Supplemental Tables/Figures:

Supplemental Table 1: Demographic Characteristics of Cohort I from Wayne State University

	Control	Heroin
N	7	8
Sex	7 M	1 F/7M
Age	46.14 ± 7.58	41.13 ± 10.13
Race	3 B/ 4 W	4 B/4 W
Brain pH	6.39 ± 0.15	6.43 ± 0.1
PMI	<24 hours	<24 hours
Toxicology ETOH present (n)	+ (4)	+ (3)
Blood EtOH levels (g/L)	0.08 ± 0.09	0.05 ± 0.08
Blood morphine levels (g/L)	n.d.	0.348 ± 0.52
Cause of Death	ASCVD(n=4), GSW (n=1), stab wound (n=1), drowning (n=1)	Heroin abuse (n=7), cardiomyopathy (n=1)

B= Black, W= White, F=female, M=male, n.d. = not detectable, ASCVD= atherosclerotic cardiovascular disease, GSW= gun shot wound.

Supplemental Table 2: Characteristics and Demographic Variables of Cohort II- Hungarian Heroin Population

	Control	Heroin
N	18	28
Sex	3 F/ 15 M	5 F/23 M
Age	35.11 ± 12.37	27.07 ± 5.26
Race	European Caucasian	European Caucasian
Brain pH	6.73 ± 0.21	6.56 ± 0.21
PMI	<24	<24
Toxicology ETOH present (n)	+ (1)	+ (3)
Blood EtOH (g/L)	0.07 ± 0.20	0.16 ± 0.49
Blood Morphine (g/L)	n.d.	0.337 ± 0.44
Cause of Death	ASCVD (14) Electric Shock (1) Viral infection (2) Pulmonary Embolus (2)	Heroin intoxication/overdose

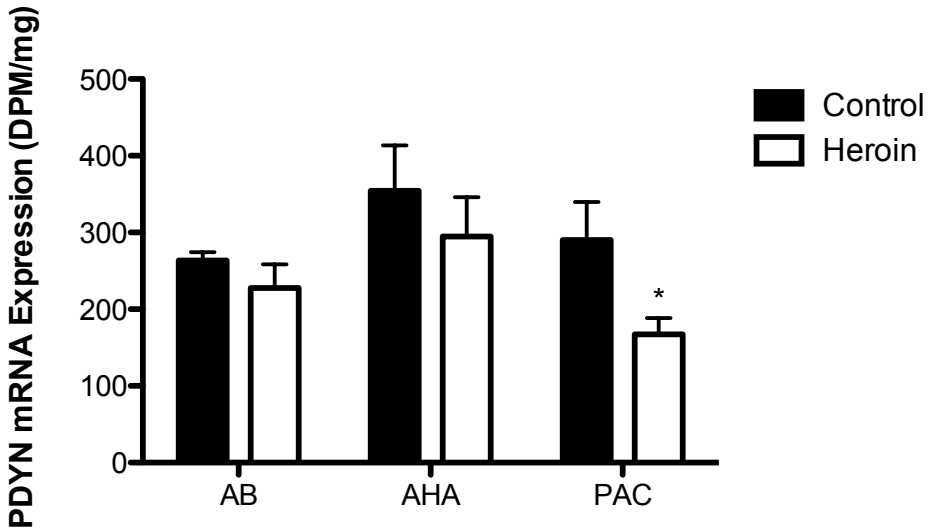
F=female, M=male, n.d. = not detectable, ASCVD= atherosclerotic cardiovascular disease.

Supplemental Table 3: Demographic Characteristics of the Major Depressive Population

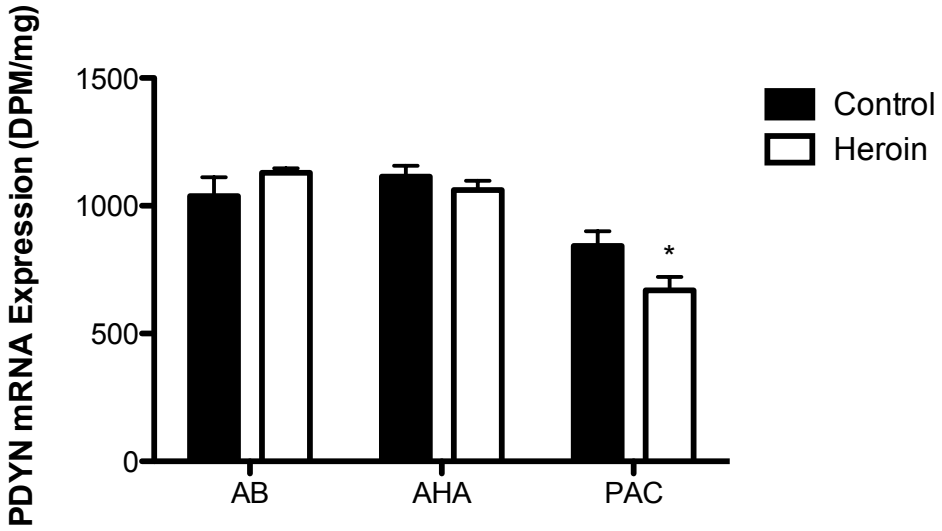
	Control	Major Depressive
N	10	14
Sex	3F/7M	6 F/8M
Age	33.10 ± 9.90	36.20 ± 12.90
Race	European Caucasian	European Caucasian
Brain pH	6.82 ± 0.10	6.83 ± 0.08
PMI	< 24 hours	<24 hours
Manner of death	Cardiac Arrest	Suicide by asphyxiation

F=female, M=male.

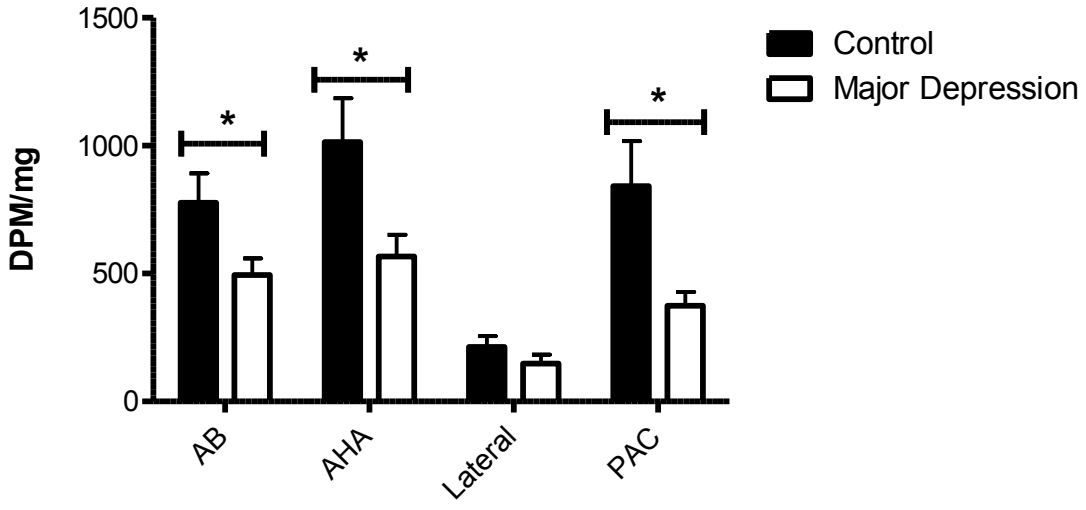
Supplemental Figure 1 - Cohort 1 Heroin abusers have reduced PDYN mRNA expression in the PAC. AB, accessory basal; AHA, amygdalohippocampal area; PAC, periamygdaloid cortex**.** *, $p<0.05$ according to ANOVA analysis. Values are expressed in DPM/mg (mean ± SEM) ($n_{Control}=7$ and $n_{Heroin}=8$).



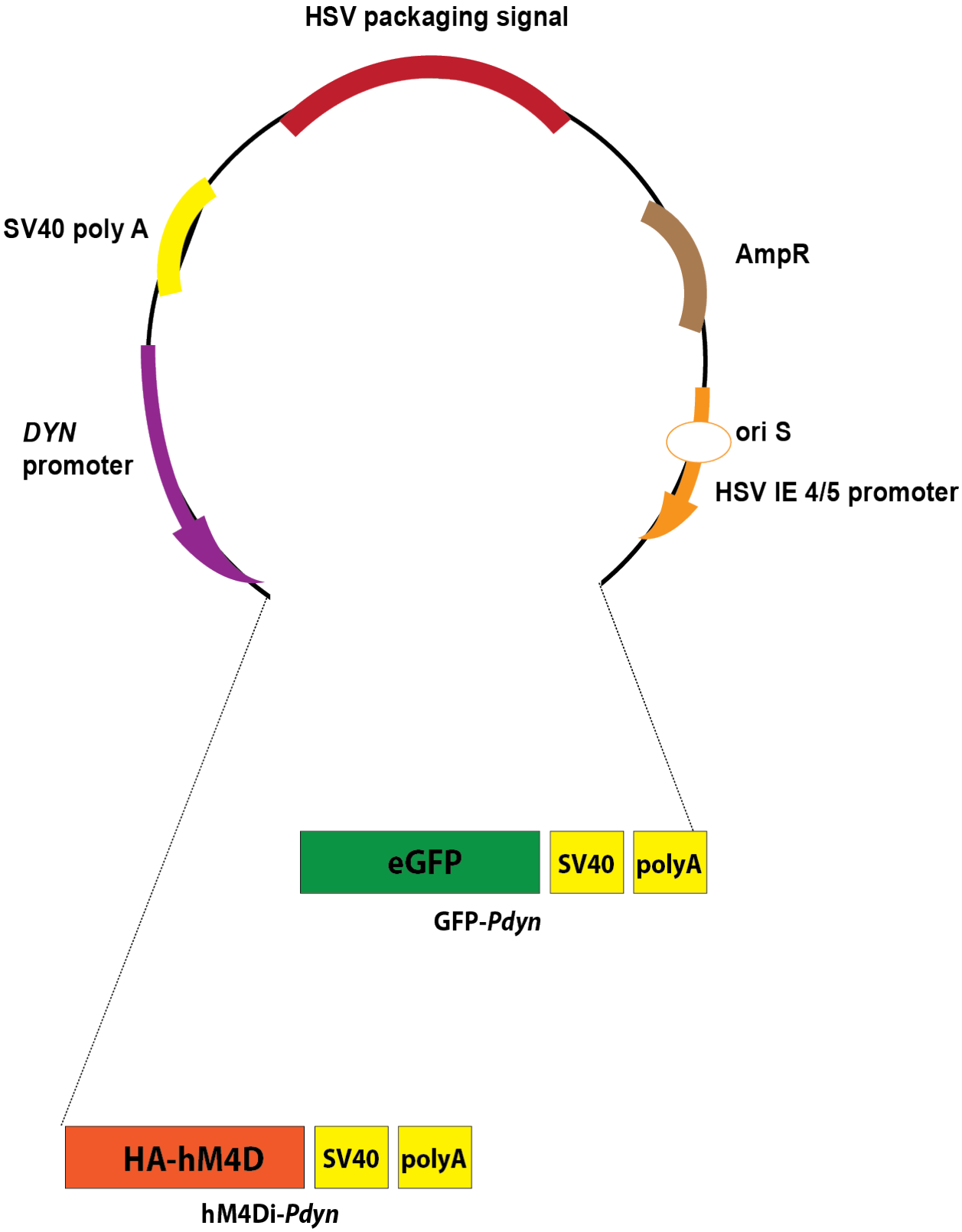
Supplemental Figure 2: Cohort II Heroin abusers have significant reduction of PDYN mRNA expression in the PAC. Values are expressed in DPM/mg (mean ± SEM). ($n_{Control}$=18 and n_{Heroin}=28) *, p<0.05 according to ANOVA or Welch's analysis.



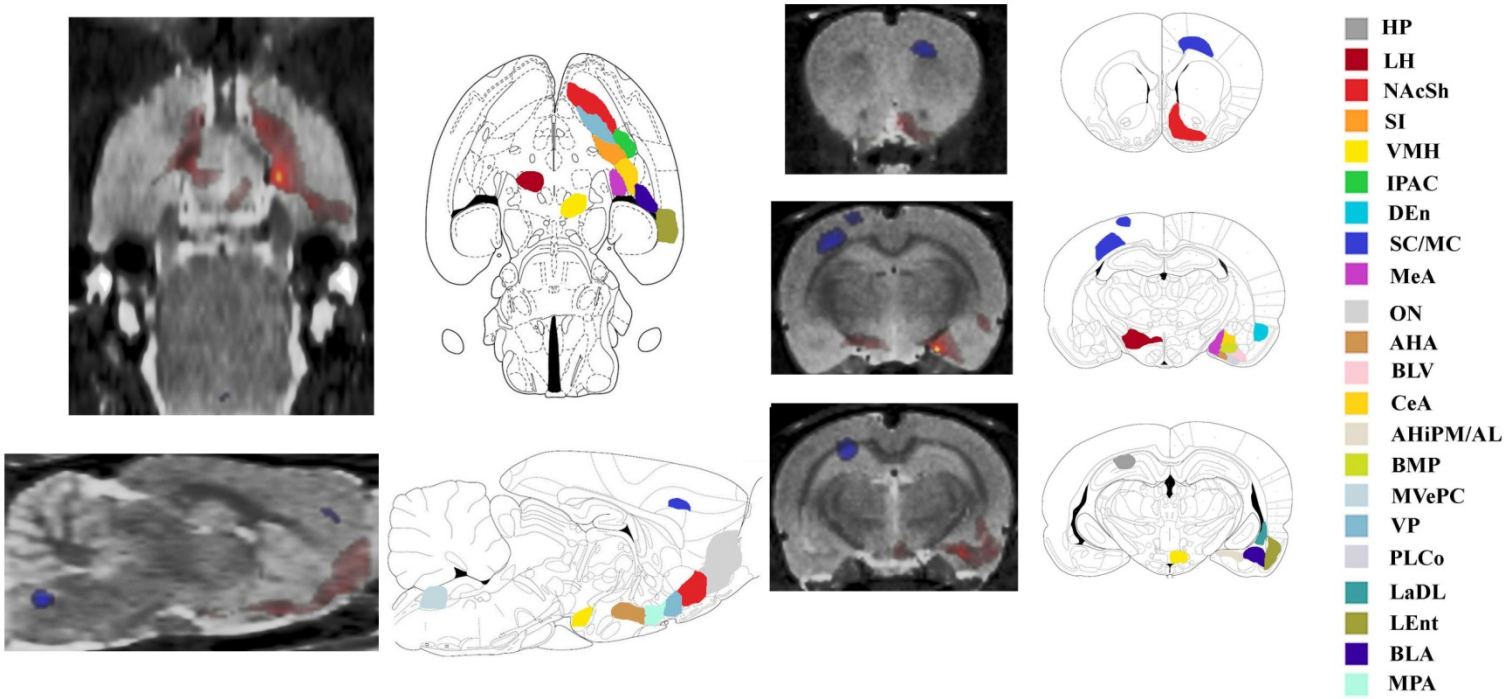
Supplemental Figure 3: MDD subjects have reduced PDYN mRNA expression in several amygdala nuclei. Values are expressed in DPM/mg as mean ± SEM ($n_{Control}$=10, n_{MDD}=14). *, p<0.05 according to an ANOVA/ Welch's analysis.



Supplemental Figure 4 – Map of viral vectors used in experiments



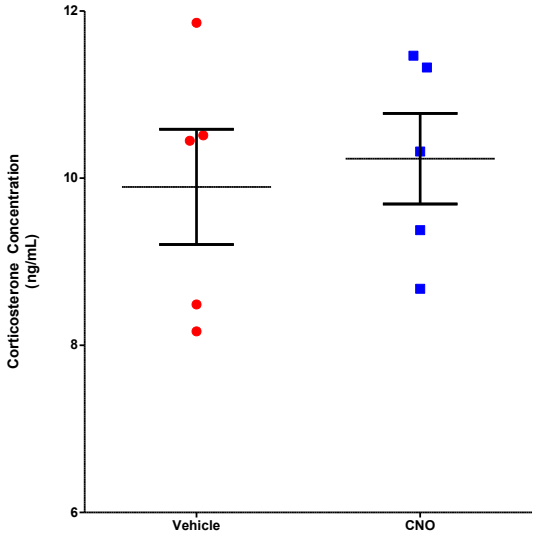
Supplemental Figure 5- Metabolic Mapping resulting from inhibitory hm4di-Pdyn infusion in the PAC using the DREAMM



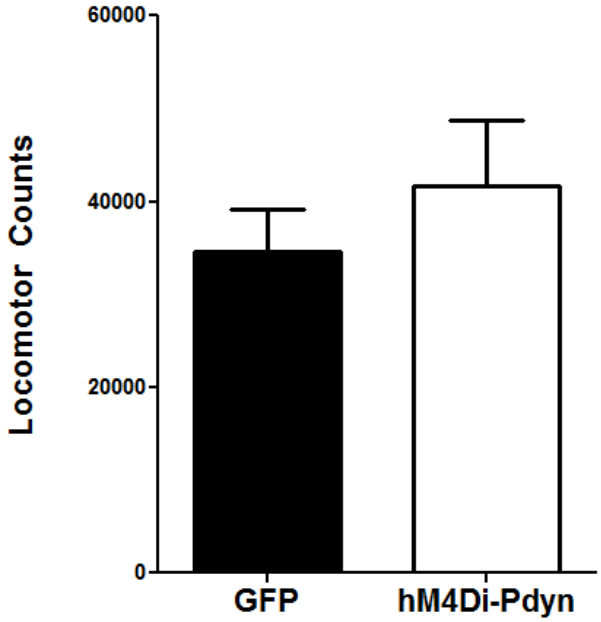
Abbreviations:

HP: Hippocampus
LH: Lateral Hypothalamus
NAcSh: Nucleus Accumbens shell
SI: substantia innominata
VMH: ventral medial hypothalamus
IPAC: interstitial nucleus of posterior limb of anterior commissure
DEn: dorsal endopiriform nucleus
SC/MC: sensory cortex/motor cortex
AHA: anterior hypothalamic area, anterior part
BLV: basolateral amygdala, ventral part
CeA: central amygdala
AHiPM/AL: amygdalaohippocampal area, posteriomedial, anterolateral
BMP: basomedial amygdala nucleus, posterior
MVePC: medival vestibular nucleus, parvicellular part
VP: Ventral pallidum
PLCO: posterolateral cortical nucleus
LaDL: lateral amygdaloid nucleus, dorsolateral part
Lent: lateral entorhinal cortex
BLA: Basolateral amygdala
MPA: medial preoptic area

Supplemental Figure 6: CNO administration has no effect on corticosterone levels in GFP-Pdyn animals (p=0.55, within subjects t-test)



Supplemental Figure 7: Total distance of rats in open field locomotor arena over a 60 minute time period



Supplemental Methods:

Analysis Used in DREADD-assisted metabolic mapping (DREAMM)

All scans were reconstructed using the *maximum a posteriori* (MAP) algorithm as previously described[8]. After reconstruction, images were spatially processed and normalized using the Pixel-wise Modeling software suite (PMOD) (PMOD Inc., Zurich, Switzerland) to a rat brain MRI template set to Paxinos & Watson stereotaxic coordinates. Constraining the reconstruction of the metabolic images into MRI-derived neuroanatomical templates, significantly improves both the sensitivity and anatomical specificity to detect alterations in FDG uptake using SPM[18,19]. As such, normalized scans were then analyzed using statistical parametric mapping (SPM) as previously described[20]. All SPM contrasts consisted of paired t-tests within each group (e.g. VEH>CNO, VEH<CNO) and were evaluated at the uncorrected p=0.05 level as per our *a priori* hypotheses. Only clusters of at least 100 contiguous voxels were reported. For quantitative analysis of regional SPM differences we modified an SPM region of interest (ROI) toolbox (MarsBaR v0.43) for use with our rat stereotaxic MRI atlas. For the CeA coordinates were: ML: 3.5→4.3, DV: 7.5→8.5, AP: -1.6→-2. For the BNST: ML: 0.8→1.3, DV: 6.8→7.2, AP: -0.8→-1.1. For the NAc Shell: ML: -0.3→-0.7, DV: 7.4→7.9, AP: 1.5→1.8. For the MeA: ML: 2.4→3.2, DV: 8.4→9, AP: -1.6→-2. Stereotaxic coordinates were entered into MarsBaR for the brain areas of interests, which allowed the extraction of individual subject data for each stereotaxically-defined brain area. Each region of interest investigated represents a voxel, which is a 3-Dimensional construction of that area and the analyses done in this area refer to changes in voxel intensity.