Supplemental Methods:

The RPOOL model was formulated because the RD model, which offers an explanation for the nature of the standard, monophasic dopamine response in the context of various steady state drugs and the drug naïve state, was unable to fit just the second phase of DA response induced by Cyam with any set of parameter values, let alone both phases together. Furthermore, attempts at deducing possible time or stimulation dependence of the standard RD model parameters (release, uptake, or rate of mass transport between the compartments) which could reproduce the Cyam response resulted in highly improbable and excessively fine-tuned time dependencies that were simply not plausible as they would have required many unknown parameters to reproduce their complex functions and that these parameters would be highly specific and fine-tuned in value to each response. This led to the conclusion that some factor was operating completely outside of the RD model to create the response, and the only obvious possibility was an additional source of DA release that was not strictly coupled to the electrical stimulation. Because there is no information on how such release would arise in pulses, we represented the release as coming from a pool of vesicles and continuing to happen after the stimulus. At 50 nM bath Cyam, the DA responses were so large and long lasting that the data could be fit with just one parameter (m) to increase the release without limit until the RPOOL was completely empty. This is not to suggest that there is in the brain no mechanism to attenuate Cyam-induced DA release (indeed our preliminary 5 nM Cyam data suggests that there is), or that diffusional restrictions are not operative on the dopamine released from the RPOOL; rather, those parameters were simply not required, under the experimental conditions, to make reasonable fits to the data.

Figure S1. Cyclic voltammograms for DA responses.

Background subtracted color plots and fast scan cyclic voltammograms of DA from a representative experiment which detected a protracted DA overflow in response to vesicular release conditions for cyamemazine (Cyam). The timepoint within the experiment is denoted by labels at the top of the figure. "Drug naive" records a DA measurement taken before Cyam was added to the superfusion fluid, while the 15 min, 180 min, and 190 min labels (+10 min) -denote the time after which Cyam was added to the superfusion fluid. The colored panels are false color plots with the color "axis" denoting current (nA), while time is on the x-axis and is denoted by scale bars at the top. The potential limits are the same throughout the experiment and are -0.4V and 1.3V. The position of the potential limits has been indicated in the first color plot and first cyclic voltammogram and omitted in the others for clarity.

Figure S2. Quantification of test pulse responses.

Test pulse responses in Fig. 3A, left were quantified by measuring the change in amplitude of the signal immediately following the second stimulation.

Figure S1

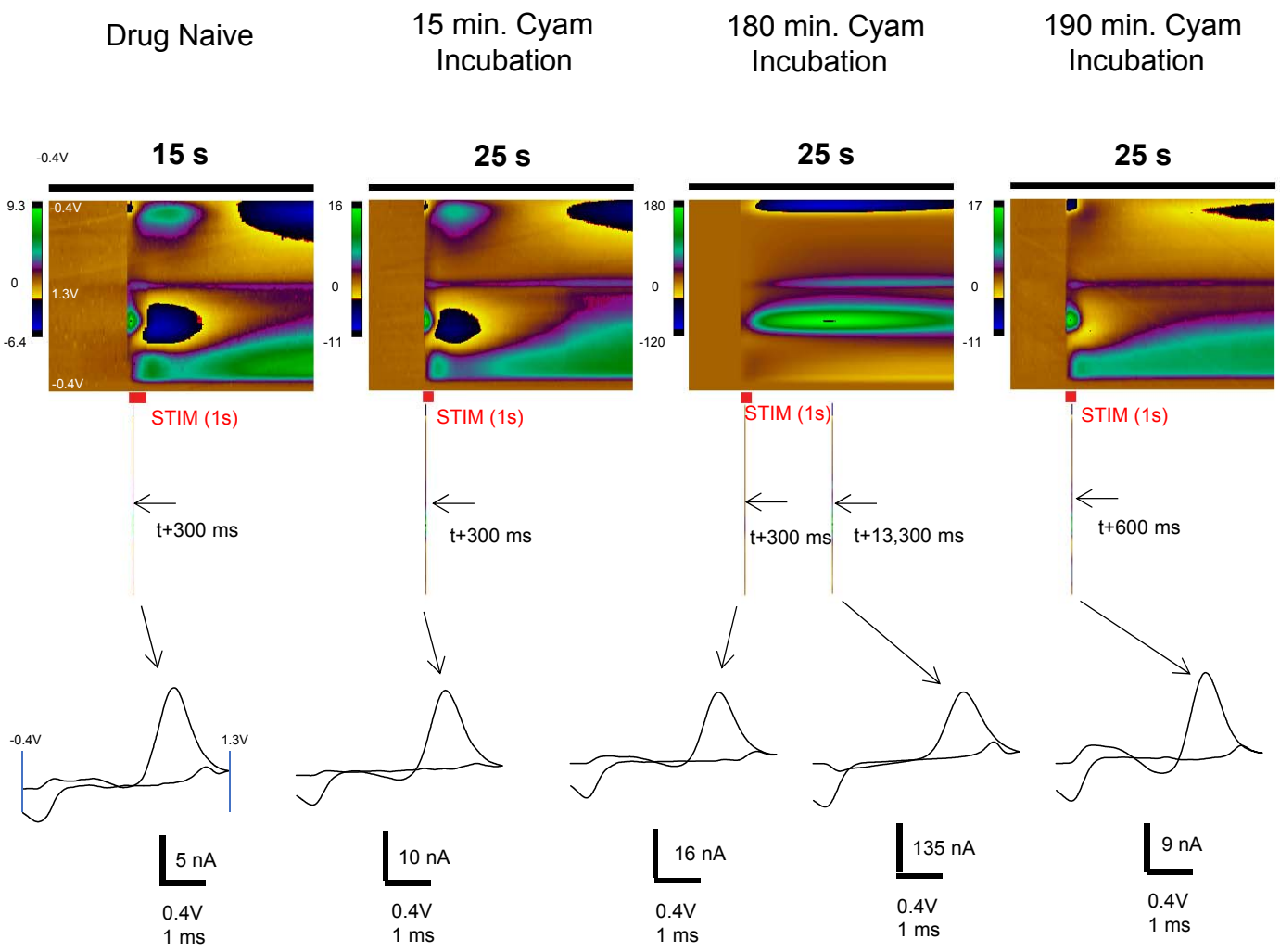
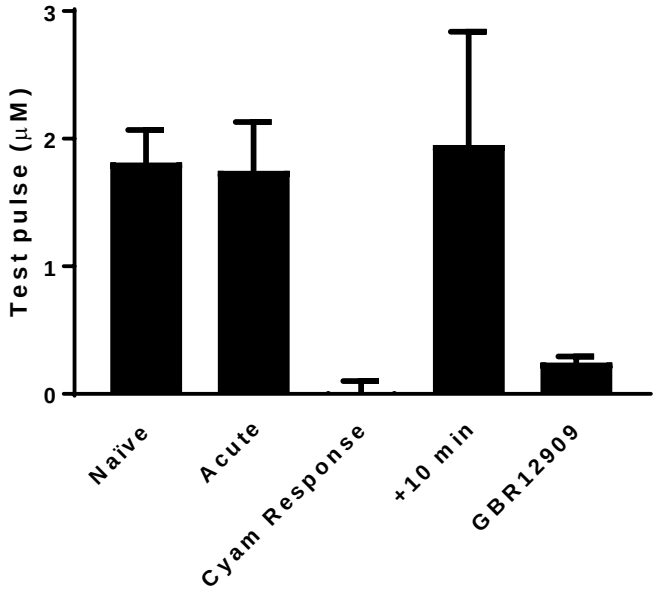

Drug Naive
15 min. Cyam Incubation
180 min. Cyam Incubation
190 min. Cyam Incubation
15 s
25 s
25 s
25 s
-0.4V
9.3
0
-6.4
1.3V
16
-11
180
-120
17
STIM (1s)
t+300 ms
t+13,300 ms
t+600 ms
1.3V
5 nA
10 nA
16 nA
135 nA
9 nA
0.4V
1 ms

Fig S2


Test pulse (μM)
3
2
1
0
Naïve
Acute
Cyam Response
+10 min
GBR12909