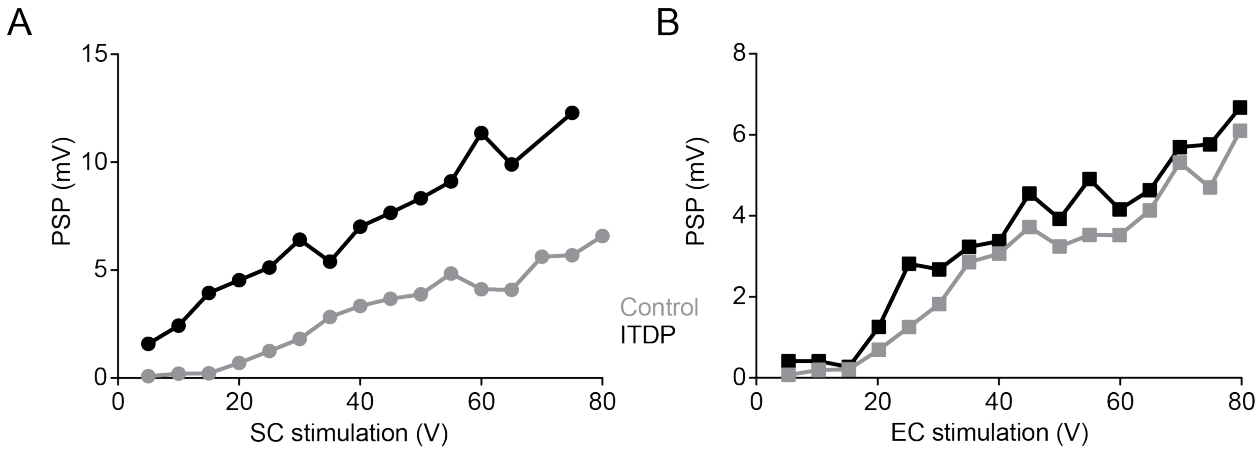

Figure S1 related to Figure 1

Stimulus intensity vs. PSP amplitudes for SC (left) and PP (right) stimulations before and after ITDP.

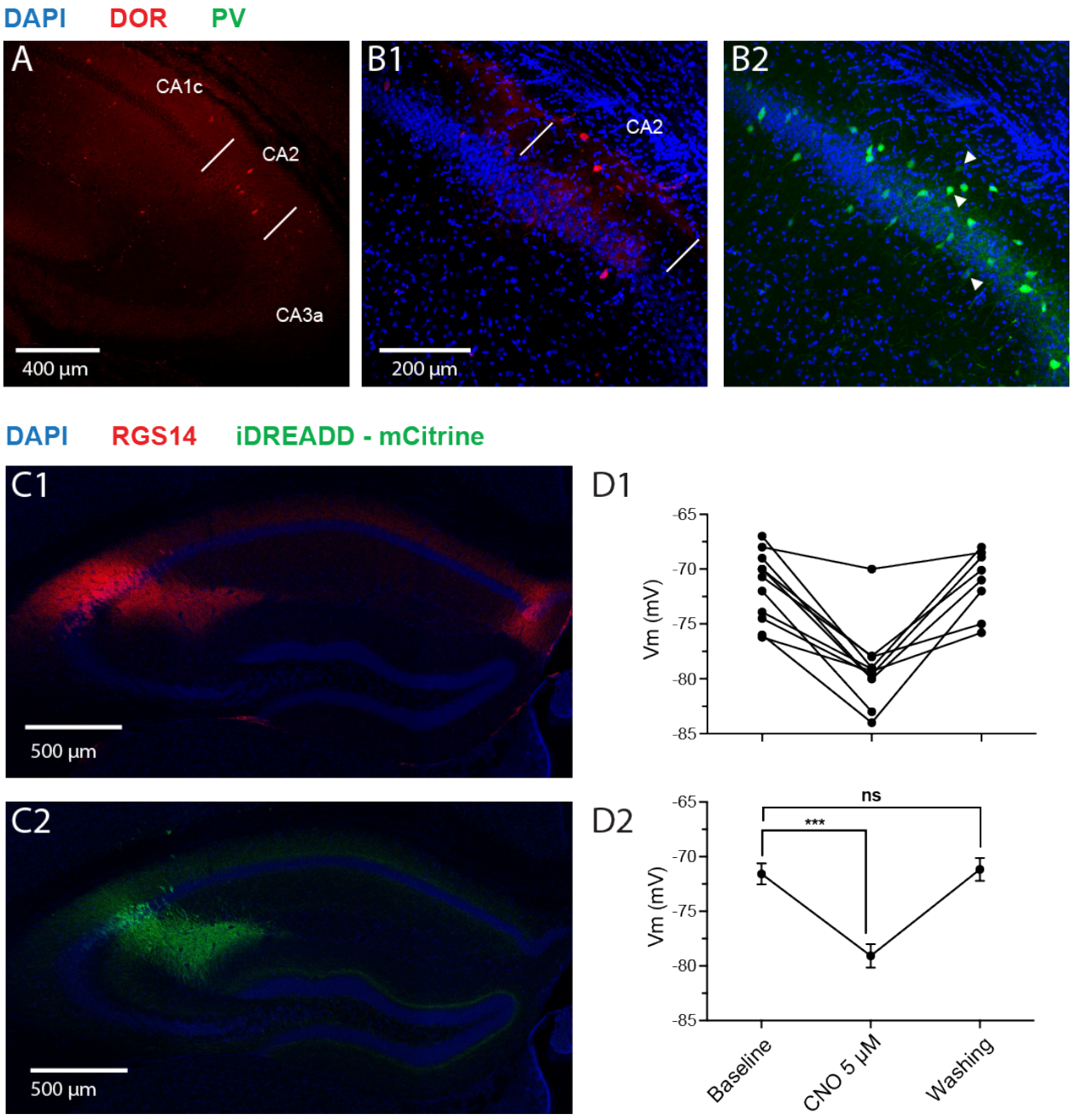

Figure S2 related to Figure 2

Double immunohistochemical labeling for DOR (red) and PV (green). **A.** View of CA2 and neighboring CA3 and CA1 regions. **B**. Expanded view of CA2. Arrowhead (**B2**) points at the PV^+ cells also positive for DOR (**B1**). In C and D, Amigo2-cre injected with cre-dependent virus expressing iDREADD and mCitrine. C. Double immunohistochemical labeling for mCitrine (green) and RGS14 (red). D Resting potential recorded in current-clamp recording of CA2 PNs before and 15 min after 5 µM CNO application. Washing was measured 25 minutes after the end of CNO perfusion.

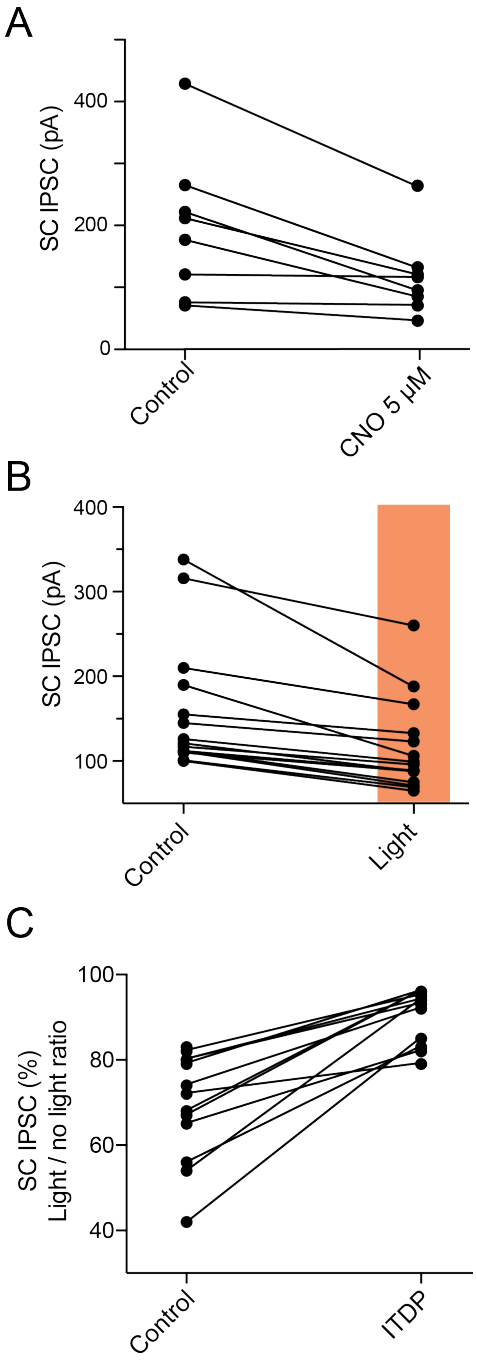

Figure S3 related to Figure 3: Silencing of PV$^+$ INs and ITDP both decrease FFI in CA2 PNs Voltage-clamp recordings at -10 mV of CA2 PN IPSCs evoked by SC stimulation. **A.** IPSC amplitudes recorded in slices from a PV-cre mouse injected with iDREADD before and after 5 µM CNO application. **B.** IPSCs in slices from a PV-cre mouse injected with Arch3.0 with or without yellow light. **C**. IPSC amplitude in slices from a PV-cre mouse injected with Arch3.0 during illumination divided by IPSC amplitude in absence of illumination, before (Control) and 30 min after induction of ITDP. Note that effect of illumination to inhibit IPSC is greatly reduced after induction of ITDP.

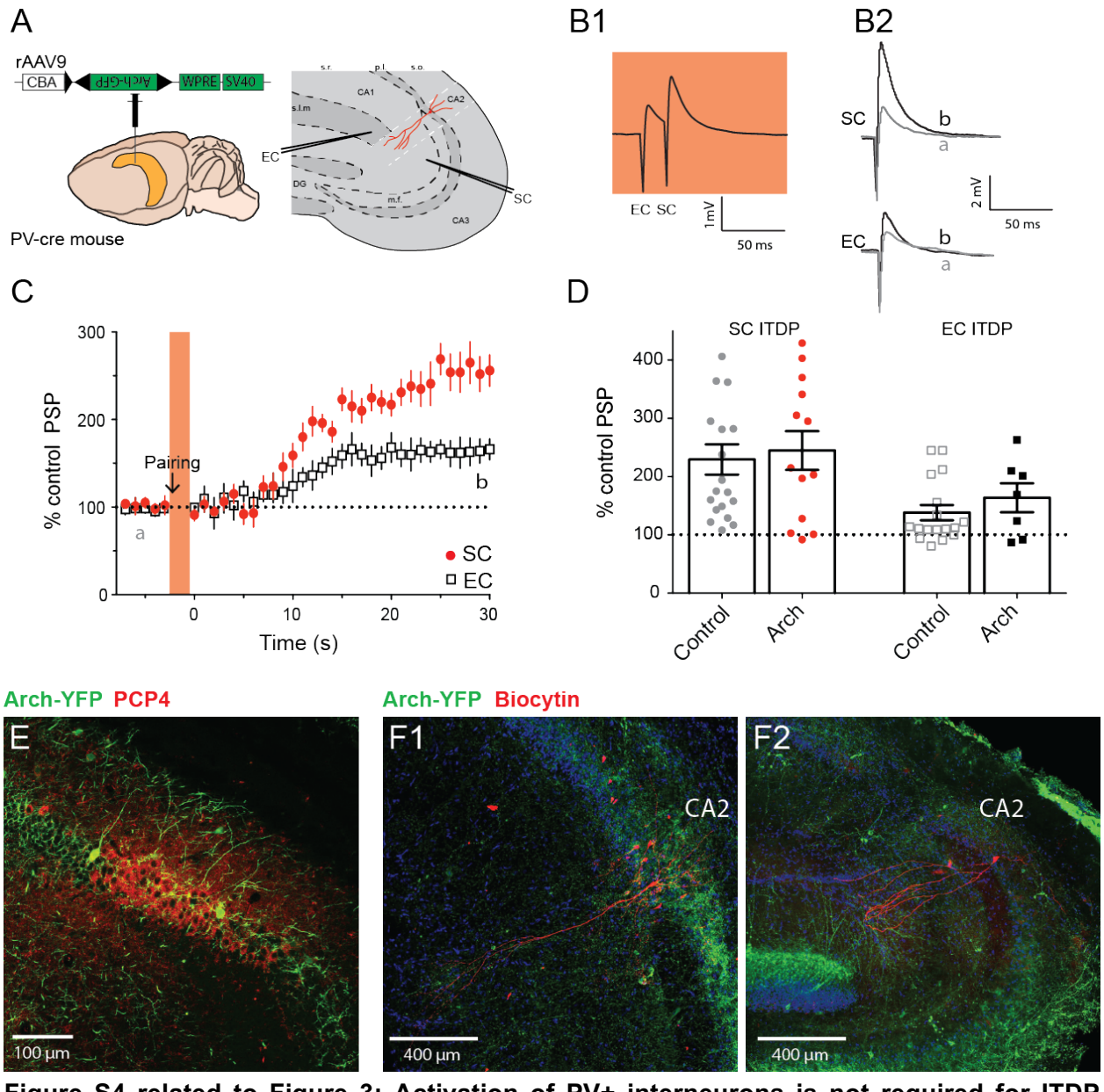

Figure S4 related to Figure 3: Activation of PV+ interneurons is not required for ITDP induction

A. Experimental design and injection site of Cre-dependent Arch3.0 expressing virus. **B.** PSPs obtained in whole-cell current-clamp configuration using electrical stimulation of EC and SC inputs. (**B1**) PSPs evoked by paired EC+SC stimulation. (**B2**) PSPs evoked by SC (top) or EC stimulation before (black) and after (grey) ITDP induction. **C.** Time course of PSP peak amplitude during ITDP. **D.** Normalized PP and SC PSP amplitude following ITDP induction by electrical pairing of EC+SC pathways during light illumination to hyperpolarize PV+ INs in PV-cre mice expressing Arch3.0 or control WT mice. Symbols show individual cells and bars show mean ± SEM. **E**. Immunohistochemistry of acute hippocampal slice stained for YFP and PCP4. **F**. Immunohistochemistry of acute hippocampal slice stained for YFP and Biocytin (cell filled during whole cell recording).

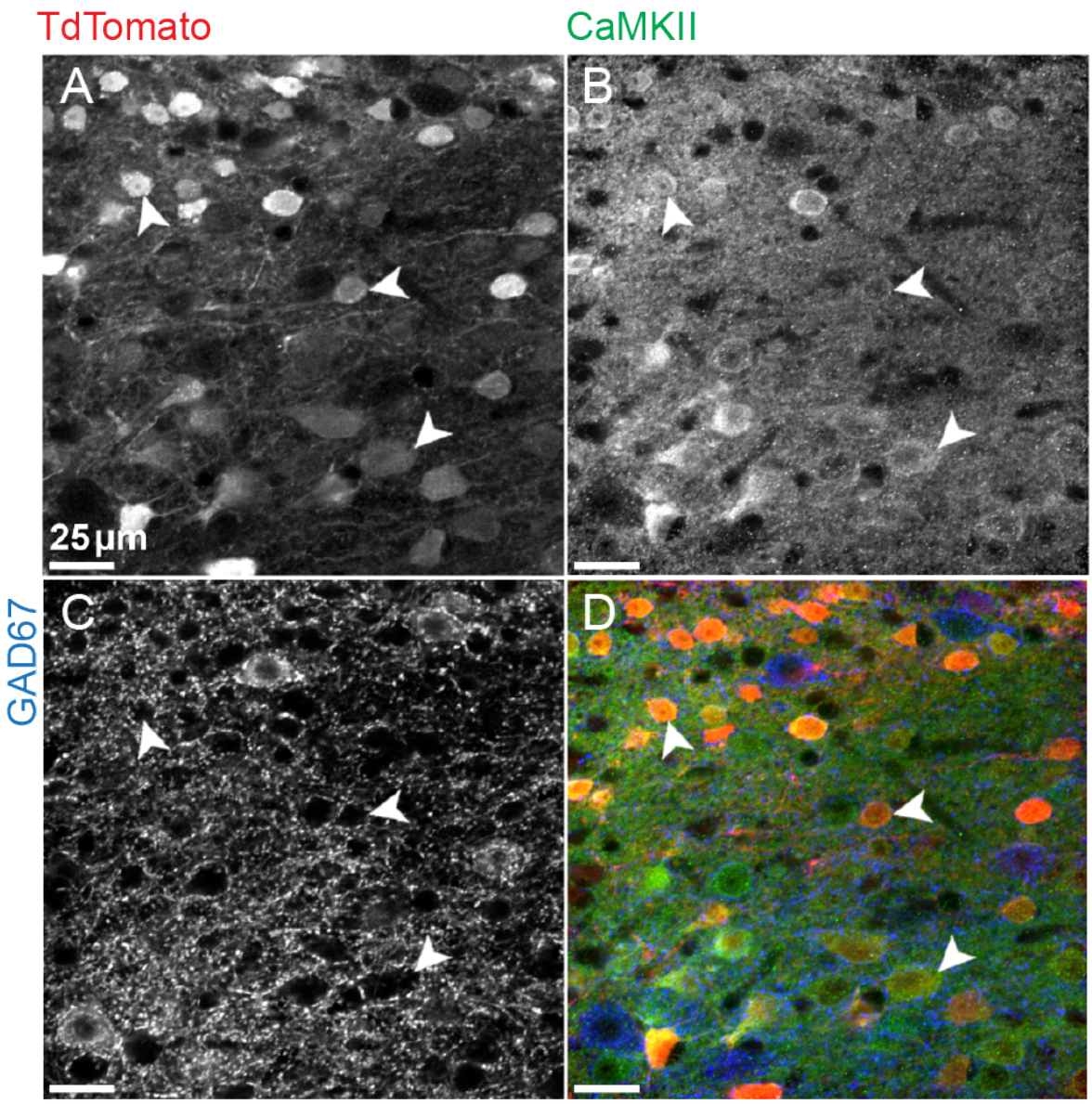

Figure S5 related to Figure 4: Expression of the ChR2 is limited to excitatory cells of the superficial layer of the MEC.

A-D. Immunohistochemistry of the MEC against TdTomato (**A**), CaMKII (B) and GAD67 (**C**). Overlap is in **D** with TdTomato in red, CaMKII in green and GAD67 in blue. Arrows point toward representative viral infected cells.

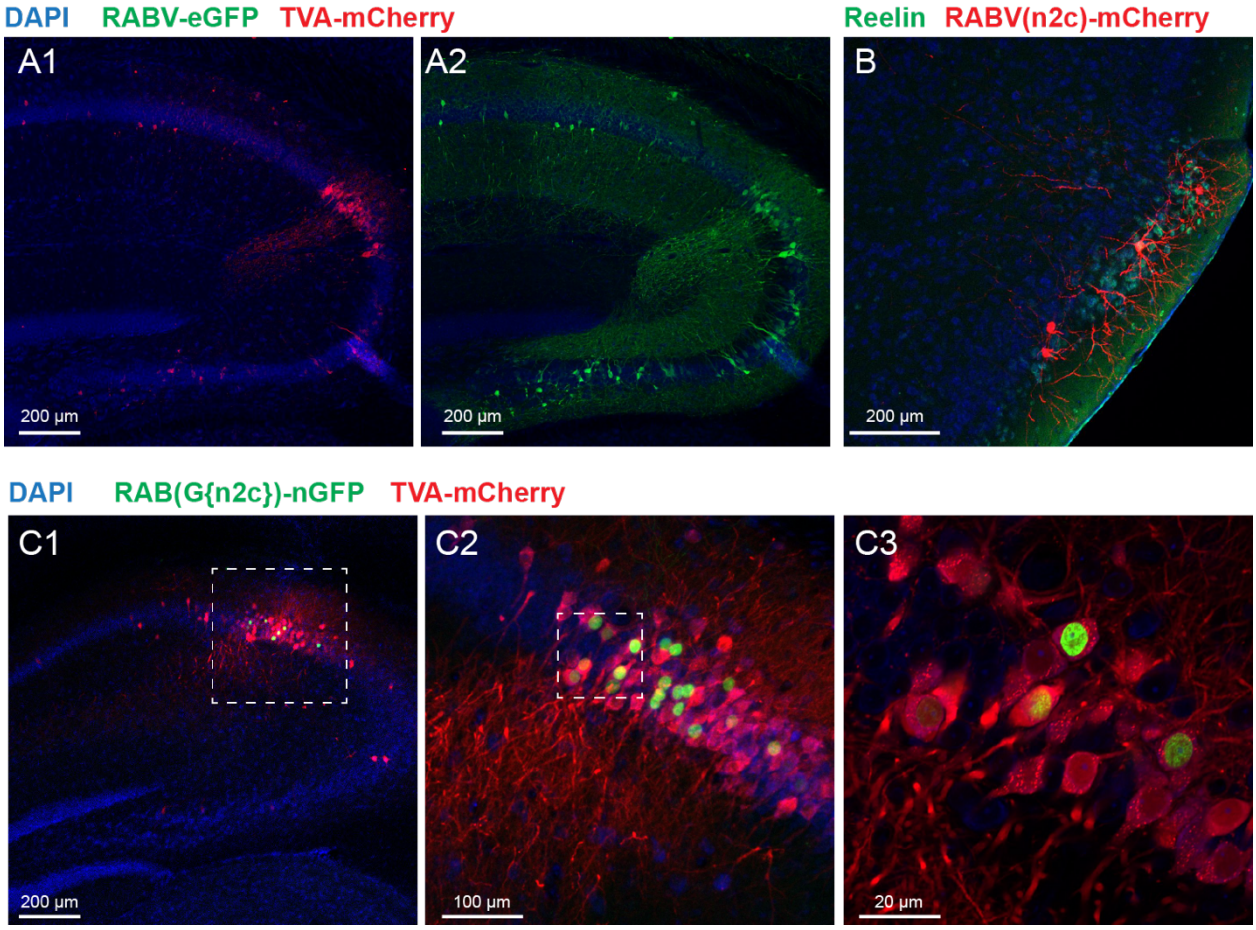

Figure S6 related to Figure 5: Expression of rabies helper virus in CA2.
A. Coronal slice of the hippocampus after injection of rAAV5 expressing TVA-mCherry and rAAV5 CAG.FLEX.RAB[G] followed by the injection of RABV$^{\Delta G}$-eGFP[EnvA] (SAD-B19 strain). **B.** Immunohistochemistry of the LEC against Reelin following expression of RABV$^{\Delta G}$–mCherry[EnvA] (CVS-N2c strain) into CA2 PNs. **C.** Coronal slice of the hippocampus after injection of rAAV5 expressing TVA-mCherry and rAAV1 FLEX.nGFP.2A.G(n2c), nGFP : histone2B-GFP fusion.

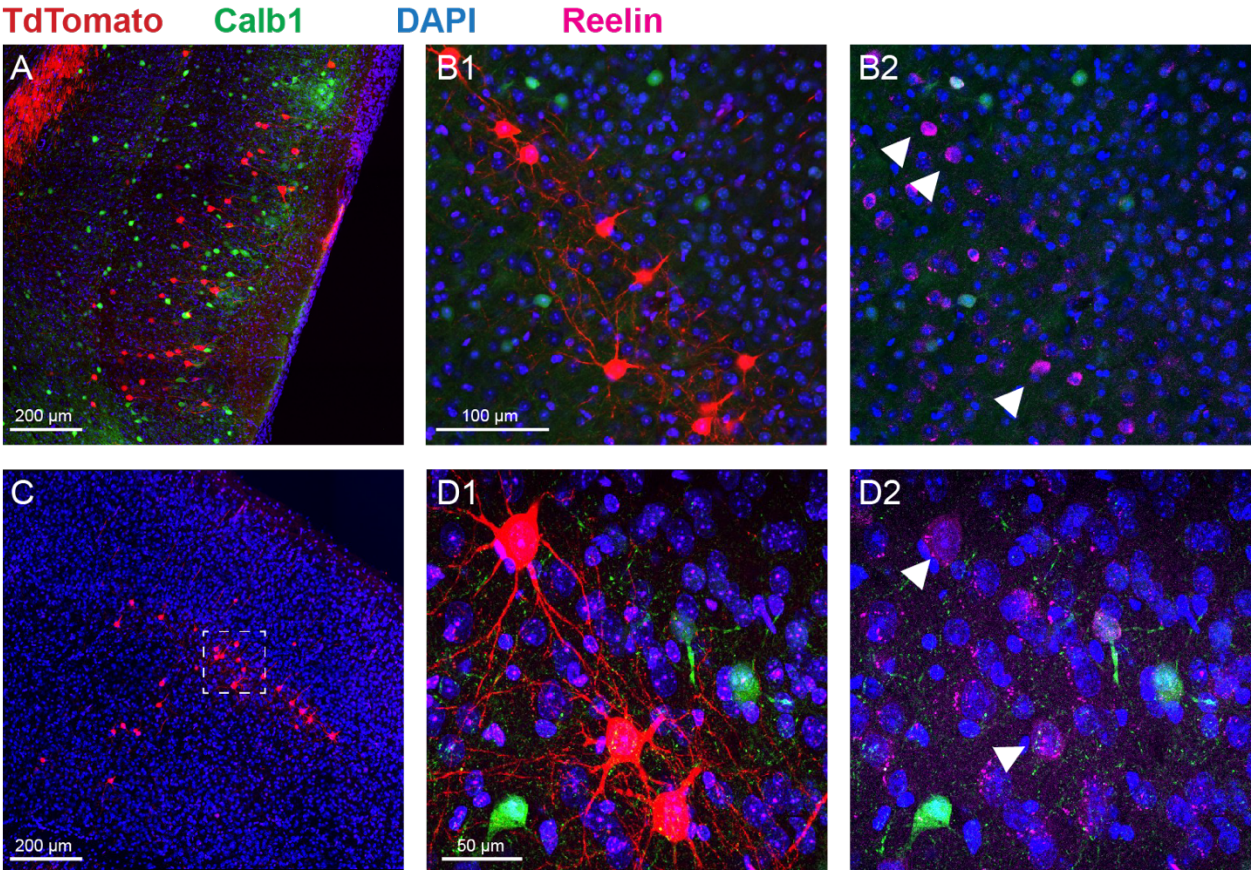

Figure S7 related to Figure 6: Expression of the Cre is restricted to the layer II stellate cells in the EC.

A-B. TdTomato expression in the EC and immunohistochemistry showing antibody staining for Calb1 and Reelin. The CAV2-Cre virus was injected in the dentate gyrus of an Ai14 mouse in which Cre expression drives TdTomato expression.

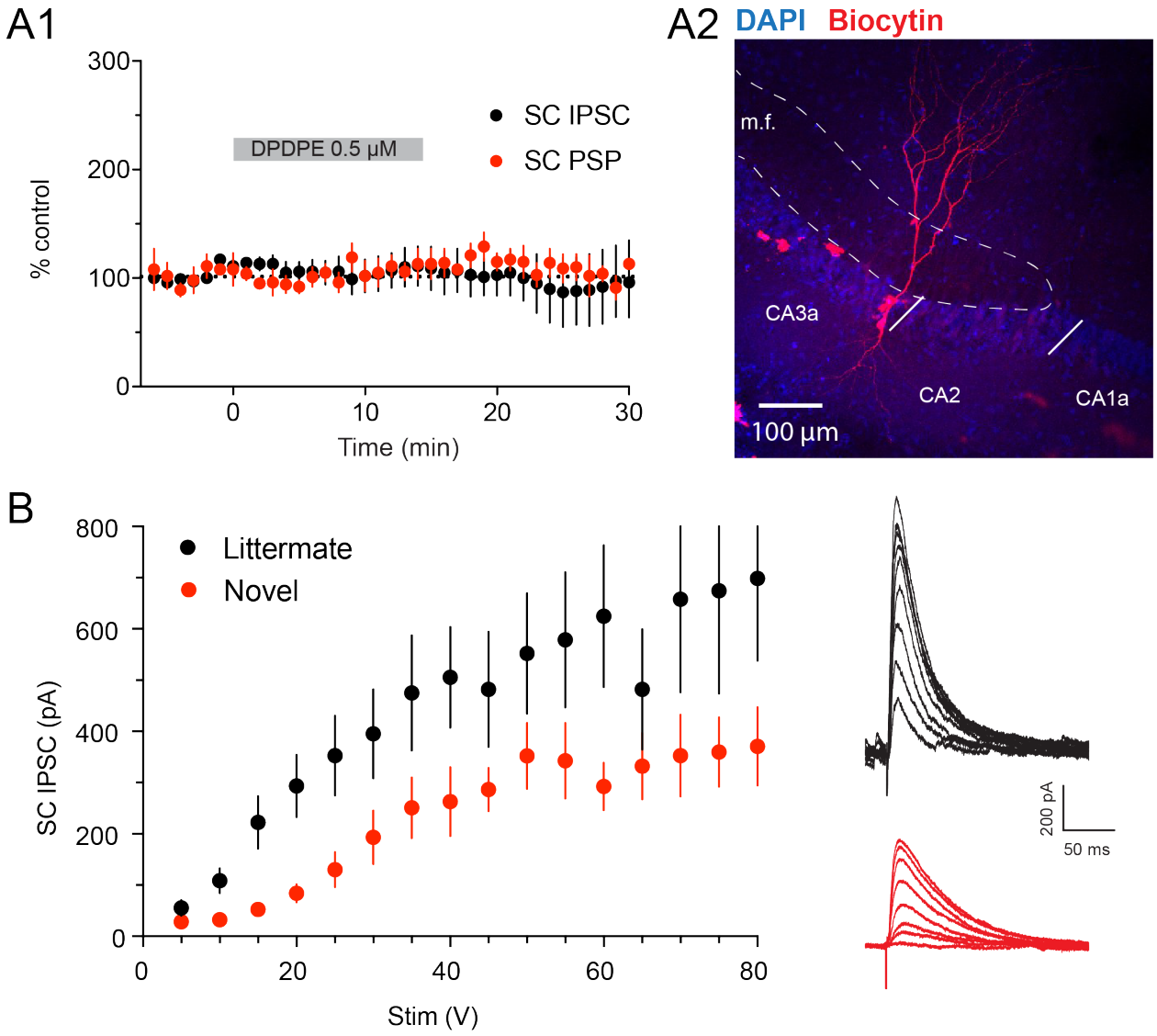

Figure S8 related to Figure 8: A. Application of the DOR agonist DPDPE has no effect on CA3a feedback. **A1.** Time course of the IPSC (black) or PSP (red) induced by SC stimulation during application of 0.5 µM DPDPE. Data are represented as mean ± SEM. **A2**. Immunohistochemistry of the acute hippocampal slice against biocytin. **B**. Voltage-clamp recording of CA2 PNs at -10 mV. The magnitude of feed-forward IPSCs recorded in CA2 PNs is plotted against different strengths of SC stimulation. IPSC amplitude is reduced in slices obtained from mice that interacted with a novel animal (red) compared to IPSC amplitude in slices obtained from mice that interacted with a familiar littermate (black).

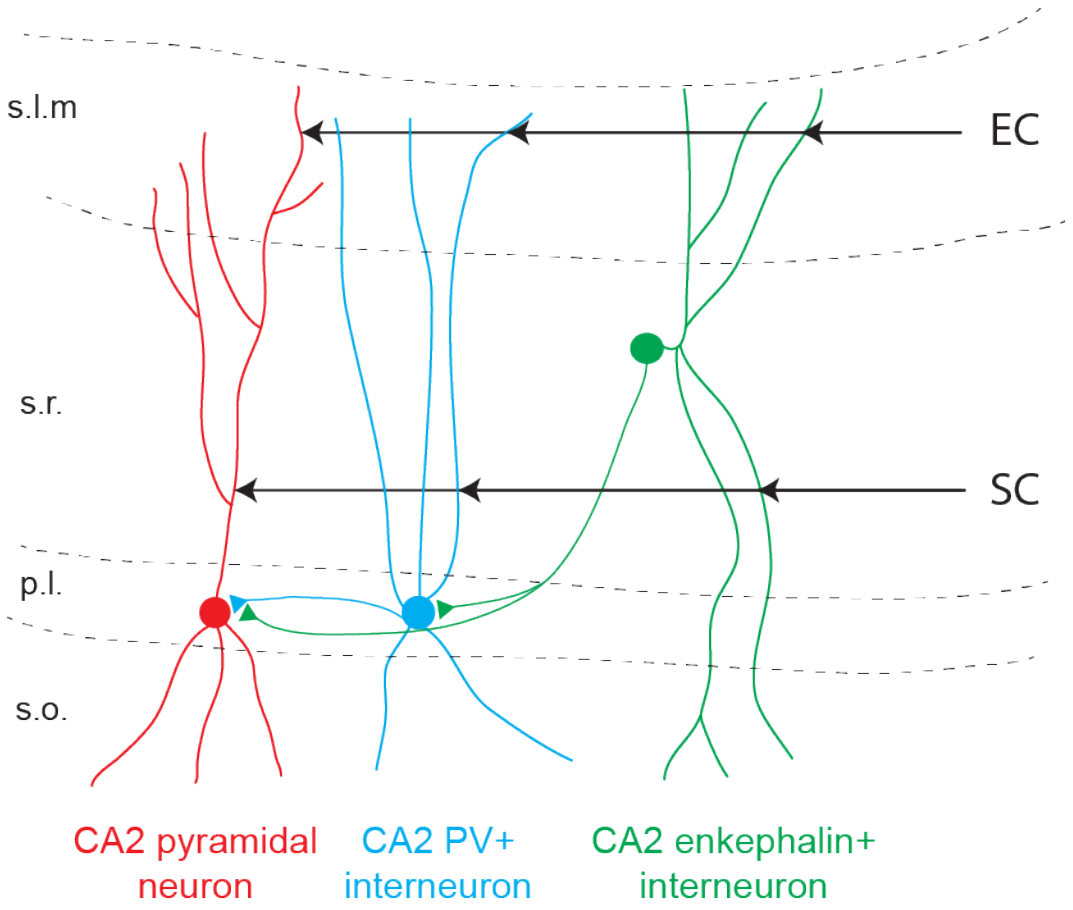

Figure S9: Schematic of the proposed circuit for CA2 ITDP.
EC and SC excitatory inputs are integrated by enkephalin-releasing interneurons. Paired activation of EC and SC inputs at an optimal -20 ms interval (EC before SC) provides sufficient excitation to trigger the release of enkephalin, which activates DORs expressed by CA2 PV+ interneurons, resulting in presynaptic inhibition of GABA release. The net effect of ITDP is therefore an enhanced excitation of the CA2 PNs by their SC (and to a lesser extent EC) inputs as a result of decreased PV interneuron-mediated feed-forward inhibition.