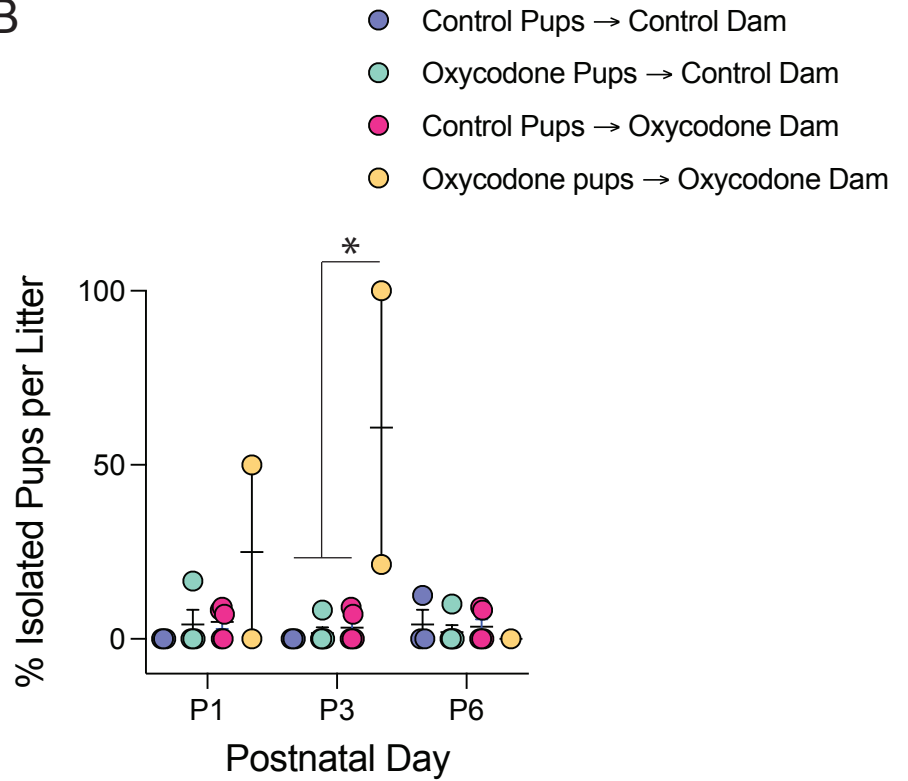
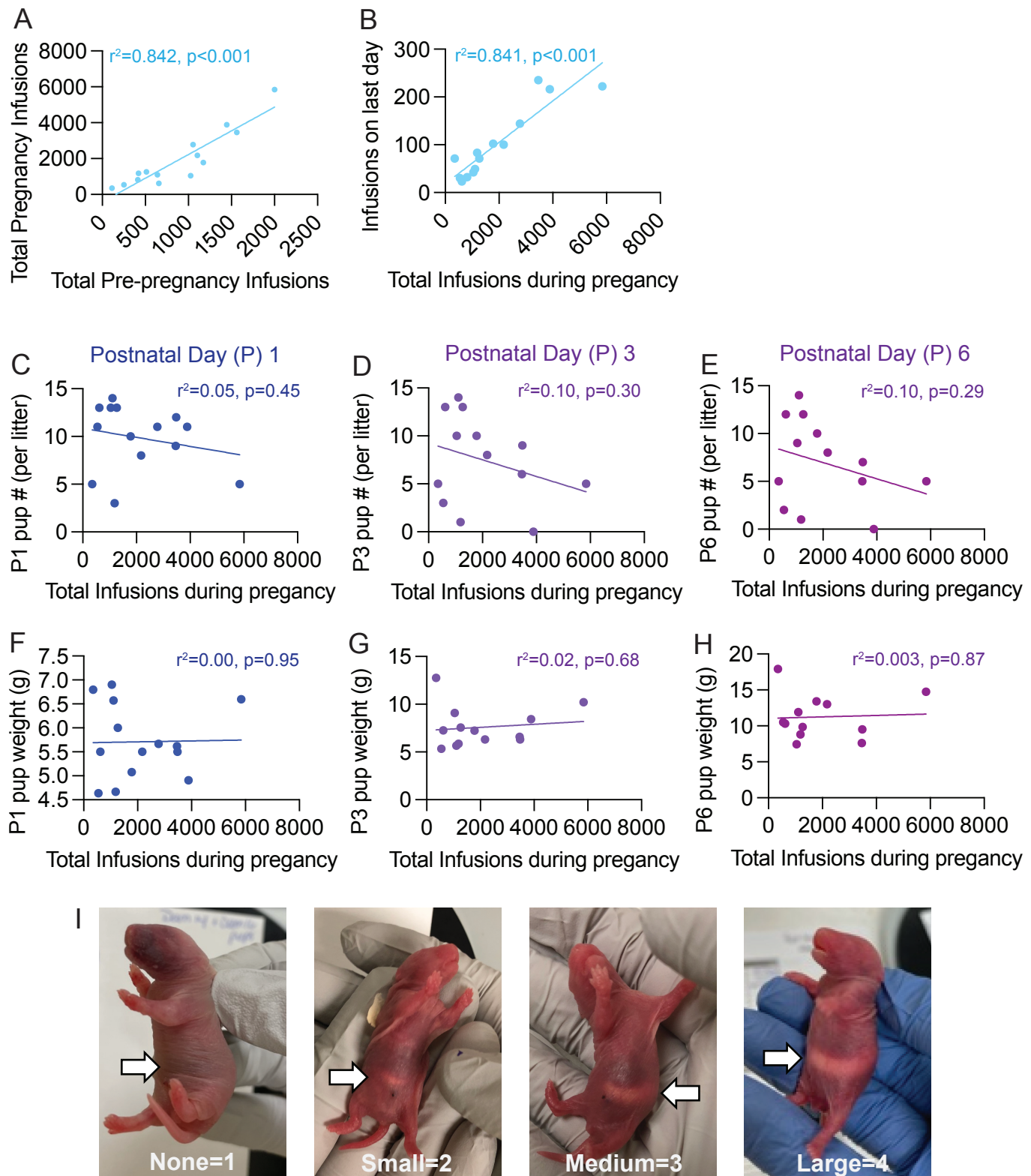
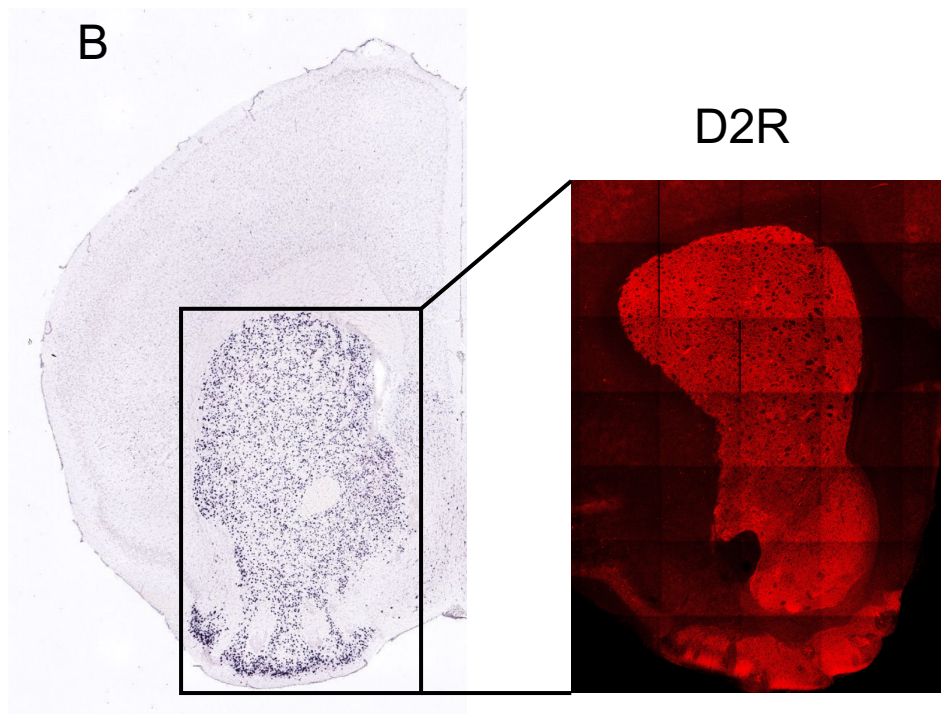
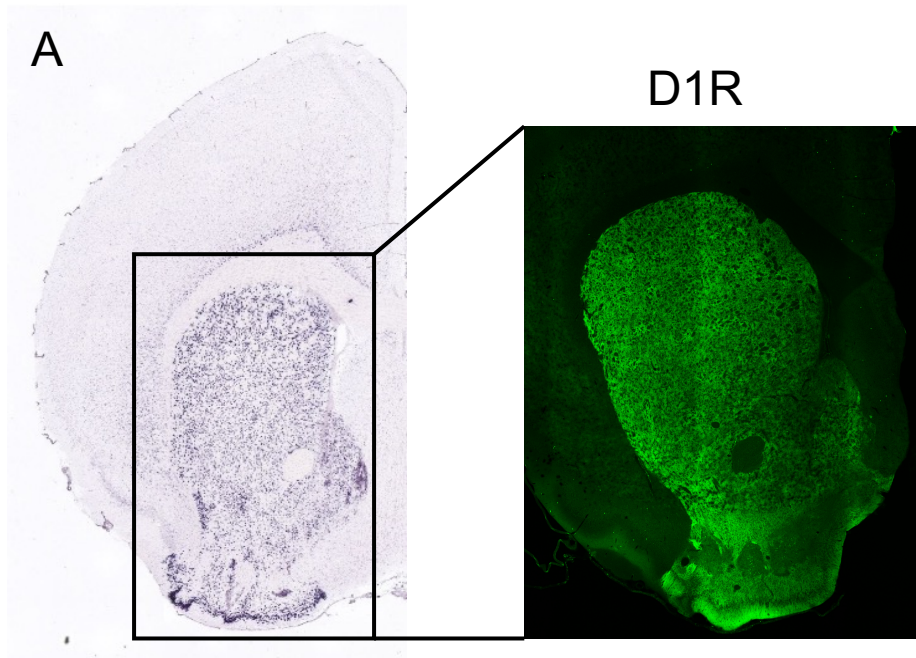


**A****B**

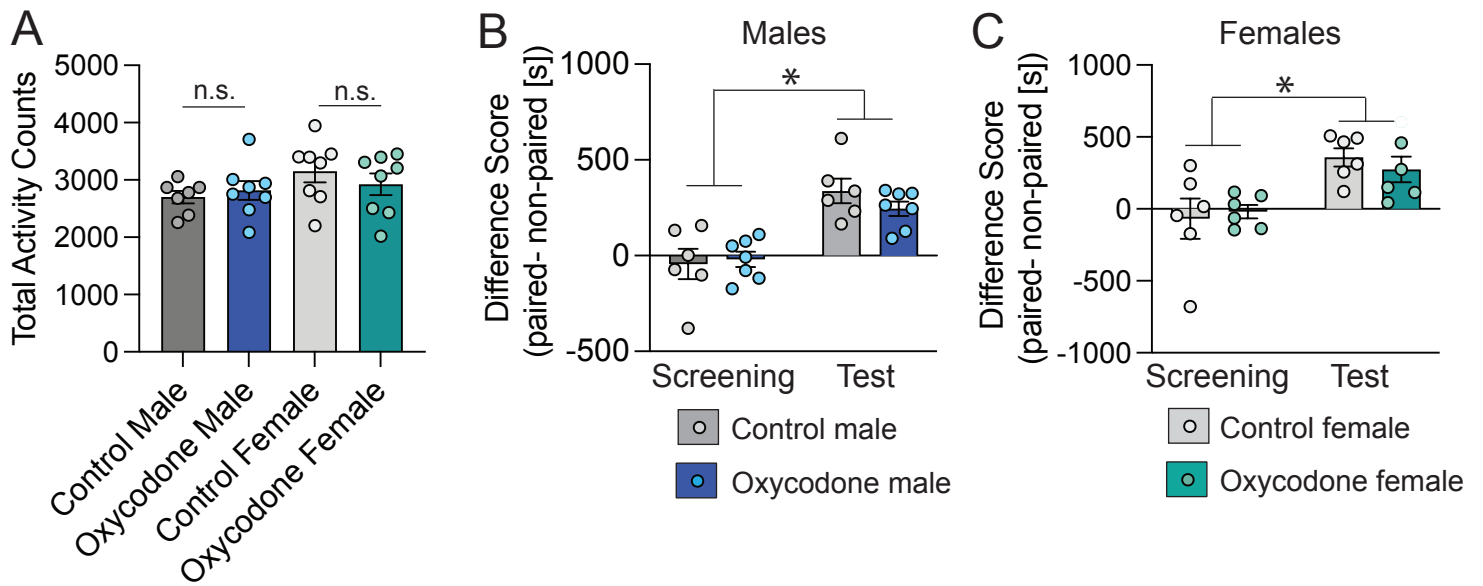
**Supplementary Figure 1. Maternal behavior in control and oxycodone-exposed dams raising control or oxycodone-exposed pups.** A cross-fostering procedure was used such that pups (either control or oxycodone-exposed in utero) were fostered to either a dam of the same treatment or a dam of the opposite treatment on postnatal day (P)0. Pup isolation was quantified by calculating the percentage of pups in each litter that were isolated from the nest at one time point at 9:00am each day. **A)** Representative image of cage with dam and isolated pup. **B)** A 3-way ANOVA (pup treatment x dam treatment x age) revealed significant main effects of all factors, as well as significant interaction effects (see Supplementary Table 1 for complete statistics). Bonferroni posthoc tests revealed that at P3, oxycodone pups reared by oxycodone dams were isolated from the nest at a higher % than all other groups (N=2-5 litters/condition). Data represented as mean +/- SEM, \*p<0.05.



**Supplementary Figure 2. Correlations between maternal oxycodone self-administration and neonatal outcomes and representative images of milk bands.** **A)** Pre-pregnancy and pregnancy infusions are highly correlated in dams self-administering oxycodone. **B)** The total number of infusions across pregnancy is highly correlated with the number of infusions dams self-administered on the last day of pregnancy before they gave birth. **C-E)** There are no significant correlations between dam infusions during pregnancy (total across pregnancy) and pup number (per litter) at postnatal day (P)1, P3, or P6. **F-H)** There are no significant correlations between dam infusions during pregnancy (total across pregnancy) and pup body weight (in grams, average per litter) at P1, P3, or P6. **I)** Representative images of milk band categorizations at P1.



**Supplementary Figure 3. Images depicting dopamine D1 and D2 receptor immunohistochemical staining in the striatum. A)** Image of *drd1* mRNA (dopamine D1 receptor) from the Allen Brain Atlas *Drd1*-RP\_Baylor\_102734 dataset compared with confocal image of D1R immunohistochemical staining in the striatum. **B)** Image of *drd2* mRNA (dopamine D2 receptor) from the Allen Brain Atlas *Drd2*-RP\_Baylor\_102735 dataset compared with confocal image of D2R immunohistochemical staining in the striatum. Images as tile-scanned 10x images taken on a Zeiss 880 Airyscan Confocal microscope.



**Supplementary Figure 4. Extended place conditioning data.** **A**) No significant differences were observed in total activity counts during the test session (2-way ANOVA (treatment x sex): treatment  $F_{(1,27)}=0.11$ ,  $p=0.75$ , sex  $F_{(1,27)}=2.66$ ,  $p=0.11$ , interaction  $F_{(1,27)}=1.02$ ,  $p=0.32$ ) as a measure of locomotor activity. **B**) In males, a main effect of session was observed such that males of both treatment conditions showed a greater preference for the drug-paired side of the chamber after conditioning (test) as compared to the screening (2-way ANOVA (treatment x session): treatment  $F_{(1,11)}=0.84$ ,  $p=0.38$ , session  $F_{(1,11)}=22.11$ ,  $p=0.0006$ , interaction  $F_{(1,11)}=0.72$ ,  $p=0.42$ ). **C**) In females, a main effect of session was observed such that females of both treatment conditions showed a greater preference for the drug-paired side of the chamber after conditioning (test) as compared to the screening (2-way ANOVA (treatment x session): treatment  $F_{(1,10)}=0.06$ ,  $p=0.81$ , session  $F_{(1,10)}=11.23$ ,  $p=0.007$ , interaction  $F_{(1,10)}=0.40$ ,  $p=0.54$ ). Data represented as mean  $\pm$  SEM, \* $p<0.05$ .

**Supplementary Table 1. Statistics for maternal care analysis.** 3-way ANOVA main and interaction effects of dam treatment [control vs. oxycodone], pup treatment [control vs. oxycodone], and age [postnatal day 1,3,6] on % of isolated pups per litter.

Comparison	F (df)	p value
Dam Treatment	$F_{(1, 31)} = 10.55$	p=0.003
Pup Treatment	$F_{(1, 31)} = 8.748$	p=0.006
Age	$F_{(2, 31)} = 3.354$	p=0.048
Dam Treatment x Pup Treatment	$F_{(1, 31)} = 7.175$	p=0.012
Dam Treatment x Age	$F_{(2, 31)} = 4.517$	p=0.019
Pup Treatment x Age	$F_{(2, 31)} = 4.449$	p=0.020
Dam Treatment x Pup Treatment x Age	$F_{(2, 31)} = 3.782$	p=0.034

**Supplementary Table 2.** Correlations between maternal oxycodone infusions during pregnancy and male offspring brain and behavioral endpoints (in oxycodone group only). Maternal infusions are the sum of infusions during pregnancy. PC: Place conditioning (Difference between seconds spend in drug-paired and un-paired sides). P: postnatal day.

Comparison	r <sup>2</sup> value	p value
Maternal infusions vs. P20 male D1R density	r <sup>2</sup> =0.11	p=0.52
Maternal infusions vs. P30 male D1R density	r <sup>2</sup> =0.39	p=0.14
Maternal infusions vs. P55 male D1R density	r <sup>2</sup> =0.03	p=0.75
Maternal infusions vs. P30 male microglial engulfment	r <sup>2</sup> =0.11	p=0.47
Maternal infusions vs. PC: Test Day 1	r <sup>2</sup> =0.08	p=0.49
Maternal infusions vs. PC: Test Day 2 (Extinction 1)	r <sup>2</sup> =0.09	p=0.48
Maternal infusions vs. PC: Test Day 3 (Extinction 2)	r <sup>2</sup> =0.01	p=0.81