Prostaglandin E2 (PGE2) is a signaling molecule derived from cell membrane lipids by the enzyme cyclooxygenase–2 (COX-2). PGE2 plays an important role in microglia activation. Research shows that microglia in turn contribute to proper brain development such as synaptic plasticity or inflammatory responses. Anomalies in the COX-2/PGE2 signaling pathway have been linked to Autism Spectrum Disorders (ASD). In this study, we examined whether abnormal PGE2 levels affect microglia activation in our ASD mouse model lacking the neuronally expressed COX-2 (COX−/−knockout). We already showed that the COX−/− offspring have autism related behavior. Here, we examined differences in sex-dependent microglial density and activation state in the brain regions associated with ASD, including the olfactory bulb, hippocampus, thalamus, prefrontal cortex and the cerebellum. We showed that at postnatal day 25 both microglial activation and density were affected in the COX2−/− model in sex-dependent and region-specific manners. Overall, COX+ mice showed elevated levels of microglial density and increased resting microglial cell quantity. A decrease in active microglial cells was seen accordingly, in all regions except the hippocampus, where COX−/− females had increased active microglial cells. Overall, these findings show that abnormal levels of PGE2 alter microglial activity across the brain. These results suggest that abnormal regulation of microglia could results in brain pathology and lead to autism.