Extrasynaptic dopamine and phasic neuronal activity

To the editor:

In a recent issue of *Nature Neuroscience*, Floresco *et al.* elegantly demonstrate that afferents to the ventral tegmental area can differentially modify the firing patterns of dopamine neurons[1]. They also report that the concentration of dopamine sampled by microdialysis during endogenous burst firing is similar to tonic firing unless dopamine uptake is blocked. From this, they deduced that dopamine does not escape the synapse during phasic firing, a conclusion we believe is flawed. To directly establish synaptic restriction would require submicron spatial resolution, which is unattainable with a 240- m microdialysis probe. Indeed, previous work showed that phasically evoked striatal dopamine cannot diffuse all the way across dialyzed tissue to a microdialysis probe while uptake is active, even though dopamine escapes the synapse (detected with a voltammetric microsensor)[2].

Floresco *et al.* argue that dopamine is contained within the synapse due to rapid removal as it encounters perisynaptic transporters. However, striatal terminals are optimized for paracrine transmission with uniformly distributed, extrasynaptic transporters[3]. Dopamine synapses are ~200 nm in radius, so outward diffusion of released dopamine takes only ~0.05 ms (ref. 4). However, dopamine released by a single impulse decays from the extracellular space with a half-life of 75 ms, and even slower for stimuli that mimic endogenous bursts[5]. This allows extrasynaptic diffusion for 5–10 m before it is removed by uptake[6]. Although this distance may not be sufficient for dopamine to reach a microdialysis probe, it permits communication with a population of receptors outside the synapse. Floresco *et al.* contend that this extrasynaptic diffusion is an artifact of highly correlated firing with electrical stimulation. However, behavioral salience endogenously elicits both highly synchronous burst firing[7] and phasic extrasynaptic dopamine[8], similar to that seen with electrical stimulation. Spatial communication is fundamental to dopamine neurotransmission, and so clarification of this controversy will permit a better understanding of the transfer of information by dopamine and the computations it encodes.

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Floresco, West and Grace reply:

Several errors are apparent in the issues raised by Drs. Phillips and Wightman. Obviously, neither a 240 m dialysis probe nor a 10 m voltammetric probe can measure intrasynaptic dopamine (DA) levels. We do not claim that "dopamine concentrations measured during bursting are similar to tonic firing unless dopamine uptake is blocked"; we report that increased tonic firing is associated with increased DA levels, whereas increased burst firing in already firing neurons is not. We concur that some DA escapes the synapse during both burst and irregular firing modes, but this unknown concentration of 'perisynaptic' DA does not contribute substantially to the slower-changing DA levels encompassing large striatal regions (*i.e.*, the classical definition of 'tonic DA'[1].

We carefully state that during bursting, reuptake "limits the amount of DA that escapes synaptic cleft, thereby occluding detection of a ... measurable increase in extracellular dopamine." We show that sustained burst firing does not impact our DA measures, implying that bursting does not play a unique role in tonic DA transmission. We conservatively state that extracellular DA measured by traditional *in vivo* neurochemistry is not altered dramatically by increases in bursting that occur without increased population activity. The distribution of reuptake sites is also unclear, given the uncertainty in labeling DA transporter intrasynaptically using pre-embedding techniques. Indeed, a primary role of intrasynaptic uptake on inactivation of DA transmission is predicted given the potent effects of psychostimulants on behavior[2] and displacement by synaptic DA release in functional imaging studies[3].

The behaving animal studies cited by the Phillips-Wightman letter[4] describe correlations between behavioral salience and "highly synchronous" bursting. However one cannot extrapolate from single-neuron recordings whether: 1) the entire population of neurons is firing spikes synchronously, or 2) the number of spontaneously firing neurons is altered. A burst recorded from one neuron at a set latency after a behaviorally relevant stimulus is not comparable to simultaneous electrical activation of the entire bundle of DA axons.

Our study shows that the DA system is compartmentalized, consisting of a synaptic (and potentially perisynaptic) compartment and a tonically maintained, extrasynaptic compartment, each of which is differentially affected by uptake processes.

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