Excessive cocaine use results from decreased phasic dopamine signaling in the striatum

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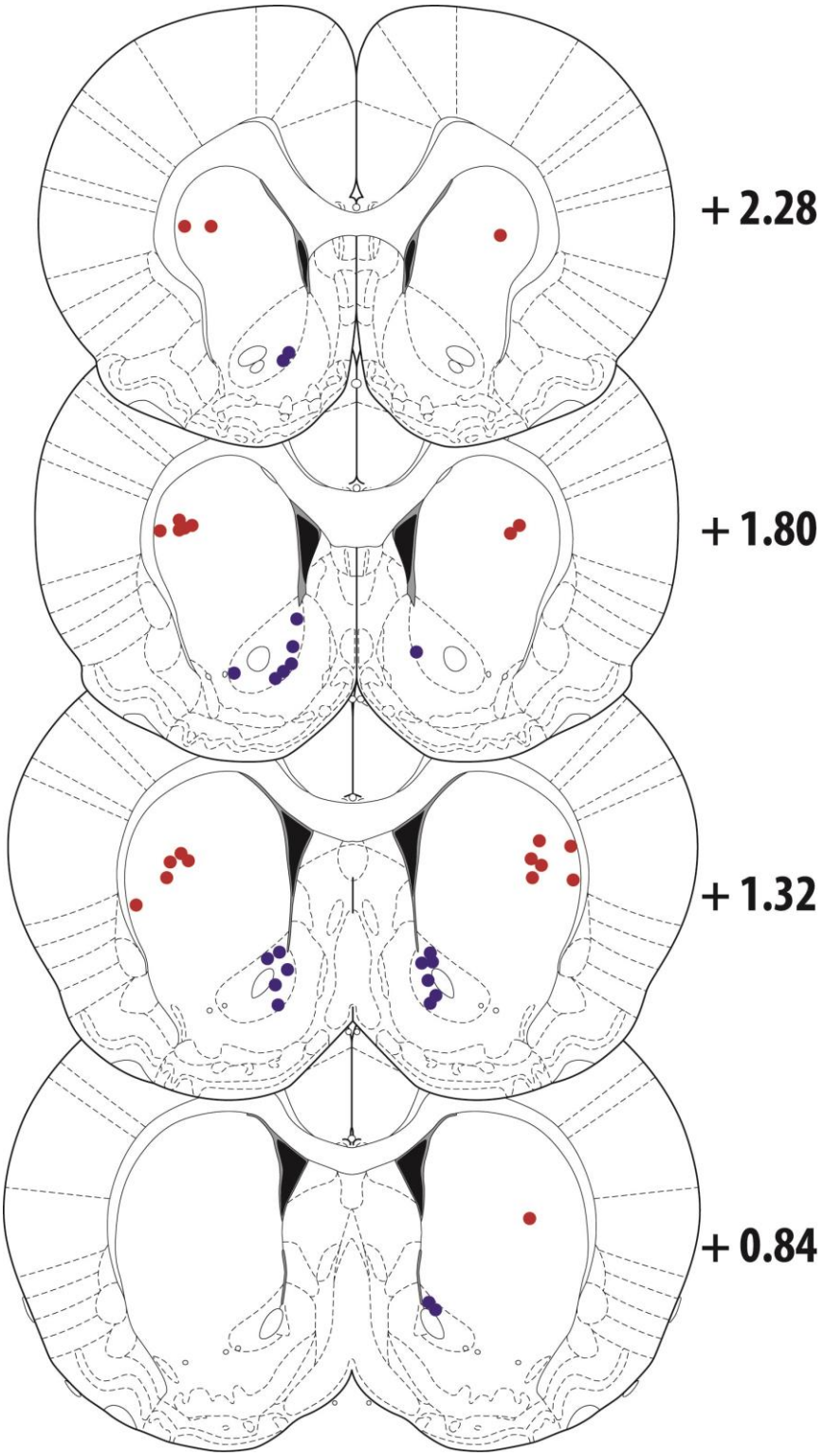
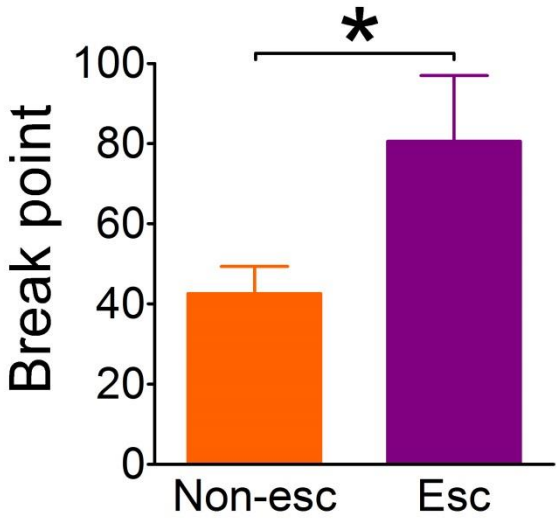
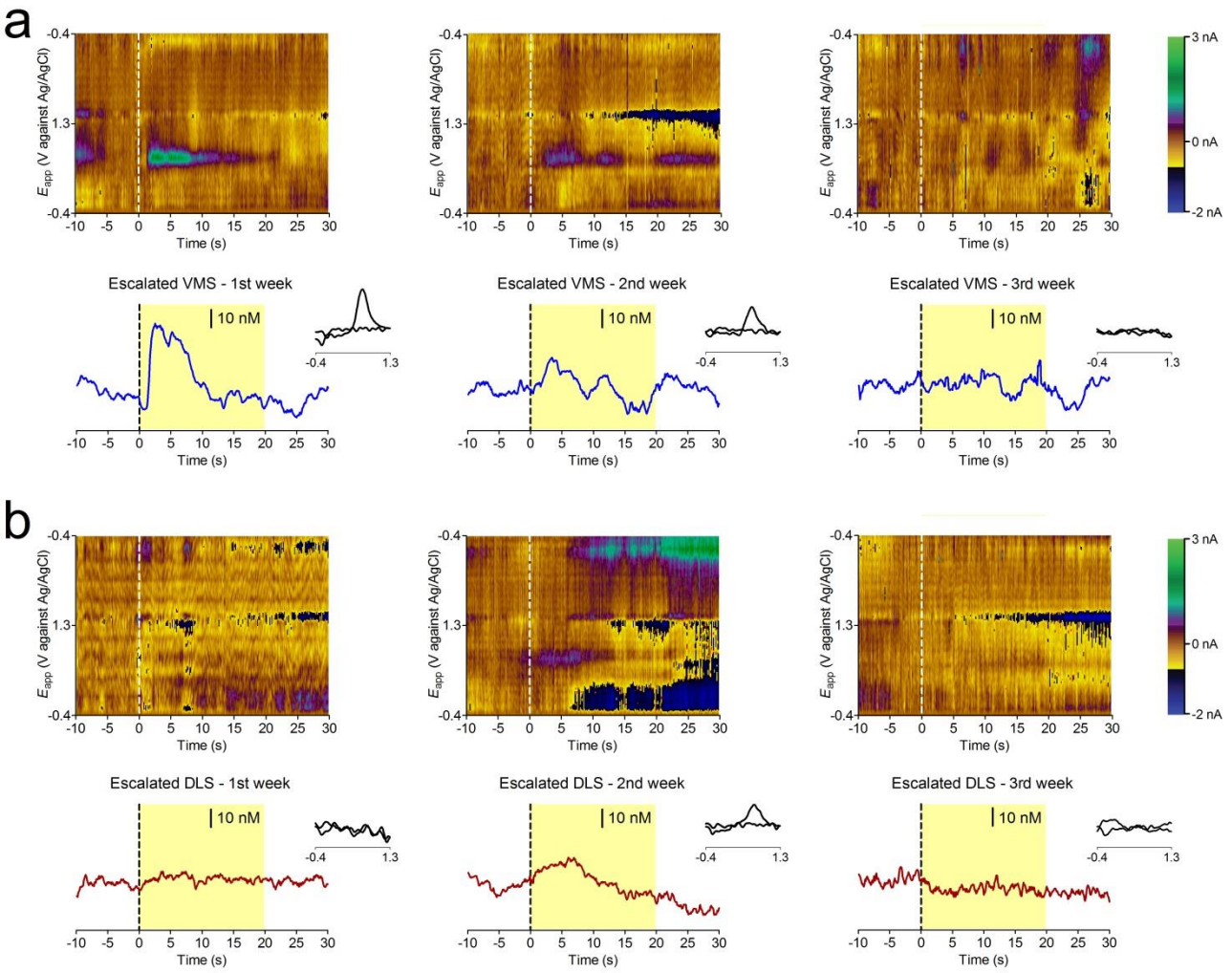


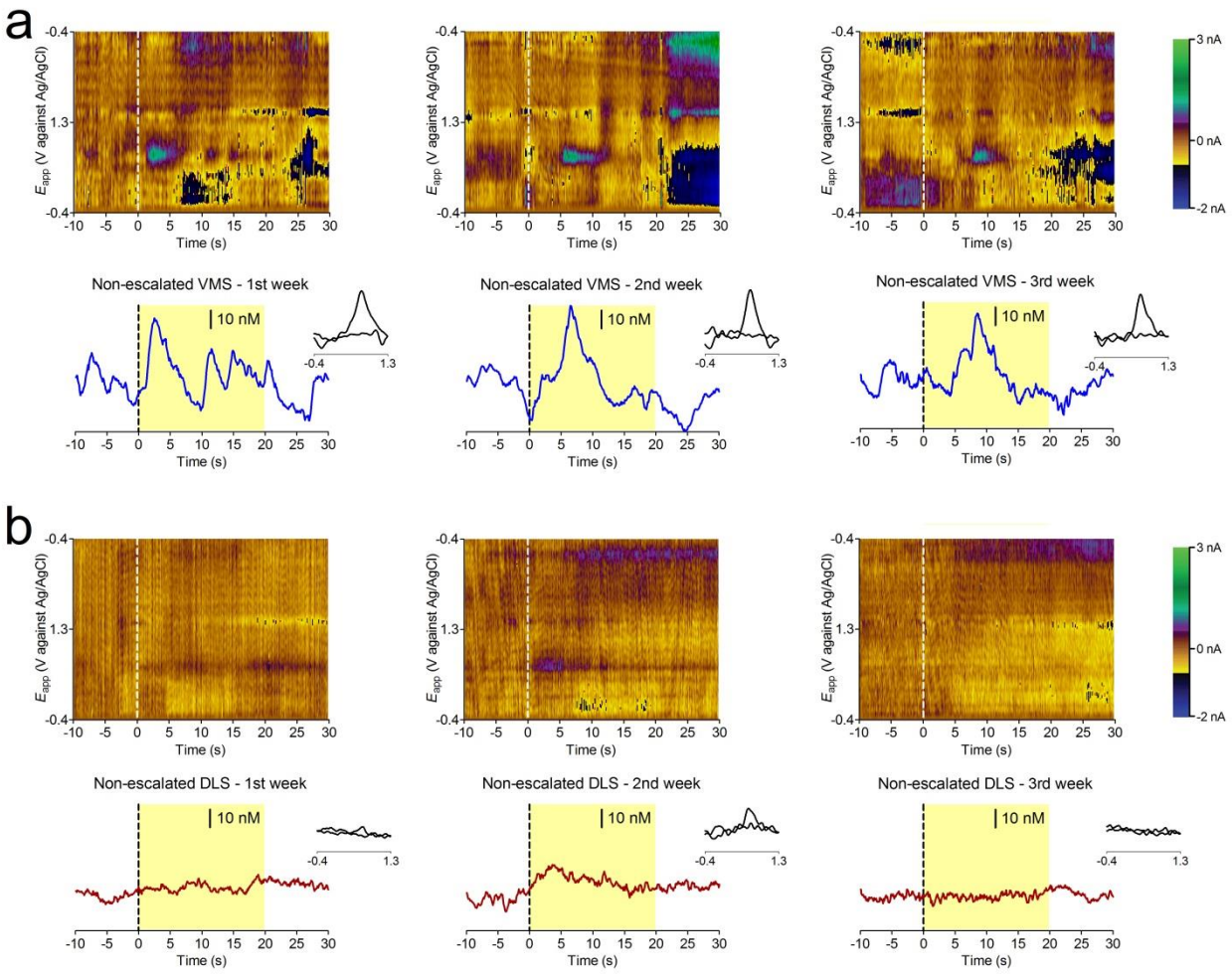
Supplementary Figure 1: **Histological verification of recording sites in VMS and DLS (1st experiment).** VMS recording sites (blue circles) were confirmed to be within the nucleus accumbens core, and DLS recording sites (red circles) were in the lateral half of the dorsal striatum. The numbers on each plate indicate distance in millimeters anterior from bregma[48].



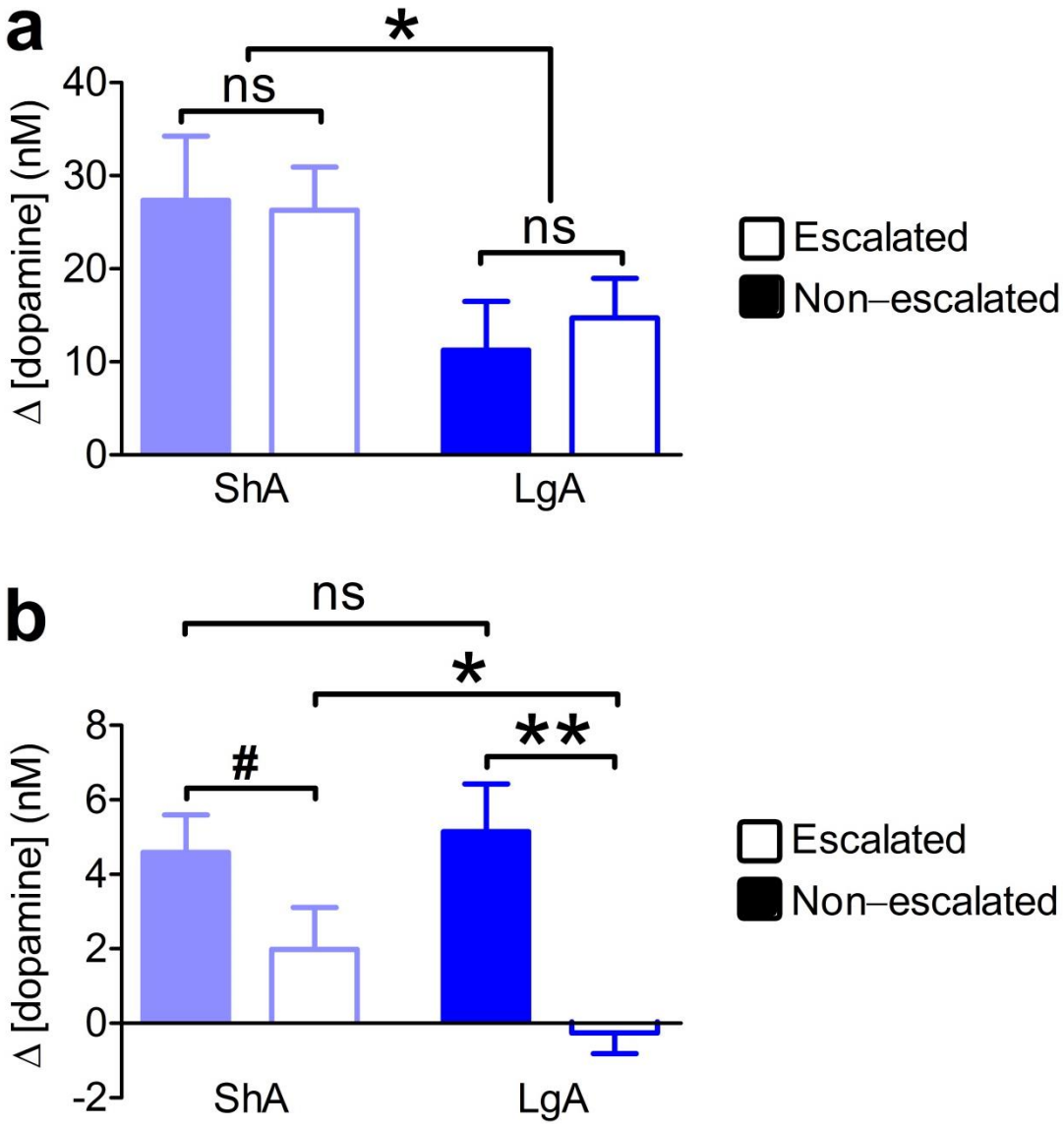
Supplementary Figure 2: **Escalated animals display increased motivation to obtain cocaine.** Subsequent to FI20 cocaine self-administration, a subset of LgA rats (n = 19) underwent progressive-ratio testing. Progressive-ratio sessions were identical to FI20 sessions except that animals were required to perform an increasing number of operant responses for successive infusions of cocaine. The break point was operationally defined as the maximum number of responses. Average break point values are depicted (mean + SEM). Escalated rats (purple bar) displayed significantly more responses (and earned more infusions) than non-escalated animals (orange bar). *$P<0.05$.



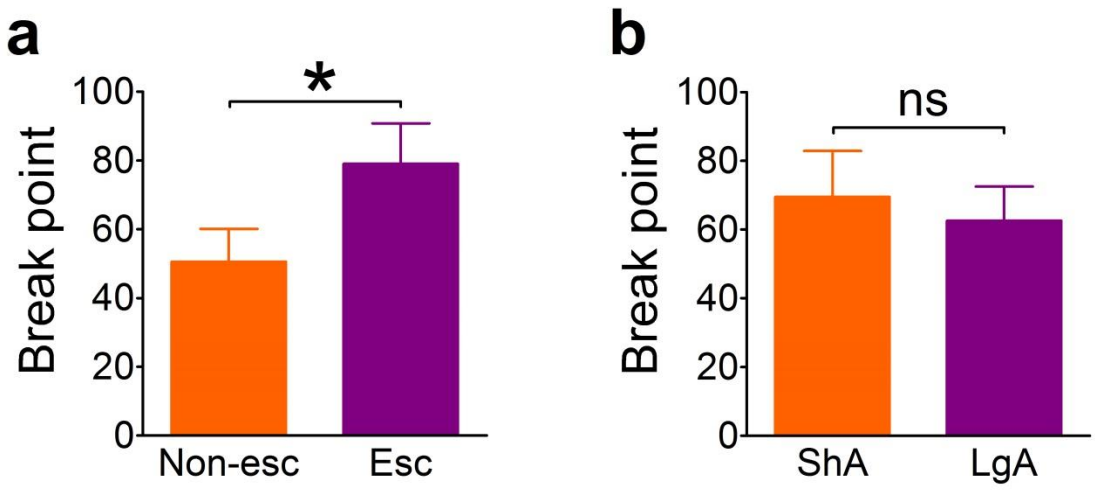
Supplementary Figure 3: **Examples of phasic dopamine release in VMS and DLS associated with an individual nose poke (single trial) into the active port for animals with escalated cocaine intake.** **a**, Pseudocolor plots (top panel), dopamine traces (bottom panel), and cyclic voltammograms (inset in bottom panel) for representative current fluctuations recorded in VMS for the period 10 seconds before an operant response (dashed line), during the subsequent 20-second presentation of the CS (yellow box; includes cocaine infusion), and 10 seconds after the offset of the CS during the first (*Left*), second (*Middle*), and third (*Right*) weeks of LgA cocaine self-administration (first hour). **b**, Pseudocolor plots (top panel), dopamine traces (bottom panel), and cyclic voltammograms (inset in bottom panel) for representative current fluctuations recorded in DLS during the first (*Left*), second (*Middle*), and third (*Right*) weeks of LgA cocaine self-administration. The color plots show current changes across the applied voltages (E_{app}; *y*-axis) over time (*x*-axis).



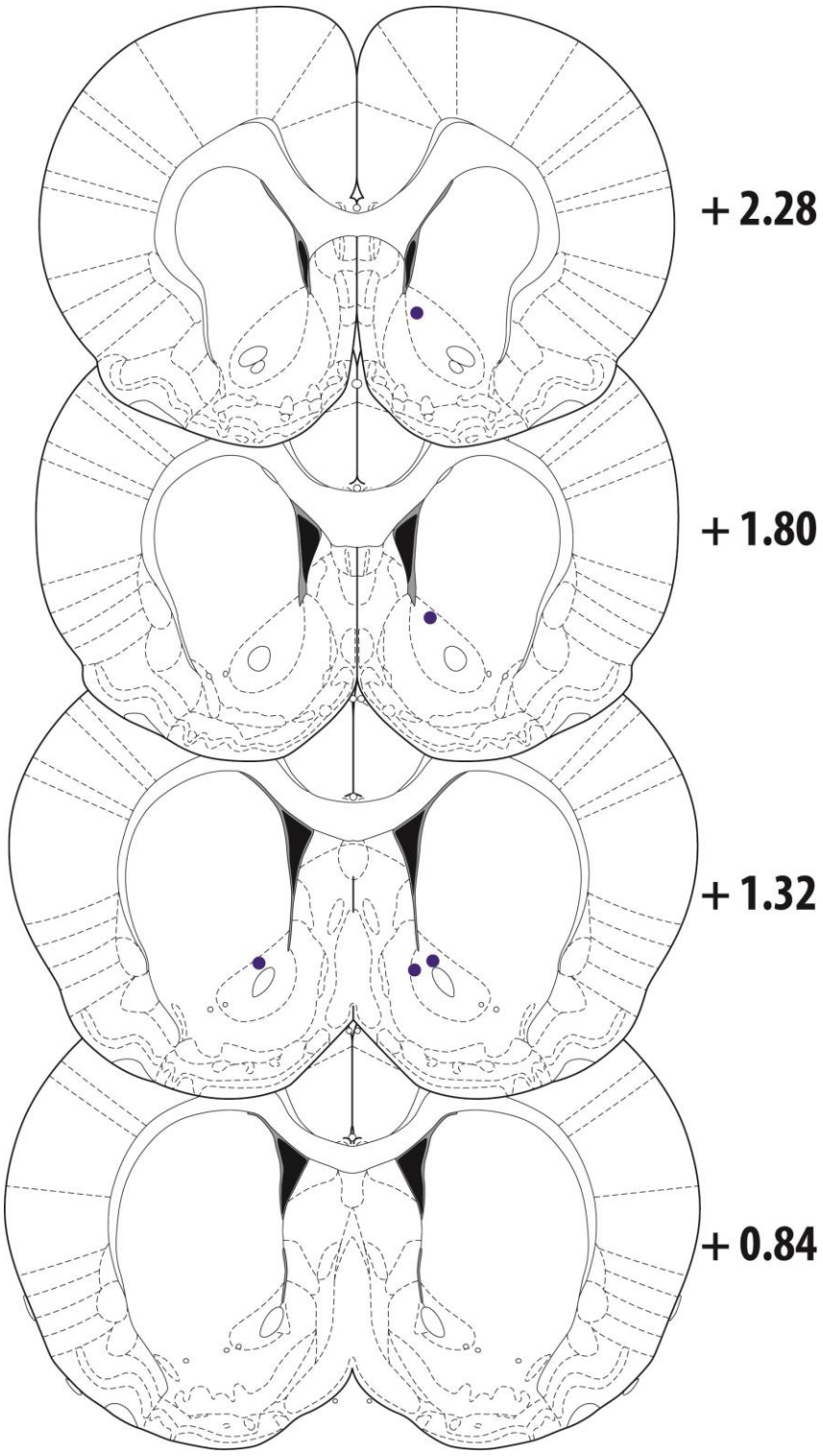
Supplementary Figure 4: **Examples of phasic dopamine release in VMS and DLS associated with an individual nose poke (single trial) into the active port for animals with non-escalated, stable cocaine intake.** **a**, Pseudocolor plots (top panel), dopamine traces (bottom panel), and cyclic voltammograms (inset in bottom panel) for representative current fluctuations recorded in VMS for the period 10 seconds before an operant response (dashed line), during the subsequent 20-second presentation of the CS (yellow box; includes cocaine infusion), and 10 seconds after the offset of the CS during the first (*Left*), second (*Middle*), and third (*Right*) weeks of LgA cocaine self-administration (first hour). **b**, Pseudocolor plots (top panel), dopamine traces (bottom panel), and cyclic voltammograms (inset in bottom panel) for representative current fluctuations recorded in DLS during the first (*Left*), second (*Middle*), and third (*Right*) weeks of LgA cocaine self-administration. The color plots show current changes across the applied voltages (E_{app}; *y*-axis) over time (*x*-axis).



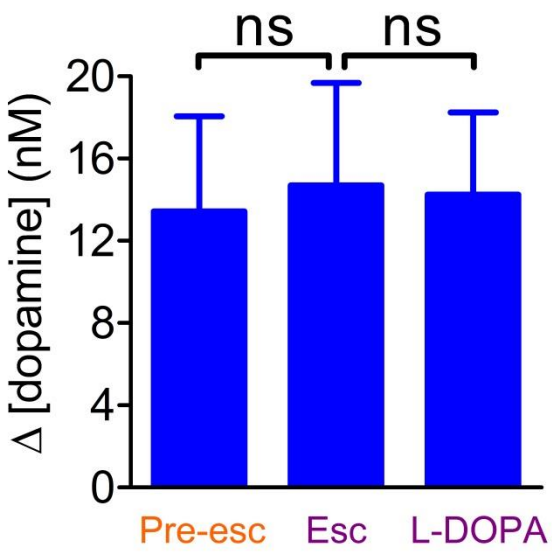
Supplementary Figure 5: **Effects of cocaine (pharmacological) and responding for cocaine delivery (behavioral) vary with access regimen (ShA/LgA) and intake pattern (Esc/Non-esc).** **a**, Average increases in extracellular concentration of dopamine in the VMS over a thirty-second period following a *non-contingent* (response-independent; no CS) intravenous infusion of cocaine (0.5 mg/kg) are depicted for non-escalated (closed bars) and escalated (open bars) animals (mean + SEM) given ShA (left) or LgA (right). Cocaine-induced dopamine release in the VMS was significantly decreased in rats given LgA compared to ShA, but release did not differ significantly between non-escalated and escalated rats ($P>0.05$). **b,** Phasic dopamine in the VMS of non-escalated animals (n = 6/16) in the third week of LgA was not different to that of non-escalated ShA rats (n = 10/16). Escalated ShA animals (n = 6/16) displayed a non-significant trend for decreased VMS dopamine compared to non-escalating ShA rats (n = 10/16); #$P = 0.094$). Escalated LgA animals exhibited less dopamine release than escalated ShA animals. Data are mean+SEM. *$P<0.05$, **$P<0.01$.



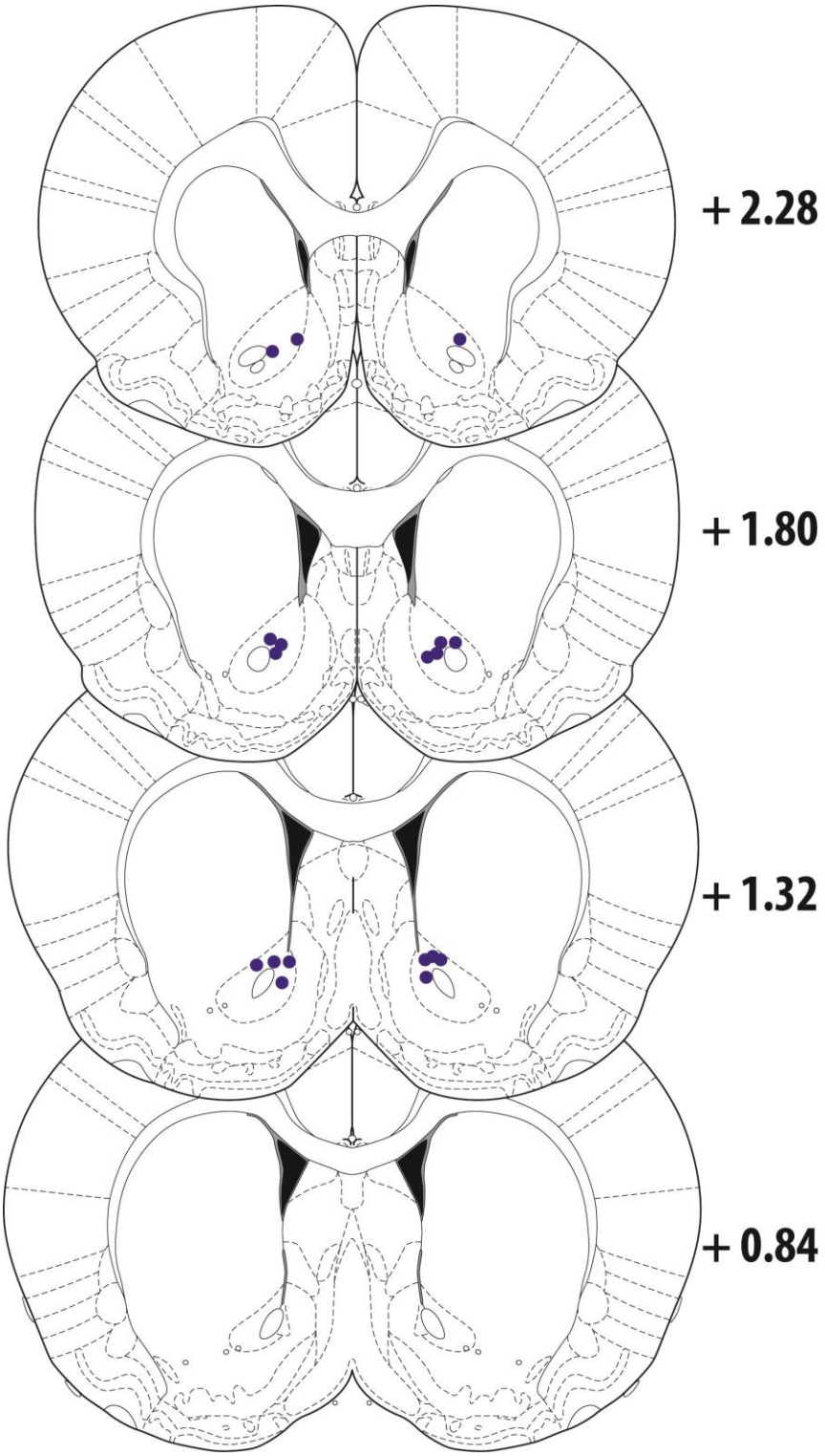
Supplementary Figure 6: **Intake pattern, but not access regimen, affects motivation to obtain cocaine.** Subsequent to FI20 cocaine self-administration, a subset of ShA and LgA rats (n = 32) underwent progressive-ratio testing. Progressive-ratio sessions were identical to FI20 sessions except that animals were required to perform an increasing number of operant responses for successive infusions of cocaine. The break point was operationally defined as the maximum number of responses. Average break point values are depicted (mean + SEM). **a**, Escalated rats (purple bar; ShA and LgA pooled) displayed significantly more responses (and earned more infusions) than non-escalated animals (orange bar; ShA and LgA). **b**, Access regimen (ShA in orange and LgA in purple) had no significant effect on the number of responses rats performed to receive an infusion of cocaine ($P>0.05$). *$P<0.05$.



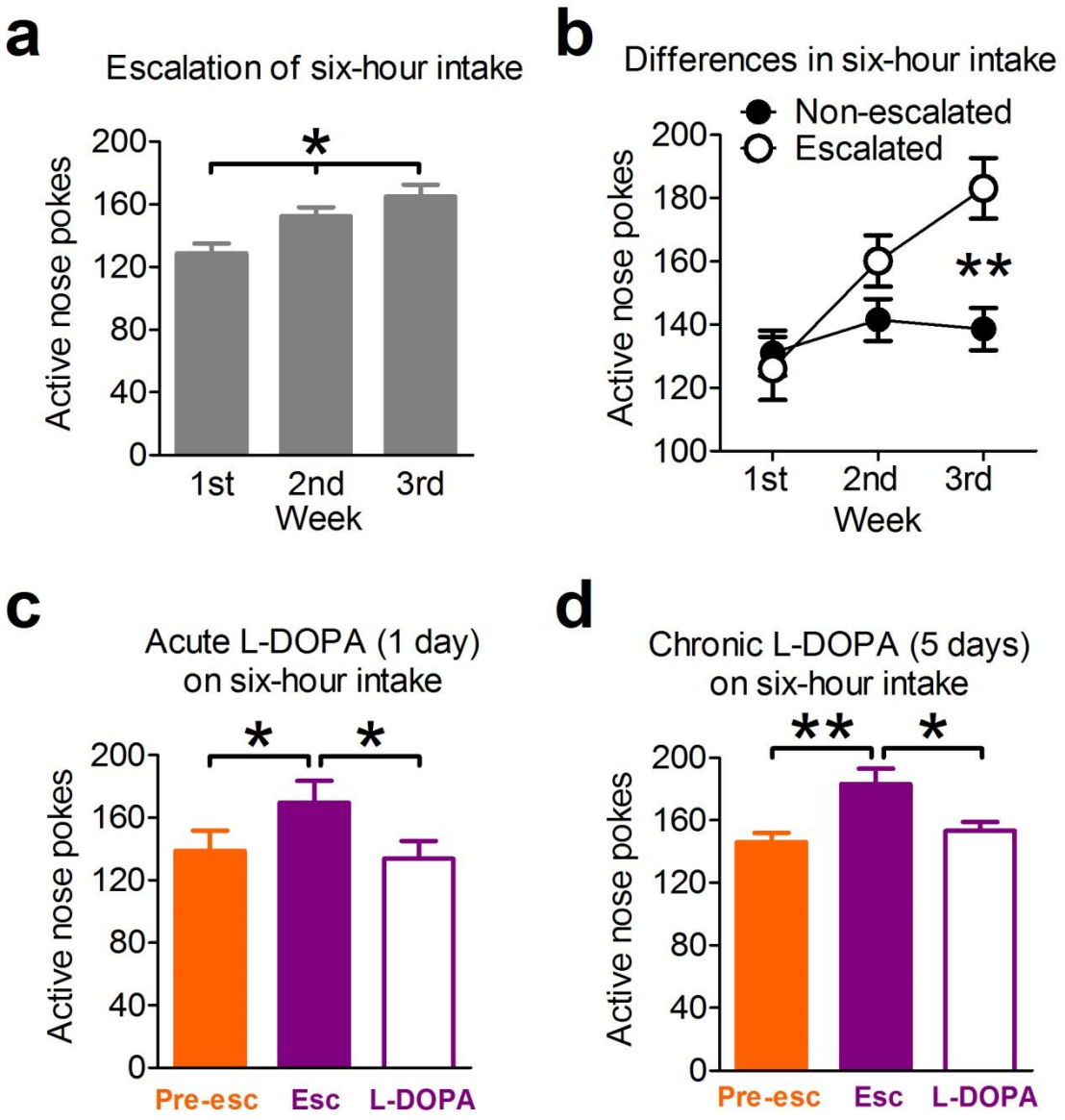
Supplementary Figure 7: **Histological verification of recording sites in VMS (2nd experiment).** VMS recording sites (blue circles) were confirmed to be within the nucleus accumbens core. The numbers on each plate indicate distance in millimeters anterior from bregma[48].



Supplementary Figure 8: **Slow changes in dopamine release in the VMS following a cocaine infusion induced by an active nose-poke response.** Increases in peak concentration of extracellular dopamine in the VMS measured during LgA cocaine self-administration sessions. Measurements were conducted over 90 seconds following an infusion of cocaine induced by a nose poke into the active hole (that occurred without additional operant responses within 90 seconds following this infusion) prior to escalation (pre-esc), after escalation (esc), and after escalation with L-DOPA treatment (L-DOPA). Average changes in such "tonic" dopamine concentration did not differ significantly from each other (ns, not significant; $P > 0.05$). Data are mean+SEM.



Supplementary Figure 9: **Histological verification of infusion sites in VMS (3rd experiment).** VMS infusion sites (blue circles) were confirmed to be within the nucleus accumbens core. The numbers on each plate indicate distance in millimeters anterior from bregma[48].



Supplementary Figure 10: **Escalation of cocaine intake and effects of L-DOPA during LgA over six hours of cocaine self-administration.** **a**, LgA animals showed a significantly increasing number of active nose pokes during six hours of cocaine self-administration across weeks (n = 24). **b**, Non-escalated animals (n = 10) showed no significant increase in cocaine intake during six hours of self-administration over the course of LgA (closed circles), whereas escalated rats (n = 14) increased their intake significantly (open circles). **c**, A single i.v. injection of L-DOPA (30 mg/kg) and Benserazide (2 mg/kg) prior to session start decreased the escalated number of active nose poke responses (purple bar) to a number (open purple bar) comparable to the pre-escalation stage (orange bar; n = 5). **d**, Repeated i.v. administration of L-DOPA (30 mg/kg) and Benserazide (2 mg/kg) on five consecutive days reliably reduced the escalated number of active nose poke responses (purple bar) and maintain the responses at a rate (open purple bar) comparable to the pre-escalation stage (orange bar; n = 5). Data are mean+SEM. *P<0.05. **P<0.01.