Brain Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres

Review

A competitive model for striatal action selection

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HIGHLIGHTS

- We propose a "competitive" model to account for how striatal output pathways shape behavior.
- This model draws on knowledge of synaptic plasticity to link action selection to reinforcement.
- This model also provides insight into how imbalances in these pathways may contribute to compulsive and avoidant disorders.

ARTICLE INFO

Keywords:
Approach
Avoidance
Striatum
Dopamine
Repetitive behavior
Drug-seeking

ABSTRACT

The direct and indirect pathway striatal medium spiny neurons (dMSNs and iMSNs) have long been linked to action selection, but the precise roles of these neurons in this process remain unclear. Here, we review different models of striatal pathway function, focusing on the classic "*go/no-go*" model which posits that dMSNs facilitate movement while iMSNs inhibit movement, and the "*complementary*" model, which argues that dMSNs facilitate the selection of specific actions while iMSNs inhibit potentially conflicting actions. We discuss the merits and shortcomings of these models and propose a "*competitive*" model to explain the contribution of these two pathways to behavior. The "*competitive*" model argues that rather than inhibiting *conflicting* actions, iMSNs are tuned to the *same* actions that dMSNs facilitate, and the two populations "compete" to determine the animal's behavioral response. This model provides a theoretical explanation for how these pathways work together to select actions. In addition, it provides a link between action selection and behavioral reinforcement, via modulating synaptic strength at inputs onto dMSNs and iMSNs. Finally, this model makes predictions about how imbalances in the activity of these pathways may underlie behavioral traits associated with psychiatric disorders. Understanding the roles of these striatal pathways in action selection may help to clarify the neuronal mechanisms of decision-making under normal and pathological conditions.

"The corpus striatum is the centre in which movements primarily dependent on volition proper tend to become organized." David Ferrier, The Functions of the Brain, 1876

1. Introduction

The striatum, a brain structure positioned at the interface between the "motivational" and "motor" systems, is well positioned to translate animal volition into action selection (Mogenson et al., 1980). Although much effort has been placed in understanding the involvement of striatal output pathways in action selection, their precise roles remain unclear. Anatomically, the striatum has two classes of output projection neurons, termed "direct" and "indirect" pathway medium spiny neurons (dMSNs and iMSNs). These cell types are named for their differential projection targets, with dMSNs projecting "directly" to the midbrain, and iMSN projecting "indirectly" to the midbrain by way of the pallidus and subthalamic nucleus (Beckstead and Cruz, 1986; DeLong, 1990; Parent et al., 1984, Alexander and Crutcher, 1990). In addition, dMSNs and iMSNs express different dopamine receptors, with dMSNs expressing the dopamine D1 receptor (D1R) and iMSNs expressing the D2 receptors (D2R; Gerfen et al., 1990). Through these receptors, dopamine can exert different cellular actions on each population, with the D1Rs causing excitatory changes in dMSNs and D2Rs causing inhibitory changes in iMSNs (Nicola et al., 2000; Tritsch and Sabatini, 2012, Shen et al., 2008).

Multiple researchers have integrated this striatal anatomy with the behavioral effects of dopamine to explain how these pathways

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https://doi.org/10.1016/j.brainres.2018.10.009
Received 4 July 2018; Received in revised form 3 October 2018; Accepted 5 October 2018

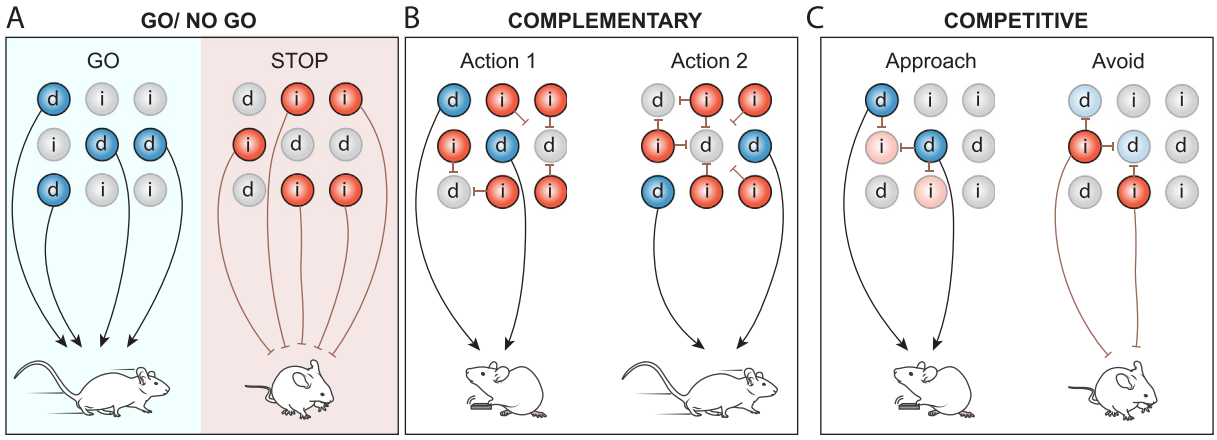

Fig. 1. Three models of striatal pathway function. (A) The GO/NO GO model posits that direct pathway MSNs (d, in blue) activation favors movement (GO) while indirect pathway MSN activation (i, in red) inhibits movement (STOP). (B) In the COMPLEMENTARY model, dMSNs (d) select and facilitate one action while iMSNs (i) concurrently suppress competing motor programs, allowing the selected action to proceed. (C) In the COMPETITIVE model, the balance of direct and indirect pathway output within an ensemble determines whether the animal approaches or avoids a stimulus.

contribute to action selection and movement. In one model, often referred to as the "classic", or "go/no-go" model (Fig. 1A), it was proposed that dMSN activation promotes movement while iMSN activation inhibits movement (Alexander and Crutcher, 1990, DeLong, 1990). This model accounts for the cellular actions of dopamine D1 and D2 receptors and predicts that conditions of high dopamine tone shifts the balance of striatal activity towards dMSNs over iMSNs. Consistent with this view, manipulations that enhance striatal dopamine, such as psychomotor simulant exposure, increase movement (Di Chiara and Imperato, 1988). Conversely, decreases in striatal dopamine, as in Parkinson's disease leads to bradykinesia (DeLong, 1990; Hornykiewicz, 1998; Obeso et al., 2010). Ablation experiments further support this model, as several groups found that selective ablation of iMSNs produced hyperactive mice (Bateup et al., 2010; Carvalho Poyraz et al., 2016; Durieux et al., 2009). Finally, optogenetic manipulations also support this model, as stimulation of iMSNs inhibited movement while stimulation of dMSNs facilitated them (Kravitz et al., 2010; Yttri and Dudman, 2016). It should be noted that the "go/no-go" model has historically focused on the dorsal striatum, and further work is needed to understand how this model applies to the ventral striatum.

Despite the heuristic utility of the "go/no-go" model, it fails to accommodate more recent data obtained with *in vivo* electrophysiology and cell-specific recordings of calcium activity. In these experiments, it was found that dMSNs and iMSNs were "co-activated" during movement initiation (Cui et al., 2013; Tecuapetla et al., 2016). This was initially puzzling: if iMSNs provide an anti-kinetic drive, why are they *activated* during movement? The observation that activity in both pathways increased during movement can be accounted for by a "*complementary*" model of striatal pathway function (Fig. 1B). This model postulates that iMSNs and dMSNs "work together" to select and facilitate appropriate behavioral responses (Mink, 1996). While this is likely true, it remains unclear *how* these cell types work together. Early views suggested dMSNs may facilitate one action, while iMSNs simultaneously suppress all competing actions (Mink, 1996; Alexander and Crutcher, 1990). This may account for why dMSNs and iMSNs are both activated when the animal moves. However, more recent work demonstrated that iMSNs have as much behavioral specificity as dMSNs in their activity patterns, making it unlikely that they are providing a blanket of inhibition over all potentially competing actions (Klaus et al., 2017; Parker et al., 2018). In addition, rather than simply inhibiting movement, iMSNs appear to promote specific behavioral strategies such as risk aversion (Zalocusky et al., 2016; Geddes et al., 2018; Klaus et al., 2017; LeBlanc et al., 2018). In sum, while both pathways are co-activated during movement, the contribution of each pathway to action selection has remained difficult to clarify.

Here, we propose a "competitive" model for action selection, which provides a theoretical framework for how these pathways work together to facilitate action selection. We hypothesize that stimuli drive cortical and thalamic ensembles that impinge on both dMSNs and iMSNs, which then "compete" via their output activity to determine the behavioral response to that stimuli. In this way, the balance of dMSN/iMSN activity determines whether the animal approaches, avoids, or remains in conflict about a stimulus (Figs. 1C and 2). This model also provides a simple link between action selection and reinforcement in which altering the synaptic strength of inputs onto iMSNs or dMSNs, via dopamine-dependent plasticity, can alter future behavioral responses to those stimuli (Fig. 2). Finally, this model provides predictions on how imbalances in striatal pathway activity may lead to specific behavioral traits that underlie psychiatric disease, such as heightened avoidance or approach of specific stimuli, which might result in action repetition. In this review, we will discuss evidence for each of these models, and argue in support of a competitive model of action selection.

2. The "classic" go/no-go model of basal ganglia function

The "go/no-go" model of basal ganglia function emerged from several convergent lines of evidence established in the later part of the 20th century. With retrograde tracing, it was found that MSNs projected to both the substantia nigra pars reticulata (SNr) and the external segment of the globus pallidus (GPe; Graybiel et al., 1979). Later analyses using double-retrograde tracers demonstrated an intriguing organization, in which striatal neurons that projected to the SNr were largely distinct from those that projected to the GPe (Beckstead and Cruz, 1986; Parent et al., 1984). These studies provided the first anatomical evidence for two parallel pathways projecting from the striatum to the SNr: (1) "direct" pathway neurons (dMSNs) that project to the SNr; and (2) "indirect" pathway neurons (iMSNs) that project "indirectly" to the SNr by way of the GPe and STN (Alexander and Crutcher, 1990; DeLong, 1990).

Around the same time, it was discovered that dopamine affected these two striatal output projections differently. First, dopamine depleted primates had reduced activity in the internal segment of the globus pallidus (GPi), but enhanced neural activity in GPe (DeLong, 1990). Why would depletion of the same transmitter cause opposing actions in two downstream targets of the striatum? Gerfen and colleagues provided a molecular answer to this question by demonstrating that dMSNs express the dopamine D1 receptor (D1R), whereas iMSNs express the dopamine D2 receptor (D2R; Gerfen et al., 1990). Finally, several groups verified that dopaminergic activation of the two receptor classes changed neuronal excitability in an opposing manner, with

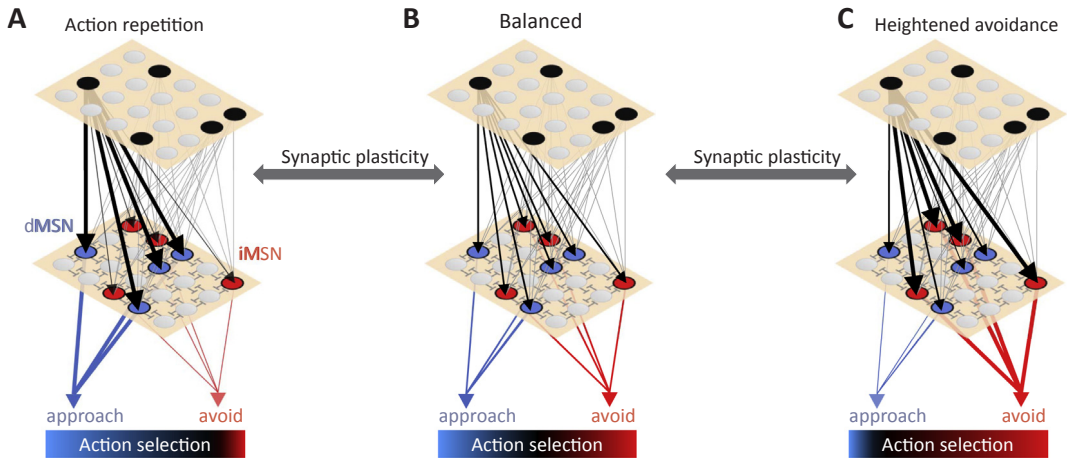

Fig. 2. Behavioral traits associated with altered striatal plasticity. (A) The enhanced and reduced excitatory drive onto dMSNs and iMSNs observed in diseases such as drug addiction, alcohol exposure and ASD might bias animals toward the repetition of certain actions, such as stimulus approach or self-directed stereotypies. (B) In naturalistic conflicts, the balanced activity of dMSNs and iMSNs ensures optimal decision-making. (C) Heightened excitatory drive onto iMSNs and reduced functionality of dMSNs may underlie animal model of social avoidance, suggesting that increased striatopallidal activity might bias animals toward stimulus avoidance.

dopamine increasing and decreasing the neuronal excitability of D1R- and D2R-expressing neurons, respectively (Nicola et al., 2000, but also see later discussion in the text). Finally, dopamine can also affect synaptic integration and plasticity at excitatory inputs (Shen et al., 2008; Surmeier et al., 2007; Tritsch and Sabatini, 2012), thus further shaping excitatory drive onto MSNs. Through multiple mechanisms, dopamine appears to promote the excitability and activity of dMSNs and inhibit those same properties in iMSNs. This can disinhibit thalamocortical and brainstem motor circuits and promote motor behavior (Albin et al., 1989; DeLong, 1990; Fig. 1A).

This "classic" model has played an integral role in understanding striatal anatomy and function, particularly in the context of movement disorders. The rigidity and bradykinesia observed in Parkinsonian patients was linked to an over-activation of the indirect pathway (Albin et al., 1989; DeLong, 1990), supporting a central prediction of the "classic" or "go/no-go" model. Multiple approaches for reducing the output of iMSNs result in hyper-locomotion, strengthening the idea that indirect pathway activity suppresses movement (Bateup et al., 2010; Carvalho Poyraz et al., 2016; Durieux et al., 2009). These findings were also supported by optogenetic studies in which the selective excitation of each pathway produced opposing changes in rodent exploratory locomotion (Kravitz et al., 2010). An elegant recent study also demonstrated that boosting striatal dopamine (via L-DOPA administration) decreased the firing rates of iMSNs, while enhancing the firing of dMSNs, in Parkinsonian mice (Ryan et al., 2018). While these studies confirm that manipulations that change the activity of these pathways *can* produce opposing actions on locomotor behavior, they do not explore how the two pathways are engaged during natural actions.

3. The "*complementary*" model of striatal function

Manipulating the activity of MSNs has been instrumental for understanding the consequences of reducing or increasing the activity of striatal pathways. However, optogenetic and chemogenetic approaches can result in non-physiological patterns of activity in the targeted neurons and synchronize large neuronal networks of neurons that might not otherwise be recruited during the expression of a specific behavioral trait (Kravitz and Optogenetics, 2013; Häusser, 2014). To address this limitation, researchers performed *in vivo* recordings from neurons of each pathway during behavior. Intriguingly, these results did not align simply with the results of optogenetic stimulation studies. For example, calcium recordings from identified dMSN and iMSN populations demonstrated that activity of *both* MSN populations were enhanced during the initiation of contraversive movements (Cui et al., 2013; Tecuapetla et al., 2014). This was initially surprising – why would the "no-go" neurons be activated during movement? Similar results were observed with electrophysiological recordings of identified neurons in a head-fixed task in rats (Isomura et al., 2013). Head-mounted microscopes were also used to record calcium activity of iMSNs and dMSNs during an open field behavior assay, and again supported this conclusion. In these recordings, it was found that compact clusters of neurons in both populations were enhanced when animals executed movements (Barbera et al., 2016). Two groups have replicated this main finding with similar methodology (Klaus et al., 2017; Parker et al., 2018), although the degree of spatial "compactness" of co-activated neurons differed among these studies. Additional recordings from these two pathways identified further correlates of movement, including body velocity, head movement speed, turn angle, and 3D action identity (Barbera et al., 2016; Cui et al., 2013; Klaus et al., 2017; Markowitz et al., 2018; Meng et al., 2018; Tecuapetla et al., 2014). Finally, in dopamine depleted animals, the balance of activity shifted towards iMSNs, consistent with early findings that supported the classic "go/no-go" model (Parker et al., 2018). Importantly, across all of these reports, iMSNs had as much specificity in their behavioral correlates as dMSNs (Klaus et al., 2017; Parker et al., 2018). Together, these results support the following conclusions: 1) both iMSNs and dMSNs are co-active during movement; 2) neurons that are closer together spatially have more correlated activity; 3) iMSNs and dMSNs have similar levels of behavioral specificity in their activity patterns.

The above data support that idea that both pathways work together to select and sculpt ongoing behavior, but it remains unclear exactly *how* they work together. In early descriptions of these two pathways, Alexander and Crutcher speculated that dMSNs select patterns of behavior for the animal to express, and iMSNs inhibit potentially conflicting patterns. They likened this to the "inhibitory surround" seen in sensory systems such as the retina and proposed that it may result in a "focusing of neural activity" in response to cortically initiated movements (Alexander and Crutcher, 1990). This view was refined by Mink in 1996, who proposed that the two striatal pathways work to broadly inhibit potentially competing motor programs, while allowing the selected action to proceed (Mink, 1996). These views, which we collectively refer to as the "complementary" model, suggested that iMSNs may act in concert to inhibit large numbers of competing actions (Fig. 1B). However, more recent recordings of individual iMSNs suggested that this view may be over-simplified. With calcium imaging, it was found that iMSNs have as much specificity in their tuning to behavioral features as dMSNs (Klaus et al., 2017; Parker et al., 2018). In addition, calcium recordings from populations of direct and indirect

MSNs demonstrated spatial "clusters" of activity in both populations, and not a broad activation of many iMSNs during movement (Barbera et al., 2016; Klaus et al., 2017; Parker et al., 2018). Finally, high resolution behavioral analyses demonstrated that both dMSNs and iMSNs are tuned to specific "syllables" of behavioral sequences (Markowitz et al., 2018), and brief manipulations of iMSN activity can shape these sequences (Geddes et al., 2018). Together, these recordings called into question the idea that iMSNs are a broadly tuned inhibitory circuit. While this has refined the possible role of iMSNs in shaping behavior, it has remained unclear *how* they contribute to action selection. Do they directly facilitate selected actions? Do they inhibit a small number of actions that are incongruous with the selected action? Or are they attempting to oppose the ongoing action, but failing to do so?

4. The "competitive" model: opposing functions of dMSN and iMSN within neuronal ensembles

To address the role of iMSNs in action selection, we propose a refinement of the above models, which accounts for the co-activation of iMSNs and dMSNs during movement, the specificity in the behavioral correlates of iMSN responses, and the effects of experimenter-controlled manipulations of dMSNs and iMSNs. As dMSNs and iMSNs receive inputs from largely overlapping brain areas (Guo et al., 2015; Wall et al., 2013), we propose that ensembles of dMSNs and iMSNs receive similar patterns of inputs, and therefore receive similar information about stimuli and selected actions (Kress et al., 2013). Rather than facilitating or opposing potentially *conflicting* actions, we propose that both dMSNs and iMSNs are tuned to the *same* action, with dMSNs providing a facilitating drive, and iMSNs providing an inhibitory drive (Fig. 1C, Fig. 2). In this way, dMSNs and iMSNs "compete" via their activity levels to determine how an animal responds to a stimulus. In an approach-avoidance framework, this may determine whether an animal approaches, avoids, or remains in conflict about a stimulus or a potential action. This model accounts for why neurons of each population are co-activated by specific stimuli, while also explaining the effects of broad manipulations of pathway activity (Bateup et al., 2010; Carvalho Poyraz et al., 2016; Durieux et al., 2009; Kravitz et al., 2012, 2010).

The competitive model also provides a simple explanation for how activity in these pathways mediates reinforcement, by drawing on cellular understanding of plasticity at projections onto dMSNs and iMSNs. We hypothesize that stimuli that result in depolarization of MSNs increase the probability of those neurons undergoing excitatory synaptic plasticity, as this appears to be a necessary component of such plasticity *in vitro* (Shen et al., 2008). Additionally, dopamine is released during unexpected outcomes (Schultz et al., 1997), and modulates synaptic plasticity to favor long-term potentiation (LTP) and long-term depression (LTD) at dMSNs and iMSNs, respectively (Shen et al., 2008). When post-synaptic depolarization is paired with pre-synaptic patterns of input from cortex and thalamus, and dopaminergic drive, those specific synapses can be potentiated. Importantly, when dMSNs "win" the competition and an animal approaches a stimulus, stimulus-linked iMSNs are also co-activated. This primes synapses onto these neurons for plasticity should the value of the outcome be greater or less than expected. Relatively small changes in synaptic strength can thereby alter action selection on subsequent experiences with that stimulus. Such plasticity mechanisms may influence future responses to the same stimulus, inherently linking action selection to reinforcement.

The existence of neuronal ensembles within the striatum has been observed with genetic tools that "tag" activated brain cells during the expression of specific behavioral traits. Moreover, manipulating the function of those neuronal ensembles can alter behavior: daunorubicin-mediated ablation of activated cells in the nucleus accumbens revealed the existence of groups of neurons that were causally involved in context-specific locomotor sensitization to cocaine (Koya et al., 2009) and reinstatement of seeking behavior (Cruz et al., 2014). This circuit specialization is associated with a specific form of excitatory synaptic plasticity, restricted to ensembles of neurons during cocaine sensitization (Koya et al., 2012). Within the dorsal striatum, methamphetamine-seeking behavior is regulated by a medially-located neuronal ensemble constituted by a mix of MSNs and other neuronal cell types (Caprioli et al., 2017) while a neuronal ensemble, mainly populated by dMSNs, is responsible for L-DOPA induced dyskinesia (Girasole et al., 2018). Thus, within the striatum, discrete neuronal ensembles may be linked to specific cues and actions, and control their evaluation, selection and execution. When viewed in light of the competitive model, ensembles may be recruited that are imbalanced towards dMSNs or iMSNs, and thereby lead to a high probability of approach or avoidance, respectively. At extremes, this may lead to pathologically high levels of approach or avoidance of specific stimuli, and underlie behaviors seen in psychiatric disorders (Fig. 2A, C).

Consistent with this proposal, in an elegant study that used spectrally resolved fiber photometry to simultaneously record population activity of iMSNs and dMSNs, the balance of activity between these pathways was the critical determinant of whether the animal continued or aborted ongoing actions (Meng et al., 2018). This study also demonstrated a lack of coordination between hemispheres, indicating that striatal neurons can be further tuned to the direction of the selected action (Cui et al., 2013, Meng et al, 2018). The importance of dopaminergic signaling for controlling approach/avoidance behavior has been demonstrated in both naturalistic and decision-making settings. In naturalistic settings, global D2R KO mice show enhanced stress-induced avoidance of anxiogenic zones (Sim et al., 2013). With refined genetic ablation, the absence of D2R from iMSNs increased iMSN output (Lemos et al., 2016), possibly through enhanced excitatory drive onto iMSNs. The D2 iMSN ablation also results in avoidance of anxiogenic areas, such as the open arms of an elevated zero maze or the center zone of an open field (LeBlanc et al., 2018). Low-power optogenetic stimulation of iMSNs also induced avoidance of such anxiogenic areas (LeBlanc et al., 2018). In a decision-making task, risk-avoidance behavior also appears to be controlled by accumbal iMSN activity: iMSNs activity was tuned to risky outcomes, and optogenetic activation of these neurons reduced risky actions in risk-taker rats (Zalocusky et al., 2016). Thus, iMSNs facilitate avoidance of stimuli, which can manifest as a generalized state of risk aversion.

As a final consideration, equivalent activation of dMSNs and iMSNs within a neuronal ensemble may put the animal in conflict, and unable to decide whether to approach or avoid a stimulus. Such conflict states can be adaptive in the face of uncertain outcomes, as it can allow more time to evaluate existing information or to allow for additional information to accrue, known as "risk assessment" (Bach, 2015; Blanchard et al., 2011). However, conflict states can also be maladaptive. Heightened drive for approach might underlie impulsive choices when an action is repeated without considerations for its consequences, or despite known negative consequences (Fig. 2A). Conversely, a generalized enhancement in avoidance of stimuli may underlies certain types of anxiety disorders (Fig. 2C). People with anxiety disorders can ruminate over even small decisions, which may result from a conflict between activity of dMSNs and iMSNs, such that neither approach nor avoidance is selected. Thus, re-interpreting the functions of dMSNs and iMSNs in a "*competitive*" conflict-resolution perspective may give insights into how the basal ganglia contribute to decision making in both normal conditions and psychiatric disorders.

5. Integrating action selection with reinforcement

Models of basal ganglia function often suggest that activity in these pathways promotes or inhibits *ongoing* actions. While optogenetic studies demonstrate sufficiency of these pathways to do so, under other conditions these pathways appear to be more involved in manipulating *future* actions. For instance, activity in many striatal neurons precedes actions, sometimes by several seconds (Cui et al., 2013; London et al., 2018). In tasks in which animals perform multiple actions to obtain the

same outcome (such as in a go/no-go task), many striatal neurons track the outcome, and not the action (Apicella et al., 1991; Schultz et al., 1993). Finally, stimulation of these pathways can drive reinforcement, and modulate the reinforcing properties of other outcomes (Carvalho Poyraz et al., 2016; Durieux et al., 2009; Kravitz et al., 2012). This demonstrates that activity in these pathways can alter the probability of future actions as well as ongoing actions.

It remains unclear how these pathways contribute to both action selection and reinforcement. In the competitive model, we propose that action selection is inherently linked to reinforcement, by increasing the probability of synaptic plasticity onto active dMSNs or iMSNs (Shen et al., 2008). One example of this is observed in optogenetic activation of dMSNs and iMSNs (Kravitz et al., 2012). In this study, optogenetic stimulation increased or decreased the probability of future contacts with the stimulus that caused the stimulation. In a refined closed-loop stimulation of these pathways, dMSN stimulation during action execution increased and decreased the velocity of fast and slow purposive movements, respectively, while iMSN activation had the opposite effect (Yttri and Dudman, 2016). Importantly, the progressive change in action velocity over time indicated a form of learning, which depended on dopamine (Yttri and Dudman, 2016). Accordingly, during a goal-directed lever press sequence, the activation of dMSNs supported ongoing performance, while iMSN stimulation facilitated task switching (Tecuapetla et al., 2016). This supports the hypothesis that at time of decision-making, the dMSNs and iMSNs convey important information about action value (Tai et al., 2012) and fits with the observation that dMSN and iMSN activity increases before execution of actions (Cui et al., 2013; London et al., 2018). In addition to reflecting ongoing actions, dMSN and iMSNs may signal the potential value associated with future actions, which can also be updated *via* synaptic plasticity at inputs onto these neurons.

6. Dopaminergic modulation of synaptic plasticity at dMSNs and iMSNs

Midbrain dopamine neurons are involved in updating the value of reward-paired cues (Schultz et al., 1997), and dopamine is a key modulator of excitatory striatal plasticity. *In vivo*, synaptic plasticity may occur at excitatory inputs of neurons that are concurrently activated during action execution and/or cue presentation. In this way, dopamine may potentiate the excitatory drive onto stimulus-recruited dMSNs, while depressing excitatory inputs onto recruited iMSNs (Shen et al., 2008). Thus, the dopamine-modulated synaptic plasticity onto ensembles of dMSNs and iMSNs may represent the neuronal substrate for reinforcement.

Synaptic plasticity at glutamatergic inputs enables for tuning of excitatory drive to refine neuronal output (Turrigiano and Nelson, 2004). Striatal MSNs, due to their hyperpolarized resting membrane potential, require strong excitatory synaptic drive to fire action potentials (Wickens and Wilson, 1998). The main excitatory inputs to MSNs arise from cortical and thalamic areas (Huerta-Ocampo et al., 2014; Wall et al., 2013), which coordinate behavioral flexibility and action selection, respectively (Kato et al., 2018; Wickens et al., 2007). Cortical and thalamic inputs are heterogeneous (Ding et al., 2008; Smith et al., 2009), and the majority of these inputs target the head of dendritic spines where they are subject to regulation by dopamine (Huerta-Ocampo et al., 2014). As a result, dopamine signaling at MSNs through D1Rs and D2Rs strongly impacts action selection (Cohen and Frank, 2009; Surmeier et al., 2007).

In vivo, different protocols of cortical stimulation can induce synaptic potentiation (Charpier and Deniau, 1997; Charpier et al., 1999) as well as depression (Reynolds and Wickens, 2000). This suggests potential differences in synaptic plasticity occurring at different neuronal subtypes. Despite the evidence that D1R blockade prevents synaptic potentiation induced by simultaneous dopamine release and synaptic stimulation (Reynolds et al., 2001; Reynolds and Wickens, 2002), it remains unknown whether the induction and expression properties of plasticity are similar at the two striatal pathways *in vivo*. In this regard, *ex vivo* electrophysiological recordings provided instrumental information about synaptic plasticity rules and the role of dopamine at identified MSN subtypes. In D1-MSNs, spike timing-dependent long-term potentiation (STDP-LTP) requires D1R activation, while STDP-induced long term depression (STDP-LTD) can be elicited only if D1Rs are blocked (Shen et al., 2008). This dopamine-dependent potentiation arises from activation of the D1R, which increases the activity of PKA-dependent signaling cascades to promote the insertion of AMPA receptors on the postsynaptic membrane (Mangiavacchi and Wolf, 2004; Tukey and Ziff, 2013). Consistently, high frequency stimulation can induce LTD in dMSNs *via* mechanisms that do not engage post-synaptic dopamine receptor signaling (Trusel et al., 2015; Wang et al., 2006). Thus, dopamine appears to favor synaptic potentiation of inputs onto dMSNs but not iMSNs.

In iMSNs, LTD is induced by cortical STDP with negative timing (Shen et al., 2008) or high-frequency macro-electrode stimulation with post-synaptic depolarization (Kreitzer and Malenka, 2005). This requires intact D2-signaling, since it is blocked by sulpiride (Kreitzer and Malenka, 2005; Shen et al., 2008), and is dependent on intracellular calcium through L-type calcium channels, with co-activation of mGluR5 activation for calcium-dependent calcium release. mGluR5 activation leads to production of endocannabanoids (eCBs), which retrogradely activate CB1 receptors on cortical terminals to reduce glutamate release (Sung et al., 2001). D2Rs might modulated modulate this plasticity through stimulating the production of eCBs to promote LTD (Giuffrida et al., 1999), and by opposing adenosine A2a signaling which promotes LTP through PKA-dependent signaling cascades (Fuxe et al., 2007; Shen et al., 2008). Interestingly, although CB1Rs are involved in mechanisms of LTD at excitatory inputs, they are also expressed by MSNs (Naydenov et al., 2014) and on GABAergic terminals (Kofalvi et al., 2005) where they modulate synaptic plasticity at GABAergic inputs (Adermark and Lovinger, 2007). Consistent with enhanced pre-synaptic glutamatergic input to iMSNs in the absence of D2Rs, frequency of miniature excitatory post-synaptic currents (mEPSCs) onto striatal neurons is increased (Cepeda et al., 2001; Robbe et al., 2002). Together these studies suggest that D2R signaling depresses excitatory input selectively onto iMSNs.

The effects of D2R signaling on the excitability of iMSNs themselves is controversial. Depletion of dopamine or blockade of D2Rs selectively increases activity of D2 MSNs measured by downstream genetic activation or electrophysiology (Bertran-Gonzalez et al., 2008; Mallet et al., 2006). However, when the D2R was selectively removed from iMSNs, firing rates of iMSNs were decreased *in vivo,* as was the intrinsic excitability of these neurons *ex vivo* (Lemos et al., 2016). Consistent with these findings, quinpirole had no effect on excitability of iMSNs *ex vivo*, suggesting a contribution of D2Rs on other striatal neuronal populations to altered excitability or compensatory adaptations following genetic ablation. Despite the reduction in their spiking activity, genetic ablation of the D2R on iMSNs increased output of these neurons, increasing lateral inhibition within the striatum and GABAergic tone in downstream pallidal structures (Lemos et al., 2016). Conversely, increasing dopamine tone (via repeated cocaine exposure) decreased the output of iMSNs locally and to pallidal structures (Creed et al., 2016; Dobbs et al., 2016) and this dopamine-dependent decrease was absent in mice in which the D2Rs have been ablated selectively from iMSNs (Dobbs et al., 2016). Together, this supports a model whereby dopamine signaling through D2Rs reduces both the excitatory transmission onto iMSNs and the output of iMSNs, thus attenuating indirect pathway function through multiple mechanisms. It should be noted that such *ex vivo* experiments make it difficult to evaluate the contribution of specific ensembles, and future experiments with *in vivo* preparations are needed to evaluate these.

Dopaminergic control of synaptic transmission is particularly relevant when considering its contribution to neurological disorders such

as Parkinson's disease. Different levels of SNc denervation differentially affected MSN synaptic plasticity in rats: while complete denervation affected both LTP and LTD, incomplete dopamine denervation only affected LTP (Paillé et al., 2010), pointing at a possible involvement of the loss of synaptic potentiation at early stages of Parkinson's disease. Furthermore, in a reserpine-induced dopamine depletion model, negative timing plasticity protocol produced LTP, instead of LTD, at iMSN inputs, while positive timing protocol at dMSNs promoted LTD, instead of LTP (Shen et al., 2008). This suggested that the reduction in dopamine levels favors weakening of dMSN inputs that would normally be potentiated, while strengthening iMSN inputs that would be depressed. Importantly, the restoration of LTD at excitatory inputs onto iMSNs ameliorates the Parkinsonian motor dysfunctions (Kreitzer and Malenka, 2007), pointing at the involvement of altered dopamine-mediated synaptic plasticity in the emergence of brain disorders.

7. Altered striatal pathway function in animal models of psychiatric disease

According to the Research Domain Criteria Initiative (RDoC), the investigation of the etiological mechanisms underlying pathological behavioral traits occurring in more than one disease might be beneficial for finding effective treatments for psychiatric disorders (Katahira and Yamashita, 2017). Further, brain disorders are often diagnosed because of the appearance of a cluster of behavioral symptoms. Alterations of glutamatergic plasticity onto defined striatal circuits have been observed in animal models of human pathologies such as drug addiction and Autism Spectrum Disorders (ASDs). These pathologies are characterized by *heightened action repetition*, including drug consumption and stereotyped behavior; for the animal models discussed below, an association between striatal dysfunctions and pathological behavioral traits has been established. Conversely, in depressive-like phenotypes induced in laboratory animals, *heightened avoidance*, in particular towards social stimuli, is also associated with striatal synaptic maladaptations, and appear opposite to the changes observed in pathologies characterized by heightened stimulus approach behavior. We therefore propose that these behavioral traits may be the result of opposing shifts in the balance of dMSNs and iMSNs within ensembles of striatal neurons that are tuned to specific stimuli (Fig. 2).

Addiction to drugs of abuse is characterized by enhanced seeking behavior, a lack of inhibitory control over drug taking, and the emergence of negative emotional states (Everitt and Robbins, 2013; Koob and Volkow, 2016). Several forms of synaptic adaptations occur in many brain regions in animal models of drug exposure that appear necessary for these behavioral changes (Luscher and Malenka, 2011). For instance, intermittent alcohol consumption potentiates excitatory transmission onto dMSNs and GABAergic transmission onto iMSNs of the DMS, respectively, enhancing and depressing direct and indirect pathway function to control alcohol seeking (Cheng et al., 2017). This may create a state in which cues that signal alcohol engage dMSNs to drive approach, while the output of avoidance-promoting iMSNs in this ensemble is diminished (Fig. 2A). Similarly, cocaine exposure enhances excitatory synaptic transmission onto accumbal dMSNs, but not iMSNs, in mice (Pascoli et al., 2012). Withdrawal from cocaine self-administration promotes input-specific forms of synaptic potentiation at dMSNs, but not iMSNs, to control different traits of cocaine seeking behavior (Pascoli et al., 2014). Consistently, the output of iMSNs is decreased after cocaine exposure (Creed et al., 2016; Dobbs et al., 2016). Intriguingly, excitatory synaptic strength on iMSNs is enhanced in mice that do not show compulsive cocaine seeking behavior (Bock et al., 2013), suggesting that maintenance of iMSN drive in an ensemble may make an animal resistant to addictive effects of cocaine. Altogether, these lines of evidence suggest that enhanced synaptic transmission onto accumbal dMSNs and reduced excitatory and/or increased inhibitory drive onto iMSNs facilitates a loss-of-control over seeking behavior, particularly when an animal experiences drug-paired stimuli (Fig. 2A).

The relationship between pathological seeking behavior and striatal synaptic dysfunctions has been demonstrated by optogenetic or electrical stimulation to reverse synaptic plasticity *ex vivo* and ameliorate behavioral symptoms *in vivo*. An induction of a long-term depression via 13 Hz stimulation of prefrontal cortex inputs onto dMSNs induces long-term depression in brain slices and abolishes cocaine seeking *in vivo* (Pascoli et al., 2014). Moreover, electrical stimulation of cortical afferences together with D1R blockade induces long-term depression *ex vivo* and abolishes cocaine-induced locomotor sensitization *in vivo* (Creed et al., 2015). These experiments indicate that potentiation of excitatory transmission onto dMSNs can modulate cocaine seeking behavior. A similar association has been also reported for alcohol seeking behavior, which can be reduced by depotentiation of prefrontal cortex inputs to dMSNs of DMS (Ma et al., 2018). Moreover, inhibition and excitation of accumbal iMSNs increases and reduces motivation for drug-intake, respectively (Bock et al., 2013), thus providing a link between reduced function of indirect striatal pathway to compulsive drug-intake.

As reported earlier, the exposure to drugs of abuse strengthens striatal ensembles responsible for the expression of drug-related behavioral traits (Koya et al., 2009; Cruz et al., 2014; Koya et al., 2012; Caprioli et al., 2017). Neurons that belong to those ensembles might be recruited by specific stimuli, such as contextual cues previously associated to drug exposure (Koya et al., 2009), and synaptic maladaptations might drive aberrant approach behavior to drug-paired stimuli, as well as the avoidance of other stimuli. Chronic intermittent alcohol exposure can also drive habitual behavior by inducing an endocannabinoid-mediated weakening, instead of strengthening, of orbitofrontal cortex excitatory inputs to dMSNs of the DMS (Gremel et al., 2016; Renteria et al., 2018). Thus, input-specific synaptic adaptations, within discrete neuronal ensembles, can strengthen approach towards drug-paired stimuli, while promoting avoidance of other stimuli.

Autism Spectrum Disorders (ASDs) constitute a class of heterogenous developmental disorders characterized by social communication deficits and stereotyped behavior (DSM-5). Importantly, at least some of the behavioral traits associated to ASD have been linked to dysfunctional striatal circuits (Fuccillo, 2016) and animal models of ASD-related genetic dysfunctions provided a link between specific striatal pathway alterations and compulsive-like behavioral traits. Among these, mutations in the *Shank3* gene in mice induced behavioral alterations reminiscent of ASD symptoms (Jiang and Ehlers, 2013; O'Connor et al., 2014). *Shank3* gene is highly expressed (as opposed to Shank1 or Shank2, for example) in striatal regions (Peça et al., 2011) and its mutation induces social behavior and compulsivity dysfunctions together with excitatory synapse alterations in mice. A genetic intervention the restored some SHANK3 expression in a full-KO improved glutamatergic deficits in the striatum while ameliorating social, anxiety-like and compulsivity-like impairments (Mei et al., 2016). More direct support for a causal link between SHANK3 mutation-induced dysfunctions in specific striatal pathways and ASD-like behavioral deficits came from a chemogenetic study. The enhancement of iMSN function rescued the compulsive self-grooming behavior in a SHANK3 full-KO mouse model (Wang et al., 2017) proving that the restoration of iMSN activity might be a valuable tool to reduce self-directed stereotypies. Furthermore, SHANK3 absence from dMSNs causes neuronal hyperexcitability accompanied by a reduction in vertical activity and a mild anxiolytic behavior (Bey et al., 2018), consistent with reduced avoidance. Repetitive behavior has also been observed in a Nlg3 KO mouse models and it is thought to originate from a reduced inhibitory tone onto dMSNs of the nucleus accumbens, which might ultimately increase dMSN output function. Accordingly, re-expression of Nlg3 in D1-expressing accumbens neurons rescues the aberrant behavioral trait (Rothwell et al., 2014). Altogether these data suggest that altered function of dMSNs and iMSNs can underlie compulsivity traits observed in some ASD animal models, which might relate to aberrant and

repetitive action selection (Fuccillo, 2016). Moreover, the altered synaptic function and excitability of striatal pathways might be caused by the aberrant formation of neuronal ensembles. Although this hypothesis is supported by the observation that the absence of the ASD-related protein MecP2 induces the formation of hyper-excitable neuronal ensembles in the hippocampus (Calfa et al., 2011), it requires further investigation within striatal circuits.

The competitive model also makes predictions about disorders that are characterized by heightened avoidance. In the chronic social defeat (CSDS) task a test mouse is repeatedly confined with an aggressor mouse and subsequently placed into an arena where it is exposed to the aggressor without physical contact (Golden et al., 2011). "Stress-susceptible" mice decrease the time spent engaging with the aggressor relative to "stress-resilient" mice. In susceptible mice, mEPSC frequency onto dMSNs was reduced, while frequency onto iMSNs was enhanced (Francis et al., 2015). This alteration in mEPSC frequency is indicative of pre-synaptic adaptations favoring heightened excitation of iMSNs relative to dMSNs. Moreover, a negative correlation between iMSN mEPSC firing frequency and time in the interaction zone suggests that the enhanced excitatory inputs to accumbal iMSNs might be responsible for avoidance of the anxiogenic area (Francis et al., 2015; Francis and Lobo, 2017). These data support the hypothesis that reduced and enhanced excitatory drive onto dMSNs and iMSNs function, respectively, results in a social avoidance phenotype (Fig. 2C). Consistent with this hypothesis, reduced activity of dMSNs, but not iMSNs, was associated with increased susceptibility to social defeat (Muir et al., 2018). While reduced dMSN output might represent a neuronal correlate for vulnerability to social stress, the diverging synaptic plasticity occurring at excitatory inputs on dMSNs and iMSNs could also represent the assignment of a negative valence to a social stimulus during aversive learning. Together, these studies implicate a shift towards iMSN over dMSN output in avoidance. Indeed, artificial activation of iMSNs *via* optogenetic stimulation also produces an avoidant phenotype (LeBlanc et al., 2018).

Although the animal models of brain disorders discussed here support the hypothesis that heightened action repetition and avoidance traits might be associated with enhanced dMSN and iMSN output within striatal networks, these traits can also co-exist in the same experimental models. For example, animal models of ASD are not only characterized by heightened stereotypies, but also with reduced approach/exploration of social stimuli (O'Connor et al., 2014). Similarly, drug addiction is associated with both heightened seeking of drugs, and negative emotional states and anhedonia (Markou and Koob, 1991). Do these deficits rely on the same striatal networks? Are different striatal networks recruited and responsible for the expression of heightened action repetition or heightened avoidance? One intriguing hypothesis is that certain environmental experiences (such as drug-exposure and chronic stress) or genetic mutations (in excitatory synaptic proteins associated with ASD and/or in dopamine receptors) might cause a rewiring of striatal neuronal networks dedicated to the execution or avoidance of certain actions in response to environmental cues. However, whether these adaptations impinge on already existing neuronal ensembles, encoding for example either approach or avoidance of certain stimuli, or whether they promote newly-formed neuronal networks is an exciting question that requires novel lines of research.

8. Conclusions and future directions

The "go-no go" model, according to which dMSNs and iMSNs promote and inhibit movement, respectively, has been highly influential in shaping basal ganglia research, especially with respect to Parkinson's disease. However, electrophysiology and optogenetic experiments support an ensemble-based model in which populations of both dMSNs and iMSNs work in concert to select actions. This led to the development of a "complementary model", in which the two pathways work together to produce behavior. While this model is consistent with *in vivo* recording data, it remains unclear *how* these pathways work together to produce actions. Early models suggested that iMSNs may form a global inhibitory signal over all potential competing actions. More recent refinements have pointed out that this arrangement is unlikely, yet have not distinguished between potential alternatives. Here, we present a "*competitive*" model that serves to unify experimental evidence on the function of these pathways in action selection. In addition, the competitive model links action selection to reinforcement and provides testable predictions for how these pathways are altered in animal models of psychiatric disease.

To investigate predictions of the competitive model, there is a need for recordings of neuronal ensembles during scenarios that promote both approach and avoidance of the same stimuli, for instance in passive and active avoidance paradigms. Such paradigms may clarify nuances that our model does not address. For example, avoiding an aversive stimulus in a passive avoidance task requires an inhibition of movement, yet is highly reinforcing. In this regard, striatal single cell-resolution calcium-imaging (Barbera et al., 2016; Klaus et al., 2017; Parker et al., 2018) and concurrent monitoring of dMSN and iMSN population activity (Markowitz et al., 2018; Meng et al., 2018) might help to understand how stimuli are represented by striatal ensembles of both dMSNs and iMSNs. Moreover, the avoidance of one stimulus can also be viewed as an approach toward a "safer" stimulus. In such case, the two stimuli might recruit two different striatal networks that are characterized by a higher iMSN and dMSN output levels, respectively.

Additionally, while most studies have focused on animals performing a limited set of actions to obtain an outcome, a more thorough evaluation of the behavioral repertoire of mice may give insights on how these pathways work to facilitate one specific action among many competing options. Finally, while many decision-making tasks are positively reinforced, we foresee a need for negative reinforcement and punishment to better explore the parameter space that these pathways encode. It may also be possible to "tag" and "track" MSN ensembles based on activation of neurons themselves, as has been done for hippocampal engrams (Liu et al., 2012; Ramirez et al., 2013), or on activation of their dopamine receptors (Lee et al., 2017), *prior to* or during action execution. These interventions would provide invaluable tools for manipulating activity of MSN ensembles and studying the relative contribution of dMSNs and iMSNs within that ensemble to behavior. Finally, the use of these tools with animal models of psychiatric disorders will enable sophisticated investigations of neuronal circuit dysfunctions and its consequences for behavior.

Acknowledgements

This work was supported by the National Institutes of Health Intramural Research Program (NIDDK). SB is supported by the EarlyPostdoc.Mobility fellowship from the Swiss National Science Foundation (SNSF; P2GEP3_174898) and by the NIDDK as supplemental visiting fellow. WF is supported by the NIH Intramural Center for Compulsive Behavior. MCC supported by the Whitehall Foundation; 2017-12-54.

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