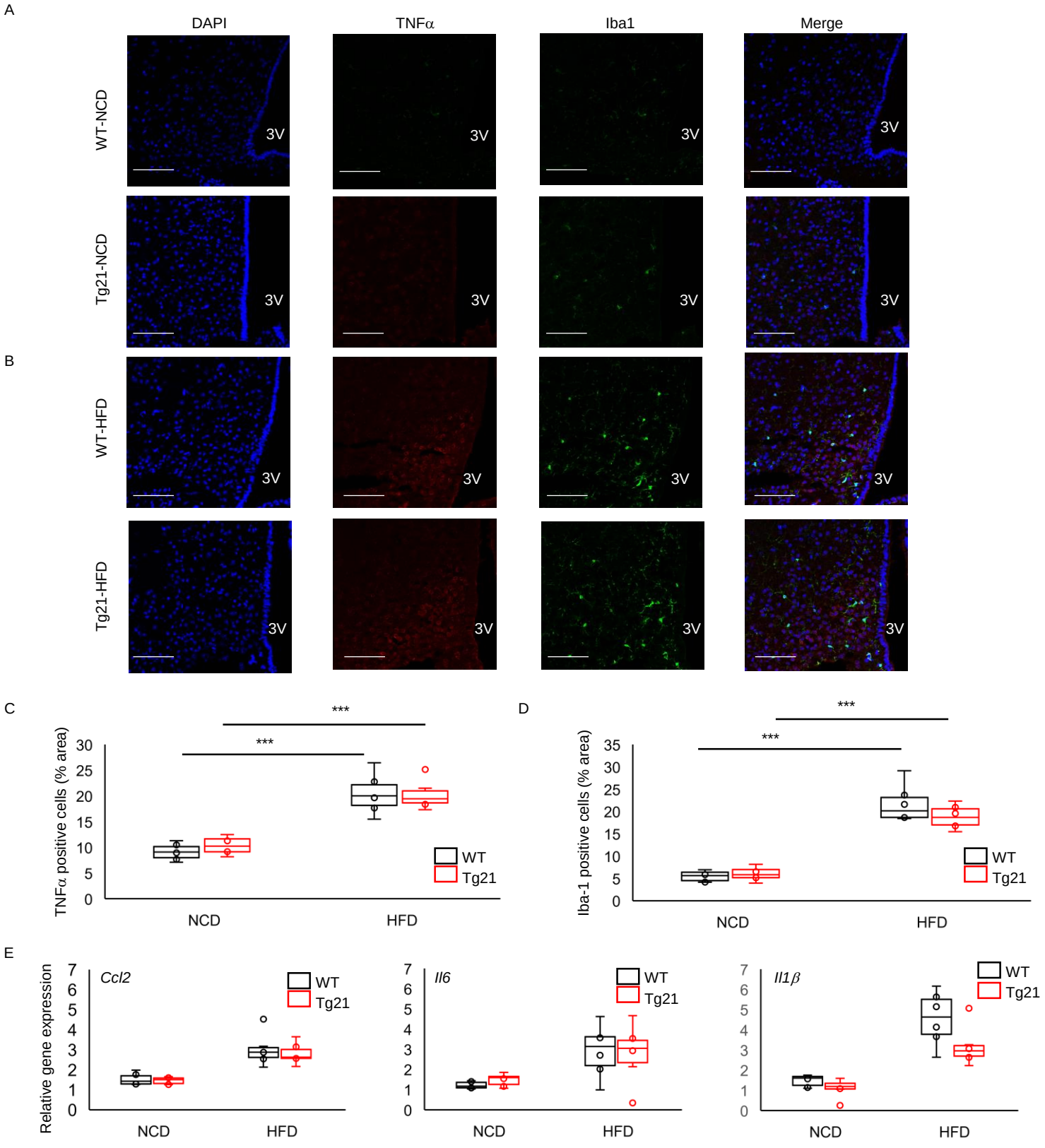
Supplementary Figures:

Supplementary Figure 1. Inflammatory and microglial cell response in the hypothalamus of female WT- and *Tg21*-mice are not different on NCD or HFD-feeding. (A, B) Representative hypothalamic sections from age-matched (8 weeks) female *Tg21*- and WT-mice during NCD (A) or after three weeks of HFD-feeding (B) stained for nuclear marker DAPI, inflammatory marker TNFα, and microglial cells marker Iba1 in MBH. (C, D) Quantification of (A) and (B) (E) Gene expression of markers *Ccl2*, *Il6*, and *Il1*β in the hypothalamus of age-matched (8 weeks) female *Tg21*- and WT-mice on NCD or after 3 weeks of HFD determined by quantitative RT-PCR, normalized to WT control mice on NCD, and adjusted to *Gapdh* gene expression. Box and whisker plots denote bounds ranging from 25^{th} to 75^{th} percentile, line represents the median, whiskers ranging from minimum to maximum values, and includes outliers. Statistical significance is indicated by *** $p<0.001$, ** $p<0.01$, *$p<0.05$ (2-way ANOVA) (n=8-10/group). Scale bar 100μm; magnification 40X, 3V: third ventricle.

Supplementary Figure 2. *Tg21*- and WT-female mice show no difference in $P2Y12^{+}$ microglial cells during NCD or HFD-feeding, and no detectable $CD169^{+}$ cells in either condition (A) Representative hypothalamic sections from age-matched (8 weeks) female *Tg21*- and WT-mice during NCD (A) or after three weeks of HFD-feeding (B) stained for nuclear marker DAPI, CD169, andP2Y12 in MBH. (C) Quantification of (A) and (B) to measure CD169- and P2Y12-positive cells. Box and whisker plots denote bounds ranging from 25^{th} to 75^{th} percentile, line represents the median, whiskers ranging from minimum to maximum values, and includes outliers. Statistical significance was tested by 2-way ANOVA (n=6-8/group). Scale bar 100μm; magnification 40X, 3V: third ventricle. Each slide is representative of n=8-10/group.

Supplementary Figure 3. *EpoR* gene deletion via *nestin*-promoter driven cre-recombinase expression is specific in the brain and not in the spleen and does not affect hematocrit. (A, B) *EpoR* gene expression in the whole brain and spleen at age 4 weeks of *nestin-cre;EpoR*$^{loxP/loxP}$ and *nestin-cre;EpoR*$^{WT/WT}$ mice normalized to WT control mice, and adjusted to *Gapdh* gene expression. (C) Hematocrit levels in *nestin-cre;EpoR*$^{loxP/loxP}$ and *nestin-cre;EpoR*$^{WT/WT}$ mice at age 4 weeks. Box and whisker plots denote bounds ranging from 25th to 75th percentile, line represents the median, whiskers ranging from minimum to maximum values, and includes outliers. Statistical significance was tested by 2-way ANOVA (n=6-8/group).

Supplementary Figure 1



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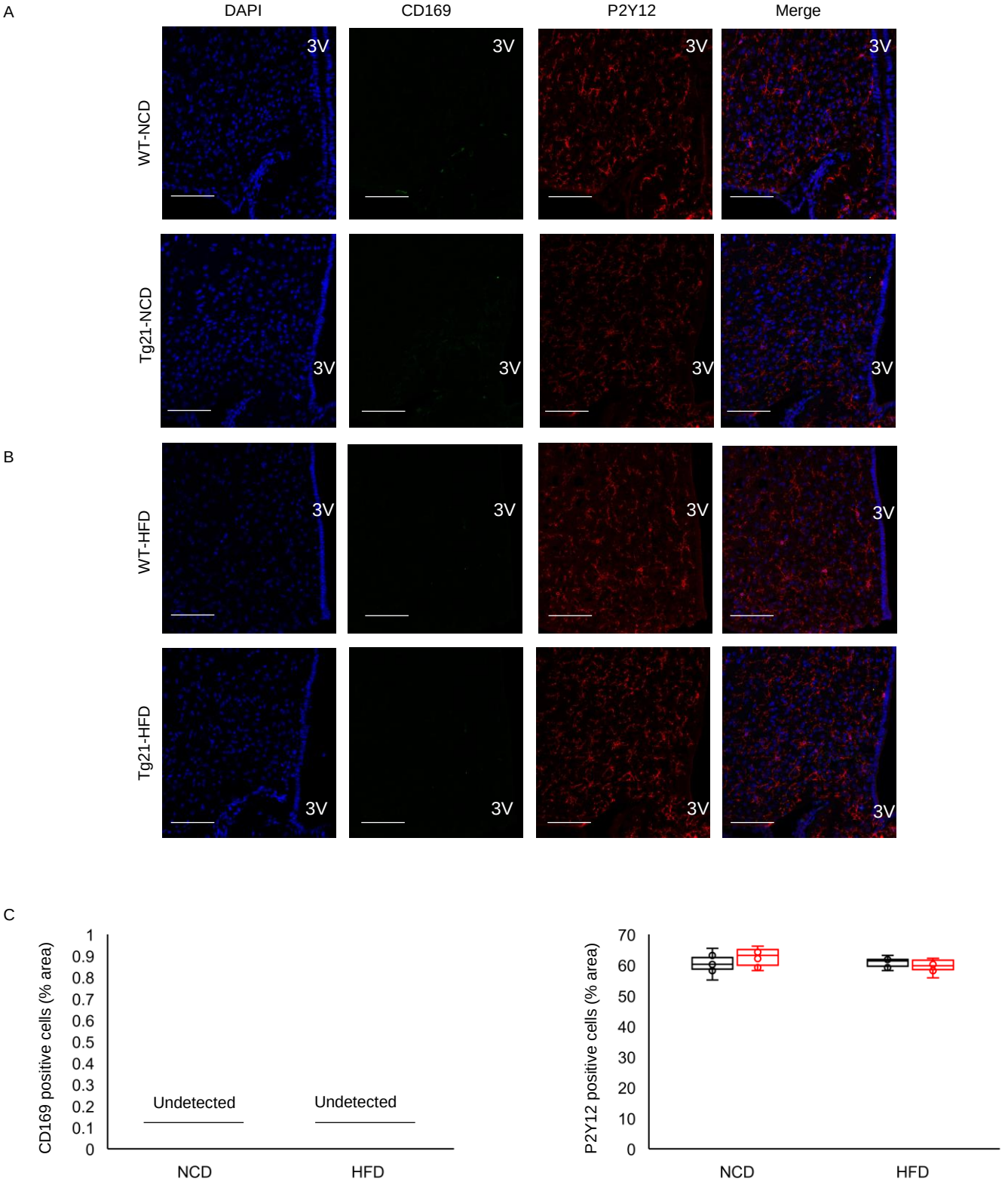
Supplementary Figure 2



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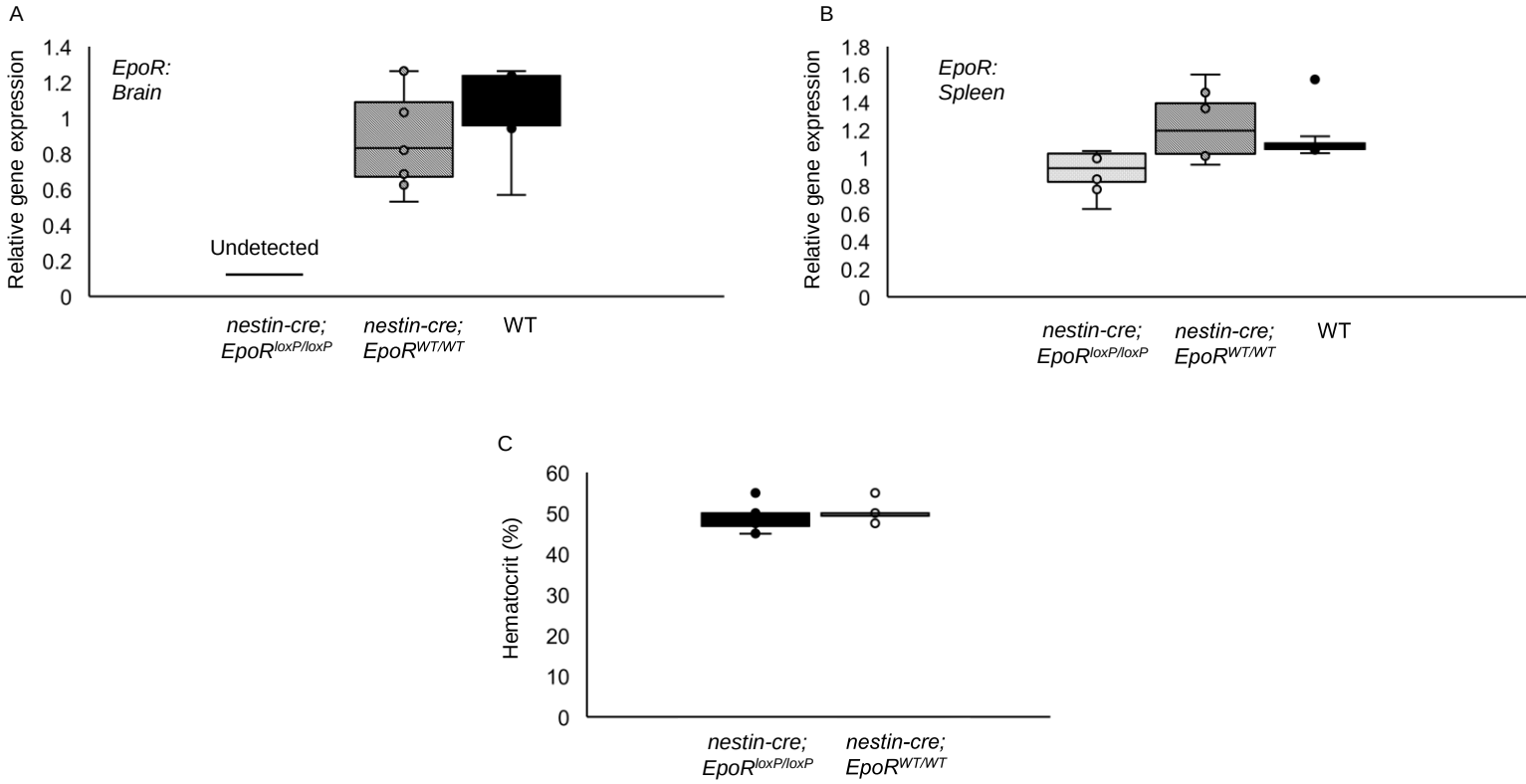
Supplementary Figure 3



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