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# Local regulation of striatal dopamine: A diversity of circuit mechanisms for a diversity of behavioral functions?

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**Abstract**

Striatal dopamine governs a wide range of behavioral functions, yet local dopamine concentrations can be dissociated from somatic activity. Here, we discuss how dopamine's diverse roles in behavior may be driven by local circuit mechanisms shaping dopamine release. We first look at historical and recent work demonstrating that striatal circuits interact with dopaminergic terminals to either initiate the release of dopamine or modulate the release of dopamine initiated by spiking in midbrain dopamine neurons, with particular attention to GABAergic and cholinergic local circuit mechanisms. Then we discuss some of the first *in vivo* studies of acetylcholine-dopamine interactions in striatum and broadly discuss necessary future work in understanding the roles of midbrain versus striatal dopamine regulation.

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## Introduction

Our knowledge of the behavioral functions of dopamine has evolved since its discovery in 1957. The earliest investigations of dopaminergic function involved pharmacological manipulations wherein local injections of 6-Hydroxydopamine (6-OHDA, which depletes dopamine) into dopaminergic nuclei generated a motor deficit exhibited by rotational behavior. Combined with foundational work that uncovered the loss of dopamine in postmortem brain tissue of patients with Parkinson's Disease [1], this pointed to a key role in motor behavior. Hypotheses of dopamine's function were subsequently broadened as intracranial self-stimulation studies suggested that dopamine subserved reward-related functions, with early microdialysis studies demonstrating increases in dopamine in response to both rewarding and aversive stimuli [2]. This was followed by ground-breaking electrophysiological recordings from Schultz and colleagues [3] showing midbrain dopamine neuron (DAN) firing rates encoded deviations from expected outcomes known as reward prediction errors. In recent years the number of functions attributed to dopamine signaling has continued to increase, including a range of disparate behaviors including regulation of motor vigor [4], scratching-induced reward [5], and auditory perception [6], to name just a few. This expansion of dopamine functions beyond movement production raises the question of whether this single neuromodulator utilizes diverse spatial and temporal regulatory mechanisms in mediating distinct behavioral processes.

One level of striatal dopamine regulation occurs via regulation of somatic DAN spiking in the midbrain [7,8]. However, results showing a disconnect between recorded somatic DAN activity and striatal dopamine release suggest further layers of regulation. This divergence has consistently been observed, first with microdialysis and more recently with fast-scan cyclic voltammetry (FSCV) and fluorescent dopamine sensors, both of which provide higher temporal precision. Recent experiments from Berke and colleagues [9] highlight this conundrum - when simultaneously recording DAN spiking in the ventral tegmental area (VTA) and dopamine sensor activity in the nucleus accumbens (NAc), they revealed value-related increases in striatal dopamine levels that did not correlate with increased midbrain DAN spiking. Here we examine an emerging

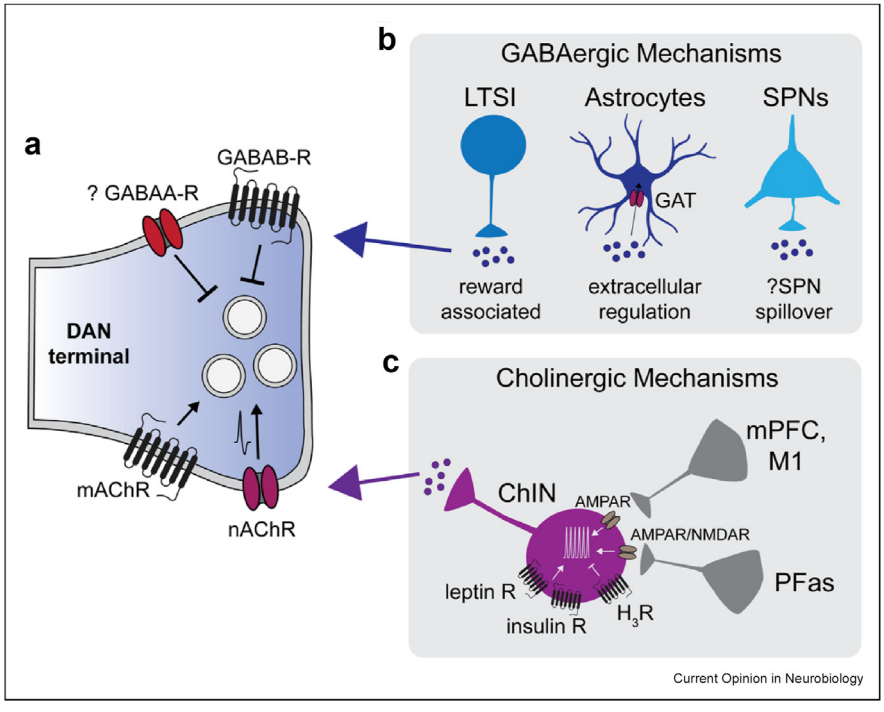
body of work that might provide mechanistic explanations for this dissociation.

To understand how local striatal regulation of dopamine may occur, we must consider the unique characteristics of dopaminergic innervation and release. Although sparse, DANs provide extensive unmyelinated innervation to target structures, particularly the striatum. A single DAN can make more than 350,000 synapses in striatum alone, and the axons are so highly branched that one axon can occupy more than 5 % of the striatal volume [10]. While only ~1/3rd of DAN varicosities contain active zone machinery like that found in glutamatergic synapses, they nevertheless release dopamine with high release probability in a relatively focal manner [8]. The local mechanisms modulating dopamine release from these sites can be homosynaptic, via responses to dopamine itself, or heterosynaptic, via responses to other signaling molecules. While a thorough catalogue of these mechanisms can be seen elsewhere [11], we focus here on how striatal circuits - including both GABAergic and cholinergic interneuron subtypes as well as their cortical and thalamic drivers - interact with DAN terminals to either initiate the release of dopamine or modulate the release of dopamine initiated by spiking in midbrain DANs (Figure 1). Then we look at some of the first *in vivo* studies of acetylcholine-dopamine interactions in striatum and broadly discuss necessary future work in understanding the roles of midbrain versus striatal dopamine regulation.

## Regulation by local circuit GABA

GABA has long been reported to modulate striatal dopamine [12]. As the striatum is primarily comprised of GABAergic cells, the vast majority of which participate in long-loop feedback circuits to the midbrain, it is challenging to align specific GABAergic sources to local dopamine modulation *in vivo*. The sources of striatal GABA may include GABAergic afferents, extrasynaptic action potential-independent spillover from spiny projection neurons (SPNs), low threshold spiking interneurons (LTSIs), GABA co-released by dopamine neurons, and ambient GABA tone set by uptake transporters or release of GABA from striatal astrocytes [12–16]. Within the striatum, GABA may act on ionotropic $GABA_A$ and/or metabotropic $GABA_B$ receptors to attenuate dopamine release. There is ultrastructural evidence for $GABA_B$ receptors on dopamine-like axons in non-human primates [18] and rats [19]. Furthermore, striatal $GABA_B$ agonism attenuates dopamine release

**Figure 1**




Cellular mechanisms for striatal control of DA release. (**a**) Key neurotransmitter receptors on striatal DAN terminals that can modulate dopamine release. Arrowheads indicate facilitation of synaptic vesicle release while straight lines indicate suppression of synaptic release. (**b**) Potential sources of GABAergic modulation include low-threshold spiking interneurons (LTSIs), regulation of extracellular GABA levels via astrocyte GABA uptake transporters (GAT), and GABA spill-over from spiny projection neurons which comprise ~95 % of striatal neurons and extensively collateralize locally. (**c**) Regulation of cholinergic-mediated DA release is impacted by both regulators of cholinergic interneuron excitability (including leptin, insulin, and H3-histamine receptors, among others) and glutamatergic drive from both cortical and thalamic projection neurons.

both *in vivo* and in acute slice [13,15,20], while $GABA_B$ antagonism potentiates dopamine [13,15,17]. These effects occur independently from nicotinic acetylcholine receptor (nAChRs) activity described in 'Regulators of cholinergic-mediated dopamine regulation' below. While this work strongly implies GABA can directly suppress dopamine release via presynaptic $GABA_B$ receptors, the evidence for modulation by $GABA_A$ has been less consistent. *In vivo*, effects of $GABA_A$ modulation on extracellular dopamine are ablated by local kainic acid lesions, which lesion striatal cell bodies while leaving afferents intact, suggesting the effects of $GABA_A$ are mediated by striatonigral feedback or striatal interneurons. Work from the España lab [15] later supported these findings, demonstrating $GABA_A$-mediated reductions in evoked dopamine release are blocked by $GABA_B$ antagonism. However, recent work from the Khaliq lab [16] using whole-cell and perforated patch recordings on DAN axons reveals further complexity, with the degree of $GABA_A$-mediated modulation potentially being a function of striatal activity level.

One unresolved issue is whether there are roles for phasic GABA in the regulation of dopamine release from DAN terminals or whether all modulatory effects are a function of the ambient or tonic levels of striatal GABA. Functionally speaking, the former could permit discrete, temporally specific modulation of striatal dopamine while the latter would be less precise, influencing dopamine levels over the time course of seconds to minutes. Recently, we demonstrated dorsal striatal LTSIs, which have phasic activity to rewarded choice outcomes, can regulate dopaminergic axons, raising the possibility of more temporally discrete dopamine control. Nevertheless, two points from our study argue against precise temporal control — (1) using a slice preparation with simultaneous excitatory optogenetic control of DAN terminals and inhibitory optogenetic control of LTSIs, we found that inhibition of LTSIs increased evoked striatal dopamine even if LTSI manipulation occurred before optically-evoked dopamine release and (2) these effects were mediated exclusively by slower $GABA_B$ receptor signaling [17]. Recent work highlighting a role of GABA uptake transporters, including those on astrocytes, which regulate tonic GABAergic control of evoked dopamine in dorsal but not ventral striatum, lends further strength to the idea of less temporally precise mechanisms for GABAergic modulation of striatal dopamine [12,14]. Resolving the respective roles of these fast and slow GABARs on dopamine release, in addition to a greater knowledge of how different striatal interneuron subtypes are modulated during behavior, will help to define the constraints of local GABAergic control of striatal dopamine.

## Regulators of cholinergic-mediated dopamine regulation

The effects of cholinergic transmission on striatal dopamine release have received considerable attention (see [21,22] for review). The two primary sources of striatal acetylcholine are local cholinergic interneurons (ChINs) and long-range projections from pedunculopontine and laterodorsal tegmental nuclei [23,24]. Although these cholinergic midbrain afferents shape action strategies [25], only ChINs directly modulate dopamine release in the striatum [26]. Several landmark papers uncovered direct, local mechanisms whereby nicotinic transmission enhanced striatal dopamine release [27—29]. Dopamine evoked by single or low-frequency electrical stimulation in acute striatal slices can be partially blocked by nAChR antagonism [27—29]. In baseline conditions, repeated electrical stimulation induces a short-term depression that limits subsequent dopamine release. However, with nAChR antagonism this suppression is lifted, leading to the hypothesis that acetylcholine action on nAChRs serves as a low-pass filter at DAN terminals [28,29]. Our understanding of how nAChRs locally control dopamine has evolved substantially in the last 15 years with the power of optogenetics. Preparations using slice FSCV with selective optogenetic activation of ChINs were sufficient to drive dopamine release independent of direct stimulation of DAN axons [21,30]. Recently, elegant direct recordings of dopamine axons in the striatum have shown that ChIN activation of dopamine axons via nAChRs generates local action potentials that broaden the area of dopamine release [31,32]. Muscarinic acetylcholine receptors also have complex contributions to cholinergic control of accumbens dopamine - $M_5$ receptors on DAN terminals enhance dopamine release while $M_2$ and $M_4$ auto-receptors on ChINs restrain cholinergic-mediated dopamine release [33].

Multiple neuromodulators, including leptin, insulin, and histamine, have recently been shown to exert local heterosynaptic control over dopamine release indirectly via ChIN modulation. Leptin is a metabolic hormone important for signaling satiety and regulating energy expenditure known to interact with the mesolimbic dopamine system. The Rice lab [34] has identified leptin receptors on ChIN cell bodies and processes and found that leptin increased evoked dopamine concentrations via increases in ChIN excitability. Insulin is another metabolic hormone classically considered a satiety signal which has also been recently shown to locally modulate striatal dopamine [35,36]. The striatum expresses abundant insulin receptors, and insulin can locally influence dopamine release either via increasing ChIN excitability or via astrocyte-released ATP directly mediating dopamine release from terminals [35,37,38]. Histamine has numerous regulatory

functions, most notably for immune responses and sleep-wake cycle control [39,40]. Recently Trudeau and colleagues [41] demonstrated that histamine $H_3$ receptors are expressed on ChINs, and activation of these $H_3$Rs reduces the firing rates of ChINs in ventral striatum, concomitant with a decrease in electrically evoked dopamine release.

A wealth of evidence shows that striatal dopamine is also under glutamatergic regulation via cortical and thalamic excitatory drive of ChINs [42–44], shown via optogenetic recruitment of these structures combined with FSCV and microdialysis measures. These studies have revealed multiple levels of circuit-specific regulation that could have unique impacts on behavior – mPFC inputs drive feed-forward striatal dopamine release to specific striatal regions [45], endocannabinoid signaling within these cortical terminals constrains feed-forward dopamine release [44], and parafascicular driven ChIN-evoked dopamine release requires both NMDAR and AMPAR activation in contrast to exclusive AMPAR requirements from cortical inputs [43]. Taken together, the data present a compelling mechanistic picture for local ChIN-mediated modulation of striatal dopamine release. In these scenarios, anything that modulates ChIN output, including changes in excitability of ChINs or their drive by excitatory projections, could potentially have strong effects on uncoupling striatal dopamine from DAN somatic spiking. However, whether and under what conditions these phenomena occur in more dynamic *in vivo* systems and what specific computational advantages they provide remains unclear (see 'New insights into local dopamine control from *in vivo* studies' below for further discussion).

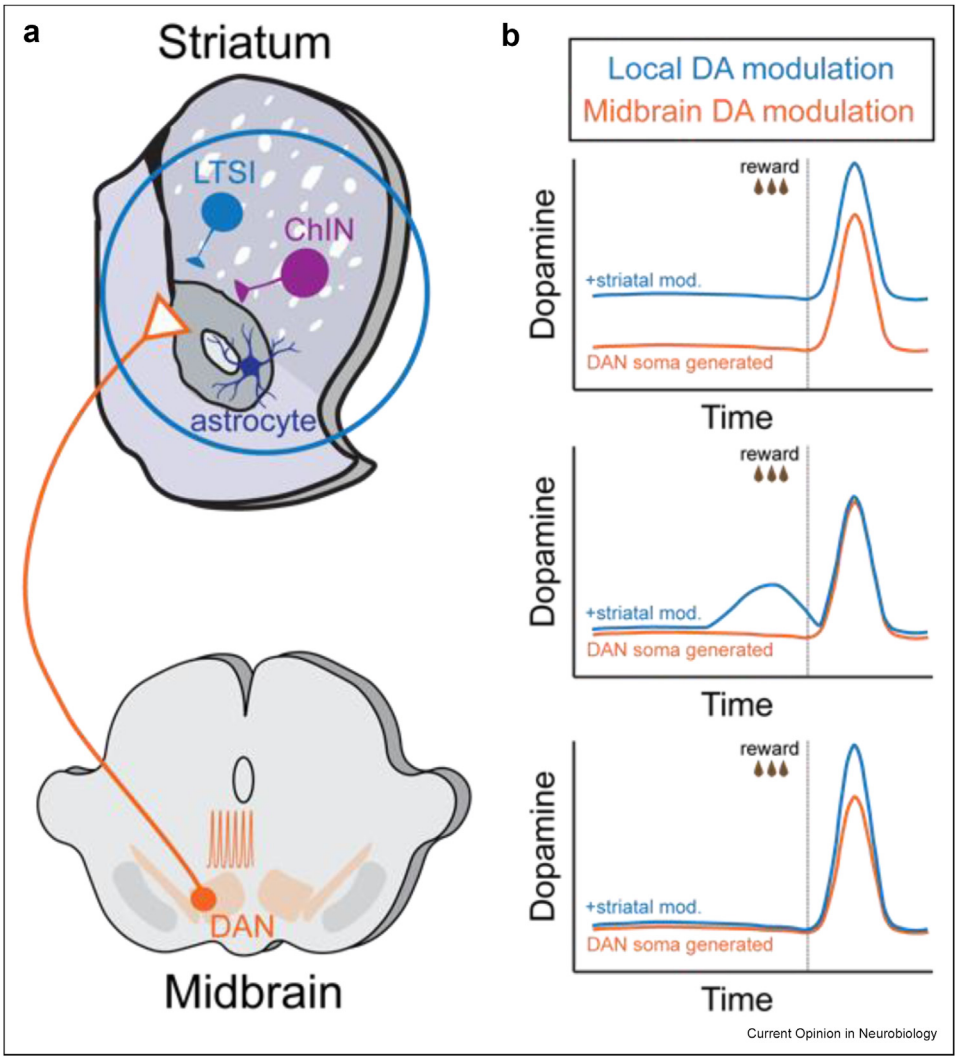
## New insights into local dopamine control from *in vivo* studies

*In vitro* preps have given us insight into multiple levels of local striatal control over dopamine, which are now being expanded upon in dynamic *in vivo* systems. The use of sensors for acetylcholine and dopamine measured via fiber photometry has provided our first insights into striatal dopamine modulation in awake behaving animals. Mohebi and colleagues [46] showed that reward approach behaviors were marked by dopamine release ramps that coincided with ramps of ChIN calcium activity, but not changing single-unit spiking activity of DANs in the lateral VTA. While this work supports the idea of local cholinergic modulation of striatal dopamine, two other studies in dorsal and ventrolateral striatum paint a more complex picture. The Sabatini and Tritsch labs [47,48] performed simultaneous imaging of dopamine and acetylcholine sensors and found these signals to be continuous anti-correlated oscillations, with the peak of the dopamine signal preceding that of acetylcholine by ~100msec. Amazingly, this relationship reproducibly appeared at rest, during locomotion, spontaneous reward delivery, and in an operant task modulated by decision history and outcome. Despite the robustness of these state-independent patterns, neither team found evidence that they were supported by local cholinergic modulation of dopamine release. Targeted disruption of acetylcholine release via tetanus toxin or genetic ablation of β2-nicotinic receptors from DANs had no impact on the robust oscillatory patterns of striatal dopamine and acetylcholine. These results however contrast with the blunting of sensory-evoked dorsal striatal dopamine transients in response to pharmacological blockade of β2 nicotinic receptors via DHβE [31]. It is presently unclear what accounts for the discrepancies between *in vivo* experiments and their relationship to the extensive *in vitro* literature which would have predicted cholinergic boosting of dopamine within the striatum. As with all *in vivo* experiments, a major caveat is that only a small subset of behavioral processes is investigated, and it remains possible that dopamine-acetylcholine interactions are relevant at discrete times or for only a subset of behavioral processes. Furthermore, these data do not invalidate the importance of local striatal dopamine-acetylcholine interactions – dopamine can inhibit striatal acetylcholine via inhibitory D2-dopamine receptor mechanisms, and perturbing these pathways disrupts choice patterns, supporting the importance of both neuromodulatory systems in regulating downstream behavior [47]. Together, these first *in vivo* insights remind us of the large task ahead in merging understanding from mechanistic acute slice studies with the function of these systems in the behaving brain.

## Looking forward: untangling how local modulation of dopamine impacts behavior

The expansive behavioral functions of dopamine have fueled searches for regulatory mechanisms that differentially impact behavior via distinct mechanisms of dopamine modulation at its striatal target. For example (Figure 2), in goal-directed choice, individuals typically control which options to select and how to perform those actions (sometimes defined as motor vigor). It is possible that either tonic levels (defined as any non-phasic signal) of dopamine or ramps that precede choice would modulate action vigor while the phasic signals at outcome would mediate reward learning (noting that some have argued pre-outcome ramps reflect a form of prediction signaling) [49,50]. In this scenario, vigor-related modulation could arise largely from local striatal dopamine regulation while outcome learning could reflect prediction error signals computed by midbrain DANs. While this dissociation of dopamine regulation may help shape both 'willingness to work' and choice selection by dopamine in the NAc [9,51], the accuracy of this model and the potential regulatory mechanisms remain elusive.

**Figure 2**




Integration of DAN somatic spiking and local DAN terminal modulation to generate behaviorally relevant DA signals in striatum. (**a**, bottom) Schematic of midbrain DAN somatic activity and (top) the potential local regulators of DAN terminals in striatum. Schematized striatal DA signal generated by DAN somatic spiking in response to unexpected reward (orange) and effects of local striatal modulation (blue). Three potential scenarios whereby local modulation further shapes this signal to alter baseline (tonic) dopamine levels (top), dopamine ramping prior to reward (middle), or outcome-associated dopamine.

In conclusion, the list of receptors on DAN terminals known to alter local dopamine release is large, including kappa-opioid [52], metabotropic glutamate [33], GABA [13,15], and acetylcholine [32,33] receptors. The regulated release of each cognate ligand in striatum is a potential opportunity to further sculpt the dopamine signals arising from spiking in the midbrain. As is clear from our first *in vivo* glimpse at acetylcholine-dopamine interactions, the combined use of viral-genetic tools to interrogate these systems while imaging dopamine within striatum during behavior will be key next steps. Furthermore, it will be necessary to delineate the potential time courses of these regulators — can local striatal modulation of dopamine only work on slow time scales, or can more phasic regulation occur as well? Addressing these two issues will provide a huge step forward in understanding how a single neuromodulator can have massively pleiotropic behavioral impacts.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Marc Fuccillo reports financial support was provided by National Institutes of Health. Elizabeth Holly 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.

## Data availability

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

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This study used Fast-scan Cyclic Voltammetry in acute slice with both electrical stimulation of striatum and optical stimulation of dopamine neuron terminals in striatum to assess local GABAergic modulation of dopamine release. It is shown that GABA and $GABA_A$ or $GABA_B$ receptor agonists can reduce the electrically stimulated release of dopamine independent of nicotine acetylcholine receptor activity. The optically stimulated release of dopamine is also shown to be reduced with application of GABA, and selective GABA receptor antagonism revealed receptor subtype specific modulation of dopamine release with $GABA_B$ receptor antagonism being sufficient to enhance release.

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This study used a combination of electrophysiological and photometric techniques in acute slice to identify mechanisms of dopamine axon modulation by $GABA_A$ receptors. The authors demonstrate axonal depolarization with $GABA_A$ agonism accompanied by reductions in axonal spike amplitude, propagation, and dopamine release. The mechanism is shown to involve sodium channel inactivation and shunting.

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This study used a combination of *in vitro* Fast-scan Cyclic Voltammetry and *in vivo* photometry to assess a role for low-threshold spiking interneurons (LTSIs) in the local modulation of dopamine release in striatum. *In vitro*, it is shown that optogenetic inhibition of LTSIs enhances optically evoked dopamine release while chemogenetic excitation of LTSIs impairs this dopamine release. Further, it is shown that this LTSI-dependent impairment of dopamine release is abolished by $GABA_B$ receptor antagonism and not $GABA_A$. *In vivo*, it is shown that LTSI inhibition enhances dopamine signaling and the rate of learning.

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This study included not only a breadth of *in vitro* techniques in acute slice preparations including functional imaging, amperometry, and electrophysiology, but it also included a photometric evaluation of dopamine in freely moving mice *in vivo*. The *in vitro* experiments revealed that nicotinic acetycholine receptor activity generates action potentials in dopamine axons that propagate and cause dopamine release in and beyond the area of acetylcholine binding. The *in vivo* experiment demonstrated impaired dopamine dynamics with the inhibition of nicotinic acetylcholine receptors.

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