with no effect of HSV-*FosB*-ZFP35-NFD [t_{12}=3.2, **P*=0.008; n=7]. **(j)** Representative heatmaps of social interaction after a subthreshold defeat stress show a preference for the interaction zone when a target mouse is present for mice injected with control virus and HSV-*FosB*-ZFP35-NFD, but not HSV-*FosB*-ZFP35-G9a.

Supplementary Figure Legends:

Supplementary Figure 1: A suite of *FosB*-ZFPs bidirectionally regulate *FosB* expression in vitro. (a) *FosB*/Δ*FosB* mRNA was significantly induced by several *FosB*-ZFP-p65 and -G9a constructs expressed in N2a cells and harvested after 48 hours. *FosB*-ZFP-NFD constructs activated gene expression to a lesser extent or not at all. Data are normalized to mock transfected cells. Complete statistics are available in Supplementary Table 3. Student's unpaired t-test: $^{\square}P<0.05$, $^{\square}P<0.10$. Data are presented as mean ± s.e.m.

Supplementary Figure 2: HSV-ZFPs specifically infect neurons in NAc and inhibit basal *FosB* expression. (a) HSV-GFP specifically infects DARPP-32 positive neurons in the NAc. White arrows indicate double labeled cells. **(b)** NAc injection of HSV-*FosB*-ZFP35-G9a repressed expression of FosB/ΔFosB in HSV infected (GFP+) cells [t_{13}=3.55, **P*=0.033; n=7, 8] compared to HSV-*FosB*-ZFP35-G9a (72 hours post HSV injection). Data are presented as mean ± s.e.m.

Supplementary Figure 3: Regulation of *FosB* expression and reward behavior by *FosB*-TALEs and a suite of additional catalytic domains fused to *FosB*-ZFP35. (a) Locations of

FosB-ZFP and -TALE binding relative to the *FosB* TSS. The location of functional SRF and CREB sites are shown. **(b)** *FosB*/Δ*FosB* mRNA expression in the NAc was significantly induced by HSV-*FosB*-TALE2-VP64 [FosB: t_8=3.03, **P*=0.016; ΔFosB: t_8=6.40, **P*=0.000; n=5], and -*FosB*-TALE3-VP64 [FosB: t_8=2.79, **P*=0.023; ΔFosB: t_8=4.01, **P*=0.004; n=5] compared to control virus. **(c)** The binding sites of the 6-finger ZFP35 and 17-RVD (repeat variable diresidue) TALE1 recognize the *FosB* promoter at overlapping sites approximately 250 bp upstream from the *FosB* TSS. **(d)** *FosB*-ZFP35-p65 [FosB: t_4=5.91, **P*=0.004; ΔFosB: t_4=26.11, **P*=0.000; n=3], -p65x2 [FosB: t_4=2.30, **P*=0.000; ΔFosB: t_4=3.46, **P*=0.026 ; n=3], -VP16 [FosB: t_4=9.04, **P*=0.001; ΔFosB: t_4=7.45, **P*=0.002 ; n=3], and -VP64 [FosB: t_4=19.40, **P*=0.001; ΔFosB: t_4=7.45, **P*=0.001; n=3] and *FosB*-TALE1-VP64 [FosB: t_4=6.80, **P*=0.002; ΔFosB: t_4=15.17, **P*=0.000; n=3] activate FosB/ΔFosB mRNA levels when expressed in Neuro2a cells and harvested after 48 hours. Data are normalized to mock transfected cells. **(e)** HSV-*FosB*-TALE1-VP64 in NAc sensitizes cocaine-induced hyperactivity over time. There is a significant interaction between day, cocaine treatment, and virus [F(3,32)=3.42, **P*=0.029]. TALE1-VP64 sensitizes the effect of cocaine on locomotor activity [main effect of day among TALE1-VP64 [F(3,35)=9.92, **P*=0.000, n=10], but not GFP control [F(3,36)=2.05, P=0.126, n=9]. HSV-GFP data are the same as in Fig. 4d-e. Heat maps show representative locomotor data within the chamber for mice over the course of repeated cocaine exposure. Data are presented as mean ± s.e.m.

Supplementary Figure 4. Differential regulation by *FosB*-ZFPs in vitro and in vivo. (a) Expression of *FosB*-ZFP35-G9a differs between N2a cells and NAc [t_6=4.50, **P*=0.004; n=3,5]. **(b)** Titration of the amount of *FosB*-ZFP35-G9a expression in N2a cells leads to a reduction in

the amount of induced mRNA expression of ΔFosB but not FosB. Using a 2-tailed Pearson correlation, we found a significant correlation between µg of transfected DNA and mRNA fold change of ΔFosB [R_{12}=0.83, *P=0.001] but not FosB [R_{12}=.66, P=0.665]. Data are presented as mean ± s.e.m.

Supplementary Figure 5: Full blots of experiment shown in Figure 1e.

Methods:

Animals and treatments. Male 7-8 week old C57BL/6J mice and 6-month old CD1 retired breeders (CD1 aggressor) were housed at 22-25°C in a 12-hr light/dark cycle and provided food and water ad libitum. Animals were housed five per cage and habituated in our facility for at least 1 week before experimentation and all tests were conducted during the light cycle. Members of the same cage were randomly assigned to different experimental groups for behavioral studies and the order of testing was distributed across groups. Wherever possible, the experimenter conducting the data analysis was blind to treatment conditions of the animals. All experiments were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee at Mount Sinai. Group size determination was based on published protocols for the behavioral paradigm in use; no statistical test was used to predetermine sample size. For repeated cocaine experiments (immunohistochemistry, chromatin immunoprecipitation [ChIP]), animals received daily injections of either saline (5 treatments saline, i.p.), or saline followed by cocaine (1 treatment saline, 4 treatments cocaine, 20 mg/kg, i.p.) and sacrificed 24 hours after the

Supplementary Table 1: Primers

Mus qRT-PCR Primers

Name	Sequence
Ankrd52 F1	CCTCTGACACCTACCGGAGA
Ankrd52 R1	TCGAGGTTCTGTCTGTTGCC
Cacnb3 F1	CAGCTACTGTGGGGTTCTGG
Cacnb3 R1	CTCCTGGCCTTCTGTTCCTG
cFos F	GGAATTAACCTGGTGCTGGA
cFos R	TGAACATGGACGCTGAAGAG
Ctbs F1	TCGCAGATGCCTGTGACTTT
Ctbs R1	GCCAGCAGGATCCTTTGAGAG
Cux2 F1	TCCAGGGTCTTCCGGACATC
Cux2 R1	CCGAGGCGACAGAACTAAGC
D15Wsu169e F1	GAGACCCAGGACGTGAAGC
D15Wsu169e R1	CATCAGGTTGCCTCCTCCAG
ΔFosB F	AGGCAGAGCTGGAGTCGGAGAT
ΔFosB R	GCCGAGGACTTGAACTTCACTCG
Dip2b F1	CTCCTCTTCCTCACTTCGCC
Dip2b R1	GTTGGGATCTGGCTGAGGTAT
FosB F	GTGAGAGATTTGCCAGGGTC
FosB R	AGAGAGAAGCCGTCAGGTTG
Fsd1l F1	GCAAGTCCCAGGAGTTACAG
Fsd1l R1	CTCTTTACAGCATCAGAAATGACAA
Gnai1 F1	ATGGGCTGCACATTGAGCG
Gnai1 R1	TGCTGTAGACCACTGCCTTG
Hcfc2 F1	ATGTACAGTGACTGCTGGGC
Hcfc2 R1	ACCATGGGCCCACATCTTTT
Hic2 F1	TGCTCACATGGTTTCTGGGC
Hic2 R1	AGCAGCCAGGACATTCTTGT
Kcnt1 F1	GGTGATGTGACGCCCAAGAT
Kcnt1 R1	CGGGGATGGGCATAGAACTC
Mef2b F1	GGGATTGGGCACCTCAAGAA
Mef2b F2	GTCTACAGCGTCCCTCGTTG
Ofcc1 F1	CACTGCAGACGGGAATCCTT
Ofcc1 R1	TTGACACTCCTGTGAGGCAC
Prrt1 F1	CGTGCACTGCTTATGTCCCT
Prrt1 R1	AGAAGCAGCAGATGGTGGTC
Prrt2 F1	GCCTTCGCTTATGCCGTC
Prrt2 R1	CCCAAGACAGCTCCCAACAG
Pth1r F1	CTGTGGGGCTTCACCATCTT
Pth1r R1	TCCCGAAGCTTAGTGGCAAG
Ptprn2 F1	TCCGCCACAACTCACACTAC
Ptprn2 R1	GAGCCGAAGGACTAGGCATC
Pygo1 F1	TGGGTTAGGAGGGCCCAATA
Pygo1 R1	TGTCATCGAACGGATTGGCA
Rps6ka5 F1	TCAGGTTCCCCTAAGAGCGA
Rps6ka5 R1	CCTTCTCTGCGTGTCCTGTT
Sardh F1	CTTGGGCCAGCAGCATTG
Sardh R1	GGGGACTTAGGGCTCCTGTA

Mus qRT-PCR Primers (continued)

Name	Sequence
Slc2a7 F1	ACAAAGAGATAGGGACACCTCTGC
Slc2a7 R1	GGACCTGAAAGACAGGACCCC
Syncrip F1	TTCGGCCGCCATTTTACAAC
Syncrip R1	CCATGGGCTCTTCAGTACCA
Tlr12 F1	GAGGGAGTACAGCCCTCAGA
Tlr12 R1	AGGGAACCCCTAGCAGAGAG
Tmem132e F1	ATCTCTACACCCTCGGACCC
Tmem132e R1	TAGGGCTAGCCTGAGTTCCC
Unc5a F1	ACCATGGAGGTCCGGATCAA
Unc5a F2	GCGACAAGGTAGCACAATGC
Vmn2r20 F1	TGTCCAGAGGGAGAGATTGC
Vmn2r20 R1	GACAATGGGTGTGTCCCGAT
Vmn2r21 F1	CCATGTCCAGAGGGAGAGGT
Vmn2r21 R1	GACAATGGGTGTGTCCCGAT

Mus qChIP Primers

Name	Sequence
cFos F	GCTGCGTACTTGCTTCTCCT
cFos R	AACATTCGCACCTGATTCAA
FosB -1250 F	ATGGGACTCAGGTTGTCAGG
FosB -1250 R	AGCCAGGGCTACACAGAGAA
FosB -500 F	GAGTTGCACCTTCTCCAACC
FosB -500 R	GGCCCAGTGTTTGTTTGGTA
FosB -250 F	ATGGCTAATTGCGTCACAGG
FosB -250 R	ACCTCCCAAACTCTCCCTTC
FosB +1 F	GCTCCCGGTTTCATTCATAA
FosB +1 R	GCAAAAAGGAAACCCACAAA

Hu qChIP Primers

Name	Sequence
FosB F	CTTTGTCTCCGGGTGGATTA
FosB R	TTCTGTCCTGATTCGCTGTG

Mus Bisulfite Sequencing Primers

F	TGAATTATTTTGTTGGGGTTGATAT
R	ATTAAAAACCTCTCCTTCCCACTTA

Supplementary Table 2
***FosB*-ZFP35 Off-Target Sites**

Gene Name	Refseq	Distance to TSS	Motif Sequence	No. Mismatch	ZFP35-NFD	ZFP35-p65
Fosb	NM_008036	-215.5	GATCCCCTCCCGCGAAGCC	0	ns	upregulated
Ankrd52	NM_172790	354.5	GAGCCCCTCCAGCGACGCC	3	ns	ns
Cacnb3	NM_007581	124.5	GACCCCCTCCCGGGAAGAc	3	ns	ns
Ctbs	NM_028836	2645.5	GGTCCCCTCCCATGAAGCC	3	ns	ns
Cux2	NM_007804	-2559.5	GCTCCCCTCGCGCGAGGCC	3	nd	nd
D15Wsu169e	NM_001168288	801.5	GAGGCCCTGCCGCGAAGCC	3	ns	ns
Dip2b	NM_001159361	333.5	GCTCCCCACCCGCGAAGCG	3	ns	ns
Fsd1l	NM_176966	392.5	GATCCCCCCACGCGAGGCC	3	ns	ns
Gnai1	NM_010305	65.5	GATCCGCGCCCGCGAATCC	3	ns	ns
Hcfc2	NM_001081218	-41.5	GAGCCCCTCCCGCCAACCC	3	ns	ns
Hic2	NM_178922	733.5	GACCCCCTCCCCCCAAGCC	3	ns	ns
Kcnt1	NM_175462	215.5	AAGCCCCTCCCGCGCAGCC	3	ns	ns
Mef2b	NM_008578	-50.5	GATGCCTTCCCGCGCAGCC	3	nd	nd
Myl7	NM_022879	1332.5	GATCCCCTGCCGCGAGGCC	2	nd	nd
Ofcc1	NM_172143	1511.5	GCTCCCCTCCCTCGTAGCC	3	nd	nd
Rps6ka5	NM_153587	372.5	ATTCCCCGCCCGCGAAgcc	3	ns	ns
Sardh	NM_138665	-799.5	GTTCCCCACCCCCGAAGCC	3	ns	ns
Slc2a7	NM_001085529	-1338.5	GATCTCCTCACGCGAAGTC	3	ns	ns
Syncrip	NM_019666	-594.5	GCTCCCCTCCCCCGCAGCC	3	ns	ns
Tlr12	NM_205823	-12.5	TTTCCCCTCCCTCGAAGCC	3	ns	ns
Tmem132e	NM_023438	2611.5	TCTCCCCTCCCCCGAAGCC	3	ns	ns
Unc5a	NM_153131	1317.5	GATCACCTCCCGGGAAGCA	3	ns	ns
Vmn2r20	NM_001104634	-2738.5	GATCCCATCCCACTAGCC	3	nd	nd
Vmn2r21	NM_001104635	-2738.5	GATCCCATCCCACTAGCC	3	nd	nd

nd not determined (no cDNA detected in NAc tissue)
ns not significant, see Extended Data Fig. 3b

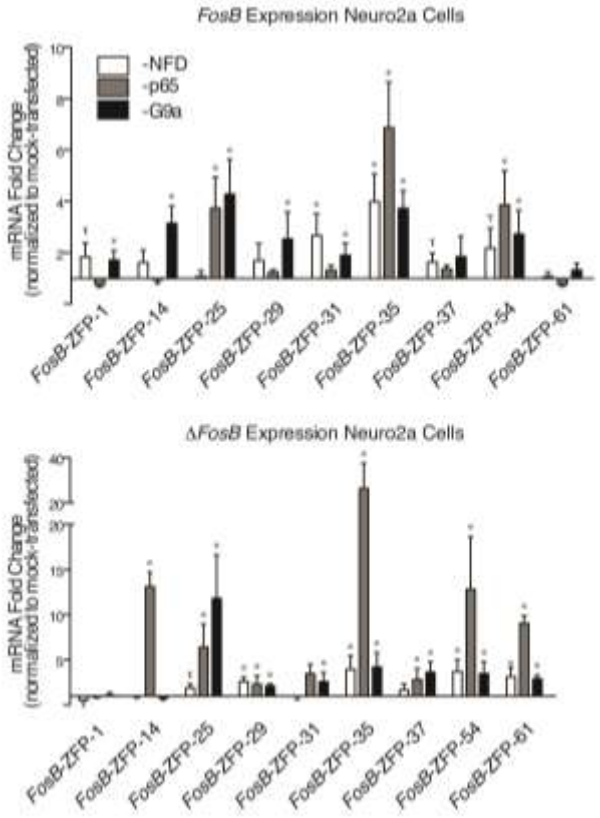
Supplementary Table 3. Extended statistics.

FIGURE 1d	t	df	Sig. (2-tailed)	n =	GFP n =
FOSB_fosb_zfp25_p65	0.178	8	0.863	5	5
dFOSB_fosb_zfp25_p65	0.541	8	0.603	5	5
FOSB_fosb_zfp25_G9a	-0.865	7	0.415	4	5
dFOSB_fosb_zfp25_G9a	-0.275	7	0.791	4	5
FOSB_fosb_zfp35_p65	2.376	7	0.049	4	5
dFOSB_fosb_zfp35_p65	3.828	7	0.006	4	5
FOSB_fosb_zfp35_G9a	-4.842	6	0.003	5	3
dFOSB_fosb_zfp35_G9a	-3.38	6	0.015	5	3
FOSB_fosb_zfp35_NFD	0.312	8	0.763	5	5
dFOSB_fosb_zfp35_NFD	0.96	8	0.365	5	5
FOSB_fosb_zfp61_p65	0.444	7	0.670	4	5
dFOSB_fosb_zfp61_p65	2.097	7	0.074	4	5
FOSB_fosb_zfp61_G9a	-2.997	8	0.017	5	5
dFOSB_fosb_zfp61_G9a	-2.364	8	0.046	5	5
FOSB_fosb_zfp61_nfd	-2.404	7	0.047	4	5
dFOSB_fosb_zfp61_nfd	-2.176	7	0.066	4	5
FOSB_p65	0.151	7	0.884	5	4
dFOSB_p65	0.802	7	0.449	5	4
FOSB_klf4_zfp_p65	-0.479	8	0.645	5	5
dFOSB_klf4_zfp_p65	-0.193	8	0.852	5	5
FOSB_vegf_zfp_G9a	-0.248	7	0.811	5	4
dFOSB_vegf_zfp_G9a	0.224	7	0.829	5	4

FIGURE 2b					
GFP TO NFD	t	df	Sig. (2-tailed)	GFP n=	NFD n=
FosB	0.378	8	0.715	5	5
DFosB	-0.516	8	0.619	5	5
Ankrd52	1.492	8	0.174	5	5
Cacnb3	1.112	8	0.298	5	5
Ctbs	-0.949	7	0.374	4	5
D15Wsu169e	-0.174	8	0.866	5	5
Dip2b	-0.615	8	0.555	5	5
Fsd1l	0.523	7	0.617	4	5
Gnai1	0.038	8	0.971	5	5
Hcfc2	-0.516	8	0.619	5	5
Hic2	-0.426	7	0.683	4	5
Kcnt1	-0.772	8	0.462	5	5
Prrt1	-0.451	8	0.664	5	5
Prrt2	-0.309	8	0.765	5	5
Pth1r	-0.583	8	0.576	5	5
Ptprn2	-0.507	8	0.626	5	5
Pygo1	-0.157	8	0.879	5	5
Rps6ka5	-0.461	8	0.657	5	5
Sardh	-0.325	8	0.754	5	5
Slc2a7	-0.272	8	0.793	5	5
Syncrip	-0.289	8	0.78	5	5
Tlr12	0.601	8	0.565	5	5
Tmem132e	1.261	7	0.248	4	5
Unc5a	-0.387	7	0.71	4	5

GFP TO p65	t	df	Sig. (2-tailed)	GFP n=	p65 n=
FosB	-4.731	7	0.002	5	4
DFosB	-4.83	7	0.002	5	4
Ankrd52	-1.648	7	0.143	5	4
Cacnb3	-0.215	7	0.836	5	4
Ctbs	0.878	6	0.414	4	4
D15Wsu169e	-0.572	7	0.585	5	4
Dip2b	-0.704	7	0.504	5	4
Fsd1l	-0.446	6	0.671	4	4
Gnai1	0.13	7	0.901	5	4
Hcfc2	-0.674	7	0.522	5	4
Hic2	0.019	6	0.985	4	4
Kcnt1	-0.504	7	0.63	5	4
Prrt1	0.06	7	0.954	5	4
Prrt2	0.007	7	0.995	5	4
Pth1r	-0.06	7	0.954	5	4
Ptprn2	0.006	7	0.996	5	4
Pygo1	0.011	7	0.991	5	4
Rps6ka5	-0.64	7	0.543	5	4
Sardh	0.093	7	0.928	5	4
Slc2a7	-0.208	7	0.841	5	4
Syncrip	-0.799	7	0.45	5	4
Tlr12	0.085	7	0.934	5	4
Tmem132e	-0.217	6	0.835	4	4
Unc5a	-0.435	6	0.679	4	4
GFP to G9a	**t**	**df**	**Sig. (2-tailed)**	**GFP n=**	**G9a n=**
FosB	2.399	8	0.043	5	5
DFosB	2.876	8	0.021	5	5
Ankrd52	1.097	8	0.304	5	5
Cacnb3	0.822	8	0.435	5	5
Ctbs	-0.541	7	0.605	4	5
D15Wsu169e	0.323	8	0.755	5	5
Dip2b	0.701	8	0.503	5	5
Fsd1l	-0.132	7	0.899	4	5
Gnai1	-0.166	8	0.873	5	5
Hcfc2	0.579	8	0.578	5	5
Hic2	0.095	7	0.927	4	5
Kcnt1	-0.386	8	0.71	5	5
Prrt1	-1.698	8	0.128	5	5
Prrt2	-0.332	8	0.748	5	5
Pth1r	0.053	8	0.959	5	5
Ptprn2	0.246	8	0.812	5	5
Pygo1	0.389	8	0.707	5	5
Rps6ka5	0.434	8	0.676	5	5
Sardh	-0.198	8	0.848	5	5
Slc2a7	0.522	8	0.616	5	5
Syncrip	-1.05	8	0.325	5	5
Tlr12	0.194	8	0.851	5	5
Tmem132e	-0.748	7	0.479	4	5
Unc5a	0.561	7	0.592	4	5

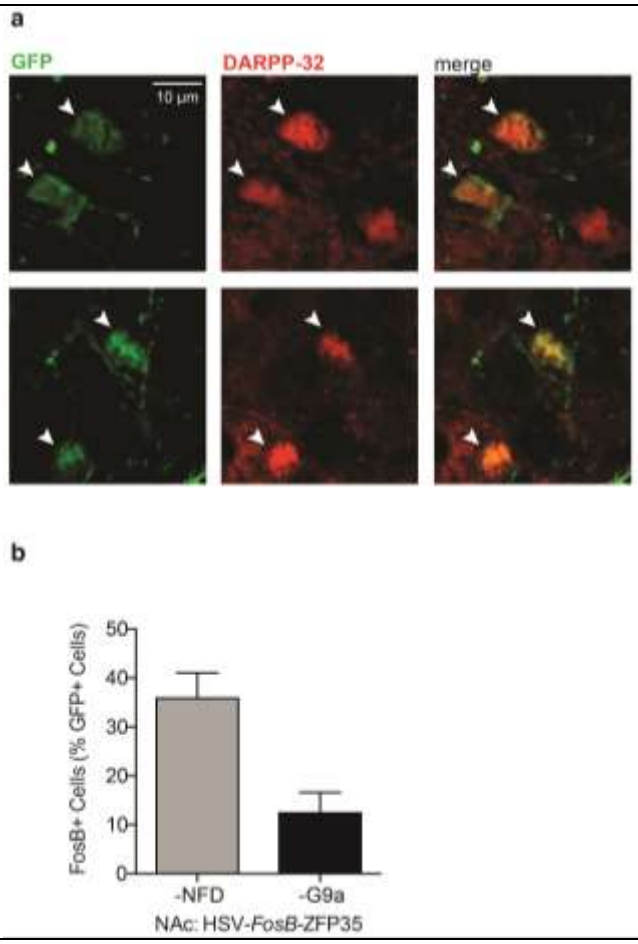
SUPP FIGURE 1					
FosB	**t**	**df**	**Sig. (2-tailed)**	**n =**	**mock n =**
FosB_1_NFD	1.868	17	0.079	6	13
FosB_1_p65	-0.666	14	0.516	3	13
FosB_1_G9a	1.958	17	0.067	6	13
FosB_14_NFD	1.36	20	0.189	9	13
FosB_14_p65	-0.192	17	0.85	6	13
FosB_14_G9a	4.142	17	0.001	6	13
FosB_25_NFD	0.273	23	0.787	12	13
FosB_25_p65	2.705	20	0.014	9	13
FosB_25_G9a	2.897	20	0.009	9	13
FosB_29_NFD	1.186	20	0.25	9	13
FosB_29_p65	0.858	17	0.403	6	13
FosB_29_G9a	2.082	17	0.053	6	13
FosB_31_NFD	2.251	20	0.036	9	13
FosB_31_p65	1.106	17	0.284	6	13
FosB_31_G9a	2.218	17	0.04	6	13
FosB_35_NFD	2.975	22	0.007	11	13
FosB_35_p65	4.208	19	0	8	13
FosB_35_G9a	4.716	19	0	8	13
FosB_37_NFD	1.807	20	0.086	9	13
FosB_37_p65	1.317	17	0.205	6	13
FosB_37_G9a	1.459	17	0.163	6	13
FosB_54_NFD	1.742	20	0.097	9	13
FosB_54_p65	3.132	17	0.006	6	13
FosB_54_G9a	2.595	17	0.019	6	13
FosB_61_NFD	0.231	17	0.82	6	13
FosB_61_p65	-0.616	14	0.548	3	13
FosB_61_G9a	1.031	17	0.317	6	13
DFosB	**t**	**df**	**Sig. (2-tailed)**	**n =**	**mock n =**
FosB_1_NFD	-2.337	17	0.032	6	13
FosB_1_p65	-0.281	14	0.783	3	13
FosB_1_G9a	0.353	17	0.728	6	13
FosB_14_NFD	0	20	1	9	13
FosB_14_p65	11.495	17	0.00	6	13
FosB_14_G9a	-0.85	17	0.407	6	13
FosB_25_NFD	1.77	23	0.090	12	13
FosB_25_p65	2.569	20	0.018	9	13
FosB_25_G9a	2.72	20	0.013	9	13
FosB_29_NFD	3.658	20	0.002	9	13
FosB_29_p65	1.961	17	0.067	6	13
FosB_29_G9a	4.553	17	0.000	6	13
FosB_31_NFD	-0.107	17	0.916	6	13
FosB_31_p65	2.833	20	0.010	9	13
FosB_31_G9a	2.278	17	0.036	6	13
FosB_35_NFD	2.13	22	0.045	11	13
FosB_35_p65	2.904	19	0.009	8	13
FosB_35_G9a	2.584	19	0.018	8	13
FosB_37_NFD	1.223	20	0.236	9	13
FosB_37_p65	2.241	17	0.039	6	13
FosB_37_G9a	3.375	17	0.004	6	13
FosB_54_NFD	2.46	20	0.023	9	13
FosB_54_p65	3.089	17	0.007	6	13
FosB_54_G9a	2.791	17	0.013	6	13
FosB_61_NFD	3.085	17	0.007	6	13
FosB_61_p65	18.966	14	0.00	3	13
FosB_61_G9a	5.545	17	0.00	6	13



Supplementary Figure 1

A suite of *FosB*-ZFPs bidirectionally regulate *FosB* expression in vitro.

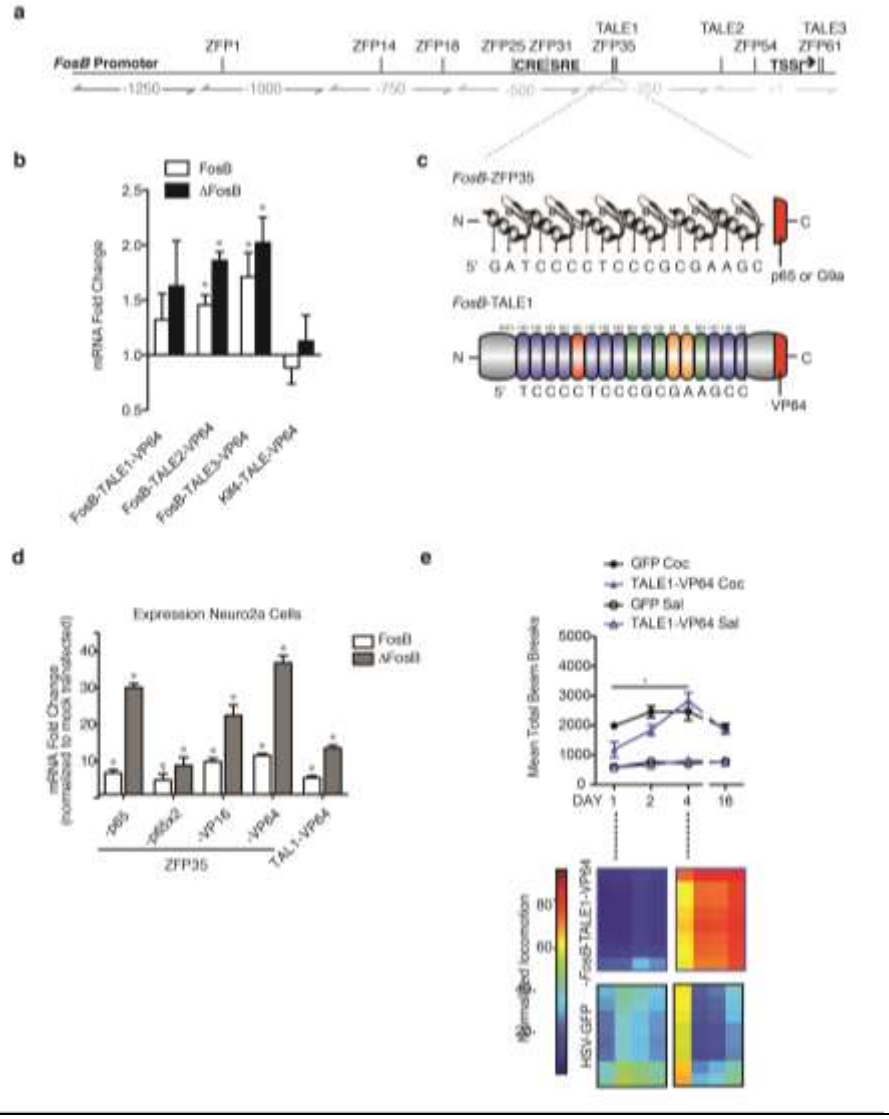
(a) *FosB*/Δ*FosB* mRNA was significantly induced by several *FosB*-ZFP-p65 and -G9a constructs expressed in N2a cells and harvested after 48 hours. *FosB*-ZFP-NFD constructs activated gene expression to a lesser extent or not at all. Data are normalized to mock transfected cells. Complete statistics are available in Supplementary Table 3. Student's unpaired t-test: $^{\square}P<0.05$, $^{\square}P<0.10$. Data are presented as mean ± s.e.m.



Supplementary Figure 2

HSV-ZFPs specifically infect neurons in NAc and inhibit basal *FosB* expression.

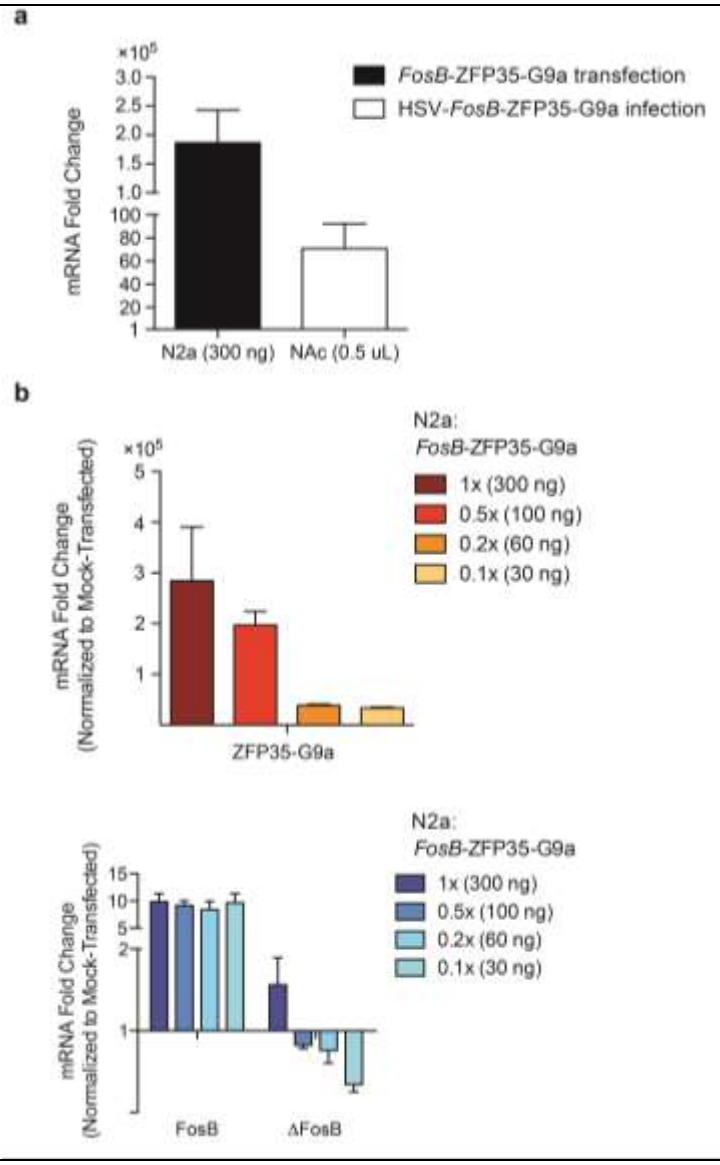
(a) HSV-GFP specifically infects DARPP-32 positive neurons in the NAc. White arrows indicate double labeled cells. **(b)** NAc injection of HSV-*FosB*-ZFP35-G9a repressed expression of FosB/ΔFosB in HSV infected (GFP+) cells [t_{13}=3.55, **P*=0.033; n=7, 8] compared to HSV-*FosB*-ZFP35-G9a (72 hours post HSV injection). Data are presented as mean ± s.e.m.



Supplementary Figure 3

Regulation of *FosB* expression and reward behavior by *FosB*-TALEs and a suite of additional catalytic domains fused to *FosB*-ZFP35.

(a) Locations of *FosB*-ZFP and -TALE binding relative to the *FosB* TSS. The location of functional SRF and CREB sites are shown. **(b)** *FosB/ΔFosB* mRNA expression in the NAc was significantly induced by HSV-*FosB*-TALE2-VP64 [FosB: t_8=3.03, **P*=0.016; ΔFosB: t_8=6.40, **P*=0.000; n=5], and -*FosB*-TALE3-VP64 [FosB: t_8=2.79, **P*=0.023; ΔFosB: t_8=4.01, **P*=0.004; n=5] compared to control virus. **(c)** The binding sites of the 6-finger ZFP35 and 17-RVD (repeat variable diresidue) TALE1 recognize the *FosB* promoter at overlapping sites approximately 250 bp upstream from the *FosB* TSS. **(d)** *FosB*-ZFP35-p65 [FosB: t_4=5.91, **P*=0.004; ΔFosB: t_4=26.11, **P*=0.000; n=3], -p65x2 [FosB: t_4=2.30, **P*=0.000; ΔFosB: t_4=3.46, **P*=0.026 ; n=3], -VP16 [FosB: t_4=9.04, **P*=0.001; ΔFosB: t_4=7.45, **P*=0.002 ; n=3], and -VP64 [FosB: t_4=19.40, **P*=0.001; ΔFosB: t_4=7.45, **P*=0.001; n=3] and *FosB*-TALE1-VP64 [FosB: t_4=6.80, **P*=0.002; ΔFosB: t_4=15.17, **P*=0.000; n=3] activate FosB/ΔFosB mRNA levels when expressed in Neuro2a cells and harvested after 48 hours. Data are normalized to mock transfected cells. **(e)** HSV-*FosB*-TALE1-VP64 in NAc sensitizes cocaine-induced hyperactivity over time. There is a significant interaction between day, cocaine treatment, and virus [F(3,32)=3.42, **P*=0.029]. TALE1-VP64 sensitizes the effect of cocaine on locomotor activity [main effect of day among TALE1-VP64 [F(3,35)=9.92, **P*=0.000, n=10], but not GFP control [F(3,36)=2.05, P=0.126, n=9]. HSV-GFP data are the same as in Fig. 4d-e. Heat maps show representative locomotor data within the chamber for mice over the course of repeated cocaine exposure. Data are presented as mean ± s.e.m.



Supplementary Figure 4

Differential regulation by *FosB*-ZFPs in vitro and in vivo.

(a) Expression of *FosB*-ZFP35-G9a differs between N2a cells and NAc [t_6=4.50, **P*=0.004; n=3,5]. **(b)** Titration of the amount of *FosB*-ZFP35-G9a expression in N2a cells leads to a reduction in the amount of induced mRNA expression of ΔFosB but not FosB. Using a 2-tailed Pearson correlation, we found a significant correlation between μg of transfected DNA and mRNA fold change of ΔFosB [R_{12}=0.83, **P*=0.001] but not FosB [R_{12}=.66, *P*=0.665]. Data are presented as mean ± s.e.m.

Supplementary Figure 5

Full blots of experiment shown in Figure 1e.