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Dopaminergic modulation of striatal neurons, circuits and assemblies

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Abstract

In recent years, there has been a great deal of progress toward understanding the role of the striatum and dopamine in action selection. The advent of new animal models and the development of optical techniques for imaging and stimulating select neuronal populations has provided the means by which identified synapses, cells and circuits can be reliably studied. This review attempts to summarize some of the key advances in this broad area, focusing on dopaminergic modulation of intrinsic excitability and synaptic plasticity in canonical microcircuits in the striatum as well as recent work suggesting that there are neuronal assemblies within the striatum devoted to particular types of computation and possibly action selection.

Overview

The basal ganglia are part of the forebrain circuitry involved in the selection of actions (Redgrave et al., 1999, Wichmann and DeLong, 2003, Cisek and Kalaska, 2010). Diseases of the basal ganglia result in a spectrum of movement and thought disorders, ranging from those characterized by a paucity of action, such as Parkinson's disease (PD), to those producing an 'exuberance' of action, such as chorea and dystonia (Mink, 2003).

How the basal ganglia contribute to action selection is poorly understood. It is generally believed that the striatum evaluates competing 'action plans' held in cortical networks and then feeds back a recommendation to cortex (through the thalamus) based upon sensory and motivational states, as well as past experience. Dopamine (DA) plays a critical role in this process, both as a modulator of cellular excitability on a moment-to-moment basis and as a modulator of long-term changes in synaptic strength that shape network activity. The review will spend much of the space allotted to it going over how dopamine shapes the function of neurons and canonical circuits in the largest of the basal ganglia nuclei – the striatum. This nucleus receives the richest dopaminergic innervation of all the nuclei in the basal ganglia and has been the most intensively studied. However, dopamine also modulates all of the other nuclei of the basal ganglia and this influence should not be under-estimated. It won't be discussed much here only because there isn't nearly as much known about it. The review

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concludes with a discussion of recent work characterizing neuronal assemblies in the striatum and their possible modulation by dopamine. These neuronal assemblies, which are dynamically constructed from the canonical circuit elements discussed in the first part of the review, might be the network representation of actions.

The striatal DA innervation

A cardinal feature of the striatum is its dense DA innervation, which arises from the midbrain (Bolam et al., 2000). This dopaminergic input is critical to shaping the activity of striatal networks. This is accomplished through activation of G-protein coupled receptors (GPCRs) for dopamine (DA) receptors distributed along the dendrites and axon terminals of both principal neurons and interneurons. The principal neurons of the striatum are GABAergic spiny projection neurons (SPNs). SPNs constitute as much as 90% of the striatal neuron population. SPNs can be divided into two approximately equally-sized populations based on axonal projections. One population – direct pathway SPNs (dSPNs) – projects axons to the nuclei at the interface between the basal ganglia and the rest of the brain, whereas the other population – indirect pathway SPNs (iSPNs) – projects only to an intermediate basal ganglia nucleus, connecting only indirectly to the interface nuclei (Gerfen and Surmeier, 2011).

Another important way in which dSPNs and iSPNs differ is in their expression of DA receptors. Five G-protein coupled receptors mediate DA signaling (D₁-D₅). These receptors are grouped into two classes based on the G-protein to which they couple: D₁, D₅ (D₁-like) receptors stimulate G_s and G_{olf} proteins, whereas D₂, D₃, and D₄ (D₂-like) receptors stimulate G_o and G_i proteins (Neve et al., 2004). G_s and G_{olf} proteins stimulate adenylyl cyclase, elevating intracellular levels of cyclic adenosine monophosphate (cAMP) and activating protein kinase A (PKA). PKA has a broad array of cellular targets, including transcription factors, voltage-dependent ion channels and glutamate receptors (Svenningsson et al., 2004). G_{i/o} proteins target voltage-dependent ion channels through a membrane-delimited mechanism, as well as enzymes like phospholipase C (PLC) isoforms (e.g. Hernandez-Lopez et al., 2000). G_i proteins also inhibit adenylyl cyclase (Stoof and Keibarian, 1984). Another important feature of the D₂-like pathway is its potent modulation by RGS (regulators of G-protein signaling) proteins that are robustly expressed in striatal neurons (Geurts et al., 2003).

All five DA receptor are expressed in the striatum, but D₁ and D₂ receptors are far and away the most abundant. These two receptors are largely segregated in dSPNs and iSPNs: D₁ receptors are expressed by dSPNs, whereas D₂ receptors are expressed by iSPNs (Gerfen et al., 1990, Surmeier et al., 1996). This dichotomy was first inferred from the effects of DA depletion on gene expression. D₁ receptor agonists restored striatal SP levels and D₂ receptor agonists restored ENK levels (Gerfen et al., 1990). In situ hybridization studies confirmed that D₁ receptor mRNA and SP colocalized in dSPNs and D₂ receptor mRNA and ENK colocalized in iSPNs. As simple as this story was, it didn't align perfectly with electrophysiological studies showing that D₁ and D₂ receptor agonists seemed both to have effects on individual striatal neurons (Surmeier et al., 1992). The simplest explanation for the physiological studies was that D₁ and D₂ receptors were co-localized in SPNs. However, the absence of any significant degree of D₁ and D₂ receptor co-localization was evident in single cell RT-PCR studies (Surmeier et al., 1996). Because these studies were not quantitative, the very modest extent of co-localization found in these studies could be attributable to the detection of low abundance transcripts that had little or no functional impact. This point has been driven home more recently by the development of BAC transgenics in which eGFP or Cre-recombinase are expressed under control of the D₁ or D₂ promoter (Gong et al., 2003). Examination of these mice has confirmed the stark segregation

of D₁ and D₂ receptor expression in direct and iSPNs (Gertler et al., 2008, Valjent et al., 2009), confirming the original hypothesis advanced by Gerfen (Gerfen et al., 1990).

What then explains the physiological data? There are two obvious alternatives to colocalization. First, because the pharmacological tools are crude and only allow the D₁- and D₂-like receptors to be discriminated, it could be that SPNs express the less abundant DA receptors (D₅, D₃, D₄). Single cell RT-PCR profiles of SPNs clearly support this view, showing that dSPNs expressed low levels of D₃ receptor mRNA and iSPNs expressed low levels of D₅ mRNA (Surmeier et al., 1996).

Another possibility that has gained more support in recent years is that DA receptor expressing striatal interneurons play an important role in regulating both types of SPN, leading to indirect responses to a global DA signal. There are four well-characterized classes of striatal interneuron: cholinergic interneurons, parvalbumin-expressing GABAergic interneurons, calretinin-expressing GABAergic interneurons and NPY/nitric oxide-expressing GABAergic interneurons (Tepper et al., 2008). Together, these interneurons constitute about 5-10% of all striatal neurons. One of them, the cholinergic interneuron, co-express D₂ and D₅ receptors (Bergson et al., 1995, Hersch et al., 1995, Yan et al., 1997) and modulate both SPN populations through muscarinic receptors (Bernard et al., 1992, Yan and Surmeier, 1996). Two other prominent interneurons, the somatostatin/neuropeptide Y (NPY) expressing GABAergic interneuron and the parvalbumin (PV) GABAergic interneuron, express D₅ DA receptors (Centonze et al., 2002, Centonze et al., 2003). To complicate matters, the PV interneuron is strongly innervated by globus pallidus neurons that express D₂ receptors (Bevan et al., 1998), creating a microcircuit that is influenced by both D₁- and D₂-class receptors (Wiltchko et al., 2010). As outlined below, there are good reasons to believe that these interneurons play important roles in regulating direct and indirect pathway activity, providing a mechanism by which a ligand for a single receptor class can have broad effects.

An additional complication is that DA terminals themselves express D₂-class autoreceptors, making the interpretation of pharmacological manipulations targeting these receptors problematic.

Thus, the striatal circuitry controlling direct and indirect pathways is complex and the impact of DA on these circuits even more so. Nevertheless, in the last decade, considerable progress has been made toward understanding both. To make the review of this work more tractable, five canonical striatal microcircuits will be considered. These basic circuits are found throughout the striatum.

The corticostriatal circuit

The most basic striatal microcircuit is the one formed by glutamatergic cortical pyramidal neurons and SPNs (Bolam et al., 2000). The synapses formed by cortical pyramidal neurons are exclusively on dendritic spines of SPNs. These spines are absent from soma and the most proximal dendrites, rising to a peak density (1-2 per micron) 50-60 microns from the soma and then falling off very gradually in density to the tips of the sparsely branching dendrites (250-400 μ m) (Wilson, 1994). Individual cortical axons are sparsely connected to any one SPN, typically making one or two en passant synapses (Parent and Parent, 2006). There is no obvious organization to the cortical synapses on the dendritic tree of SPNs, but this could simply be that this organization is difficult to see, as the striatum lacks the lamination characteristic of other regions where this is apparent (e.g., cerebral cortex).

New techniques are revealing the extent of differences between dSPNs and iSPNs (Lobo et al., 2006, Heiman et al., 2008, Meurers et al., 2009). The functional implications of this

dichotomy are only beginning to be understood. One dichotomy that is readily interpretable is in the somatodendritic anatomy (Gertler et al., 2008). In rodents, the total dendritic length of iSPNs is significantly less than that of dSPNs (Fig. 1). This difference is due to iSPNs having on average two fewer primary dendrites than dSPNs. This difference in surface area, in the absence of any obvious difference in spine density, suggests that dSPNs receive roughly 50% more glutamatergic input than iSPNs. This also makes iSPNs more excitable, as judged by both somatic current injection and activation of nominally the same number of corticostriatal axons (Flores-Barrera et al., 2010). Thus, although SPNs have long been thought to a single type of neuron, there are clear differences between dSPNs and iSPNs.

The neuromodulatory effects of DA on dSPN/iSPNs parallel this dichotomy in intrinsic excitability. Both SPNs have a similar core physiological phenotype. At rest, SPNs are dominated by inwardly rectifying, Kir2 K⁺ channels that hold the membrane potential near the K⁺ equilibrium potential (~-90 mV), far from spike threshold (Wilson, 1993, Shen et al., 2007). This is the so-called 'down-state'. In response to excitatory glutamatergic synaptic input from the cerebral cortex, SPNs depolarize. If this input lacks spatial or temporal convergence, the constitutively open Kir2 K⁺ channels shunt this synaptic current, minimizing the cellular response. However, if this input is highly convergent, the glutamatergic synapses can overwhelm the Kir2 channels and promote their closure (Wilson and Kawaguchi, 1996). Closure of dendritic Kir2 K⁺ channels and inactivation of neighboring Kv4 (A-type) K⁺ channels leads to a dramatic elevation of the input impedance of SPN dendrites and a reduction in their electrotonic length, as revealed with ionic Kir2 channel blockers (Wilson, 1993, Reyes et al., 1998, Day et al., 2008). With this, the SPN somatic membrane reaches a potential near spike threshold. This 'up-state' can last hundreds of milliseconds. It is during this up-state that SPNs spike. These spikes are typically not correlated with the transition to the up-state, suggesting that they are driven by an independent synaptic input (Stern et al., 1998).

DA modulates the glutamatergic synapses responsible for the transition to the up-state and the ion channels controlling spiking. The qualitative features of the modulation depend upon which DA receptor is being stimulated. As originally hypothesized on the basis of changes in gene expression induced by DA depletion (Gerfen et al., 1990), D₂ receptor signaling impedes the up-state transition and diminishes up-state spiking in indirect pathway SPNs, whereas D₁ receptor signaling does precisely the opposite in dSPNs (Surmeier et al., 2007). The responses to suprathreshold corticostriatal stimulation, which elicit plateau potentials similar to *in vivo* up-states, are modulated by D₁ and D₂ receptor agonists in the same way (Flores-Barrera et al., 2011). How this happens is still being unraveled, but some elements of the formula have been defined. In the somatic region where spikes are generated, activation of D₂ receptor signaling reduces inward, depolarizing currents through Cav1 (L-type) Ca²⁺ channels and Nav1 Na⁺ channels, while increasing outward, hyperpolarizing K⁺ channel currents (Surmeier et al., 1992, Kitai and Surmeier, 1993, Greif et al., 1995, Schiffmann et al., 1998, Hernandez-Lopez et al., 2000, Olson et al., 2005). D₂ receptor stimulation also decreases dendritic Ca²⁺ entry through voltage-dependent channels (Day et al., 2008, Flores-Barrera et al., 2010, Higley and Sabatini, 2010a).

Complementing these alterations in the gating of voltage-dependent ion channels is a reduction in glutamatergic signaling. Although it is not clear whether they are located pre- or postsynaptically (Yin and Lovinger, 2006), D₂ receptor stimulation diminishes presynaptic release of glutamate by cortical afferents (Flores-Hernández et al., 1997, Bamford et al., 2004). In large part, this modulation depends upon the production of endocannabinoids and activation of presynaptic CB1 receptors (see below). Activation of D₂ receptors also has been reported to decrease AMPA receptor currents in SPNs (Cepeda et al., 1993, Hernandez-Echeagaray et al., 2004). This could be accomplished by D₂ receptor triggered

dephosphorylation of GluR1 subunits, which should promote trafficking of AMPA receptors out of the synaptic membrane (Hakansson et al., 2006). However, recent work using glutamate uncaging on proximal dendritic spines failed to find any acute effect of D₂ receptor stimulation on AMPA receptor currents (Higley and Sabatini, 2010b). What Higley and Sabatini did find was that D₂ receptor activation decreased NMDA receptor currents, in keeping with the general pattern of D₂ receptor effects.

D₁ receptor signaling has almost diametrically opposing effects on dSPNs. D₁ receptor stimulation and PKA activation increases somatic Cav1 L-type Ca²⁺ channel currents and decreases somatic K⁺ currents (Kitai and Surmeier, 1993, Surmeier et al., 1995, Galarraga et al., 1997, Gao et al., 1997, Hernandez-Lopez et al., 1997). In addition, D₁ receptor signaling decreases the opening of Cav2 Ca²⁺ channels that control activation of Ca²⁺-dependent, small conductance K⁺ (SK) channels that slow repetitive spiking in SPNs (Surmeier et al., 1995, Vilchis et al., 2000). All three of these effects serve to increase spiking of dSPNs with somatic depolarization. The only apparently incongruent modulation is the one that was described first showing D₁ receptor signaling decreased, excitatory Na⁺ currents (Calabresi et al., 1987). This observation was confirmed by voltage clamp work showing that D₁ receptor signaling reduces Na⁺ channel availability without altering the voltage-dependence of fast activation or inactivation (Surmeier et al., 1992). Subsequent work has shown that PKA phosphorylation of the pore-forming subunit of the Na⁺ channel promotes activity dependent entry into a non-conducting, slow inactivated state that can be reversed only by membrane hyperpolarization (Carr et al., 2003, Chen et al., 2006). It is likely that the D₁ receptor modulation is mediated by phosphorylation of somatic Nav1.1 channels, as axon initial segment Nav1.6 channels are not efficiently phosphorylated by PKA (Scheuer and Catterall, 2006) and Na⁺ channels do not extend any significant distance into the dendrites of SPNs (Day et al., 2008). Given this restricted site of action and its time and voltage-dependence, it's reasonable to hypothesize that this effect simply acts as a brake on the spike-promoting effects of D₁ receptors on Ca²⁺ and K⁺ channels (as well as glutamergic signaling described below).

A number of studies suggest that D₁ receptor signaling has positive effects on AMPA and NMDA receptor function and trafficking, in contrast to D₂ receptors. For example, D₁ receptor activation of PKA enhances surface expression of both AMPA and NMDA receptors (Snyder et al., 2000, Sun et al., 2005, Hallett et al., 2006). The precise mechanisms underlying the trafficking remains unknown but the tyrosine kinase Fyn and the protein phosphatase STEP (striatal-enriched-phosphatase) appear to be important regulators of surface expression of glutamate receptors (Braithwaite et al., 2006). Trafficking and localization might also be affected by a direct interaction between D₁ and NMDA receptors (Dunah et al., 2000, Lee et al., 2002, Scott et al., 2006). Rapid D₁ receptor effects on glutamate receptor gating have been more difficult to see physiologically. Although PKA phosphorylation of the NR1 subunit is capable of enhancing NMDA receptor currents (Blank et al., 1997), the presence of this modulation in SPNs is controversial. In neurons where the engagement of dendritic voltage-dependent ion channels has been minimized by dialyzing the cytoplasm with cesium ions, D₁ receptor agonists have little or no discernible effect on AMPA or NMDA receptor mediated currents (Nicola and Malenka, 1998). However, in SPNs where this has not been done, D₁ receptor stimulation appears to rapidly enhance currents evoked by NMDA receptor stimulation (Cepeda et al., 1993). The difference between these results suggests that the effect of D₁ receptors on NMDA receptor currents is largely indirect and mediated by voltage-dependent dendritic channels that are taken out of play by more effectively clamping dendritic voltage. Indeed, blocking Cav1.3 L-type Ca²⁺ channels, which open in the same voltage range as NMDA receptors attenuates the D₁ receptor mediated enhancement of NMDA receptor currents (Liu et al., 2004).

In healthy rodents, the ambient level of extracellular striatal DA is thought to be in the low nanomolar range (reflecting the basal pacemaking of DA neurons innervating the striatum), rising into near micromolar ranges with burst spiking of DA neurons (Bass et al., 2010). Because D₂ receptors exist primarily in a high affinity state in the striatum, ambient, nanomolar concentrations of DA are sufficient to tonically inhibit iSPNs, and perhaps, several types of interneuron. Conversely, transient elevation of DA into the micromolar range activates low affinity D₁ receptors on dSPNs, increasing their excitability. Hence, it appears that under basal conditions, the intrinsic differences in excitability of dSPNs and iSPNs (described above) are counterbalanced by a tonic D₂ receptor inhibition of iSPNs. This will tend to balance the responsiveness of direct and indirect pathways to cortical signals - which is a key feature of classical models of basal ganglia function (Albin et al., 1989). This also suggests that any variation in extracellular DA created by drugs or disease states, like Parkinson's disease, might disrupt this balance (see below).

Although intuitively appealing, this simple model fails to take into account DA regulation of striatal interneurons. What is known about this important component of the striatal network is discussed briefly below.

As important as the impact of DA is on the moment-to-moment activity of the corticostriatal network, it also has important part to play in regulating long-term changes in synaptic strength. There are several recent reviews that cover this ground (Surmeier et al., 2007, Kreitzer and Malenka, 2008, Wickens, 2009, Gerfen and Surmeier, 2011), so only the major points bearing on the dichotomy between direct and indirect pathways will be discussed here. At the outset, it must be acknowledged that nearly all of what has been described as corticostriatal synaptic plasticity is truly glutamatergic synaptic plasticity, as corticostriatal and thalamostriatal glutamatergic synapses have not been reliably distinguished. With that caveat in mind, we'll follow the convention and assume that what has been described applies to the corticostriatal synapse formed on a dendritic spine.

The best characterized form of SPN synaptic plasticity is long-term depression (LTD). Unlike the situation at many other synapses, striatal LTD induction requires pairing of postsynaptic depolarization with moderate to high frequency afferent stimulation at physiological temperatures (Lovinger et al., 1993, Kreitzer and Malenka, 2005). Typically for the induction to be successful, postsynaptic L-type calcium channels and mGluR5 receptors need to be co-activated. Both L-type calcium channels and mGluR5 receptors found near glutamatergic synapses on MSN spines, making them capable of responding to local synaptic events (Testa et al., 1994, Carter and Sabatini, 2004, Day et al., 2006, Carter et al., 2007). The induction of LTD requires the postsynaptic generation of endocannabinoids (ECs) (Gerdeman et al., 2002). ECs diffuse retrogradely to activate presynaptic CB1 receptors and decrease glutamate release probability. Both of the abundant striatal ECs – anandamide and 2-arachidonylglycerol (2-AG) – are involved in the metabolic mechanisms responsible for EC production (Giuffrida et al., 1999, Gao et al., 2010, Lerner et al., 2010, Tanimura et al., 2010). A key question about the induction of striatal LTD is whether activation of D₂ receptors is necessary. Activation of D₂ receptors is a potent stimulus for anandamide production (Giuffrida et al., 1999). However, recent work showing the sufficiency of L-type channel opening in EC-dependent LTD (Adermark and Lovinger, 2007), makes it clear that D₂ receptors play a modulatory – not obligatory – role. The real issue is the role of D₂ receptors in LTD induction using synaptic stimulation. Studies have consistently found that in iSPNs, D₂ receptor activation is necessary (Wang et al., 2006, Kreitzer and Malenka, 2007, Shen et al., 2008). This could be due to the need to suppress A2a adenosine receptor signaling that could impede efficient EC synthesis and LTD induction (Fuxe et al., 2007, Shen et al., 2008). Indeed, Lerner et al. demonstrate quite

convincingly that antagonism of A2a receptors promotes EC-dependent LTD induction in iSPNs (Lerner et al., 2010).

The question then is can EC-dependent LTD be induced in dSPNs that do not express D₂ receptors? When a minimal local stimulation paradigm is used, LTD does not appear to be induced in these SPNs (Kreitzer and Malenka, 2007, Shen et al., 2008). However, using macroelectrode stimulation, EC-dependent LTD is readily inducible in identified dSPNs (Wang et al., 2006), consistent with the high probability of SPN induction seen in previous work (Calabresi et al., 2007). In this circumstance, LTD induction was dependent upon D₂ receptors. But how? There are a couple of possibilities. One is that D₂ receptor stimulation reduces DA release through a presynaptic mechanism, preferentially reducing stimulation of D₁ receptors that oppose the induction of LTD in direct pathway neurons (Shen et al., 2008). The other possibility is that for LTD to be induced in dSPNs, acetylcholine release and postsynaptic M₁ muscarinic receptor signaling must fall (Wang et al., 2006). Recent work by Tozzi et al. has confirmed this earlier inference and extended it to highlight the interaction between A2a and D₂ receptors in the regulation of cholinergic interneuron activity.

Long-term potentiation (LTP) at glutamatergic synapses is less well characterized because it is more difficult to induce in the *in vitro* preparations typically used to study plasticity. Most of the work describing LTP at glutamatergic synapses has been done with sharp electrodes (either *in vivo* or *in vitro*), not with patch clamp electrodes in brain slices that afford greater experimental control and definition of the cellular and molecular determinants of induction. Previous studies have argued that LTP induced in SPNs by pairing HFS of glutamatergic inputs and postsynaptic depolarization depends upon co-activation of D₁ and NMDA receptors (Calabresi et al., 2007). The involvement of NMDA receptors in LTP induction is clear. The necessity of D₁ receptors is another matter. If this were the case, there would be no LTP in iSPNs – an unlikely situation. Again, the advent of BAC transgenic mice has provided an invaluable tool for unraveling this puzzle. In dSPNs, the induction of LTP at glutamatergic synapses is dependent upon D₁ DA receptors (Pawlak and Kerr, 2008, Shen et al., 2008). However, this is not the case in iSPNs (Flajolet et al., 2008, Shen et al., 2008). In them, LTP induction required activation of A2a adenosine receptors. These receptors are robustly expressed in the indirect pathway and have a very similar intracellular signaling linkage to that of D₁ receptors; that is, they positively couple to adenylyl cyclase and protein kinase A (PKA). Acting through PKA, D₁ and A2a receptor activation leads to the phosphorylation of DARPP-32 and a variety of other signaling molecules, including MAPKs, linked to synaptic plasticity (Svenningsson et al., 2004, Sweatt, 2004).

In addition to the convergence of PKA and NMDA receptor signaling (presumably through CaMKII), the induction of corticostriatal LTP also requires activation of receptor tyrosine kinases. Both fibroblast growth factor (FGF) and brain derived neurotrophic factor (BDNF) receptors have been implicated in corticostriatal LTP induction (Flajolet et al., 2008, Jia et al., 2010). How these receptor tyrosine kinases interact with the other obligate signaling pathways involved in LTP induction and whether they are operative at all glutamatergic synapses remains to be determined.

Although most of the induction protocols for synaptic plasticity that have been used to study striatal plasticity are heroic, involving sustained, strong depolarization and/or high frequency synaptic stimulation that induces dendritic depolarization, they do make the necessity of postsynaptic depolarization clear. In a more physiologically relevant setting, what types of depolarization are likely to gate induction? One possibility is that spikes generated in the axon initial segment (AIS) propagate into dendritic regions where synapses are formed. Recent work has shown that STDP is present in SPNs (Fino et al., 2005, Pawlak

and Kerr, 2008, Shen et al., 2008). But there are reasons to believe that this type of plasticity is relevant for only a subset of the synapses formed on SPNs. SPN dendrites are several hundred microns long, thin and modestly branched. Their initial 20-30 microns are largely devoid of spines and glutamatergic synapses. Glutamatergic synapse and spine density peaks near 50 microns from the soma and then modestly declines with distance (Wilson, 2004). Because of their geometry and ion channel expression, AIS generated spikes rapidly decline in amplitude as they invade SPN dendrites (as judged by their ability to open voltage-dependent calcium channels), producing only a modest depolarization 80-100 microns from the soma. This is less than half the way to the dendritic tips (Day et al., 2008), arguing that a large portion of the synaptic surface area is not normally accessible to somatic feedback about the outcome of aggregate synaptic activity. High frequency, repetitive somatic spiking improves dendritic invasion, but distal (>100 microns) synapses remain relatively inaccessible, particularly in dSPNs (Day et al., 2008).

In the more distal dendritic regions, what controls plasticity? The situation in SPNs might be very similar to that found in deep layer pyramidal neurons where somatically generated bAPs do not invade the apical dendritic tuft (Golding et al., 2002). In this region, convergent synaptic stimulation is capable of producing a local calcium spike or plateau potential that produces a strong enough depolarization to open NMDA receptors and promote plasticity. Calcium imaging using 2PLSM has shown that there is robust expression of both low threshold Cav3 and Cav1 Ca²⁺ channels – in addition to NMDA receptors – in SPN dendrites (Carter and Sabatini, 2004, Day et al., 2006, Carter et al., 2007), a result that has been confirmed using cell-type specific gene profiling (Day et al., 2006). If distal dendrites are capable of regenerative activity, they could also be important to the induction of plasticity in SPNs. SPN dendrites do appear to be active in some circumstances (Kerr and Plenz, 2002, Vergara et al., 2003, Carter and Sabatini, 2004, Kerr and Plenz, 2004, Flores-Barrera et al., 2010) and this activity does not appear to arise from the somatic and proximal dendrites of adult SPNs (Wilson and Kawaguchi, 1996). Moreover, from this latter study, it is clear that SPNs are not bistable in the absence of synaptic stimulation.

One possible scenario is that distal SPN dendrites are bistable when NMDA receptors are active during synaptic stimulation. If this is the case, spatial convergence of glutamatergic inputs onto a distal dendrite could induce a local plateau potential capable of pulling the rest of the cell into depolarized state – like an up-state. Doing so would collapse the electrotonic structure of SPNs (Wilson, 1992), enhancing the impact of excitatory input anywhere on the dendrite. The lack of temporal correlation between up-state transitions and EPSP-driven spike generation (Stern et al., 1998) is consistent with this scenario. Indeed, recent work by our group has shown that distal dendrites of both types of SPN are capable of regenerative activity (Plotkin et al., 2011). Using two photon uncaging of glutamate (2PLUG) (Carter and Sabatini, 2004, Higley and Sabatini, 2010b) to probe specific dendritic regions of identified SPNs, it was found that about halfway from the base to the tip of a SPN dendrite, 2PLUG at 10-15 adjacent spines can evoke long lasting plateau potentials that are virtually identical to up-states, at least from the standpoint of somatic membrane potential. These up-states were dependent upon an interaction between NMDA receptors and voltage-dependent Ca²⁺ channels (Cav3, Cav2.3). The ability of distal, but not proximal, dendrites to generate these plateau potentials appears to reflect their elevated expression of Cav3 channels their increased input resistance (due to dendritic tapering).

This discovery has fundamental implications for how the striatal circuit is wired and controlled by corticostriatal signals. Rather than requiring hundreds or thousands of temporally convergent inputs that are spatially distributed across the dendritic tree of SPNs, up-state transitions require only a handful of temporally and spatially convergent inputs onto a single dendrite. Obviously, this changes the types of cortical signal SPNs will be sensitive

to and dramatically increases SPN pattern recognition capacity (e.g., Poirazi and Mel, 2001). Because regenerative events engage NMDA receptors that are central to LTP induction (and synapse stability), this capacity will promote the clustering of co-active synapses in dendritic microdomains (10-20 micron stretches of dendrite). Because the dendritic plateaus are regulated by D₁, D₂ and A2a receptor signaling in the expected way, they provide a means by which afferent activity alone can induce changes in the strength of distal synapse, complementing how plasticity is induced in the proximal dendrites. Unpublished work by our group using 2PLUG stimulation of distal dendritic sites has confirmed this hypothesis, showing in iSPNs that co-activation of NMDA, A2a and TrkB receptors leads to potentiation of a subset of distal synapses.

In vivo studies of striatal synaptic plasticity have provided an important counterpoint to the perspectives based upon reduced *in vitro* preparations. The pioneering work of Charpier and Deniau (Charpier and Deniau, 1997, Charpier et al., 1999) demonstrated that with more intact input, LTP was readily inducible in SPNs. More recently, it has been shown that the sign of synaptic plasticity in SPNs is influenced by anesthetic and presumably the degree of cortical synchronization in corticostriatal projections (Stoetzner et al., 2010). In particular, in barbiturate-anesthetized rats, 5Hz stimulation of motor cortex evokes LTP in the striatum, but in awake animals the same stimulation induced LTD. A challenge facing the field is how to bridge these observations. Because glutamatergic connections are sparse, it is virtually impossible to reliably stimulate a collection of synapses onto a particular SPN dendrite with an electrode in a brain slice. Optogenetic techniques might provide a feasible alternative strategy, but these approaches are not well-suited to high frequency stimulation of axons. It also will be critical to determine the roles of proximal and distal dendritic synaptic input in the regulation of this activity. At present, nothing is known about the origins or properties of these two types of input. For example, it is not clear whether they originate from the same cortical and thalamic ensembles.

The feedback striatal circuit

SPNs have a richly branching recurrent axon collateral that arborizes in the neighborhood of its parent cell body (Kawaguchi et al., 1989). This feedback could provide the substrate for lateral inhibition (Groves, 1983) and has figured prominently in several models of striatal processing (Beiser et al., 1997). However, the functional significance of this feedback circuit has been controversial. In large measure, this is because the synapses formed by recurrent collaterals are largely onto distal dendrites of other SPNs (Wilson and Groves, 1980, Bolam et al., 1983), making their physiological effects difficult to see with a somatic electrode (Jaeger et al., 1994). Using paired patch clamp recordings from neighboring SPNs, it has been possible to more reliably see the effects of collateral activation (Czubayko and Plenz, 2002, Tunstall et al., 2002, Koos et al., 2004, Taverna et al., 2008), but the percentage of synaptically connected neighbors has been small (~10-15%) in randomly selected SPNs in brain slices. Using D₁ and D₂ BAC transgenic mice to direct sampling, it was found that although iSPNs project to both themselves and direct pathway SPN dSPNs, direct pathway SPN dSPNs connect essentially only with other direct pathway SPN dSPNs (Taverna et al., 2008). The percentage of SPNs showing demonstrable connectivity doubled when sampling was not random. DA modulates GABA release at recurrent collateral synapses. D₂ receptor stimulation decreases GABA release, whereas D₁ receptor stimulation increases release (Guzman et al., 2003, Tecuapetla et al., 2007, 2009). Given that D₂ receptors should be active at basal extracellular DA levels, the feedback circuit of the indirect pathway should be depressed, disinhibiting dendritic integration. A transient elevation in striatal DA should preferentially activate D₁ receptors, leading to enhanced GABA release at collaterals formed between direct pathway SPN dSPNs, enhancing lateral inhibition of dendritic integration. Because D₁ receptor stimulation enhances the somatodendritic excitability of dSPNs, the

collateral modulation should in principle promote the type of population sculpting typically envisioned for lateral inhibition (Beiser et al., 1997). Conversely, a transient drop in striatal DA should enhance GABA release at collaterals formed by the iSPNs. Because this drop elevates the somatodendritic excitability of indirect pathway SPNs, the collateral modulation should promote a similar type of population sculpting, but one favoring a subset of strongly activated indirect pathway SPN iSPNs (Tecuapetla et al., 2009). The critical gap in this scenario is the lack of compelling data about how dendritic GABAergic synapses shape synaptic integration in SPNs, although this gap is beginning to be filled (Flores-Barrera et al., 2010).

The feedforward corticostriatal circuit

Fast-spiking (FS), PV GABAergic interneurons receive a prominent glutamatergic input from cortical pyramidal neurons and, in turn, convey this activity through perisomatic synapses to both dSPNs and iSPNs (Kita, 1993, Bennett and Bolam, 1994, Koos and Tepper, 1999, Gittis et al., 2010, Planert et al., 2010), thus being strategically located to control neuronal spiking. This feed-forward inhibition is thought to contribute to action selection by suppressing SPN activity in circuits associated with unwanted actions (Kita et al., 1990, Parthasarathy and Graybiel, 1997, Gage et al., 2010). In the striatum and other circuits, FS-PV neurons contribute to fast gamma oscillations (Whittington and Traub, 2003, Berke, 2009), which in the motor system are pro-kinetic, making movements easier (Hutchison et al., 2004). Although both types of SPN are targeted in this circuit, paired recordings in BAC mice have found some preferential connectivity of FS interneurons with dSPNs (Gittis et al., 2010), although this has not been seen in all studies (Planert et al., 2010).

One of the major projections to FS interneurons originates from GPe neurons that are preferentially controlled by iSPNs (Rajakumar et al., 1994, Spooren et al., 1996, Bevan et al., 1998). This feedback loop complements the one formed by collateral projections of SPNs. D₂ receptor agonists depress the GABAergic inputs to FS interneurons (Bracci et al., 2002, Centonze et al., 2003, Sciamanna et al., 2009, Gage et al., 2010), which are presumably derived in large measure from GPe neurons which express D₂-class receptors (Hoover and Marshall, 2004). This dual control of the feedback by D₂ receptors in indirect pathway and GPe neurons suggests that its function is attenuated by basal DA, but capable of rapid facilitation if DA levels fall. This suppression of the GABAergic feedback circuit complements the elevation in FS interneuron excitability mediated by postsynaptic D₅ receptors.

Somatostatin (SOM)/neuropeptide Y (NPY)/nitric oxide synthase (NOS) GABAergic interneurons also form another, less well studied, part of the feedforward corticostriatal circuit (Tepper et al., 2008, Tepper et al., 2010). Because these interneurons respond to intrasomatic current injection with persistent plateau potentials and rebound, low threshold spikes, they are often referred to as PLTS interneurons (Kawaguchi, 1993, Tepper et al., 2010). If these interneurons are like the SOM expressing, Martinotti interneurons of cortex (Wang et al., 2004), their innervation of distal dendrites could make it difficult to accurately judge their importance using somatic electrodes, as with SPN recurrent collaterals. What should allow a more accurate estimation of their functional role is to examine the effect on synaptic integration. An intriguing study by Flores-Barrera et al. (2010) found that cortical stimulation produced a shunting inhibition in iSPNs that reduced summation of concurrent EPSPs, whereas the same stimulation produced a weaker response in dSPNs that was often depolarizing. It is tantalizing to hypothesize, particularly in light of the work of Gittis et al. and Planert et al. described above, that these responses to cortical stimulation were a consequence of engagement of SOM/NPY/NOS interneurons contacting distal dendrites of

SPNs. Because these interneurons express D₅ receptors, this regulation should be influenced by DA (Centonze et al., 2002).

The feedforward thalamostriatal circuit

The other major glutamatergic projection to the striatum originates in the thalamus (Smith et al., 2004). The synapses formed by this projection are found both on dendritic shafts and spine heads, in the same regions as those formed by the corticostriatal projection. In contrast to the corticostriatal synapses, those formed by thalamic axons have a high release probability, making them well-suited to signaling transient events (Ding et al., 2008). Another major target of this projection is the cholinergic interneuron. Like the corticostriatal feedforward circuit involving FS interneurons, the thalamostriatal projection makes a feedforward connection to SPNs through cholinergic interneurons (Ding et al., 2010). With a burst of thalamic activity like that seen after presentation of a salient stimulus, cholinergic interneurons exhibit a burst-pause pattern of activity that enhances the somatic excitability of both SPNs (Perez-Rosello et al., 2005, Pisani et al., 2007), but preferentially enhances the dendritic excitability of iSPNs by decreasing Kir2 K⁺ channel opening (Shen et al., 2007). As noted above, reducing Kir2 K⁺ channel opening increases dendritic input resistance and the ability to sum corticostriatal inputs. The role of DA in regulating the thalamostriatal projection to SPNs has not been systematically explored. However, DA potently modulates the activity of cholinergic interneurons through D₂ and D₅ receptors. D₂ receptors suppress the ongoing pacemaking activity of interneurons (Maurice et al., 2004) and diminished acetylcholine release (DeBoer et al., 1996, Ding et al., 2006). D₅ receptors complement this modulation by enhancing GABAergic responsiveness (Yan and Surmeier, 1997, Deng et al., 2007).

Cholinergic interneurons also might enhance FS interneuron GABAergic input to SPNs, as FS interneurons express nicotinic receptors (Koos and Tepper, 2002, Sullivan et al., 2008, Xiao et al., 2009b). As described above, FS interneurons potently inhibit SPNs. However, a direct demonstration of a functional connection between cholinergic interneurons and FS interneurons is lacking (Tepper et al., 2010). Interestingly, a recurrent GABAergic input to cholinergic interneurons does not depend upon nicotinic receptors (Sullivan et al., 2008), suggesting that there are alternative networks containing GABAergic neurons that might influence SPNs.

Striatal cell assemblies

How are these canonical microcircuits assembled to control striatal target structures, like the GP during action selection? This is a daunting question. Hebb created a theoretical framework in which this question could be approached over 60 years ago (Hebb, 1949, Harris, 2005). He posited that long-term synaptic plasticity is the initial stage of a series of processes that store information by shaping the connectivity of brain microcircuits into cell-assemblies (CAs). CAs have been envisioned as the building blocks of sensory and motor representations (Huyck, 2001, Harris et al., 2003, Harris, 2005, Dragoi and Buzsaki, 2006, Pastalkova et al., 2008).

However, demonstrating the existence of CAs in living tissue has not been trivial. To date, the evidence that CAs exist is indirect and based upon the assumption that experience-dependent correlations in spiking reflect the formation of CAs. For example, correlations between the spiking of an individual neuron (or small group of neurons) and field potentials (reflecting aggregate neural activity in a region) is taken as evidence of CAs (e.g., Sakurai, 1996, Berke et al., 2004, Costa et al., 2006, Ballion et al., 2009). Experiments using voltage-sensitive dyes also suggest that groups of neuron can be co-activated in stereotyped ways

under certain conditions, indicating the presence of CAs (Grinvald et al., 2003, Grinvald, 2005). Another manifestation of CAs is thought to be the existence of recurring patterns of activity in a population of neurons in response to a single stereotyped input. This recurring, patterned activity is thought to be shaped by activity-dependent, long-term synaptic plasticity of the sort described above (Abeles et al., 2004, Grinvald, 2005, Harris, 2005).

Correlated or synchronized spiking among neurons has been observed in many nuclei (e.g., Petersen and Sakmann, 2000, Doupe et al., 2004, Carrillo-Reid et al., 2008, Li et al., 2010). In some cases, synchronization is on the millisecond timescale (Diesmann et al., 1999, Leger et al., 2005, Robbe et al., 2006). However, in most cases, synchrony is on a slower timescale, leading to some ‘jitter’ in spike timing (Calvin and Stevens, 1968, Shadlen and Newsome, 1994, Grinvald et al., 2003, Kostal et al., 2007). The correlation in spiking is envisioned to arise from activity being propagated through the network in a particular, patterned way – a way that is determined by the elements in the network and the strength of the synaptic connections between them (Grinvald et al., 2003, Doupe et al., 2004, Carrillo-Reid et al., 2008, Pastalkova et al., 2008, Uhlhaas et al., 2009). The strength of the synaptic connections, which dictate the correlations in activity, is hypothesized to be sculpted by experience through the mechanisms of LTP/LTD.

Recurring, patterned activity also has been seen, albeit less frequently (Hebb, 1949, Cossart et al., 2003, Grinvald et al., 2003, Abeles et al., 2004, Grinvald, 2005). These repeated, closed loop activity patterns much arise from networks that have re-entrant or cyclical architecture (Hebb, 1949, Harris et al., 2003, Sporns and Kötter, 2004). Recurrent, patterned activity, also called “phase sequences”, have been observed in cortical circuits (Tsodyks et al., 1999); this kind of activity is hypothesized to be a substrate of working memory (Hebb, 1949, Pastalkova et al., 2008). These types of circuit have the property of compositionality (Hammer, 2003). That is, they possess a “syntax” that allows reconfiguration, resulting in the expansion or contraction of the number of participating neurons (Carrillo-Reid et al., 2009). Compositionality implies that the network contains a modularity that allows small groups of neuron (modules) to be brought into or removed from an active circuit (Bienenstock and Geman, 1995, Hammer, 2003, Abeles et al., 2004). In the case of the striatum, these modules might be the canonical microcircuits described above. Neuromodulators, like DA, that shape synaptic transmission and its integration, could serve to control the excitability of these canonical modules and the compositional properties of striatal CAs (Jáidar et al., 2010). For example, on a short time scale, DA modulation of dendritic excitability and up-state transitions could dictate which SPNs participate in a CA at any one point in time. On a longer time scale, DA modulation of corticostriatal synaptic strength through LTP/LTD mechanisms could determine the SPNs participating in a particular CA.

Are there striatal CAs capable of recurrent, closed loop activity?

From a theoretical standpoint, the striatal network has many of the canonical features required to generate this kind of activity.

First, as described above, synaptic connections within the striatum is capable of undergoing experience-dependent, long-term changes in strength, as required of a Hebbian CA. Although plasticity at the corticostriatal glutamatergic synapse formed with SPNs is the best studied, similar sorts of plasticity exist at other synaptic connections within the striatum (Adermark and Lovinger, 2009, Rueda-Orozco et al., 2009), suggesting that the mechanisms are in place to allow experience to shape connectivity and CA composition.

Second, as outlined above (the feedback striatal circuit) there are recurrent collateral connections between SPNs. This type of connection is necessary to establish neuronal pools,

or aggregates, whose synchronous activity underlie network states (Sporns et al., 2002, Grillner, 2006). Whether recurrent collaterals subserve this function in the striatum is controversial, but this might simply be a consequence of our reliance upon a weak outcome measure (e.g., somatic IPSPs) that is not really indicative of their function in an intact network. An indication that this is the case comes from recent work showing that their blockade abolishes the reverberation of network states in the striatum (Carrillo-Reid et al., 2008). Moreover, weakening these connections by DA deprivation (Taverna et al., 2008, Tecuapetla et al., 2009) tends to abolish microcircuit dynamics by leaving a single dominant network state that traps most active neurons (Jáidar et al., 2010).

Third, the striatum possesses strong canonical feedforward and feedback networks involving interneurons (Sporns et al., 2002, Grillner, 2006). Activity in interneurons can be recorded in several network states and they appear to be capable of synchronizing SPNs (Fig. 2) (Carrillo-Reid et al., 2008). As noted above, DA (and, hence, experience) modulates the activity of interneurons and their connections. Reverberation, or repetitive activity patterns could shape network activity in way that enhances the ability of a particular cortical or thalamic input to activate a CA and to reduce variability in the temporal pattern of CA activity; this synaptic sculpting might also reduce the ‘completeness’ of the input pattern needed to activate a CA. A similar scenario has been postulated in the cortex (Feldmeyer et al., 2005, Yoshimura and Callaway, 2005, Yoshimura et al., 2005, Feldmeyer et al., 2006).

Fourth, the striatum possesses autonomously active, pacemaking interneurons (Grillner et al., 2005b) (Fig. 2A). Pacemaking is one way to establish recurrent CA activity (Grillner 2006) (Fig. 2B). As noted above, striatal cholinergic interneurons are autonomous pacemakers, but other GABAergic interneurons might also possess this property (Koos and Tepper, 1999, Berke et al., 2004, Ding et al., 2010, Tepper et al., 2010) (Fig. 2C). The reciprocal connections between cholinergic and GABAergic interneuron pools (Koos and Tepper, 2002, Sullivan et al., 2008, Fino and Venance, 2011) might create sustained network activity (Fig. 2A). For this to be the case, fast, ligand-gated excitatory synapses must exist at one of the synapse in the network. Nicotinic ACh receptors found on FS interneurons fit this bill (Koos and Tepper, 2002, Xiao et al., 2009a) and other types of fast receptor might be present at cholinergic synapses (Sullivan et al., 2008). Thus, the striatum has the circuit elements necessary to sustain autonomous network activity. It should be noted that autonomous recurrent activity can also be generated by networks were the connections are ‘hard-wired’ or innate. These networks have been called Central Pattern Generators (CPGs) (Brown, 1911, Grillner, 2006). In contrast to CPGs, the connections which underlie autonomous activity in CAs are thought to be “acquired” through experience-dependent synaptic plasticity (Grillner et al., 1981, Guertin and Hounsgaard, 1998).

Although much remains to be done, there is growing evidence that these four canonical elements of the striatum result in to correlated and recurrent CA activity in the striatum. For example, robust recurrent bursting has been seen in the striatum, both *in vivo* (Herrling et al., 1983) and *in vitro* (Vergara et al., 2003), following elevation of extracellular NMDA concentration to increase network excitability; the same manipulation (unilateral NMDA administration) induces contralateral turning behavior, establishing a link between recurrent bursting and a motor representation (Ossowska and Wolfarth, 1995). The ability of an unstructured ‘drive’, like elevation of extracellular NMDA concentration, to induce patterned striatal activity is strong evidence of CAs. More recently, by using a combination of electrophysiology and dynamic calcium imaging, which allows the activity of dozens of cells to be monitored simultaneously, we have recently demonstrated that SPNs display correlated spiking in response to a stereotyped input and even display recurrent patterns of activity (Carrillo-Reid et al., 2008). These recurrent patterns of activity followed Hamiltonian or Eulerian trajectories, excluding the possibility that this behavior was

fortuitous or random. Furthermore, ex vivo interrogation of striatal tissue from over-trained rodents show clear signs of CA creation (Yin et al., 2009).

Thus, there are good reasons to believe that the canonical circuit elements needed to create CAs are present in the striatum and that striatal CAs can be activated under certain circumstances. What role these CAs play in the striatum remains to be determined. It has been hypothesized that both CPG-like circuits controlling innate movements, like postures and facial expressions, (Ekman et al., 1992, Grillner et al., 2005a) and CAs controlling learned voluntary movements and habits (Graybiel, 2008, Obeso et al., 2008) co-exist within the striatum (or basal ganglia). Testing this conjecture will require methods that allow the activity of CAs to be mapped over time and with changes in experience; it will also be necessary to selectively activate CAs while monitoring behavioral outcomes. Although this experimental situation seemed distant only a few years ago, optical approaches that allow the activity in large collections of neurons to be monitored and the stimulation of collections of neuron based upon molecular phenotype or connectivity are rapidly bringing it within reach.

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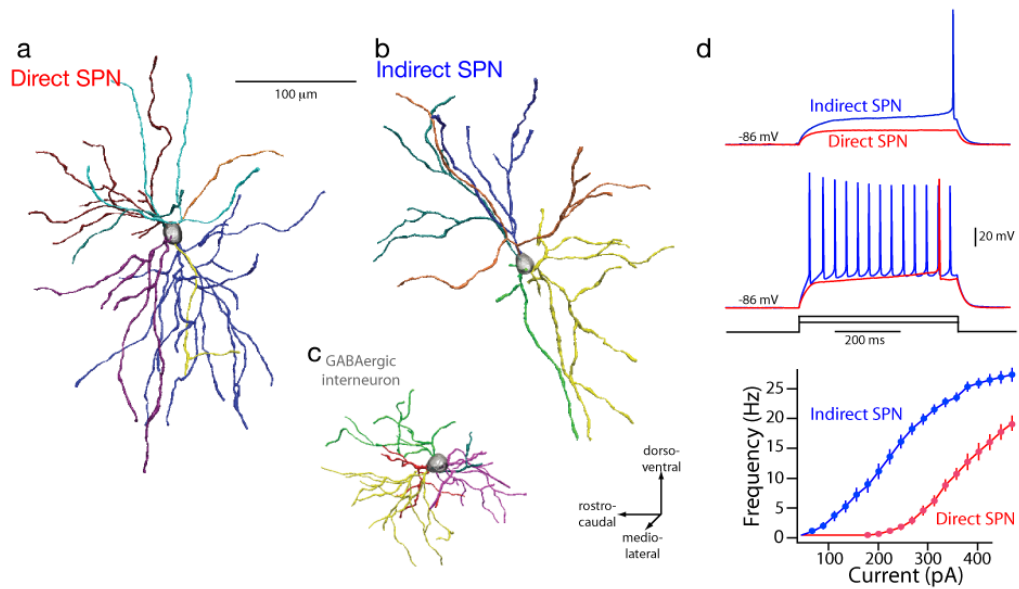
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Highlights

- Dopamine regulates striatal excitability in a cell-type specific manner.
- Dopamine modulates synaptic plasticity in different ways.
- We review the main types of canonical striatal microcircuits.
- Cell assemblies might underlie canonical microcircuits and action selection.
- We discuss how striatal cell assemblies might be regulated by dopamine.

**FIGURE 1.**

Dichotomous anatomy and physiology of direct and indirect pathway SPNs. Reconstructions of biocytin-filled direct (a) and indirect pathway (b) SPNs from P35–P45 BAC transgenic mice; a GABAergic interneuron (c) is included for comparison. The different dendrites are color coded to allow regions of overlap to be interpreted. The dendrites of SPNs were not oriented in any particular direction or plane. Intracellular current injection consistently revealed that indirect pathway SPNs were more excitable than direct pathway SPNs. Current amplitudes at near rheobase for each cell type were used to illustrate the differences; note that these values were remarkably consistent within a population. (d) Summary of the responses of direct and indirect pathway SPNs to a range of intracellular current steps; indirect pathway SPNs were more excitable over a broad range of injected currents. From Gertler et al., 2008.

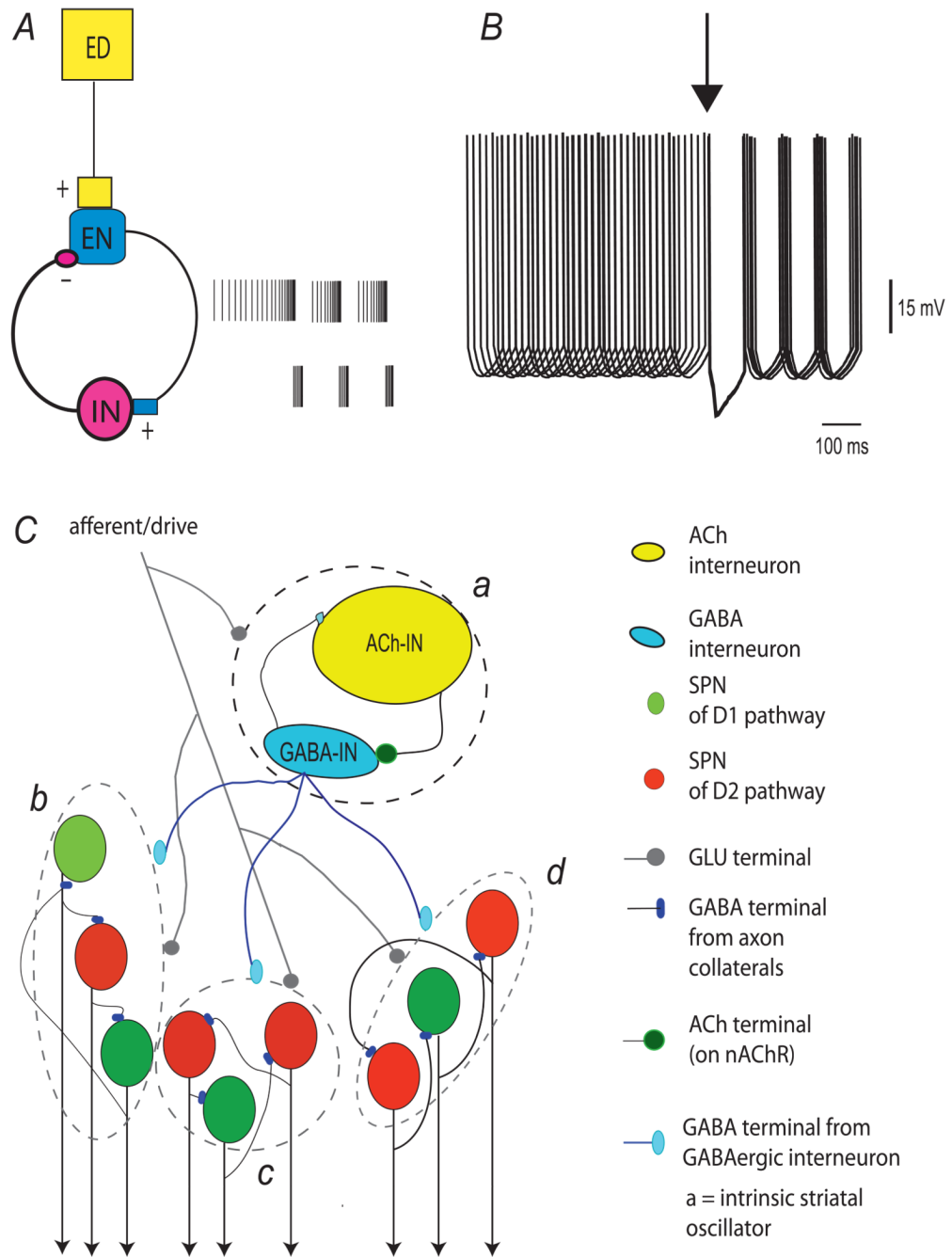


FIGURE 2. Schematic summary of a hypothetical mechanism for activating spontaneous dynamics in striatal cell assemblies as related with the canonical striatal microcircuit. **A.** A basic oscillatory mechanism capable of generating recurrent firing patterns. An excitatory drive or input (ED: yellow box) is capable to activate selected fast-ligand gated synapses, e.g., previously potentiated by LTP, in a pool of excitatory neurons (EN, blue symbol) according to intensity/concentration. EN are connected to a pool of inhibitory neurons (IN, pink symbol) through fast-ligand gated synapses such that when active they immediately excite the pool of IN which in turn transiently inhibits the pool of EN. The basic mechanism for recurrent firing depicted is almost counterphase. However, according to variables such as

synaptic force and intrinsic membrane currents, phase locking may have phase variances. This basic oscillator has been described in various places, e.g., the subthalamic-pallidum loop (Bevan et al., 2002), the reticular-relay thalamic loop (Steriade, 1999), etc. Recurrent firing may be on as long as ED is on, or else, if pacemaking properties of the neurons that conform the oscillator are turned on (Grillner, 2006). Loops between neurons pools that are mutually connected through fast-ligand gated synapses in the striatal microcircuit can be though as conformed by cholinergic interneurons connecting to GABAergic interneurons through nicotinic ACh receptors (nAChR)(Koos and Tepper, 2002). Some interneuron classes connect back to the cholinergic interneurons through fast-ligand gated GABAergic synapses (Fino and Venance, 2011). B. A basic mechanism to synchronize pools of SPNs through the oscillator. Irregular or regular firing unsynchronized neurons, or silent neurons, may receive a strong inhibitory input from a pool of inhibitory interneurons which is known as making a mesh united by electrical and chemical synapses. A strong inhibition resets the network so that when leaving the IPSP many recipient neurons fire in synchrony (Baufreton et al., 2009). An alternative mechanism arises from the glutamate co-release of cholinergic interneurons (Higley et al., 2011). C. Explaining recurrent and alternating network states in the striatal microcircuit. a) Represents the intrinsic oscillator made up by the cholinergic interneurons and any of several classes of GABAergic interneurons. These interneurons may exhibit pacemaking properties according to context. Dashed circle indicates that the excitatory drive may impinge on many of the neuron pools represented by the symbols. Afferent inputs or a continuous excitatory drive turn on these pools according to intensity and location. b-d) Dashed lines enclose represented pools of SPNs (10-40 neurons) recruited by the oscillator as explained in B. These pools have mixtures of direct and iSPNs (unpublished) which are interconnected according to certain rules (Taverna et al., 2008). The synchronized firing of these neuron pools underlie the networks states (peaks of spontaneous synchronization) that alternate their activity in regular and fixed patterns such as reverberating cycles of activity. That is the three pools represented may alternate their activity in a fixed sequence. They are not anatomically separated as in the scheme, but most probably intermingled (Carrillo-Reid et al., 2008). Alternation of activity among the pools may be explained either by a sequential activation of oscillators, or more likely, to a recovery variable that stops synchronized activity within a pool. This recovery variable is under study but may emerge from intrinsic properties, e.g., repolarizing K^+ -currents (see above) and inhibitory interconnections among SPNs. In any case the sequence of network states that show a reverberating cycle is orchestrated by GABAergic interneurons, that unlike SPNs, are active during each network state (Carrillo-Reid et al., 2008).