The Role of Dopamine in Training Automaticity

Talia N. Lerner, Andrew J. Miller-Hansen, and Priscilla Ambrosi

Abstract Habits and motor skills serve to automate routine behaviors, allowing the fast and fluid execution of complex tasks while reducing cognitive load. However, automatic behaviors can be difficult to override and can become problematic when circumstances change. Therefore, the healthy brain must carefully adjudicate which actions to automate. In this chapter, we review the evidence that dopamine signals in the dorsal striatum control transitions from goal-directed behavior to automatic or habitual behavior. We examine how dopamine release related to the development of automaticity is regulated, what effects dopamine has on downstream striatal synaptic plasticity and circuit function, and how the role of dopamine in orchestrating downstream circuit function and behavior changes after automaticity is acquired.

Keywords Dopamine · Striatum · Basal ganglia · Habit · Motor skill · Automaticity · Learning · Synaptic plasticity

1 Introduction

Habits and motor skills serve to automate routine behaviors, allowing the fast and fluid execution of complex tasks while reducing cognitive load. However, automation comes at the cost of behavioral flexibility. Automated action sequences that were previously beneficial can become maladaptive if action-outcome contingencies shift. For example, excessive habit formation is thought to contribute to disruptive

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repetitive behavior and persistent reward-seeking even in the face of adverse consequences, behaviors that occur in disorders such as obsessive-compulsive disorder (OCD) and addiction. Therefore, the healthy brain must carefully adjudicate which actions to automate. How does it do so?

Key brain areas involved in habit formation and motor skill acquisition have been identified: the dorsomedial striatum (DMS; caudate in primates) is required for the early acquisition of action-outcome associations, whereas the dorsolateral striatum (DLS; putamen in primates) is required for transitions to automation involving stimulus-response learning. The roles of these key brain areas were first established using lesion studies in rodents. In these studies, lesions of the DLS impaired habit formation, whereas lesions of DMS impaired goal-directed behavior and enhanced habit formation (Yin et al., 2004, 2005; Yin & Knowlton, 2006).

These studies used operant training on a random interval task to elicit habitual behavior, defined as behavior that is insensitive to outcome devaluation. Random interval tasks are not the only tasks that can be used to elicit habits. For example, other studies have used signaled fixed ratio ("discrete ratio") tasks to elicit habits (Vandaele et al., 2017), studied overtraining in a T-maze task (Thorn et al., 2010), or examined the learning of ordered sequences of actions (Turner et al., 2022; for a more expansive review of behaviors used to elicit habits, see Lerner, 2020). In vivo recording studies during these various habit formation tasks largely confirm the importance of DLS for habit formation. As actions transition to habitual control, DLS engagement increases while DMS engagement decreases or remains steady (Thorn et al., 2010; Gremel & Costa, 2013; Vandaele et al., 2019; Smith et al., 2021).

Motor skill acquisition, which also involves the development of automaticity, appears to rely on similar brain regions as habit formation. Lesions of DMS impair early learning on the accelerating rotarod test of motor skill acquisition, but mice can attain good performance with continued training, presumably due to intact DLS function. In contrast, lesions of DLS impair learning on the accelerating rotarod and other motor skill tasks permanently (Yin et al., 2009; Dhawale et al., 2021; Wolff et al., 2022). In vivo recording studies during the learning and consolidation of skill on the accelerating rotarod task also largely align with what has been observed for habit formation. Namely, the number of behavior-modulated neurons in DMS increases in early training and fades in late training, whereas the number of behavior-modulated neurons in DLS increases in late training (Yin et al., 2009).

Although the details across many studies of habit formation and motor skill acquisition differ, the general theme is consistent: a shift from DMS-dependent behavior to DLS-dependent behavior occurs with the emergence of automaticity. How does this shift occur? In this chapter, we examine evidence for the hypothesis that dopamine drives changes in striatal circuitry relevant to automaticity and that dopamine circuits are a critical mediator for the transfer of information between striatal subregions required for transitions to automaticity to occur.

2 DLS Dopamine as a Controller of Transitions to Automaticity

Lesion and recording studies show that shifts towards automaticity require the DLS. Likewise, dopamine signaling in DLS appears required for this shift. Lesions of DLS-projecting dopamine neurons using the selective neurotoxin 6-OHDA impair habit formation (Faure et al., 2005). Dopamine receptor blockers infused into the DLS also impair habit formation and motor skill acquisition (Yin et al., 2009). Ablating Aldh1a1+ dopamine neurons, a molecularly-defined subpopulation of dopamine neurons which primarily projects to DLS, prevents motor skill acquisition in the accelerating rotarod task while causing only very minimal disruption of general motor function (Sgobio et al., 2017; Wu et al., 2019).

Why is dopamine signaling in the DLS so critical to automaticity transitions? Dopamine is a critical controller of downstream striatal circuit function. Dopamine receptors are robustly expressed in striatal neurons, including spiny projection neurons (SPNs), which make up ~90% of the neurons in the striatum, as well as fast-spiking interneurons (FSIs), low-threshold spiking interneurons (LTSIs), and cholinergic interneurons (ChIs) (Kreitzer, 2009). Dopamine receptors are G-Protein Coupled Receptors (GPCRs) that are divided into two primary subclasses: (1) D1-like receptors (D1, D5), which are G_s-coupled, and (2) D2-like receptors (D2, D3, D4), which are $G_{i/o}$-coupled. SPNs generally express either D1 receptors (and participate in the "direct pathway," projecting directly to the output nuclei of the basal ganglia) or D2 receptors (and participate in the "indirect pathway," projecting directly to the globus pallidus external segment and only indirectly to the basal ganglia output nuclei; Fig. 1). FSIs and LTSIs primarily express D5 receptors, while ChIs primarily express D2 and some D5. D3 and D4 are largely not expressed in the dorsal striatum, although D3 receptors are expressed in the ventral striatum (Bouthenet et al., 1991; Meador-Woodruff et al., 1996). Dopamine D2 receptors are also notably expressed presynaptically at dopamine axon terminals in the striatum, where they inhibit dopamine release and promote dopamine reuptake through dopamine transporters (Ford, 2014). Thus, dopamine is well-positioned to influence striatal circuit function by a variety of mechanisms and sites of action, but disentangling the many effects of dopamine on different cell types within the striatal microcircuit, and how these effects may interact with each other and change with learning, is quite complicated.

Dopamine can exert relatively fast actions on SPNs, for example, controlling the excitability of D1-SPNs (Lahiri and Bevan, 2020). In addition to affecting SPN activity acutely, dopamine also strongly regulates long-term synaptic plasticity in the striatum. Excitatory glutamatergic inputs from the cortex and thalamus synapse onto both D1- and D2-SPNs (Doig et al., 2010; Wall et al., 2013; Huerta-Ocampo et al., 2014; Guo et al., 2015), and the potentiation and/or depression of these excitatory synapses have long been implicated as key features of habit formation and motor skill learning (Fig. 1). Long-term potentiation (LTP) of excitatory inputs to D1-SPNs requires D1 receptor activation. Long-term depression (LTD) of excitatory

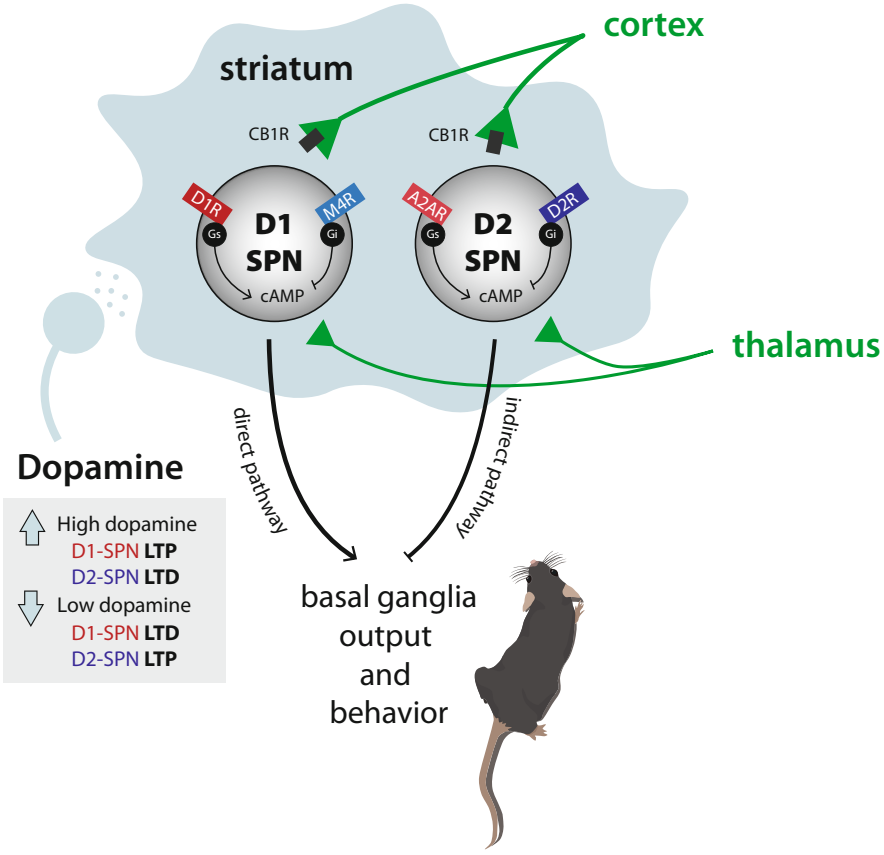

Fig. 1 Synaptic plasticity onto DLS neurons during transitions to automaticity. Long-term synaptic plasticity of excitatory inputs onto the DLS neurons, including D1- and D2-SPNs, has been strongly implicated in transitions to automaticity. The DLS receives excitatory inputs from the cortex and thalamus. Some differences exist between these inputs. For example, cortical inputs express presynaptic cannabinoid CB1 receptors while thalamic inputs do not. Dopamine release within the striatum affects D1- and D2-SPNs differently, due to their expression of different dopamine receptors. D1 dopamine receptors (D1Rs) on D1-SPNs are G_s-coupled and stimulate cAMP production, whereas D2 dopamine receptors (D2Rs) on D2-SPNs are $G_{i/o}$-coupled and inhibit cAMP production. Therefore, high dopamine levels are expected to promote conditions for D1-SPN LTP and D2-SPN LTD. Low dopamine levels are expected to promote conditions for D1-SPN LTD and D2-SPN LTP. However, in each type of SPN, other neuromodulator receptors are positioned to counterbalance dopamine signaling. D1-SPN express $G_{i/o}$-coupled M4 acetylcholine receptors, for instance, while D2-SPNs express G_s-coupled A2A adenosine receptors. As a result, the balance of synaptic plasticity occurring in each cell type will be determined by a complex milieu of neuromodulation in combination with the activity of excitatory inputs from the cortex and thalamus. Ultimately, changes in D1- and D2-SPN activity due to these synaptic plasticity events will control the output of the striatum (via the direct pathway from D1-SPNs and the indirect pathway from D2-SPNs) to basal ganglia output nuclei and drive changes in behavior

inputs to D2-SPNs requires D2 receptor activation. Therefore, conditions of high dopamine should promote D1-SPN LTP and D2-SPN LTD. Conditions of low dopamine should promote the opposite: D1-SPN LTD and D2-SPN LTP (Kreitzer & Malenka, 2008; Surmeier et al., 2009; Lerner & Kreitzer, 2011).

Given the critical role that striatal dopamine release plays in the development of automatic behavior, it is important to understand the anatomy of dopamine projections to the dorsal striatum as well as how the natural patterns of activity in these projections during learning control in vivo dopamine release.

3 Anatomy of Dopamine Projections to the DLS

Striatal dopamine signals arise due to the release of dopamine by dopaminergic inputs to the striatum from the midbrain. Dopamine neurons in the midbrain—including the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA)—form highly complex axonal arborizations in the striatum. Although single cell tracing studies show how large and complex these arborizations can be, covering in some cases more than 1 mm across the rat striatum (Matsuda et al., 2009), other studies designed to look at the collateralization of dopamine axons find that they generally project to restricted striatal subregions. For example, a dopamine neuron that projects to DMS may have a large axonal arborization covering a broad area within DMS, but the axon collateralizes minimally to DLS or to the ventral striatum (Lerner et al., 2015). Consistent with the view that individual dopamine neurons innervate specific striatal subregions, studies of molecular diversity in dopamine neuron subpopulations have identified molecular markers for subsets of dopamine neurons that follow topographical projection patterns (Poulin et al., 2018), and studies of dopamine release from these molecularly-defined subtypes indicate that local dopamine release is closely related to the activity of cell bodies that innervate that area (Azcorra et al., 2022). Therefore, we can conclude that dopaminergic projections to the midbrain are arranged as largely parallel circuits, perhaps designed to deliver distinct information to different striatal subregions specializing in learning separable aspects of motivated behavior.

Key to the question of transitions to automaticity is the question of what information is transmitted by which dopamine cell types to the DLS (Fig. 2). In general, DLS-projecting dopamine neurons are located across the medial-lateral span of the SNc, largely in the ventral tier (Lerner et al., 2015; Farassat et al., 2019; Pereira Luppi et al., 2021). These ventral tier SNc dopamine neurons express the transcription factor Sox6 and have generally been observed to transmit motor-related information, such as movement starts, rather than reward-related activity (Jin & Costa, 2010; Howe & Dombeck, 2016; Dodson et al., 2016; da Silva et al., 2018; Pereira Luppi et al., 2021). A subset of the ventral tier Sox6+ SNc dopamine neurons are Aldh1a1+. This Aldha1a1+ subset is the most vulnerable to degeneration in Parkinson's disease (Cai et al., 2014), although by the time of

Parkinson's disease diagnosis, that is, when classic Parkinsonian motor symptoms are evident, almost all ventral tier dopamine neurons are dead (Surmeier et al., 2017).

Interestingly, Aldh1a1+ dopamine neurons preferentially innervate striosomes (also known as patches), which are histochemically defined areas of the striatum with high mu-opioid receptor expression (Brimblecombe & Cragg, 2017) (Fig. 2). Striosomes make up ~10% of the striatum. Unlike the rest of the dorsal striatum (known as the matrix), striosomes receive input from more limbic areas such as prelimbic cortex and the bed nucleus of the stria terminalis and send outputs directly back to SNc dopamine neurons as well as to the lateral habenula (Smith et al., 2016; Brimblecombe & Cragg, 2017; Hong et al., 2019; McGregor et al., 2019). Striosomes may play a role in habit formation and motor skill acquisition (Lawhorn et al., 2009; Nadel et al., 2020). Given that ablation of Aldh1a1+ dopamine neurons does not cause overt motor symptoms, but does disrupt motor skill acquisition (Wu et al., 2019), it may be that striosome dopamine signaling has a distinct function in transitions to automaticity.

In addition to receiving dopaminergic input from the ventral tier of the SNc, the DLS also receives some dopaminergic input from VTA dopamine neurons (Lerner et al., 2015; Howe & Dombeck, 2016) (Fig. 2). Single axon imaging by Howe and Dombeck (2016) indicates that reward-related signals in DLS primarily arise from this minority of VTA axons. Future work will be required to define the importance of these reward-related VTA dopamine signals in the DLS for transitions to automaticity.

4 In Vivo Activity of Dorsal Striatal Dopamine Circuits During Transitions to Automaticity

Measurements of dopamine transmission in vivo are important for understanding when behavior-linked dopamine release events occur so that we can build models of how these release events might coordinate transitions to automaticity. There are two major approaches for monitoring dopamine release in vivo with relatively good (behaviorally relevant) temporal precision: fast-scan cyclic voltammetry (FSCV) and imaging or fiber photometry of fluorescent sensors. FSCV uses a carbon fiber electrode cycling through various potentials to detect extracellular dopamine based on a redox signature. Imaging and fiber photometry are optical approaches for detecting fluorescence emitted either from dopamine sensors (e.g., dLight, GRAB-DA (Cosme et al., 2018)) or from neuronal activity indicators (e.g., GCaMP (Looger & Griesbeck, 2012)) expressed in dopamine cell bodies or axon terminals. As a third approach that does not directly monitor dopamine release, one can use in vivo electrophysiology to examine dopamine cell body firing patterns with excellent temporal precision. In vivo electrophysiology can provide an excellent readout of dopamine cell body activity, but it can be difficult to "tag" dopamine neurons according to their

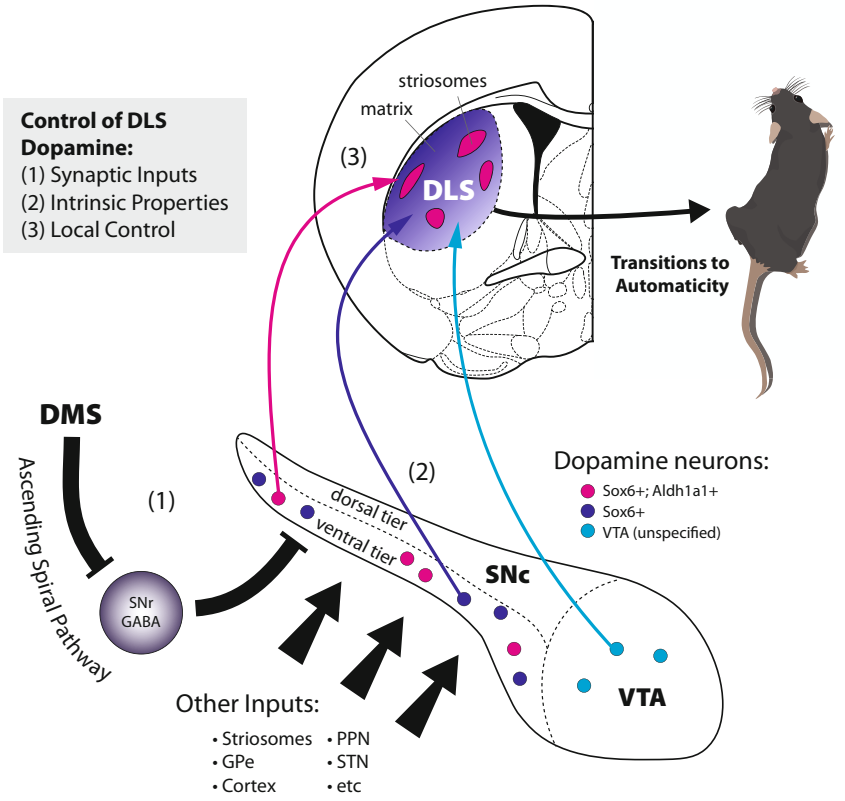

Fig. 2 Control of DLS dopamine release: anatomy, physiology, and circuit function. DLS dopamine is required for transitions to automaticity. Most DLS-projecting dopamine neurons are located in the ventral tier of the substantia nigra pars compacta (SNc) and express the transcription factor Sox6 (dark blue circles). A subset of Sox6+ dopamine neurons also express Aldha1a1 (magenta circles). This subpopulation of dopamine neurons preferentially innervates the striosomes within the DLS and is required for learning on the accelerating rotarod task, but its role in habit formation has not been determined. A small number of dopamine neurons in the ventral tegmental area (VTA) also project to DLS (cyan circles). These DLS-projecting VTA dopamine neurons are of an unspecified molecular subtype. They may be important for communicating reward-related information to the DLS. Dopamine release by DLS-projecting dopamine neurons may be regulated on a number of levels: via (1) changes in input activity or synaptic plasticity at inputs that alter firing patterns, (2) changes in dopamine neuron excitability and intrinsic properties controlling firing rates, and (3) local control of terminals by presynaptic receptors. Notable synaptic inputs to dopamine neurons include direct inputs from striosome D1-SPNs in the striatum and inputs from the globus pallidus external segment (GPe), cortex (primarily motor and somatosensory cortices), pedunculopontine nucleus (PPN), and subthalamic nucleus (STN), among others. One potentially important disynaptic input pathway for modulating the activity of DLS-projecting dopamine neurons is the "ascending spiral" pathway by which DMS activity (from matrix D1-SPNs) may relieve tonic inhibition of DLS-projecting dopamine neurons by substantia nigra pars reticulata (SNr) GABA neurons

projection targets to determine the ultimate downstream release sites of dopamine. Although many studies have examined in vivo dopamine transmission in the ventral striatum, fewer have probed in vivo dopamine transmission in the dorsal striatum, especially during transitions to automaticity. However, there are some interesting observations arising from the recent literature, which may require a readjustment of models on how DLS dopamine supports transitions to automaticity.

In a pioneering study of the in vivo activity of SNc dopamine neurons during learning, Jin and Costa (2010) used in vivo electrophysiology to record dopamine cell body activity during the learning of a fixed action sequence (a fixed ratio of 8 lever presses per reward, performed in a rapid sequence). They found patterns of phasic dopamine neuron firing emerging with learning at the initiation and termination of the action sequence, suggesting that dopamine helps "chunk" action sequences to be automated. The projection targets of SNc dopamine neurons recorded in this study were not determined; however, start/stop activity was observed in both DMS and DLS SPNs, perhaps indicating the dopamine signal is sent to both regions. The habitual nature of this action performance was not determined, and fixed ratio tasks in general do not lead to robust habit formation.

Another very interesting study of dopamine activity in the dorsal striatum was conducted by Hamid et al. (2021), who examined GCaMP activity in DMS and DLS dopamine axons during learning through a large chronic imaging window over the dorsal striatum. They observed directional waves of dopamine axon activity in response to rewards. In a Pavlovian task, these reward-associated waves progressed from DLS to DMS, whereas in an instrumental task, the waves progressed from DMS to DLS (Hamid et al. 2021). The authors suggested that DMS-to-DLS dopamine waves during the performance of an instrumental task could serve as a mechanism for credit assignment in action-outcome learning, allowing animals to tie specific aspects of their behavior to eventual reward. Such a mechanism is intuitively related to goal-directed behavior; however, DMS-DLS waves could also, over time, participate in a mechanism that controls transitions to automaticity with repeated experience. This specific study did not explicitly test for habit formation or motor automaticity after long-term training on an instrumental task, so it is still unclear if DMS-DLS dopamine waves are involved in transitions to automaticity or only in goal-directed instrumental responding.

Another study examining GCaMP activity in DMS and DLS dopamine axons via fiber photometry in mice found that DLS dopamine axon dynamics change over time in a random interval operant task, a task that generally leads to habit formation. However, strong associations between DLS dopamine dynamics and habit formation in individual mice were not observed (Seiler et al., 2022). Instead, changes in DMS dopamine were found to drive operant responding and transitions towards punishment-resistant reward-seeking. Van Elzelingen et al. (2022) took a similar but different approach to Seiler et al. (2022), using FSCV in rats to examine changes in dopamine release during a random interval operant task. They used a novel two-step task in which a random interval schedule on one lever (a "seeking"

lever) allowed access to a second lever (a "taking" lever) that would then lead to reward delivery on a fixed ratio 1 schedule (1 lever press for reward). They verified that their task leads to habit formation using a sensory-specific satiety test and additionally showed that the most habitually acting rats come to prefer the seeking lever to the taking lever with extended training, despite the seeking lever being less proximal to reward delivery. Nevertheless, like Seiler et al. (2022), van Elzelingen et al. (2022) observed that DMS, not DLS, dopamine transients were related to responding on and preferring the seeking lever, linking DMS dopamine to habit formation. These results are puzzling, given a preponderance of other evidence that DLS dopamine and circuit function are required for habit formation. However, they may still be consistent with a model in which DMS-dependent associative learning precedes habit formation and do not rule out that there is an additional requirement for DLS dopamine.

It is possible that DLS dopamine signals required for transitions to automaticity are not temporally linked to specific actions. Perhaps, tonic extracellular levels of DLS dopamine could serve simply as a necessary permissive signal for automaticity transitions. Here, there is a curious distinction in the dopamine requirements for habit formation and motor skill acquisition. Mice that lack NMDA receptors in dopamine neurons, and which therefore lack the dopamine neuron burst firing that gives rise to phasic dopamine signals in the striatum, have impaired habit formation (Wang et al., 2011). However, surprisingly, they have intact motor skill acquisition (Zweifel et al., 2009). According to these data, phasic DLS dopamine transients might be important for habit formation but not motor skill acquisition. However, even these phasic transients required for habit formation do not necessarily need to correspond to rewards or reward-predicting cues. Rather, since most phasic DLS dopamine activity is closely tied to motor behavior (Jin & Costa, 2010; Howe & Dombeck, 2016; Dodson et al., 2016), phasic DLS dopamine could be playing its primary role in behavioral chunking and the refining of action sequences. Such a motor-related role for DLS dopamine could allow it to train the performance of habitual action sequences, which are not (by definition) closely linked with reward outcomes. A very interesting recent study of DLS dopamine signaling during spontaneous locomotor behavior showed that DLS dopamine transients that occur in the absence of reward can still reinforce simple behavioral elements of locomotion and exploration in an open field (Markowitz et al., 2023). These data could be consistent with a role for DLS dopamine in the assignment of motivational value to actions, i.e., DLS dopamine could be a mechanism for assigning "action salience" as suggested by Berridge (2021). Further studies of DLS dopamine dynamics in a broader array of tasks, including both habit formation and motor skill acquisition tasks, and in combination with simultaneous tracking of subsecond motor "syllables" making up complex behavioral sequences (Markowitz et al., 2018, 2023) will likely be clarifying. Further optogenetic investigations examining the temporal dynamics of DLS dopamine required for automaticity transitions would also be useful.

5 Mechanisms Controlling DLS Dopamine Release

If DLS dopamine release is required for transitions to automaticity, it is natural to ask what mechanisms control this release. Dopamine release is controlled at several levels: (1) global control of phasic firing activity at cell bodies by synaptic inputs, (2) global control of phasic firing activity at cell bodies through changes in intrinsic properties, and (3) local control of dopamine terminals within the striatum (Fig. 2). The global vs. local distinction refers to changes in dopamine neuron firing patterns, which will propagate globally (though likely not perfectly) throughout the axonal arborization of a dopamine neuron vs. changes occurring locally at dopamine terminals in the striatum, which may be restricted to small subregions of an axonal arborization. Because of this distinction, monitoring the activity of dopamine neuron cell bodies alone may not be sufficient to understand how patterns of downstream dopamine release control behavior. The importance of global vs. local mechanisms for controlling dopamine release in the striatum is a topic of ongoing debate, as we discuss below.

First, we will discuss the idea of local control, which is relatively new. Given the large axonal arborizations of dopamine neurons, local control is an appealing mechanism by which dopamine release might be regulated in smaller functional areas within the striatum. In rats, simultaneous electrophysiological recordings of dopaminergic neurons in VTA and imaging of dopamine release in the nucleus accumbens, where most VTA axons project, revealed increases in dopamine release that did not follow increases in the cell body firing rate (Mohebi et al., 2019). One possible mechanism underlying this dissociation is acetylcholine-mediated modulation of dopaminergic terminals in the striatum. ChIs make axo-axonic synapses onto dopamine terminals (Kramer et al., 2022) and can trigger both action potentials (Liu et al., 2022) and dopamine release (Threlfell et al., 2012; Cachope et al., 2012; Liu et al., 2022) by activating nicotinic acetylcholine receptors (nAchRs) expressed on dopamine terminals. Despite the growing evidence that acetylcholine *can* trigger dopamine release from dopamine terminals in the striatum, it is unclear *when*, *where*, and *how* this phenomenon impacts in vivo circuit function and behavior. Acetylcholine-mediated dopamine release requires a synchronous activation of ChIs (Threlfell et al., 2012; Cachope et al., 2012), which can be achieved using optogenetics, but may not occur physiologically. In two studies specifically examining DLS, the activity in dopamine terminals closely followed the somatic activity in SNc (Azcorra et al., 2022) and dopamine release was undisturbed by perturbations in cholinergic signaling (Krok et al., 2022). Thus, it is not clear that local acetylcholine modulation of dopamine terminals is critical for DLS dopamine function and transitions to automaticity.

Dopamine itself is also a known regulator of local dopamine release in the striatum, acting through D2 autoreceptors expressed on presynaptic terminals. The activation of D2 autoreceptors leads to an overall decrease in dopamine release via fast and slow mechanisms, such as lowering the excitability of presynaptic terminals and increasing the rate of dopamine uptake (Zhang & Sulzer, 2012; Nolan et al.,

2020). Interestingly, basal D2 receptor occupancy is heterogeneous in the striatum, leading to compartmentalized responses to changes in dopamine levels through this mechanism. Higher D2 receptor occupancy would lead D2 receptor-expressing cells to be less responsive to phasic increases in dopamine, but perhaps more sensitive to decreases in dopamine release. One study in mice suggested that basal occupancy is higher in the dorsal vs. ventral striatum, but did not discriminate between DMS and DLS (Gowrishankar et al., 2018).

Besides releasing dopamine, dopamine terminals in the striatum co-release the inhibitory neurotransmitter GABA (Tritsch et al., 2012), which may have its own local effects on dopamine release through presynaptic GABA receptors. GABA decreases dopamine release in the striatum via presynaptic $GABA_A$ and $GABA_B$ receptors expressed on dopamine terminals (Lopes et al., 2019). The activation of $GABA_A$ receptors in particular leads to depolarization-dependent inactivation of sodium channels and shunting inhibition in dopamine axons, which attenuate propagating spikes on a distance-dependent manner (Kramer et al., 2020). In addition, $GABA_A$ receptor activation lowers dopamine release probability during "burst-like" dopamine terminal stimulation (Patel et al., 2022). Notably, the role of D2 autoreceptors and axonal GABA receptors on striatal dopamine terminals has mostly been studied in acute brain slices. Thus, the importance of these mechanisms for transitions to automaticity remains unclear.

Despite potential local tuning of dopamine release by the mechanisms described above, dopamine release in DLS is primarily related to the firing of DLS-projecting dopamine cell bodies (Azcorra et al., 2022). Dopamine neurons fire in two modes: tonic and phasic. Tonic firing is regular low-frequency firing (<10 Hz) driven by cell autonomous pacemaking mechanisms. Although these pacemaking mechanisms are still under some debate, major regulators are L-type Cav1.3 calcium channels, small-conductance calcium-activated potassium (SK) channels, and Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) channels (Surmeier et al., 2005; Puopolo et al., 2007; Guzman et al., 2009; Shin et al., 2022). DLS-projecting SNc dopamine neurons are particularly robust in their expression of HCN channels (Lammel et al., 2011; Lerner et al., 2015). Pacemaking in DLS-projecting dopamine neurons is also more sensitive to manipulations of Cav1.3 than pacemaking in DMS-projecting dopamine neurons (Shin et al., 2022). Therefore, changes in HCN or Cav1.3 expression or function could impact tonic firing patterns of DLS-projecting dopamine neurons and change tonic dopamine levels in DLS.

Tonic extracellular levels of dopamine in the striatum are maintained by dopamine pacemaking (in combination with local regulatory mechanisms of dopamine release in the striatum), and some level of tonic dopamine is likely to be permissive for learning. However, most theories of dopamine function posit that phasic dopamine release is critical for associative learning to occur. Unlike pacemaker firing, which arises cell autonomously (in the absence of synaptic inputs), phasic dopamine neuron firing requires excitatory synaptic input to activate AMPA and NMDA glutamate receptors (Blythe et al., 2007, 2009). Relief of inhibition onto dopamine neurons can also facilitate burst firing (Lobb et al., 2011). Finally, cholinergic inputs to dopamine neurons may play a dichotomous role in

the lateral vs. medial SNc. Cholinergic inputs activate dopamine neurons in the lateral SNc, which tend to be DLS-projecting, by activating postsynaptic nicotinic acetylcholine receptors and by promoting glutamate transmission indirectly. Meanwhile, cholinergic inputs inhibit dopamine neurons in the medial SNc, which can be DMS- or DLS-projecting, through GABA co-release and/or indirect activation of other GABAergic inputs to these dopamine neurons (Lerner et al., 2015; Estakhr et al., 2017; Farassat et al., 2019).

Phasic firing of dopamine cell bodies evokes phasic dopamine transients in the striatum that are important for learning. As mentioned above, mice lacking NMDA receptors in dopamine neurons have reduced phasic firing and a deficit in habit learning (Wang et al., 2011) although they are capable of learning the accelerating rotarod (Zweifel et al., 2009). Phasic dopamine transients in DLS have been observed in response to rewards (Schultz et al., 1997; Matsumoto & Hikosaka, 2009; Lerner et al., 2015; Seiler et al., 2022; van Elzelingen et al., 2022, among others) and may also play a role in reinforcing spontaneous behavioral elements in the absence of reward (Markowitz et al., 2023).

Further research into the identities of specific excitatory, inhibitory, and neuromodulatory inputs to DLS-projecting dopamine neurons and their roles in controlling behaviorally relevant DLS dopamine release events will be informative. A general idea of the sources of monosynaptic inputs to DLS-projecting dopamine neurons is available, thanks to anatomical tracing using synapse-specific rabies-based viral methods (Lerner et al., 2015; Menegas et al., 2015). A limitation of these studies is that they have examined inputs to DLS-projecting dopamine neurons in general, without regard to the molecular identities of the dopamine neurons or their specific locations within the SNc or VTA. Nevertheless, these studies have revealed a wide range of input structures to DLS-projecting dopamine neurons of importance to understand and examine for their roles in behavior. A large number of inputs to DLS-projecting dopamine neurons are inhibitory and arise from basal ganglia structures including the striatum, globus pallidus external segment, and substantia nigra pars reticulata. Accordingly (and in line with previous estimates that ~70% of inputs are inhibitory (Bolam & Smith, 1990; Tepper & Lee, 2007; Henny et al., 2012)), DLS-projecting dopamine neurons experience a nearly constant barrage of inhibition (Lerner et al., 2015). In contrast, excitatory inputs arise from a limited set of sources, which include the cortex (primarily motor and somatosensory cortices), subthalamic nucleus (STN), pedunculopontine nucleus (PPN), and the dorsal raphe (DR; which sends a mixed glutamatergic/serotonergic projection). Excitatory inputs to SNc dopamine neurons from PPN, a brainstem nucleus important for movement, form onto dopamine cell bodies and are positioned to closely control firing (Galtieri et al., 2017). Inputs from other sources, such as STN and cortex, synapse onto dendrites, where their influence on dopamine neuron firing patterns is likely subject to modulation by other inputs or changes in dendritic excitability. For instance, the ability of these dendritic excitatory inputs to control firing patterns in dopamine neurons might be modulated by changes in calcium activity in dopamine dendrites (Hage & Khaliq, 2015; Evans et al., 2017).

Long-term synaptic plasticity at inputs to dopamine neurons may also be relevant for learning and transitions to automaticity. Only a few studies have examined plasticity at inputs to SNc dopamine neurons (and none have differentiated DLS-projecting dopamine neurons from other populations in SNc). However, a 100 Hz stimulation of STN inputs to SNc dopamine neurons, when paired with postsynaptic depolarization, induces NMDA receptor-dependent LTP (Overton et al., 1999), while spike timing-dependent protocols can produce LTP of NMDA receptor currents (Harnett et al., 2009). Observations of the slow recruitment of phasic dopamine signaling in DLS with behavioral training suggest that there is some mechanism that slowly engages DLS dopamine signaling over time (Willuhn et al., 2012; Seiler et al., 2022). Long-term synaptic plasticity at inputs to DLS-projecting dopamine neurons could provide such a mechanism, so better characterizing this plasticity, including the molecular mechanisms and timing relative to changes in behavior, is an important area for future investigation in understanding transitions to automaticity.

In terms of inhibitory inputs to DLS-projecting SNc dopamine neurons, inputs from striatal SPNs (which are inhibitory projection neurons) are very robust, representing 50% of the monosynaptic inputs to SNc dopamine neurons (Watabe-Uchida et al., 2012; Lerner et al., 2015). Monosynaptic inputs to DLS-projecting SNc dopamine neurons arise from DLS, DMS, and nucleus accumbens, but are strongest from DLS (Lerner et al., 2015). These monosynaptic inputs arise largely from D1-SPNs located in the striosomes, which synapse onto dopamine neuron dendrites in elaborate "bouquet" structures (Crittenden et al., 2016; McGregor et al., 2019; Evans et al., 2020). Striosomes have been linked to habits and motor skills (Lawhorn et al., 2009; Nadel et al., 2020), but whether they achieve this regulation of transitions to automaticity via their control over DLS dopamine signaling is not well understood.

Another prominent and important inhibitory input to DLS-projecting dopamine neurons arises from the substantia nigra pars reticulata (SNr). The SNr is the primary output nucleus of the basal ganglia in rodents (the internal segment of the globus pallidus plays a homologous role in primates). In addition to inhibiting SNc dopamine neurons, SNr GABA neurons send output signals to many other brain areas (McElvain et al., 2021) and may serve to coordinate behavioral output with dopaminergic feedback to the striatum. Unlike striatal SPNs, which have very low spontaneous firing rates (<1 Hz), SNr GABA neurons exhibit tonic firing rates ~25-30 Hz and therefore provide tonic inhibitory input to dopamine neurons (Atherton & Bevan, 2005). The relief of this tonic inhibitory input is hypothesized to disinhibit dopamine neurons and lead to dopamine release in the striatum.

D1-SPNs in the matrix of the striatum, neurons that comprise the "direct pathway" (Fig. 1), synapse onto SNr GABA neurons. Therefore, while striosome D1-SPNs are positioned to inhibit dopamine neurons, matrix D1-SPNs are positioned to disinhibit them (Evans et al., 2020). Indeed, disinhibitory circuits from the striatum to the SNr to the SNc exist in the mouse brain and can connect striatal subregions to themselves (DMS to DMS dopamine, DLS to DLS dopamine) and

to adjacent striatal subregions (DMS to DLS dopamine, DLS to DMS dopamine) (Ambrosi & Lerner, 2022).

The idea that activity in one striatal subregion could influence dopamine release in an adjacent striatal subregion is particularly exciting when considering the implications for transitions to automaticity. As noted above, transitions to automaticity are marked by transitions from DMS engagement in behavior towards DLS engagement in behavior, a process that is likely dopamine dependent. If DMS activity regulates DLS dopamine release through a disinhibitory circuit (sometimes termed the "ascending spiral" (Haber et al., 2000)), this would provide a mechanism for the transition (Fig. 2). Indeed, DMS-mediated disinhibition of DLS dopamine has long been proposed as a mechanism for regulating transitions to automaticity (Haber et al., 2000; Yin & Knowlton, 2006; Belin & Everitt, 2008; Lüscher et al., 2020), but evidence specifically linking the function of this disinhibitory circuit to behavior is currently lacking and questions remain about the ability of this circuit to effectively control the firing rates of DLS-projecting dopamine neurons (Ambrosi & Lerner, 2022). The ascending spiral hypothesis is consistent with observations that DMS lesions slow motor skill acquisition (Yin et al., 2009); however, it is inconsistent with the observation that DMS lesions accelerate rather than inhibit habit learning (Yin et al., 2004). The apparent acceleration of habit learning in DMS-lesioned animals could be due to an impairment of goal-directed control such that normally covert habit-related plasticity is revealed behaviorally, but the result still implies that the ascending spiral is not required for habitual control to manifest. More studies are still required to determine the contribution of the ascending spiral pathway to transitions to automaticity. It will also be illuminating to understand how disinhibitory circuits controlling DLS dopamine activity coordinate with other inputs to dopamine neurons, both excitatory and inhibitory.

6 Evidence for Dopamine-Dependent Long-Term Synaptic Plasticity in the Dorsal Striatum Related to Transitions to Automaticity

Dopamine release is dynamically modulated and patterns of release can evolve with learning, as detailed above. The exact timing of dopamine release in the striatum during behavior may be very important since it can function to open and close narrow time windows for long-term synaptic plasticity of excitatory inputs (Yagishita et al., 2014).

Strong evidence links dopamine-dependent long-term plasticity of excitatory inputs to the dorsal striatum to habit formation and motor skill acquisition. This evidence comes in several forms, including experiments manipulating numerous striatal neuromodulators important for plasticity, experiments manipulating signaling pathways in SPNs important for plasticity, and electrophysiology studies looking directly for evidence of striatal plasticity in trained animals.

First, in addition to the studies cited above, which found that impairments of DLS dopamine transmission interfere with automaticity transitions, it has been found that manipulations of other striatal neuromodulators known to coordinate with dopamine to control long-term striatal plasticity can also disrupt transitions to automaticity (for reviews detailing the molecular mechanisms of dopamine-dependent striatal plasticity, see Kreitzer & Malenka, 2008; Surmeier et al., 2009; Lerner & Kreitzer, 2011). For example, endocannabinoid CB1 receptors and adenosine A2A receptors, which coordinate with dopamine D2 receptors to induce D2-SPN LTD (Fig. 1; Lerner et al., 2010; Lerner & Kreitzer, 2012), are required for habit formation (Hilário et al., 2007; Yu et al., 2009; Gremel et al., 2016; Li et al., 2016).

Dopamine receptors are GPCRs that influence downstream signaling pathways in SPNs. G_s-coupled D1 receptors increase adenylyl cyclase activity and $G_{i/o}$-coupled D2 receptors decrease adenylyl cyclase activity. Mice lacking a striatal-enriched form of adenylyl cyclase, AC5, have impaired dopamine-dependent corticostriatal plasticity and impaired behavioral flexibility (in a response-learning task) and skill learning (in the accelerating rotarod task) (Kheirbek et al., 2009). These results links known dopamine receptor signaling pathways to plasticity and learning. Mice lacking NMDA receptors in the striatum, a knockout that prevents corticostriatal LTP, have severely impaired learning on the accelerating rotarod (Dang et al., 2006; Beutler et al., 2011) and poor operant learning (Jin & Costa, 2010; Beutler et al., 2011; Geddes et al., 2018). However, mice lacking NMDA receptors only in D2-SPNs have largely intact accelerating rotarod learning (Lambot et al., 2016), implying that NMDA receptor-dependent LTP in D1-SPNs is more important for training automaticity than NMDA receptor-dependent LTP in D2-SPNs. In fact, another study showed that mice lacking TRPV1 receptors lack a form of LTD in D2-SPNs and have impaired habit formation (Shan et al., 2015), implicating LTD in D2-SPNs as an important form of striatal plasticity involved in training automaticity. Unfortunately, none of these studies of knockout mouse lines isolated the knockouts to DLS or compared them to specific knockouts in other striatal subregions. Thus, it is somewhat difficult to conclude if plasticity in DLS is the only plasticity process affected by the manipulation and contributing to the observed behavioral changes.

In a groundbreaking study, more directly addressing evidence for long-term synaptic plasticity in the DLS in motor skill acquisition, ex vivo recordings were taken from mice that had been trained on the accelerating rotarod task. Evoked field potentials and excitatory postsynaptic potential (EPSP) slopes in DLS were larger in extensively trained vs. naïve, minimally trained, or yoked mice, suggesting that DLS LTP specific to motor skill acquisition had occurred in vivo (Yin et al., 2009). Furthermore, "saturation" experiments showed that it was more difficult to saturate DLS LTD in ex vivo brain slices from mice that had performed extended rotarod training compared to naïve mice and mice with limited training. The implication of these experiments is that excitatory synapses onto DLS neurons were further away from the floor of their possible range of strengths (i.e., had undergone in vivo LTP) in mice that had acquired and practiced motor skills more extensively. Although most of the experiments in Yin et al. (2009) were conducted in mixed populations of D1- and D2-SPNs, a final experiment in identified SPNs found that while the

effects on EPSP slopes were observed to some extent in both D1- and D2-SPNs, a significant effect was observed only in D2-SPNs. This finding—indicating a primary role for LTP in D2-SPNs in motor skill acquisition—is in conflict with the finding that mice lacking NMDA receptors in D2-SPNs learn the accelerating rotarod fairly well (Lambot et al., 2016). Nevertheless, it is intriguing to think about the mechanisms for consolidation of stereotyped motor sequences. Lambot et al. (2016) did observe that the D2-SPN NMDA receptor knockout mice turned around more on the rotarod (despite not falling), an indication that they did not learn the same stereotyped motor sequence as control mice. Lambot et al. (2016) also observed that D2-SPN NMDA receptor knockouts were impaired on a different fine motor skill task involving reaching through a narrow slot. Therefore, D2-SPN LTP may be particularly important not for initial gross motor learning but for fine motor skill consolidation meeting some (admittedly vague) definition of motor automaticity.

A similar approach to Yin et al. (2009)—training mice and looking for ex vivo evidence of plasticity—has also been taken by subsequent studies. Hawes et al. (2015) used a T-maze task to train rats and then prepared ex vivo slices to examine whether LTP or LTD could be induced in the DMS or DLS following minimal vs. extensive training. Since habitual performance in the T-maze task involves subjects consistently turning in one direction, the authors examined plasticity according to whether it occurred in the hemisphere ipsilateral or contralateral to the habitual turning direction. Mixed effects were found indicating both early and late plasticity changes in DMS and a reduction in the ability to induce LTD in late trained rats in the ipsilateral hemisphere (Hawes et al., 2015). The results for DLS are at odds with Yin et al. (2009), which indicated it was easier, not harder, to induce DLS LTD in slices from extensively trained animals. Differences between these studies include the model organism (mice vs. rats), the behavior (accelerating rotarod vs. T-maze), and the specificity of examining ipsilateral vs. contralateral hemispheres (completed in Hawes et al., but not relevant to Yin et al., given the difference in the behavioral paradigm). Though both studies are consistent in arguing for the importance of long-term excitatory synaptic plasticity in the DLS for transitions to automaticity, further studies are required to understand if the forms of plasticity that participate in learning vary systematically according to specific experimental design factors.

Another study by O'Hare et al. (2016) examined corticostriatal responses from mice trained on a random interval operant paradigm to induce habits. Using calcium imaging in brain slices to examine the responses of both D1- and D2-SPN in DLS to cortical stimulation, they found that both SPN types displayed increased event amplitudes in habitually acting mice. This study, conducted in mice as in Yin et al. (2009), is consistent with in vivo LTP having occurred at excitatory cortical synapses onto both D1- and D2-SPNs and with this LTP being related to automaticity transitions. The extent to which a mouse expressed habitual behavior also correlated strongly with a shift in relative *timing* between the two SPN types: in habitually acting mice, D1-SPNs responded to cortical stimulation faster than D2-

SPNs (O'Hare et al., 2016). How this shift in timing is achieved mechanistically is not yet entirely clear, but may involve changes in feed forward inhibition from FSIs (O'Hare et al., 2017). Timing is an exciting additional factor to consider when evaluating the downstream circuit effects of corticostriatal synaptic plasticity.

The tests conducted by Yin et al. (2009) and others measuring changes at synapses following training are powerful, but they involve post hoc ex vivo measurements of striatal plasticity. There is, however, also direct evidence that activity-dependent long-term plasticity occurs in vivo at corticostriatal synapses (Charpier & Deniau, 1997; Ma et al., 2018; Bariselli et al., 2020) and that it is required for specialized skill learning to control neuroprosthetic devices through volitional control of motor cortex activity (Koralek et al., 2012).

7 Influence of Dopamine on Downstream D1- and D2-SPNs

How does dopamine ultimately control downstream striatal function to regulate transitions to automaticity? Given the differing affinities of various dopamine receptors for their ligand, behaviorally-linked increases and decreases in dopamine may have different effects on D1- and D2-SPNs over the course of learning, differentially regulating plasticity and sculpting task involvement. In general, D1-like dopamine receptors are thought to have lower affinity for dopamine than D2-like dopamine receptors (Marcellino et al., 2012). The difference in affinities implies that D2 receptors are more likely to be occupied by dopamine at basal tonic levels. Decreases in dopamine (either transient dips linked to specific behavioral events, or conditions that lower extracellular tonic dopamine) could reduce receptor occupancy. D1 receptors are less likely to already be occupied without phasic dopamine signaling. Therefore, phasic dopamine signals may be more likely to impact D1 receptor-dependent striatal plasticity (i.e., LTP at synapses onto D1-SPNs). There are caveats to this theory. One important one is that both D1 and D2 receptors can exist in high- and low-affinity states in vivo (Richfield et al., 1989). Even if D2 receptors are more likely to maintain high-affinity states, this balance between states could dynamically shift depending on the conditions of an experiment (e.g., the stage of learning, or the stress levels of the animal). Another caveat is that the importance of receptor binding affinities could be overwhelmed by slow unbinding kinetics and high abundances of both types of receptors (Hunger et al., 2020).

Given these uncertainties, it is important to have studies directly designed to disambiguate the roles of D1- and D2-SPNs in automaticity transitions. Specific ablations of D1- or D2-SPNs in DMS vs. DLS using selective expression of the diphtheria toxin receptor found differing roles for the two SPN subtypes in these two striatal subregions (Durieux et al., 2012). Ablating D1-SPNs in DMS had no effect but ablating D2-SPNs in DMS impaired early learning on the accelerating rotarod. Late performance was not impaired. Ablating D1-SPNs in DLS impaired learning throughout the training. Ablating D2-SPNs in DLS had no effect. Despite

the observed effects of ablating DMS D2-SPNs and DLS D1-SPNs during training, local ablations of D1- and D2-SPNs in either DMS or DLS had no effect on rotarod performance when the ablations were done after extensive training on this task (i.e., after motor skill consolidation had occurred). This result looking at SPN ablations after training is particularly interesting in light of a parallel observation for dopamine neurons already noted above—that although ablating Aldh1a1+ dopamine neurons, which project to DLS, before motor skill learning prevents learning, ablating these same dopamine neurons after motor skill consolidation does not impair expert performance (Wu et al., 2019). Together, these results suggest that dopamine-dependent plasticity in D1- and D2-SPNs is important for *learning* and *transitions to automaticity*, but not necessarily for the retrieval of procedural memories necessary for the *performance* of learned actions and habits.

In considering the roles of D1- and D2-SPN activity in automaticity transitions, it is also helpful to examine the actual patterns of D1- and D2-SPN activity in vivo during such transitions. Historically, it has been difficult to differentiate D1- and D2-SPNs in vivo for recordings; however, more recent technical approaches have made such studies possible. One approach is "opto-tagging," in which D1- or D2-SPNs are genetically identified using cre mouse lines and induced to express the excitatory opsin ChR2. Intracranially, implanted "optrodes" can then be used to record SPN activity and to test if recorded neurons are light-sensitive, thereby identifying them as either D1- or D2-SPNs. Jin et al. (2014) used this approach to compare the activities of D1- and D2-SPNs during the execution of well-learned rapid action sequences consisting of eight lever presses. They found that both D1- and D2-SPNs often showed start/stop activity (at the beginning or end of the action sequence), but that D1-SPNs were more likely to show sustained activity through the action sequence, whereas D2-SPNs were more likely to be inhibited through the action sequence (Jin et al., 2014). Recordings were performed across the dorsal striatum, not distinguishing between DMS and DLS. Further studies by Geddes et al. (2018) used a similar approach to examine the learning of more complicated action sequences combining two lever presses, each on the left and right sides of a reward port (left-left-right-right sequence). As in Jin et al. (2014), D1-SPNs showed sustained activity and D2-SPNs showed sustained inhibition during the execution of the action sequence. Additionally, they found that D1-SPNs were more likely to encode the initiation of the overall action sequence (left-left-right-right), whereas D2-SPNs were more often selectively activated during switches between left and right lever pressing in the middle of the overall sequence. They concluded that D2-SPNs may play a role in coordinating subsequences of behavior, allowing switches between modes like left and right lever pressing that can occur within the overall sequence of behavior that is ultimately rewarded (Geddes et al., 2018).

Another approach to distinguishing D1- and D2-SPN activity in vivo is imaging. Calcium sensors can be expressed exclusively in either D1- or D2-SPNs using specific mouse lines (e.g., D1-cre and A2A-cre) to allow for imaging of known populations. Calcium imaging studies have poorer temporal resolution than elec-

trophysiology but the advantage of providing spatial information, which can be tracked across days of learning. Parker et al. (2018) have shown the utility of this approach examining the activities of D1- and D2-SPNs under conditions of dopamine loss and supplementation with the dopamine precursor levodopa (Parker et al., 2018). They found that the activity of spatially clustered ensembles of D1- and D2-SPNs was important for predicting the motor consequences of these dopamine manipulations. However, DMS, and not DLS, was examined in this study, and transitions to automaticity were not the focus.

Similar analysis of D1- and D2-SPN activity by fiber photometry, which lacks single cell spatial resolution, has caveats (Legaria et al., 2022), but can still be informative. An analysis of D1- and D2-SPN activity in DLS during fine timescale movements using fiber photometry found that the two cell types encode nonredundant information at fine timescales (ms to sec), despite being similar at longer timescales (sec to min) (Markowitz et al., 2018). The findings were confirmed with single cell imaging, which revealed ensemble encoding in DLS similar to that described by Parker et al. (2018) in DMS. These fine timescale representations of motor activity in DLS cells may be important for sequenced behaviors, especially motor skills requiring precise timing.

Self-stimulation studies examining the roles of D1- and D2-SPNs in reinforcement learning are also interesting to consider as they can reveal the causal relationships of these cell types in shaping behavioral outcomes. Optogenetic self-stimulation of D1-SPNs in either DMS or DLS is reinforcing and action-specific, in concordance with theories of direct pathway circuit function (Kravitz et al., 2012; Vicente et al., 2016). In contrast, self-stimulation of D2-SPNs is more complicated, with results differing by a striatal subregion. Mice avoid self-stimulating DMS D2-SPNs (Kravitz et al., 2012) but pursue self-stimulating DLS D2-SPNs (Vicente et al., 2016). Additionally, unlike self-stimulation of D1-SPNs, self-stimulation of DLS D2-SPNs is not action-specific. Rather, mice generalized their learning, pressing both an active and an inactive lever (Vicente et al., 2016). The differing roles of D2-SPNs in DMS and DLS in reinforcement could be related to the overall differing functions of DMS and DLS in goal-directed and habitual behavior, respectively. Decreases in dopamine that allow LTP of excitatory inputs to D2-SPNs would promote action discrimination in DMS but generalization in DLS. A generalization function in DLS could relate to habitual behavior provoked by contextual cues in the absence of specific behavioral goals. Indeed, mice self-stimulating D2-SPNs in DLS were found to be insensitive to contingency degradation, consistent with a habit phenotype (Vicente et al., 2016).

Further work on the specific activity patterns of D1- and D2-SPNs in DMS and DLS during habit formation and motor skill acquisition will continue to be informative in building models for transitions to automaticity. It is imperative to understand how dopamine in DMS and DLS functions to shape downstream striatal circuits to control learning transitions and the consolidation of procedural memories.

8 Possible Roles for Striatal Interneurons in Mediating Transitions to Automaticity

The roles of striatal interneurons in mediating transitions to automaticity are unclear. However, given that striatal interneurons express dopamine receptors and play important roles in regulating striatal microcircuit function, it is an area worthy of further investigation.

8.1 Fast-Spiking Interneurons (FSIs)

FSIs are inhibitory striatal interneurons that receive excitatory inputs from the cortex and thalamus and synapse primarily onto SPN cell bodies, providing powerful feedforward inhibition (Mallet et al., 2005; Kreitzer, 2009; Gittis et al., 2010; Owen et al., 2018). Although FSIs synapse onto both D1- and D2-SPNs, there is a bias towards D1-SPNs (Gittis et al., 2010). FSIs express D1 dopamine receptors and are acutely excited by dopamine (Bracci et al., 2002). Excitatory inputs to FSIs can undergo spike timing-dependent plasticity, although the dopamine dependence of this plasticity is not defined (Fino et al., 2008). In rats trained on a T-maze task, FSIs showed opposite patterns of activity as compared to SPNs. While SPNs showed task-boundary activity patterns (at the starts and stops of trials), FSIs showed mid-task activation (Martiros et al., 2018). In mice trained on an operant procedure designed to elicit habit formation, FSIs in the DLS from habitually acting mice had greater intrinsic excitability than FSIs from goal-directed mice (O'Hare et al., 2017). The chemogenetic inhibition of these highly excitable FSIs in habitually acting mice impaired the expression of already learned habitual behavior (O'Hare et al., 2017). This evidence certainly suggests a permissive role of FSIs in allowing already learned habitual behavior, but it does not speak to the question of whether FSIs are required for the acquisition of habits. In another study, FSIs were selectively ablated prior to learning on the accelerating rotarod task for motor skill acquisition, and this ablation *did not* disrupt learning, suggesting that FSIs do not meaningfully contribute to transitions to automaticity, at least in the case of motor skills (Owen et al., 2018). However, FSI inhibition did slow the transition from an allocentric (hippocampal-dependent) to an egocentric (striatal-dependent) performance on a T-maze task, perhaps suggesting a more prominent role for FSIs in coordinating learning transitions between the striatum and the hippocampus. Owen et al. (2018) disrupted FSI function broadly across the dorsal striatum, so the identified function of FSIs in egocentric learning might be related to a change in either DMS or DLS function. Lesioning the posterior DMS leads to an increased reliance on egocentric learning (Yin and Knowlton 2004), so it is possible that the disinhibition of posterior DMS function by FSI ablation would produce the opposite effect, preventing egocentric learning.

8.2 Low-Threshold Spiking Interneurons (LTSIs)

LTSIs are inhibitory striatal interneurons that are also known for their expression of neuropeptides such as somatostatin and neuropeptide Y, and their production of the gaseous neuromodulator nitric oxide due to their expression of nitric oxide synthase. LTSIs form long-range connections onto the distal dendrites of SPNs (Straub et al., 2016). Their long-range connectivity might position these interneurons to coordinate activity between striatal subregions; however, their role in transitions to automaticity is unknown. The work by Holly et al. (2019) investigating the function of LTSIs in DMS has shown that LTSI activity in DMS naturally decreases over the course of DMS-dependent goal-directed operant learning. Enhancing DMS LTSI activity inhibits goal-directed learning (Holly et al., 2019), an effect that may be mediated by inhibition of DMS dopamine release (Holly et al., 2021). Expanding studies of LTSI function into the DLS is a critical need in the field, as is examining the importance of neuropeptide signaling by this cell type.

8.3 Cholinergic Interneurons (ChIs)

ChIs are striatal interneurons that release acetylcholine, which can activate nicotinic acetylcholine receptors (nAChRs) primarily expressed by presynaptic dopamine terminals within the striatum, as well as muscarinic acetylcholine receptors (mAChRs) primarily expressed by SPNs and other striatal interneurons. Activation of mAChRs on SPNs, particularly M4 receptors on D1-SPNs, is thought to regulate synaptic plasticity at SPN inputs (Fig. 1; Surmeier et al., 2009; Lerner & Kreitzer, 2011). ChIs exhibit regular spontaneous firing activity and are therefore often identified as "tonically active neurons" (TANs) during in vivo electrophysiology recordings. In such recordings, TANs in the dorsal striatum are observed to pause their regular firing during behaviorally relevant events like reward-predicting cues (Zhang & Cragg, 2017). Pauses in response to reward-predicting cues are acquired during learning. This neural adaptation likely depends on dopamine and could be related to dopamine-dependent synaptic plasticity of excitatory inputs to ChIs (Suzuki et al., 2001; Fino et al., 2008; Zhang & Cragg, 2017). Some research has explored the relationship between ChIs and habits. Chemogenetic inhibition of ChIs in DLS can promote behavioral flexibility during learning (Amaya & Smith, 2021), but chemogenetic activation does not accelerate habit formation (Aoki et al., 2018). After habit formation, ablation of ChIs in DLS does not affect the expression of habits, but chemogenetic activation can enhance behavioral flexibility (Aoki et al., 2018). These results are somewhat confusing, since both inhibition and activation of ChIs can promote behavioral flexibility, but perhaps they arise due to differing roles for DLS ChIs during habit formation vs. the expression of habitual behaviors. It has also been found that mice lacking the vesicular acetylcholine transporter (VAChT), and which therefore lack acetylcholine release from ChIs, are prone to

habit formation (Favier et al., 2020). However, this effect appears mediated by impairments of ChI function in DMS, which could reduce reliance of the animal's behavior on goal-directed control and thereby increase reliance on habits indirectly. More research is needed to understand how ChIs coordinate DLS microcircuit function through transitions to automaticity and how dopamine-dependent plasticity at inputs to ChIs might contribute to their changing roles in behavior across learning.

9 Dopamine's Role in the Acquisition vs. Expression of Automatic Behaviors

Dopamine is important for transitions to automaticity. However, it is not necessarily important for the expression of automatic behaviors once learned. For example, as mentioned above, ablating Aldh1a1+ DLS-projecting dopamine neurons prevents mice from *learning* the accelerating rotarod task, but ablation of these cells *after* motor skill acquisition does not impair skilled performance (Wu et al., 2019). Interestingly, human Parkinson's disease patients, who display profound dopamine neurodegeneration and significant motor dysfunction by the time of diagnosis, are still able to maintain skilled performance on complex motor tasks learned before disease onset (e.g., riding a bike, https://youtu.be/aaY3gz5tJSk) until much later stages of the disease (Snijders & Bloem, 2010). Disentangling the requirement of dopamine for motor learning vs. motor performance will help us understand and treat Parkinson's disease, but also presents an experimental challenge since lesions or other permanent disruptions of dopamine signaling often affect both learning and performance. Studies specifically designed to dissociate the acquisition vs. expression of automatic behaviors can shape future thinking and study design.

One approach to disentangling dopamine's role in motor performance from its role in motor learning is to ask whether an experimental manipulation affecting dopamine signaling causes behavioral changes immediately (indicating dopamine was required for performance) or only in an experience-dependent manner (indicating that experience-dependent learning and long-term dopamine-dependent plasticity are required to see the effects; Fig. 3a). In one study, Leventhal et al. (2014) infused a D1 and D2 antagonist into the DLS of rats extensively trained in a two-alternative forced choice task. This pharmacological block of DLS dopamine signaling did not cause an immediate crash in accuracy in the task, but evoked a progressive decrease in accuracy dependent on performing the task and lasting beyond the drug's acute effects (Leventhal et al., 2014). This slow, progressive loss of performance suggests a learning effect, in which a maladaptive form of plasticity is taking place when the task is performed in the absence of dopamine signaling. A similar result has been shown with the accelerating rotarod task (Beeler et al., 2010). In this case, the authors used Pitx3-deficient mice that have almost no dopaminergic cells in the SNc and have a 90% reduction in striatal dopamine levels. These mice have no obvious motor deficits in their homecage, but a profound deficit

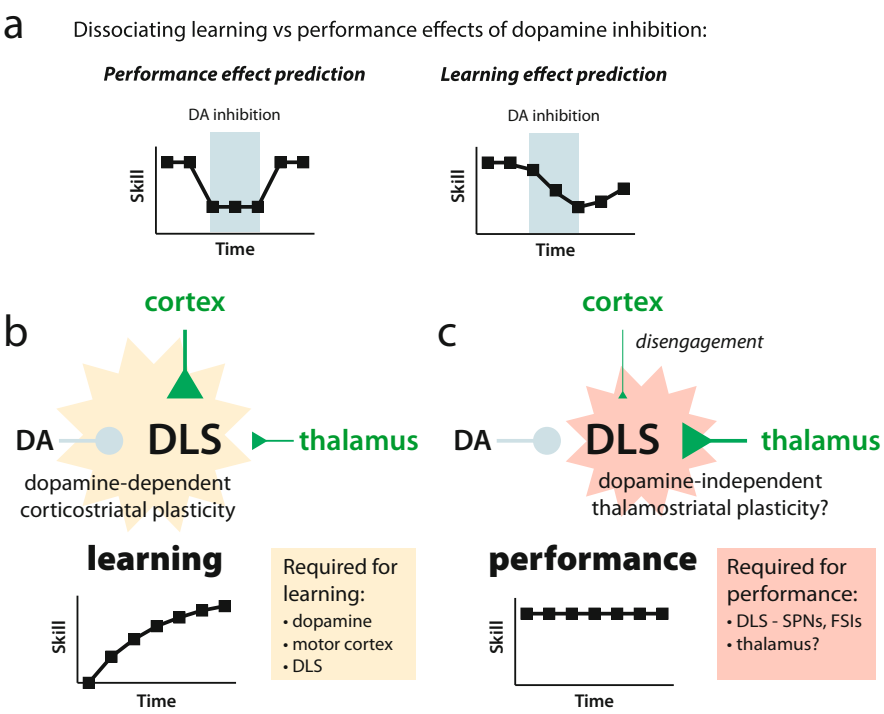

Fig. 3 Role of DLS dopamine in transitions to automaticity and the expression of automatic behaviors. (**a**) To dissociate between the effects of dopamine inhibition on the skilled performance of a motor skill task vs. an effect on learning, one can examine the time course of behavioral effects. If dopamine is required to perform a skill, dopamine inhibition should cause an immediate drop in performance that also recovers immediately when dopamine inhibition is ended. If dopamine inhibition degrades skilled motor performance by creating conditions for maladaptive synaptic plasticity and learning, the effects should be slow and experience-dependent in their onset, and slow to recover after dopamine inhibition is ended. So far, several studies support the model that DLS dopamine plays a primary role in learning. (**b**) During the initial stages of learning, skilled performance increases rapidly. The learning of motor skills and habits seems to rely primarily on dopamine-dependent corticostriatal plasticity. (**c**) After skilled performance asymptotes, the DLS still seems to be important for performance (i.e., the expression of automatic behaviors). However, several studies support the notion that corticostriatal inputs disengage from the control of behavior and that dopamine is no longer required for performance. One theory, requiring further testing, is that cortical inputs "tutor" thalamic inputs to the DLS, allowing thalamostriatal synapses to assume control of automatic behaviors after learning has occurred. This consolidation phase may be independent of dopamine or may depend on yet-to-be-clarified dopamine-dependent mechanisms

in the learning of the accelerating rotarod task. Their learning could be rescued by treatment with levodopa, the dopamine precursor often used to treat Parkinson's disease. Once levodopa administration was stopped, their performance did not immediately plummet, but instead declined slowly. Interestingly, experience was required for the deficit in dopamine to cause a decline in rotarod performance. Time

off levodopa treatment before subsequent training did not matter—mice started rotarod performance post-levodopa treatment at a level comparable to their last day of training completed on levodopa. All mice then showed the same progressive decrease in performance over several rotarod sessions performed without levodopa. This study underscores the experience-dependent effects of low/absent dopamine on skilled motor performance, which can help explain the "long-duration response" to levodopa therapy in Parkinson's disease, wherein there is a slow buildup of improvement on levodopa and a gradual degradation of effects if treatment is ceased (Beeler et al., 2010; Anderson & Nutt, 2011). A follow-up study (Beeler et al., 2012) showed a similar learning effect in response to dopamine receptor antagonism. Both D1 and D2 receptor antagonists impaired initial rotarod learning; however, a D2 receptor antagonist (but not a D1 receptor antagonist) had a long-lasting impact on skilled performance after antagonist administration was ceased. This study proceeded to implicate aberrant LTP at glutamatergic inputs onto D2-SPNs in long duration task impairment. Interestingly, preventing this aberrant D2-SPN LTP by co-administration of an A2A receptor antagonist with the D2 antagonist (Fig. 1) prevented the long-lasting effects of D2 receptor antagonism.

In another study, Bova et al. (2020) provided a test of the learning vs. performance question using optogenetic manipulations of SNc dopamine neurons while rats performed a skilled reaching task dependent on more dexterous forelimb movements. This study asked if manipulations of SNc dopamine cell activity affected reach kinematics only during trials with optogenetic manipulation (which would suggest in role in performance), or if there was an effect of the history of optogenetic manipulation of dopamine during previous trials on current reaches (consistent with dopamine's role in motor learning; Fig. 3a). They showed a strong effect of dopamine history, which occurred only when optogenetic manipulations were applied during reaches and not when the manipulations were applied between reach movements. Interestingly, although reach kinematics initially changed slowly with optogenetic manipulations of dopamine, once rats had learned to operate under both light-on and light-off conditions over several training sessions, immediate trial-by-trial effects on reach kinematics were resolved. The role that Bova et al. (2020) observed for dopamine in controlling rapid shifts between different reach trajectories is perhaps consistent with a role for controlling sequences and switches in subsequences of well-learned behaviors as in Geddes et al. (2018). Nonetheless, overall, these studies all provide strong support for the idea that DLS dopamine guides adaptive plasticity underlying motor learning rather than strictly permitting the execution of learned skills.

If dopamine plays a primary role in the acquisition but not necessarily the expression of automatic behaviors, then where are memories of automatic behaviors stored? This issue is far from settled. On the one hand, if the striatum and downstream basal ganglia nuclei are specialized for learning, skill or habit memories would be expected to be stored outside the basal ganglia, perhaps in the motor cortex. This view is supported by the observation that inhibiting basal ganglia output areas can leave the execution of already-learned motor sequences intact (Desmurget & Turner, 2010). In fact, lesions of basal ganglia output in humans—

pallidotomies—have been performed historically in Parkinson's disease patients and can improve symptoms (Cif & Hariz, 2017) though they impair motor learning (Brown et al., 2003; Obeso et al., 2009). On the other hand, several studies in rodents suggest that motor cortex is dispensable for skilled motor performance (Kawai et al., 2015; Hwang et al., 2019, 2021; Dhawale et al., 2021) and that the engagement of motor cortex inputs to DLS during motor skill acquisition declines with training (Kupferschmidt et al., 2017), seemingly ruling out that motor cortex is a nonredundant site of motor skill memory storage. As an alternative, Wolff et al. (2022) proposed that thalamic inputs to the striatum are a site of storage and that thalamic inputs assume control of DLS function from cortical inputs with training (Wolff et al., 2022). This account is plausible, given what we know about the role of dopamine in long-term synaptic plasticity of excitatory inputs to DLS SPNs. Cortical inputs to DLS have been shown to express several forms of plasticity that can be modulated by dopamine including endocannabinoid-dependent LTD (Kreitzer & Malenka, 2005; Wu et al., 2015). Thalamic inputs, on the other hand, show negligible endocannabinoid-dependent LTD, but rather exhibit dopamine-independent forms of spike timing-dependent plasticity (Wu et al., 2015). Together, these findings support a model in which dopamine modulates the synaptic plasticity underlying motor learning at corticostriatal synapses, which are necessary for the acquisition of automaticity, but later become unnecessary for its performance (Fig. 3b-c). Corticostriatal synapses that have undergone learning-related dopamine-dependent plasticity could then "tutor" thalamostriatal synapses through dopamine-independent plasticity mechanisms, resulting in animals' ability to continue to perform motor skills without motor cortex or dopaminergic inputs to the striatum being present. Theoretical models have proposed such mechanisms, whereby motor memories could be stored in DLS after cortical tutoring and disengagement either at intra-striatal synapses (Murray & Escola, 2017) or at thalamostriatal synapses (Murray & Escola, 2020). Further experiments will be necessary to confirm the predictions of such models, especially the specific timelines of dopamine-dependent and dopamine-independent events in DLS that would underlie transitions in DLS circuit function supporting automaticity.

10 Conclusion

In summary, DLS dopamine is important for training automaticity (including habits and motor skills), but not necessarily for the expression of automaticity. Although aberrant dopamine signaling may provoke aberrant plasticity and degrade habit representations, a total lack of dopamine does not in itself impair the expression of fully learned and consolidated habits and motor skills. Future studies of the role of dopamine in transitions to automaticity are necessary in several areas. It will be important to determine the precise nature of dopamine signals promoting automaticity, what upstream circuits generate these dopamine signals, and the mechanisms by which these dopamine signals influence striatal synaptic plasticity

and orchestrate downstream shifts in striatal microcircuit function. Shedding light in these areas of investigation will impact our understanding of dopamine-related disorders such as addiction, OCD, and Parkinson's disease.

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