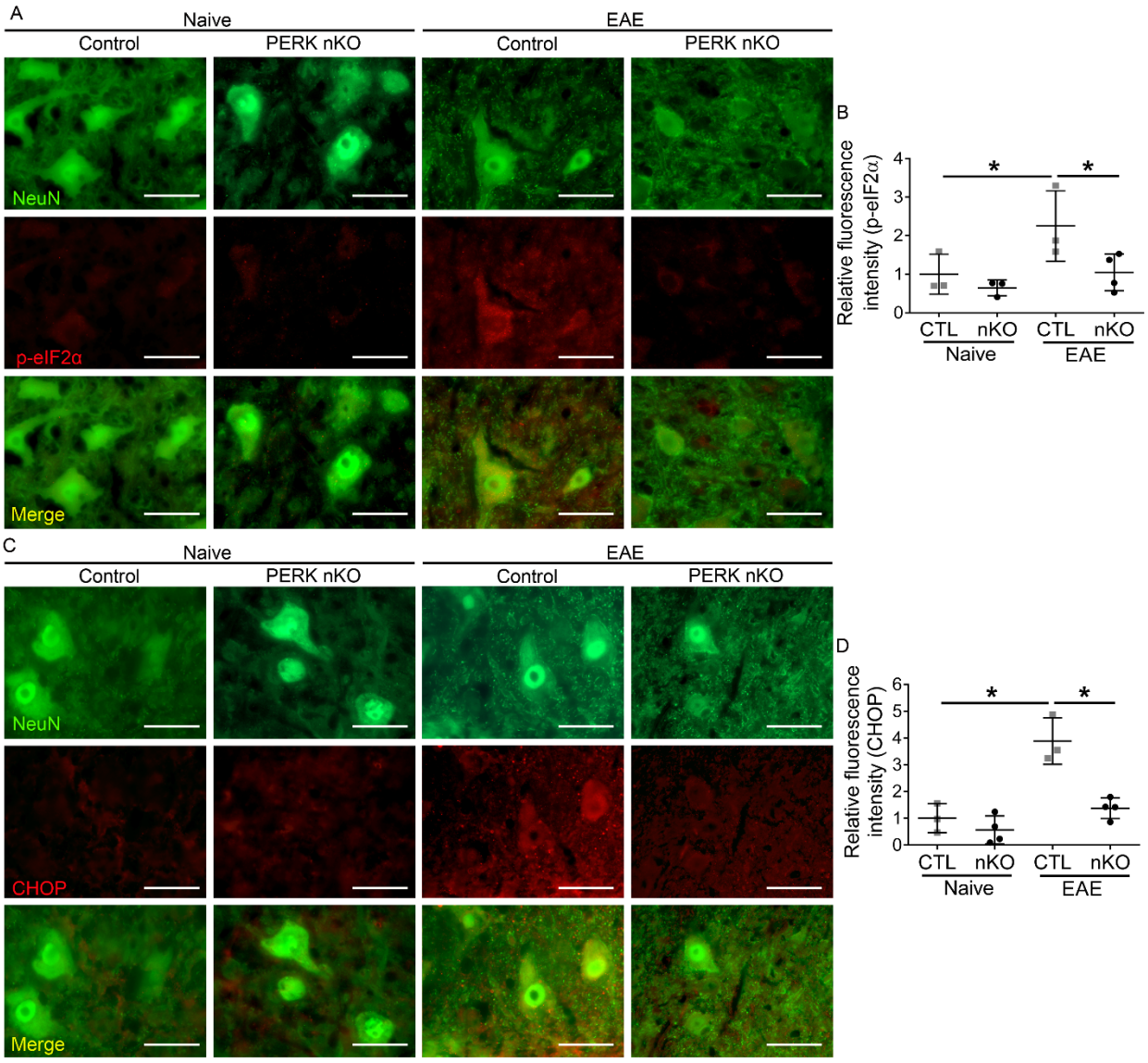
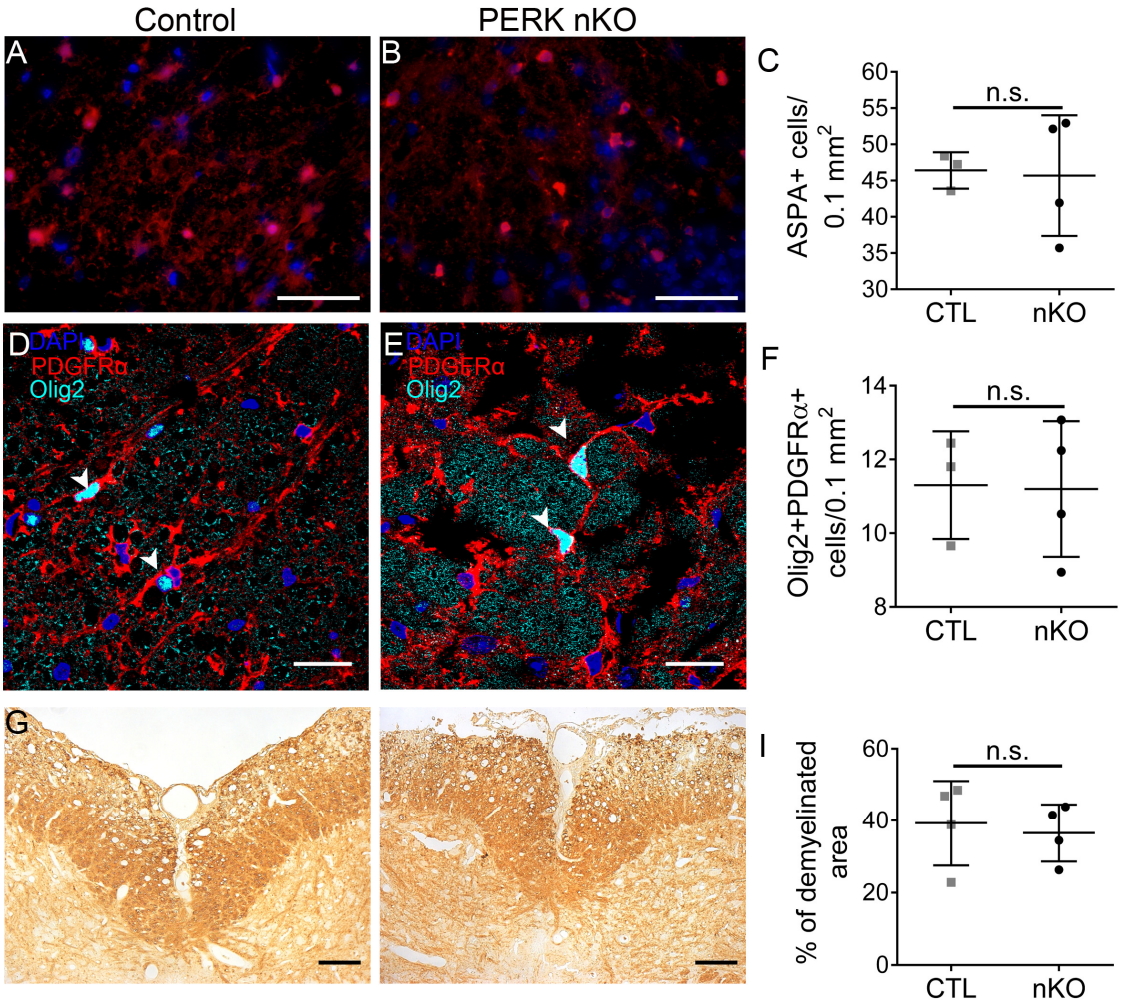
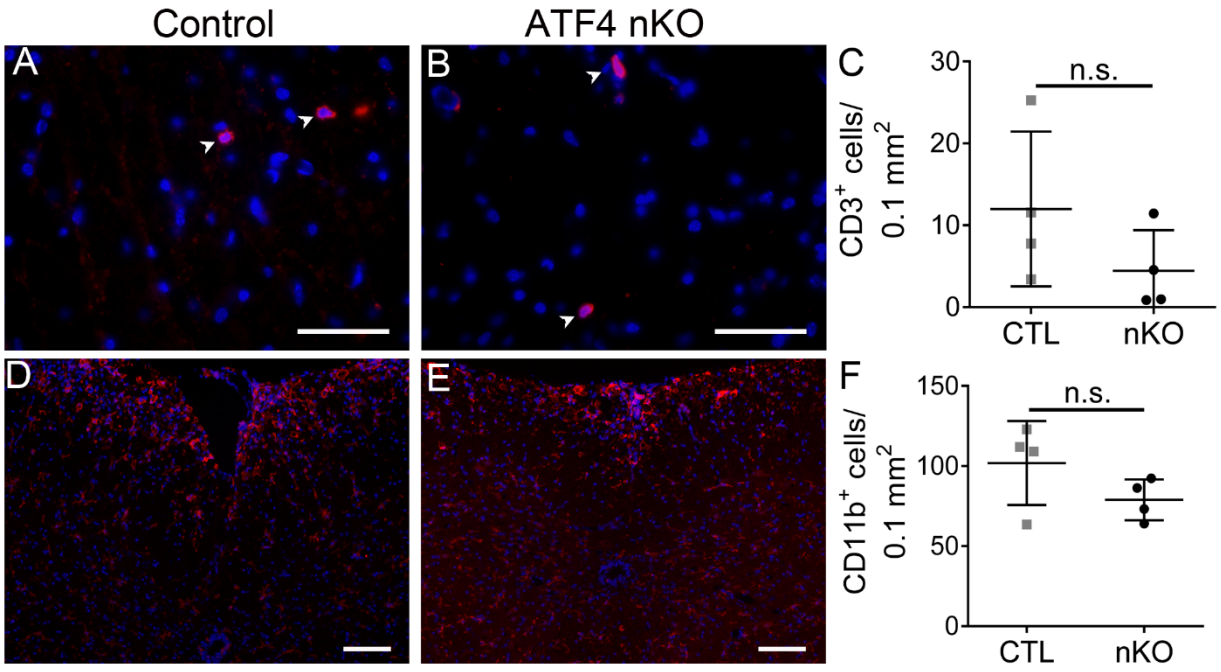


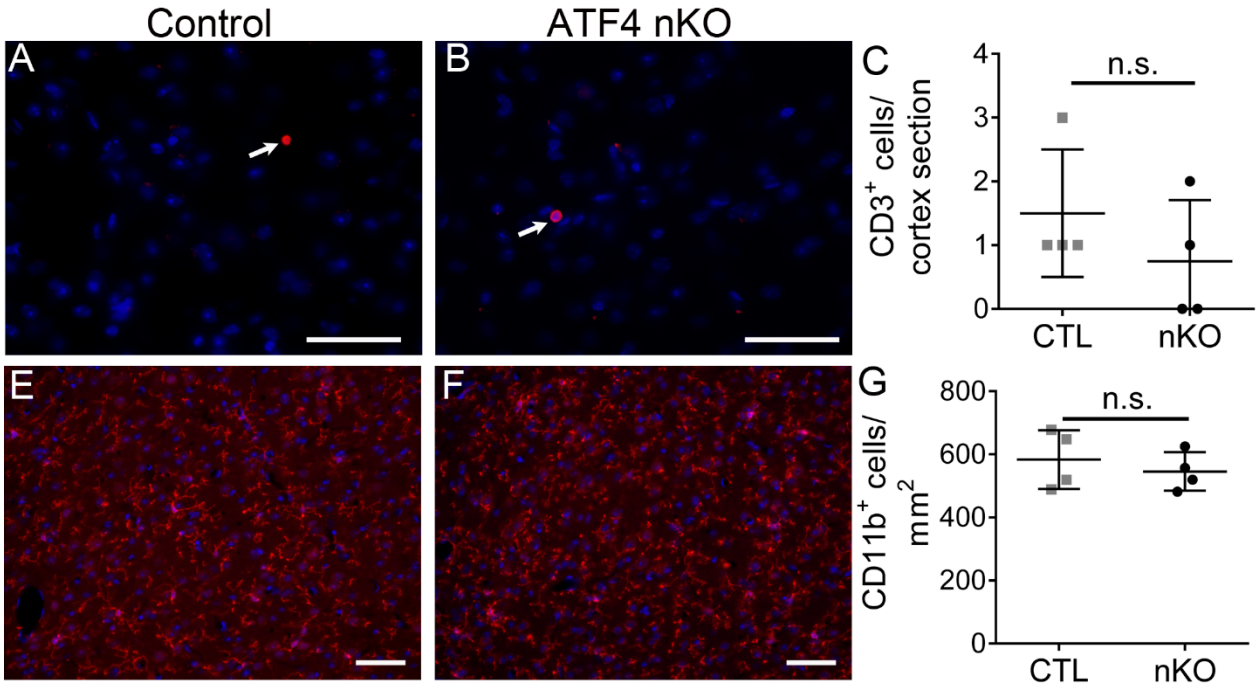
Supplemental figure 1. Neuron-specific PERK inactivation diminished the elevation of p-eIF2α and CHOP in neurons in the lumbar spinal cord during EAE. A, B. NeuN and p-eIF2α double immunostaining showed that the level of p-eIF2α was markedly increased in neurons in the lumbar spinal cord of control EAE mice at PID 22 compared to naïve mice. Importantly, the p-eIF2α level in neurons was noticeably reduced in PERK nKO mice with EAE compared to control EAE mice at PID 22. **C, D.** NeuN and CHOP double immunostaining showed that the level of CHOP was markedly increased in neurons in the lumbar spinal cord of control EAE mice at PID 22 compared to naïve mice. Importantly, the CHOP level in neurons was noticeably reduced in PERK nKO mice with EAE compared to control EAE mice at PID 22. Scale bars: 50 μm. N = 3-4 animals. Error bars represent SD. Statistical analyses were done with a 1-way ANOVA with a Tukeys posttest, $*P < 0.05$.



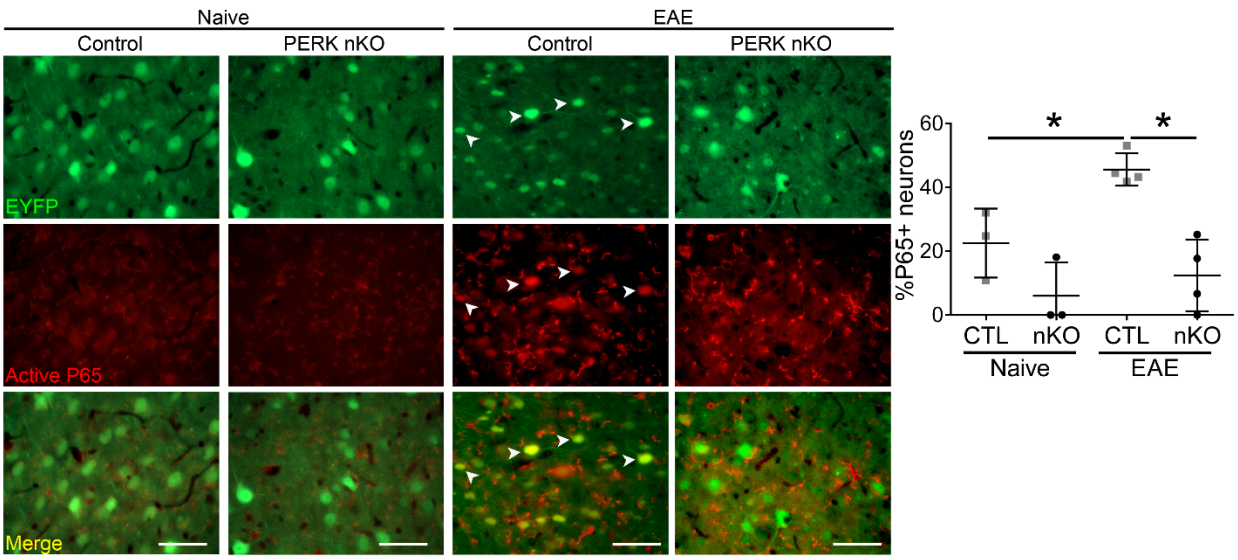
Supplemental figure 2. Neuron-specific PERK inactivation did not affect oligodendrocyte loss or demyelination in the lumbar spinal cord of EAE mice at the peak of disease. A, B, C. ASPA immunostaining revealed that neuron-specific PERK inactivation did not significantly influence oligodendrocyte loss in the lumbar spinal cord of EAE mice at PID 22. **D, E, F.** PDGFRα and Olig2 double immunostaining revealed that neuron-specific PERK inactivation did not significantly change the number of OPCs that were positive for both PDGFRα and Olig2 (arrows) in the lumbar spinal cord of EAE mice at PID 22. **G, H, I.** MBP IHC revealed that neuron-specific PERK inactivation did not significantly affect the degree of demyelination in the lumbar spinal cord of EAE mice at PID 22. Scale bars: A, B, 50 μm; D, E, 20 μm; G, H, 100 μm. N = 3-4 animals. Error bars represent SD. Statistical analyses were done with a two-tailed t-test, n.s. not significant.



Supplemental figure 3. Neuron-specific ATF4 inactivation did not influence inflammation in the lumbar spinal cord during EAE. A, B, C. CD3 immunostaining showed that neuron-specific ATF4 inactivation did not significantly change the number of T cells (arrowheads) in the lumbar spinal cord of EAE mice at PID 60. **D, E, F.** CD11b immunostaining showed that neuron-specific ATF4 inactivation did not significantly change the number of macrophages/microglia in the lumbar spinal cord of EAE mice at PID 60. Scale bars: A, B, 50 μm; D, E, 100 μm. N = 4 animals. Error bars represent SD. Statistical analyses were done with a two-tailed *t*-test, n.s. not significant.



Supplemental figure 4. Neuron-specific ATF4 inactivation did not influence inflammation in the primary motor cortex during EAE. A, B, C. CD3 immunostaining showed that neuron-specific ATF4 inactivation did not significantly change the number of T cells (arrows) in the layer V of the primary motor cortex in EAE mice at PID 60. **D, E, F.** CD11b immunostaining showed that neuron-specific ATF4 inactivation did not significantly change the number of macrophages/microglia in the layer V of the primary motor cortex in EAE mice at PID 60. Scale bars: 50 µm. N = 4 animals. Error bars represent SD. Statistical analyses were done with a two-tailed *t*-test, n.s. not significant.



Supplemental figure 5. Neuron-specific PERK inactivation impaired NF-κB activation in neurons during EAE. Active form of p65 immunostaining showed that the number of EYFP positive neurons that were positive for the active form p65 (arrows) was significantly increased in the layer V of the primary motor cortex in control EAE mice compared to naïve mice at PID 22, but was significantly reduced in PERK nKO mice with EAE compared to control EAE mice. Scale bars: 50 μm. N = 3-4 animals. Error bars represent SD. Statistical analyses were done with a 1-way ANOVA with a Tukeys posttest, $*P < 0.05$.