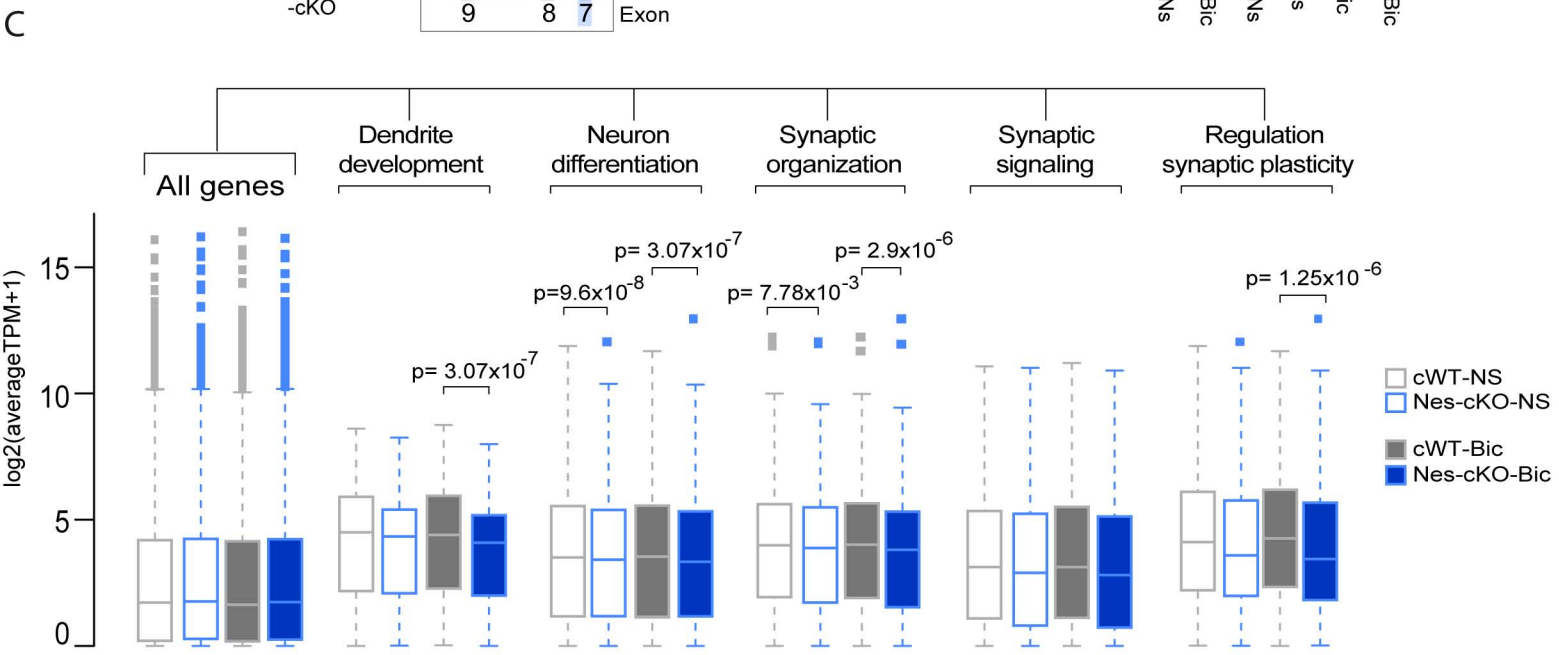
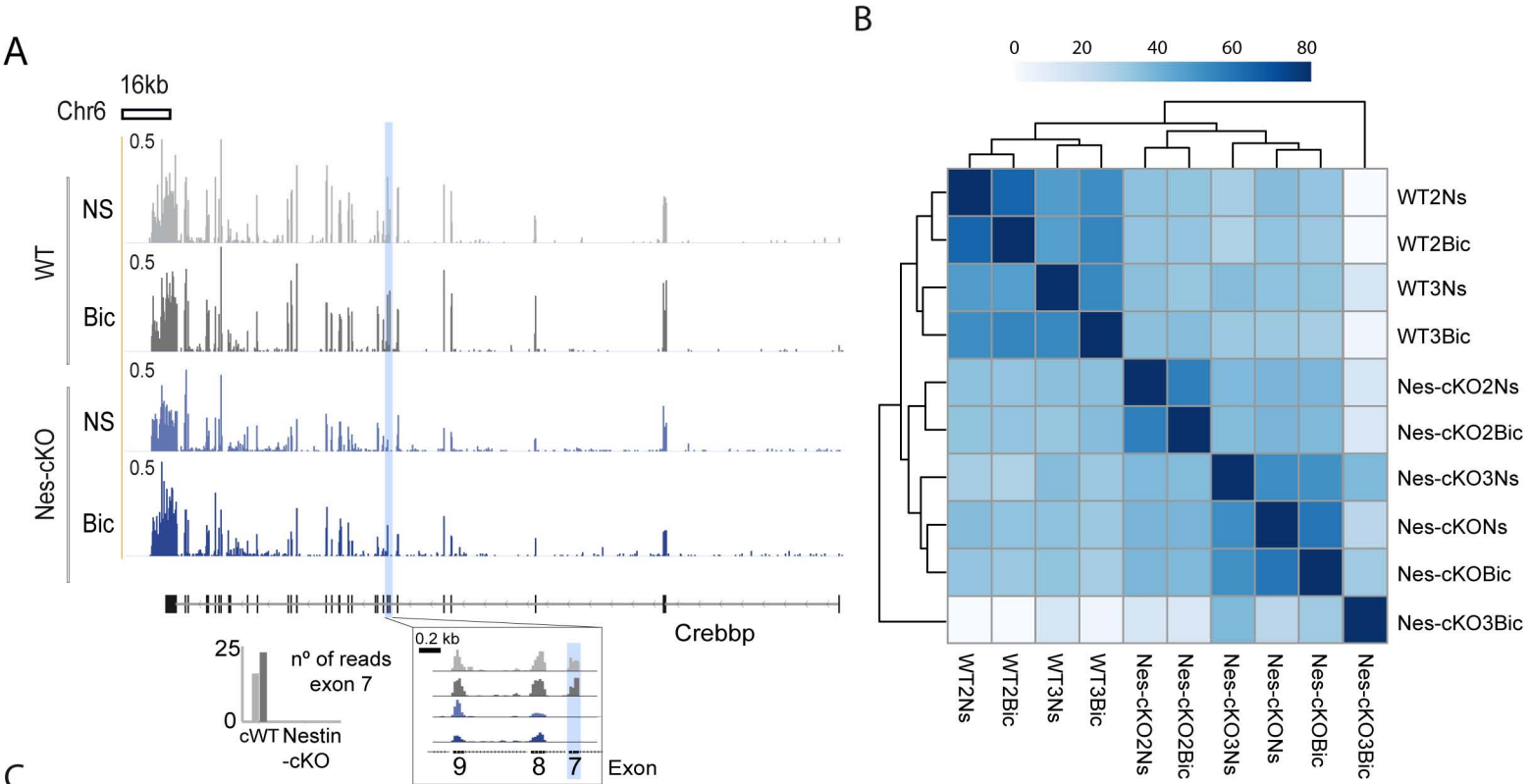
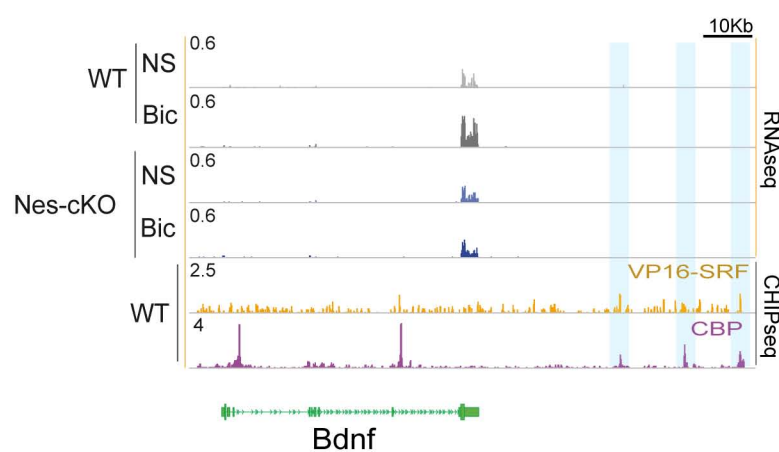
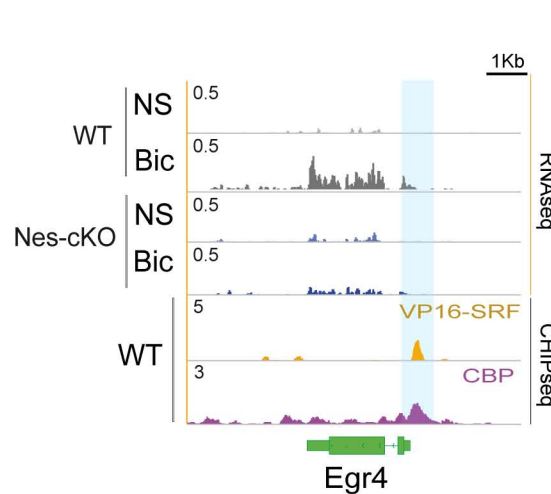
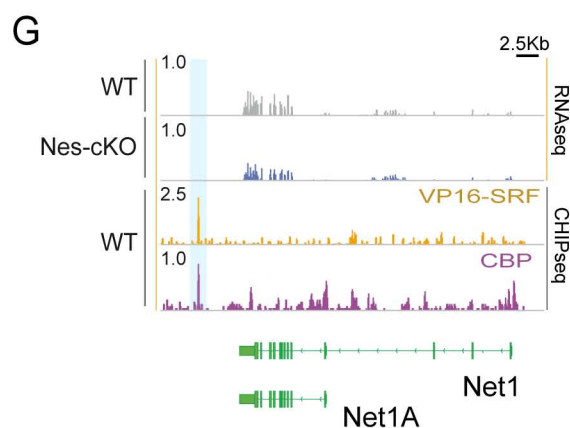
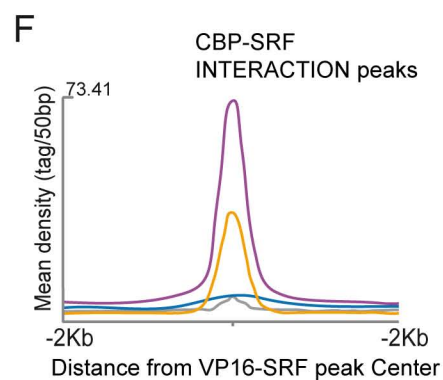
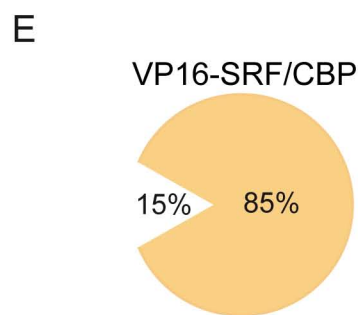
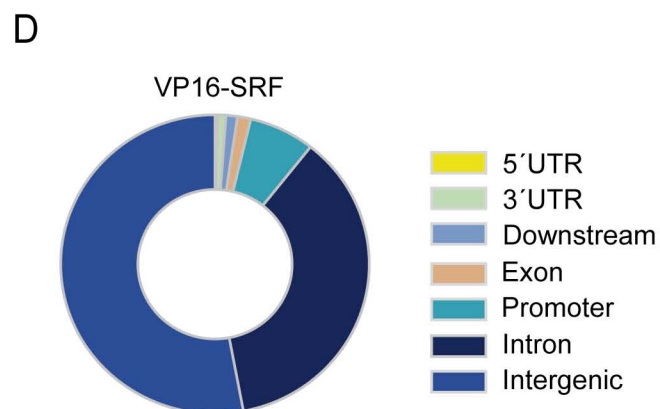
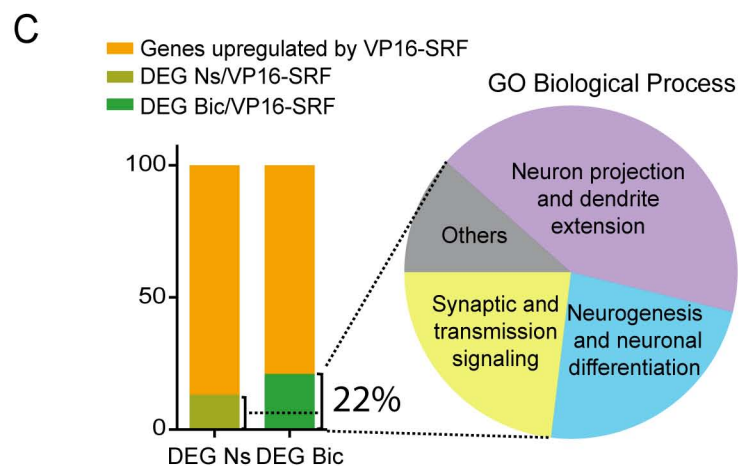
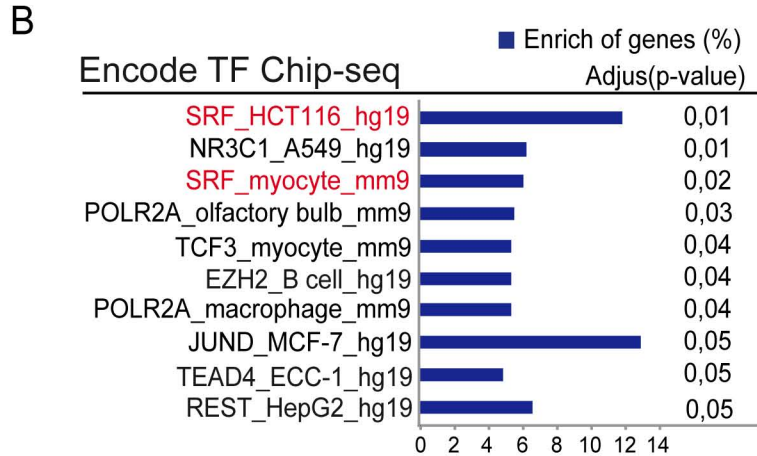
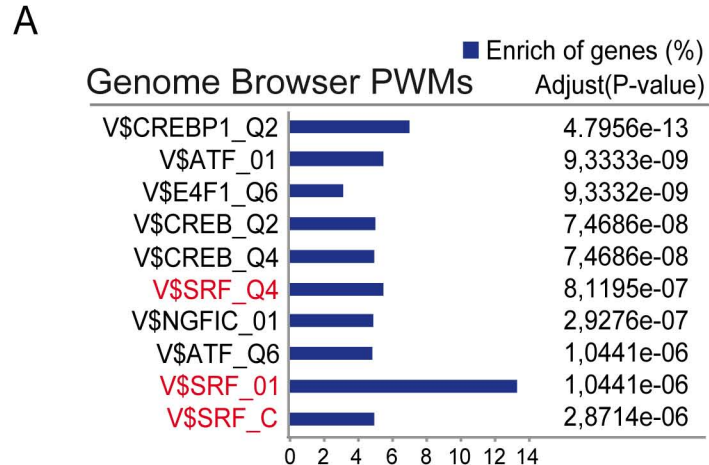


**Supplemental Figures**

**Supplemental Figure S1 Impaired activity-induced transcription and structural changes in Nes-cKO neurons.** **A.** IGV snapshot of the *Crebbp* locus and quantification of the number of reads mapping to exon 7. The difference between Nes-cKO and cWT neurons confirms the specific ablation of exon 7 in PNCs from Nes-cKO embryos. **B.** Correlation between RNA-seq samples. Colors represent the Pearson correlation coefficients ( $R^2$ ), from low (0) to high (80) correlation. **C.** Box plot depicting the total reads into genes belonging to the indicated biological processes. *P* values were determined using the Wilcoxon non-parametric test.



**Supplemental Figure S2 related to Figure 5. Enhancing SRF-dependent transcription of neuronal growth-related genes reverses the synaptic deficits associated with CBP loss.** **A.** TFBS-enrichment analysis based on UCSC Genome Browser position weight matrices (PWMs) identifies SRF as the TF showing the largest enrichment in the promoters of downregulated genes in Nes-cKO neurons after Bic-stimulation. **B.** TFBS-enrichment analyses based on TF Chip-seq data generated in the ENCODE project identifies SRF as the TF showing the most significant enrichment. **C.** Genes upregulated by VP16-SRF (left bar graph) and downregulated in CBP-deficient neurons are related to neuronal growth and plasticity according to GO enrichment analyses (right sector graph). **D.** Mapping of VP16-SRF binding in hippocampal neurons. The sector diagram shows the distribution among gene features. **E.** Sector graph representing the percentage of genes annotated with both VP16-SRF and CBP peaks (85%), or only VP16-SRF peaks (15%). The distance thresholds for annotation to a given gene are 5 Kb upstream and 1 Kb downstream. **F.** The kernel plot depicts CBP (purple) at VP16-SRF (orange) occupancy peaks. The CBP distribution is represented upstream (+ 2 Kb) and downstream (-2Kb) of the center of the VP16-SRF peak. Blue: input for the CBP sample; gray: input for the VP16-SRF sample. **G-H.** Additional IGV snapshots of DEGs in non-stimulated (G) and Bic-stimulated PNCs (H) showing the co-localization of CBP and VP16-SRF at regulatory regions of DEGs in Nes-cKO neurons.



### **Inventory of Supplemental Tables**

**Table S1 related to Figure 4.** Analysis of differentially expressed genes between genotypes (Nes-cKO vs cWT PNCs).

**Table S2 related to Figure 4.** Analysis of differentially expressed genes in cWT PNCs (non-stimulated vs Bic-stimulated).

**Table S3 related to Figure 4.** Analysis of differentially expressed genes in Nes-cKO PNCs (non-stimulated vs Bic-stimulated).

**Table S4 related to Figure 5.** VP16-SRF genome occupancy in the chromatin of hippocampal PNCs.