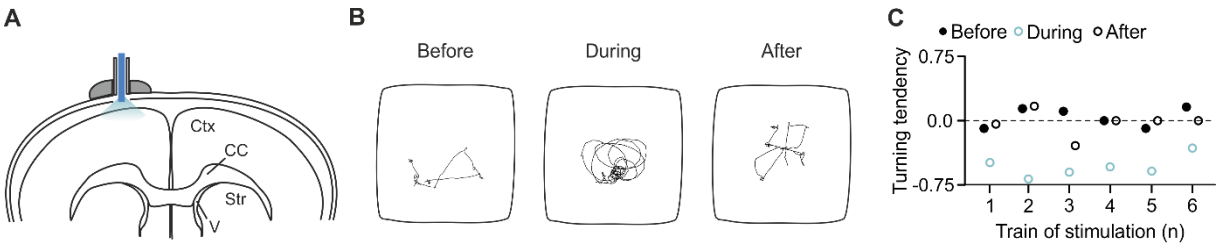
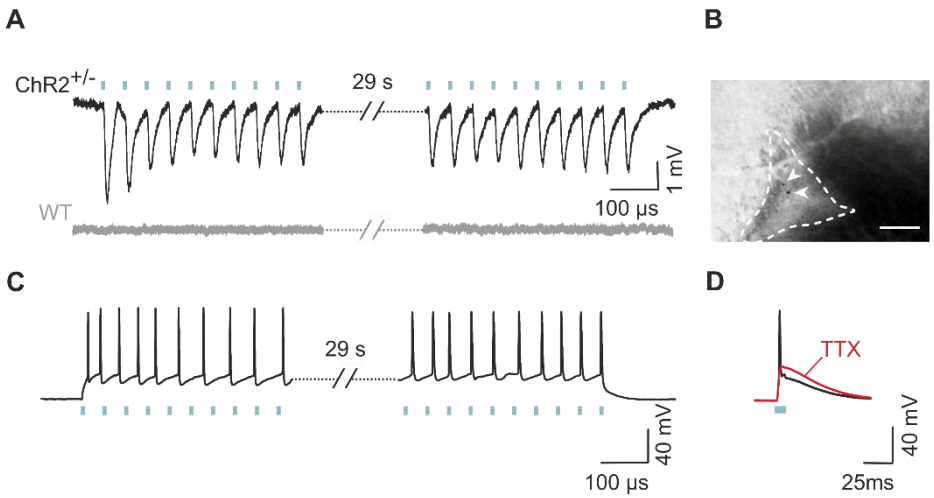


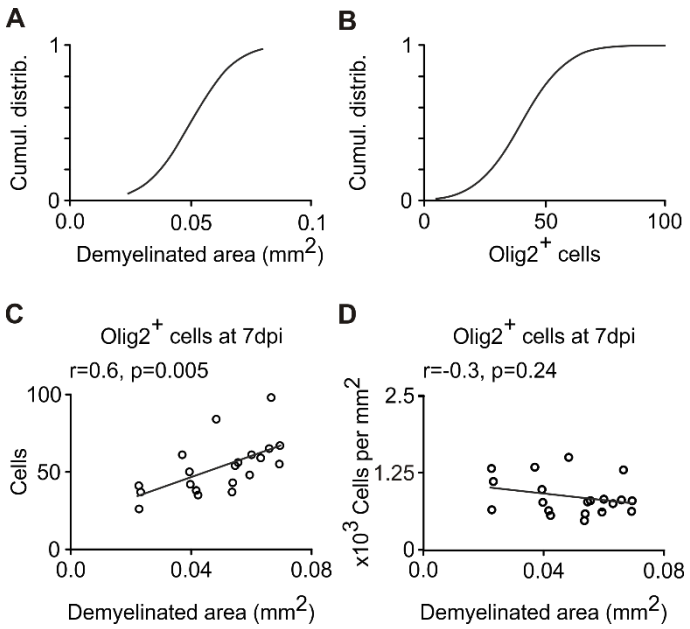
Supplemental Figure 1. *In vivo* cortical photostimulation altering motor behavior

A. Scheme of the optogenetic stimulation at the pial surface of the motor cortex (Ctx: cortex, CC: *corpus callosum*, Str: striatum, V: ventricle). **B**. Representative open-field trajectory maps (30 sec) Before, During and After a photostimulation train for a single mouse (10 ms light pulses at 20 Hz for 30 s and ~1 mW output as in Figure 1). Note the circling behavior during the photostimulation. **C**. The turning tendency before, during and after photostimulation trains (30 s periods) for the same mouse revealing motor behavior changes during each train (this behavior was reproducible in n=3 mice while n=2 other mice displayed strong seizure behavior).



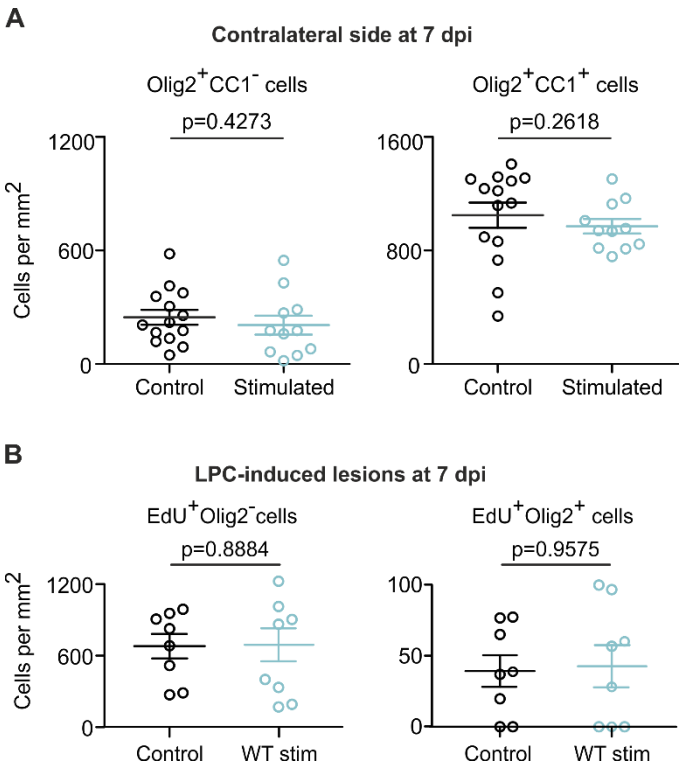
Supplemental Figure 2. Local field potentials (LFPs) *in vivo* upon a 30 s photostimulation train and action potential discharges of channelrhodopsin-2 (ChR2)-expressing pyramidal neurons in acute slices

A. LFPs are evoked during a 30 s photostimulation train (blue bars) inside the demyelinated lesion in an anesthetized mouse (n=13 mice). **B.** Differential Interference Contrast (DIC) image of a coronal slice showing a lysophosphatidylcholine (LPC)-induced demyelinated lesion (dashed lines). The position of the electrode marked with carbon particles was inspected in acute slices performed after in vivo recordings. The presence of carbon particles inside the lesion (white arrowheads) confirms the correct position of its tip during in vivo recordings (n=13 mice). Scale bar: 100 µm. **C**. Current-clamp recording of a layer V ChR2-expressing pyramidal neuron during a photostimulation train of 30 s (blue bars, 10 ms pulse at 20 Hz and ~1 mW output) in acute brain slices. Photo-induced action potential discharges are sustained until the end of the train (n=9 patched cells). **D**. Bath application of tetrodotoxin (TTX; 1 µM) in the same cell blocks the action potential generation but does not affect direct ChR2-induced depolarization (red).



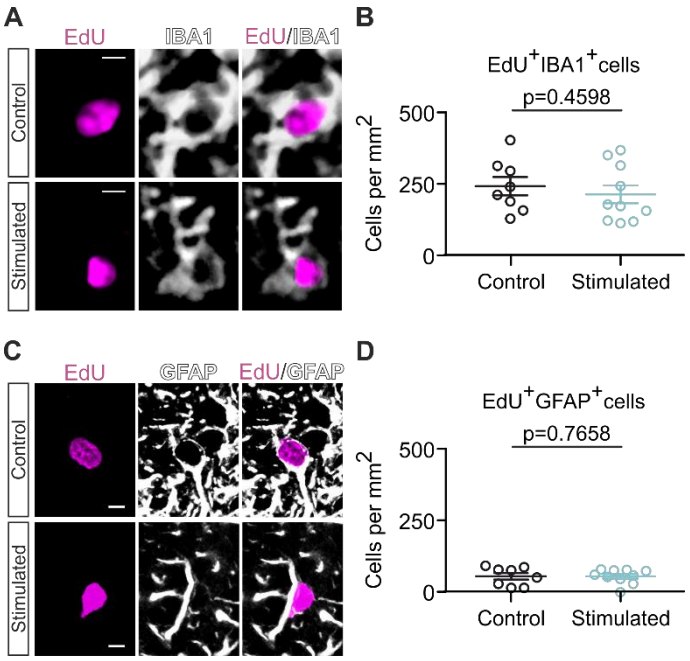
Supplemental Figure 3. Characterization of lysophosphatidylcholine (LPC)-induced demyelinated lesions

A, B. Cumulative distributions of demyelinated areas (**A**) and Olig2$^+$ cell numbers in LPC-induced lesions (**B**) at 7 dpi. **C, D**. Olig2$^+$ cell numbers (**C**) and densities (**D**) as a function of demyelinated areas (Pearson correlation test). Note that the Olig2$^+$ cell density does not correlate with the size of the lesion (**D**).



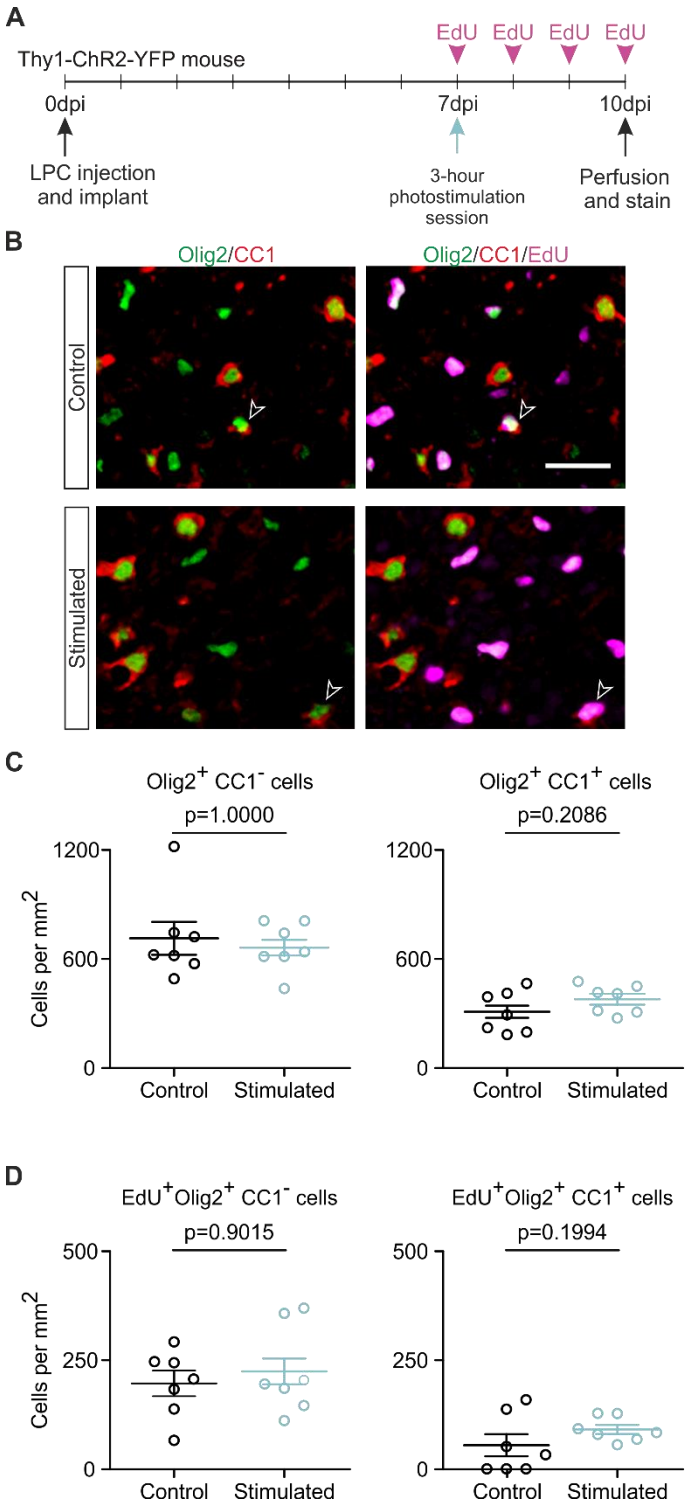
Supplemental Figure 4. Lack of cell density changes in the contralateral side of Thy1-ChR2-YFP photostimulated mice and in lesions of wild-type (WT) photostimulated mice at 7 dpi.

A. Densities of Olig2$^+$/CC1$^-$ OPCs (left) and Olig2$^+$/CC1$^+$ OLs (right) in the contralateral corpus callosum in Control and Stimulated mice at 7 dpi. n.s. p>0.05 (n=14 and n=11, respectively; U= 62 and U=56, respectively; two-tailed Mann Whitney U Test). **B.** Densities of EdU$^+$/Olig2$^-$ cells (left) and EdU$^+$/Olig2$^+$ OPCs (right) in lesions of Control and WT photostimulated (WT stim) mice at 7 dpi. n.s. p>0.05 (n=8 for both conditions; U= 34 and U=32, respectively; two-tailed Mann Whitney U Test).



Supplemental Figure 5. Photostimulation did not modify 5-Ethynyl-2´-deoxyuridine (EdU)-positive microglia and astrocytes at 7dpi

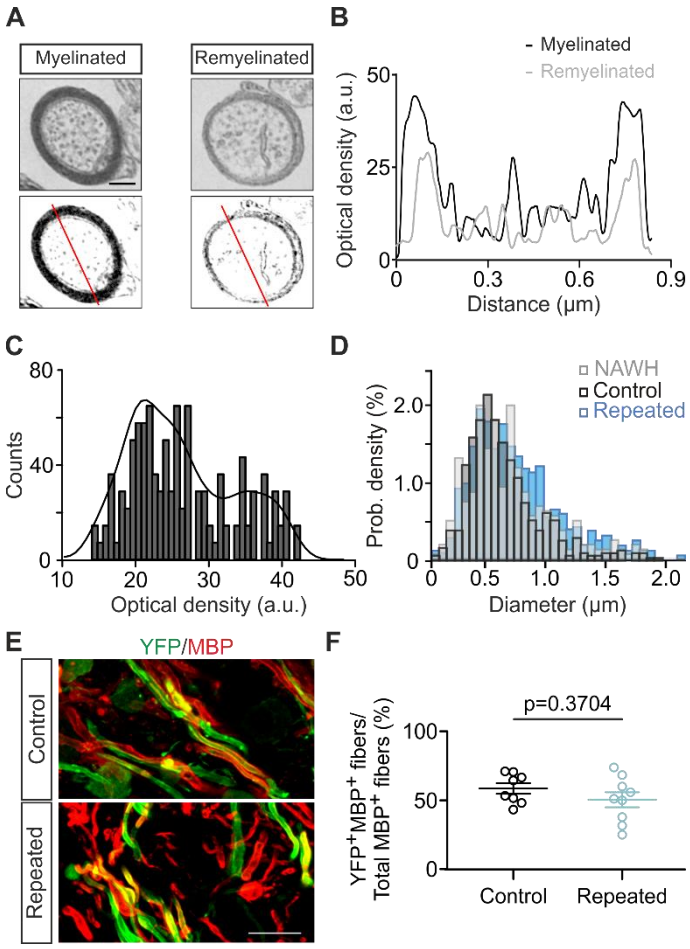
A, C. EdU (magenta), IBA1 (white; **A**) and GFAP (white; **C**) cells stained at 7 dpi in control (Control) and after a single photostimulation session (Stimulated) in LPC-induced lesions. Colors are pseudo-colors, and correspond to Alexa-405 (405 nm excitation) for IBA1, Alexa-480 (480 nm excitation) for GFAP and Alexa-647 (647 nm excitation) for EdU. Scale bar: 5 µm. **B, D**. Densities of $EdU^+/IBA1^+$ microglia (**B**) and $EdU^+/GFAP^+$ astrocytes (**D**) at 7 dpi in control and photostimulated mice. Note the lack of effect of the stimulation (n=8 for Controls and n=10 for Stimulated mice; U= 31 and U=36, respectively; two tailed Mann-Whitney Test).



Supplemental Figure 6. A single photostimulation session at 7 dpi did not affect either OPC or OL densities at 10 dpi.

A. Experimental design with a 3h photostimulation session at 7 dpi and perfusion at 10 dpi. **B**. Olig2 (green), CC1 (red) and 5-Ethynyl-2´-deoxyuridine (EdU; magenta) cells stained at 10

dpi in control LPC-induced lesions (Control) and after a photostimulation session at 7 dpi (Stimulated). Note the few number of $EdU^+/Olig2^+/CC1^+$ OLs (arrowheads) inside the lesions in both conditions. Scale bars: 25 µm. Note that colors are pseudo-colors and correspond to Alexa-405 (405 nm excitation) for Olig2, Alexa-480 (480 nm excitation) for CC1 and Alexa-647 (647 nm excitation) for EdU. **C**. Density of $Olig2^+/CC1^-$ OPCs (left) and $Olig2^+/CC1^+$ OLs (right) at 10 dpi in control and after a photostimulation session at 7 dpi (n=7 for both Control and Stimulated lesions; U= 18.00 and U=72.50, respectively; two tailed Mann-Whitney Test). **D**. Density of $EdU^+/Olig2^-$ (top) and $EdU^+/Olig2^+$ (bottom) cells at 10 dpi in control and after a photostimulation session at 7 dpi (U=20.00 and U=11.00, respectively; two tailed Mann-Whitney Test). Note that no changes in the density of EdU^+ oligodendroglia occurs with this protocol.



Supplemental Figure 7. Identification of myelinated *vs* remyelinated axons in *corpus callosum*

A. Representative electron micrographs of a myelinated axon (left, top) and a remyelinated axon (right, top). Same images after a renyi-entropy thresholding treatment (bottom). Scale bar: 0.2 µm. **B.** Myelin optical density profiles of the same axons showed in **A**. The *x*-axis corresponds to the red lines in **A**. **C.** Distribution of myelin optical densities of a repeated photostimulated demyelinated lesion. **D**. Distribution of axon diameters for normal appearing white matter (NAWM), control and repeated lysophosphatylcholine (LPC)-induced lesions at 14 dpi (D=0.2571, p=0.168 for NAWM *vs* control, D=0.2000, p=0.441 for NAWM *vs* repeated, D=0.2513, p=0.093 for control *vs* repeated; Kolmogorov-Smirnov test). **E**. Confocal images of YFP^+ (green) and MBP^+ (red) fibers inside the lesion at 14 dpi. Scale bars: 10 µm.

F. Percentage of YFP^+/MBP^+ fibers expressing ChR2 with respect to the total number of MBP^+ fibers at 14 dpi in Control and after Repeated photostimulation (n=8 and n=9, repectively; U= 26.00; two tailed Mann-Whitney Test).