Supplemental Methods.

MeDIP Assay. Because real time PCR threshold cycle (Ct) values for the background (control immunoprecipitation with mouse serum) MeDIP-qPCR measurements tend to be greater than 37 (which cannot be reproducibly measured) we used MeDIP DNA fractions' Ct value normalized to the Input DNA to compare experimental samples.

For MeDIP followed by real-time PCR assay the calculations were performed using following procedure:

1. Each MeDIP DNA fractions' Ct value was normalized to the Input DNA fraction Ct value for the same qPCR Assay (ΔCt) to account for sample preparation differences using:

   ΔCt [normalized MeDIP] = (Ct [MeDIP] - (Ct [Input] - Log2 (Input Dilution Factor))

   Normalized MeDIP Ct values were then averaged for replicate samples.

2. % Input for each MeDIP fraction (linear conversion of the normalized MeDIP ΔCt) was calculated using the following formula:
   % Input = 2 (-ΔCt [normalized ChIP])

3. Finally, the difference between the normalized experimental sample (S2) and the control sample (S1) MeDIP fraction Ct values (ΔΔCt) was determined using
   ΔΔCt [S2-S1] = ΔCt [S2:normalized ChIP] - ΔCt [S1:normalized ChIP]

4. Differential Occupancy Fold Change (linear conversion of the second ΔΔCt to yield a fold change in site occupancy) was calculated:
   Fold Change in Occupancy = 2 (-ΔΔCt [S2-S1])

Brain Dissections. Specific regions were identified and macrodissected using their approximate mouse stereotaxic coordinates according to Mouse Brain Atlas (NAc, bregma +1.10mm; PFC ~ +2 to Bregma at posterior surface; VTA, bregma -3.64mm). Briefly, brains were positioned in a 1mm mouse brain matrix (ASI Instruments, Warren, MI, USA) abutting a razor blade placed in the first slot. The slot nearest the boundary of medulla was the first landmark. Next, double-edged razor blades were placed in slots one and two mm anterior to that boundary. Next, razor blades were placed in slots one, two and three mm posterior to blade at anterior surface. The anterior set of three blades was removed from the block. Proceeding anterior to posterior, the first section was discarded. From second section (~ +2 to Bregma at posterior surface), cortex was cut from dorsal half of section. From third section (~ +1 to Bregma at posterior surface), the nucleus accumbens was removed. Hypothalamus was dissected from the section in between blade 3 and 4. The slab was placed flat and the cuts were placed on either side of the optic chiasm and dorsal to the third ventricle. The posterior set of blades was removed from the block and VTA/SN region was dissected.

Table 1. List of TaqMan probes (ABI, Foster City, CA, USA) used for gene expression assays.

Gene Symbol	***Gene Name***	***RefSeq mRNA***	***TaqMan Assay ID***
Th	tyrosine hydroxylase	NM_009377.1	Mm00447557_m1
Slc6a3	dopamine reuptake transporter	NM_010020.3	Mm00438388_m1
Drd1a	dopamine receptor D1A	NM_010076.1	Mm02620146_s1
Drd2	dopamine receptor 2	NM_010077.1	Mm00438541_m1
Ppp1r1b	dopamine- and cyclic AMP-regulated phosphoprotein	NM_144828.1	Mm00454892_m1
Comt	catechol-O-methyltransferase	NM_007744.1	Mm00514377_m1
Pomc	pro-opiomelanocortin-alpha	NM_008895.3	Mm00435874_m1
Pdyn	prodynorphin	NM_018863.3	Mm00457573_m1
Penk	preproenkephalin	NM_001002927.2	Mm01212875_m1
Oprk1	opioid receptor, kappa 1	NM_011011.1	Mm01230885_m1
Oprm1	opioid receptor, mu 1	NM_001039652.1	Mm01188089_m1
Oprd1	opioid receptor, delta 1	NM_013622.3	Mm01180757_m1
Actb	B-Actin	NM_007393.1	4352933E
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase	NM_008084.2	4352932E

Table 2. List of primers (SABiosciences, Frederick, MD, USA) used for MeDIP analysis.

Gene Symbol	***Gene Name***	***Chromosome RefSeq #***	***TSS Position***	***Assay Position***	***SABiosciences ID***
Th	Tyrosine hydroxylase	NC_000073.4	142709356	-378	GPM052099(-)01A
Slc6a3	Dopamine reuptake transporter	NC_000079.4	74002749	-398	GPM030478(-)01A
Penk1	Preproenkephalin	NC_000070.4	4065592	-248	GPM048569(-)01A
Oprm1	Opioid receptor, mu 1	NC_000076.4	3557732	-142	GPM041465(-)01A
Gapdh	Glyceraldehyde 3-phosphate dehydrogenase	NC_000072.4	125131222	-399	GPM050651(-)01A
IGX1A Neg Ctrl	900 kb ORF-free intergenic region	NC_000072.4	N/A	9746275	GPM00001C(-)01A