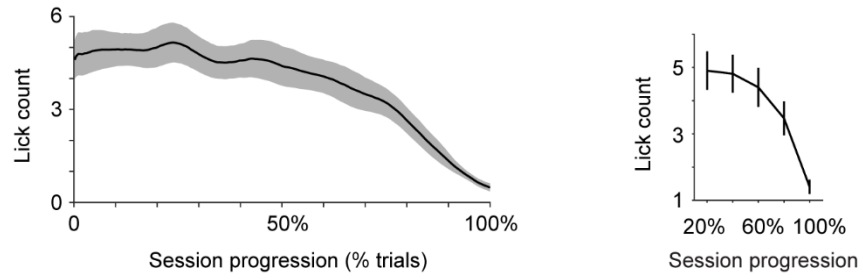
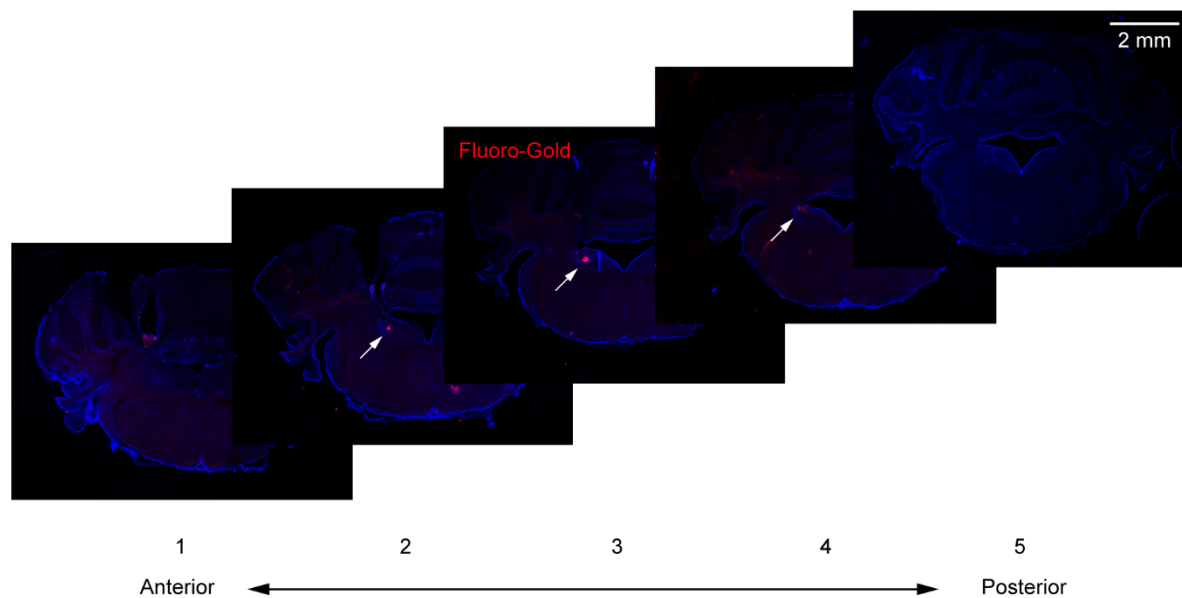


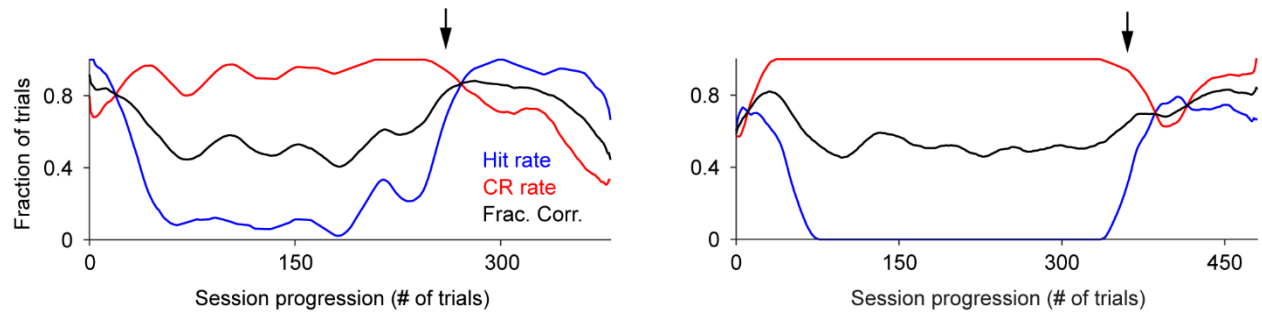
**Figure S1.** IS rate was positively correlated with Hit rate (a), and negatively correlated with CR rate (b). Dashed lines: linear fitting.



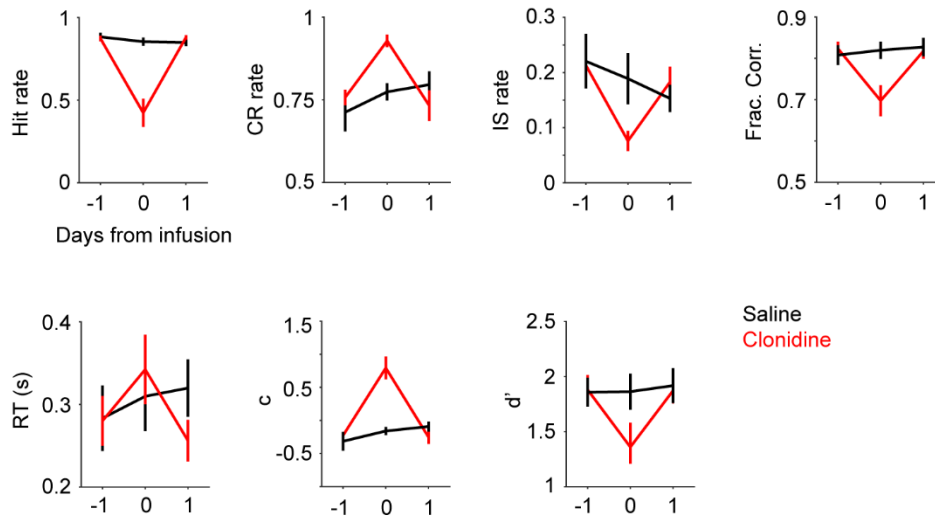
**Figure S2.** Lick count decreased as task progressed within sessions. Left: normalized single-session trajectory of lick count, mean  $\pm$  s.e.m. Right: averaged every 20% progression. Lick count is defined as the total number of licks emitted in each trial.



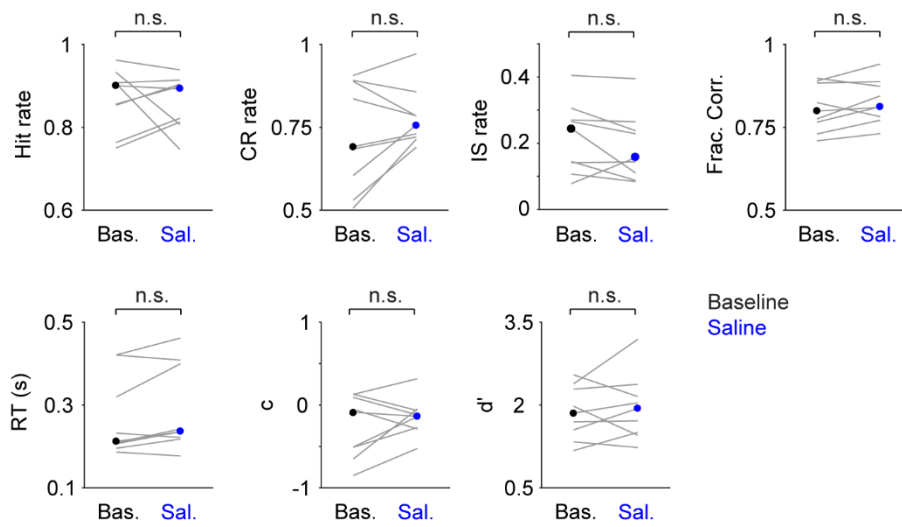
**Figure S3.** 5 consecutive 100  $\mu$ m coronal sections from a mouse where 300 nL Fluoro-Gold was locally infused. Arrows point to visible Fluoro-Gold (red) in sections 2-4. Fluoro-Gold in the most anterior and posterior sections (1 and 5) is very faint.



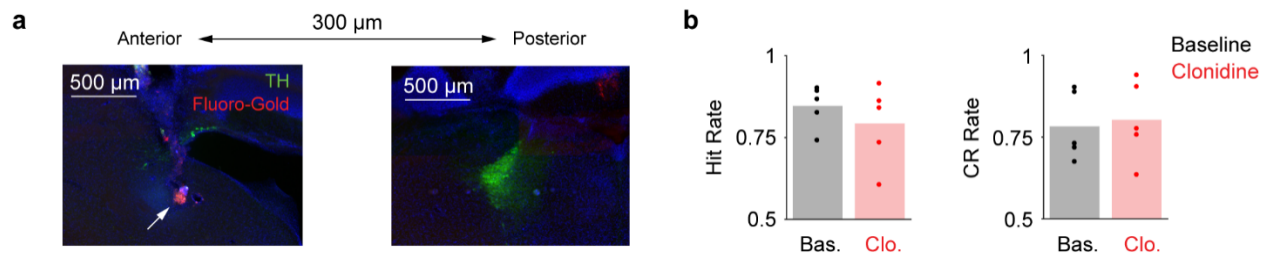
**Figure S4.** Two example behavior sessions of localized clonidine infusion showing that mouse behavior tended to recover later in the session (Hit rate increased and CR rate decreased), indicated by the arrows.



**Figure S5.** Mean Hit rate, CR rate, IS rate, Fraction Correct, RT, decision bias (c) and detection sensitivity (d') for 3 consecutive days ( $\pm$  s.e.m.). Black: saline, n = 6; Red: clonidine, n = 8.

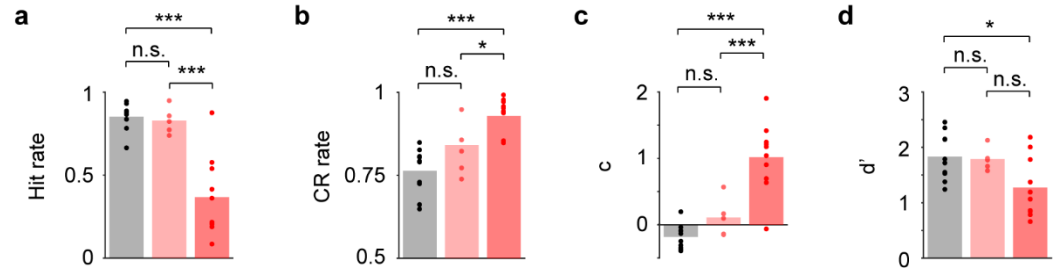


**Figure S6.** Localized saline infusion did not affect behavior. Hit rate,  $P = 1$ , Signed rank = 22; CR rate,  $P = 0.20$ , Signed rank = 11; IS rate,  $P = 0.13$ , Signed rank = 36; Frac. Corr.,  $P = 0.16$ , Signed rank = 10; RT,  $P = 0.055$ , Signed rank = 6;  $c$ ,  $P = 0.30$ , Signed rank = 13;  $d'$ ,  $P = 0.65$ , Signed rank = 18.  $n = 9$ .



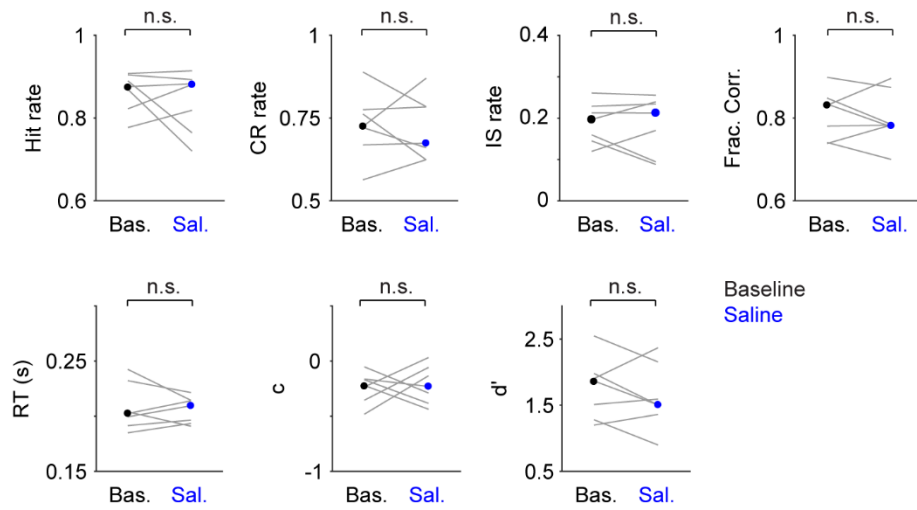
**Figure S7.** Clonidine minimally affected behavior when the infusion was outside of LC. **a.** Example histological sections showing off-target infusion. The location of drug infusion was estimated by Fluoro-Gold (red), which is ~300 μm anterior to the LC (green). **b.** Hit and CR rates during baseline and off-target clonidine sessions (Hit rate, 0.85 ± 0.03 vs. 0.79 ± 0.05; CR rate, 0.78 ± 0.05 vs. 0.80 ± 0.05, mean ± s.e.m., n = 5).

Baseline  
 Clonidine 5 mM  
 Clonidine 10 mM

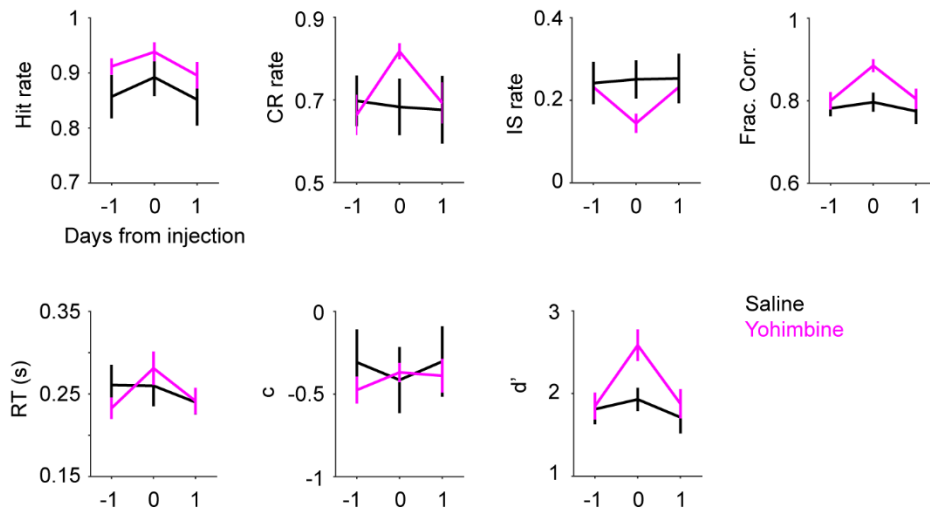


**Figure S8.** Hit rate, CR rate, decision bias (c) and detection sensitivity (d') for baseline (black, n = 10), 5 mM clonidine (light red, n = 5), and 10 mM clonidine (red, n = 10) sessions. **a.** Hit rate: one-way ANOVA,  $F(2,22) = 23.97$ ,  $P = 3.0e-6$ . Baseline vs. 5 mM,  $P = 0.70$ ; Baseline vs. 10 mM,  $P = 3.5e-6$ ; 5 mM vs. 10 mM,  $P = 4.0e-4$ . **b.** CR rate: one-way ANOVA,  $F(2,22) = 18.69$ ,  $P = 1.8e-5$ . Baseline vs. 5 mM,  $P = 0.18$ ; Baseline vs. 10 mM,  $P = 1.2e-5$ ; 5 mM vs. 10 mM,  $P = 0.013$ . **c.** Decision bias: one-way ANOVA,  $F(2,22) = 26.47$ ,  $P = 1.4e-6$ . Baseline vs. 5 mM,  $P = 0.36$ ; Baseline vs. 10 mM,  $P = 1.2e-6$ ; 5 mM vs. 10 mM,  $P = 6.6e-4$ . **d.** Detection sensitivity: one-way ANOVA,  $F(2,22) = 4.39$ ,  $P = 0.025$ . Baseline vs. 5 mM,  $P = 0.98$ ; Baseline vs. 10 mM,  $P = 0.029$ ; 5 mM vs. 10 mM,  $P = 0.12$ . All post-hoc pairwise tests were Tukey-Kramer.

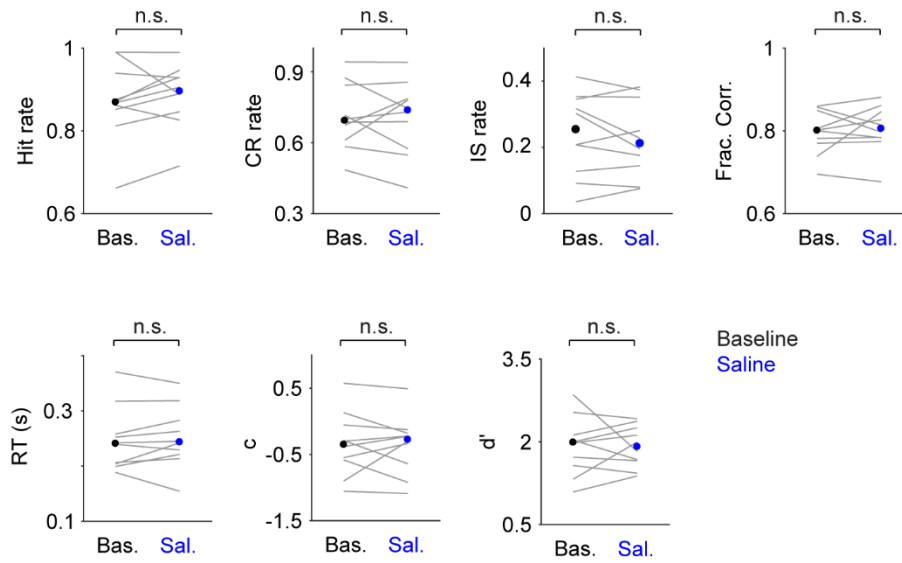




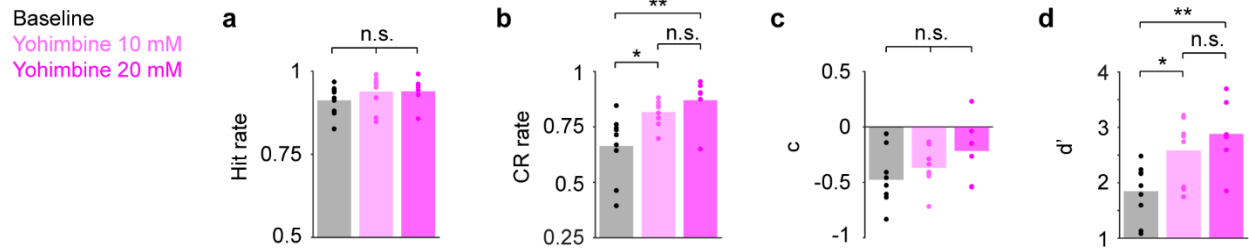
**Figure S9.** Systemic saline administration did not affect behavior. Hit rate,  $P = 0.81$ , Signed rank = 16; CR rate,  $P = 1$ , Signed rank = 14; IS rate,  $P = 0.70$ , Signed rank = 16.5; Frac. Corr.,  $P = 0.81$ , Signed rank = 16; RT,  $P = 0.69$ , Signed rank = 17;  $c$ ,  $P = 0.58$ , Signed rank = 10;  $d'$ ,  $P = 0.47$ , Signed rank = 19.  $n = 7$ .



**Figure S10.** Mean Hit rate, CR rate, IS rate, Fraction Correct, RT, decision bias ( $c$ ) and detection sensitivity ( $d'$ ) for 3 consecutive days ( $\pm$  s.e.m.). Black: saline,  $n = 7$ ; Magenta: yohimbine,  $n = 9$ .



**Figure S11.** Localized saline injection did not affect behavior. Hit rate,  $P = 0.32$ , Signed rank = 17; CR rate,  $P = 0.92$ , Signed rank = 29; IS rate,  $P = 0.70$ , Signed rank = 32; Frac. Corr.,  $P = 0.63$ , Signed rank = 22; RT,  $P = 0.43$ , Signed rank = 19;  $c$ ,  $P = 0.77$ , Signed rank = 31;  $d'$ ,  $P = 0.86$ , Signed rank = 25.  $n = 10$ .



**Figure S12.** Hit rate, CR rate, decision bias (c) and detection sensitivity (d') for baseline (black, n = 9), 10 mM yohimbine (light magenta, n = 9), and 20 mM yohimbine (magenta, n = 6) sessions. **a.** Hit rate: one-way ANOVA,  $F(2,21) = 0.89$ ,  $P = 0.42$ . Baseline vs. 10 mM,  $P = 0.48$ ; Baseline vs. 20 mM,  $P = 0.53$ ; 10 mM vs. 20 mM,  $P = 1.0$ . **b.** CR rate: one-way ANOVA,  $F(2,21) = 7.36$ ,  $P = 0.0038$ . Baseline vs. 10 mM,  $P = 0.021$ ; Baseline vs. 20 mM,  $P = 0.0055$ ; 10 mM vs. 20 mM,  $P = 0.66$ . **c.** Decision bias: one-way ANOVA,  $F(2,21) = 2.17$ ,  $P = 0.14$ . Baseline vs. 10 mM,  $P = 0.61$ ; Baseline vs. 20 mM,  $P = 0.18$ ; 10 mM vs. 20 mM,  $P = 0.45$ . **d.** Detection sensitivity: one-way ANOVA,  $F(2,21) = 6.9$ ,  $P = 0.0047$ . Baseline vs. 10 mM,  $P = 0.029$ ; Baseline vs. 20 mM,  $P = 0.0061$ ; 10 mM vs. 20 mM,  $P = 0.58$ . All post-hoc pairwise tests were Tukey-Kramer.

Saline				
Mouse number	1		2	
	Left	Right	Left	Right
TH positive cells	453	442	586	577
TH/c-fos double positive cells	40	41	117	132
c-fos expression level (%)	8.8	9.3	20.0	22.9
	P = 0.41		P = 0.051	

**Table S1.** Quantification of c-fos expression to examine the effect of localized saline infusion on LC activity in 2 awake mice. Saline was infused in the left LC. The right LC serves as a basal level control. Permutation test was performed ( $10^5$  iterations) to compare c-fos expression levels between the left and right LC in individual mice.