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Supplemental information

Cocaine disrupts action flexibility via glucocorticoid receptors

Michelle K. Sequeira, Kathryn M. Stachowicz, Esther H. Seo, Sophie T. Yount, and Shannon L. Gourley

Supplementary Materials

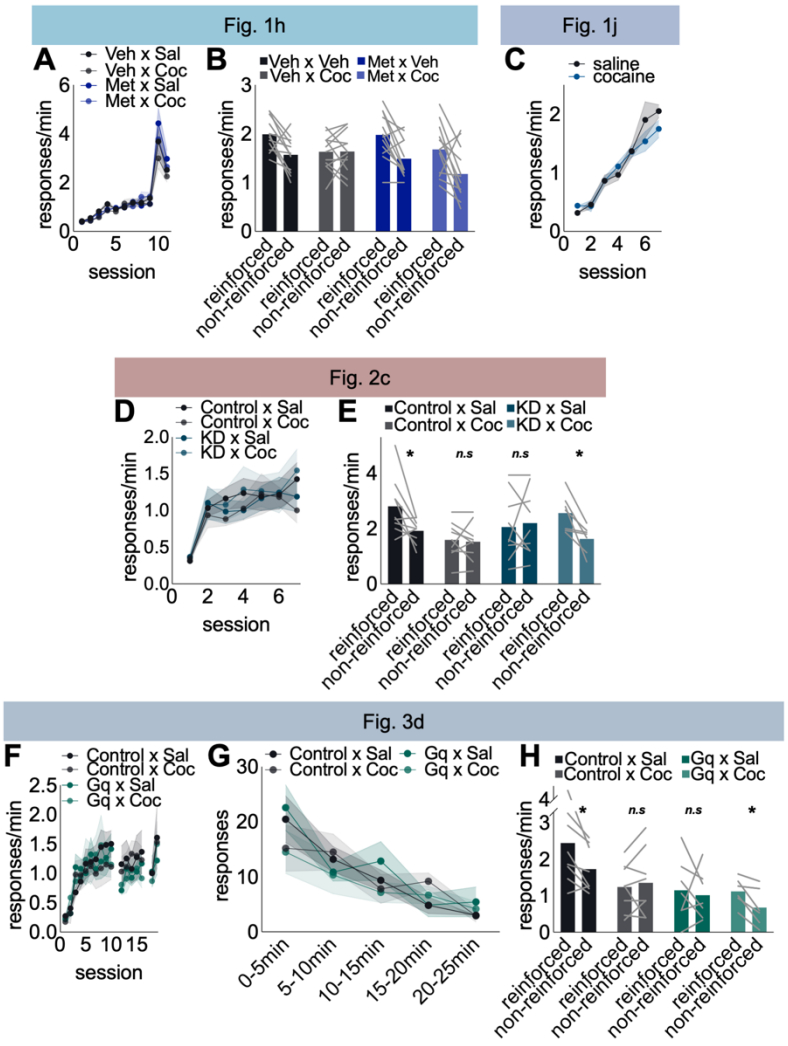

Fig. S1. Response rates, with correspondence to the main text indicated. (a) Mice were trained until criteria were met [main effect of session $F_{(8,37)}$=33.38, p<0.001; session x cocaine x metyrapone interaction $F_{(8,37)}$=2.00, p=0.07]. (b) Response rates at the choice test [aperture x metyrapone interaction $F_{(1,44)}$=3.86, p=0.056; aperture x cocaine x metyrapone interaction $F_{(1,44)}$=2.23, p=0.14]. (c) Mice were trained until criteria were met [main effect of session $F_{(6,9)}$=77.48, p<0.001; session x cocaine interaction $F_{(6,9)}$=0.60, p=0.72]. (d) Mice were trained until criteria were met [main effect of session $F_{(6,25)}$=13.65, p<0.001; session x cocaine x *Nr3c1* condition interaction $F_{(6,25)}$=1.12, p=0.35]. (e) Response rates at the choice test [aperture x cocaine x *Nr3c1* condition interaction $F_{(1,30)}$=5.42, p=0.03]. (f) Mice were trained until criteria were met (session 1-10). There were no differences between the groups [main effect of session $F_{(9,18)}$=4.09, p=0.005; session x cocaine x DREADD interaction $F_{(9,18)}$=0.78, p=0.64]. Mice were

placed back into the operant chambers to reignite responding after cocaine exposure and trained until criteria were met (session 11-15). There were no differences between the groups [main effect of session $F_{(4,23)}$=3.84, p=0.02; session x cocaine x DREADD interaction $F_{(4,23)}$=0.53, p=0.71]. Responding was once again reignited after the test for response flexibility (session 16-17). There were no differences between the groups [main effect of session $F_{(1,26)}$=11.62, p=0.002; session x cocaine x DREADD interaction $F_{(1,26)}$=0.85, p=0.37]. (g) All mice decreased responding across the non-reinforced session [main effect of time $F_{(4,120)}$=20.71, p<0.001; time x cocaine x DREADD interaction $F_{(4,120)}$=0.05, p=1.0]. (h) Response rates at the choice test [aperture x cocaine x DREADD interaction $F_{(1,25)}$=4.67, p=0.04]. *p<0.05. Means (±SEMs if indicated) + connected grey lines representing individual mice.

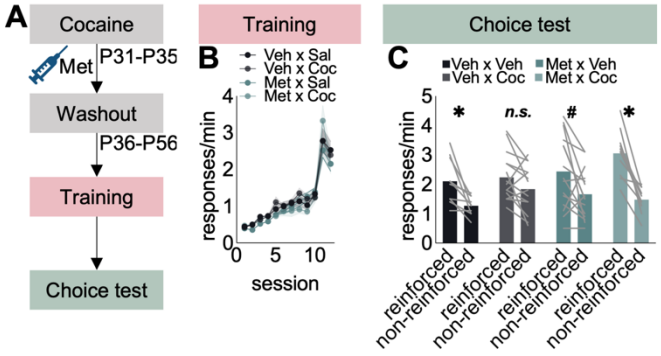

Fig. S2. Inhibiting CORT synthesis in mice exposed to cocaine in adolescence protects flexible behavior (associated with main text Fig. 1). (a) Experimental timeline. "P" refers to postnatal day. (b) Mice were trained to respond for food. Response rates in training [main effect of cocaine $F_{(1,46)}$=0.001, p=0.97; main effect of metyrapone $F_{(1,46)}$=2.33, p=0.13; main effect of session $F_{(9,414)}$=56.08, p<0.001, session x cocaine x metyrapone interaction effect $F_{(9,414)}$=2.95, p=0.002]. The Met x Sal group responded more during session 9 and the Coc x Sal group responded more during sessions 5 and 9. There were no differences between the groups by the end of training. (c) Adolescent cocaine exposure impaired action flexibility, but blocking CORT synthesis protected action flexibility in cocaine-exposed mice [aperture x cocaine x metyrapone interaction effect $F_{(1,46)}$=4.13, p=0.048]. n=10-15 mice/group, *p<0.05, #p=0.07. Bars and connected dots represent means (+SEMs if indicated), and gray lines represent individual mice.

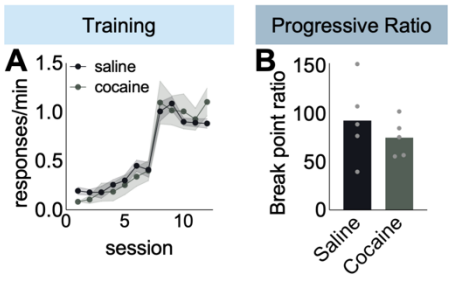

Fig. S3. Cocaine does not obviously impact motivation to respond for food pellets (associated with main text Fig. 1). (a) Mice were trained to respond for food at one aperture. Response rates in training [main effect of cocaine $F_{(1,8)}$=0.002, p=0.970; main effect of session $F_{(11,88)}$=54.08, p<0.001; session x cocaine interaction effect $F_{(11,88)}$=0.895, p=0.549]. (b) Following training, they were tested on a progressive ratio schedule of reinforcement. Break point ratios did not differ between groups [t_8=0.876, p=0.407]. n=5 mice/group. Bars and connected dots represent means (±SEMs if indicated), and unconnected dots represent individual mice.

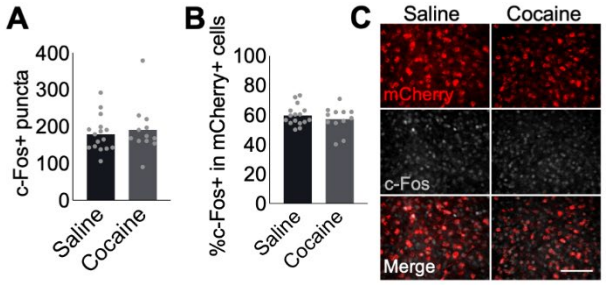

Fig. S4. Cocaine does not impact immediate-early gene levels in memory trace neurons at the choice test (associated with main text Fig. 3). (a) Cocaine does not impact c-Fos counts in the VLO [$t_{(26)}$=0.54, p=0.59], measured following the choice test. (b) c-Fos co-localization with mCherry-expressing cells (*i.e.*, memory trace cells) is also not impacted by cocaine [$t_{(26)}$=0.84, p=0.41]. (c) Representative mCherry and c-Fos. Scale bar=50μm. n=12-16 sections/group. Means + grey dots indicating individual data points.