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What, If, and When to Move: Basal Ganglia Circuits and Self-Paced Action Initiation

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Abstract

Deciding what to do and when to move is vital to our survival. Clinical and fundamental studies have identified basal ganglia circuits as critical for this process. The main input nucleus of the basal ganglia, the striatum, receives inputs from frontal, sensory, and motor cortices and interconnected thalamic areas that provide information about potential goals, context, and actions and directly or indirectly modulates basal ganglia outputs. The striatum also receives dopaminergic inputs that can signal reward prediction errors and also behavioral transitions and movement initiation. Here we review studies and models of how direct and indirect pathways can modulate basal ganglia outputs to facilitate movement initiation, and we discuss the role of cortical and dopaminergic inputs to the striatum in determining what to do and if and when to do it. Complex but exciting scenarios emerge that shed new light on how basal ganglia circuits modulate self-paced movement initiation.

Contents

INTRODUCTION

We live and survive through interactions with our environment, which require the ability to generate movements. Coordinated movements rely on intact motor centers in the brainstem and spinal cord. For example, specific brainstem circuits can generate coordinated limb movements or locomotor behaviors (Esposito et al. 2014, Caggiano et al. 2018). However, those circuits need input from other brain areas to evaluate when and how these behaviors should be performed (Arber & Costa 2018). What other circuits and mechanisms are required for these behaviors to be initiated in the correct order, the right context, and the right moment? Moreover, how can purposive movements—i.e., actions that are aimed at achieving specific goals rather than responses to antecedent stimuli—be initiated without depending on explicit external triggers? The importance of the underlying mechanisms is evident from neurological disorders that perturb self-initiated movements and action selection. Patients with Parkinson's disease (Parkinson 2002), who suffer from the degeneration of dopamine neurons of the substantia nigra pars compacta (SNc) (Carlsson et al. 1958, Hornykiewicz 1963), often have profound difficulties in self-initiating movements. However, in certain contexts where strong external cues are used, movement can be triggered (Rubinstein et al. 2002, Snijders et al. 2012). Other movement dysfunctions such as Huntington's disease and levodopa-induced dyskinesias are characterized by excessive movements that affect both the selection and timing of actions (Donaldson et al. 2012). Profound changes in movement patterns can also be found in obsessive-compulsive disorder, where individuals are stuck doing the same action, or in attention-deficit/hyperactivity disorder, which manifests as aberrant switching between actions.

At the core of these functions and dysfunctions are basal ganglia circuits and their glutamatergic and dopaminergic inputs, which integrate information about internal state, context, and motor plans to select the most appropriate behaviors. Basal ganglia output circuits, that is, the substantia nigra pars reticulata (SNr) and the internal segment of the globus pallidus, keep downstream motor centers under tonic inhibitory control (Redgrave et al. 1999, Hikosaka et al. 2000, Grillner et al. 2013), thus preventing the occurrence of involuntary movements that would otherwise emerge as a result of the ongoing driving inputs from motor-related brain circuits such as the motor cortex or colliculus (Hikosaka et al. 2000). The striatum, which is the largest basal ganglia input nucleus,

modifies this widespread tonic inhibition during voluntary action in a specific way to support the desired movement. In this process, the striatum continuously samples inputs from frontal, sensory, and motor cortices and related thalamic areas. These inputs provide information about current goals, context, alternative actions, and related costs (Gremel & Costa 2013, Li et al. 2015) and, through specific corticostriatal activation, allow the initiation of a particular action in the right context. Cortex-to–basal ganglia information flow is strongly modulated by dopamine transients, which both signal reward prediction errors (RPEs) important for reinforcement learning (Montague et al. 1996, Schultz et al. 1997, Watabe-Uchida et al. 2017) and facilitate the initiation and modulate the vigor of self-paced movements (Mazzoni et al. 2007, Howe & Dombeck 2016, da Silva et al. 2018). Thus, the basal ganglia are in a central position to modulate different aspects of movement initiation like the selection, timing, and invigoration of upcoming movements (Redgrave et al. 1999, Dudman & Krakauer 2016, Thura & Cisek 2017).

Existing models of basal ganglia motor function have been strongly influenced by attributing movement-facilitating and movement-suppressing roles to striatonigral and striatopallidal projections, respectively (Albin et al. 1995). However, recent experimental findings challenge this prokinetic versus antikinetic dichotomy (Cui et al. 2013; Jin et al. 2014; Tecuapetla et al. 2014, 2016; Yttri & Dudman 2016) and suggest that more detailed models are required that consider, for example, ensemble-level descriptions of movement-related activity (Barbera et al. 2016, Klaus et al. 2017, Parker et al. 2018), their fine-scale temporal modulations (Markowitz et al. 2018), and how these ensembles jointly regulate downstream circuits and behavior (Alexander & Crutcher 1990, Turner & Desmurget 2010).

Thus, the generation of self-initiated movements, which is essential for flexible behaviors, involves the interplay between different brain circuits. Here we describe new insights into striatal, cortical, and dopaminergic mechanisms that underlie this important process, as well as some open questions.

THE STRIATUM AND SELF-PACED MOVEMENT INITIATION

Self-paced movement initiation is associated with premovement activity in the motor cortex, including in neurons that project within the telencephalon [i.e., intratelencephalic (IT)] and via the pyramidal tract (PT) to brainstem and spinal cord motor centers (Romo & Schultz 1992, Lemon 2008, Kaufman et al. 2014, Svoboda & Li 2018). Similarly, other motor control centers in the midbrain and brainstem also show activity before movement (Buford & Davidson 2004, Thompson & Felsen 2013). The basal ganglia tonically inhibit thalamocortical and motor centers via GABAergic projections and prevent activity in those motor centers from leading to unwanted or wrongly timed movements (Hikosaka et al. 2000). The dorsal striatum constitutes a crucial component in the regulation of basal ganglia outputs. That is, striatal spiny projection neurons (SPNs) gather information about planned movements from the cortex, as well as sensory and other contextual information, and translate it into specific changes in the basal ganglia outputs. Accordingly, many striatal neurons increase activity at movement onset (Jog et al. 1999, Hikosaka et al. 2000, Jin & Costa 2010, Cui et al. 2013, Jin et al. 2014) with a substantial fraction of SPNs being selectively active during self-initiated movements (Schultz & Romo 1992, Jin et al. 2014).

Classically, the striatum is thought to project to downstream nuclei through two major projection patterns. About half of the SPNs form the striatonigral pathway that directly innervates basal ganglia output nuclei (i.e., the direct pathway), whereas the remaining SPNs are part of the striatopallidal pathway that reaches basal ganglia outputs indirectly (i.e., the indirect pathway) via the globus pallidus external segment (GPe) and subthalamic nucleus (STN). Direct pathway spiny projection neurons (D1-SPNs) express D1-type dopamine receptors, and indirect pathway spiny

projection neurons (D2-SPNs) coexpress D2-type dopamine and adenosine A2a receptors (Gerfen et al. 1990). The profile of dopamine receptor expression makes D1-SPNs more excitable and D2-SPNs less excitable in response to dopamine (Gerfen et al. 1990, Planert et al. 2013). Furthermore, the difference in efferent connectivity suggests that D1- and D2-SPNs can exert opposing effects on basal ganglia outputs. Early interpretations of this organization recognized that this could underlie very different implementations for action selection and initiation (Alexander & Crutcher 1990, Hikosaka et al. 2000, Gerfen & Surmeier 2011). This resulted in a classical model that attributes a pro- versus antikinetic function to direct and indirect pathways, respectively, where the activity of D1-SPNs would facilitate movement and be high during movement, whereas the activity of D2-SPNs would inhibit movement and therefore be lower during movement (**Figure 1*a***). Conversely, during immobility, activity in D2-SPNs would be higher and activity in D1-SPNs would be lower (**Figure 1*a***). This model is supported by optogenetic (Kravitz et al. 2010) and pharmacogenetic (Alcacer et al. 2017) manipulation experiments in which the activation of many D1-SPNs leads to more movement and activation of many D2-SPNs to less movement. However, cell type–specific recording experiments, which do not interfere with the normal activity in those neurons, reveal that both D1- and D2-SPNs are more active during movement than during immobility (Cui et al. 2013, Isomura et al. 2013, Jin et al. 2014, Tecuapetla et al. 2014, Barbera et al. 2016, Klaus et al. 2017, Markowitz et al. 2018, Parker et al. 2018). Thus, these studies show increased activity in D1- and D2-SPNs during movement, and importantly, they show very low activity in both populations during immobility, indicating that immobility is not associated with high activity in striatopallidal SPNs. Furthermore, they show that during normal movement the activity of both neuron types increases with a similar temporal profile (Jin et al. 2014). These findings are consistent with other models that predict that both pathways should be concomitantly active during movement (**Figure 1*b***). For example, certain models suggest a so-called support/suppress scenario in which the two pathways work in concert to facilitate the desired movements while simultaneously suppressing competing actions (Mink 1996, Hikosaka et al. 2000). While the classical rate model postulates that the inhibitory and disinhibitory effects of direct and indirect pathways are exerted on the same basal ganglia output neurons in SNr, this model suggests that coactive direct and indirect pathways exert their effect on different basal ganglia output neurons, with the direct pathway inhibiting specific neurons to release the desired movement, and the indirect pathway disinhibiting other neurons to suppress competing movements. Other models suggest that both pathways can be concomitantly active but that their relative activity levels and relative timing influence activity in basal ganglia output nuclei (**Figure 1*c***). These models are discussed in more detail below.

While the coactivation of both pathways might still be compatible with variations of the movement-facilitating versus movement-inhibiting views, an elegant experiment by Yttri & Dudman (2016) showed that the stimulation of either pathway can increase or decrease movement speed in subsequent trials depending on whether neurons during fast or slow movement trials were stimulated (**Figure 1*d***). Furthermore, the optogenetic manipulation of either D1- or D2-SPN activity before movement increases the latency for action initiation (Tecuapetla et al. 2016). These results do not support the simple pro- versus antikinetic dichotomy of D1- and D2-SPN function, but they are compatible with the idea that D1-SPNs support the desired action whereas D2-SPNs suppress alternative actions. However, detailed measurements of the spatiotemporal activity of SPN ensembles during natural behavior demonstrate that neurons in both pathways are rather action-specific, and consequently, the patterns of activity of neurons in each pathway are different for each action (Klaus et al. 2017, Markowitz et al. 2018, Parker et al. 2018) (**Figure 2*a*,*b***). Conversely, although the activity of SPNs is modulated by the speed of the movement (Costa et al. 2004, Rueda-Orozco & Robbe 2015), this activity does not seem to be speed-specific across

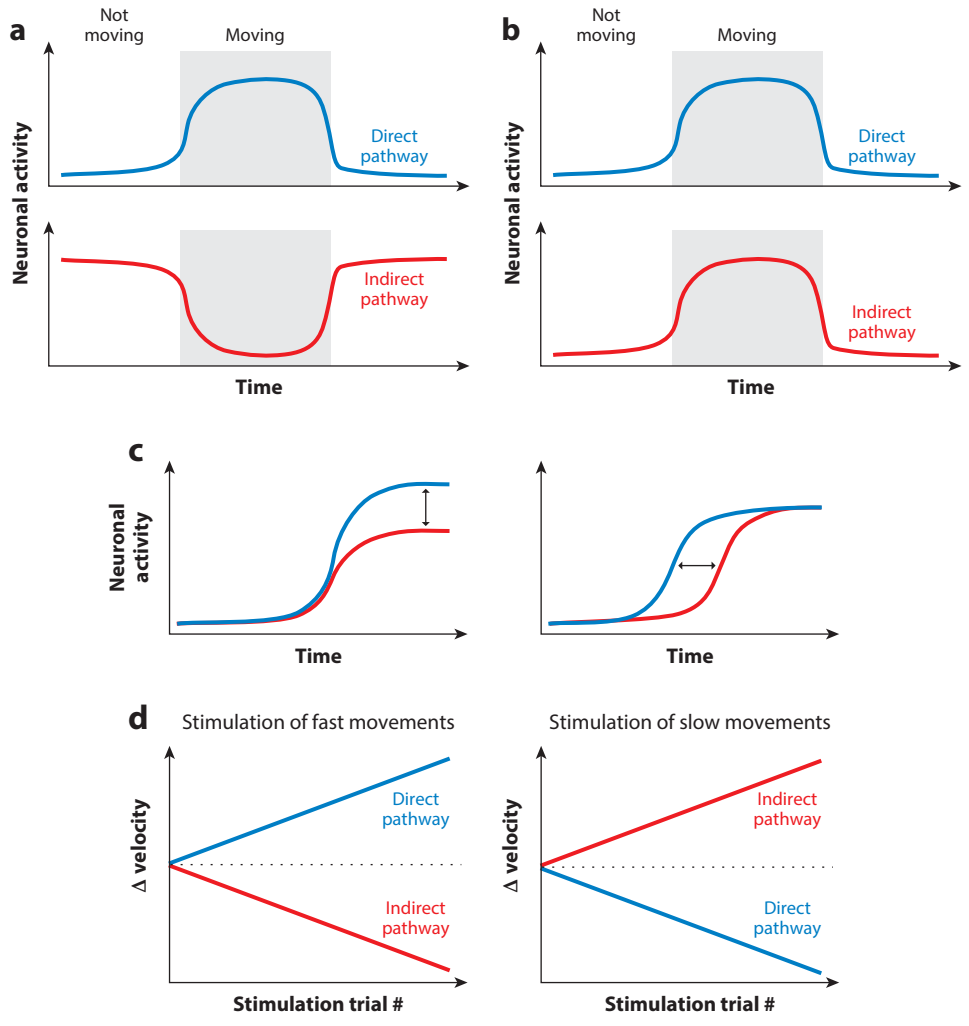

Figure 1

Potential scenarios of how activity in direct and indirect pathway neurons in the striatum is related to movement. (*a*) The pro- versus antikinetic model suggests that D1-SPN activity is higher during movement and D2-SPN activity is lower during movement, and vice versa during immobility. (*b*) Other models suggest that both pathways are more active during movement to select the particular desired movement. Cell type–specific recordings show that both pathways increase their activity during movement and are less active during immobility. (*c*) Variations of panel *b* in which both pathways are more active during movement, but changes in the relative amount or temporal profile of the activity lead to changes in movement. Panel *c* adapted from Jin et al. (2014). (*d*) D1-SPN and D2-SPN stimulation have opposing effects on movement speed, but either pathway can increase or decrease movement speed over subsequent trials depending on whether neurons during fast or slow movement trials are stimulated, respectively. Panel *d* adapted from Yttri & Dudman (2016) with permission from Nature. Abbreviations: D1-SPN, direct pathway spiny projection neuron; D2-SPN, indirect pathway spiny projection neuron; SPN, spiny projection neuron.

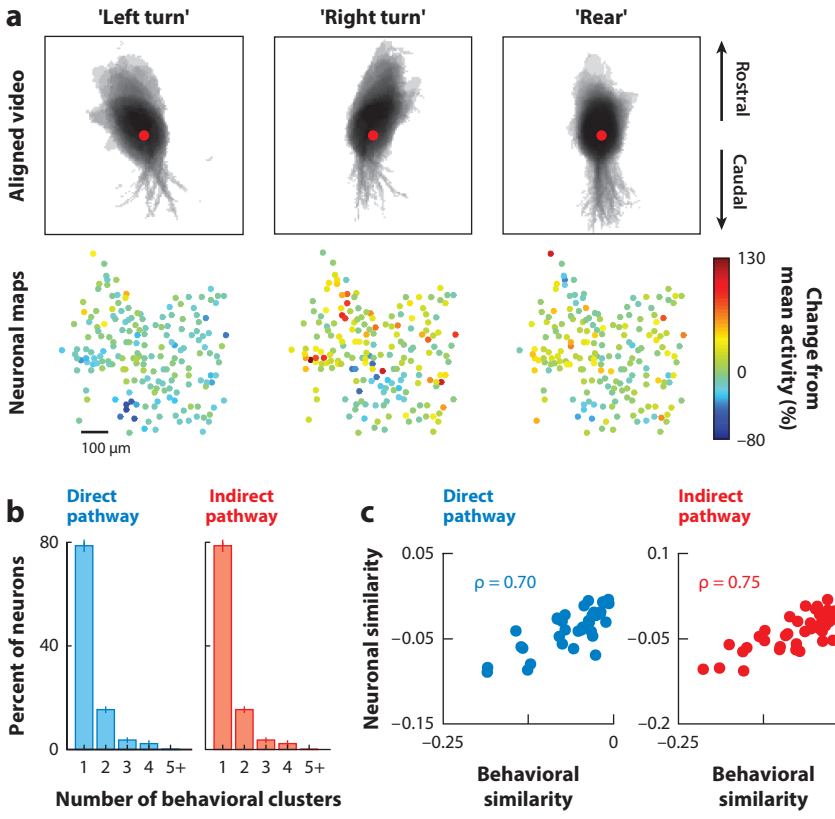

Figure 2

Striatal D1-SPNs and D2-SPNs have action-specific activity. (*a*) Different actions have different corresponding neuronal activity patterns in the striatum. (*b*) Most SPNs of both pathways that respond during movement have action-specific tuning; that is, they are significantly active only during one particular movement. (*c*) Similarity between neural patterns is related to the similarity between movements. ρ denotes Spearman correlation coefficient between behavioral and neuronal similarity. Abbreviations: D1-SPN, direct pathway spiny projection neuron; D2-SPN, indirect pathway spiny projection neuron; SPN, spiny projection neuron. Figure adapted from Klaus et al. (2017).

different movements but rather works on top of action-specific activity to modulate the speed of the corresponding movements (Jin et al. 2014). Consistently, the similarity between neuronal patterns is related to the similarity between the actions that are being performed (**Figure 2*c***) rather than the similarity between the speeds at which different movements are performed (Klaus et al. 2017). This suggests that when an organism initiates a specific action, the indirect pathway is not a general suppressor of all other competing actions, but rather, it can have a more specific role (Tecuapetla et al. 2016, Klaus et al. 2017). An alternative possibility would be that the indirect pathway is necessary to suppress rather specific unwanted muscle activations when initiating a specific movement, while direct activation of the STN-to-SNr projection from the cortex would play a role in general movement suppression (Mink 1996, Aron & Poldrack 2006, Schmidt et al. 2013, Fife et al. 2017). At any rate, these observations call for different models of how direct and indirect projection pathways work in concert during movement initiation.

The role of these striatal projection pathways may be different during movement initiation versus action evaluation and the control of ongoing action strategies. For example, in addition to

movement, SPNs encode action value (Samejima et al. 2005), and pathway-specific manipulations and recordings suggest that D1- and D2-SPNs may relay relative positive and negative values, respectively (Tai et al. 2012, Shin et al. 2018, Nonomura et al. 2018). Furthermore, perturbations of D2-SPN activity during action initiation increase the likelihood of switching to a different action, whereas comparable changes in D1-SPN activity lead to a delay in initiation but not a switch in behavior (Tecuapetla et al. 2016). This latter difference between the two pathways could be mediated by a different innervation of downstream targets, including thalamic and cortical circuits. Evidence for this hypothesis comes from experiments that recorded activity in the primary motor cortex while stimulating the two striatal pathways in a cued lever-pressing task (Oldenburg & Sabatini 2015). That is, the stimulation of D1-SPNs can increase cortical activity across all layers, predominantly in lever press–related neurons. In contrast, D2-SPN stimulation transiently excites neurons in more superficial layers (involved in thalamocortical and corticocortical processing) that show little or no lever press–related modulation of activity. These results suggest that there are still aspects to be uncovered in how direct and indirect projections connect to basal ganglia outputs and thalamocortical circuits (see, e.g., Saunders et al. 2015).

Taken together, the results reviewed here suggest that the coordinated spatial and temporal activation of specific SPN ensembles are crucial for the proper selection and initiation of actions. This raises the question of which mechanisms regulate SPN firing at both the single neuron and the ensemble level. A characteristic feature of SPNs is their distinctively low firing rate even during cortical activation (Berke et al. 2004, Sippy et al. 2015). This is a result of inward-rectifying conductances (Nisenbaum & Wilson 1995) and inhibitory synaptic inputs that counterbalance glutamatergic excitation (Blackwell et al. 2003, Pidoux et al. 2011, Reig & Silberberg 2014). Intrastriatal inhibition arises from various classes of local interneurons (Koós & Tepper 1999) as well as from axon collaterals between SPNs (Czubayko & Plenz 2002, Tunstall et al. 2002). Accordingly, striatal interneurons and lateral SPN inhibition have been implicated in normal and perturbed movement initiation (Dobbs et al. 2016, Klaus & Plenz 2016, Tecuapetla et al. 2016). Notably, many of these features are modulated by dopamine, which can shape the balance between the direct and indirect pathways and influence motor behavior (Planert et al. 2013, Dobbs et al. 2016, Parker et al. 2018). Indeed, accumulating evidence suggests that self-paced movement initiation is regulated by dopamine in a very dynamic fashion. Overall, the striatum, which requires sufficient glutamatergic and dopaminergic evidence for information transmission, provides an ideal architecture for action selection and initiation.

DOPAMINE INPUT TO STRIATUM AND SELF-PACED MOVEMENT INITIATION

Dopamine neurons are present in different regions of the brain. From the mesencephalon to the olfactory bulb, dopamine neurons can be found in nine distinctive areas (Dahlström and Fuxe groups A8–16) (Dahlström & Fuxe 1964, Björklund & Dunnett 2007). Among these areas, the SNc (A9 cell group) has been extensively studied since it was discovered that the degeneration of these neurons was the pathological hallmark of Parkinson's disease (Foix & Nicolesco 1925, Hassler 1938). Impairment in self-paced movement initiation and slowness of movement (bradykinesia) are striking symptoms in Parkinson's disease (Jankovic 2008) and in animal models of striatal dopamine depletion (Carli et al. 1985, Sotnikova et al. 2005, Panigrahi et al. 2015), and they are alleviated by levodopa administration. This obvious link between the loss of SNc neurons and movement impairment motivated researchers to record the activity of these neurons in behaving animals.

Seminal experiments in behaving monkeys revealed that the majority of putative SNc dopamine neurons increased their firing transiently after the presentation of stimuli that could elicit behavior reactions (Schultz 1986, Schultz & Romo 1990). The interpretation at the time was that dopamine neurons would participate in setting a state where actions would occur (Schultz & Romo 1990). Later, this interpretation was revised when it was postulated that the phasic activity of dopamine neurons resembled an RPE (Mirenowicz & Schultz 1994, Montague et al. 1996, Schultz et al. 1997). The concept of RPEs emerged from early learning experiments and theories (Kamin 1969, Rescorla & Wagner 1972) and was explicitly incorporated in reinforcement learning algorithms (Sutton & Barto 1981) that became increasingly explanatory. Prediction error models postulate that learning is maximal when there is an unexpected outcome, and indeed, dopamine neurons were shown to be phasically activated by rewarding stimuli or reward-predicting stimuli, but this activation was dependent on the unpredictability of the stimuli (Mirenowicz & Schultz 1994, Waelti et al. 2001), thus offering a neural support to prediction error algorithms. These studies, and the fact that the activation of midbrain dopamine neurons is sufficient to reinforce actions (Corbett & Wise 1980), shifted the focus on dopamine away from motivation and movement to learning. The RPE function of dopamine neurons, and their role in learning, has been extensively studied in the last few decades, with robust findings implicating phasic dopamine release in reward-based learning (for a recent review, see Watabe-Uchida et al. 2017). More recently, this role was confirmed by specific optogenetic manipulations of midbrain dopamine neurons (Tsai et al. 2009, Witten et al. 2011, Kim et al. 2012, Stauffer et al. 2016). However, recent studies confirmed that phasic activity of classified SNc dopamine neurons (Jin & Costa 2010) and subsecond fluctuations in dopamine levels in the striatum (Phillips et al. 2003, Wassum et al. 2012) occur before or around the initiation of self-paced learned actions. Furthermore, when a conditioned stimulus signals a rat to stay immobile for a certain amount of time in order to obtain a reward, the transient increase of dopamine happens when the rat initiates the movement to collect the reward and not when the conditioned stimulus appears (Syed et al. 2015), suggesting that the role for transient dopamine neuron activity in movement transitions should be revisited.

Besides the well-established role of dopamine neurons in learning, there is extensive evidence suggesting a role for dopamine neurons in other functions, namely in motivation and movement invigoration, in both rodents and humans (Berke 2018). For example, blocking D2 receptors decreases the effort that mice are willing to spend working for a food reward (Salamone et al. 1991), while blocking dopamine reuptake has the opposite effect (Yohn et al. 2016). Also, dopamine transporter–knockout mice exhibit reduced movement within a few minutes after the injection of α-methyl-*p*-tyrosine (an irreversible inhibitor of tyrosine hydroxylase) (Sotnikova et al. 2005). Bradykinesia in Parkinson's disease patients seems to be a combination of both deficits in movement initiation and a tendency to select less vigorous movements (Berardelli et al. 2001, Mazzoni et al. 2007), with similar observations in animal models where the nigrostriatal pathway is impaired (Panigrahi et al. 2015). Based on this finding, it has been argued that motor motivation is one of the main roles of nigrostriatal projections of dopamine neurons (Mazzoni et al. 2007).

Learning and motivation are clearly different functions. Motivation through behavioral activation and invigoration is a function that looks forward to energize behavior in anticipation of future reward, while learning looks back to previous states and actions and updates their values (Berke 2018). Because these functions are quite distinct, it has been a challenge to reconcile them. The widely accepted view is that the role of dopamine neurons in motivation and movement is supported by their tonic or sustained activity that changes slowly on a scale from several seconds to minutes, while their role in reward prediction is mostly attributed to phasic (i.e., subsecond) changes in activity (Niv et al. 2005, Schultz 2007). However, several observations demonstrated that the phasic activity of dopamine neurons is diverse and not fully explained by RPE. Besides

phasic activity neurons around behavioral transitions (Schultz 1986, Jin & Costa 2010), dopamine neurons have been shown to be phasically activated by both appetitive and aversive events, responding in a way that reflects the salience but not the value of the events (Matsumoto & Hikosaka 2009). Salience-coding dopamine neurons also respond to alerting events (Bromberg-Martin et al. 2010, Nomoto et al. 2010, Schultz 2010), with responses that depend on salience, surprise, novelty, arousal, and attention and are attenuated if stimuli are repeated in a predictable way (Bromberg-Martin et al. 2010). These novelty/salience neurons seem to also be anatomically distinct, and many project specifically to the posterior tail of the striatum (Menegas et al. 2017). Moreover, it was recently recognized that the phasic response of RPE coding dopamine neurons to stimuli has two components: an initial component that codes salience and is present for all kinds of stimuli and a second component that codes RPE (Nomoto et al. 2010, Schultz 2016).

Taken together, these data suggest that the function of phasic dopamine neuron activity may not be exclusively related to RPE. An alternative could be that phasic dopamine activity, even the first component of RPE coding neurons, is also important for preparing or motivating actions. Moreover, although minute-to-minute quantification of dopamine levels in the ventral striatum reflects reward rate, a relationship can still be found between subsecond dopamine level fluctuations and how willing a rat is to engage in a task (Hamid et al. 2016). Furthermore, these transient and fast changes before the performance of learned actions are not just reporting reward rates or how activated an animal is. Transient subsecond manipulations that increase striatal dopamine increase the probability of engaging in learned actions (Phillips et al. 2003, Hamid et al. 2016). Interestingly, in a two-arm bandit task, the optogenetic activation of dopamine neurons promoted the initiation of a trial when rats were not engaged but did not change the probability that the same action (left or right) was repeated in the next trial. However, transiently activating dopamine neurons after the rats had chosen right or left increased the probability of them repeating the same choice in the following trial (Hamid et al. 2016). This exemplifies how both learning and action initiation can be produced by fast and transient changes in dopamine activity.

In summary, a variety of experiments revealed that transient changes of dopamine levels in the striatum can also be related to action initiation. However, until recently, these experiments were performed in the context of reward-based tasks, and so it is possible that actions, as stimuli, that predict reward would elicit transient dopamine activity.

However, transient changes in the activity of dopamine neurons and their terminals in the dorsal striatum have also been described preceding self-paced initiation of movements outside the context of reward-based tasks (Dodson et al. 2016, Howe & Dombeck 2016, da Silva et al. 2018) (**Figure 3*a***). This transient activity of dopamine neurons before movement initiation was found to be not very action specific (**Figure 3*b***), with individual dopamine neurons being transiently active before different actions (da Silva et al. 2018), suggesting that the action specificity of striatal neurons (**Figure 2**) does not arise from dopamine inputs. Furthermore, the transient activity of particular dopamine neurons before movement initiation correlates with the vigor of the movement to be initiated (**Figure 3*c***). This activity preceding movement initiation seems to have a causal role because brief optogenetic activation of SNc dopamine neurons (Barter et al. 2015, da Silva et al. 2018) or their terminals in the dorsal striatum (Howe & Dombeck 2016) promotes movement initiation, while the inhibition of SNc dopamine neurons decreases the probability of movement initiation in mice (da Silva et al. 2018) (**Figure 3*d***). Furthermore, movements initiated after the brief optogenetic activation of SNc dopamine neurons are more vigorous, while movements initiated during optogenetic inhibition are less vigorous (da Silva et al. 2018). Importantly, precisely timed optogenetic manipulations of SNc dopamine neurons during movement did not change ongoing movements, perhaps indicating a more specific role for their activity for action transitions than previously acknowledged (da Silva et al. 2018).

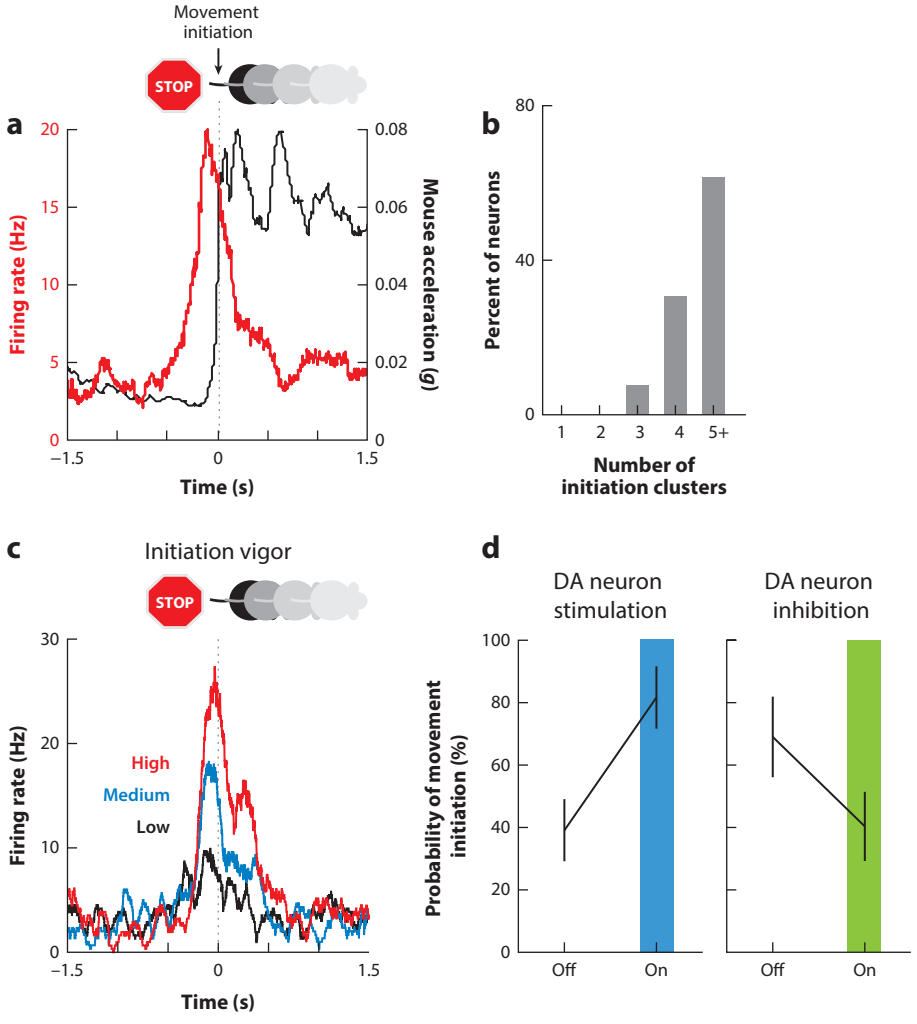

Figure 3

Transient activity of dopamine neurons precedes movement initiation and modulates the probability and vigor of movement initiation. (*a*) Example of a dopamine neuron with a transient increase in activity (*red*) before the initiation of self-paced movements (*black*) while mice explored an open field. (*b*) In contrast to SPNs (see **Figure 2*b***), dopamine neurons that are movement initiation related are generally not action specific because most of them increase their activity before different types of movement initiation. (*c*) The activity of some movement initiation dopamine neurons is associated with the vigor of the upcoming movement. In this example, a vigor-related neuron has a higher increase in activity before higher vigor movements (*red*) than before medium (*blue*) or lower vigor movements (*black*). (*d*) Optogenetic activation of SNc dopamine neurons with ChR2 increases the probability of movement initiation (*left*), while optogenetic inactivation with ArchT decreases the probability of movement initiation (*right*). Abbreviations: ArchT, archaerhodopsin; ChR2, channelrhodopsin; DA, dopamine; SNc, substantia nigra pars compacta; SPN, spiny projection neuron. Figure adapted from da Silva et al. (2018).

Taken together, these more recent findings suggest that transient changes in dopamine may work on top of sustained release to rapidly increase the probability of movement initiation and transition between movement states and to modulate the vigor of future movements.

CORTEX INPUT TO STRIATUM AND SELF-PACED MOVEMENT INITIATION

Despite its active role in movement initiation, the striatum is not a driver of basal ganglia output activity. Instead, SPNs require excitatory inputs and are heavily populated by glutamatergic synapses, most of which arise from the cortex (Huerta-Ocampo et al. 2014). Consequently, increases in striatal activity are preceded by cortical activity during the initiation of movements (Schultz & Romo 1992, Seo et al. 2012). However, the striatum does not simply relay a motor plan present in the motor cortex (Li et al. 2015) to downstream areas but integrates these activities with sensory and cognitive information (Pidoux et al. 2011, Reig & Silberberg 2014, Gremel & Costa 2013, Stalnaker et al. 2016). This is achieved through convergent projections from multiple cortical areas, which in the dorsal striatum are provided by topographically aligned motor and somatosensory cortices as well as the frontal cortex (Hintiryan et al. 2016, Hooks et al. 2018).

The convergence of cortical inputs at the mesoscopic scale is at least partly reflected at the level of individual SPNs. Direct functional evidence for this comes from whole-cell recordings that demonstrate integration from different cortical areas within single SPNs in vitro (Hooks et al. 2018) and in vivo (Reig & Silberberg 2014). Single SPNs receive inputs from a few thousand cortical synapses (Wilson 1995). Importantly, despite the overall convergence of cortical inputs within a given striatal region, neighboring SPNs can sample independently from individual cortical axons as observed using single-axon tracing (Zheng & Wilson 2002). Although only relatively few coordinated glutamatergic inputs are required to drive SPNs into a prolonged dendritic plateau potential (Plotkin et al. 2011), stronger inputs are necessary for SPNs to fire. Taken together, this architecture suggests that SPNs have some shared access to cortical information and can tune their responsiveness to very specific combinations of cortical inputs. This picture is in line with the spatiotemporal organization of SPN ensemble activities during natural movements (Klaus et al. 2017, Parker et al. 2018) and the observation that many striatal neurons do not show movement-related activities per se but fire in a context-dependent manner (Hikosaka et al. 2000). Furthermore, groups of SPNs that are coactive during a specific action (**Figure 2*a*,*b***) have more cross-correlated activity overall (i.e., not only during the preferred action; see **Figure 4*a***). SPNs are relatively hyperpolarized and require substantial glutamatergic inputs to fire, which suggests that groups of striatal neurons active during the same action receive common input (i.e., the same individual cortical neurons or connected cortical neurons project to coactive striatal neurons during the same action; a similar argument could be made for thalamic inputs). Thus, groups of cortical and striatal neurons may form preferentially connected modules that could be the basis for the action-specific patterns of activity (**Figure 4*b***).

The overall pattern of corticostriatal connectivity suggests that corticostriatal circuitry may be a suitable substrate to translate specific cortical states (i.e., movement plans, contextual information, etc.) into specific changes in basal ganglia outputs for movement initiation. And even in cases where the cortex may have already selected a specific motor plan (Seo et al. 2012), the basal ganglia are still required to evaluate it against additional contextual information and to commit to executing it (Thura & Cisek 2017).

Interestingly, self-initiated actions are preceded by neuronal activities in the cortex and striatum by hundreds of milliseconds to several seconds (Romo et al. 1992, Schultz & Romo 1992, London et al. 2018). This implies that premovement activities can reverberate through

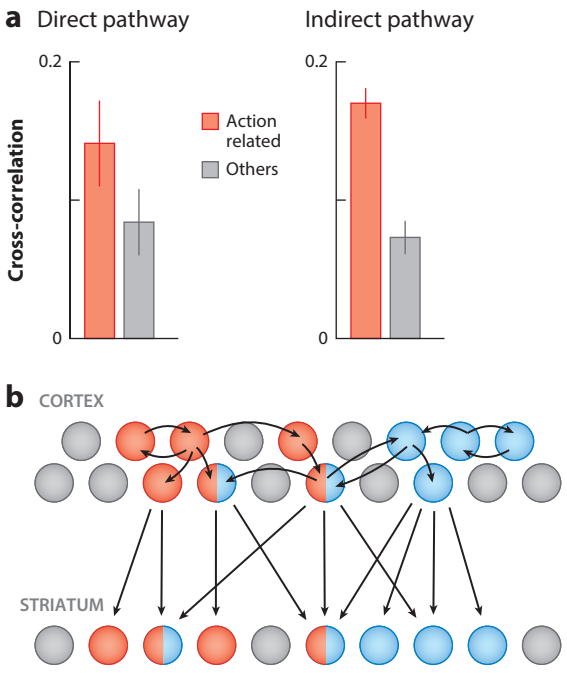

Figure 4

Excitatory cortical inputs are a major driver of striatal dynamics. (*a*) Cross-correlation between spiny projection neurons (SPNs) that are coactive during the same action is higher than between neurons that are not coactive during the same action, even in periods when the action is not being executed. Panel *a* adapted from Klaus et al. (2017). (*b*) This suggests that striatal neurons that are coactive during the same action share cortical inputs, either from the same cortical projections between action-related cortical neurons that project divergently to action-related SPNs or from cortical neurons that are preferentially connected. The colored circles indicate neurons related to two different actions (*blue* and *red*, respectively).

cortex–basal ganglia–thalamocortical loops, which have propagation latencies of about 200–250 ms (Oldenburg & Sabatini 2015, Klaus & Plenz 2016). Thus, the cortex can employ the basal ganglia in different modes. That is, it can modulate brainstem motor centers through direct projections and via the basal ganglia in a feedforward manner to execute movements given a motor plan and the right contextual information. In addition, the basal ganglia can provide feedback to thalamocortical circuits. Such feedback could flow in a closed loop (i.e., reaching the same cortical region where the activity originated from) or in open loops (i.e., reaching cortical regions that were not driving the corresponding basal ganglia circuits) (see, e.g., Haber & Calzavara 2009). Future studies that investigate those different scenarios will be needed for a complete understanding of cortex–basal ganglia circuits in movement and beyond.

It is important to note that cortical inputs to the striatum can arrive from different populations, for example, IT and PT neurons (Reiner et al. 2010, Shepherd 2013). While both types are active during movement planning, a specific motor command arises mainly in PT neurons before movement onset (Svoboda & Li 2018). Interestingly, it is not necessarily the average firing rate but rather the ensemble dynamics that have a profound influence on movement initiation (Kaufman et al. 2014). Thus, understanding IT and PT connectivity to downstream circuits (Hooks et al. 2018) and their dynamical organization in relation to basal ganglia circuits will be important avenues for future studies.

OTHER INPUTS TO STRIATUM

The second major source of glutamatergic inputs to the dorsal striatum, besides the cortex, comes from various thalamic nuclei, most notably the center median, parafascicular, and medial dorsal thalamus (Jones & Leavitt 1974, Wall et al. 2013, Smith et al. 2014). Some thalamic projection properties to SPNs and striatal interneurons have been extensively described anatomically and functionally (Ding et al. 2008, Wall et al. 2013, Smith et al. 2014). However, recent advances in viral tracing techniques reveal new details about the connectivity motifs between different thalamic, cortical, and striatal regions (Guo et al. 2015, Hintiryan et al. 2016, Hunnicutt et al. 2016, Hooks et al. 2018). Thus, thalamic inputs to the striatum might serve distinct functions based on origin and striatal target, that is, whether D1- or D2-SPNs or striatal interneurons are targeted. Thalamostriatal projections show strong alterations in Parkinson's disease (Smith et al. 2014) that are causally related to the motor deficits observed under chronic dopamine depletion (P.R.L. Parker et al. 2016). And although the precise role of the thalamus during self-paced movement initiation is not well understood, evidence suggests that the striatum receives input from thalamic areas necessary for movement preparation in sensory-guided decisions (Guo et al. 2017), and it has been recently shown that the inhibition of specific thalamostriatal projections perturbs action initiation (Díaz-Hernández et al. 2018). Furthermore, the thalamus may complement movement- and goal-specific cortical information with activities that support movement switching (Smith et al. 2011, Kato et al. 2018) or movement initiation during certain conditions, such as when an action has relatively low value (Minamimoto et al. 2005).

Additional excitatory afferents to the dorsal striatum, the posterior part in particular, arise from the basolateral amygdala (Kelley et al. 1982, Pan et al. 2010). This projection may modulate striatal activity depending on internally generated goals and the emotional context (Hernádi et al. 2015, Maeda et al. 2018). In rodents, the posterior striatum differs from the anterior part in that it receives fewer motor inputs (Hooks et al. 2018, Jiang & Kim 2018) and unique dopamine projections from a small set of lateral SNc neurons that reinforce avoidance (Menegas et al. 2018).

In addition to the various excitatory inputs, the striatum receives GABAergic inhibitory projections, in particular from the GPe (Bevan et al. 1998, Mallet et al. 2012, Guo et al. 2015). Prototypical GPe neurons project mainly to downstream basal ganglia nuclei but also innervate the striatum (Gittis et al. 2014). These GPe neurons fire at a high rate and are most likely modulated by D2-SPNs. A second source of GABAergic GPe (so-called arkypallidal) neurons provides strong and exclusive projections to the striatum (Mallet et al. 2012). Compared to prototypical GPe neurons, these neurons fire at a lower rate and have all the characteristics to globally reset striatal action representation during action cancelation (Mallet et al. 2016). New insights have been gained in recent years into the molecular subdivisions and downstream connectivity of these cell types (Saunders et al. 2016, Mastro et al. 2017). Investigating neuronal circuits at this level and studying their functional relevance will be important for understanding basal ganglia function.

MODELS OF HOW MODULATION OF BASAL GANGLIA OUTPUTS CAN INFLUENCE MOVEMENT INITIATION

The tonic inhibition by basal ganglia of thalamocortical circuits and executive motor centers in the brainstem and spinal cord (Grillner et al. 2013) serves at least two functions. It allows for simultaneous representations of potential motor commands without uncontrolled translation into movements (Redgrave et al. 1999, Hikosaka et al. 2000). Furthermore, it allows for more flexible access to the motor output centers, for example, the activation of the same motor output by different upstream modules or in different contexts (Redgrave et al. 1999).

Conceptually different models have been proposed to explain how tonic basal ganglia outputs are modulated by upstream circuits. The so-called rate model has at its core the opposing and symmetric effects of the direct and indirect pathways on downstream circuits (Albin et al. 1995; see also DeLong & Wichmann 2009). This model predicts the pro- versus antikinetic effects described above, that is, D1-SPN activity is low during immobility and high during movement and the opposite is true for D2-SPNs (**Figure 1*a***). The rate model does not make any predictions about how specific actions could be selected by the striatum. Thus, Mink (1996) and Hikosaka et al. (2000) proposed models that postulate the concurrent activity of D1- and D2-SPNs and in which specific ensembles of D1-SPNs can support the initiation of a specific action, whereas activity in D2-SPNs provides a more general suppression of alternative actions via the GPe and STN (i.e., spatially focused disinhibition of basal ganglia outputs). This model has been described above as the support/suppress model. It is important to note that D2-SPNs may be involved in a more specific form of movement suppression (Majid et al. 2013, Collins & Frank 2014), and other circuits like the hyperdirect pathway (i.e., cortex-to-STN-to–basal ganglia outputs) could implement a more general inhibition of movements (Mink 1996). Other models have postulated that even if D1- and D2-SPN activity is concurrent, direct pathway activity would inhibit the SNr before indirect pathway activity would arrive via GPe/STN, and hence there would be a window of disinhibition of basal ganglia output targets. Conversely, if indirect activity would precede direct pathway activity, this window would not exist. In this so-called race model, the timing of the activity in the two pathways will strongly determine their effect on basal ganglia outputs (Schmidt et al. 2013, O'Hare et al. 2016). The above models do not attempt to incorporate other types of neuronal dynamics, such as changes in synchrony or functional connectivity, which have been observed under pathological conditions (Goldberg et al. 2002, Costa et al. 2006, Hammond et al. 2007, Cruz et al. 2009, Parker et al. 2018) and which are likely to be at play under normal conditions. However, recent advances in cell type–specific recording techniques of neural ensembles with single-cell resolution have provided new insights into the spatial and temporal dynamics of cortical and basal ganglia circuits during movement (Barbera et al. 2016, Klaus et al. 2017, da Silva et al. 2018, Parker et al. 2018) and call for updated models of striatal function.

Nonetheless, irrespective of exactly how direct and indirect pathways exert their influence in basal ganglia output circuits, a certain view of how basal ganglia circuits and their inputs contribute to action selection and movement initiation is emerging. In **Figure 5**, we present two scenarios depicting how cortical and dopamine inputs could jointly regulate striatal dynamics during action initiation. In one case, two alternative motor plans in the cortex (**Figure 5*a***) are integrated with contextual and other information as well as dopamine inputs in the striatum. If dopamine input is low, striatal output is not sufficient to disinhibit motor centers, resulting in subthreshold motor output despite the presence of cortical activity (**Figure 5*a***). In the presence of stronger phasic dopamine, specific striatal ensembles become active depending on the specific cortical (and other) inputs, resulting in either action A or B (**Figure 5*a***). Importantly, action specificity arises from the pattern of cortical inputs, whereas dopaminergic inputs modulate the probability of the input arising from the cortex at that moment to cause the striatal neurons to fire (i.e., to be selected) by modulating their excitability. Furthermore, even in cases where a particular plan emerges more clearly in the cortex, dopamine input is still needed to activate the striatal neurons above threshold, hence leading to action initiation (**Figure 5*b***). This is consistent with studies showing that cortical dynamics that prepare movement can emerge in the absence of movement execution (see also Kaufman et al. 2014) and also that the basal ganglia may be needed to initiate movements that are selected somewhere else (Thura & Cisek 2017).

The above models help to relate aspects of cortical and basal ganglia activities to behavior, but they are formulated based on rather simplistic anatomical and functional connectivity and

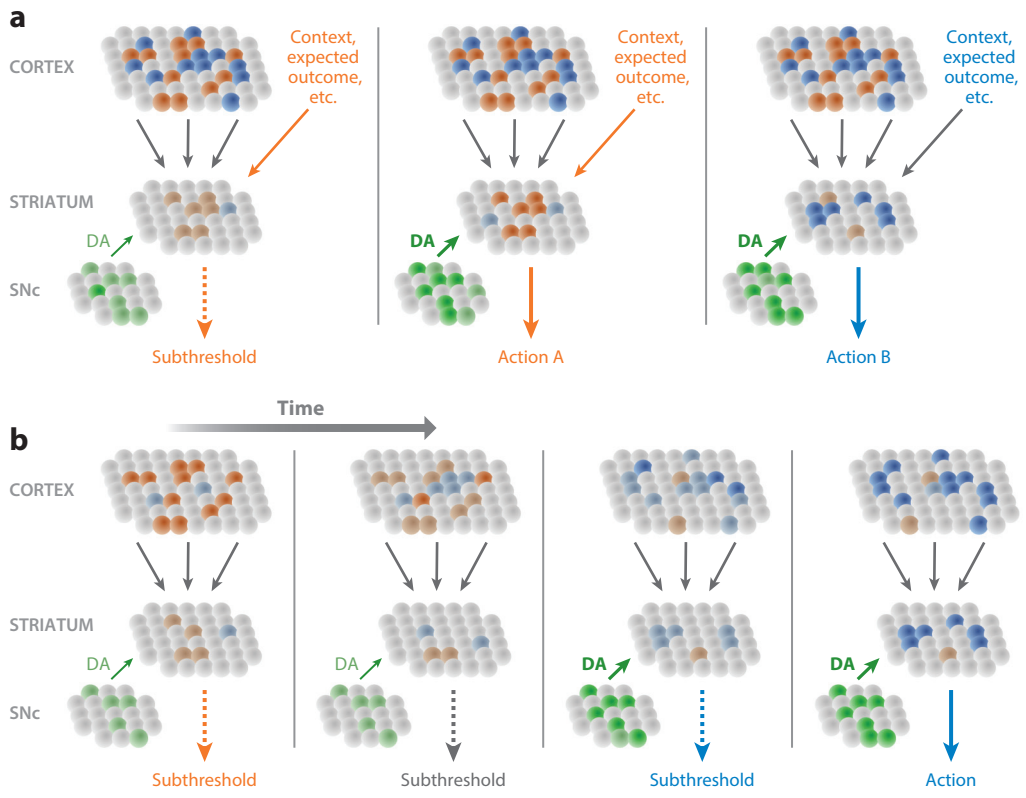

Figure 5

Selection and timing of self-paced actions. (*a*) The motor cortex can represent alternative actions (*orange* and *blue*) and drives specific striatal ensembles, depending on the context, expected outcomes, behavioral needs, and related costs (i.e., what to do). DA neurons are less action-specific but modulate the excitability of SPNs. (*b*) Even if an action plan emerges more clearly from the cortex, DA is required for the proper activation of striatal neurons. Thus, the timing of self-paced actions is controlled by the convergence of excitatory inputs and DA release (i.e., when to do it). Abbreviations: DA, dopamine; SNc, substantia nigra pars compacta; SPN, spiny projection neuron.

lack potentially important basal ganglia connections. As shown in **Figure 6**, even an incomplete account of the current knowledge of the connectivity in cortex–basal ganglia–thalamocortical circuits involves substantially more projections, collateralizations, and feedback loops than acknowledged by current models.

MODELS OF HOW DOPAMINE INFLUENCES MOVEMENT INITIATION

The evidence we described above defies the models that argue that dopamine influences movement only on a slow timescale of seconds to minutes. Transient subsecond changes in dopamine neuron activity or dopamine release have been shown to be involved in motivation and movement initiation (Jin & Costa 2010, Syed et al. 2015, Dodson et al. 2016, Hamid et al. 2016, Howe & Dombeck 2016, Coddington & Dudman 2018, da Silva et al. 2018). This revives an old question: How do we reconcile dopamine-related functions with dopamine's role in movement and reward prediction? One hypothesis is that RPE coding and movement-related dopamine neurons exist

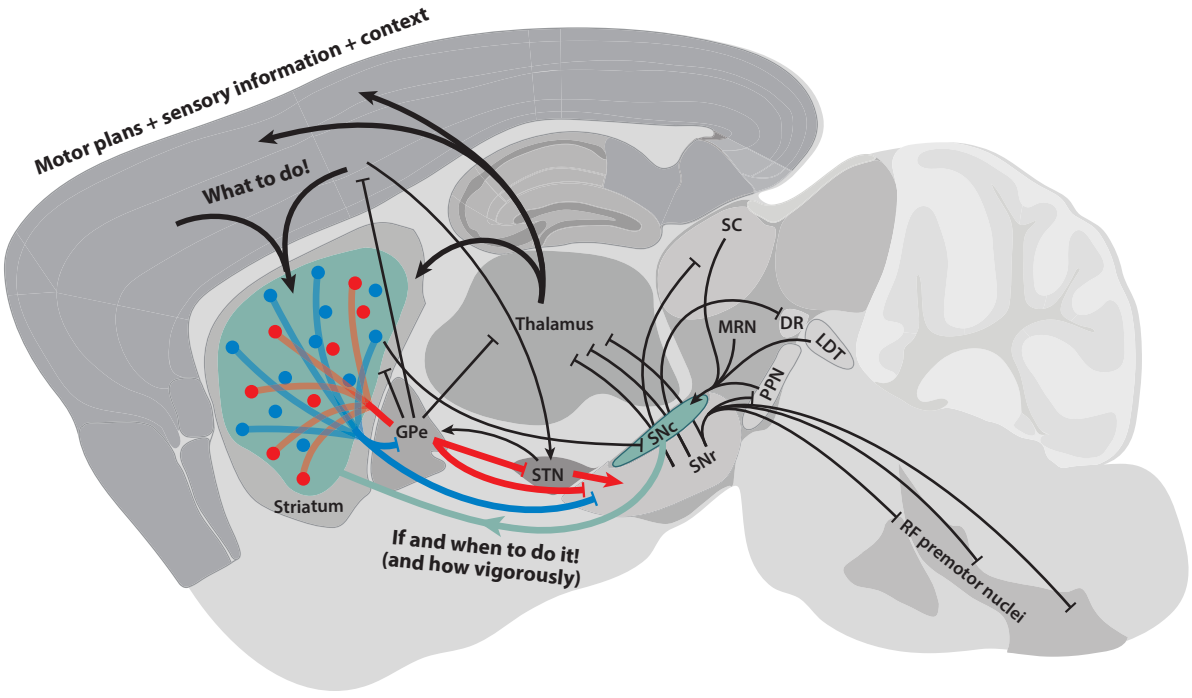

Figure 6

Models of basal ganglia function should have updated connectivity. A representation of other known projections in addition to the typical direct (*blue*), indirect (*red*), and nigrostriatal (*green*) pathways reveals a more complex circuitry. Direct projections from SPNs to SNc dopamine neurons; collateral projections from direct pathway neurons to the GPe; GPe projections directly to the cortex, thalamus, and striatum; brainstem inputs to the SNc; and SNr projections directly to brainstem nuclei are examples of projections that are less often considered when conceiving functional models of basal ganglia circuitry, and that challenge existing models. The understanding of how the basal ganglia influence movement selection and initiation should incorporate these projections. Abbreviations: DR, dorsal raphe; GPe, globus pallidus external segment; LDT, laterodorsal tegmental nucleus; MRN, median raphe nucleus; PPN, pedunculopontine nucleus; RF, reticular formation; SC, superior colliculus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; SPN, spiny projection neuron; STN, subthalamic nucleus. Anatomical structures were obtained from the Allen Mouse Brain Atlas (Lein et al. 2007) using API (**http://api.brain-map.org/api/v2/svg_download/100884129?groups=28**).

within different basal ganglia loops (limbic, associative, and sensorimotor) (Hunnicutt et al. 2016) defined by specific inputs and preferential projection areas. Supporting this hypothesis, dopamine neurons that project to the dorsal striatum seem to be more associated with movement, while dopamine neurons that project to the ventral striatum carry responses that seem to be more related to reward and RPE (Howe & Dombeck 2016, N.F. Parker et al. 2016). Consistently, the activity of the cholinergic neurons that project from the pedunculopontine nucleus (PPN) to the SNc dopamine neurons has the ability to modulate locomotion, while the activity of PPN or laterodorsal tegmental nuclei cholinergic neurons that project to the ventral tegmental area exerts reward-related effects (Xiao et al. 2016). However, other studies found dopamine neurons with movement-related and reward-related activity within the same area of the SNc (da Silva et al. 2018). This suggests that different dopamine subpopulations with different inputs and outputs can coexist in the same area (Poulin et al. 2018, Saunders et al. 2018). In fact, recent work has shown that genetically defined subpopulations of dopamine neurons can coexist within the same area but have different projection profiles (Poulin et al. 2018). Although, on average, dopamine activity increases before movement initiation (da Silva et al. 2018), dopamine neurons related

to movement initiation also have heterogeneous profiles, with some being transiently excited and others inhibited (Dodson et al. 2016, da Silva et al. 2018) and with part of this heterogeneity being attributed to differences in the anatomical distribution of midbrain dopamine neurons (Dodson et al. 2016).

Another hypothesis is that dopamine could switch between motivational and RPE functions by local regulation within the striatum. In this sense, cholinergic interneurons in the striatum could be poised to dynamically switch the effect of dopamine release in the striatum between motivational and learning functions (Berke 2018).

As we discussed above, dopamine neuron phasic activity does not only reflect RPE. However, it is possible that dopamine neurons within different loops may subserve different functions even if they do similar computations (Lau et al. 2017). It could be that the prediction error function that was clearly identified within reward-related loops is also present within other functional loops like the ones involved in movement promotion and invigoration. Transient changes in the activity of dopamine neurons before movement initiation could therefore be seen as transitions between states, with the activity of these neurons coding an unsigned state prediction error (SPE) akin to the unsigned sensory prediction error or SPE found in salience-coding dopamine neurons. This signal before transitions between behavioral states could represent the difference between desired states and the current state (or the predicted sensory consequences of the movement and the current sensory input). Moreover, such an initiation or switch signal may work to facilitate the state transition at the same time and also establish a forward eligibility trace at the corticostriatal synapses that were involved in that state transition, facilitating their potentiation if a positive outcome would be encountered in the future. Such a mechanism would signify that this prediction error before movement initiation could be useful to encode the learning rate for that action; that is, expected movement transitions would be less likely to be reinforced than unexpected movement transitions.

From the discussion above, it is very striking that although dopamine neurons have activity that modulates movement, the activity of dopamine neurons does not code movement per se. We propose that dopamine input to the striatum modulates if and when to do something and how vigorously to do it by modulating the excitability of SPNs (Kravitz et al. 2010, Tecuapetla et al. 2016), which concomitantly receive the information about the motor plan (what to do) via glutamatergic inputs from the cortex and/or thalamus (**Figure 5**). Thus, dopamine would be gating and invigorating movements that were planned elsewhere (Wong et al. 2015, Thura & Cisek 2017), an idea that is consistent with the observation that dopamine neuron activity is not highly action specific (da Silva et al. 2018). In this sense, dopamine activity would not encode the speed of movement per se but maybe allow for more effortful actions, which are planned, for example, in the motor cortex that has speed-related activity (Costa et al. 2004). This could be achieved by influencing the activity in the striatum and, indirectly, the activity of downstream circuits like the brainstem cell populations that modulate the speed of locomotion (Capelli et al. 2017). Exactly how dopamine transients at movement initiation may influence SPN excitability is still not clear. Given the differential effect of dopamine in the modulation of D1- and D2-SPN excitability, it may even seem contradictory that movement initiation, which is associated with the coactivation of both the direct and indirect pathways, is modulated by transient dopamine release. One possibility is that dopamine release normalizes the activity of D2-SPNs, which are more excitable to begin with, to that of D1-SPNs. Another possibility is that the effects of dopamine are coadjuvated by the corelease of other transmitters. At any rate, the temporal dynamics of receptors and downstream second messenger systems, as well as the affinity of each receptor type, should be considered. It is important to note that D1- and D2-type receptors have different affinities, with the high-affinity D2 receptors likely being occupied at lower concentrations. Thus, transient increases in

dopamine release might mostly recruit the lower-affinity D1 receptors, promoting the activation of D1-SPNs by coordinated cortical or thalamic inputs (Surmeier et al. 2007). It is also relevant to note that although many SPNs of both pathways respond specifically during action initiation, others respond throughout the execution of the action (Jin et al. 2014, Sales-Carbonell et al. 2018). In this respect, it seems that although a similar proportion of D1- and D2-SPNs are active during action initiation, more D1-SPNs than D2-SPNs seem to have sustained activity during action execution (Jin et al. 2014). This seems to suggest that D1- and D2-SPNs that are active just at the start either have different inputs or respond differently to dopaminergic and glutamatergic modulation than those responding during execution.

Many of the points discussed above may help us to understand apparent discrepancies in the relation of midbrain dopamine neurons and movement initiation between different studies (Dodson et al. 2016, Hamid et al. 2016, Howe & Dombeck 2016, Coddington & Dudman 2018, da Silva et al. 2018). For example, different studies may target different anatomical regions or different cell types within midbrain dopamine neurons. Also, the physiological levels of dopamine release in the striatum needed for behavioral transitions necessarily depend on the concomitant levels of cortical/thalamic inputs, and hence different contexts may lead to easier or more difficult behavioral transitions upon dopamine release.

MOVEMENT INITIATION INDEPENDENT OF BASAL GANGLIA CIRCUITS

Even patients with advanced Parkinson's disease can transiently exhibit apparently normal movements following emotional or physical stress, typical involving life-threatening situations [so-called paradoxical kinesia (see, e.g., Bonanni et al. 2010)]. In addition, sensory cueing has been successfully used to overcome impairments in movement initiation in some of these patients (Rubinstein et al. 2002). Also, the execution of overtrained movements can become less dependent on dopamine (Yin et al. 2009). Nevertheless, in some situations this dopamine independence can still require the basal ganglia and the actions to be triggered by strong glutamatergic inputs, for example, in response to strong cues or for overtrained movements. In other situations, other motor control centers such as cerebellar pathways or brainstem motor control circuits might be triggered directly, even by cortical input, but independently of the basal ganglia (Schlesinger et al. 2007).

It makes sense that the evaluative process carried out by the basal ganglia may not be adequate in certain situations with immediate impact on survival. In such situations, the implementation of the motor program needs to be fast (e.g., escape responses to predator attacks). To achieve this, dedicated circuits involving the projections of the lateral hypothalamus to the periaqueductal gray mediate predative and evasive behaviors, putatively by integrating sensorimotor information from the central amygdala (Li et al. 2018). Such a circuit is well placed to determine the initiation of an action plan without the contribution of the basal ganglia. It also may be advantageous, in situations where an action is trained over and over, for it to be selected and executed independently of an evaluative process by the basal ganglia, by, for example, directly linking cortical circuits representing the sensory inputs to motor plans (Wickens et al. 2007).

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