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Investigating Striatal Function through Cell-Type-Specific Manipulations

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Abstract

The striatum integrates convergent input from the cortex, thalamus, and midbrain, and has a powerful influence over motivated behavior via outputs to downstream basal ganglia nuclei. Although the anatomy and physiology of distinct classes of striatal neurons has been intensively studied, the specific functions of these cell subpopulations have been more difficult to address. Recently, application of new methodologies for perturbing activity and signaling in different cell types *in vivo* has begun to allow direct tests of the causal roles of striatal neurons in behavior.

Keywords

Striatum; BAC transgenic; Optogenetics; Medium Spiny Neuron; Cholinergic Interneuron; Fast-Spiking Interneuron

Introduction

The basal ganglia (BG) are a highly conserved, and thus presumably critical, feature of vertebrate brain organization (Reiner et al., 1998). The striatum is the largest component of the BG, and striatal function has been of great interest since the discovery that prominent movement disorders such as Parkinson's disease (PD) and Huntington's disease (HD) involve striatal deficits. Yet the function of the striatum and the BG in general remain a contentious issue.

In the widely-cited standard model, the BG are central to action selection: the context-dependent facilitation of appropriate movements (or action sequences) and suppression of alternatives (Albin et al., 1989, Mink, 1996, Redgrave et al., 1999). According to this line of thinking, the BG play a fundamental role in decision-making and ongoing motor performance, with adaptive learning occurring as long-term changes in synaptic strength in the striatum or other BG nuclei. Support comes from the robust motor impairments caused by striatal disorders (including PD and HD), as well as studies showing that focal striatal

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inactivation can disrupt highly-trained choice behavior (e.g. (Packard and McGaugh, 1996, Atallah et al., 2007, Gage et al., 2010).

At the other extreme, the BG are thought to have no role in making choices. Instead, they help to train *other* circuits to perform action selection, and also have a role in appropriately assigning effort (“vigor”) to actions selected by those other circuits (Shadmehr and Krakauer, 2008, Turner and Desmurget, 2010). Supporting this scheme are findings that damage to BG output nuclei do not have a major impact on many aspects of motor coordination and performance, except to cause movements that are slower and too small (Desmurget and Turner, 2008, 2010). BG damage is known to cause specific implicit learning deficits across a wide range of species, from songbirds to humans (Brainard and Doupe, 2000, Obeso et al., 2009).

A major goal of current and future research is to rigorously test these broad competing hypotheses, as well as more specific aspects of BG models. In particular, the standard BG framework (Albin et al., 1989, DeLong, 1990, Gerfen, 1992) is largely built around two key features of striatal organization: 1) that the “direct” (striatonigral) and “indirect” (striatopallidal) outputs from striatum serves to facilitate (Go) and suppress (NoGo) motor output respectively, and 2) that dopamine acts to excite direct pathway striatal neurons (via D1 receptors) and inhibit indirect pathway neurons (via D2 receptors). Both of these statements are known to be considerable simplifications, which nonetheless account for many, but not all observations (Boraud et al., 2002).

While striatal function has been studied using traditional methods such as lesions, pharmacological manipulations, or electrophysiological recordings of unidentified cell types, the roles of specific striatal cell types has been more difficult to discern. Instead, their role in normal and pathological behavior has been deduced indirectly from changes in cell morphology, gene expression, or targeted lesions of downstream structures. While such methods have yielded important insights, precisely perturbing specific types of neurons in behaving animals has been an important, challenging goal. Pharmacological methods represent the most common strategy for accomplishing this aim, and have the advantage of being relatively transient and reversible. However, receptor expression is typically not restricted to single cell types, and drugs themselves are rarely specific to one type of receptor, particularly at the doses required to ensure adequate tissue penetration. Additionally, even if a receptor is expressed by just a single cell type, it can be expressed both pre- and postsynaptically in the same structure (e.g. postsynaptically on dendrites, and presynaptically in local axon collaterals). Genetic methods can provide a more focused alternative for achieving cell-type specific manipulations. Genetically-specified expression of toxins or toxin receptors, modified neurotransmitter receptors, or optogenetic proteins all provide an effective means for manipulating neuronal function. Among these, optogenetic approaches offer particular advantages, in that they enable rapid and reversible control of spiking on the millisecond timescale, but can also present pitfalls to be avoided. Here, we review studies that have successfully applied genetic targeting methods to understand the function of specific striatal cell types in behavior.

Organization of striatal circuits

Different striatal subregions receive inputs from distinct cortical areas, and correspondingly participate in distinct aspects of behavioral control. Very roughly, putamen in primates (dorsal/lateral/posterior striatum in rodents) is a component of “sensorimotor” circuits, caudate (dorsal/medial striatum in rodents) participates in “associative” circuits, and nucleus accumbens (NAc core and shell; ventral/anterior striatum) is part of “limbic” circuitry (McGeorge and Faull, 1989, Brog et al., 1993). Nonetheless in most respects striatal

architecture appears relatively homogeneous, suggesting that there is a core striatal computation that can operate on various forms of information.

The vast majority of neurons (>95%) throughout the striatum are GABAergic medium spiny projection neurons (MSNs). About half of these are direct-pathway MSNs that express dopamine D1 receptors, substance P and dynorphin, and project to basal ganglia output nuclei (D1 MSNs). The others are indirect-pathway MSNs that express D2 receptors and enkephalin, and project to the lateral globus pallidus (D2 MSNs) (Beckstead, 1988, Gerfen et al., 1990, Gerfen, 1992, Smith et al., 1998, Bertran-Gonzalez et al., 2010). Observations in mice expressing fluorescent proteins under control of specific promoters indicate that D1 vs D2 segregation is virtually complete (Matamales et al., 2009). The main exception is in the NAc shell, where ~17% of MSNs coexpress both D1 and D2 receptors (Bertran-Gonzalez et al., 2008), that can form heteromers with potentially unique properties (Perreault et al., 2011). Intermingled among the MSNs are several rarer subpopulations, including large aspiny cholinergic interneurons (1–2% of neurons), GABAergic parvalbumin-positive fast-spiking interneurons (FSIs; ~1%) (Luk and Sadikot, 2001) and GABAergic somatostatin- and NPY-positive low-threshold spiking interneurons ~1%; (Rymar et al., 2004). MSNs have been a major focus of research because they are numerous and form the sole output of the striatum. Striatal output from both direct and indirect pathways is integrated in basal ganglia output nuclei, with some functional evidence for convergence of both pathways onto the same population of neurons (Nambu et al., 2000, Kolomiets et al., 2003, Beurrier et al., 2006).

Interneurons have received less attention because they represent only a small fraction of neurons and are therefore much harder to study. Nevertheless, they are thought to have critical roles organizing striatal output (Gage et al., 2010, Berke, 2011), and have steadily gained prominence. Finally, another likely-critical feature of striatal organization is the division between focal zones called patches or striosomes (that stain intensely for μ -opioid receptors, and receive more limbic inputs) and the surrounding matrix (that stains intensely for acetylcholinesterase; (Graybiel and Ragsdale, 1978). These distinct compartments have long been hypothesized to have distinct roles in motor control (Canales and Graybiel, 2000) though such ideas have so far proven difficult to test.

Manipulations of striatal projection neurons

In normal animals D1 MSNs and D2 MSNs are difficult to distinguish. In brain slices, they have a similar appearance under the light microscope. In vivo, MSNs have generally similar waveforms, and are typically quiescent outside of a specific combination of context, cues and action (Hollerman et al., 2000). The development and application of BAC transgenic mice has been instrumental in distinguishing these subtypes, using either D1 or M4 lines to identify direct pathway MSNs, and D2 or A2A lines to identify indirect pathway MSNs (Gong et al., 2003, Gong et al., 2007). Experiments based on these lines have revealed that D1 and D2 MSNs actually exhibit significant differences in dendritic morphology (Gertler et al., 2008), excitability (Kreitzer and Malenka, 2007, Gertler et al., 2008), gene expression (Lobo et al., 2006, Heiman et al., 2008), response to local GABAergic input (Flores-Barrera et al., 2010), and mechanisms of plasticity (Kreitzer and Malenka, 2007, Shen et al., 2008). Together, these distinct properties are thought to endow each subtype with unique functions within the BG network. In the classical Albin-DeLong model, D1 and D2 MSNs have opposing influences over behavior because the direct and indirect pathways reconverge to provide opposite regulation of BG output nuclei, which normally inhibit thalamocortical circuits. The overall notion that D1 MSNs promote while D2 MSNs restrain behavior has been a major focus of studies that manipulate these cell populations, both because of the

centrality of this idea to the classical model and because gross changes in behavioral activity are relatively easy to assess.

Some of the first relevant genetic manipulations were dopamine receptor knockouts. Mice lacking D2 receptors display reduced spontaneous activity, and slowness in behavioral tests resembling PD (Baik et al., 1995), consistent with the classical model simplification that D2 receptor activation normally acts to inhibit MSNs of the indirect “NoGo” pathway, although a later study implicated background strain and other factors in this phenotype (Kelly et al., 1998). By contrast D1 knockouts showed less dramatic changes in spontaneous activity, either displaying no change compared to wild-types (Drago et al., 1994) or a mild hyperactivity not predicted by the classical model (Xu et al., 1994b). Removal of D1 receptors does interfere with the psychomotor-activating effects of stimulant drugs like cocaine (Xu et al., 1994a), consistent with the idea that these drugs increase behavioral output largely by driving the direct Go pathway. Another striking feature of the D1 knockouts is that they fail to feed normally after weaning, which might arise from a deficit in learning how to obtain and consume standard lab food. Overall, the effects of dopamine receptor knockouts seem consistent with the idea that D2 receptors are higher-affinity receptors whose tonic stimulation by baseline dopamine is important for facilitating behavior (with dips in dopamine perhaps prompting NoGo learning). By contrast, D1 receptors are thought to reside in a lower-affinity state and to be less involved in spontaneous activity. They have been proposed to be engaged when brief increases in dopamine cell firing prompt behavioral switching and reward-based learning (Richfield et al., 1989, Dreyer et al., 2010), although there is still very little direct evidence for this scheme.

Other genetic studies have targeted different aspects of intracellular signalling in D1- and D2-MSNs. Two studies recently showed that the sphingosine-1-phosphate receptor Gpr6 is selectively expressed in striatopallidal cells where it can stimulate cAMP production (i.e. in opposition to D2 receptor activity) (Lobo et al., 2007, Heiman et al., 2008). Gpr6 knockout mice appeared normal in many tests of locomotor activity and motor learning, but showed faster acquisition of operant lever-pressing for sugar pellets, as if they had enhanced motivation to perform the task (Lobo et al., 2007). Another study examined the consequences of deleting a target of dopamine signaling in D1 and D2 MSNs, DARPP-32 (Bateup et al., 2010). The authors found that in both subtypes of MSNs, deletion of DARPP-32 led to a loss of long-term potentiation (LTP), which is an NMDAR-dependent form of synaptic plasticity observed in the striatum (Calabresi et al., 1992, Shen et al., 2008). When DARPP-32 was deleted from D1 MSNs, a reduction in basal activity was observed, as well as a reduction in the locomotor response to cocaine; opposite results were observed in D2 MSNs. Loss of NMDARs in D1 MSNs also results in impaired responses to psychostimulants, namely amphetamine sensitization (Beutler et al., 2011). Interestingly, Beutler et al. found that loss of NMDARs in D2 MSNs normalized sensitization in mice already lacking NMDARs in D1 receptors, arguing that: (1) the balance of activity in direct and indirect pathways is critical for establishing sensitization, and (2) that the mechanism underlying sensitization does not require NMDAR-dependent LTP in MSNs, consistent with a potential role for striatal long-term depression (LTD) in this process (Thomas et al., 2001).

While targeting receptors or signaling pathways in D1 or D2 MSNs is informative, these pathways are involved in multiple aspects of cellular function, and it is not always clear how neural activity in vivo is affected by such manipulations. An alternative genetic strategy involves the selective expression of toxins to generate cell-type specific lesions or inactivation. The first application of this technology to MSNs used expression of diphtheria toxin in dopamine D1-expressing neurons (Drago et al., 1998), which yielded robust ablation of D1 MSNs. This produced motor abnormalities more severe than those seen in the

D1 receptor knockouts, including slowed movements consistent with the classical model. However, while such hypoactivity was observed in young pups, older pups showed hyperactivity (Wong et al., 2000), and a subsequent study in which toxin expression was restricted to postnatal development also found hyperactivity (Gantois et al., 2007), as part of a generally milder phenotype. Such results serve to emphasize the necessary interpretive caveats that accompany manipulations over extended periods of development, especially when not restricted to specific cell types (e.g. all D1-cells, not just D1-MSNs).

Improved temporal and spatial control can be achieved by combining genetic manipulations with intrastratial injections of virus or toxin. This approach enhances specificity, as targeting can be both cell-type- and (sub)region-specific. On the other hand, manipulations of (for example) dorsolateral striatum will likely have different effects than manipulations of dorsomedial striatum or NAc, and targeting the whole striatum can require many injection sites. Sano et al. (Sano et al., 2003) successfully targeted striatal D2-expressing cells by generating mice that express interleukin-2 receptor alpha subunit (IL-2R α) under control of the D2 receptor gene, and injecting an immunotoxin that kills IL-2R α -expressing cells into six sites in both dorsomedial and dorsolateral striatum. As predicted by the classical model, loss of D2 MSNs greatly enhanced locomotor activity. Similar results were obtained using a different method for selective cellular ablation, targeted expression of diphtheria toxin receptor followed by intrastratial injection of diphtheria toxin. By expressing the toxin receptor under the adenosine A2AR promoter (which is selectively expressed by D2-MSNs), (Saito et al., 2001) were able to achieve a near-complete ablation of D2-MSNs throughout striatum, or a more focused effect in the NAc. Near-complete D2-MSN removal produced strong and persistent hyperactivity, confirming the results of Sano et al. and providing further support for the idea that the indirect pathway tonically inhibits movement. More restricted D2-MSN removal in NAc did not cause hyperactivity but did cause an enhancement of amphetamine-driven conditioned place preference (CPP). This result begins to connect the D1/D2-MSN distinction to the extensive literature on NAc and reward-related learning (Berridge & Robinson 2003).

To achieve a more reversible version of selective D1-/D2-MSN manipulations, Hikida et al. combined genetic, viral and pharmacological methods (Hikida et al., 2010). They used mice in which tetanus toxin (a neurotoxin that interferes with synaptic transmission by cleaving vesicular fusion proteins) was controlled by promoter elements that bind the tetracycline transactivator (tTA). Multiple sites in dorsal striatum and NAc were injected with a virus that encoded tTA under either a substance P promoter (for D1-MSNs) or enkephalin promoter (for D2-MSNs). tTA is repressed by drugs such as doxycycline, so they raised mice with doxycycline in their food and water. To selectively shut down D1 or D2 MSN transmission in adult mice, the authors withdrew the doxycycline for 2–4 weeks. Their results broadly supported the classical model: unilateral suppression of direct (striatonigral) transmission caused spontaneous rotation towards the injected side (ipsiversive rotation), while suppression of indirect (striatopallidal) output caused contraversive rotation. Both direct and indirect pathways were found to be important for acute cocaine-induced locomotion, with a greater role of the direct pathway in progressive locomotor sensitization to cocaine. The direct pathway was also preferentially involved in reward-based learning (CPP), while the indirect pathway was preferentially involved in learning to avoid an action after punishment (inhibitory avoidance test). In principle, these learning deficits could have arisen either by blocking the behavioral impact of plasticity at excitatory synapses onto MSNs, or by interfering with the induction of “downstream” plasticity (at MSN terminals, or in downstream nuclei). It would be interesting to use the reversibility of the Hikida et al. approach to distinguish between such possibilities.

Although these toxin studies provided the first solid pieces of evidence for the function of D1 and D2 MSNs, the relatively slow time course (1 week +) of inactivation limits their utility for dissecting neuronal function on rapid timescales. Several new methods offer still more rapid, selective, and reversible changes in D1 or D2 MSN activity. The expression of synthetic G-protein-coupled receptors (termed RASSLs: Receptors Activated Solely by Synthetic Ligands, or DREADDs: Designer Receptor Exclusively Activated by Designer Drugs) enables the regulation of neural activity in vivo, following administration of a selective (and otherwise biologically inert) drug that activates that receptor (Coward et al., 1998, Armbruster et al., 2007). This approach was taken by Ferguson et al. (Ferguson et al., 2010), who achieved expression of a Gi-coupled receptor (hM4D, a DREADD based on the human muscarinic M4 receptor) in D1 or D2 MSNs in the rat striatum using a Herpes simplex virus with promoter elements for enkephalin or dynorphin. Injections into dorsomedial striatum yielded changes in the threshold and persistence of locomotor sensitization in response to amphetamine. Expression of hM4D in D1 MSNs resulted in inhibition of neural activity and a reduction in the persistence of locomotor sensitization, whereas hM4D in D2 MSNs resulted in enhanced sensitization. Similar to the study of Durieux et al, these results indicate that activity in D1 or D2 MSNs may be critical for plastic changes that occur in response to adaptive (or in this case, maladaptive) forms of behavioral plasticity. However, the use of designer GPCRs to study behavior does have several caveats. It is not clear how the viral overexpression of exogenous GPCRs impacts their cellular localization, their coupling to intracellular signaling pathways, or sequestration of G-proteins or other interacting proteins. Thus, while synthetic GPCRs can regulate neural activity, they may exert a plethora of other effects that could influence cellular function in unpredictable ways.

Perhaps the most precise method for manipulating neural activity in a specific, reversible, rapid, and minimally-invasive way is the use of optogenetic methods (Zhang et al., 2007a, Zhang et al., 2007b). In particular, expression of channelrhodopsin-2 (ChR2) in subsets of neurons in vivo enables the direct control of neural activity on the millisecond timescale with light. Two recent studies have expressed ChR2 in D1 or D2 MSNs in the dorsomedial striatum (Kravitz et al., 2010) or nucleus accumbens (Lobo et al., 2010) using D1- and D2-Cre BAC transgenic mice, combined with Cre-dependent viral expression, and examined the behavioral consequences of increased spiking in these two cell populations in the context of motor function and reward. The Kravitz et al. results are remarkably consistent with the classical Albin-DeLong model of basal ganglia function. In the dorsal striatum, activation of D2 MSNs induces a constellation of features that resemble parkinsonism: (1) voluntary initiation of locomotion is decreased, (2) time spent immobile is increased, and (3) the velocity of fine movements is decreased. In contrast, activation of D1 MSNs yields precisely the opposite results (Kravitz et al., 2010). In the nucleus accumbens, Lobo et al., 2010 found no immediate locomotor effects of stimulating either D1- or D2-MSNs, although stimulating D1 MSNs did increase locomotion in mice previously sensitized with repeated cocaine (stimulating D2 MSNs still had no effect). Stimulating D1- or D2-MSNs in NAc did not appear to be intrinsically rewarding, as neither produced CPP. However, D1 MSN stimulation enhanced the degree of CPP produced by cocaine, whereas D2 MSN stimulation reduced cocaine CPP. Together these results provide further support for the idea that D1- and D2-MSNs oppositely influence movement in dorsal striatum, and oppositely influence reward-related learning in NAc.

While ChR2 expression provides a highly-specific method for activating neurons, it should be noted that its application is not without caveats (see (Yizhar et al., 2011) for a detailed primer). The most widely used H134R variant of ChR2 expresses exceptionally well in most neuronal types, but it has relatively slow kinetics (τ_{off} : 15–20 ms), shows marked desensitization (40–60%), and has some calcium permeability (Lin, 2011). Therefore it must

be applied with caution to studies involving repetitive stimulation, since distortions in postsynaptic current amplitudes have been noted, particularly when illumination is delivered to axon terminals (Zhang and Oertner, 2007). Although variants of ChR2, such as ChETA or ChIEF, have been developed to address some of these issues (Lin et al., 2009, Gunaydin et al., 2010, Berndt et al., 2011), they have not been as extensively tested. Another important consideration is the indirect effect of ChR2 stimulation on local microcircuitry. For example, in the striatum, optogenetic activation of D2-MSNs elicits significant lateral inhibition of other MSNs (likely both D1- and unlabeled D2-MSNs), whereas optogenetic activation of D1-MSNs induces far less lateral inhibition (Kravitz and Kreitzer, unpublished observations), consistent with their connectivity in vitro (Taverna et al., 2008). Such problems become even more salient in structures with recurrent excitatory connections. Finally, strong optogenetic stimulation of a striatal subregion is liable to produce highly artificial patterns of synchrony within groups of neurons, which could disrupt rather than mimic natural information processing. This problem can be somewhat mitigated by using lower power stimulation to avoid imposing a specific pattern of firing, but rather make cells more likely to spike in response to synaptic input (Kravitz et al. 2010). Ultimately however, no stimulation technique, including optogenetic stimulation, can be expected to fully preserve or recapitulate naturally-occurring, complex activity patterns within neural networks.

Striatal interneurons

In comparison to MSNs, far less is known about the function of striatal interneurons. A focus of much early research were the cholinergic cells, known anatomically as large aspiny interneurons and electrophysiologically as tonically active neurons (TANs). One early tool developed to selectively inactivate cholinergic neurons was ethylcholine mustard aziridinium ion (AF64A) (Mantione et al., 1981). Although the specificity of putative cholinergic neurotoxins is a major problem, injections of AF64A into the striatum resulted in impaired performance on a passive avoidance task (Sandberg et al., 1984), but no changes in spontaneous locomotor behavior. Other toxins have been directly targeted to cholinergic interneurons (Hikida et al., 2001), resulting in enhanced sensitivity to cocaine and enhanced CPP. More recently, the physiological and behavioral effects of selective manipulation of striatal cholinergic interneurons were investigated using optogenetic approaches in the NAc (Witten et al., 2010). Strikingly, no obvious motor deficits were observed during transient inhibition of cholinergic interneurons. However, a moderate dose of cocaine was found to enhance their activity, and directly activating these interneurons with ChR2 enhanced the frequency of inhibitory currents onto MSNs. This process appears to be required for normal cocaine-CPP, since artificially reducing cholinergic activity with the light-activated chloride pump halorhodopsin reduced CPP. At face value, the results from the optogenetics experiments appear inconsistent from the lesion experiments. However, differences in acute versus chronic manipulation of the cholinergic system may explain these discrepancies. For example, a chronic reduction in cholinergic tone could reduce the excitability of D2 MSNs (Shen et al., 2007), which might promote CPP induction. In any case, both toxin and optogenetic evidence suggests that normal cholinergic tone is not required for relatively normal locomotor activity. Rather, cholinergic signalling appears to modulate learning (Morris et al., 2004). It will be useful to determine how the enhanced inhibitory currents on MSNs induced by cholinergic interneurons/cocaine might be involved in the control of synaptic plasticity.

The role of other interneuron types in the striatum remains even more mysterious. Two recent optogenetic studies have implicated parvalbumin-positive FSIs in sensory-evoked response precision and gamma rhythms (Cardin et al., 2009, Sohal et al., 2009). FSIs in striatum are tonically active (Berke et al. 2004) and also participate in striatal fast

oscillations (Berke 2009). However, in dorsolateral striatum where FSIs are enriched, gamma oscillations are not robust (Berke et al., 2004). Moreover, FSIs do not even appear to mediate constant rapid inhibition of MSN spiking in awake behaving animals (Gage et al., 2010), raising a number of questions about their function in vivo. One set of potentially useful tools for selectively targeting FSIs are drugs that target calcium-permeable (GluR2-lacking) AMPARs. Unlike philanthotoxin, which also block NMDARs (Brackley et al., 1993), dicationic adamantane derivatives such as IEM-1460 (Magazanik et al., 1997) are potent and selective inhibitors of calcium-permeable AMPARs that are highly enriched in FSIs in the striatum. We have recently demonstrated that infusion of IEM-1460 into dorsolateral striatum selectively reduces FSI activity and induces dystonia-like dyskinesias (Gittis et al, submitted manuscript). However, these behavioral abnormalities are not accompanied by overall changes in MSN firing, suggesting that FSIs may play a more subtle and complex role in coordinating the activity of behaviorally-relevant ensembles of MSNs that are critical for proper motor function.

Conclusions

Results using a variety of methods to selectively target D1 or D2 MSNs in behaving animals have yielded remarkably consistent results. Activation of D1 MSNs enhances locomotion and CPP. Activation of D2 MSNs induces parkinsonian motor deficits and decreases CPP. In contrast, lesions or inactivations of D1 MSNs lead to slowed movements, reduced sensitization to psychostimulants, and reduced CPP, whereas loss of D2 MSN function yielded hyperactivity, enhanced sensitization and CPP, as well as a reduction in passive avoidance. One common thread is that manipulations of dorsal striatum influenced motor behavior, whereas manipulations of NAc altered simple forms of conditioned learning (e.g. CPP). However, the precise function of MSNs in distinct subregions during these types of behaviors has not been well characterized. The function of interneurons is even less well understood, although they must ultimately act by modulating excitability, plasticity, or coordination of MSNs. Together, current evidence suggests that *at the level of the striatum*, the classical model appears to hold true. Nevertheless, the impact of direct and indirect pathways on downstream nuclei is surely more complex than suggested by a simple box-and-arrow rate model. Moreover, nearly every assay thus far has focused on robust changes in simple motor behaviors, crude learning tests, or responses to drugs, which greatly limits the insight provided into normal striatal function. Indeed, the classical Albin-DeLong model may be particularly useful for understanding basal ganglia dysfunction, when aberrant changes in the direct or indirect pathways results in behavioral abnormalities. A major remaining challenge for the future is to determine how the striatum contributes to normal, adaptive behaviors, such as decision making, reward-dependent learning and action selection.

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Highlights

- Cell-type specific manipulations enable insight into striatal function
- Several techniques have been used to knockout, ablate, or inactivate striatal neurons
- Optogenetic methods have enabled selective stimulation of striatal neurons
- A remarkable convergence of results indicates unique functions for D1 MSNs, D2 MSNs, and striatal interneurons

Table 1

Manipulations of Striatal Cell Types

Cell Type	Subregion	Targeting Method	Manipulation	Behavior	References
D1 MSNs	Striatum	Conditional knockout	NMDAR deletion	Loss of sensitization	Beutler et al. 2011
D1 MSNs	Striatum	Conditional knockout	DARPP-32 deletion	Hypoactivity, reduced psychostimulant response	Bateup et al. 2010
D1 MSNs	Dorsomedial striatum	Virus + drug	Activate Gi signaling	Reduced sensitization	Ferguson et al. 2010
D1 MSNs	Striatum	Transgenic + virus	Cell inactivation	Reduced sensitization, CPP	Hikida et al. 2010
D1 MSNs	NAc	Transgenic + virus	Optogenetic stimulation	Enhanced CPP	Lobo et al. 2010
D1 MSNs	Dorsomedial striatum	Transgenic + virus	Optogenetic stimulation	Hyperactivity	Kravitz et al. 2010
D2 MSNs	Striatum	Knockout	GPR6 deletion	Faster acquisition of operant task	Lobo et al. 2007
D2 MSNs	Striatum	Conditional knockout	DARPP-32 deletion	Hyperactivity, enhanced psychostimulant response	Bateup et al. 2010
D2 MSNs	Dorsal striatum	Transgenic + virus	Cell ablation	Hyperactivity	Sano et al. 2003
D2 MSNs	Striatum or NAc	Transgenic + virus	Cell ablation	Hyperactivity, enhanced CPP (NAc lesion)	Durieux et al. 2009
D2 MSNs	Striatum	Transgenic + virus	Cell inactivation	Reduced passive avoidance	Hikida et al. 2010
D2 MSNs	Dorsomedial striatum	Virus + drug	Activate Gi signaling	Enhanced sensitization	Ferguson et al. 2010
D2 MSNs	Dorsomedial striatum	Transgenic + virus	Optogenetic stimulation	Hypoactivity	Kravitz et al. 2010
D2 MSNs	NAc	Transgenic + virus	Optogenetic stimulation	Reduced CPP	Lobo et al. 2010
Cholinergics	Striatum	Toxin	Cell ablation	Reduced passive avoidance	Sandberg et al. 1984
Cholinergics	NAc	Toxin	Cell ablation	Enhanced sensitization, CPP	Hikida et al. 2001
Cholinergics	NAc	Transgenic + virus	Optogenetic inhibition	Loss of CPP	Witten et al. 2010
FSIs	Dorsolateral striatum	Pharmacology	Cell inactivation	Dystonia, dyskinesia	Gittis et al. submitted