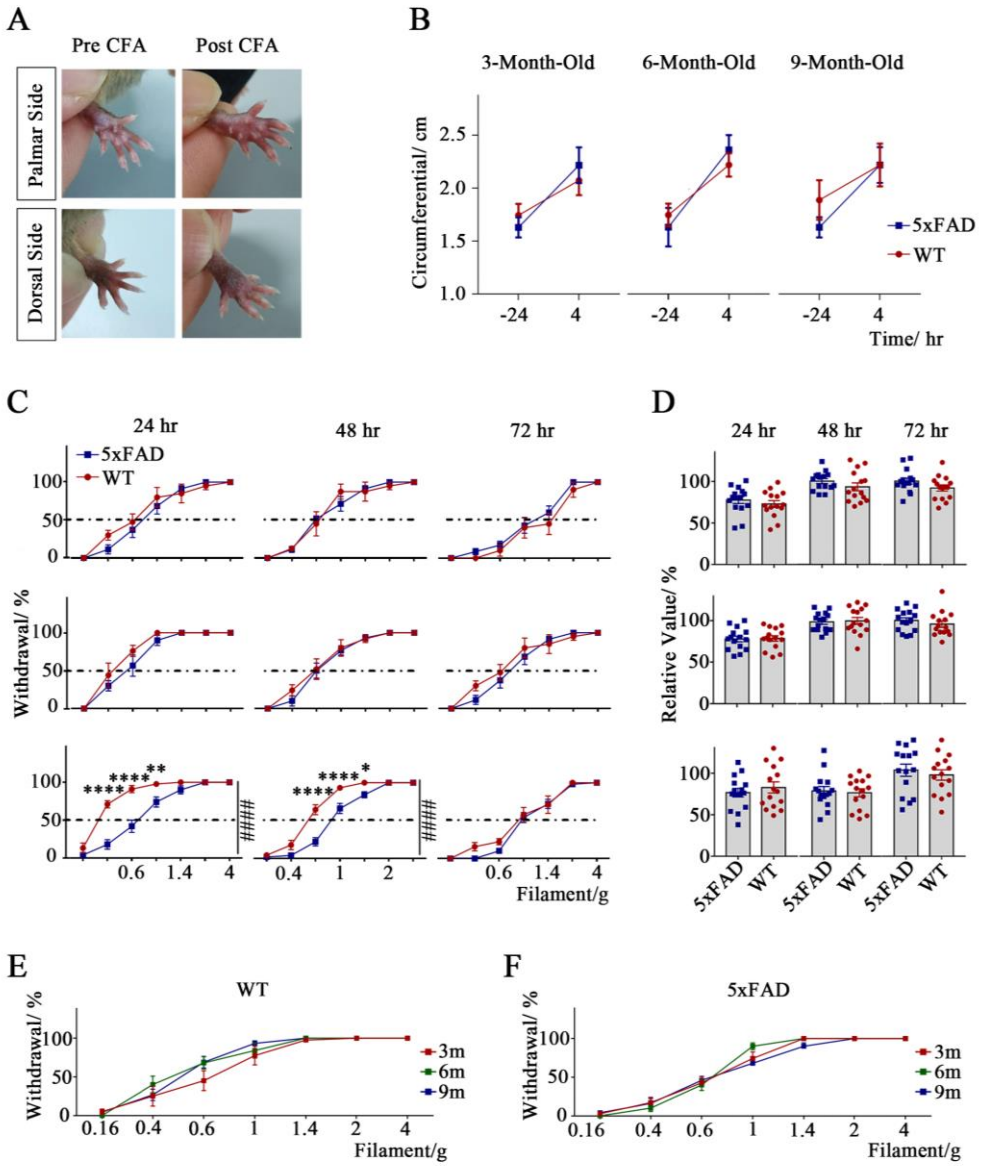
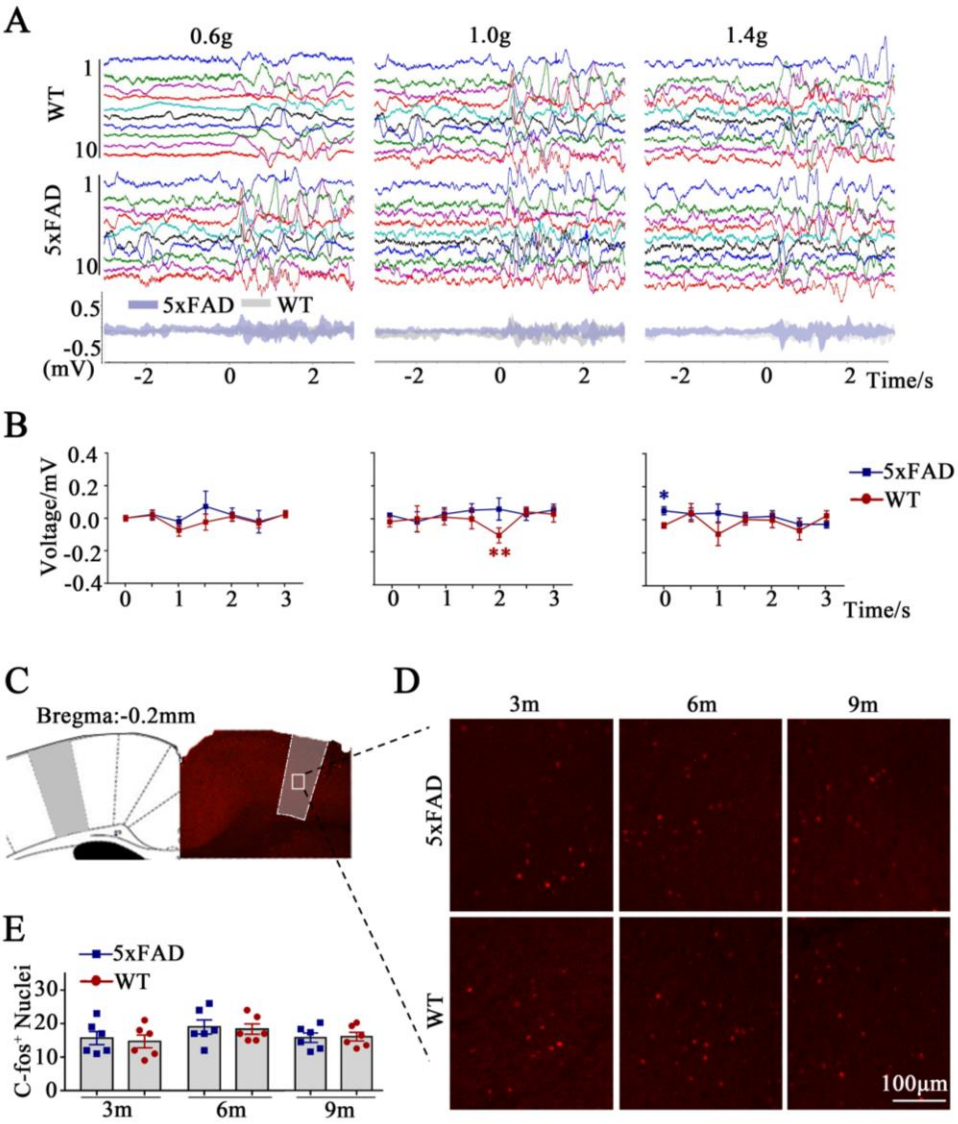
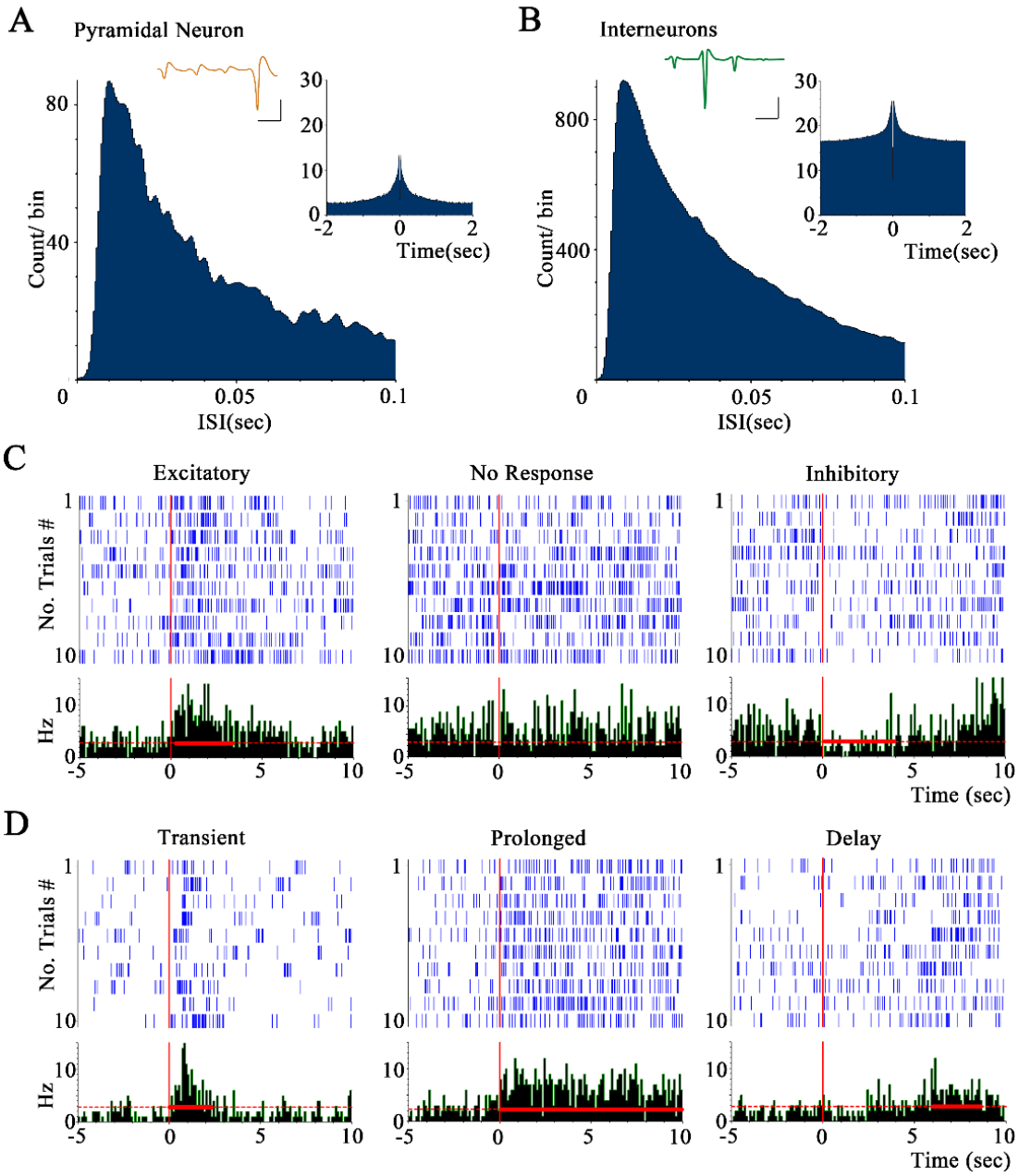


Supplemental Figure 1. The inflammation and pain response post-CFA in each group. (A) Representative images of paw pre- and post-CFA injection. **(B)** Paw circumference of 5×FAD mice and WT mice at 3-m (left), 6-m (middle) and 9-m-old (right) (n=7 per group, $P > 0.05$, unpaired t-test). **(C)** The withdrawal percentage of all groups 24 h, 48 h and 72 h post-CFA injection (3-m: 5×FAD, n = 8; WT, n = 7) (top), (6-m: 5×FAD, n = 6; WT, n = 5) (middle), (9-m: 5×FAD, n = 10; WT, n = 9) (bottom). (5×FAD vs WT: *$P < 0.05$; **$P < 0.01$; ****$P < 0.0001$, unpaired *t*-test). Two-way ANOVA was performed post CFA to investigate the effects of genotype. 9m post 24 h ($F (1, 119) = 71.67$, ####$P < 0.0001$) and 9-m post 24 h ($F (1, 119) = 50.96$, ####$P < 0.0001$). **(D)** Relative values of inflamed paw (Mean

intensity$^{post\text{-}CFA}$/Mean intensity$^{pre\text{-}CFA}$) at 24 h, 48 h and 72 h after CFA in WT and 5×FAD mice. (Each groups vs Baseline: n=15 per group, $P > 0.05$, unpaired *t*-test). **(E** and **F)** Comparison of withdrawal percentage 4 h post CFA injection between different ages (3-m: 5×FAD, n = 8; WT, n = 7), (6-m: 5×FAD, n = 6; WT, n = 5), (9-m: 5×FAD, n = 10; WT, n = 9). ($P > 0.05$, Two-way ANOVA).



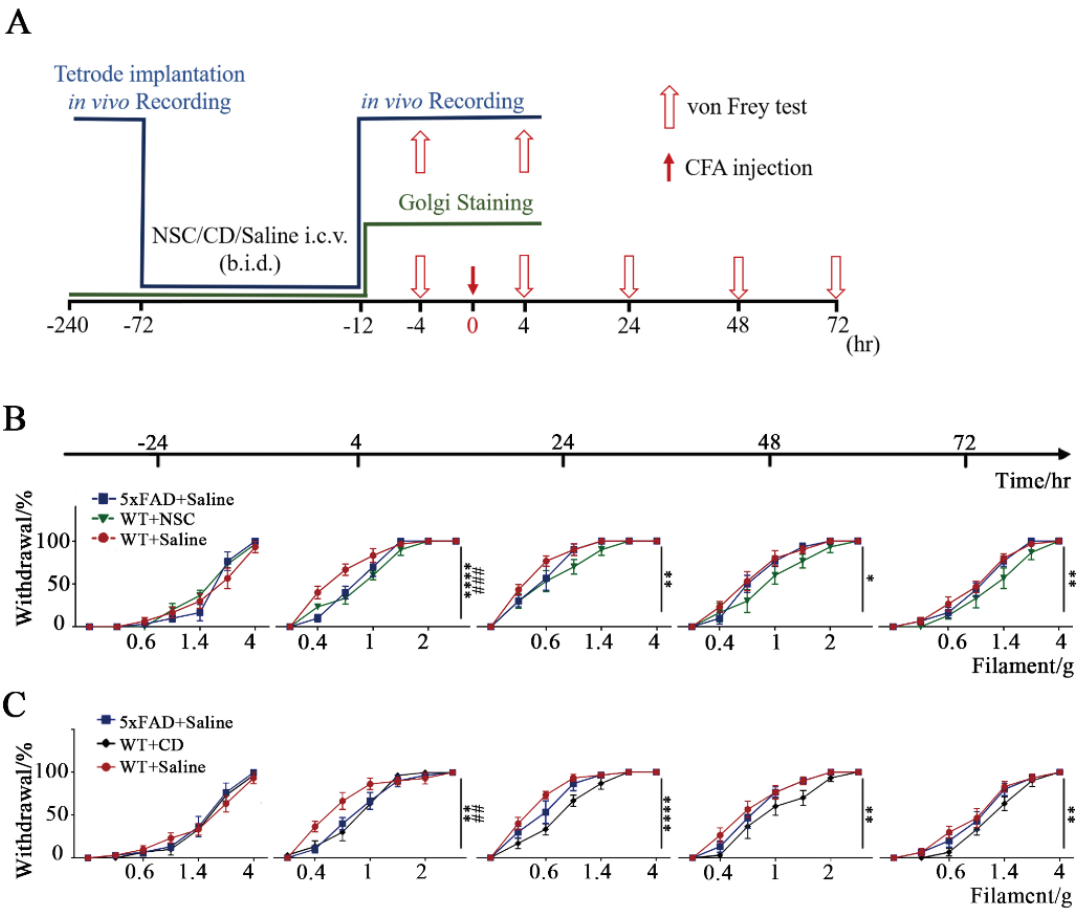
Supplemental Figure 2. Similar CFA-induced LFP alteration and c-Fos expression in S1 between WT and 5×FAD mice. (**A**) Each intensity stimulus (0.6 g, 1.0 g and 1.4 g) is applied for 10 times (top) and the grey and blue areas represent the SEM voltage (bottom). (**B**) The amplitude values of voltages are calculated for every 500 ms after stimulus. (WT: $^{**}P < 0.01$; 5×FAD: $^{*}P < 0.05$; unpaired *t*-test). (**C**) The schematic of S1 (grey shaded area) and the selected area analysed (white solid line). (**D**) Representative image of c-Fos expression in S1 brain region. (**E**) Comparison of c-Fos^{+} nuclei in S1 4 h post CFA injection. (n=6 per group, $P > 0.05$; unpaired *t*-test).



Supplemental Figure 3. Classification of excitatory pyramidal neurons.

(**A** and **B**) Inter spike interval (ISI) histograms and auto-correlograms (inset) of a putative pyramidal neuron (A) and putative interneuron (B) recorded in layer IV/V of ACC. The putative pyramidal cell has wider and more asymmetrical waveform with lower firing rate. The putative interneuron has narrower waveform and higher firing rate. Scales: 1ms, 0.2mV. (**C**) Representative peri-event rasters of responsive excitatory neuron (left), no response neuron (middle) and responsive inhibitory neuron (right). (**D**) Classification of transient neuron (left), prolonged neuron (middle) and delay neuron (right) from excitatory neurons recorded in ACC. The recorded

neurons with increased activity during the filament stimuli were divided into three groups based on the characterization of firing time: instantaneously units (firing to the stimuli within 3 seconds), prolonged units (firing to the stimuli within 3 seconds and last for 5 seconds) and delayed units (firing 5 seconds later to the stimuli).



Supplemental Figure 4. The withdrawal response changed under NSC/CD treatment. (A) Schematic of NSC/CD treatment experimental design. The tetrode implantation surgery conducted 240 h pre-CFA and then the neuronal activity was recorded in *vivo* when the animal is recovered (NSC/CD/Saline injection, twice a day). **(B)** and **(C)** The percentage of paw withdrawal in each group of 6-m mice (n=6 in each group). Two-way ANOVA was performed to investigate the effects of drugs. 5×FAD + saline vs WT + saline in NSC trail: (4 h: F (1, 70) =11.9, ###P = 0.001); 5×FAD + saline vs WT + saline in CD trail: (4 h: F (1, 70) =10.35, ##P = 0.002); WT + saline vs WT + NSC (4 h: F (1, 70) =21.18, ****P < 0.0001; 24 h: F (1, 70) =9.524, **P = 0.0029; 48 h: F (1, 70) =6.318, *P = 0.0143; 72h: F (1, 70) =8.403, **P = 0.005). WT + saline vs WT + CD (4 h: F (1, 70) =9.901, **P = 0.0024; 24 h: F (1, 70) =36.68, ****P < 0.0001; 48 h: F (1, 70) =11.5, **P = 0.0011; 72h: F (1, 70) =10.64, **P = 0.0017).