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Review

How dopamine enables learning from aversion

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Dopamine is heavily studied for its role in reward learning, but it is becoming increasingly appreciated that dopamine can also enable learning from aversion. Dopamine neurons modulate their firing and neurotransmitter release patterns in response to aversive outcomes. However, there is considerable heterogeneity in the timing and directionality of the modulation. Open questions remain as to the factors that determine this heterogeneity and how varying patterns of responses to aversion in different dopamine-receptive brain regions contribute to value learning, decision-making, and avoidance. Here, we review recent progress in this area and highlight important future directions.

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Introduction

Most dopamine neurons fire when unexpected rewards are received [1,2]. Dopamine responses to unexpected rewards are heavily studied for their roles in supporting learning from positive reinforcement. As cues and actions that lead to rewards are identified, dopamine responses shift toward representing predictive stimuli, reinforcing behaviors that lead to beneficial outcomes.

Dopamine is also proposed to allow organisms to weigh the potential benefits of their actions against potential downsides, supporting cost–benefit decision-making [3,4]. However, to properly support cost–benefit assessments that involve the risk of loss or punishment, the dopamine system needs access to information about these aversive outcomes. Therefore, researchers have increasingly probed the dopamine system to assess its responses to aversion and to determine its role in aversive learning.

Dopamine neurons respond heterogeneously to aversive stimuli

Dopamine research over the last 15 years has demonstrated that dopamine neurons modulate their firing and neurotransmitter release in response to aversive stimuli such as electrical shocks, air puffs, and aversive tastes [5–11]. However, there is considerable heterogeneity among subpopulations of dopamine neurons in the timing and directionality of modulation. Some dopamine neurons *decrease* their activity during aversive stimuli, and some *increase* their activity (for review, see Ref. [5]) (Table 1). In aversive Pavlovian conditioning experiments, for example, de Jong et al. [7] found that while dopamine signaling is suppressed by aversive cues and outcomes in many nucleus accumbens (NAc) subregions, it is increased specifically in the NAc ventromedial shell.

Both decreases and increases in dopamine concentrations in downstream dopamine-receptive brain regions may be computationally meaningful and have consequences for circuit function (Figure 1). Dopamine decreases during aversive stimuli conform to reward prediction error models in which punishments can often be understood as negative reward prediction errors (i.e. moments when outcomes are worse than expected). Dopamine increases during punishment could be compatible with salience encoding [12,13]. Alternatively, there could be encoding of aversive salience (the desire to avoid a predicted aversive outcome) or encoding of threat prediction error [7,13,14]. Distinguishing between these possibilities will be important. Since the answer may differ for subpopulations of dopamine neurons, these subpopulations must be carefully delineated in future studies.

Defining dopamine neuron subpopulations

Reaching agreed-upon definitions of heterogeneous dopamine neuron subpopulations is desirable to ensure reproducibility across studies and provoke productive debate about function. Defining subpopulations by distinct gene expression patterns is an approach that holds

Table 1

Summary of recent studies examining dopamine responses to aversive cues and outcomes across varying striatal subregions.

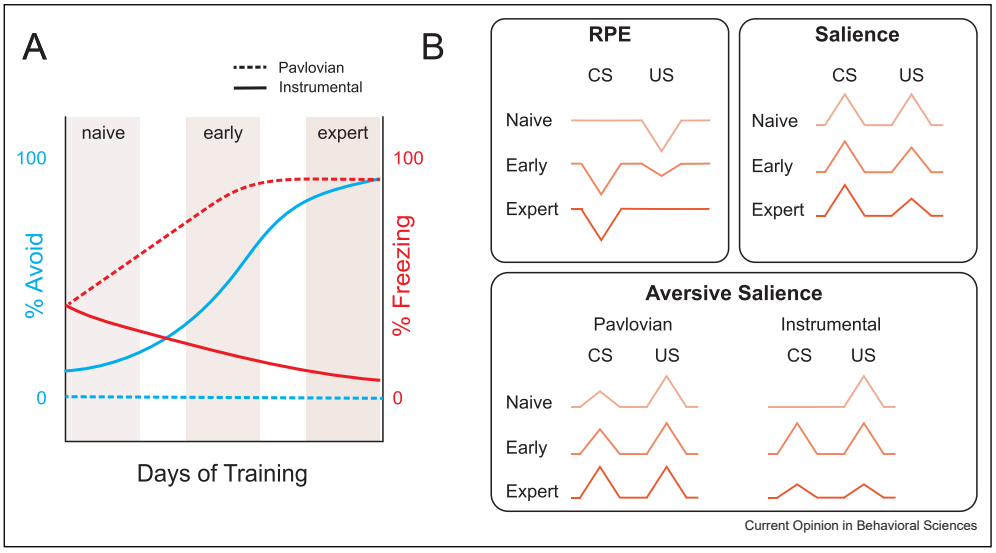
Aversion paradigm	Behavior	Reference	Species	Recording technique	Recording site	Main outcomes
Unpredictable aversive stimuli	Unpredicted footshock	Brischoux et al., 2009	Rats	Single-unit recordings; putative DA	VTA	Dorsal VTA neurons inhibited by shock Ventral VTA neurons excited by shock
	Unpredicted footshock	Lerner et al., 2015	Mice	Fiber photometry; GCaMP in projection-defined DA neurons	SNc	SNc→DMS neurons inhibited by shock SNc→DLS neurons excited by shock
	Unpredicted footshock, quinine, and tail pinch	Yuan et al., 2019	Mice	Fiber photometry; DA sensor or GCaMP in DA axons	NAc (multiple subregions)	DA/DA axons increased by aversion in NAc ventromedial shell Mixed results in other subregions
	Unexpected air puffs	Menegas et al., 2018	Mice	Fiber photometry; GCaMP in DA axons	NAc core, TS	NAc core axons inhibited by air puffs TS DA axons excited by air puffs
	Unpredicted footshock and quinine	Kutlu et al., 2021	Mice	Fiber photometry; DA sensor	NAc core	NAc core DA increased by shock and by high levels of quinine
	Unpredicted air puff	Azcorra et al., 2023	Mice	Fiber photometry; GCaMP in DA axons (molecular subtypes)	Striatum	Calb1+, Anxa1+ DA axon activity excited by air puff Vglut2+ DA axon activity inhibited by air puff
	Unpredicted air puff	Amo et al., 2023	Mice	Fiber photometry; glutamate sensor + GCaMP in DA neurons (VTA), DA sensor (NAc)	VTA and NAc ventrolateral core	VTA Glu release increased by air puff VTA DA neurons inhibited by air puff NAc DA release decreased by air puff
Aversive pavlovian conditioning	Visual cues predicted air puff with varying probability	Matsumoto & Hikosaka, 2009	Nonhuman Primate	Single-unit recordings; putative DA	Midbrain (SNc/VTA)	DA neurons were found that were inhibited by the predictive cues and air puffs, as expected at the time, but another population was excited by the cues and air puffs.
	Tone cue predicted footshock	Oleson et al., 2012	Rat	Fast-scan cyclic voltammetry	NAc core	DA release decreased by the predictive cue, 24 hours after conditioning
	Tone cue predicted footshock	Badrinarayan et al., 2012	Rat	Fast-scan cyclic voltammetry	NAc core and medial shell	Core: DA release decreased by cue Medial shell: DA release increased by cue
	Tone cue predicted footshock	de Jong et al., 2019	Mouse	Fiber photometry; GCaMP in DA axons	NAc (multiple subregions)	Core: DA axon activity decreased by cue + shock Dorsomedial Shell: DA axon activity decreased by cue + shock Ventromedial shell: DA axon activity increased by cue + shock Lateral Shell: DA axon activity unchanged by cue, decreased by shock
	Light + tone cue predicted footshock	Stelly et al., 2019	Rat	Fast-scan cyclic voltammetry	NAc core/medial shell	DA release decreased by cue + shock, increased during safety period
	Tone cue predicted footshock	Steinberg et al., 2020	Mouse	Fiber photometry; GCaMP in DA neurons	SNL	SNL DA neuron activity increased cue + shock
	Tone cue predicted footshock, shock omission, and extinction	Kutlu et al., 2021	Mice	Fiber photometry; DA sensor	NAc core	DA release decreased by cues DA release increased by shock, greater responses for 80% probability over 100% DA increases lessen with shock omission and extinction
	Tone cue predicted footshock, shock omission, and extinction	Salinas-Hernandez et al., 2023	Mouse	Fiber photometry; GCaMP in DA axons	NAc (multiple subregions)	Anteromedial NAc: DA axon activity decreased by cue + shock, increased by shock omission Lateral and ventral NAc: DA axon activity increased by cue + shock + shock omission

Table 1 (*continued*)

Aversion paradigm	Behavior	Reference	Species	Recording technique	Recording site	Main outcomes
						Posteromedial NAc: DA axon activity unchanged by cue + shock, increased by shock omission
Active avoidance (instrumental conditioning)	Shuttle avoidance	Lopez et al., 2024	Mice	Fiber photometry; DA sensor	NAc (multiple subregions)	Core: DA decreased by cues + shocks, cue decreases become larger with learning, DA increased by shuttling to safety Ventromedial shell: DA increased by cues + shocks, cue increases grow in early learning, fade with expert performance.
	Lever press avoidance	Oleson et al., 2012	Rat	Fast-scan cyclic voltammetry	NAc core	Core DA release decreased on failed avoidance trials but increased on successful avoidance trials DA increased during safe periods after lever press
	Lever press avoidance	Stelly et al., 2019	Rat	Fast-scan cyclic voltammetry	NAc core/medial shell	Rats were categorized as learners or nonlearners. DA release decreased during cue for both groups (stronger for nonlearners). DA release increased during safety for both groups (stronger for learners). Elevated DA release for shock off if it occurred unexpectedly early.
	Learned helplessness (reduction in shock escape after inescapable shocks)	Wu et al., 2021	Mice	Fiber photometry; GCaMP in DA neurons	VTA	DA neuron activity initially decreased during inescapable shock and increased at shock-end. By the end of inescapable shocks, DA neuron activity at shock-end was blunted. Restoration of the shock-end signal restored shock escape behavior.
	Nosepoke avoidance; light cue at shock termination	Kutlu et al., 2021	Mice	Fiber photometry; DA sensor	NAc core	DA release similarly increased by the cue pre- and post-avoidance training. DA release for shock higher post-training, DA release for safety higher pretraining.
Other	Novel object interaction task	Menegas et al., 2018; Akiti et al., 2022	Mice	Fiber photometry; GCaMP in DA axons (Menegas) or DA sensor (Akiti)	TS	TS DA axon activity and TS DA release increase during retreat from a novel object
	Nosepoke to receive air puff	Yawata et al., 2023	Mice	Fiber photometry; DA sensor	NAc core/lateral shell	DA increased for voluntary administration of air puffs in an impoverished environment

DA, dopamine; DLS, dorsolateral striatum.

Figure 1



Dopamine may play diverse computational roles in aversion learning. **(a)** Schematic showing how Pavlovian and instrumental aversive learning behaviors differ as training progresses. During Pavlovian aversive learning, subjects learn associations between a conditioned stimuli (CS) and an aversive unconditioned stimuli (US) but cannot control US exposure. Freezing behavior increases and plateaus (red dashed line), while avoidance actions do not develop (blue dashed line) since they are not part of the task design. During instrumental aversive learning, subjects learn a CS–US association and then learn to react to the CS to prevent or stop aversive stimuli. The successful performance of this avoidance behavior steadily increases over training (blue solid line), while freezing decreases over time (red solid line). **(b)** Schematic showing predicted dopamine dynamics during aversive learning under various theories of dopamine function. If dopamine encodes reward prediction error (RPE; *top left*), then dopamine should decrease in response to the US early in training, shifting toward the CS as CS–US associations form. If dopamine encodes salience (*top right*), then both the CS and US should trigger increases in dopamine release. Initial responses to the CS will occur due to novelty and remain salient due to CS–US associations. As the CS becomes more informative, US-related dopamine release may decline. Some dopamine subcircuits may also encode aversive salience, also known as fearful salience, the aversive counterpart to incentive salience. Here, the predictions for Pavlovian versus instrumental learning differ (*bottom)*. In Pavlovian learning (no control over the US), the CS becomes highly salient as a fear-inducing predictor of an aversive outcome. In instrumental learning (US is avoidable), the CS will initially become a fear-inducing predictor of an aversive outcome but will later lose this property as most aversive outcomes are avoided. The US remains aversive when experienced later in training but may lack aversive salience due to well-understood rules for controllability.

promise in bringing clarity to the field, but knowledge of gene expression differences must be interfaced with circuit and systems neuroscience perspectives. One recent exemplary effort focused on motor and reward representations in dopaminergic projections to the dorsal striatum and found a unique class of Anxa1+ dopamine neurons that encode movement (responses correlated with accelerations on a treadmill) but not reward (no responses for unexpected water delivery in thirsty mice) [15]. A similar approach could likely be taken to define aversion-encoding dopamine subpopulations. For example, positive-going dopaminergic responses to aversive events have been reported in NAc core, NAc ventromedial shell, and dorsolateral striatum [7,10–12,16,17], so searching for molecular markers for aversion- or salience-encoding dopamine neurons within these projection-defined populations may prove fruitful in understanding how to interpret these responses.

Dopamine and aversive learning

Aversive outcomes facilitate the learning of actions that can be taken to avoid such experiences in the future. Avoidance actions can be either passive (avoiding scenarios associated with aversive outcomes) or active (engaging in behaviors that proactively prevent aversive outcomes from occurring). Dopamine responses to aversive stimuli have been characterized reasonably well, but a major frontier remains in understanding how dopamine responses to these stimuli are utilized to guide various types of learning.

Remarkably, the dopaminergic dependence of avoidance learning may be preserved across species in organisms with very simple nervous systems. In *C. elegans*, a tiny nematode worm with only four pairs of dopamine neurons, two of these four pairs were found to specifically participate in natural bacterial avoidance behavior induced by physiological stress [18].

In rodents, dopamine in the NAc Core has received particular attention for its role in active avoidance. In a task where rodents could perform a lever press to prevent footshock during a brief warning cue, NAc Core dopamine increased during cues where an avoidance

action was performed but decreased during cues with no avoidance action [19]. Optogenetic stimulation of NAc Core dopamine terminals promoted avoidance [20]. Consistently, Lopez et al. [17] found that although NAc Core dopamine reliably decreased in response to a warning cue, it increased specifically when an avoidance action (in this case, crossing to a safe chamber) was performed. Thus, it is important to differentiate in time when warning cues and avoidance actions take place in time during a task to disambiguate related neural responses. In Lopez et al. [17], decreases in NAc Core dopamine in response to warning cues deepened as avoidance learning progressed, while decreases in response to shock itself on unsuccessful avoidance trials lessened, consistent with a notion of reward or safety prediction error previously proposed by Stelly et al. [21]. Another study found that NAc Core dopamine is also increased when expected aversive outcomes are omitted, which could be interpreted as a positive reward or safety prediction error. However, other experiments in this study showed increases in NAc Core dopamine for aversive stimuli, and the authors therefore proposed that the dopamine signals they had recorded were encoding perceived salience [16]. Sources of variability in the reported direction of NAc Core dopamine signaling are not clear, but small differences in anatomical location, especially when comparing across different model organisms (e.g. rats vs mice) and different recording techniques (e.g. voltammetry vs fiber photometry) will be important to explore further to align the literature (for a comparison of aversion-related dopamine findings by behavioral event, species, recording site, and recording technique, see Table 1).

Consistent with findings from aversive Pavlovian conditioning experiments [7,22], Lopez et al [17] found that dopamine in the NAc ventromedial shell increased for shocks and warning cues during active avoidance learning. However, unlike under Pavlovian conditioning, during avoidance learning, NAc ventromedial shell dopamine representations of warning cues waned late in training, as aversive outcomes were consistently avoided. These findings contrast with findings from the NAc Core (where warning cue representations strengthened with avoidance learning). Importantly, these findings constrain models of NAc ventromedial shell dopamine function in avoidance learning to processes important for early learning, such as aversive salience. In contrast, the NAc Core or other striatal regions may participate in consolidating avoidance rules through reward prediction error (Figure 1).

Moving beyond the NAc, yet further dopamine neuron subpopulations are important for alerting organisms to potential threats, thereby guiding behavior away from these stimuli. For example, dopamine release in the tail of the striatum (TS) suppresses engagement with novel objects [14,23]. When TS dopamine neurons are ablated, animals interact more with novel objects, suggesting that dopamine in this region facilitates cautionary behavior and threat avoidance in the absence of learning about explicit warning cues.

Aversive outcomes also guide learning and decision-making in scenarios involving conflict between seeking rewards and avoiding aversion. Dopamine release in the dorsomedial striatum (DMS) tracks an animal's willingness to endure punishment to obtain rewards [24]. TS dopamine release can also influence an animal's tendency to pursue rewards in the presence of potential threats. In the TS, activation of direct and indirect pathway striatal neurons oppose each other to balance threat avoidance with reward pursuit [25]. Together, these findings suggest that multiple aspects of the dopamine system and its downstream targets in the dorsal striatum are crucial in weighing risks and rewards during complex decision-making tasks.

Finally, a recent study analyzed how dopamine may be involved under atypical circumstances in which aversive stimulation is actively pursued [26]. This study observed that mice would sometimes seek aversive air puffs in impoverished environments, suggesting a motivation to seek information or sensory stimulation despite aversive qualities. Accordingly, dopamine increased in the ventrolateral striatum (approximately in the NAc core/lateral shell) right before air puff-seeking nosepokes. These observations could be consistent with novelty or salience encoding [12,27] and are notable in the context of designing tasks to isolate aversion encoding from salience. Experiments that can manipulate the same sensory stimuli to be perceived as rewarding or aversive may be especially informative.

A role for neurotransmitter co-release in aversion encoding by dopamine neurons

A building understanding of dopamine neuron heterogeneity at the level of neurotransmitter release [28–31] is adding to our understanding of aversion encoding by dopamine neurons. Notably, a recent study by Warlow et al. [31] suggested that dopamine released from ventral tegmental area (VTA) dopamine neurons that co-release glutamate is aversive, driving place avoidance. Meanwhile, glutamate release from these same neurons is reinforcing. Of note, VGLUT2+ VTA dopamine neurons project primarily to the NAc medial shell, adding to mounting but not conclusive evidence that at least a subset of dopamine signals in the NAc medial shell, especially the ventromedial shell, may specifically signal aversion [7,17,32] (Table 1).

More work is needed to determine how neurotransmitter co-release from dopamine neurons contributes to

behavior. Careful molecular biology and synaptic physiology work in VTA and substantia nigra pars compacta (SNc) dopamine neurons suggests that the co-release of dopamine, glutamate, and gamma-aminobutyric acid (GABA) can be independently regulated by differing presynaptic release machinery [33,34]. This independent regulation of release in neurons from naïve mice could provide a molecular basis for plasticity mechanisms that alter the balance of co-release as learning progresses.

How do dopamine neuron inputs shape responses to aversion?

Monosynaptic input tracing using modified rabies viruses has provided valuable insights into how inputs to different dopamine neuron subtypes influence their responses to punishment. VTA, SNc, and substantia nigra pars lateralis (SNL) dopamine neurons each display distinct input connectivity motifs [11,35–37], and further differences between subregions or cell types are likely. Recently, Salinas-Hernandez et al. [38] used rabies tracing to identify differences between inputs to dopamine neurons projecting to the anterior versus posterior medial NAc. They found that inputs to VTA dopamine neurons from the dorsal raphe are critical for fear extinction learning by modulating dopamine signaling in the anterior medial NAc.

Although rabies tracing is useful, it has limitations, including cell-type tropisms, activity dependence, and the inability to measure synaptic strength or other properties. 'Opto-seq' [39] is a recently developed and complementary approach, which also provides a global unbiased perspective. In Opto-Seq, selected inputs to dopamine neurons are optogenetically stimulated, then patterns of immediate-early gene expression among neuronal subtypes are read out by signal-nucleus RNA sequencing. This approach can be used to identify new molecular markers for functionally relevant dopamine neuron subpopulations as well as identify their key input structures. It could be applied to understanding dopamine responses to aversion if inputs known to carry aversive information to dopamine neurons were stimulated.

Another innovative new approach called 'DART' (drug acutely restricted by tethering) [40] allows specific local pharmacology that can be used to target and modulate inputs to dopamine neurons. Using DART, Burwell et al. [41] blocked $GABA_A$ receptors on VTA dopamine neurons and observed a surprising acceleration of fear extinction, perhaps due to changes in the detection of punishment omission.

While Burwell et al. [41] examined inhibitory inputs to dopamine neurons, another recent study [42] examined excitatory inputs by expressing a glutamate sensor in VTA. During aversive air puffs, glutamate in lateral VTA is increased, but downstream dopamine release in the NAc lateral shell is inhibited. This effect can be explained by the activation of glutamatergic inputs onto inhibitory GABA neurons in the VTA during aversion, inhibiting dopamine neurons.

Although many glutamatergic inputs representing aversive information synapse primarily onto VTA GABA neurons, some synapse directly onto dopamine neurons. One example is glutamatergic lateral hypothalamus (LH-Glut) neurons, which synapse specifically onto dopamine neurons projecting to the NAc ventromedial shell. LH-Glut inputs are required for the positive-going responses of NAc ventromedial shell-projecting dopamine neurons to aversive events. Stimulating these inputs causes place avoidance [7].

Finally, SNL dopamine neurons receive a unique motif of inputs [37]. The roles of these inputs are not yet well understood, but some recent research shows that salience information may be communicated from the central amygdala, which is important for learning from both rewarding and aversive outcomes [23,43,44].

How do downstream circuits read out dopamine responses to aversion?

Equally important to understanding how inputs shape dopamine responses is understanding how output structures read out dopamine signals to refine behavior. Recent studies have been particularly productive in dissecting how distinct striatal projection neuron (SPN) subtypes in the NAc, which express abundant dopamine D1 and D2 receptors, are involved in representations of aversion and avoidance learning. In single-unit recordings, NAc SPNs respond heterogeneously to aversive stimuli and associated cues [45]. Some SPN populations appear to specifically signal aversion, and genetic markers for these populations are becoming apparent. Tshz1 is a transcription factor that marks a primarily D1 receptor-expressing SPN population within the striosome/patch compartment of the striatum that is specifically excited by aversion [46–48]. Inhibiting Tshz1+ SPNs in the dorsal striatum impairs avoidance learning [47]. Meanwhile, Cartpt+ SPNs in the NAc medial shell are inhibited by reward [49]. Activation of either Tshz1+ or Cartpt+ SPNs induces place avoidance, suggesting these SPN types may play important roles in allowing learning from aversion [47,49]. This work adds an important functional perspective on the types of instrumental behaviors that genetically heterogeneous SPN subtypes may support [48,50–52].

The Cartpt+ SPN population includes D1- and D2-receptor-expressing SPNs. A key question is how D1- and D2-SPNs interact to produce avoidance learning. Recent research on the NAc microcircuits required for aversive

learning has described a mechanism in which aversive stimuli evoke substance P release from D1-SPNs, which activates cholinergic interneurons. Acetylcholine, in turn, promotes potentiation at glutamatergic synapses onto D2-SPNs [53,54]. How dopamine contributes to this circuit mechanism by layering additional levels of control over D1- and D2-SPN plasticity remains to be determined.

Understanding the interaction between D1- and D2-SPN activity in aversive learning is essential for explaining their coactivation during behavior [55,56]. Fiber photometry experiments measuring calcium reporter fluorescence in D1- and D2-SPNs report co-activity during movement, reward, and aversion [17,55], which may reflect common excitatory input patterns [57,58]. Despite this shared input, SPNs expressing different dopamine receptors (G_s-coupled D1 vs G_i-coupled D2) respond oppositely to dopamine, leading to nuanced and potentially opposing functional changes that affect learning over time. Along these lines, recent literature suggests phasic dopamine's primary role might be to modulate the timing of synaptic plasticity events rather than immediate changes in SPN excitability [59–63].

Moving forward: relevance for depression and addiction

Understanding how dopamine signaling contributes to learning from aversion has implications for psychiatry, including for depression, addiction, and other disorders. For example, recent findings suggest that dopamine responses at the termination of an aversive stimulus are important for motivated behavior to escape aversion, with likely relevance for depression. Wu et al. [64] found that VTA dopamine responses to the termination of shock diminished during repeated uncontrollable shocks, and that the reduction of this dopamine response to aversion is related to the development of learned helplessness. A complementary finding from Dong et al [65] showed that elevations of dopamine in the NAc lateral shell at the termination of chronic restraint stress support active coping in the forced swim test.

In addiction-relevant paradigms where 'compulsive' (i.e. punishment resistant) reward-seeking is observed, strong reward-evoked dopamine transients can promote continued reward-seeking behavior even under threat of punishment [24,66,67]. Dopamine's additional roles in aversive instrumental learning may also be important for understanding how animals incorporate knowledge of aversive contingencies during conflict paradigms. Understanding the operation of dopamine signals during aversion may also inform models of relapse and withdrawal in addiction. The extent to which withdrawal states engage different aspects of the aversive-responsive dopaminergic machinery is not well understood, but recent evidence suggests that the medial and lateral NAc shell show distinct responses, indicating region-dependent machinery [68]. Although it was recently reported that the expression of mu-opioid receptors in VTA is not required for somatic symptoms of opioid withdrawal [69], a relationship with affective symptoms is still likely. In all, applications of basic discoveries about the role of dopamine in aversive learning stand to improve treatment approaches in psychiatry across several diagnostic categories.

CRediT authorship contribution statement

G.C.L. and T.N.L.: Conceptualization and Writing. **T.N.L.:** Supervision.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

Talia N Lerner reports financial support was provided by National Institutes of Health. Gabriela C Lopez reports financial support was provided by National Institutes of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- • of special interest
- •• of outstanding interest

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This study used advanced behavioral tracking and machine learning approaches to identify complex behavioral interactions of mice with novel objects. Novelty induces competing motivations to explore and to protect against potential unknown risks. Ablating dopamine neurons that project to the TS during these novelty-induced behaviors revealed that TS dopamine suppresses engagement with novel objects, which the authors propose is due to representations of threat prediction error or salience. This study highlights how noncanonical dopamine signaling in the TS — an understudied striatal subregion — is tuned to calibrate avoid and approach behaviors as animals explore new situations and change as familiarity develops.

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This study is a rich exploration of the functional differences between dopamine neurons based on genetic subtypes. Dopamine neuron subtypes in the SNc were identified by the expression of one of three genes: Anxa1, Calb1, and Vglut2. The Anxa1+ dopamine neuron subtype was a novel identification of a subset of Aldh1a1+ dopamine neurons. This population is notable for its strong encoding of motor information and relative lack of reward and aversion responses compared to other dopamine neuron subtypes. This study shows a way forward in defining dopamine neuron functional heterogeneity, where differences might be observable not only by projection site but also by gene expression patterns that contribute to physiological function.

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