	1,5	4,2	1,7

		Open	Center	Close	Close edge
Rat	Group (before injection)	%	%	%	%
3	PTD4-PI3KAc	10,2	14,7	75,1	26,1
4	PTD4-PI3KAc	10,4	18,9	70,7	6,2
7	PTD4-PI3KAc	4,5	22,3	73,2	15,3
8	PTD4-PI3KAc	2,5	10,5	86,9	14,9
13	PTD4-PI3KAc	0,5	5,2	94,3	21,8
14	PTD4-PI3KAc	16,9	24,7	58,1	7,3
15	PTD4-PI3KAc	33,2	19,5	47,2	11,1
19	PTD4-PI3KAc	10,9	29,3	59,7	10,7
20	PTD4-PI3KAc	5,2	22,3	72,1	8,1
21	PTD4-PI3KAc	6,3	17,1	76,6	8,9
22	PTD4-PI3KAc	9,1	12,5	78,4	13,6
	<b>Mean</b>	10,0	17,9	72,0	13,1
	<b>SEM</b>	2,7	2,1	4,0	1,9

0,954815 0,851855 0,974490

## Supplementary Figure legends

**Supplementary Figure S1. PTD4-PI3KAc increases phospho-Akt levels.** The phosphorylated PDGF-C-terminus p85 interaction domain was fused to a transduction domain (PTD4). **A)** The ability of PTD4-PI3KAc to activate PI3K-Akt signaling pathway was quantified by measuring Ser-473 phospho-Akt levels in SH-SY5Y cells. Cells were serum starved 16 hours prior to peptide addition and phospho-Akt levels were measured at 30, 60, 90, 180 and 360 minutes after peptide addition. As a control of possible transduction effects, PTD4 peptide was employed (50  $\mu\text{g/ml}$ ). **B)** Quantification indicates that PTD4-PI3KAc raises phospho-Akt levels and remains stable during the 180-360 minutes interval (207-219 % respectively). Statistically different from the PTD4 treatment, two way ANOVA,  $p= 0.0092$ .  $n= 6$ .

**Supplementary Figure S2. Visualization of pre- and post-synaptic markers.** Cultured 21 div hippocampal neuron immunostained against Bassoon (green) and PSD95 (red). Right: High magnification of inset on the dendrite shown on the left. Note the coincident pre- and postsynaptic signals (white arrow). Only cases of coincident markers were used in the quantitative data reported in the main text. Scale bar 10  $\mu\text{m}$ .

**Supplementary Figure S3. Spine density varies as a function of distance from soma** **A)** Confocal image of a basal CA1 dendrite. Changes in the density of spines depend of the distance from soma. Notice the lack of spines in the initial dendritic segment. Scale bar 5  $\mu\text{m}$ . **B)** Spine density was quantified as the number of spines every 10  $\mu\text{m}$  of dendritic length and related to the distance from soma. In agreement with previous studies, spine density reaches a constant density value at around 40  $\mu\text{m}$  from soma. **C)** Representative coronal hippocampal rat brain sections indicating the place of stereotaxic injections (arrow) in control (left) and PTD4-PI3KAc treated (right) animals. Sections were counterstained with DAPI to stain nuclei. DG: dentate gyrus, sr: stratum radiatum, or: stratum oriens, sp: stratum pyramidale. Scale bar: 250  $\mu\text{m}$ .



**Supplementary Figure S4. Most dendritic spines harbor synapses.** Left: Hippocampal GFP-Actin transfected neuron stained with Synapsin antibody. Right: High magnification of inset on the left. Note that Synapsin signal is adjacent to most GFP-labelled dendritic spines. Scale bar 10  $\mu\text{m}$ .

**Supplementary Figure S5. Elevated Plus Maze.** The percentage of time that the animals spent in the open arms is indicative of their anxiety level. According to this variable animals were divided in order to obtain groups with similar average mean times. **A)** CFC: Graph plot of the average time spent in the open, closed or center of the arms. Notice that there is not statistically differences between groups (PTD4 or PTD4-PI3KAc). **B)** Same as representation for the animals employed in the AFC test.

**Supplementary Figure S6. Elevated Plus Maze** **A)** Summary table of the EPM results previous to the CFC test with its statistical analysis. **B)** Summary table of the EPM results previous to the FCT test with its statistical analysis.

**Supplementary Movie S1:** Contextual fear conditioning test. Video showing a CSF injected control rat (left cage) and a PTD4-PI3KAc injected rat (right cage) one day after fear conditioning training. Note the difference in the freezing response of the PI3K-treated rat with respect to the control animal.

**Supplementary Movie S2:** Video showing the same animals as in movie S1, 24 hours later during the contextual change. Control rat (left cage) and a PTD4-PI3KAc injected rat (right cage). Notice how both animals perform similarly in the new context.