Review

Functional roles of neurotransmitters and neuromodulators in the dorsal striatum

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The dorsal striatum, with its functional microcircuits galore, serves as the primary gateway of the basal ganglia and is known to play a key role in implicit learning. Initially, excitatory inputs from the cortex and thalamus arrive on the direct and indirect pathways, where the precise flow of information is then regulated by local GABAergic interneurons. The balance of excitatory and inhibitory transmission in the dorsal striatum is modulated by neuromodulators such as dopamine and acetylcholine. Under pathophysiological states in the dorsal striatum, an alteration in excitatory and inhibitory transmission may underlie dysfunctional motor control. Here, we review the cellular connections and modulation of striatal microcircuits and propose that modulating the excitatory and inhibitory balance in synaptic transmission of the dorsal striatum is important for regulating locomotion.

The dorsal striatum is best known for its role in decision-making, especially in action selection and initiation through the convergence of sensorimotor, cognitive, and motivational information (DeLong 1990; Smith et al. 1998; Balleine et al. 2007). As the primary input of the basal ganglia, the striatum receives glutamatergic inputs from the cortex and thalamus and in turn projects GABAergic outputs to the globus pallidus and substantia nigra pars reticulata (SNr). Inputs from the cortex and thalamus both form excitatory synaptic connections on medium spiny neurons (MSN) in which cortical afferents are from the sensory, motor, and associational cortex (Bolam et al. 2000), and thalamic afferents are from the intralaminar thalamic nuclei (Doig et al. 2010). These glutamatergic inputs are then processed in the dorsal striatum where numerous connections between various types of neurons exist. Thus, the complexity of neuronal circuits has made it difficult to elucidate the functional roles of the striatum. Recently, studies focused on interneurons that reside in the dorsal striatum have characterized the physiological features and functional connections. For example, parvalbumin-expressing fast-spiking interneurons (PV-FSI) and neuropeptide-Y positive low-threshold spiking interneurons (NPY-LTS) form synaptic connections with MSNs and regulate the firing activity of the principal neuron MSNs (Koos and Tepper 1999; Gittis et al. 2010; Chuhma et al. 2011). These interneurons were shown to have distinct firing patterns and connections, and thus they may exert different effects on MSNs. Other crucial connections are the cholinergic, dopaminergic, and serotonergic axons that strongly innervate the dorsal striatum. These projections are essential for modulating striatal circuits and disruption of such signaling can result in movement impairments and neurological disorders such as Huntington's disease (Lovinger 2010). This review summarizes recent reports of the microcircuits present in the dorsal striatum, although serotonergic signaling is excluded, and suggests a putative role for striatal microcircuits in motor dysfunction and/or hyperactivity that often accompany psychiatric disorders

such as attention deficit/hyperactivity disorder (ADHD) and autism.

Circuits: Glutamatergic and GABAergic transmission

Corticostriatal circuit: Direct/indirect pathway

MSNs constitute >90% of the dense GABAergic striatal neuron population and can be subdivided into two main classes: the direct-pathway (striatonigral) and indirect-pathway (striatopallidal) MSNs. The striatonigral MSNs (D₁-MSN) express high levels of both D₁ dopamine (DA) receptors and M4 muscarinic receptors and project directly to the internal globus pallidus (GPi in primates, GPM in rodents) and SNr. Striatopallidal MSNs (D₂-MSN) highly express D₂ dopamine receptors and adenosine A_{2A} receptors and project to the external globus pallidus (GPe in primates, GP in rodents). Direct and indirect pathways act in opposition to one another to control movement, which indicates segregated information processing (Albin et al. 1989; DeLong 1990). Compelling evidence of this segregation has been obtained from studies in bacterial artificial chromosome (BAC) transgenic mice (Gong et al. 2003). The existence of synaptic connections between direct- and indirect-pathway MSNs was reported only recently. However, the functional significance of these connections is yet to be characterized.

Cell-type specific whole-cell voltage clamp recordings have revealed distinct physiological properties in D₁- and D₂-MSNs in BAC transgenic mice. D₂-MSNs have a higher NMDA/AMPA (2-amino-3-hydroxy-5-methyl-4-isoxazol propionic acid/N-Methyl-D-aspartate) ratio. Also, a greater paired-pulse ratio (PPR) value than that of D₁-MSN indicates that corticostriatal inputs to D₂-MSNs have a higher probability in neurotransmitter release (Ding et al. 2008). Further, membranes of D₂-MSNs are intrinsically more excitable than those of D₁-MSNs (Kreitzer and Malenka 2007), which is supported by an anatomical comparison of somatodendritic trees, where the surface area of D₁-MSNs is larger than that of D₂-MSNs (Gertler et al. 2008).

Once the striatonigral direct-pathway circuit receives glutamatergic inputs from the sensorimotor cortex, GABAergic

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D₁-MSNs, which project directly to GABAergic neurons in the GPI and SNr, are activated. Thus, GABAergic GPI and SNr neurons, which in turn send axons to motor nuclei of the thalamus, become inhibited. The net effect of this information flow is a disinhibition of excitatory thalamocortical projections. Since the GPI is involved in axial and limb movements and the SNr in head and eye movements, activation of the striatonigral pathway is predicted to promote action selection and movement. The striatopallidal indirect-pathway circuit also receives glutamatergic inputs from the cortex. Glutamatergic input onto GABAergic D₂-MSNs inhibits GABAergic pallidal neurons of the GPe, whereupon the target of the GPe neurons, the glutamatergic neurons of the subthalamic nucleus (STN), are disinhibited. Disinhibition of excitatory STN neurons could activate inhibitory output neurons of the GPI and SNr, resulting in a net effect of an inhibition of excitatory thalamocortical projection neurons. This would then lead to a reduction of cortical premotor drive and inhibition of movement.

A compelling number of studies of synaptic plasticity in corticostriatal synapses have been reported, but an in-depth examination of these studies is beyond the scope of this review. Long-term depression (LTD), long-term potentiation (LTP), and spike-timing dependent plasticity (STDP) occur in these types of synapses (Calabresi et al. 1992a,b; Centonze et al. 2001; Fino et al. 2005; Wang et al. 2006; Pawlak and Kerr 2008). Endocannabinoid-dependent LTD (Gerdeman et al. 2002) is much better characterized than NMDAR-dependent or NMDAR-independent LTP because it occurs more frequently than LTP under conditions of high-frequency stimulation (HFS) and depolarization pairing protocol. Whether the properties of synaptic plasticity differ between direct and indirect pathways is unclear.

Thalamostriatal circuit

The existence of profuse striatal projections from the entire intralaminar nuclear complex was first characterized in a cell degeneration study conducted in primates (Cowan and Powell 1956). Yet, properties of the thalamostriatal projection were much less well understood than those of the corticostriatal circuit. However, a recent approach designed to preserve thalamostriatal axons in brain slices cut in oblique horizontal planes has enabled studies to distinguish physiological properties of thalamostriatal and corticostriatal projections (Smeal et al. 2007). The study in rat oblique horizontal slices proposed dissimilar physiological properties in presynaptic release probability; PPRs of thalamostriatal connections were higher than those of corticostriatal connections. However, another study in mice reported an opposing result, i.e., the PPR in corticostriatal synapses was higher than that in thalamostriatal synapses (Ding et al. 2008, 2010). In addition, the NMDA/AMPA ratio in corticostriatal synapses was higher than that in thalamostriatal synapses, but no distinguishing feature existed between synapses formed between thalamostriatal axons and D₁- or D₂-MSNs. A recent study did show that the number of synapses formed along D₁-MSNs from the thalamus is regulated by an interaction between Semaphorin 3E (Sema3E) secreted from thalamostriatal axons and Plexin-D1 receptors expressed on D₁-MSNs (Ding et al. 2012).

Selective ablation of thalamostriatal axons originating from the parafascicular thalamic nuclei revealed that thalamostriatal axons were not significantly involved in motor-skill learning and spontaneous activity in mice (Kato et al. 2011). Compared with corticostriatal projections, thalamostriatal projections were shown to form fewer synapses on MSNs, but these synapses significantly influenced local striatal circuits by glutamatergic transmission on cholinergic interneurons (Ding et al. 2010).

Local GABAergic circuits: Parvalbumin-expressing fast-spiking interneurons and neuropeptide-Y positive low-threshold spiking interneurons

The GABAergic interneurons in the striatum form feed-forward inhibitory synaptic connections on both MSNs and neighboring interneurons (Ding et al. 2010). The neighboring interneurons have been largely classified into two groups: parvalbumin positive fast-spiking interneurons (PV-FSI) and neuropeptide-Y expressing low-threshold spiking interneurons (NPY-LTS). Although interneurons constitute a very small population of the dorsal striatum compared to that of MSNs, the minority exerts powerful inhibitory effects on MSNs through GABAergic transmission. Studies have shown that FSIs form multiple synapses, roughly ranging from 135 to 541 in number, on MSNs. One FSI could delay the generation of action potentials in MSNs by a single inhibitory postsynaptic current (IPSC) (Koos and Tepper 1999). FSIs both receive and respond to cortical input faster than MSNs (Kawaguchi 1993), and in turn can exert fast inhibitory actions on both types of MSNs (Planert et al. 2010). BAC transgenic mice in which GABAergic interneurons can be identified showed that FSIs preferentially target direct-pathway MSNs over indirect-pathway MSNs (Gittis et al. 2010). In addition, it is important to note that there is a prominent distinction between the actions of GABA_A receptors in direct- and indirect-pathway MSNs; currents through GABA_A receptors always depressed the response to corticostriatal stimulation in D₂-MSNs, whereas they helped to depolarize the response in D₁-MSNs (Flores-Barrera et al. 2010). Thus the differing nature of synaptic response in each type of MSN may reflect distinct FSI synaptic connectivity; however, a thorough observation needs to be done.

LTS interneurons, which express NPY, somatostatin (SOM), and nitric oxide synthase (NOS) (Gallarraga et al. 2007), are much less characterized than FSIs because of their sparse connection to MSNs, cholinergic interneurons, and FSIs (Kawaguchi 1993; Gittis et al. 2010). Although SOM-positive GABAergic terminals have been observed on the dendrites of MSNs (Kubota and Kawaguchi 2000), it has been difficult to explain their functional role. Interestingly, under dopamine depletion states, GABAergic inhibition onto MSNs by LTS interneurons was shown to become potentiated (Dehorter et al. 2009). This distinct set of neurons is thought to modulate striatal circuits by releasing neuromodulators such as NPY, SOM, and NO in a spatial and temporal manner rather than as a fast synaptic transmission (O'Donnell and Grace 1997; West and Grace 2004; Gallarraga et al. 2007). For example, one study reported that D₁ receptor signaling in the dorsal striatum was upregulated in mice deficient of nitric oxide synthase, and this was accompanied with abnormal social behavior and hyperactivity (Tanda et al. 2009).

GABAergic interneurons in the dorsal striatum are seemingly crucial for facilitating fine movement, as GABAergic dysfunction in the striatum has been linked with hyperkinetic movements like dystonia, tics, and chorea (Levy and Hallett 2002). In experiments where the GABAergic network was interfered, GABA_A antagonists elicited tic-like movement and other types of dyskinesia (McCairn et al. 2009; Worbe et al. 2009). A more recent study reported that the selective pharmacological inhibition of FSIs leads to robust dystonia-like impairments (Gittis et al. 2011b). Also, previous studies have shown that a state of dopamine depletion induces a rapid shift of FSI connectivity within the striatum (Salin et al. 2009) by increasing synaptic connections with indirect-pathway MSNs (Gittis et al. 2011a). This may result in synchronous firing of indirect-pathway MSNs that could resemble a pathological network oscillation observed in patients of Parkinson's disease (Vida et al. 2006; Assisi et al. 2007; Atallah and Scanziani 2009).

Neuromodulators: Dopamine and acetylcholine (ACh)

Modulation of the corticostriatal pathway by dopamine

Dense innervation of mesencephalic dopaminergic axons modulates the excitability of striatal MSNs, GABAergic interneurons, and cholinergic interneurons. The modulatory action of dopamine differs depending on the cell types because each cell type expresses distinct types of dopamine receptor classes in different combinations. Dopamine receptors are classified into two groups: the D₁-like and D₂-like receptors. D₁-like receptors consist of D₁ and D₅ receptors, and D₂-like receptors consist of D₂, D₃, and D₄ receptors. Dopamine receptors are G-protein coupled receptors that act through G-proteins, which modulate ion channels and therefore alter the intrinsic property of the cell membrane. D₁ and D₅ receptors activate stimulatory G_{s/olf} proteins, while D₂, D₃, and D₄ stimulate inhibitory G_{i/o} proteins (Okada et al. 1990; Neve et al. 2004). G_s and G_{olf} proteins in turn stimulate adenylyl cyclase, which elevates the intracellular level of the secondary messenger cAMP, thus activating PKA and its broad range of cellular targets, such as transcription factors and voltage-gated ion channels. On the other hand, G_o and G_i proteins inhibit adenylyl cyclase (Stoof and Kebabian 1984) and target voltage-dependent ion channels, for example through a membrane-delimited G-protein mechanism.

Dopamine's effect on principal MSNs has received significant attention because of the distinctive pool of dopamine receptor expression on MSN membranes. In D₁-MSNs, D₁ receptors act through G_s and G_{olf}, and therefore dopamine triggers activation of PKA due to an enhanced level of cAMP. PKA has been shown to increase L-type Ca²⁺ channel currents (Gao et al. 1997; Hernandez-Lopez et al. 1997) and decrease somatic K⁺ currents (Kitai and Surmeier 1993). Furthermore, activation of the D₁ receptor reduces GABA_A receptor currents through a PKA/DARPP-32/PP1 signaling cascade (Flores-Hernandez et al. 2000), and D₁ receptor signaling inhibits the opening of the Ca_v2 Ca²⁺ channels that activate Ca²⁺-dependent small conductance K⁺ channels (Vilchis et al. 2000). Overall, the dopamine modulation on direct-pathway MSNs serves to increase spiking and somatic depolarization.

D₂ receptor signaling, which is dominant in indirect pathways, reduces Na_v1 and Ca_v1 L-type channel currents, but increases outward hyperpolarizing K⁺ channel currents (Greif et al. 1995; Schiffmann et al. 1998; Hernandez-Lopez et al. 2000). Moreover, D₂ receptor activation decreases dendritic Ca²⁺ currents through voltage-dependent channels (Higley and Sabatini 2010). Such actions of D₂ dopamine receptors align with the notion that D₂ receptor signaling is inhibitory and reduces the excitability of indirect-pathway MSNs. In addition, some studies have shown that D₂ receptor signaling reduces presynaptic glutamate release (Bamford et al. 2004; Yin and Lovinger 2006).

The widespread action of dopamine in the dorsal striatum affects interneurons as well. Dopamine can modulate local GABAergic neurons; FSIs can become excited by dopamine through D₂ and D₅ receptors. Studies have shown that D₅ receptor activation depolarizes the membrane potential of FSIs (Bracci et al. 2002; Centonze et al. 2003). Also, D₂ receptor agonists reduced presynaptic GABAergic neurotransmission in FSIs (Gage et al. 2010), which mostly originate from GPe neurons that express D₂ receptors (Bevan et al. 1998; Hoover and Marshall 2004).

Cholinergic interneurons can be modulated by dopamine through D₂ and D₅ receptors. D₂ receptor activation has been reported to suppress cholinergic autonomous firing activity by inhibiting voltage-dependent Na⁺ channels (Maurice et al.

2004) or reducing hyperpolarization-activated depolarizing currents through HCN channels (Deng et al. 2007). D₂ receptors also mediate the inhibition of Ca_v2.2 Ca²⁺ channels, ultimately reducing membrane excitability (Cabrera-Vera et al. 2004). Conversely, D₅ receptor activation depolarizes cholinergic interneurons through a cAMP-dependent pathway (Aosaki et al. 1998).

Modulation of interneurons and MSNs by acetylcholine

Acetylcholine (ACh) is another major neuromodulator supplied by large aspiny cholinergic interneurons that are tonically active (<10 Hz) in the striatum (Bolam et al. 1984). Although aspiny cholinergic interneurons constitute a small fraction of the total population, they also have a dense and widespread innervation of dendritic arbors in the striatum, contributing to a constituent background level of ACh as the acetylcholinesterase present in the extracellular matrix degrades the residual ACh.

Nicotinic ACh receptors (nAChR) expressed on presynaptic dopaminergic terminals can regulate dopamine release locally by initiating depolarization and calcium signaling to enhance dopamine release. ACh pulses arriving at dopaminergic terminals are degraded rapidly by acetylcholinesterase, thus minimizing the level of nAChR desensitization and allowing cholinergic activity to regulate dopaminergic axon terminals locally and release dopamine in an action-potential dependent manner (Zhou et al. 2001). In addition, recent studies have evaluated that the triggering force of dopamine release from axon terminals in the striatum by cholinergic interneurons is dominant over ascending dopaminergic somata firing (Cachope and Pereda 2012; Threlfell et al. 2012).

In addition, cholinergic interneurons may recruit distinctive sets of GABAergic circuits to modulate MSN output activity. ACh was shown to depolarize FSIs directly through nAChRs and attenuate their GABAergic inhibition on MSNs by presynaptic muscarinic acetylcholine receptors (mAChR) on FSI terminals (Koos and Tepper 2002). More recently, a study showed that activation of a novel inhibitory NPY-neurogliaform by nicotinic synaptic inputs from cholinergic interneurons contributes to slow inhibitory currents in MSNs (English et al. 2011).

In the case of MSNs, the principal neurons mainly express the muscarinic form of acetylcholine receptors, M1-like (M1 and M5) and M2-like (M2, M3, and M4) (Bernard et al. 1992). The M1-like receptors stimulate G_{q/11}, which in turn activates phospholipase C (PLC) (Berstein et al. 1992) and protein kinase C (PKC) (Perez-Burgos et al. 2008), while M2-like receptors are coupled to G_{i/o} proteins which inhibit adenylyl cyclase, thus reducing cAMP levels (McKinney et al. 1989) and inhibiting Ca²⁺ channels (Yan and Surmeier 1996). M1 receptors are highly enriched in both striatopallidal and striatonigral MSNs, and M4 receptors are expressed preferentially in striatonigral MSNs (Ince et al. 1997). M2 and M3 receptors are present in glutamatergic terminals of cortical projections (Ding et al. 2010).

M1 receptor activation on MSNs ultimately alters intrinsic excitability by modulating voltage-gated channels. Potassium currents through A-type K_v4, Kir2, and KCNQ potassium channels are reduced by M1 receptor activation (Galarraaga et al. 1999; Shen et al. 2005) and are accompanied by a shift in voltage-dependent activation and inactivation (Akins et al. 1990; Nakamura et al. 1997). Also, M1 negatively regulates Ca_v1.3 channels by activating phospholipase C and protein phosphatase 2B (PP-2B), and inhibits Ca_v2.1 channels (Perez-Rosello et al. 2005; Perez-Burgos et al. 2010).

Cholinergic interneurons also express M2 and M4 receptors, which function as autoregulators. The activation of M2-class receptors results in a rapid reduction of N- and P-type Ca²⁺ currents

through a membrane-delimited pathway that stimulates $G_{i/o}$ proteins (Yan and Surmeier 1996).

Striatal-based learning

It has been clearly shown that the dorsal striatum can play a critical role in learning and memory. Early studies first suggested the involvement of striatum in instrumental conditioning and response-based learning (Divac et al. 1967). Later studies using excitotoxic lesions, drug-based approaches, or in vivo recording of neuronal activity have provided evidence that the dorsal striatum plays a role in skill learning and instrumental conditioning involving both goal-directed and habitual responding (Yin et al. 2005b, 2008; Yin and Knowlton 2006; Wickens et al. 2007; Grahn et al. 2008). Otherwise, it could be the striatum as a whole which is involved in most types of learning. However, until this point, very little is known about learning-induced plasticity in striatal microcircuits or how that memory is stored.

Goal-directed behavior during instrumental conditioning in rodents initiates with the association between a specific action and outcome and is prone to the degradation of action–outcome contingency or outcome revaluation (Balleine and Dickinson 1998). With extensive training, performance becomes habitual and no longer sensitive to degradation or devaluation (Dayan and Balleine 2002). This shift in learning is thought to be mediated by different subregions of the dorsal striatum; converging projections from the medial prefrontal cortex to the rodent dorsomedial striatum mediate the acquisition of goal-directed actions (Balleine and Dickinson 1998; Corbit and Balleine 2003; Balleine 2005; Yin et al. 2006), while projections from the sensorimotor cortex to the dorsolateral striatum mediate the acquisition of habits (Jog et al. 1999; Killcross and Coutureau 2003; Barnes et al. 2005). Consistent with results from lesion studies, direct injection of NMDAR antagonist into the dorsomedial striatum prevented goal-directed learning; in other words, the behavior was insensitive to devaluation (Yin et al. 2005a). In the dorsolateral striatum, on the other hand, excitotoxic lesions impaired habit learning (Yin et al. 2004; Hilario et al. 2007).

Receptors involved with striatal synaptic plasticity have been implied to be crucial for striatal-based learning. One study showed that CB1 receptor deletion impaired habit learning while action–outcome learning remained intact (Hilario et al. 2007). This could indicate a role for endocannabinoids in habit learning and the possible involvement of CB1-mediated striatal LTD. Also, the role of A_{2A} receptors seems important for promoting habit learning as A_{2A} receptor knockout mice were only able to show goal-directed behavior (Yu et al. 2009).

Given the fact that the neuronal population is heterogeneous, it is important to understand whether information is differently encoded by striatopallidal and striatonigral MSN pathways during instrumental conditioning. A study in the dorsomedial region using viral expression of channelrhodopsin-2 in D_1 - and D_2 -Cre mouse lines somewhat illustrates this point (Kravitz et al. 2012). In an operant chamber, where mice were trained to receive light stimulation in response to a lever press, selective activation of striatonigral MSNs induced persistent reinforcement, whereas striatopallidal MSNs induced transient punishment.

This type of segregated encoding is observed during skill learning as well. Studies have shown that task-related firing during the early phase of skill learning develops in the dorsomedial region and gets more prominent in the dorsolateral as performance of the skill becomes automatized (Costa et al. 2004; Hernandez et al. 2006; Tang et al. 2007). A more recent study observed that these regional and training-specific changes were reflected as an enhanced excitatory synaptic transmission prefer-

entially in the striatopallidal MSNs of the dorsolateral region (Yin et al. 2009).

The modulation of excitatory and inhibitory balance in locomotion

Concerted excitatory and inhibitory transmission activities in the CNS are essential for processing sensory information and cognitive function. Neuropsychiatric disorders such as autism, attention deficit/hyperactivity disorders (ADHD), and schizophrenia, and neurological disorders such as Parkinson's disease and epilepsy are often associated with an imbalance of excitatory and inhibitory neurotransmissions (Eichler and Meier 2008; Wang et al. 2010).

Dysfunction in the dorsal striatum, embedded with complex microcircuits galore, has been associated with neurological disorders, including Parkinson's disease, Huntington's disease, and psychiatric disorders such as obsessive–compulsive disorders (OCD) (Mink 2003; Welch et al. 2007). More recently, growing evidence has raised the possibility of striatal dysfunction associated with ADHD and autism (Durstion et al. 2003; Lou et al. 2004; Di Martino et al. 2011; Peca et al. 2011). Interestingly, a notable number of mouse models for neuropsychiatric disorders share a common phenotype of elevated locomotor activity (Bolivar et al. 2004; Welch et al. 2007; Dzirasa et al. 2010; Penagarikano et al. 2011; Won et al. 2012). A study in mice deficient of contactin-associated protein-like 2 (*CNTNAP2*) reported that hyperactivity and perseveration could be rescued by risperidone, a dopamine D_2 receptor agonist, while social deficits remained impaired. This selective rescue clearly suggests a segregated pathway underlying motor dysfunction of psychiatric disorders (Penagarikano et al. 2011). Although an excitatory/inhibitory (E/I) balance has often been linked to explain psychiatrically disordered states, a direct examination of E/I balance in the dorsal striatum under such states and its relevance to hyperactivity has not been attempted. Here we pool the results of recent studies and propose a functional role for the striatal microcircuits in motor impairment accompanied by neuropsychiatric disorders.

A balance of dopaminergic and cholinergic systems in the striatum has been suggested and studies have shown that an imbalance between these two systems can result in movement disorders in either hyperkinetic or hypokinetic aspects. For example, early observations of hyperactivity in the *weaver* mouse, a naturally occurring mutant mouse, reported a significant reduction of dopamine in the striatum (Schmidt et al. 1982). Interestingly, when dopamine receptor agonists were applied, hyperactivity was further increased, suggesting a supersensitization of dopamine receptors as a consequence of dopamine deficiency. In addition, mice deficient of M1 receptors exhibited both hyperactivity and elevated rearing activity, along with enhanced dopamine transmission in the striatum (Hamilton et al. 1997; Gerber et al. 2001). Recently, altered cholinergic control over dopamine release has been shown to directly result in hyperactivity in $\alpha 6^{L9/S}$ mice. Such mice have hypersensitive nicotinic $\alpha 6\alpha 4\beta 2^*$ channels that augment DA release from DA fibers during burst-firing in the dorsal striatum (Drenan et al. 2010). On the other hand, it has been reported that dopaminergic dysfunction and elevated cholinergic tone underlie hypokinetic movements of Parkinson's disease and several forms of dystonia (Augood et al. 2004; Clement et al. 2012). Thus, it seems that enhanced dopaminergic tone, stemming most likely from attenuated cholinergic signaling, results in hyperactivity. Given that the role for dopamine and acetylcholine is to alter membrane excitability of both principal neurons and interneurons in the striatum, it is important to understand how they alter E/I transmission in the dorsal striatum under psychiatrically disordered states.

Figure 1. Imbalance of dopaminergic and cholinergic modulation can result in movement impairment. (A) Abnormal dopamine release and enhanced FSI activity may strengthen the output D₁-MSN pathway and thus promote excessive locomotion. (B) Dopamine depletion triggers FSI circuit reorganization by reducing FSI connections to D₁-MSNs. In this case, the strength of the D₂-MSN pathway may become more dominant than that of the D₁-MSN pathway, resulting in reduced locomotion. (FS) fast-spiking interneuron, (Ch) cholinergic interneuron, (D₁) D₁-MSN, (D₂) D₂-MSN, (GPe) external globus pallidus, (GPI) internal globus pallidus, (STN) substantia nigra.

Cortical input to the dorsal striatum is the initial step and this is where FSIs seem to play an important role to mediate cortically driven striatal activity (Stern et al. 1998; Murer et al. 2002; Berke et al. 2004). In vivo gamma oscillations (30–80 Hz) in the striatum are confined to FSIs and coherent gamma oscillations between those connections in both anesthetized and awake states (Berke 2009; Sharott et al. 2009). Given that FSIs receive convergent input from the cortex and respond faster, allowing feed-forward inhibition on MSNs (Ramanathan et al. 2002; Mallet et al. 2005), it is most likely that the fast striatal oscillations will act in a broad coordinated manner to bring about rapid fluctuations of membrane potentials of MSNs that determine spiking during motor coordination (Plenz and Kitai 1998; Hasenstaub et al. 2005).

Differences in GABAergic transmission caused by a neuromodulatory network can have a strong influence over synaptic inputs to MSNs. More specifically, a loss of FSI-mediated control of MSN spike timing in pathophysiological states can result in impaired locomotion. In dopamine-depleted states, local field potential (LFP) recordings show a decreased power of gamma oscillation and an increased power of low-frequency oscillation in the dorsal striatum (Costa et al. 2006; Burkhardt et al. 2009). Given that dopamine increases FSI activity by depolarization (Bracci et al. 2002), such depletion could restrain FSIs from transition to up states where the power of high frequencies is enhanced (Schulz et al. 2011). In addition, dopamine depletion leads to HCN channelopathy in neurons of the external globus pallidus (GPe), which tend to fire in a synchronized fashion, while intrinsic autonomic firing is attenuated (Chan et al. 2011). Such synchronized neurons in the GPe project to FSIs (Bevan et al. 1998) and this could further impair gamma-frequency firing. Likewise, subsequent loss of dopamine dynamically remodels the microcircuits of FSIs by increasing synaptic contact with both striatonigral and striatopallidal MSNs (Salin et al. 2009; Gittis et al. 2011a). Thus, loss of dopamine may result in the broad range of hypolocomotion by reducing FSI activity and gamma oscillations, perhaps hindering direct-pathway MSNs from readily firing in response to cortical input. Consistent with this is a pharmacological study where selective inhibition of striatal FSIs led to dystonia in mice (Gittis et al. 2011b).

On the other hand, elevated dopaminergic tone in the dorsal striatum may almost do just the opposite. In vivo recordings of FSIs show that firing rates increase in response to amphetamine (a dopamine transporter blocker) and are positively correlated to enhanced locomotion (Wiltchko et al. 2010). In another pharmacological/recording study, FSI firing activity positively correlates with drug-induced hyperlocomotion, caused by a combination of methamphetamine and endocannabinoid CB₁ receptor antagonist, in the nucleus accumbens (Morra et al. 2010). Thus, dopamine may enhance the readiness of FSIs to fire in a coordinated manner with cortical input. In addition, gap junctions can determine firing rates of FSIs as well. It has been proposed that gap junctions reduce FSI firing rates by shunting when synaptic inputs are present (Hjorth et al. 2009) and studies in mice deficient of connexin31.1 observe hyperactivity (Dere et al. 2008). Given that GABAergic inhibition contributes

differently to cortically evoked D₁- or D₂- MSN firing (Flores-Barrera et al. 2010), it is possible that increased FSI activity could augment the length of a depolarized state in direct-pathway MSNs leading to excess locomotion (Fig. 1).

Alteration of glutamatergic transmission in the dorsal striatum by blockade of NMDARs may have a role in hyperactivity. Aberrant gamma oscillation throughout the mouse brain, including the dorsal striatum, is observed when psychotomimetics, such as ketamine or MK-801, are systemically applied (Hakami et al. 2009). Hyperactivity in striatal specific NR1 subunit deficient mice is correlated with a reduction of striatal gamma oscillation and, interestingly, hyperactivity can be reduced by either applying D₁ or D₂ receptor agonists (Ohtsuka et al. 2008). Such NMDAR hypofunction induced hyperactivity is thought to result from a reduced number of functional dopamine receptors (Ohtsuka et al. 2008). Examining the consequences of cell-type specific NMDAR hypofunction in the dorsal striatum might be needed to explain the state of hyperactivity.

Studying the excitatory and inhibitory balance in the dorsal striatum is likely to expand our understanding of motor dysfunction (specifically, hyperactivity) that accompanies neurological and psychiatric disorders. Perhaps additional examination of FSIs at the level of channels, such as voltage-gated sodium and potassium channels (Korotkova et al. 2010; Sciamanna and Wilson 2011; Verret et al. 2012), might better explain how membrane potentials of FSIs oscillate and alter under pathological states induced by an impaired balance of neuromodulators. Furthermore, manipulating specific cell types using mouse Cre-lines and optogenetic tools could provide a method for direct observation of hyperactivity.

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