DOPAMINE SIGNALING

Double threat in striatal dopamine signaling

In this issue of Nature Neuroscience, Menegas et al. demonstrate a role for midbrain dopamine neurons projecting to the tail of the striatum in encoding stimulus novelty and threat avoidance. From this study emerges a model whereby distinct dopaminergic projections to striatum influence behavior along at least two axes, one representing value and one representing threat.

Cody A. Siciliano, Fergil Mills and Kay M. Tye

"What does dopamine do?" For many decades, dopamine was predominantly thought of as a 'pleasure' neurotransmitter, mediating hedonic reward in response to stimuli such as food, sex, and drugs of abuse. Over time, additional evidence suggested more diverse roles for dopamine, including in learning and even aversion[1]. More recently, interest in the diverse functions of dopamine has been reignited[2,3], and it is becoming increasingly clear that there may be no single answer to the question of what dopamine does; dopamine can be found throughout the brain across functionally distinct brain regions and, to make matters more complicated, can be involved in different functions even within a single brain region[4].

The proposed roles for dopamine in reward and reinforcement learning are based largely on studies examining dopamine neuron firing in the ventral midbrain and dopamine signaling in ventral striatum (VS)[5]. Classic studies have shown that dopamine release in VS (which includes the nucleus accumbens) can be driven by reward or by cues conditioned to predict reward[6]. Dopamine neuron activity has been further conceptualized in the 'reward prediction error' hypothesis, which proposes that dopamine reports the difference between expected and actual reward outcomes to mediate learning[7,8]. In dorsal striatum, dopamine signaling has additionally been implicated in action selection and initiation, as well as in habit learning[9]. Because most of this work has focused on relatively anterior parts of striatum, little is known about the role of dopamine in more posterior regions such as the tail of striatum (TS). Menegas and colleagues have been pioneers in studying this region, having first identified a distinct subpopulation of dopamine neurons in the substantia nigra pars lateralis (SNL) that project to TS[10] and subsequently demonstrated that dopamine terminals in TS are preferentially engaged by novel stimuli[11]. Together, these studies demonstrated that dopamine neurons projecting to TS are anatomically and functionally distinct from 'canonical' striatal dopamine circuits. Yet the precise role of role dopamine terminals in TS in guiding behavioral responses to novel or aversive stimuli remained unclear.

In the present study[12], the authors begin by examining dopamine terminal activity in VS or TS in mice exposed to stimuli of variable valence and intensity. They observe that dopamine terminals in VS are activated by reward and that the magnitude of this response tracks the relative size of the reward, suggesting that, consistent with previous results, these terminals may encode value. Also consistent with value coding, terminal activity in VS is inhibited by aversive stimuli, such as an airpuff or the bitter tastant quinine, or by aversive outcomes, such as the omission of an expected reward. Importantly, dopamine terminal activity in VS is specifically driven by stimuli of non-neutral valence, rather than by any salient stimulus, such that activity is not strongly modulated by neutral auditory tones presented at varying intensities. In stark contrast, dopamine terminal activity in TS does not track value, but instead appears to track the novelty and intensity of stimuli. Dopamine terminal responses to reward delivery in TS are small and do not scale with the magnitude of reward. Additionally, dopamine terminals in TS respond to neutral tones and scale with sound intensity. Interestingly, although dopamine terminal activity in TS increases in response to certain aversive stimuli or outcomes (airpuff or loud tone), it is relatively unresponsive to others (bitter taste or reward omission).

Based on the observed dopamine terminal responses in TS, the authors hypothesize that this circuit may encode the novelty and intensity of stimuli (Fig. 1). This model is supported by a series of experiments that manipulate dopamine terminal activity in TS. First, dopamine terminal stimulation in TS is sufficient to act as punishment and produces behavioral avoidance in a dopamine-dependent manner. Furthermore, ablation of dopamine terminals in TS by application of the catecholamine-specific neurotoxin 6-OHDA reduces retreat behavior during investigation of a novel object. Importantly, while 6-OHDA lesions demonstrate that dopamine transporter expressing neurons are involved, they do not distinguish between dopamine-dependent and dopamine-independent functions of these neurons, such as those driven by co-release of glutamate. To support the specific necessity for dopamine, the authors use mice lacking the vesicular glutamate transporter 2 (vGlut2; required for glutamate release) specifically in dopamine neurons, and show that retreat behavior remains intact. Further supporting the idea that this circuit mediates potential threat avoidance, dopamine terminal activity in TS increases during exploration of a novel object in a manner time-locked to bouts of retreat away from (and not approach toward) the object. The authors conclude that dopamine terminals in TS selectively encode stimuli that may indicate a proximal threat and that they function to reinforce retreat or avoidance behavior—a very different role from that of VS terminals (Fig. 1). One might further speculate that a determining factor in TS dopamine terminal responses to aversive stimuli is the potential for bodily harm, which calls for immediate action. Ethologically, a loud noise or sudden rush of air is likely to be associated with the rapid approach of a potential predator (a localizable, potentially avoidable threat). Similarly, when exploring a novel environment or object, where outcomes are difficult to predict, immediate escape or retreat responses are critical for survival. In contrast, while ingestion of a bitter tastant or omission of an expected reward carry a negative valence, they are not intrinsically associated with imminent bodily harm. Thus, such aversive stimuli or outcomes might signal that it would be beneficial to modify the current strategy, but do not require an immediate response.

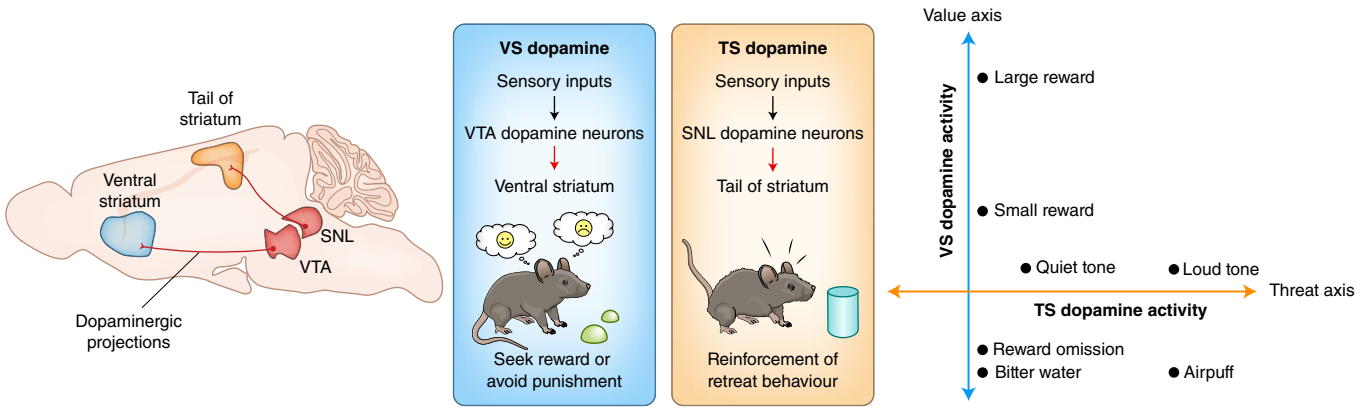

Fig. 1 | Dopamine terminals in VS and TS report distinct features of salient stimuli. Dopamine terminals in VS primarily originate from neurons in the ventral tegmental area (VTA), while those in TS originate from SNL. These two anatomically distinct dopamine circuits work to guide behavior toward maximizing reward while minimizing exposure to threatening stimuli. Dopamine terminals in VS track the magnitude of reward and are inhibited by aversive stimuli. In contrast, dopamine terminal activity in TS tracks the intensity of novel stimuli and is activated by aversive stimuli that promote retreat, but not by aversive stimuli not associated with potential imminent bodily harm. These data support a model whereby VS and TS dopamine circuits encode stimuli on separate axes of reinforcement, with VS dopamine signaling value and TS dopamine signaling threat

This study also highlights the importance of assessing circuit activity in response to a range of stimuli with varying intensity and valence, to fully elucidate the coding rules of a given circuit. In this case, Menegas et al. systematically present several outcomes or stimuli of different valence, novelty, modality, and salience. By integrating findings across all of these stimuli, the authors elegantly show that this population does not encode aversiveness per se, but monotonically tracks the novelty and intensity of a stimulus. This approach should inform the interpretation of other studies assessing circuit-based coding rules, many of which apply a single reward and a single aversive stimulus, each at a fixed intensity. For example, had the authors only presented quinine, they may have concluded that this population does not encode aversive events. Similarly, had they only presented an airpuff, they may have concluded that this pathway preferentially encodes aversive outcomes; yet, neither of these conclusions would have fully captured the coding rules of the population.

Axonal recordings are often used as means to assess the activity of a specific neuronal projection based on the assumption that activity at synaptic terminals is a reflection of activity in the associated cell bodies. However, this is not necessarily the case for dopamine neurons, where transmitter release is often decoupled from action potential activity due to local modulatory mechanisms occurring at the terminals[13]. Here Menegas et al. record calcium transients in both the cell bodies and terminals of TS-projecting dopamine neurons, and find that, in this case, activity is indeed similar between the two. While calcium signals at dopamine terminals have been shown to track dopamine release measured directly by fast-scan cyclic voltammetry[14], calcium influx and transmitter release are not always linearly related in dopamine terminals[15], and it will therefore be important for future studies to assess this relationship across a range of conditions. Further, it will also be informative to assess the heterogeneity of dopamine neurons in the SNL to determine whether SNL neurons that project elsewhere share the features of TS-projecting neurons.

Together, these findings offer new, exciting insights toward a revised model of midbrain dopamine neurons and renew interest in a long-overlooked part of striatum. It seems clear that the behavioral functions of dopamine are too diverse to have a single answer to the question of what dopamine does. Instead, we may need to consider this question in the context of specific projections and local microcircuit computation where dopamine is present. ❐

Cody A. Siciliano[1], Fergil Mills[1,2] and Kay M. Tye[1,2]*

[1]*The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA.* [2]*The Salk Institute for Biological Sciences, La Jolla, CA, USA.*

**e-mail: kaytye@mit.edu*

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Competing interests

The authors declare no competing interests.