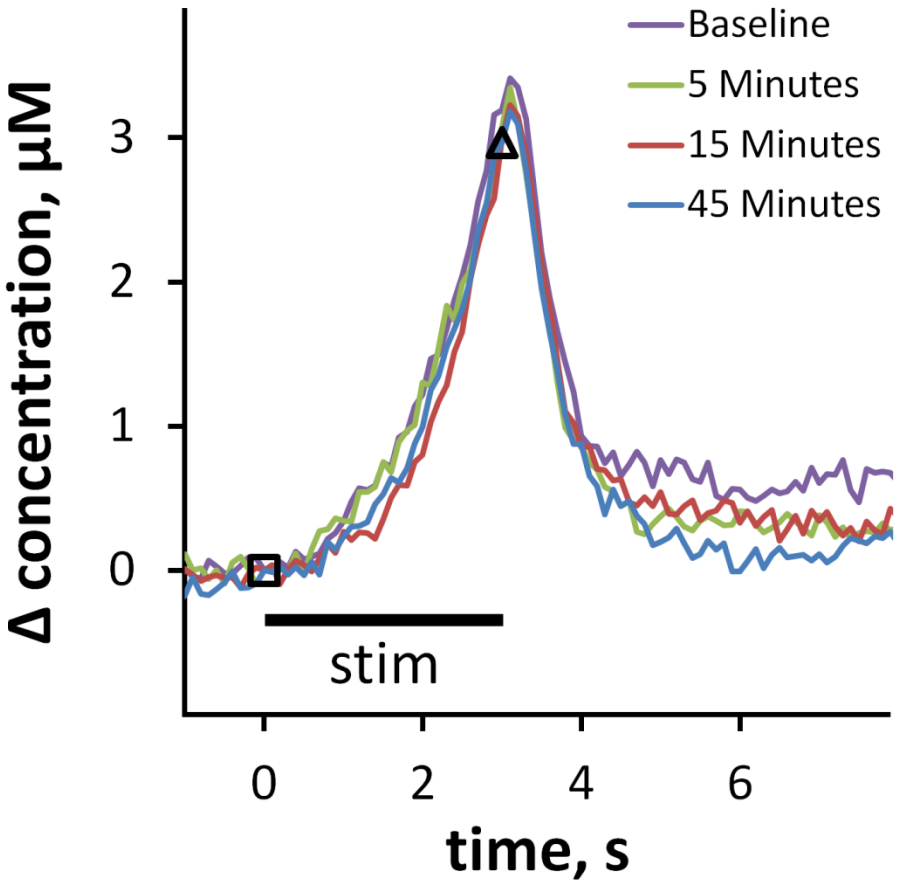
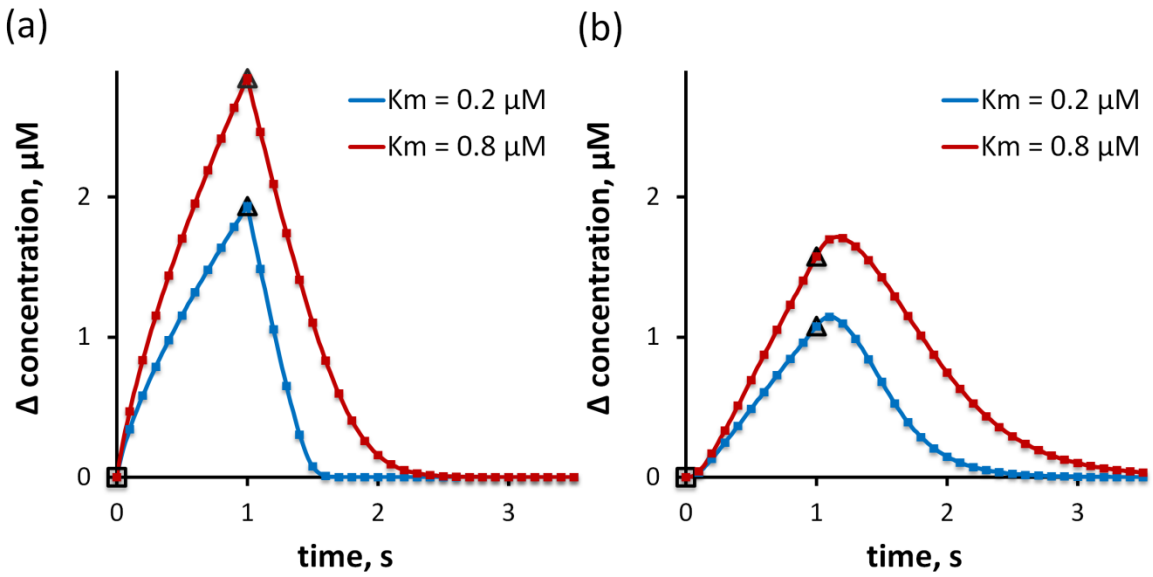



**Supplementary Figure 1:** The kinetic response of the slow domain is reproducible over time. Shown here are the evoked DA overflow responses to consecutive 3 sec, 60Hz stimulations in the slow domain of a single rat without altering the stimulation or working electrode positions or parameters. The initial response delay and linear clearance rate are consistent after 5, 15, and 45 minutes following collection of the baseline reading at t = 0.




**Supplementary Figure 2:** Simulations, according to equation 1, modeling the effect of increasing $K_M$ do not reproduce the observed effects of nomifensine in the fast domain. Fig S2a) The simulation modeling an increase in $K_M$ from 0.2 µM to 0.8 µM (representative of competitive DAT inhibition by nomifensine) in the absence of diffusion does not produce the overshoot and subsequent slowing of linear clearance observed in the fast domain. Fig S2b) Incorporation of a 10 µm diffusional gap into the model produces a small symmetrical distortion at the beginning and end of stimulation which also fails to mimic the large asymmetric overshoot observed in the fast domain after nomifensine.

**Supplementary Information**

**The stability of evoked DA in the rat striatum**

This study relies on comparisons of evoked DA responses in individual rats before and after the administration of nomifensine. This common practice relies on the well-known stability of evoked DA responses in the rat striatum (see references in main text). Prior studies have mainly focused on fast type responses recorded after optimization of the electrode placement. Fig S1 illustrates the stability of the slow responses by means of a representative example of multiple slow responses collected in an individual rat at 5, 15, and 45 minutes after an initial, baseline response. The delay in onset of the response and the rate of DA clearance after the end of the stimulus are both consistent.

**Using Equation 1 to model competitive DAT inhibition**

Equation 1 of the main text is a mathematical model used frequently to quantitatively evaluate evoked DA responses in terms of the intrinsic kinetic parameters $[DA]_p$, $V_{max}$, and $K_M$. A main theme of this study is that this standard model does not comprehensively fit the collection of evoked responses recorded in both the fast and slow domains, before and after the administration of nomifensine. This points to a major conclusion of our study, i.e. that nomifensine appears to do more than just increase $K_M$. In this Supplementary Information document, we present modeled evoked responses, with and without the effects of a diffusion gap, to examine the contrast between the modeled and measured results.

Fig S2a shows evoked responses calculated with Equation 1 using some standard stimulus conditions (60 Hz, 1 s) and intrinsic kinetic parameters ($[DA]_p$ = 0.1 µM, $V_{max}$ = 5 µM/s, and $K_M$ = 0.2 µM and 0.8 µM: these two values of $K_M$ are typical pre-and post-nomifensine values). It is important to emphasize that these modeled responses are presented only to illustrate their essential features, not as a fit to any of the measured responses reported in the main text.

The rising phase of the modeled responses are always 'curved-downwards,' i.e. the response rate decreases as the stimulus proceeds. Mathematically, this occurs because the rate of evoked release, $f \cdot [DA]_p$, is constant while the rate of DA clearance, $\frac{V_{max} \cdot [DA]}{[DA] + K_M}$, increases as the DA concentration increases. Whereas the modeled responses are curved-downwards, the measured slow responses are 'curved-upwards,' i.e. they begin slowly but get faster as the stimulus proceeds. This contrast between the modeled and measured responses is the basis for the statement in the main text that model does not predict the measured slow responses.

Fig S2a compares responses modeled with two different values of $K_M$ to predict the actions of a competitive uptake inhibitor. A key point is that competitive uptake inhibition is not expected to substantially alter the initial slope of the clearance phase of the response. This is the basis for claiming, as we do in the main text, that the decrease in clearance slope of the fast responses caused by nomifensine is paradoxical. A slight decrease in initial slope might be expected if the pre-drug response did not reach sufficient concentrations to exceed $K_M$, but the fast responses well exceed the reported $K_M$.

In the case of fast responses, nomifensine did not alter the rising phase of the stimulus response during the 200 ms stimulus. This is another observation inconsistent with the model, which predicts that the slope of the response should increase when the rate of clearance decreases. In the case of Fig S2a, the signal is increased nearly 40% after the first 100 ms of the stimulus (see the first "data point" on the modeled responses).

Fig S2b repeats the calculation in Fig S2a but includes the effect of a 10 µm diffusion gap between the electrode and the site of DA release and uptake. A finite element simulation algorithm was used to calculate the diffusion effect. A diffusion gap in the in vivo experiments might arise from the use of Nafion films (which were not used in this study) or as consequence of penetration injury caused by the electrode. Fig S2b shows two important features of the response delays expected in the

presence of a diffusion gap. First, the modeled delays when the stimulus starts and stops are symmetrical: in Fig S2b the delays are both about 200 ms. Second, the delay even from a diffusion gap as large as 10 µm should be relatively minor, i.e. only about 200 ms and far smaller than the 800 ms observed in fast domains after nomifensine. These features of the modeled response delays, i.e. that they are symmetrical and relatively minor, is the basis for claiming, in the main text, that the delays observed by voltammetry in the striatum do not conform to diffusion gap expectations. First, the delays are symmetrical and, especially in the fast domains post-nomifensine, are much longer than can be explained be even a large diffusion gap. The EM result (Fig 7 of the main text) shows that any diffusion gap due to penetration injury is much smaller than 10 µm.