Neurochemistry International 124 (2019) 200–214

Contents lists available at ScienceDirect

Neurochemistry International

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

It takes two to tango: Dorsal direct and indirect pathways orchestration of motor learning and behavioral flexibility

Patricia Bonnavion[a,**,1], Elisa Pozuelo Fernández[a,1], Christophe Varin[a], Alban de Kerchove d'Exaerde[a,b,*]

[a] Laboratory of Neurophysiology, Université libre de Bruxelles, ULB Neuroscience Institute ULB-UNI, Brussels, Belgium
[b] WELBIO, Wavre, Belgium

A B S T R A C T

The striatum as the main entry nucleus of the basal ganglia is long known to be critical for motor control. It integrates information from multiple cortical areas, thalamic and midbrain nuclei to refine and control motion. By tackling this incredible variety of input signals, increasing evidences showed a pivotal role, particularly of the dorsal striatum, in executive functions. The complexity of the dorsal striatum (DS) in its compartmentalization and in the nature and origin of its afferent connections, makes it a critical hub controlling dynamics of motor learning and behavioral or cognitive flexibility. The present review summarizes findings from recent studies that utilize optogenetics with complementary technologies including electrophysiology, activity imaging and tracing methods in rodents to elucidate the functioning and role of discrete regions and specific pathways of the DS in behavioral flexibility, with an emphasis on the processes leading to initial action sequence or serial order learning and reversal learning.

1. Introduction

Executive functions consist of multiple high-level cognitive processes that include planning, problem-solving, decision-making, working memory, strategy evaluation or behavioral control and adaptation. The latter can be defined as behavioral or cognitive flexibility, which is a broad concept that refers to the ability to adapt one's cognitive representations, and hence behavior, to environmental changes, which is essential for daily living and often survival.

Behaving in a flexible manner requires multiple operations involving inhibition of old pre-learned responding, search for novel effective strategies, and maintenance of these new strategies. The concept of behavioral flexibility emerged from animal learning studies (Dickinson, 1981) in which animals face choices influenced by future reward outcomes. There are different assays to measure behavioral flexibility in human and non-human primates, as well as in rodents, using reversal learning, strategy- or set-shifting, or inhibitory control or self-control tasks. Reversal learning allows to measure a simpler form of behavioral flexibility entailing shifts between different stimulus–reward associations within one dimension (Iversen and Mishkin, 1970; Dias et al., 1996). Classically, a dominant strategy is formed and must be reversed due to changes in reward contingencies. First, a conditional stimulus is associated with a response leading to a reward (e.g. left lever press) in the presence of a second unrewarded stimulus (e.g. right lever press). Once the association is acquired to form a dominant strategy over multiple trials, the stimulus-reward contingency is unexpectedly reversed, and subjects are required to reverse their preference switching to the previously unrewarded stimulus as the cue (e.g. right lever press). Similarly, strategy-shifting also consists in a change in response strategy but the attention is solicited by stimuli from multiple dimensions through visual, tactile, olfactory or spatial cues at the same time (Roberts et al., 1988; Dias et al., 1996; Brigman et al., 2005). In these paradigms, the first rule focuses on one type of stimulus for example visual discrimination differing in color (one color is rewarded but not the other) while tactile stimuli are irrelevant. The strategy-shift would then require a tactile discrimination, such as different textures, and visual stimuli become irrelevant. Therefore in strategy-shifting, subjects are required to shift between multidimensional attention sets to succeed, while in reversal learning subjects are required to adapt their response in accordance with changes in stimulus-reward contingencies, within one dimension. In "self-control" or tasks assessing response inhibition, another aspect of behavioral flexibility is examined. In brief, subjects here are required to withhold or inhibit their actions in anticipation of reward. In this regard, these different assays intrinsically involve various brain mechanisms, although some overlap. One characteristic trait that reflects this aspect is the perseverative responding

* Corresponding author. Laboratory of Neurophysiology, Université libre de Bruxelles, ULB Neuroscience Institute ULB-UNI, Brussels, Belgium
** Corresponding author.
E-mail addresses: pbonnavi@ulb.ac.be (P. Bonnavion), adekerch@ulb.ac.be (A. de Kerchove d'Exaerde).
[1] Co-first authors, equally contributed to the work.

https://doi.org/10.1016/j.neuint.2019.01.009
Received 18 November 2018; Received in revised form 12 December 2018; Accepted 8 January 2019
Available online 16 January 2019
0197-0186/

that can be measured in the three various paradigms we described. Perseverance as a trait of behavioral inflexibility can either correspond to a deficit in erasing old pre-learned strategy or impairments in the acquisition of a novel one. In this review, we do not intend to cover all aspects and assays of behavioral/cognitive flexibility. We will be specific in naming the tasks and assays probing behavioral flexibility, mostly focusing on initial serial order learning and reversal learning procedures in rodents, as model system to identify neural substrates and circuits of behavioral flexibility operations.

Behavioral inflexibility that includes impairments in reversal learning, is a common feature of many psychiatric illnesses and neurodegenerative disorders such as schizophrenia, attention-deficit/hyperactivity-disorder (ADHD), drug addiction, depression, Parkinson's or Huntington's diseases (Owen et al., 1992; Lawrence et al., 1999; Swainson et al., 2000; Cools, 2001; Rogers and Robbins, 2001; McLean et al., 2004; Fillmore and Rush, 2006; Waltz and Gold, 2007; Murray et al., 2008; Clark et al., 2009; Shell et al., 2018). Along with brain impairments associated with these diseases, a large literature has shown that across species, the frontal lobe and the basal ganglia (BG) play fundamental roles in enabling the different aspects of behavioral flexibility (Kirkby, 1969; Kolb, 1977; Pisa and Cyr, 1990; Owen et al., 1992; Eslinger and Grattan, 1993; Roberts et al., 1994; Wise et al., 1996; Dias et al., 1996, 1997; Birrell and Brown, 2000; Swainson et al., 2000; Collins et al., 2000; Monchi et al., 2001; Cools, 2001; Crofts et al., 2001; Barense et al., 2002; Chudasama and Robbins, 2003; McLean et al., 2004; Ragozzino, 2007; Waltz and Gold, 2007; Floresco et al., 2008). A key advantage of the paradigms we described above is that it allows to identify the types of error induced by a particular brain region alteration, whether they are due to deficits in suppressing old pre-learned responding, acquisition of novel strategies, or maintenance of novel strategies. Globally, lesions or inactivations of the frontal lobe typically lead to increased perseverative responding of the initial strategy during either a reversal or strategy shift. Primary loss-of-function studies further dissecting the function and necessity of various cortical and sub-cortical regions attributed distinct involvements of discrete regions of the cortex and the striatum in the different aspects of behavioral flexibility. Hence, reversal learning would be critically dependent upon the orbitofrontal cortex (OFC) (McAlonan and Brown, 2003; Ragozzino, 2007; Ghods-Sharifi et al., 2008). In contrast, strategy-shifting would be further mediated by the medial prefrontal cortex (mPFC) as shown by strategy-shifting deficits when mPFC is inactivated while reversal learning is not affected (Birrell and Brown, 2000; Stefani et al., 2003; Ragozzino, 2007; Bissonette et al., 2008; Floresco et al., 2008; Ostlund et al., 2009). Thus, OFC and mPFC would differentially contribute to different components or operations of behavioral flexibility.

Downstream from cortical regions, damage to the DS, which is made of the caudate and putamen nuclei, in animals or patients with Parkinson's or Huntington's diseases is associated with impairments in both reversal learning and strategy-shifting (Owen et al., 1992; Lawrence et al., 1999; Ragozzino et al., 2002a, 2002b). According to its cortical inputs, the DS can be subdivided into the associative, dorsomedial striatum (DMS) corresponding to primate caudate nucleus, receiving afferents mainly from prefrontal and associative cortices, and the sensorimotor dorsolateral striatum (DLS), homologous to primate putamen, receiving afferents from sensorimotor cortical areas (Graybiel, 2008). Thus, both the OFC and mPFC project to the DMS. Interestingly, loss-of-function studies of DS sub-regions showed that the DMS would play a broader role than either the OFC or the mPFC do alone in behavioral flexibility (Ragozzino, 2007). Inactivation of the DMS leads to deficits in both reversal learning and strategy-shifting (Ragozzino et al., 2002a, 2002b) without affecting initial discrimination learning. Damage to the DMS impairs learning and maintenance of new strategies after the strategy shift. Hypothesis postulated thereafter is that the DMS, in coordination with different cortical areas, may link a particular response pattern with a specific strategy, which allows the reliable execution of the new strategy as well as the continual inhibition of previously relevant strategies (Ragozzino, 2007). In contrast to OFC and mPFC, DMS inactivation does not increase perseverative responding (Ragozzino, 2007). Similar observations in a strategy-shifting assay were made when inactivating the core region of the ventral striatum (VS) or *Nucleus Accumbens* (NAc) that also disrupt shifting from one strategy to another (Floresco et al., 2006). However lesions of the NAc has no impact on reversal learning performance (Castañé et al., 2010). The lateral sector of the DS, the DLS, was shown to be particularly important in the automatization of tasks and habit formation (Yin et al., 2004, 2009; Rueda-Orozco and Robbe, 2015; O'Hare et al., 2016). Importantly, the DLS plays a seminal role in sequence or serial order learning as shown by severe impairments in the acquisition of a simple sequence after DLS lesion while DMS lesion has no impact (Yin, 2010). Despite this strong effect, DLS damage does not impair reversal performance but facilitates extinction of responding in the old rewarded strategy (Castañé et al., 2010). Thus, there may be here two dissociable aspects of behavioral flexibility: while DLS impairment does not affect the acquisition of novel reversed strategy, it still impact on the extinction, which reflects a form of inhibitory control. A classical view of the DS mode of operation in learning proposes that through its compartmentalization, the DS would execute complementary functions in motor learning and behavioral flexibility where the DMS would support goal-directed learning, rapidly acquired and responsive to changes in choice outcomes, which would be then gradually supplanted by the DLS mediating stimulus-driven habitual performance (Graybiel, 2008; Balleine et al., 2009).

However, to further our understanding on the role of the DS and define the striatal processes underlying motor learning and reversal learning, we also have to integrate another dimension in the cellular complexity of the striatum. The striatum is composed to 95% of two categories of GABAergic medium-sized spiny neurons (MSNs) also called striatal projection neurons (SPNs), and to the remaining 5% of cholinergic and three types of GABAergic interneurons including Fast Spiking Interneurons (FSI) (Butcher and Hodge, 1976; Chang et al., 1981, 1982; Gerfen et al., 1985; Kawaguchi et al., 1990; Kawaguchi, 1993; Bennett and Bolam, 1993; reviewed in Silberberg and Bolam, 2015). MSNs are subsequently divided into two intermingled populations: dopaminergic receptor type D1-expressing neurons giving rise to the striatonigral direct pathway (dMSNs), projecting directly to downstream BG nuclei including the internal *Globus Pallidus* (GPi) or *Substantia Nigra pars reticulata* (SNr); and dopaminergic receptor type D2- and adenosine (A2A) receptor-expressing neurons forming the striatopallidal indirect pathway (iMSNs), projecting to the GPi and SNr via the external *Globus Pallidus* (GPe) and the subthalamic nucleus (STN) (Beckstead and Cruz, 1986; Kawaguchi et al., 1990; Gerfen et al., 1990; Schiffmann et al., 1991; reviewed in Gerfen and Surmeier, 2011; Lanciego et al., 2012; Nelson and Kreitzer, 2014). Considering this cellular diversity and the complexity of striatal input/output organization, many of the previous studies using lesions and local pharmacological inactivation approaches set numerous limitations due to lack of specificity onto the different cell types and pathways involved, hiding most of striatal processes in the acquisition and execution of behavioral flexibility. Thanks to the vast development of transgenic tools and optogenetic systems, every component of the DS can be specifically targeted, in each compartment. The following chapters will depict the latest findings on the encoding and contributions of the two main projecting cell populations of the DS in initial motor sequence learning and reversal learning in rodents, obtained mainly through optogenetic approaches consisting in 1) imaging or recording from in vivo optogenetically-tagged cells in behaving animals, and 2) controlling sub-populations activities to assess their respective role in behavioral responding. Finally, we will present some studies integrating, on top of these sophisticated approaches, the function of specific synaptic connections to defined striatal cell populations or to discrete regions of the DS in motor learning.

2. Neuronal correlates of motor learning in the dorsal striatum

The essence of many behaviors is organized into complex sequence of actions, which implies a selection of elements of action executed in a particular order and precise timing. Humans and animals have this extraordinary ability to develop new learning organized into precise sequences of movements. Based on past experience, complex skills can be produced with more accuracy and efficiency in face of an ever-changing environment. Several lines of evidences suggest that the motor circuit of the BG, and particularly the DS, play an important role in these motor planning and learning processes involving sequential behaviors (Graybiel, 1998; Yin and Knowlton, 2006; Balleine et al., 2009; Hilario et al., 2012; Jin and Costa, 2015). The BG has been proposed to be critically involved in the "proceduralization" of action sequences or "chunking" referring to the capacity to recall as a whole a series of actions/elements in a hierarchical manner (Graybiel, 1998). During sequence learning, many neurons of the striatum, or more largely in the BG, develop a sequence-related activity (Jin and Costa, 2015). There are neurons showing increased phasic activity during the execution of every element of the sequence, some neurons selectively encoding initiation (start), termination (stop) or both (sequence boundary) but a few, and neurons exhibiting sustained oscillation firing or remain silent throughout the whole period of sequence execution (Jin and Costa, 2015, see Table 1). These observations indicated that the BG circuits can encode action sequence as modules or chunks (Jin et al., 2014).

Furthermore, this sequence-related activity is differentially expressed in direct and indirect BG pathways, notably during the execution of action sequence (Jin and Costa, 2015). As depicted above, the striatum contains a majority of intermingled MSNs, organized into the direct (dMSNs) and indirect (iMSNs) projection pathways. Classical models of BG motor control describe a loop in which motor cortex sends glutamatergic inputs to the striatum, and is in turn influenced by the BG through inhibitory outputs to the thalamus. Striatal pathways are thought to be functionally opposing by either increasing or reducing thalamo-cortical activation to promote or suppress motor action (Albin et al., 1989; DeLong, 1990). The neural substrates that mediate these antagonistic effects are thus thought to be the dMSNs and iMSNs, where dMSNs disinhibit thalamo-cortical activity whereas iMSNs inhibit it, implying that movement initiation would relate to activation of dMSNs, while movement inhibition would relate to activation of iMSNs (Albin et al., 1989; DeLong, 1990). These theories were largely supported by the development of genetic and optogenetic approaches implemented in striatal sub-populations. Hence, since the development of bacterial artificial chromosome (BAC) transgenic mice, it became possible to assess the respective role of dMSNs and iMSNs, first, in motor control. To control, record or image specifically with optogenetic tools these populations, two BAC cre-recombinase driver lines can be used: D1-cre mice (Gong et al., 2007) and A2A-cre mice (Durieux et al., 2009) showing specific cre expression in dMSNs and iMSNs, respectively (Durieux et al., 2011, 2012). Indeed, D2 promoter (Gong et al., 2003, 2007) initially used to target iMSN, was also found to lead to protein expression in striatal cholinergic interneurons (CINs) and in presynaptic DA neurons (Bertran-Gonzalez et al., 2008; Matamales et al., 2009). Along with the canonical model, the first genetic manipulations in which d- and i-MSNs function has been selectively disrupted by the deletion of a key striatal signaling phosphoprotein, DARPP-32 (Bateup et al., 2010), or by selective lesions (Durieux et al., 2009, 2012), showed that either way, lesions or loss of function in dMSNs reduced basal locomotor activity, while it increased it when targeting iMSNs. These results were consistent with the interpretation that activation of dMSNs normally exerts a stimulatory effect on locomotion while iMSNs exert an inhibitory tone. This classical model also supports many BG-related disorders and explains as well the mechanisms by which symptoms of Parkinson's disease are improved by deep brain stimulation restoring somehow the imbalance of activity within the BG

Table 1
Preferential sequence related-activity of individual striatal GABAergic projection neurons.

Authors	Striatal region & cells	Start[1]	Stop[2]	Sequence boundary[3]	Sequence execution[4]	Method
	DLS					
Jin et al. (2014)	dMSNs	+ + +	+ + +	+	+ + +/−	ChR2-opto tagging in vivo electrophysiology
	iMSNs	+ + +	+ + +	+	− − −/+	
	Dorso-central to DMS					
Cui et al. (2013)	dMSNs	+ + +	−* (inactive state)	na	+ + (active state)	Optogenetic imaging GCaMP3
	iMSNs	+ + +	−* (inactive state)	na	+ + (active state)	
	DLS					
Isomura et al. (2013)	Putative D1 (mRNA)	+ + +	+ + (hold)	na	+ + + (movement)	Juxtacellular in vivo electrophysiology (rat)
	Other	+ + +	+ + (hold)	na	+ + + (movement)	
	Dorso-central to DMS					
Geddes et al. (2018)	dMSNs	+ + +	+ + +	na*	+ +/− and + (switch)	ChR2-opto tagging in vivo electrophysiology
	iMSNs	+ +	+ +	na*	− − −/+ and + + + (switch)	
	Dorso-central to DLS					
Sales-Carbonell et al. (2018)	Indistinct MSNs	+ + +	+ + +	+ + + (running start-stop)	Progressive + + +/− (running)	In vivo electrophysiology (mice)
	DLS					
Martiros et al. (2018)	Indistinct MSNs	+	+	+	↘ + (same neurons as start/stop & boundary)	In vivo electrophysiology DLS & motor cx (rats)

Elements of the sequence are dissected into [1] Sequence initiation (start); [2] Sequence termination (stop); [3] Sequence initiation and termination (boundary); [4] Whole period of sequence execution. (+) sign represents a semi-quantitative report of each striatal cell population showing a preferential increase in firing activity. (−) sign represents a semi-quantitative report of each striatal cell population showing a preferential decrease in firing activity or no activity*. In the sequence execution panel, the firing activity of the neuronal population characterized on the left side of the (/) symbol represents the predominant firing pattern, while on the right side of the (/) figures the firing pattern of a sub-population of cells. na: not-applicable for the behavioural task performed or not specified whether start/stop-related activity is start only, stop only or both*. ↘ +: Less active units from neurons exhibiting a preferential start and stop activity (as well as sequence boundary) during the middle of the trials.

network (Da Cunha et al., 2015). Follow-up studies using optogenetic stimulating approaches further confirmed this view on an opposite and bidirectional control of movement (Kravitz et al., 2010; Yttri and Dudman, 2016) as optogenetic activation of dMSNs in the DMS resulted in increased locomotion and velocity together with a significant reduction in immobile states, while photostimulation of DMS iMSNs decreased velocity and elicited more arrests or immobile states (Kravitz et al., 2010; Yttri and Dudman, 2016). However, in another study applying bidirectionnal optogenetic control of d- and i-MSNs in the DLS on action initiation, Tecuapetla and colleagues found a more versatile role for d- and i-MSNs, respectively, having complementary contributions rather than opposite (Tecuapetla et al., 2016). In a lever press task, photoinhibition of the direct and indirect pathways both resulted in increasing the latency to initiate action sequence, suggesting that both pathways are necessary for action initiation (Tecuapetla et al., 2016). Surprisingly, photostimulations of d- and i-MSNs before the onset of action initiation also impaired action sequence initiation (Tecuapetla et al., 2016). These data suggested that balanced activity between both pathways and/or specific patterns of activity, rather than rate of firing, may be critical for appropriate action sequence initiation. By further dissecting photostimulated-evoked behavior, the researchers found that optogenetically activating d- or i-MSNs either slowed or aborted action initiation as the animals switched to other behaviors, respectively. A similar distinction could be made when applying optogenetic control during action performance (Tecuapetla et al., 2016). This study is not consistent with a simple “Go” pro-kinetic action of the direct pathway, and “No-Go” anti-kinetic properties of the indirect pathway. The authors rather positioned their results in this view attributing a complementary role of both pathways with the direct pathway supporting the initiation and execution of the desired action, while the indirect pathway would permit it by inhibiting competing actions.

This alternative model has also been built up based on investigations examining the behavioral correlates of neural activity in both populations in behaving animals. As mentioned earlier, the neural activity within the DS exhibits a variety of response patterns in sequential motor behavior, and distinct sequence-related activity were found in d- and i-MSNs (Jin et al., 2014). The way to selectively monitor the activity from d- or i-MSNs uses a combination of in vivo electrophysiological recordings with channel rhodopsin (ChR2)-assisted optogenetic photo-tagging identification of individual cells in behaving mice, using the different cre-lines mentioned above (Jin et al., 2014). Using this approach, Jin and colleagues observed that a majority of dMSNs displays sequence-related sustained firing activity while a majority of iMSNs shows sequence-related inhibited firing activity during action sequence execution (Jin et al., 2014, see Table 1). These results are consistent with what the model would predict: dMSNs would be more active during movement to facilitate it, while iMSNs would be inhibited and active during lack of movement. Importantly, the target regions that receive GABAergic innervation from d- and i-MSNs (in the SNr and GPe, respectively) behave in a symmetric way, confirming that the two BG pathways display opposite activity during the execution of motor sequences. Importantly, in contrast to the classical model, the researchers highlighted a similar proportion of d- and i-MSNs (~40%) co-active during action initiation and action termination (Jin et al., 2014), demonstrating that both pathways show concomitant activity on specific actions. Co-activation of d- and i-MSNs during action initiation was already observed using optogenetic imaging approach with genetically-encoded fluorescent calcium indicators (GCaMP) in the same cre-lines monitoring the activity of d- and i-MSNs in a lever-press task (Cui et al., 2013, see Table 1) or during self-paced movements (Klaus et al., 2017). A cooperative contribution to spatiotemporal control of voluntary movements was also suggested from an in vivo juxtacellular electrophysiological study led in rats subjected to a reward-based motor action (Isomura et al., 2013, see Table 1). A recent study using a multicolor calcium imaging fiber-photometry in the DLS recorded d-MSNs (green fluorescence) and i-MSNs (red fluorescence) separately or simultaneously in the mouse during spontaneous 3D motor sequence (Markowitz et al., 2018). Their recordings highlighted that both populations encode the sequences of spontaneous motor behaviors and that the DLS is necessary to combine motor sequences (Markowitz et al., 2018). Altogether, these recent findings converge into an alternative model proposing that the activation of the two pathways is fundamental for action selection (Hikosaka et al., 2000; Mink, 2003). As mentioned earlier, the model's theory argues that co-activation of both pathways would permit a selection of the desired motor program driven by dMSNs, while iMSNs would inhibit competing motor programs (Hikosaka et al., 2000; Mink, 2003).

In the last ten years, growing evidences indicated that, upon the behavioral context, both striatal populations can either have antagonistic effects or these effects can be occluded when the animal is not moving or the two populations can work in a complementary manner for controlling actions (Cui et al., 2013; Isomura et al., 2013; Jin et al., 2014; Tecuapetla et al., 2016; Geddes et al., 2018). This is also illustrated by how striatal activity modulates primary motor cortex (Oldenburg and Sabatini, 2015). In this study, Oldenburg and Sabatini examined the effects of optogenetic stimulations of d- and i-MSNs on primary motor cortex activity when mice perform a lever-pressing task. First, they found that activation of d- and i-MSNs enhances and suppresses, respectively, firing rates of units in the motor cortex, consistent with the classical model of BG/cortex interactions. However, they also found that these effects in response to d- and i-MSNs stimulation were heterogeneous, asymmetric and context-dependent. Unexpectedly, the authors found that iMSNs stimulation excites transiently a sub-population of cortical cells (~30%). Both populations can thus be excitatory on a sub-population of M1 cells. Furthermore, the task-related activity of cortical neurons that are highly sensitive to d-MSNs stimulation is different from that of neurons that are highly sensitive to i-MSNs stimulation (Oldenburg and Sabatini, 2015). These results highlighted a variety of responses in superficial M1 cells and suggested that d- and i-MSNs have selective and non-antagonistic effects on distinct cortical neurons, and that d- and i-MSNs modulate motor cortex activity through separate multisynaptic pathways.

Very few studies dissecting behavioral correlates of d- and i-MSNs activity in action sequence learning are available for now, and to date, in our knowledge, no such study has been yet performed in a reversal learning or strategy-shifting procedure. Recently, Geddes and collaborators investigated how d- and i-MSNs in the central region of the DS encode a heterogeneous action sequence across different behavioral levels (Geddes et al., 2018). The task consisted in executing a specific lever-press sequence in an operant chamber equipped with two lever presses. Mice were trained and required to press a specific spatiotemporal combination “left-left-right-right” in order to earn a reward. Electrophysiological procedures combined with optogenetic ChR2-phototagging in D1-and A2A-ChR2 transgenic lines in the DS, were applied when the animals were trained and performing the rewarded-sequence pattern. Similarly to previous studies, the authors found that, at the sequence-level, a sub-population of both d- and i-MSNs exhibit a start/stop-related activity, although it was less frequent in iMSNs (Geddes et al., 2018, see Table 1). Also, at the element level (e.g. each lever press) another sub-population of d- and i-MSNs show sustained or inhibited activity, respectively, consistently with the classical model. Interestingly, a larger proportion of iMSNs exhibited a selective activity when switching from the left to the right lever. This switch-related activity appears after the last press in the left sequence and cease before the onset of the first right lever press (Geddes et al., 2018). These observations further highlight the functional heterogeneity within each MSNs population displaying distinct yet complementary roles: while d- and i-MSNs are both involved in element-level action execution, dMSNs are more likely to signal sequence initiation and termination, whereas iMSNs preferentially encode the transition between subsequences. An interesting notion that was developed in this study is that rather than competing or cooperating for individual motor output, the direct and

indirect pathways encode dynamics of the sequence execution and would coordinate to dynamically control action sequences at different levels, possibly in a hierarchical manner. Another recent study would further support this alternative encoding mechanisms of the DS: MSNs would continuously monitor movement dynamics providing an action-by-action representation of the ensemble of movements associated with the execution of a learned sequence in a run-and-stop task (Sales-Carbonell et al., 2018). An interesting point raised in this study is the importance of the method used to classify neurons in distinct functional groups based on their firing rate modulations, and that when neurons are considered individually, or as ensembles, different functional groups can appear and separate (Sales-Carbonell et al., 2018). A similar approach relying on large-scale recordings of calcium transients in the dorsal striatum and applied to spontaneous locomotion in an open field highlighted analogous points in respect with the functional organization of DS MSNs (Barbera et al., 2016). This study revealed that the activity of some d- and i-MSNs is highly synchronized within spatially compact clusters of cells that display a similar organization for either d- or i-MSNs. Moreover these clusters of MSNs appear to sequentially correlate with distinct phases of locomotor activity from movement initiation to movement termination, but also with mapping action space (Klaus et al., 2017), suggesting a functional specialization of distinct MSN clusters within the DS, and that the sequential activation and deactivation of these clusters would be critical for proper motor coordination. Using large-scale chronic recordings to test whether the distinction of a given neuronal ensemble evolves during learning, automatization and reversal would be very informative.

Resolving the encoding mechanisms of the DS is a complex task, it becomes quite accepted that we need to go beyond the classical model with its simple classification of d- and i-MSNs as pro-kinetic and anti-kinetic pathways, respectively, which does not fully account for the activities of these cells in vivo. Further studies should be led in consideration of the different medio-lateral sub-regions of the DS in regards to their inputs, in the different MSNs populations in specific behavioral paradigms. Along with this idea adding a layer of complexity, Reig and Silberberg (2014) have shown by in vivo whole-cell recordings that MSNs in the DMS are able to integrate multimodal sensory information (visual and tactile) in contrast to DLS MSNs, integrating only one modality (tactile) (Reig and Silberberg, 2014). These differences in sensory input may underlie contrasting patterns of activity in the DMS versus DLS that develop concurrently but with different dynamics during learning and task performance (Thorn et al., 2010).

Considering these different scales, striatal processes occurring during flexibility responses remain largely unknown. Whether opposite or cooperative functions of d- and i-MSNs would also apply to reversal learning or strategy-shifting is unclear. Still, although correlative studies between neuronal activity and behavioral tasks or brains states are extremely important to understand how the different striatal sub-populations encode information, these approaches cannot provide causal links. Both correlative and causal approaches are extremely informative. Optogenetic activation/inactivation experiments applied to MSNs allowed to directly delve into the causal role of the different sub-populations in behavior and recently informed more specifically on the role of d- and i-MSNs in action sequence learning and reversal learning.

3. Optogenetic control of medium spiny neurons of the dorsal striatum in motor learning

In this chapter, we will review the studies using optogenetic control of MSNs in the context of action sequence learning or serial order learning, and reversal learning. While some optogenetic activations of d- and i-MSNs supported and confirmed the pro- and anti-kinetic hypothesis of the classical model of BG motor control (Kravitz et al., 2010; Sippy et al., 2015; Yttri and Dudman, 2016), we saw that other studies were raising different roles (Tecuapetla et al., 2016) depending which striatal territory could be targeted and how photo-stimulations of each population were applied in paired with behavior, which will be further addressed in this section in various paradigms.

As introduced above, lesion and inactivation studies led to show that the lateral and medial regions of the DS are engaged in different functions: the DLS being critical in the acquisition of serial order learning, automatization of a new motor skill and habit learning (Yin, 2010), while the DMS drives goal-directed behavior and is essential for reversal learning and strategy-shifting (Ragozzino et al., 2002a, 2002b) without affecting initial discrimination learning. Selective lesions of d- or i-MSNs in the DLS and DMS also led to provide direct evidences for dissociation between neuronal sub-types and striatal sub-regions in the regulation of motor learning and novelty or drug-induced motor responses (Durieux et al., 2012). First, DMS-selective MSNs ablations have a critical impact on locomotor activity and attentional processes assessed by novel object exploration test in which dMSNs and iMSNs stimulate and inhibit locomotion and novelty recognition, respectively, while similar ablations in the DLS have no effect on these behaviors (Durieux et al., 2012). Second, DMS iMSNs were found to be required for early motor learning, while DLS dMSNs are necessary in the progressive motor skill acquisition from the initial to the late learning stages (Durieux et al., 2012). These findings suggested that d- and i-MSNs work in concert to promote acquisition of a new motor skill where: activation of dMSNs in the sensorimotor striatum (DLS) is necessary to develop correct motor strategies for progressive automatization of the task, while activation of iMSNs in the associative striatum (DMS) would inhibit competing actions. During later skill learning stage, as attention to action is less required, DMS iMSNs would progressively disengage while DLS dMSNs remain necessary for habit learning. This theory is also well-supported by respective DMS/DLS activity dynamics showing a surge of activity in the DMS on the first stages of the task acquisition that decreases as training progresses, while DLS activity increases with training and correlates with improving performances (Thorn et al., 2010).

In action sequence learning, an optogenetic approach tackling the respective contributions of d- and i-MSNs in the DLS provided causal proofs that a serial order learning task requires a disparity of striatal pathway favoring DLS dMSNs (Rothwell et al., 2015). First, Rothwell and colleagues genetically-targeted the expression of an inwardly rectifying potassium channel, Kir2.1, to selectively and robustly inhibit spiking activity of either d- or i-MSNs in the DLS and subsequently tested their necessity to acquire a serial order task (Rothwell et al., 2015). The task consists in pressing two levers in a serial order (A » B) to obtain a reward, and MSNs inactivation was performed before behavioral training. The overall performance of the AB sequence failed by inhibiting dMSNs, but not iMSNs. When dMSNs were inactivated, mice could not complete the second step of the sequence, making a high percentage of incorrect AA sequence while other types of incorrect responses (BB or BA) were unaffected (Rothwell et al., 2015). Thus, to identify the dynamic changes in their task, the authors calculated two measures of accuracy at first and second step of the sequence. First step accuracy was defined as the fraction of all trials that begin with a correct first step (AB + AA), and second step accuracy was defined as the percentage of all trials beginning with a correct first step that were subsequently completed with a correct second step (AB/AB + AA). When DLS dMSNs are inhibited, the second step accuracy is significantly decreased, while first step accuracy is unchanged. Importantly, these first results demonstrated that DLS dMSNs are critical for completion of responses in serial order, while iMSNs aren't necessary. This alteration was confirmed to be very specific to the performance of a learned sequence as it had no “side” effect on mice locomotion, motivation, perseveration or response switching (Rothwell et al., 2015). Indeed, only DLS dMSNs-inactivated mice were subjected to a discrimination task in which either left or right response was rewarded, while the other inactive. After training, contingencies were reversed and DLS dMSNs-inactivated mice normally switched their responses, which is consistent with the evidence that excitotoxic lesions

of the entire DLS do not impair reversal learning in rodents (Castañé et al., 2010). Interestingly, inhibition of DLS iMSNs produced a transient but significant improvement in second step accuracy (Rothwell et al., 2015), which can still point a role in sequence completion.

Next, to test the preferential involvement of the direct pathway in serial order task performance, the researchers implemented optogenetic tools to bilaterally activate respectively DLS d- and i-MSNs in pair with the behavior (Rothwell et al., 2015). This approach leads to a disbalanced activation of one striatal pathway versus the other. However, the authors reported that optogenetic stimulation of DLS dMSNs induced mild dyskinesia disrupting the ongoing behavior by increasing the latency to respond leading to inconclusive results. In contrast, photostimulation of DLS iMSNs (10 Hz, 5 ms pulse) did not induce such motor impairments and led to a frequency-dependent decrease in the percentage of correct AB sequences when stimulation was applied either before the first step or between steps. Similarly to dMSNs Kir2.1-induced inactivation, this impairment is associated with an increase of incorrect AA responses but not in BB nor BA responses leading to a significant decrease in second step accuracy but not in first step. Here again, the authors verified whether such stimulation of DLS iMSNs had any impact on general tendencies to repeat or switch responses, which would confound interpretation of serial order performance. Likewise Kir2.1-inhibition of dMSNs, photostimulation of iMSNs did not alter response latency and rate, or accuracy during a reversal task indicating that perseveration or response switching is not affected (Rothwell et al., 2015). The authors concluded from these impaired performances either due to direct dMSNs inhibition or iMSNs photostimulation, leading to either isolate or boost the indirect pathway, that sequence completion would require a disparity in striatal pathway that favors DLS dMSNs. Besides, they also found an asymmetric response in experience-dependent plasticity between motor cortex M2 inputs and DLS neurons after serial order learning that shows an increase in synaptic strength between M2 and dMSNs that was not detected on iMSNs (Rothwell et al., 2015, see further details in section III). Altogether these results would highlight a predominant role of DLS dMSNs in performing and completing action sequence learning.

However, another recent study using optogenetic control of MSNs sub-populations in action sequence learning rather proposes that dMSNs and iMSNs distinctly relay different sequence elements in a hierarchical manner to ensure accurate learning (Geddes et al., 2018). The purpose of this paper was to elucidate how a learned action sequence is organized and identify the neural substrates underlying it with a focus on d- and i-MSNs of the DS, principally located in the DLS portion. The target sequence required to execute for obtaining a reward consists in pressing in a serial order the left lever, twice, followed by the right lever, twice (L > L > R > R). The reward was still attributed in case of extra presses besides this combination, as long as the sequence contained the consecutive LLRR pattern. The authors first examined the effects of selective lesions of d- and i-MSNs on the acquisition of this response, which resulted in marked impairments (Geddes et al., 2018). It is important to note that the diffusion of the lesion performed here is quite important on the medio-lateral coordinate, ending up in affecting more globally the DS (DLS + DMS) rather than DLS itself. Still, dMSNs-lesioned mice showed impairments in initiating the left sequence leading to abolish the execution of the target sequence LLRR, while iMSNs-lesioned mice showed much less impairments in initiating or terminating the sequence but their ability to switch from left to right was dramatically reduced (Geddes et al., 2018). These data are consistent with the previous study highlighting a role for dMSNs in controlling the overall sequence, but not iMSNs. However, it also suggests distinct roles of d- and i-MSNs in controlling action sequences by preferentially mediating sequence-versus subsequence-level execution, respectively.

Next, Geddes and colleagues employed optogenetic stimulations of either d- or i-MSNs more specifically in the DLS while the animals are performing the sequence already learned, and tested the consequences of acute state-paired stimulation on the subsequent sequence structure (Geddes et al., 2018). Constant pulses of light (500 ms) were sent bilaterally in the DLS of D1-ChR2 or A2A-ChR2 expressing mice at each step of the sequence on the lever press. Photostimulations of DLS dMSNs at the first or second left press of the sequence induced a repetition of the left press. Although it inserted an extra left press, animals were still able to execute and terminate the target sequence. This repetition also happened following the second right press but surprisingly did not appear following the first right press. This observation led the authors to suggest that optogenetic modulation of the sequence through dMSNs is state-dependent. Stimulation on the first right press would have no effect due to the likelihood of pressing right again, which would also account for the first left press. However, the authors interpreted the latter response as a facilitation of the starting subsequence especially since that the insertion of the extra left press was counterbalanced by a shortening of the right subsequence, making the duration of the overall sequence unchanged (Geddes et al., 2018). In contrast, photostimulations of DLS iMSNs applied on the first left or right press cut the following action to terminate the sequence to LRR or LLR, respectively. When photostimulations were applied on the second left or right press, when a natural switch was expected, there were no effect and sequence remained intact (Geddes et al., 2018). These results were consistent with neuronal recording of iMSNs preferentially exhibiting high activity during subsequence left-to-right switch (Geddes et al., 2018), and also suggest that iMSNs do not only act through general motor inhibition. Altogether these optogenetic manipulations of DLS d- and i-MSNs have distinct effects on the global sequence structure by adding or removing single actions, respectively. The authors proposed that not only element- and sequence-level structures would be maintained independently, but the left and right subsequences would also be controlled separately. In addition, the fact that the right subsequence has been adjusted to maintain an appropriate total sequence length when stimulating DLS dMSNs on the left subsequence, suggests that learned action sequence is likely organized in a temporal hierarchical manner with a possible temporal encoding at both local subsequence-level and global sequence-level with separate modes of control involving both the direct and the indirect pathways. However, there is no direct report or tests on general aspects of locomotion or perseverative responding that these manipulations could cause such as dyskinesia (Rothwell et al., 2015) or response repetition especially with DLS dMSNs stimulations. Besides, a follow-up study testing the effects of similar closed-loop optogenetic control of d- and i-MSNs on reversal switching of this sequence learning, in the DLS versus DMS, would greatly advance our understanding on the respective role of these subpopulations in each striatal territories.

Our lab recently investigated the respective roles of the d- and i-MSNs of the DLS in the acquisition of a new sequence learning in a reversal task using optogenetics in a chronic manner (Laurent et al., 2017). We generated a disbalance in BG activity by over-activating or boosting each pathway during the reversal process, and test the consequences of this perturbation on the animals' performance and ability to learn a new sequence. As DMS and DLS are critical for new skill learning and habit formation, respectively, our manipulation in the DLS here intended to perturb or interfere with the automatization process that has taken place on the previously learned sequence, and test whether it impacts and allows the reversal learning. Although the DLS is expected to intervene in a second order compared to DMS, we found a direct impact on the acquisition of the new reversed sequence. In a two-lever operant task, mice were trained to execute a L1L2 sequence response in order to earn a reward (Laurent et al., 2017). In this sequence learning process, the L1L2 sequence proportion of all other possible sequence (L2L1, L1L1, L2L2) reflect the correct responses and acquisition of the dual action order. The L2L2 sequence was the most common error made at the beginning of the trials representing the repetition of the more proximal action to reward, but subsequently decreases with training. Next, once the animals were stable in their performances with

minimal incorrect responses after two weeks, the rewarded sequence was switched to L2L1. At the same time, optogenetic pulsing stimulations were applied either on DLS dMSNs or DLS iMSNs, over the whole 90 min test session without being strictly paired with lever presses actions (20 Hz, 5 ms pulse, delivered by trains of 20 sec with a 10 sec pause). Over two weeks training, all animals (stimulated and unstimulated controls) gradually learned to reverse the sequence (Laurent et al., 2017) and in contrast with previous DLS photostimulation effects (Tecuapetla et al., 2016), we did not observe any action sequence abortion when stimulating DLS d- or i-MSNs. Therefore, optogenetic activations of DLS d- and i-MSNs have no impact on the learning performances of the reversal sequence in agreement with lesions studies of the DLS that do not interfere with reversal learning (Castañé et al., 2010). However, the mice that received optogenetic stimulation of DLS iMSNs exhibited a lower proportion of correct responses and delay in acquiring the reversal sequence, while DLS dMSNs photostimulations induced a facilitation in the acquisition of the new sequence, characterized by a higher proportion of correct responses occurring earlier in the training (Laurent et al., 2017). The proportion of incorrect responses was also analyzed revealing again that the new proximal action to reward (L1L1) was the most common error made in controls at the beginning of the trials but reduces over time. However, this error was more frequently observed in DLS iMSNs activated mice, while it was significantly less occurring in DLS dMSNs activated mice across the whole training in comparison to control mice (Laurent et al., 2017). This mostly frequent error occurring with DLS iMSNs photostimulation remained frequent at a random proportion with the other types of error within the group, which discard the possibility of a general inability to discriminate the various sequences. Similarly, it is unlikely that the photostimulations induce more repetitive responses as the proportion of L2L2 sequence gradually reduced over time. This analysis led us to suggest that activation of DLS iMSNs leads to a selective deficit connecting different actions to form a correct memory. Interestingly, DLS lesions showed a facilitation in the extinction of responding in the old rewarded strategy (Castañé et al., 2010). These facilitating effects of the DLS lesion in the extinction of an old pre-learned sequence might thus rather be due to the absence of iMSNs. Interestingly, the deficits we generated with optogenetic activation of iMSNs (Laurent et al., 2017) are quite relevant to certain disease pathophysiology displaying behavioral inflexibility traits and in which the indirect pathway might be predominantly impaired, such as in schizophrenia (Simpson et al., 2010), or in other words, over-activation of the indirect pathway might be preferentially involved in certain aspects of behavioral inflexibility.

Altogether this study not only highlighted distinct roles of d- and i-MSNs in the acquisition of a dual action order but also revealed a critical influence of the DLS in sequence-switching learning process through two separates modes of control via the direct and indirect pathways. It would be thus very informative in future studies to develop concomitant recordings of DMS neurons during reversal process applying the same perturbation of the DLS sub-populations. Indeed, this study also suggests that not only a balanced activity of both pathways is necessary to execute an appropriate behavior or reversal learning, but also that a coordinated activity in the DLS and in the DMS, and in their respective downstream targets, may be also necessary to ensure flexibility. Consistently with parallel contributions of DLS and DMS rather than sequential involvement, optogenetic inhibition of DLS neurons was found to improve early discrimination performances in a visual discrimination task using a touchscreen platform (Bergstrom et al., 2018). DLS photoinhibition was continuously applied from stimulus presentation to reward collection. Concomitantly to an increase in early performances, DLS-photoinhibited mice exhibited a decrease in error rate and an increase in win-stay and lose-shift behaviors. The latter might indicate that inhibiting the DLS could facilitate action selection by improving the use of the previous trial outcome to drive current choice. To dissect the relative contribution of d- and i-MSNs in early learning, the same optogenetic inhibition was replicated specifically on both subpopulations. The inhibition of DLS dMSNs mostly mimicked the effects observed after whole DLS inhibition whereas the specific inhibition of DLS iMSNs only resulted in a decrease in early error rate. These results highlight the complex relationship between DLS d- and i-MSNs during early learning that can be, according to the behavioral trait considered, either competitive or cooperative. However, the inhibition of DLS iMSNs and dMSNs both resulted in a decrease in late discrimination performances that was not observed for total DLS inhibition, which was not further discussed by the authors. Interestingly, functional neuroanatomy revealed that DLS dMSNs inhibition resulted in enhanced Arc expression –a marker of synaptic plasticity– in the prelimbic cortex and DMS, thus suggesting enhanced synaptic plasticity in these two regions. As a conclusion the authors proposed that the DLS is recruited and influences behavior from the outset of learning, reflecting the ongoing construction of novel stimulus-response associations that are ultimately automated and aligned between the DMS and the DLS to build so-called meta-actions (Bergstrom et al., 2018). Alternatively, and in agreement with the sequential model of DMS to DLS learning, one may postulate that the effects observed here might result from interferences from DLS-dependent habits and well-learned actions competing with formation of novel associations occurring in the DMS.

Along with this consideration on parallel or sequential contributions of DMS and DLS, the participations of cortical and thalamic projections to the distinct striatal territories in these learning processes have to be addressed. As mentioned earlier Rothwell and colleagues showed that excitatory synapses from the motor cortex to dMSNs, preferentially, in the DLS are necessary for serial order learning (Rothwell et al., 2015). Moreover, the genetic deletion of NMDA receptors connecting to striatal MSNs is sufficient to decrease the learning rate of certain sequence, suggesting that striatal plasticity is necessary for appropriate organization of sequential actions (Jin and Costa, 2010; Jin et al., 2014). Plus, more specifically, NMDA inactivation in iMSNs was shown to reduce habituation to novelty, delay goal-directed learning, suppress associative behavior, and impair fine motor learning (Lambot et al., 2016). Therefore, deciphering the participation of the excitatory cortico- and thalamo-striatal synapses to identified-cell populations of the striatum, in its respective territory, in serial order learning and reversal learning remains critical.

4. Role of dorsal striatum afferences in motor learning and flexibility

The striatum works as a core center where information from different brain regions converge. This information is mediated by a variety of neurotransmitters including monoamines, aminoacids, peptides or gaseous signaling molecules (reviewed in Burke et al., 2017). However, the striatal function is shaped primarily by two important glutamatergic inputs coming from the neocortex and the thalamus, and dopaminergic inputs from the midbrain (reviewed in Lanciego et al., 2012; Nelson and Kreitzer, 2014). These connections not only modulate both types of MSNs and interneurons' activity but also other terminals via axon-axonic synapses (Burke et al., 2017). The following sections review what has been learned so far about the influences of cortical, thalamic and dopaminergic afferent neurons to the DS, in its different DLS/DMS territories when addressed, in motor learning and flexibility.

4.1. Corticostriatal pathway

The striatum receives topographically organized projections from nearly all regions of the cerebral cortex (Hintiryan et al., 2016). Corticostriatal excitatory projections originate from two types of neurons: intratelencephalic (IT) neurons, which project exclusively to ipsi- and contralateral striatum and cortex, and pyramidal tract (PT) neurons, which project to ipsilateral striatum and cortex, and other brain regions such as the thalamus or brainstem but do not project to contralateral striatum (Hooks et al., 2018). Whether these neurons project differently

to dMSNs or iMSNs remains unclear. Some studies showed that dMSNs neurons preferentially receive input from IT neurons, whereas iMSNs receive greater inputs from PT neurons (Lei et al., 2004; Reiner et al., 2010; Morita, 2014). An other anatomical study showed no significant difference in the cortical targeting between d- and i-MSNs (Wall et al., 2013) while a functional study using recordings of striatal neurons when optogenetically activating both corticostriatal projections showed a preferential targeting of dMSN by PT neurons (Kress et al., 2013). Traditionally, cortical GABAergic neurons projecting to the striatum were not considered to be a component of the canonical corticostriatal network because they were identified only in the prefrontal, somatosensory, and retrosplenial cortices (Lee et al., 2014; Jinno and Kosaka, 2004). However, recent studies have shown direct GABAergic projections to the striatum from the motor and auditory cortices providing inhibitory inputs to both d- and i-MSNs that influence both pathways output functions (Rock et al., 2016; Melzer et al., 2017).

How cortical projections to different regions of the striatum affect flexibility is still unclear. As introduced above, early lesion studies highlighted the importance of prefrontal cortical areas, such as the mPFC and OFC, in tasks requiring adaptation to new situations (Birrell and Brown, 2000; McAlonan and Brown, 2003; Stefani et al., 2003; Ragozzino, 2007; Bissonette et al., 2008; Floresco et al., 2008; Ghods-Sharifi et al., 2008; Ostlund et al., 2009). However, these studies showed heterogeneous results that may depend on the task performed and the inherent limitations of the lesion and pharmacological inactivation techniques, including low spatial and temporal resolutions, and possible involvement of compensatory mechanisms.

The importance of mPFC in behavioral adaptation was recently investigated with optogenetics. Marton and colleagues used a strategy-shifting task including audio-visual switch in which mice alternate between auditory and visual cues to obtain a reward (Marton et al., 2018). Then the task consists in first reinforcing the auditory cue (sound), while the visual cue (light) is irrelevant. Once the mice perform well enough (80% correct during a 10-trial block), the rule was switched such that the light cue is now rewarded and the sound cue can be ignored. Optogenetic inhibition was implemented in mPFC neurons with a viral vector expressing the archaerhodopsin (ArCh3.0) under the ubiquitous neuronal promoter human synapsin. Photoinhibitions were applied while the mice were already trained during the last 10 auditory trials and during the visual trials. While optogenetic inhibition of mPFC did not affect the on-going performances, it completely prevented the animals from switching to the visual rule, showing that inhibiting the mPFC impairs certain forms of behavioral flexibility (Marton et al., 2018).

Another study has recently assessed this question in a cell- and circuit-specific manner through optogenetic control of mPFC projections to the DMS (Nakayama et al., 2018). Indeed, using different GENSAT cre driver lines targeting specific neuron types in the mPFC, the authors showed that the corticostriatal projection neurons located in layer V of the mPFC are critical and specialized in controlling behavioral flexibility. To target those neurons, the authors used the transgenic Colgalt2-cre mice transfected with a cre-dependent ArCh3.0-expressing virus. Photoinhibitions were applied on axon terminals in the DMS to ensure that the observed behavioral changes resulted from specific inactivation of corticostriatal projections (Nakayama et al., 2018). Mice are trained in a reversal task including a binary choice in which mice had to identify the correct port, out of two, which offers a 75% of probability to deliver the reward. When choice accuracy in the last 10 trials reached 80%, the rewarded port was switched to the other that offered only a 15% reward probability. Pyramidal neuron terminals in the DMS were optogenetically-inhibited at different time points during the pre-start and during the pre-choice. The pre-start manipulation allows to measure whether the photoinhibition impacts on premature responding (a readout of motor impulsivity), while the other rather targets the effects on animal choice response. Inhibition of mPFC pyramidal neuron terminals in the DMS does not affect impulsive behavior but induce a biased choice response to either right or left port independently of the rewarded option (Nakayama et al., 2018). This study demonstrated that mPFC layer V neurons→DMS are critical to regulate behavioral flexibility.

Regarding the OFC, in our knowledge, the use of specific optogenetic circuit-control of OFC striatal projections has still not been used to refine the role of this pathway in behavioral flexibility. However, it has been investigated in the context of obsessive-compulsive disorder (OCD). Interestingly, optogenetic stimulations of the lateral OFC and its terminals in the DS (central region) alleviate abnormal repetitive and compulsive behavior, but also normalized impaired striatal microcircuit dynamics in a mouse model of OCD (Burguière et al., 2013).

Functions of motor cortex inputs to the DLS were also questioned with circuit-projection specific inactivation and optogenetic stimulations. As mentioned earlier, Rothwell and colleagues showed the importance of dMSNs in the DLS for completion of a learned sequence and they next investigated whether synaptic inputs from motor cortex to the DLS are critical in this process (Rothwell et al., 2015). They specifically inhibited M1→DLS or M2→DLS projections by injecting in the DLS a rabies virus expressing the cre-recombinase which is taken up by axons and retrogradely transported to starter cells in the motor cortex. This approach was combined with the injection of a cre-dependent inhibitory Kir2.1-potassium channel in M1 or M2 neurons. As explained earlier, mice were subjected to a sequence learning task which consisted in pressing two levers in a serial order (A » B) to obtain a reward. Viral injections took place once mice were already trained in this task. The authors found that inhibition of M1→DLS projecting neurons had little effect on sequence performances, while inhibition of M2→DLS cortical projections dramatically decreased the percentage of correct AB sequences (Rothwell et al., 2015). These results suggested that inhibited mice had difficulties to initiate the primary action of the sequence, and highlighted the necessity of M2 inputs to the DLS to initiate and execute correctly a sequence of action. Next, they also tested the sufficiency of M2 inputs activation to the DLS to modulate sequence learning with optogenetic stimulations. Depending on when the stimulation is applied, between responses or before the first response, activation of M2→DLS terminals can either impair or improve performances, respectively, by increasing the likelihood of performing the first response of the sequence (Rothwell et al., 2015). While inhibition of these projections impairs the initiation of the primary action, activation can lead to its repetition. Finally, to evaluate the function of M2→DLS excitatory synapses after sequence learning, the authors performed acute brain slice whole-cell recordings of d- and i-MSNs in the DLS after behavioral training and optogenetically controlled excitatory postsynaptic currents (EPSCs) from M2 terminals with the channelrhodopsin variant, ChIEF. To assess synaptic strength between M2 and d- or i-MSNs, they measured AMPA/NMDA ratio when optically evoking EPSCs from M2 terminals and found an increased ratio exclusively in dMSNs of trained animals, which was not seen in iMSNs. Altogether, these experiments suggested that dMSNs in DLS were critical for sequence completion (see section II) as their activity is potentiated by excitatory inputs from the M2 (Rothwell et al., 2015).

In addition to causal studies using optogenetic inhibition/activation control of specific circuits, correlative approaches monitoring the real-time activity dynamics of associative and sensorimotor cortical projections to DS by fiber photometry during motor skill learning were recently performed in mice (Kupferschmidt et al., 2017). Importantly, the authors evidenced that associative and sensorimotor inputs are concurrently active during the first stages of motor learning while they reduce activity in a dissociable manner as actions are refined into skills. To develop this study, the authors monitored mPFC→DMS and M1→DLS presynaptic inputs activity using fiber photometry in transgenic Emx1-cre mice transfected with a cre-dependent virus expressing GCaMP6s. GCaMP6s indicator was thus expressed in mPFC and M1 pyramidal neurons and their dorsal striatal inputs. After optical fiber implantation above the DMS and DLS the neural activity is assessed

from both mPFC→DMS and M1→DLS somas and presynaptic inputs in freely moving mice during different phases of a rotarod task. They showed that mPFC→DMS pathway is weakly engaged (little active) on the first training trials but rapidly increases and peaks by final trials during the first day of training. However, once the action is learned after several days, mPFC→DMS pathway disengages as measured by low calcic activity. These results suggest a transient engagement of mPFC→DMS projection neurons that may underlie the preferential engagement of the DMS in early learning stages (Yin et al., 2009; Durieux et al., 2012). Furthermore, mPFC→DMS input disengagement selectively correlated with and predicted subsequent learning performances, suggesting that mPFC inputs to DMS may gate the acquisition of skills. Unexpectedly, M1→DLS pathway was shown to be strongly engaged during the naive and early learning stages, and incrementally disengages across training (Kupferschmidt et al., 2017). This strong initial engagement of the M1→DLS pathway suggests that sensorimotor circuits also serve important roles during early learning and thus question the classical theory by which neural control of actions shifts from DMS to DLS circuits across learning (Graybiel, 2008), in agreement with the discussion we developed earlier in reversal learning task (Laurent et al., 2017, see section II). However, no correlation was observed between M1→DLS inputs activity dynamics and learning performance in this task.

Altogether, these studies highlighted the importance and dynamics of prefrontal and motor corticostriatal inputs to the different striatal territories to specific aspects of behavior. These studies confirm that the prefontral areas of the cortex sending projections to the DMS do not affect the acquisition of motor or instrumental conditioning tasks. However, these projections are critical for behavioral adaptations in face of changes in the environment and new learning. Nevertheless, motor areas, projecting to both DMS and DLS, are also important to acquire and develop motor learning performances. Thus, different information from the environment is transmitted from different cortical areas to the DS that governs divergent actions downstream.

In conclusion to gain further insights in the understanding on the encoding and respective role of each MSNs population in regards to their differential cortical inputs, especially in behavioral flexibility paradigms, future studies, mixing the cutting-edge techniques we reported in this review, should be used to selective control each specific inputs of both MSN populations.

4.2. Thalamostriatal pathway

Although most models of the basal ganglia emphasize the importance of the connection from the cerebral cortex to the striatum, the thalamus also shares strong connections with the striatum. Indeed, anatomical studies showed that corticostriatal and thalamostriatal synapses formed on MSNs are nearly equal in number (Doig et al., 2010). In addition, emerging evidences suggest that thalamostriatal inputs play an important role in modulating corticostriatal inputs (Ding et al., 2010).

The main source(s) of thalamostriatal projections are intralaminar thalamic nuclei, but substantial inputs from midline (Van der Werf et al., 2002) and ventral motor nuclei (Erro et al., 2001) have also been described. Intralaminar nuclei are divided into “rostral intralaminar nuclei”, composed of the central medial (CeM), paracentral (PC) and centrolateral nuclei (CL), and the “caudal intralaminar group” that includes the centromedian (CM) and parafascicular (Pf) nuclear complex in human and non-human primates. Although the CM is not clearly delineated in rodents, the lateral part of the Pf is considered the homolog of the primate CM, whereas the medial Pf displays strong similarities with the Pf in primates (Groenewegen and Berendse, 1994; Smith et al., 2004). Within the striatum, afferents from Pf establish asymmetric synapses principally with dendritic shafts of both types of MSNs (Smith et al., 2004; Raju et al., 2006; Lacey et al., 2007) and several types of striatal interneurons (Assous et al., 2017).

The implications of CM and Pf in behavioral flexibility have been analyzed in several lesion and pharmacological studies. Brown and colleagues studied the influence of the Pf in behavioral flexibility by pharmacologically inactivating the Pf through infusion of the GABA agonists, baclofen and muscimol, and examined the effects on reversal learning in rats (Brown et al., 2010). In a cross maze task, Pf inactivation impaired place reversal learning by selectively increasing regressive errors that measure the ability to maintain a new choice after initially shifting away from the previously relevant choice pattern. Interestingly, in a subsequent experiment, the authors proposed that DMS CINs exert a key role in relaying Pf inputs regulation of reversal learning by measuring acetylcholine (ACh) release in the DMS by in vivo microdialysis during reversal learning (Brown et al., 2010). They first showed an increase in ACh DMS levels during reversal learning, and then that Pf inactivation prevents it. The relationship between Pf striatal projections and CINs was further supported by anatomical (Guo et al., 2015; Reiner and Deng, 2016) and functional studies confirming that Pf neurons directly project to DMS (Alloway et al., 2014) and that lesion of the Pf alters specifically DMS CINs firing activity, as opposed to CINs located in the DLS or MSNs in the DMS (Bradfield et al., 2013). In addition, Bradfield and colleagues assessed the effect of excitotoxic NMDA-induced bilateral lesion of the Pf on a goal-directed learning protocol including a contingency reversal procedure. They also examined the effects of asymmetrical lesions to disconnect the Pf from the DMS, and the effects of pharmacological blockade of cholinergic activity on the same behavior (Bradfield et al., 2013). They found that, in all cases, either with bilateral lesion of the Pf, by disconnecting the Pf-DMS pathway (specific to the posterior region of the DMS), or by reducing the DMS cholinergic activity, there is a deficit in goal-directed learning after changes in action-outcome contingencies evidenced by rats' inability to encode new contingencies. However, the initial acquisition of goal-directed actions is not affected (Bradfield et al., 2013). Altogether these results suggest that the behavioral deficits resulting from Pf-DMS disconnection are predominantly induced by changes in CINs function in the posterior DMS. The authors proposed that rather than affecting new learning, deficit in cholinergic function induced interference between both new and existing action-outcome encoding in the posterior DMS. Consistently with these results on striatal cholinergic function, specific ablation of CINs in the DMS impairs reversal learning in set-shifting (Aoki et al., 2015). Although Pf lesion has an asymmetric effect on CINs and MSNs' firing activity, its effects or associated compensatory mechanisms on the global local network activity including GABAergic interneurons, d- and i-MSNs and their interconnectivity (collaterals) (Burke et al., 2017), and its response to cortical inputs should be further investigated.

Recently, Kato and colleagues examined the role and necessity of CL thalamostriatal neurons in reversal learning and attentional set-shifting using a selective neural pathway targeting technique in mice (Kato et al., 2018). This technique consists in injecting into the DS (central region) a lentiviral vector that has retrograde gene transfer properties and that encodes a receptor for a recombinant immunotoxin. Injection of the toxin in the CL enabled to eliminate selectively CL neurons, preserving the Pf ones. Selective ablation of CL→DS neurons impairs response selection and disturbs flexible switching. Using a two-lever choice visual discrimination task, the authors examined 1) task acquisition when inducing the lesion before the training and 2) task performance when inducing the lesion once the task was acquired. Ablation of CL→DS neurons did not alter the acquisition of the task (1) but impaired the performance (response accuracy) if the lesion was done once the task was acquired (2). This demonstrates that CL thalamostriatal neurons are important for response selection but not initial learning on sensory discrimination. However, the effect of pathway ablation on response accuracy (2) can be recovered during repetitive sessions. Moreover, the authors assessed the effects of the lesion on reversal learning and set-shifting abilities by replacing a visual discrimination task by a place discrimination strategy. As the lesion did not affect the

acquisition of the task, ablations were performed before training and once the animals were trained, one group was subjected to reversal test and another to set-shifting. In the reversal test, ablated mice exhibited slower performances to switch levers and needed more sessions to reach the criterion validating the task compared with controls. In set-shifting, the increase of correct responses in ablated mice was impaired and further sessions were also necessary to reach the criterion. These results indicated that the CL thalamostriatal neurons are required not only for reversal learning but also for attentional set-shifting where they may facilitate behavioral switching. In addition to the lesion, the authors induced a reversible inactivation of the CL→DS pathway using chemogenetic. Using the same retrograde lentivirus encoding the cre-recombinase, they injected a cre-dependent virus carrying the mutated muscarinic receptor for inhibitory DREADD control (hM4Di) in the CL, allowing specific inhibition of CL→DS projections. Interestingly, the acute inhibition of CL→DS neurons also altered behavioral flexibility in the reversal learning and attentional set-shifting tasks, but did not affect the response selection during the performance phase of visual discrimination (2) in contrast to the ablation. Such discrepancies might be due to compensatory mechanisms. Nevertheless, these results highlighted a key role of thalamostriatal inputs from the CL in the regulation of DS functions, notably in behavioral flexibility. However, the nature of the striatal target cells involved in these processes remains to be identified.

Interestingly another form of flexibility measured by response inhibition (see introduction) seems to involve Pf→DMS projections. Chemogenetic inhibition of the Pf→DMS pathway during a five-choice serial reaction time task, assessing both spatio-temporal attention and inhibitory control (motor impulsivity), was shown to induce an increase in perseverative responses when the stimulus predictability was reduced, while premature (anticipated) responding or attention measurements were unaffected (Saund et al., 2017). This perseverance trait is an indication of compulsivity, which can arise from altered response inhibition. The behavioral deficit elicited by inactivation of the Pf→DMS pathway here shows high specificity since other performance indices were not altered suggesting that the Pf→DMS pathway may be preferentially involved in certain aspects of behavioral flexibility.

A very recent study combining electrophysiological and optogenetic approaches was performed to assess the implication of thalamostriatal projections to DMS and DLS in initiation and execution of a sequence of movements (Diaz-Hernandez et al., 2018). First, Diaz-Hernandez and colleagues identified by retrograde viral approaches that Pf and thalamic ventroposterior (ThVP) neurons present a preferential innervation for the DMS and DLS, respectively, which was functionally confirmed by performing MSNs ex vivo whole-cell recordings combined with optogenetic stimulation of Pf and ThVP projections. Second, to assess whether neurons from Pf and ThVP modulate their activity during initiation or execution, they recorded the activity of thalamostriatal neurons identified by anti-dromic photo-tagging while animals initiated and executed a sequence of movements. To do so, ChR2 was expressed in glutamatergic thalamic neurons of either Pf or ThVP from VGluT2-cre mice implanted with an electrode array above the expression site. In addition, optical fibers were placed either in the DMS or DLS to anti-dromically activate and tag Pf neurons projecting to the DMS or ThVP neurons projecting to the DLS. The operant task consisted in learning a sequence of eight consecutive lever presses to earn a reward. Electrophysiological recordings performed in trained animals showed that both pathways displayed activity modulation during the initiation and execution of the sequences of lever presses, but the Pf→DMS neurons contained a larger proportion of units modulated during initiation while the ThVP→DLS neurons contained more units modulated during the execution. Moreover, the authors performed linear regression analysis in order to establish a relationship between the recorded activity and behavioral parameters, such as latency to start a sequence (initiation phase) and number of presses in the sequence (execution). They observed that Pf→DMS neurons contained more units correlated with the initiation while ThVP→DLS neurons contained more units correlated with the execution. Finally, to test the necessity of thalamostriatal projection for initiation and execution, they optogenetically inhibited the thalamostriatal terminals either before the initiation or during the execution of a sequence of movements. Optogenetic inhibition of Pf→DMS or ThVP→DLS terminals before the start of the sequence both increased the latency to initiate the sequence. However, only inhibition of ThVP→DLS increased the number of presses. On the other hand, only optogenetic inhibition of ThVP→DLS during execution had behavioral impairments characterized by an increased number of lever presses in the sequence. Altogether, these results indicated that both Pf→DMS and ThVP→DLS contribute to proper action initiation, and the later additionally contributes to the proper execution of learned sequence of movements.

In conclusion, these papers highlighted a key contribution of the thalamus as a source of striatal modulation as well as distinct involvement of singular thalamic nuclei with respect to their specific projections to DS sub-regions. However, the function of their specific actions directly on either d- or i-MSNs and indirectly through striatal interneurons is still underexplored in comparison to cortical inputs. Also knowing that both thalamic inputs and cortical inputs converge into single MSNs, it would be of great interest to dissect their synergistic or competitive interactions in the context of learning and flexibility to adjust behavioral outcome in an ever-changing environment.

4.3. Dopaminergic afferences

Midbrain DA neurons are mainly located in the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc). The striatum receives massive DA inputs from VTA DA neurons projecting principally to the VS, and from the medial and lateral SNc projecting principally to the DMS and the DLS, respectively (Lammel et al., 2014). Indeed, despite this topography, there is a considerable overlap in projection targets because individual DA neurons have widespread striatal projections (Vogt Weisenhorn et al., 2016). Midbrain DA neurons are heterogeneous not only regarding their axonal projections but also their morphological (e.g. variable dendrite architecture), molecular (GABA and glutamate co-release) and electrophysiological properties (Wolfart et al., 2001; Neuhoff et al., 2002; Amendola et al., 2012; Tritsch and Sabatini, 2012; Henny et al., 2012; Chuhma et al., 2018). In addition, DA neurons can be excited by both rewarding and aversive stimuli, suggesting that DA neurons participate in distinct circuits mediating partially distinct functions (Lammel et al., 2014; Morales and Margolis, 2017).

As previously mentioned, behavioral flexibility is mediated by prefrontal connections to the striatum. However, evidences from Parkinson's disease patients exhibiting flexibility impairments with increased perseverative errors point out an involvement of striatal DA signaling (Hughes et al., 2013; Lange et al., 2017). Because both DS and VS receive prefrontal cortex and DA projections, it is unclear whether DA signaling to either one or both of these regions would be preferentially involved in these flexibility alterations. Pharmacological and lesion approaches have shown the implication of DA in flexibility processes. For example, high or low doses of psychostimulants increasing DA levels impair reversal learning performance (Clarke et al., 2011; Idris et al., 2005). However, other studies using intermediate doses showed no effect or even opposite results (Daberkow et al., 2013) consistent with the idea that cognitive performances and DA levels follow an inverted U-shaped function (Cools and D'Esposito, 2011). Conversely, reducing DA levels by pharmacological depletion of DA neurotransmission in the DMS impairs odor-guided reversal learning, without affecting initial discrimination learning (O'Neill and Brown, 2007). A similar depletion targeting more largely the DS induces a deficit in the acquisition of a visual discrimination task, and alters the acquisition of a new rule in a set-shifting task in mice (Parikh et al., 2016). Another study using DA-deficient mice showed similar results in

a water U-maze paradigm where mice had to shift from an initially acquired escape strategy to a new strategy (Darvas and Palmiter, 2011). Interestingly, restoration of DA signaling in the VS of these mice corrected certain behavioral deficits including restoring the proper initial strategy to escape but still failed to acquire a new strategy to escape during the set-shifting test, suggesting that VS DA signaling may not be involved in new strategy learning.

To further illustrate specialized functions of DA signaling in the striatum, a recent study combining optogenetic and fiber photometry aimed at investigating reward and choice encoding in DA axon terminals in the DMS and NAc in mice highlighted key differences between these regions (Parker et al., 2016). Importantly, DA axons terminals activities in the DMS and NAc present preferential increase to choice and reward, respectively. Another study also using optogenetics and fiber photometry in combination with retrograde viral tracing tackled distinct roles of DA SNc projections to the DMS and DLS (Lerner et al., 2015). First, SNc DA neurons project to non-overlapping striatal subregions: medial cells to DMS and lateral ones to DLS. Lateral and medial cells also exhibit different intrinsic electrophysiological properties upon their axonal projection sites (Lerner et al., 2015). Interestingly, DMS and DLS are reciprocally connected with the very same DA neurons that project back to these SNc sub-fields. Furthermore, the authors described strong DLS projections to DA SNc→DMS projecting neurons, implying a support for lateral to medial information flow that would be interesting to further explore. Based on the variety of DA responses to reward and aversion, Lerner and colleagues examined distinct functions of SNc→DMS and SNc→DLS projecting neurons by recording their activity following either appetitive or aversive stimuli. To do so, they employed a retrograde targeting approach by co-injecting a CAV-cre virus in the DMS or DLS and a cre-dependent virus carrying a GCaMP6f construct in the SNc. Strikingly, SNc→DMS DA neurons showed a decrease of activity in response to aversive stimuli while SNc→DLS DA neurons showed an increase of activity. However, both populations responded similarly to appetitive stimuli. These observations demonstrated that the differences in the representations of aversive stimuli among subsets of SNc DA neurons depend on their projection target.

In addition to signaling actually occurring appetitive or aversive cues, DA neurons also play a key role in operant learning in particular through the formation of a so-called reward prediction error (Keiflin and Janak, 2015). A recent and elegant study evaluated how DA influences choice selection in operant task where mice were trained to select between two alternative actions (lever presses) according to internally monitored temporal information (Howard et al., 2017). In this task, every trial starts with the extension of both levers that are subsequently retracted for either 2 or 8 sec. The duration of lever retraction indicates the rewarded lever. This task allows to study dynamics of action selection processes in a self-paced manner, as animals rely on internal monitoring of time to get a reward. Indeed behavioral tracking of mice during levers retraction during long-duration trials reveals that their preference seems biased toward the short-duration lever during the first half of lever retraction period, and then evolves to a bias toward the long-duration option. Fast-scan cyclic voltammetry measurements of DA released in the central DS revealed an increased DA concentration throughout short-duration trials, and, regarding long-duration trials, DA concentration is initially increased during the first seconds following levers retraction and then drops to levels below baseline until levers extension. DA levels seem to follow a similar kinetic than behavioral preference toward one lever or the other. In vivo electrophysiological recordings of optogenetically-tagged DA cells in the SNc demonstrated that the firing activity of a majority of DA cells displays the same profile as DA concentration in the DS during both short- and long-duration trials. The introduction in trained animals of a new unrewarded probe trial two times longer than the long-duration trial (16 sec), unrevealed two different dynamics of DA concentration in the DS associated with different lever choices: when DA remains below baseline levels, mice chose the long-duration lever; when DA concentration returns to baseline levels, mice chose the short-duration lever. The above results would thus indicate that the release of DA in the DS might be predictive of ongoing lever preference. Following these correlative evidences, the authors next tested the causative influence of DA on action selection using optogenetic manipulation of SNc DA neurons. First, SNc DA cells or their terminals in the DS were stimulated during 1sec immediately before levers extension 2sec, 4sec, or 8sec after levers retraction. No change in preference was observed for the 2sec- or the 8sec-long trials, preferences remained identical to those after short- or long-duration trials, respectively. However, for 4sec-long trials, DA neurons or DA terminals stimulation resulted in a change in preference toward the short-duration option. Additionally, optogenetic stimulation of DA SNc neurons at different time points during long-duration trials resulted in a shift in preference toward the short-duration option with the exception of stimulations occurring early (0–2sec) during the retraction period and stimulation occurring immediately before lever extension (7sec). Oppositely, following the same procedure, the optogenetic inhibition of DA SNc cells produced a shift in preference toward the long-duration option only when it occurred early during the levers retraction period when DA concentration normally increases. Altogether, the above study highlighted that DA signaling within the DS is a key element driving and modulating action selection processes. To explain their observations, authors posit that the nigrostriatal dopamine might integrate information across multiple brain centers essential to decision processing and send this integrated signal to efferent brain structures, including the DS, for shaping action selection.

These recent studies contributed to support the fact that the midbrain DA complex does not form a homogeneous group with respect to anatomy, physiology, molecular identity, sensitivity to various stimuli, and functions. Part of this heterogeneity is related to distinct targeting in the DS, in its DMS and DLS sub-territories that, as mentioned earlier, are specifically involved in some aspects of action sequence learning, reversal learning and flexibility. On top of DS regional specialization, DA signaling also critically drives action sequence learning or reversal learning, as DA signaling dynamics shape behavioral outcome in front of a given situation. Deciphering DA signaling heterogeneity should be addressed in future studies with a particular focus on striatal subregions as well as its specific effect on subpopulations of d- and i-MSNs that might be oppositely affected by changes in DA levels. Moreover DA signaling in the DS could also strongly modulate cortico-thalamic inputs as the terminals of these afferences also bear dopamine receptors strongly adjusting synaptic transmission properties.

5. Conclusion

The development of optogenetic tools to control and image neuronal activity in the last decade offered multiple possibilities to specifically examine the functions of BG circuits and more particularly those of striatal cell populations. We reviewed here that the classical BG model on motor control is undergoing some refinements as growing evidences from recordings of individual neuron firing activity show a high level of heterogeneity within each MSNs populations and that both pathways are co-engaged in discrete behaviors (see Table 1) and can be synchronized in compact clusters of cells displaying a similar organization. The question of whether optogenetic control of MSNs either support or question the BG model can vary on where in the DS and how photostimulations were applied in pair with behavior. It is noteworthy that photostimulations induce synchronization of neuronal activity, which can naturally happen occasionally but is also inconsistent with the intra-population heterogeneity in firing activity observed in vivo, in freely moving animals. Further efforts should be made in identifying new markers or tools allowing to distinguish these different intra MSNs subpopulations in order to better characterize their causal role. In addition, it is also important to keep in mind that optogenetic excitations may disrupt the spontaneous neuronal activity engaged during the task.

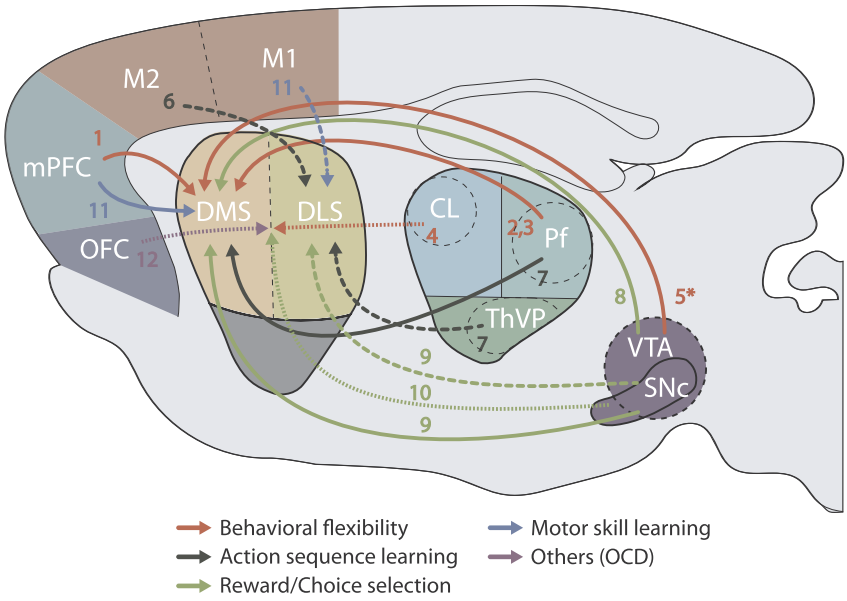

Fig. 1. Schematic representation of cortical, thalamic and dopaminergic afferences to the dorsal striatum associated with their behavioral implication. Dashed arrows indicate projections to the DLS, solid arrows projections to the DMS and dotted arrows projections to the central DS. Colored arrows indicate various behaviors and numbers correspond to the references cited below.
*DA depletion performed in the DMS.

Behavioral flexibility	**1.** Nakayama et al., 2018	Control reversal learning
	2. Bradfield et al., 2013	Involved in strategy-shifting learning
	3. Saund et al., 2017	Control response inhibition
	4. Kato et al., 2018	Necessary for reversal and set-shifting learning
	5*. O'Neill and Brown, 2007	DMS DA required for reversal learning
Action sequence learning	**6.** Rothwell et al., 2015	M2→DLS dMSNs preferentially involved
	7. Diaz-Hernandez et al., 2018	Pf→DMS and ThVP→DLS : action initiation ThVP→DLS : action execution
Reward/Choice selection	**8.** Parker et al., 2016	Association to choice and reward
	9. Lerner et al., 2015	Association to appetitive and aversive stimuli.
	10. Howard et al., 2017	Association to ongoing action selection
Motor skill learning	**11.** Kupferschmidt et al., 2017	Both mPFC→DMS and M1→DLS : early stages in rotarod task
Others (OCD)	**12.** Burguière et al., 2013	Involved in repetitive and compulsive behavior

Therefore, complementary experiments assessing both excitatory and inhibitory optogenetic approaches to test the sufficiency and necessity of target cells, respectively, to one given behavioral response, are rather informative and more insightful to better delineate the roles and contributions of striatal populations. Alternatively, we highlighted recent studies using multiple combinations of tracing tools and optogenetics allowing to study behavioral correlations and/or causal roles of specific inputs to the striatum. These studies contributed to highlight a sophisticated role of discrete regions and pathways in the DS notably in action sequence learning and specialized aspects of behavioral flexibility (see Fig. 1). These approaches will provide a critical gain of knowledge in the near future by integrating a specific targeting of MSNs allowing to track and retrogradely control specific inputs to each MSNs population in distinct striatal territories. Along with these discoveries, multiplying simultaneous recording/control of DLS and DMS neurons in behaving animals will also improve our understanding on how the DS operate to form and modulate action learning, habit formation and flexibility.

Other layers of complexity we could hardly developed here refer to the anatomical features of the striatum: 1) the intrastriatal circuitry involving a variety of interneurons (CINs (see Amalric's lab's paper entitled "Contribution of cholinergic interneurons to striatal pathophysiology in Parkinson's disease" in this issue), parvalbumin-positive fast-spiking GABAergic interneurons, FSIs, and somatostatin-positive low-threshold-spiking interneurons LTSIs) (Burke et al., 2017), 2) the existence of a collateral plexus formed by MSNs short-range axonal projections (Burke et al., 2017), and 3) the neurochemical organization of the striatum into striosomes (patches) and matrix. Concerning the critical influence of interneurons, a recent study performing in vivo simultaneous recordings in the motor cortex and DLS neurons in rats subjected to a sequenced lever-press task showed that MSNs and FSIs have complementary representations of the full learned action while motor cortex's neurons encode sub-components of the sequence (Martiros et al., 2018). Furthermore, FSIs in the DS were shown to exert a feed-forward inhibitory control of bursting activity on MSNs that regulates plasticity and facilitates sequence learning (Owen et al., 2018). Thus FSIs and CINs (as evoked above notably in thalamic influences to the DS) would have critical contributions but many open questions remain on their functions and mechanisms by which they regulate MSNs activity and plasticity, and how this local network would establish some sort of hierarchical control system analogous to neocortical or hippocampal interneurons that critically shape information processing. On the other part, the functional outcome of striosome and matrix compartments of the striatum remain poorly understood, although recent findings revealed distinct consequences for striatal synapse function (Brimblecombe and Cragg, 2017). However, Friedman and colleagues performed optogenetic photoinhibition of prelimbic cortex (PL) afferences to the DMS that preferentially innervate striosomes, and anterior cingulate cortex (ACC) afferences to the DMS that preferentially project to the matrix (Friedman et al., 2015). Inhibition of the predominantly striosome-targeting PL→DMS pathway favored a behavioral approach to high-cost options. In contrast, inhibition of the predominantly matrix-targeting ACC→DMS pathway induces approaches to higher benefits options, suggesting that the matrix in the DMS is involved in evaluating the benefit of the goals and may be less specific to cost-benefit integration. The authors proposed that the striosomes might influence not only ongoing value-based decision-making but also mood states and state-dependent control of motivation.

Overall the use of novel technological tools led to considerably improve our understanding of the basic rules and function of DS and its sub-compartments (see Fig. 1). Efforts should now be pushed forward to decipher the exquisite complexity of striatal functioning and information encoding in various behaviors and in relation with the complexity of sensory and higher-order cortical and thalamic inputs, the intricacies

of striatal regional components and cellular diversity, and modulatory factors originating from outside the basal ganglia loop.

Acknowledgement

PB is a Scientific Collaborator from the FRS-FNRS and was supported by the European Marie Sklodowska-Curie Actions, EPF was supported by a FRIA PhD fellowship from the FRS–FNRS and Van Buuren funds, CV is a postdoctoral fellow from the FRS–FNRS and AKE is a Research Director of the FRS–FNRS (Belgium) and an investigator of WELBIO. This study was supported by F.R.S. - FNRS (Belgium), Simone and Pierre Clerdent Foundation (Belgium).

References

Albin, R.L., Young, A.B., Penney, J.B., 1989. The functional anatomy of basal ganglia disorders. Trends Neurosci. 12, 366–375.
Alloway, K.D., Smith, J.B., Watson, G.D.R., 2014. Thalamostriatal projections from the medial posterior and parafascicular nuclei have distinct topographic and physiologic properties. J. Neurophysiol. 111, 36–50.
Amendola, J., Woodhouse, A., Goaillard, J., 2012. Ca 2+/cAMP-sensitive covariation of I_A and I_H voltage dependences tunes rebound firing in dopaminergic neurons. J. Neurosci. 32, 2166–2181.
Aoki, S., Liu, X.A.W., Zucca, A., Zucca, S., Wickens, J.R., 2015. Role of striatal cholinergic interneurons in set-shifting in the rat. J. Neurosci. 35, 9424–9431.
Assous, M., Kaminer, J., Shah, F., Garg, A., Koos, T., Tepper, J.M., 2017. Differential processing of thalamic information via distinct striatal interneuron circuits. Nat. Commun. 8, 15860.
Balleine, B.W., Liljeholm, M., Ostlund, S.B., 2009. The integrative function of the basal ganglia in instrumental conditioning. Behav. Brain Res. 199, 43–52.
Barbera, G., Liang, B., Zhang, L., Gerfen, C.R., Culurciello, E., Chen, R., Li, Y., Lin, D.T., 2016. Spatially compact neural clusters in the dorsal striatum encode locomotion relevant information. Neuron 92, 202–213.
Barense, M.D., Fox, M.T., Baxter, M.G., 2002. Aged rats are impaired on an attentional set-shifting task sensitive to medial frontal cortex damage in young rats. Learn. Mem. 9, 191–201.
Bateup, H.S., Santini, E., Shen, W., Birnbaum, S., Valjent, E., Surmeier, D.J., Fisone, G., Nestler, E.J., Greengard, P., 2010. Distinct subclasses of medium spiny neurons differentially regulate striatal motor behaviors. Proc. Natl. Acad. Sci. Unit. States Am. 107, 14845–14850.
Beckstead, R.M., Cruz, C.J., 1986. Striatal axons to the globus pallidus, entopeduncular nucleus and substantia nigra come mainly from separate cell populations in cat. Neuroscience 19, 147–158.
Bennett, B.D., Bolam, J.P., 1993. Characterization of calretinin-immunoreactive structures in striatum of the rat. Brain Res. 609, 137–148.
Bergstrom, H.C., Lipkin, A.M., Lieberman, A.G., Pinard, C.R., Gunduz-Cinar, O., Brockway, E.T., Taylor, W.W., Nonaka, M., Bukalo, O., Wills, T.A., Rubio, F.J., Li, X., Pickens, C.L., Winder, D.G., Holmes, A., 2018. Dorsolateral striatum engagement interferes with early discrimination learning. Cell Rep. 23, 2264–2272.
Bertran-Gonzalez, J., Bosch, C., Maroteaux, M., Matamales, M., Herve, D., Valjent, E., Girault, J.-A., 2008. Opposing patterns of signaling activation in dopamine D1 and D2 receptor-expressing striatal neurons in response to cocaine and haloperidol. J. Neurosci. 28, 5671–5685.
Birrell, J.M., Brown, V.J., 2000. Medial frontal cortex mediates perceptual attentional set shifting in the rat. J. Neurosci. 20, 4320–4324.
Bissonette, G.B., Martins, G.J., Franz, T.M., Elizabeth, S., Schoenbaum, G., Powell, E.M., 2008. Double dissociation of the effects of medial and orbital prefrontal cortical lesions on attentional and affective shifts in mice. J. Neurosci. 28, 11124–11130.
Bradfield, L.A., Bertran-gonzalez, J., Chieng, B., Balleine, B.W., 2013. The thalamostriatal pathway and cholinergic control of goal-directed Action : interlacing new with existing learning in the striatum. Neuron 79, 153–166.
Brigman, J.L., Bussey, T.J., Saksida, L.M., Rothblat, L.A., 2005. Discrimination of multidimensional visual stimuli by mice: intra- and extradimensional shifts. Behav. Neurosci. 119, 839–842.
Brimblecombe, K.R., Cragg, S.J., 2017. The striosome and matrix compartments of the striatum: a path through the labyrinth from neurochemistry toward function. ACS Chem. Neurosci. 8, 235–242.
Brown, H.D., Baker, P.M., Ragozzino, M.E., 2010. The parafascicular thalamic nucleus concomitantly influences behavioral flexibility and dorsomedial striatal acetylcholine output in rats. J. Neurosci. 30, 14390–14398.
Burguière, E., Monteiro, P., Feng, G., Graybiel, A.M., 2013. Optogenetic stimulation of lateral orbitofronto-striatal pathway suppresses compulsive behaviors. Science 340, 1243–1247.
Burke, D.A., Rotstein, H.G., Alvarez, V.A., 2017. Striatal local circuitry: a new framework for lateral inhibition. Neuron 96, 267–284.
Butcher, L.L., Hodge, G.K., 1976. Postnatal development of acetylcholinesterase in the caudate-putamen nucleus and substantia nigra of rats. Brain Res. 106, 223–240.
Castañé, A.A., Theobald, D.E.H., Robbins, T.W., 2010. Selective lesions of the dorsomedial striatum impair serial spatial reversal learning in rats. Behav. Brain Res. 210, 74–83.
Chang, H.T., Wilson, C.J., Kitai, S.T., 1981. Single neostriatal efferent axons in the globus pallidus: a light and electron microscopic study. Science 213, 915–918.
Chang, H.T., Wilson, C.J., Kitai, S.T., 1982. A Golgi study of rat neostriatal neurons: light microscopic analysis. J. Comp. Neurol. 208, 107–126.
Chudasama, Y., Robbins, T.W., 2003. Dissociable contributions of the orbitofrontal and infralimbic cortex to pavlovian autoshaping and discrimination reversal Learning : further evidence for the functional heterogeneity of the rodent frontal cortex. J. Neurosci. 23, 8771–8780.
Chuhma, N., Mingote, S., Yetnikoff, L., Kalmbach, A., Ma, T., Ztaou, S., Sienna, A., Tepler, S., Poulin, J., Ansorge, M., Awatramani, R., Kang, U.J., Rayport, S., 2018. Dopamine neuron glutamate cotransmission evokes a delayed excitation in lateral dorsal striatal cholinergic interneurons. eLife 7, e39786.
Clark, L., Chamberlain, S.R., Sahakian, B.J., 2009. Neurocognitive mechanisms in depression: implications for treatment. Annu. Rev. Neurosci. 32, 57–74.
Clarke, H.F., Hill, G.J., Robbins, T.W., Roberts, A.C., 2011. Dopamine, but not serotonin, regulates reversal learning in the marmoset caudate nucleus. J. Neurosci. 31, 4290–4297.
Collins, P., Wilkinson, L.S., Everitt, B.J., Robbins, T.W., Roberts, A.C., 2000. The effect of dopamine depletion from the caudate nucleus of the common marmoset (Callithrix jacchus) on tests of prefrontal cognitive function. Behav. Neurosci. 114, 3–17.
Cools, R., 2001. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cerebr. Cortex 11, 1136–1143.
Cools, R., D'Esposito, M., 2011. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol. Psychiatry 69, 113–125.
Crofts, H.S., Dalley, J.W., Collins, P., Van Denderen, J.C., Everitt, B.J., Robbins, T.W., Roberts, A.C., 2001. Differential effects of 6-OHDA lesions of the frontal cortex and caudate nucleus on the ability to acquire an attentional set. Cerebr. Cortex 11, 1015–1026.
Cui, G., Jun, S.B., Jin, X., Pham, M.D., Vogel, S.S., Lovinger, D.M., Costa, R.M., 2013. Concurrent activation of striatal direct and indirect pathways during action initiation. Nature 494, 238–242.
Da Cunha, C., Boschen, S.L., Gómez, -A.A., Ross, E.K., Gibson, W.S.J., Min, H.K., Lee, K.H., Blaha, C.D., 2015. Toward sophisticated basal ganglia neuromodulation: review on basal ganglia deep brain stimulation. Neurosci. Biobehav. Rev. 58, 186–210.
Daberkow, D.P., Brown, H.D., Bunner, K.D., Kraniotis, S.A., Doellman, M.A., Ragozzino, M.E., Garris, P.A., Roitman, M.F., 2013. Amphetamine paradoxically augments exocytotic dopamine release and phasic dopamine signals. J. Neurosci. 33, 452–463.
Darvas, M., Palmiter, R.D., 2011. Contribution of striatal dopamine signaling to the modulation of Cognitive Flexibility. Biol. Psychiatry 69, 704–707.
DeLong, M.R., 1990. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 13, 281–285.
Dias, R., Robbins, T.W., Roberts, A.C., 1996. Dissociation in prefrontal cortex of affective and attentional shifts. Nature 380, 69–72.
Dias, R., Robbins, T.W., Roberts, A.C., 1997. Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin card sort test: restriction to novel situations and independence from “On-Line” processing. J. Neurosci. 17, 9285–9297.
Diaz-Hernandez, E., Contreras-Lopez, R., Sanchez-Fuentes, A., Ramirez-Jarquin, J., Tecuapetla, F., 2018. The thalamostriatal projections contribute to the initiation and execution of a sequence of movements. Neuron 100, 739–752.
Dickinson, A., 1981. Conditioning and associative learning. Br. Med. Bull. 37, 165–168.
Ding, J.B., Guzman, J.N., Peterson, J.D., Goldberg, J.A., Surmeier, D.J., 2010. Article thalamic gating of corticostriatal signaling by cholinergic interneurons. Neuron 67, 294–307.
Doig, N.M., Moss, J., Bolam, J.P., 2010. Cortical and thalamic innervation of direct and indirect pathway medium-sized spiny neurons in mouse striatum. J. Neurosci. 30, 14610–14618.
Durieux, P.F., Bearzatto, B., Guiducci, S., Buch, T., Waisman, A., Zoli, M., Schiffmann, S.N., de Kerchove d'Exaerde, A., 2009. D2R striatopallidal neurons inhibit both locomotor and drug reward processes. Nat. Neurosci. 12, 393–395.
Durieux, P.F., Schiffmann, S.N., d'Exaerde, A. de K., 2011. Targeting neuronal populations of the striatum. Front. Neuroanat. 5, 40.
Durieux, P.F., Schiffmann, S.N., de Kerchove d'Exaerde, A., 2012. Differential regulation of motor control and response to dopaminergic drugs by D1R and D2R neurons in distinct dorsal striatum subregions. EMBO J. 31, 640–653.
Erro, M.E., Lanciego, J.L., Arribas, J., Gimenez-Amaya, J.M., 2001. Striatal input from the ventrobasal complex of the rat thalamus. Histochem. Cell Biol. 115, 447–454.
Eslinger, P.J., Grattan, L.M., 1993. Frontal lobe and frontal-striatal substrates for different forms of human cognitive flexibility. Neuropsychologia 31, 17–28.
Fillmore, M.T., Rush, C.R., 2006. Polydrug abusers display impaired discrimination-reversal learning in a model of behavioural control. J. Psychopharmacol. 20, 24–32.
Floresco, S.B., Ghods-Sharifi, S., Vexelman, C., Magyar, O., 2006. Dissociable roles for the nucleus Accumbens core and Shell in regulating set shifting. J. Neurosci. 26, 2449–2457.
Floresco, S.B., Block, A.E., Tse, M.T.L., 2008. Inactivation of the medial prefrontal cortex of the rat impairs strategy set-shifting, but not reversal learning, using a novel, automated procedure. Behav. Brain Res. 190, 85–96.
Friedman, A., Homma, D., Gibb, L.G., Graybiel, A.M., Friedman, A., Homma, D., Gibb, L.G., Amemori, K., Rubin, S.J., Hood, A.S., Riad, M.H., Graybiel, A.M., 2015. A corticostriatal path targeting striosomes controls decision-making under conflict article a corticostriatal path targeting striosomes controls decision-making under conflict. Cell 161, 1320–1333.
Geddes, C.E., Li, H., Jin, X., 2018. Optogenetic editing reveals the hierarchical organization of learned action sequences. Cell 174, 32–43.
Gerfen, C.R., Surmeier, D.J., 2011. Modulation of striatal projection systems by dopamine. Annu. Rev. Neurosci. 34, 441–466.

Gerfen, C.R., Baimbridge, K.G., Miller, J.J., 1985. The neostriatal mosaic: compartmental distribution of calcium-binding protein and parvalbumin in the basal gangia and monkey. Proc. Natl. Acad. Sci. Unit. States Am. 82, 8780–8784.
Gerfen, C.R., Engber, T.M., Mahan, L.C., Susel, Z., Chase, T.N., Monsma, F.J., Sibley, D.R., 1990. D_1 and D_2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 250, 1429–1432.
Ghods-Sharifi, S., Haluk, D.M., Floresco, S.B., 2008. Differential effects of inactivation of the orbitofrontal cortex on strategy set-shifting and reversal learning. Neurobiol. Learn. Mem. 89, 567–573.
Gong, S., Zheng, C., Doughty, M.L., Losos, K., Didkovsky, N., Schambra, U.B., Nowak, N.J., Joyner, A., Leblanc, G., Hatten, M.E., Heintz, N., 2003. A gene expression atlas of the central nervous system based on bacterial artificial chromosomes. Nature 425, 917–925.
Gong, S., Doughty, M., Harbaugh, C.R., Cummins, A., Hatten, M.E., Heintz, N., Gerfen, C.R., 2007. Targeting cre recombinase to specific neuron populations with bacterial artificial chromosome constructs. J. Neurosci. 27, 9817–9823.
Graybiel, A.M., 1998. The basal ganglia and chunking of action repertoires. Neurobiol. Learn. Mem. 119–136.
Graybiel, A.M., 2008. Habits, rituals, and the evaluative brain. Annu. Rev. Neurosci. 31, 359–387.
Groenewegen, H.J., Berendse, H.W., 1994. The specificity of the “nonspecific” midline and intralaminar thalamic nuclei. Trends Neurosci. 17, 52–57.
Guo, Q., Wang, D., He, X., Feng, Q., Lin, R., Xu, F., 2015. Whole-brain mapping of inputs to projection neurons and cholinergic interneurons in the dorsal striatum. PLoS One 10, e0123381.
Henny, P., Brown, M.T., Northrop, A., Faunes, M., Ungless, M.A., Magill, P.J., Bolam, J.P., 2012. Structural correlates of heterogeneous in vivo activity of midbrain dopaminergic neurons. Nat. Neurosci. 15, 613–619.
Hikosaka, O., Takikawa, Y., Kawagoe, R., 2000. Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol. Rev. 80, 953–978.
Hilario, M., Holloway, T., Jin, X., Costa, R.M., 2012. Different dorsal striatum circuits mediate action discrimination and action generalization. Eur. J. Neurosci. 35, 1105–1114.
Hintiryan, H., Foster, N.N., Bowman, I., Bay, M., Song, M.Y., Gou, L., Yamashita, S., Bienkowski, M.S., Zingg, B., Zhu, M., Yang, X.W., Shih, J.C., Toga, A.W., Dong, H.W., 2016. The mouse cortico-striatal projectome. Nat. Neurosci. 19, 1100–1114.
Hooks, B.M., Papale, A.E., Paletzki, R.F., Feroze, M.W., Eastwood, B.S., Couey, J.J., Winnubst, J., Chandrashekar, J., Gerfen, C.R., 2018. Topographic precision in sensory and motor corticostriatal projections varies across cell type and cortical area. Nat. Commun. 9, 3549.
Howard, C.D., Li, H., Geddes, C.E., Jin, X., 2017. Dynamic nigrostriatal dopamine biases action selection. Neuron 93, 1436–1450.
Hughes, L.E., Altena, E., Barker, R.A., Rowe, J.B., 2013. Perseveration and choice in Parkinson ’ s Disease : the impact of progressive frontostriatal dysfunction on action decisions. Cerebr. Cortex 23, 1572–1581.
Idris, N.F., Repeto, P., Neill, J.C., Large, C.H., 2005. Investigation of the effects of lamotrigine and clozapine in improving reversal-learning impairments induced by acute phencyclidine and D-amphetamine in the rat. Psychopharmacology (Berl) 179, 336–348.
Isomura, Y., Takekawa, T., Harukuni, R., Handa, T., Aizawa, H., Takada, M., Fukai, T., 2013. Reward-modulated motor information in identified striatum neurons. J. Neurosci. 33, 10209–10220.
Iversen, S.D., Mishkin, M., 1970. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. Exp. Brain Res. 11, 376–386.
Jin, X., Costa, R.M., 2010. Start/stop signals emerge in nigrostriatal circuits during sequence learning. Nature 466, 457–462.
Jin, X., Costa, R.M., 2015. Shaping action sequences in basal ganglia circuits. Curr. Opin. Neurobiol. 33, 188–196.
Jin, X., Tecuapetla, F., Costa, R.M., 2014. Basal ganglia subcircuits distinctively encode the parsing and concatenation of action sequences. Nat. Neurosci. 17, 423–430.
Jinno, S., Kosaka, T., 2004. Parvalbumin is expressed in glutamatergic and GABAergic corticostriatal pathway in mice. J. Comp. Neurol. 477, 188–201.
Kato, S., Fukabori, R., Nishizawa, K., Okada, K., Yoshioka, N., Sugawara, M., Maejima, Y., Shimomura, K., Okamoto, M., Eifuku, S., Kobayashi, K., 2018. Action selection and flexible switching controlled by the intralaminar thalamic neurons. Cell Rep. 22, 2455–2468.
Kawaguchi, Y., 1993. Physiological, morphological, and histochemical characterization of three classes of interneurons in rat neostriatum. J. Neurosci. 13, 4908–4923.
Kawaguchi, Y., Wilson, C.J., Emson, P.C., 1990. Projection subtypes of rat neostriatal matrix cells revealed by intracellular injection of biocytin. J. Neurosci. 10, 3421–3438.
Keiflin, R., Janak, P.H., 2015. Dopamine prediction errors in reward learning and addiction: from theory to neural circuitry. Neuron 88, 247–263.
Kirkby, R.J., 1969. Caudate nucleus lesions and perseverative behavior. Physiol. Behav. 4, 451–454.
Klaus, A., Martins, G.J., Paixao, V.B., Zhou, P., Paninski, L., Costa, R.M., 2017. The spatiotemporal organization of the striatum encodes action space. Neuron 95, 1171–1180.
Kolb, B., 1977. Studies on the caudate-putamen and the dorsomedial thalamic nucleus of the rat: implications for mammalian frontal-lobe functions. Physiol. Behav. 18, 237–244.
Kravitz, A.V., Freeze, B.S., Parker, P.R.L., Kay, K., Thwin, M.T., Deisseroth, K., Kreitzer, A.C., 2010. Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature 466, 622–626.
Kress, G.J., Yamawaki, N., Wokosin, D.L., Wickersham, I.R., Shepherd, G.M.G., Surmeier, D.J., 2013. Convergent cortical innervation of striatal projection neurons. Nat. Neurosci. 16, 665–667.
Kupferschmidt, D.A., Juczewski, K., Cui, G., Johnson, K.A., Lovinger, D.M., 2017. Parallel , but dissociable , processing in discrete corticostriatal inputs encodes skill learning parallel , but dissociable , processing in discrete corticostriatal inputs encodes skill learning. Neuron 96, 476–489.
Lacey, C.J., Bolam, J.P., Magill, P.J., 2007. Novel and distinct operational principles of intralaminar thalamic neurons and their striatal projections. J. Neurosci. 27, 4374–4384.
Lambot, L., Chaves Rodriguez, E., Houtteman, D., Li, Y., Schiffmann, S.N., Gall, D., de Kerchove d'Exaerde, A., 2016. Striatopallidal neuron NMDA receptors control synaptic connectivity, locomotor, and goal-directed behaviors. J. Neurosci. 36, 4976–4992.
Lammel, S., Lim, B.K., Malenka, R.C., 2014. Neuropharmacology Reward and aversion in a heterogeneous midbrain dopamine system. Neuropharmacology 76, 351–359.
Lanciego, L., Luquin, N., Obeso, A., Lanciego, J.L., Luquin, N., Obeso, J.A., 2012. Functional neuroanatomy of the basal ganglia. Cold Spring Harb. Perspect Med. 2, a009621.
Lange, F., Seer, C., Kopp, B., 2017. Cognitive flexibility in neurological disorders : cognitive components and event-related potentials. Neurosci. Biobehav. Rev. 83, 496–507.
Laurent, M., De Backer, J.-F., Rial, D., Schiffmann, S.N., de Kerchove d'Exaerde, A., 2017. Bidirectional control of reversal in a dual action task by direct and indirect pathway activation in the dorsolateral striatum in mice. Front. Behav. Neurosci. 11, 256.
Lawrence, A.D., Sahakian, B.J., Rogers, R.D., Hodges, J.R., Robbins, T.W., 1999. Discrimination, reversal, and shift learning in Huntington's disease: mechanisms of impaired response selection. Neuropsychologia 37, 1359–1374.
Lee, A.T., Vogt, D., Rubenstein, J.L., Sohal, V.S., 2014. A class of GABAergic neurons in the prefrontal cortex sends long-range projections to the nucleus Accumbens and elicits acute avoidance behavior. J. Neurosci. 34, 11519–11525.
Lei, W., Jiao, Y., Del Mar, N., Reiner, A., 2004. Evidence for differential cortical input to direct pathway versus indirect pathway striatal projection neurons in rats. J. Neurosci. 24, 8289–8299.
Lerner, T.N., Shilyansky, C., Davidson, T.J., Evans, K.E., Beier, K.T., Zalocusky, K.A., Crow, A.K., Malenka, R.C., Luo, L., Tomer, R., Deisseroth, K., 2015. Intact-brain analyses reveal distinct information carried by SNc dopamine subcircuits article intact-brain analyses reveal distinct information carried by SNc dopamine subcircuits. Cell 162, 635–647.
Markowitz, J.E., Gillis, W.F., Beron, C.C., Neufeld, S.Q., Robertson, K., Bhagat, N.D., Peterson, R.E., Peterson, E., Hyun, M., Linderman, S.W., Sabatini, B.L., Datta, S.R., 2018. The striatum organizes 3D behavior via moment-to-moment action selection. Cell 174, 44–58.
Martiros, N., Burgess, A.A., Graybiel, A.M., 2018. Inversely active striatal projection neurons and interneurons selectively delimit useful behavioral sequences. Curr. Biol. 28, 560–573.
Marton, T., Seifikar, H., Luongo, F.J., Lee, A.T., Sohal, V.S., 2018. Roles of prefrontal cortex and mediodorsal thalamus in task engagement and behavioral flexibility. J. Neurosci. 38, 2569–2578.
Matamales, M., Bertran-Gonzalez, J., Salomon, L., Degos, B., Deniau, J.M., Valjent, E., Hervé, D., Girault, J.A., 2009. Striatal medium-sized spiny neurons: identification by nuclear staining and study of neuronal subpopulations in BAC transgenic mice. PLoS One 4, e4770.
McAlonan, K., Brown, V.J., 2003. Orbital prefrontal cortex mediates reversal learning and not attentional set shifting in the rat. Behav. Brain Res. 146, 97–103.
McLean, A., Dowson, J., Toone, B., Young, S., Bazanis, E., Robbins, T.W., Sahakian, B.J., 2004. Characteristic neurocognitive profile associated with adult attention-deficit/hyperactivity disorder. Psychol. Med. 34, 681–692.
Melzer, S., Gil, M., Koser, D.E., Michael, M., Huang, K.W., 2017. Distinct corticostriatal GABAergic neurons modulate striatal output neurons and motor activity article distinct corticostriatal GABAergic neurons modulate striatal output neurons and motor activity. Cell Rep. 19, 1045–1055.
Mink, J.W., 2003. The basal ganglia and involuntary movements: impaired inhibition of competing motor patterns. Arch. Neurol. 60, 1365–1368.
Monchi, O., Petrides, M., Petre, V., Worsley, K.J., Dagher, A., 2001. Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. J. Neurosci. 21, 7733–7741.
Morales, M., Margolis, E.B., 2017. Ventral tegmental area: cellular heterogeneity, connectivity and behaviour. Nat. Rev. Neurosci. 18, 73–85.
Morita, K., 2014. Differential cortical activation of the striatal direct and indirect pathway cells : reconciling the anatomical and optogenetic results by using a computational method. J. Neurophysiol. 112, 120–146.
Murray, G.K., Cheng, F., Clark, L., Barnett, J.H., Blackwell, A.D., Fletcher, P.C., Robbins, T.W., Bullmore, E.T., Jones, P.B., 2008. Reinforcement and reversal learning in first-episode psychosis. Schizophr. Bull. 34, 848–855.
Nakayama, H., Ibanez-Tallon, I., Heintz, N., 2018. Cell-type-specific contributions of medial prefrontal neurons to flexible behaviors. J. Neurosci. 38, 4490–4504.
Nelson, A.B., Kreitzer, A.C., 2014. Reassessing models of basal ganglia function and dysfunction. Annu. Rev. Neurosci. 37, 117–135.
Neuhoff, H., Neu, A., Liss, B., Roeper, J., 2002. I h channels contribute to the different functional properties of identified dopaminergic subpopulations in the midbrain. J. Neurosci. 22, 1290–1302.
O'Hare, J.K., Ade, K.K., Sukharnikova, T., Van Hooser, S.D., Palmeri, M.L., Yin, H.H., Calakos, N., 2016. Pathway-specific striatal substrates for habitual behavior. Neuron 89, 472–479.
O'Neill, M., Brown, V.J., 2007. The effect of striatal dopamine depletion and the adenosine A2Aantagonist KW-6002 on reversal learning in rats. Neurobiol. Learn. Mem.

88, 75–81.
Oldenburg, I.A., Sabatini, B.L., 2015. Antagonistic but not symmetric regulation of primary motor cortex by basal ganglia direct and indirect pathways. Neuron 86, 1174–1181.
Ostlund, S.B., Winterbauer, N.E., Balleine, B.W., 2009. Evidence of action sequence chunking in goal-directed dorsomedial prefrontal cortex. J. Neurosci. 29, 8280–8287.
Owen, A., James, M., Leigh, P., Summers, B., Marsden, C., Quinn, N., Lange, K., Robbins, T., 1992. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 115, 1727–1751.
Owen, S.F., Berke, J.D., Kreitzer, A.C., 2018. Fast-spiking interneurons supply feedforward control of bursting, calcium, and plasticity for efficient learning. Cell 172, 683–695.
Parikh, V., Naughton, S.X., Yegla, B., Guzman, D.M., 2016. Impact of partial dopamine depletion on cognitive flexibility in BDNF heterozygous mice. Psychopharmacology (Berl) 233, 1361–1375.
Parker, P.R.L., Lalive, A.L., Kreitzer, A.C., Parker, P.R.L., Lalive, A.L., Kreitzer, A.C., 2016. Pathway-specific remodeling of thalamostriatal synapses in parkinsonian mice. Neuron 89, 734–740.
Pisa, M., Cyr, J., 1990. Regionally selective roles of the rat's striatum in modality-specific discrimination learning and forelimb reaching. Behav. Brain Res. 37, 281–292.
Ragozzino, M.E., 2007. The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. Ann. N. Y. Acad. Sci. 1121, 355–375.
Ragozzino, M.E., Jih, J., Tzavos, A., 2002a. Involvement of the dorsomedial striatum in behavioral flexibility: role of muscarinic cholinergic receptors. Brain Res. 953, 205–214.
Ragozzino, M.E., Ragozzino, K.E., Mizumori, S.J.Y., Kesner, R.P., 2002b. Role of the dorsomedial striatum in behavioral flexibility for response and visual cue discrimination learning. Behav. Neurosci. 116, 105–115.
Raju, D.V., Shah, D.J., Wright, T.M., Hall, R.A., Smith, Y., 2006. Differential synaptology of vGluT2-containing thalamostriatal afferents between the patch and matrix compartments in rats. J. Comp. Neurol. 499, 231–243.
Reig, R., Silberberg, G., 2014. Multisensory integration in the mouse striatum. Neuron 83, 1200–1212.
Reiner, A., Deng, Y., 2016. Organization of corticostriatal projection neuron types. In: Handbook of Behavioral Neuroscience, pp. 405–422.
Reiner, A., Hart, N.M., Lei, W., Deng, Y., Galarraga, E., Nacional, U., 2010. Corticostriatal projection neurons – dichotomous types and dichotomous functions. Front. Neuroanat. 4, 142.
Roberts, A.C., Robbins, T.W., Everitt, B.J., 1988. The effects of intradimensional and extradimensional shifts on visual discrimination learning in humans and non-human primates. J. Exp. Psychol. Sect. B 40, 321–341.
Roberts, A.C., Salvia, M De, Wilkinson, L.S., Collins, P., Muir, J.L., Everitt, B.J., Robbins, T.W., 1994. 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin Card Sort Test: possible interactions with subcortical dopamine. J. Neurosci. 14, 2531–2544.
Rock, C., Zurita, H., Wilson, C., Apicella, A., 2016. An inhibitory corticostriatal pathway. eLife 9, e15890.
Rogers, R.D., Robbins, T.W., 2001. Investigating the neurocognitive deficits associated with chronic drug misuse. Curr. Opin. Neurobiol. 11, 250–257.
Rothwell, P.E., Hayton, S.J., Sun, G.L., Fuccillo, M.V., Lim, B.K., Malenka, R.C., 2015. Input- and output-specific regulation of serial order performance by corticostriatal circuits. Neuron 88, 345–356.
Rueda-Orozco, P.E., Robbe, D., 2015. The striatum multiplexes contextual and kinematic information to constrain motor habits execution. Nat. Neurosci. 18, 453–462.
Sales-Carbonell, C., Taouali, W., Khalki, L., Pasquet, M.O., Petit, L.F., Moreau, T., Rueda-Orozco, P.E., Robbe, D., 2018. No discrete start/stop signals in the dorsal striatum of mice performing a learned action. Curr. Biol. 28, 3044–3055.
Saund, J., Dautan, D., Rostron, C., Urcelay, G.P., Gerdjikov, T.V., 2017. Thalamic inputs to dorsomedial striatum are involved in inhibitory control: evidence from the five-choice serial reaction time task in rats. Psychopharmacology (Berl) 234, 2399–2407.
Schiffmann, S.N., Jacobs, O., Vanderhaeghen, J.J., 1991. Striatal restricted adenosine A2 receptor (RDC8) is expressed by enkephalin but not by substance P neurons: an in situ hybridization histochemistry study. J. Neurochem. 57, 1062–1067.
Shell, J., Beaulieu, L., Pothier, B., Dobson, K., Drapeau, M., 2018. Is flexibility always associated with mental health? A study of coping and depression. Arch. Psychiatr. Psychother. 20, 7–11.
Silberberg, G., Bolam, J.P., 2015. Local and afferent synaptic pathways in the striatal microcircuitry. Curr. Opin. Neurobiol. 33, 182–187.
Simpson, E.H., Kellendonk, C., Kandel, E., 2010. A possible role for the striatum in the pathogenesis of the cognitive symptoms of schizophrenia. Neuron 65, 585–596.
Sippy, T., Lapray, D., Crochet, S., Petersen, C.C.H., 2015. Cell-type-specific sensorimotor processing in striatal projection neurons during goal-directed behavior. Neuron 88, 298–305.
Smith, Y., Raju, D.V., Pare, J., Sidibe, M., 2004. The thalamostriatal system : a highly specific network of the basal ganglia circuitry. Trends Neurosci. 27, 520–527.
Stefani, M.R., Groth, K., Moghaddam, B., 2003. Glutamate receptors in the rat medial prefrontal cortex regulate set-shifting ability. Behav. Neurosci. 117, 728–737.
Swainson, R., Rogers, R.D., Sahakian, B.J., Summers, B.A., Polkey, C.E., Robbins, T.W., 2000. Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. Neuropsychologia 38, 596–612.
Tecuapetla, F., Jin, X., Lima, S.Q., Costa, R.M., 2016. Complementary contributions of striatal projection pathways to action initiation and execution. Cell 166, 703–715.
Thorn, C.A., Atallah, H., Howe, M., Graybiel, A.M., 2010. Differential dynamics of activity changes in dorsolateral and dorsomedial striatal loops during learning. Neuron 66, 781–795.
Tritsch, N.X., Sabatini, B.L., 2012. Dopaminergic modulation of synaptic transmission in cortex and striatum. Neuron 76, 33–50.
Van der Werf, Y.D., Witter, M.P., Groenewegen, H.J., 2002. The intralaminar and midline nuclei of the thalamus . Anatomical and functional evidence for participation in processes of arousal and awareness. Brain Res. Rev. 39, 107–140.
Vogt Weisenhorn, D.M., Giesert, F., Wurst, W., 2016. Diversity matters – heterogeneity of dopaminergic neurons in the ventral mesencephalon and its relation to Parkinson's Disease. J. Neurochem. 139, 8–26.
Wall, N.R., DeLaParra, M., Callaway, E.M., Kreitzer, A.C., 2013. Differential innervation of direct- and indirect-pathway striatal projection neurons. Neuron 79, 347–360.
Waltz, J.A., Gold, J.M., 2007. Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. Schizophr. Res. 93, 296–303.
Wise, S.P., Murray, E.A., Gerfen, C.R., 1996. The frontal cortex-basal ganglia system in primates. Crit. Rev. Neurobiol. 10, 317–356.
Wolfart, J., Neuhoff, H., Franz, O., Roeper, J., 2001. Differential expression of the small-conductance , calcium- activated potassium channel SK3 is critical for pacemaker control in dopaminergic midbrain neurons. J. Neurosci. 21, 3443–3456.
Yin, H.H., 2010. The sensorimotor striatum is necessary for serial order learning. J. Neurosci. 30, 14719–14723.
Yin, H.H., Knowlton, B.J., 2006. The role of the basal ganglia in habit formation. Nat. Rev. Neurosci. 7, 464–476.
Yin, H.H., Knowlton, B.J., Balleine, B.W., 2004. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. Eur. J. Neurosci. 19, 181–189.
Yin, H.H., Mulcare, S.P., Hilário, M.R.F., Clouse, E., Holloway, T., Davis, M.I., Hansson, A.C., Lovinger, D.M., Costa, R.M., 2009. Dynamic reorganization of striatal circuits during the acquisition and consolidation of a skill. Nat. Neurosci. 12, 333–341.
Yttri, E.A., Dudman, J.T., 2016. Opponent and bidirectional control of movement velocity in the basal ganglia. Nature 533, 402–406.