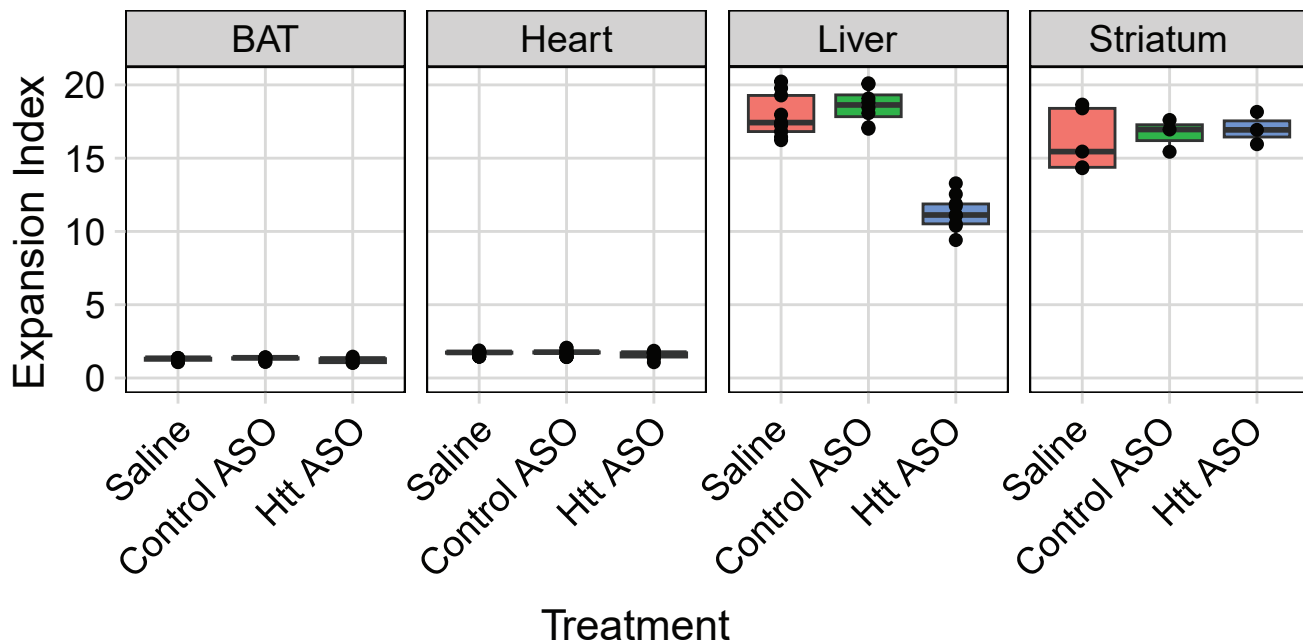
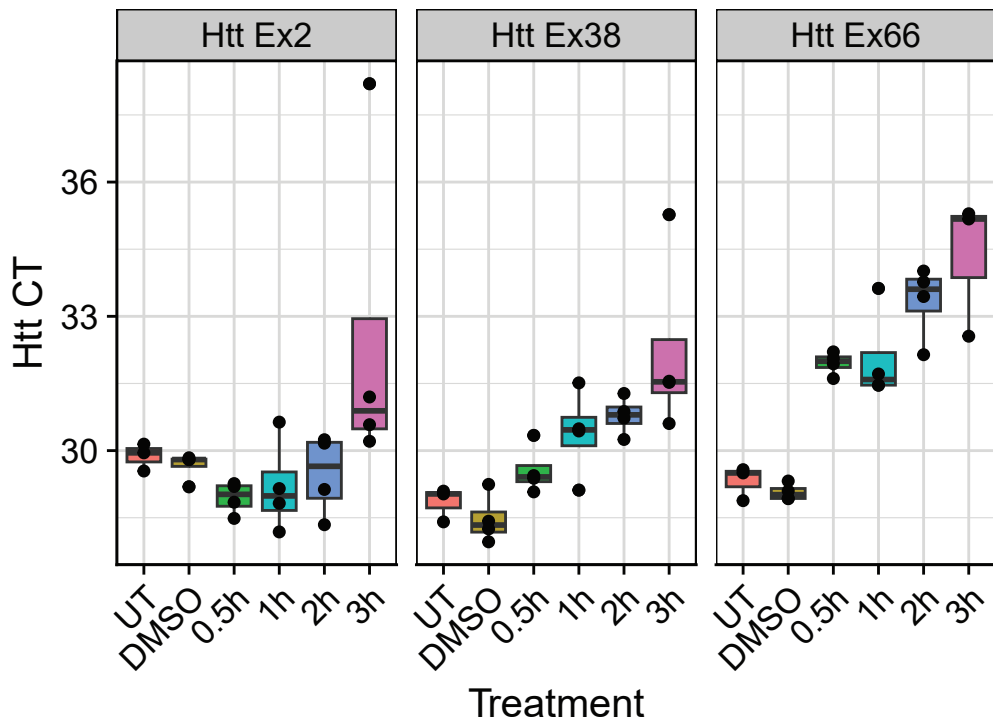
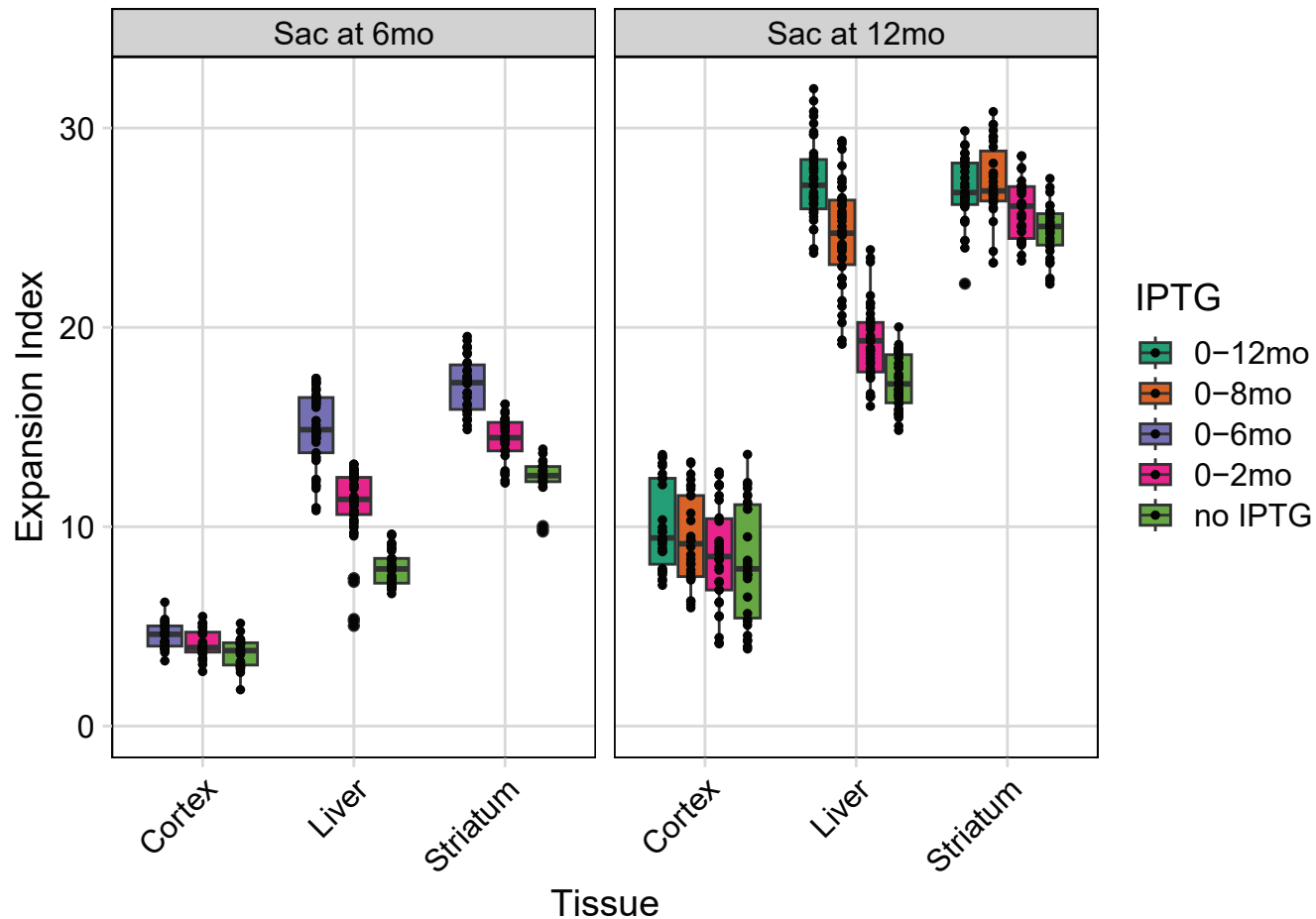




Supplementary Figure 1: Peripheral ASO treatment does not reduce instability in tissues other than liver. Brown adipose tissue (BAT) and heart are stable tissues with very low baseline instability and are not affected by *Htt* ASO treatment. Striatum is an unstable tissue, but *Htt* ASO is dosed peripherally and cannot cross the blood-brain barrier, so instability is unaffected. Liver is both unstable and accessible by the ASO, and its instability is markedly reduced by ASO treatment. $n = 3-12/\text{arm}$.



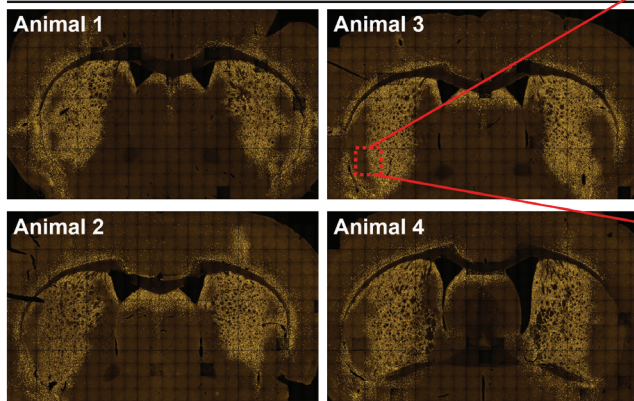
Supplementary Figure 2: Actinomycin D treatment leads to robust reductions in Htt pre-mRNA. In AML12 cells (RRID:CV-CL_0140), pre-mRNA qPCR signal for Htt RNA decreases with increasing lengths of treatment with actinomycin D, a known transcriptional inhibitor. $n = 4/\text{arm}$.



Supplementary Figure 3: Complete, cross-tissue, LacO dataset. Expansion index decreases with longer windows of *Htt* repression, i.e., shorter windows of IPTG treatment. This effect is seen in cortex, liver, and striatum, and in mice sacrificed at both 6 and 12 months of age. $n = 8-21/\text{arm}$.

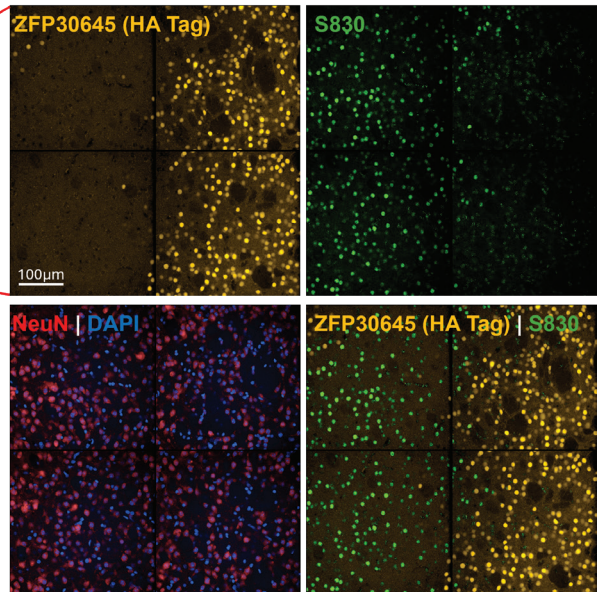
A

ZFP30645

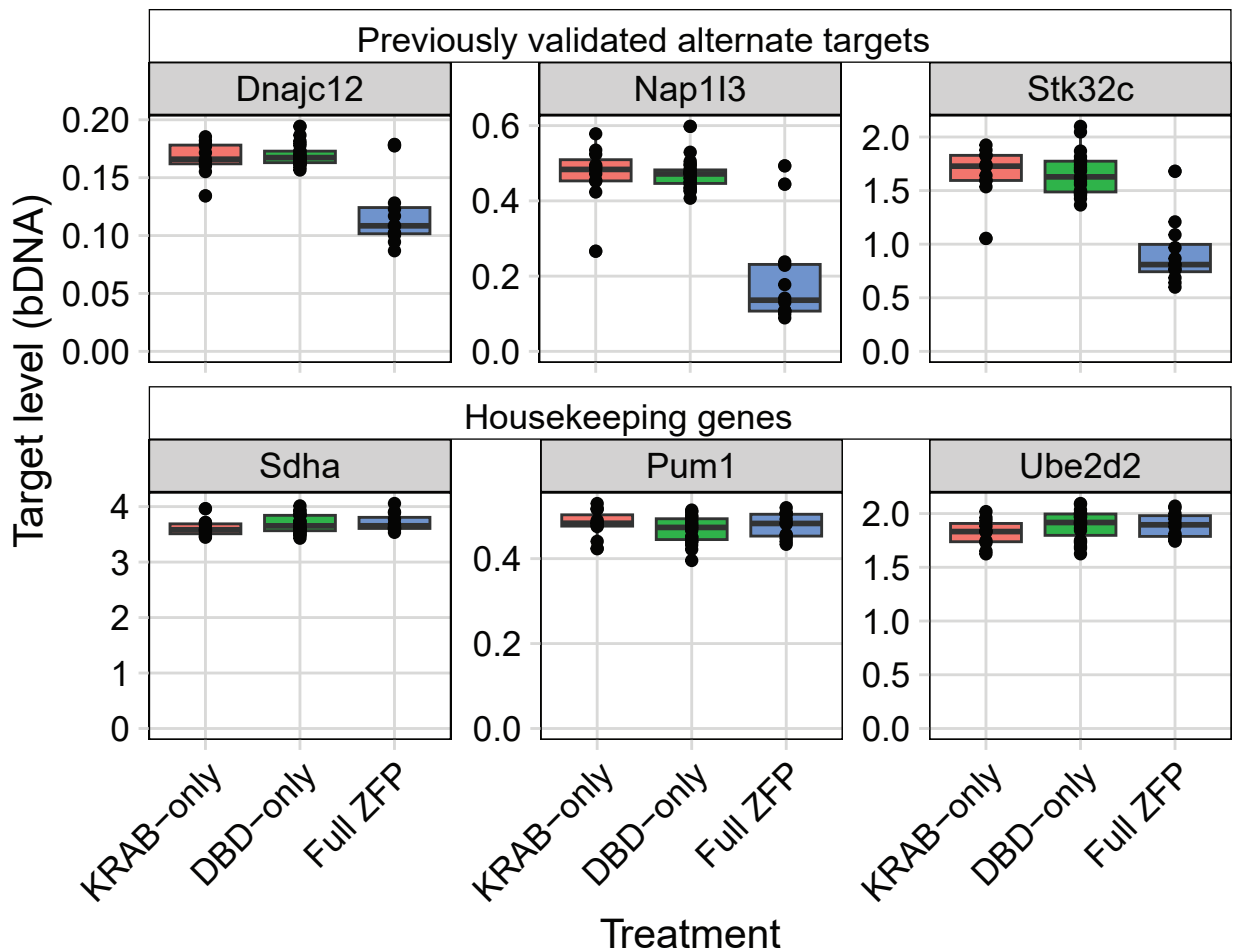


Loss of mHTT signal in the hemisphere injected with the active zinc finger ZFP30645

B



C



Supplementary Figure 4: Experimental validation of the KRAB-only and DBD-only derivative ZFP constructs. A) HA-tag staining showing successful distribution of ZFP into the striatum. B) Immunohistochemical staining showing loss of mHTT in the transduced area. C) bDNA panel showing reduction after full ZFP treatment, but not DBD-only, of previously validated alternate target genes, and no effect of any construct on housekeeping genes. $n = 11-12/arm$.