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Dopaminergic modulation of striatal networks in health and Parkinson's disease

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In the last couple of years, there have been significant advances in our understanding of how dopamine modulates striatal circuits underlying goal-directed behaviors and how therapeutic interventions intended to normalize disordered dopaminergic signaling can go awry. This review summarizes some of the advances in this field with a translational focus on Parkinson's disease.

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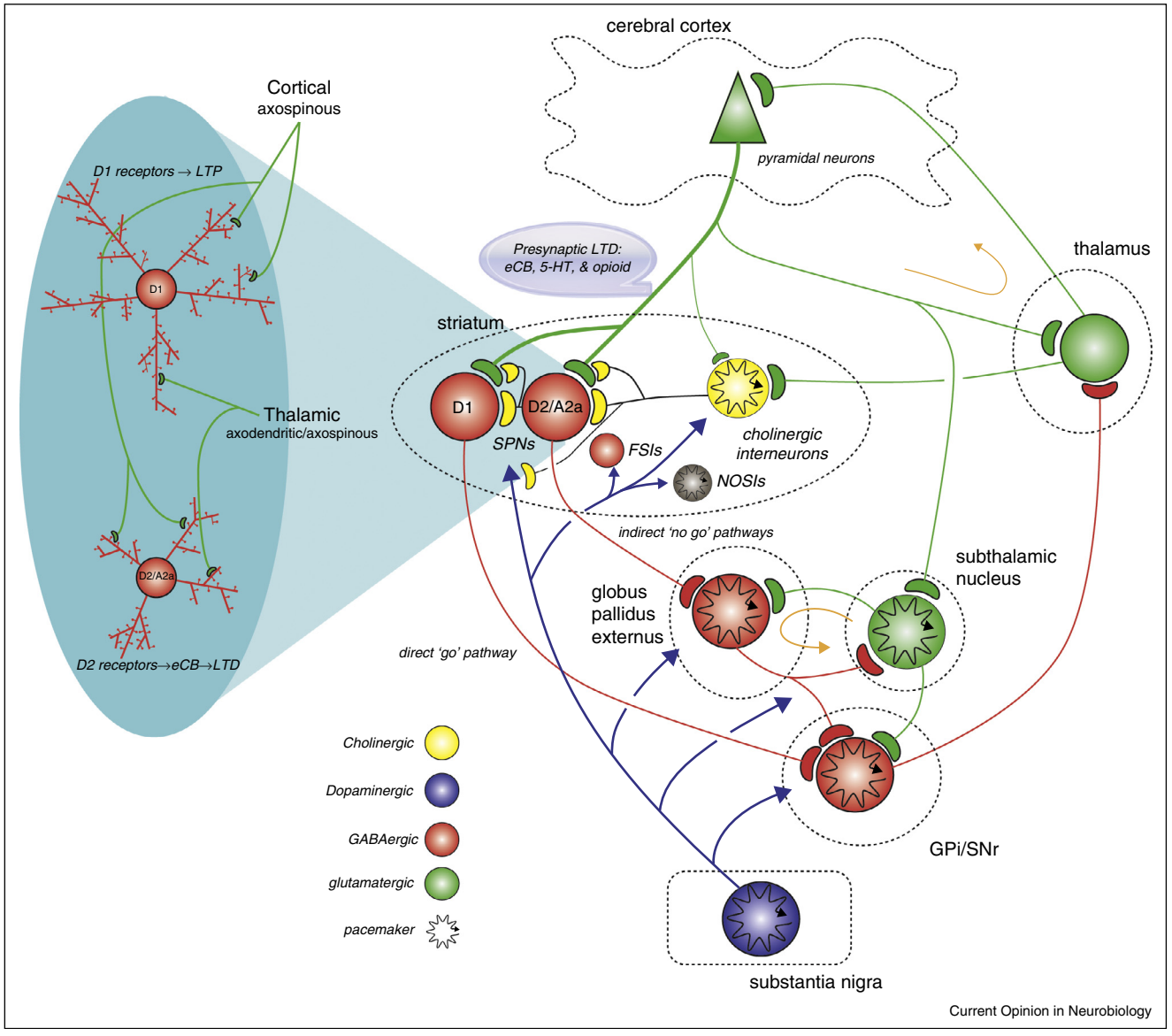
Dopamine is one of the most studied neuromodulators in the nervous system. Last year, over 5000 papers were published that had dopamine as a key word. One of the most studied of the brain regions affected by dopamine is the basal ganglia; nearly 700 of the 5000 dopamine papers in 2013 had 'basal ganglia' as a keyword. The reason for this focus is relatively straightforward. Not only are the basal ganglia important to goal-directed behavior and habit formation, they are also implicated in a wide range of diseases, including Parkinson's disease (PD), Huntington's disease, schizophrenia, dystonia, attention-deficit-hyperactivity-disorder, and depression. Alterations in dopaminergic signaling are involved in most, if not all, of these disorders, making it crucial to understand its normal role and how it goes awry in disease.

Dopaminergic neurons in the substantia nigra pars compacta (SNc) innervate all of the nuclei of the basal ganglia, most prominently the striatum (Figure 1). The striatum is the largest of the basal ganglia nuclei, serving as the principal recipient of information reaching the basal ganglia. The striatal innervation is diverse but is derived primarily from cortical and thalamic regions [1]. Dopamine modulates the responsiveness of principal GABAergic spiny projection neurons (SPNs) to these inputs, as well as the strength of corticostriatal synapses. SPNs that project directly to the interface nuclei of the basal ganglia — direct pathway SPNs (dSPNs) — express primarily D_1 dopamine receptors (D1Rs), which increase intrinsic excitability and promote long-term potentiation (LTP) at glutamatergic corticostriatal synapses. SPNs that project indirectly to the interface nuclei — indirect pathway SPNs (iSPNs) — express primarily D_2 dopamine receptors (D2Rs) that decrease their intrinsic excitability and promote long-term depression (LTD) at corticostriatal synapses. By inhibiting GABAergic neurons in the interface of the basal ganglia (substantia nigra pars reticulata and the internal segment of the globus pallidus), dSPNs gate thalamocortical circuits and action selection, leading it to be referred to as the 'go' pathway [2]. Conversely, by dis-inhibiting these same neurons, iSPNs suppress action selection making it the 'no-go' pathway (Figure 1). By bi-directionally modulating these two SPN populations, dopamine is thought to not only regulate ongoing choices about what to do and not to do, but also to lay down a memory of the consequences of those choices that help guide future behavior. Several studies in the last few years have confirmed the basic features of this model [3–5]. That said, beautiful work by Costa's group [6••] has shown that dSPNs and iSPNs are concurrently active at movement initiation, suggesting that these two pathways do not simply compete for control the basal ganglia output but act in a coordinated way to promote some actions and suppress others.

In PD, this dopaminergic innervation of the striatum is lost. In the classical model, this leads to hyper-activity in iSPNs and hypo-activity in dSPNs, resulting in dis-inhibition of basal ganglia outputs and suppression of movement. Although this model has been remarkably robust, it has its limitations. One is that the spatiotemporal pattern of activity in the striatum and in other parts of the basal ganglia, which is not captured in the model, is crucial to normal movement control and the motor symptoms of the disease [7]. Another major shortcoming is that it fails to account for the ability of neurons and neural circuits to adapt to sustained perturbations in activity. These homeostatic forms of plasticity are generally thought to diminish network dysfunction, but might, in certain circumstances, lead to unexpected and undesirable consequences. This short review will focus on work in the last few years that have provided new insight into the mechanisms by which dopamine regulates SPNs and how this is altered in PD states, particularly the dyskinetic

Figure 1



Circuit diagram depicting basal ganglia circuitry and forms of presynaptic LTD and postsynaptic LTP. The blue blowout to the left of the circuit diagram highlights features of D1 receptor expressing dSPNs (top) and D2 receptor expressing iSPNs (bottom) with dSPNs having larger dendritic arbors than iSPNs. Both dSPNs and iSPNs receive glutamatergic input from the cortex and thalamus; cortical innervation is primarily axospinous and thalamic axodendritic as depicted, albeit not exclusively.

state. A number of more detailed and comprehensive reviews have appeared that complement the narrow focus here [8–10].

Size matters — dopamine and neuronal morphology

For decades, it was thought that from the standpoint of somatodendritic anatomy and intrinsic excitability, SPNs were essentially all alike. But since the advent of bacterial artificial chromosome (BAC) transgenic mice that allow dSPNs and iSPNs to be reliably sampled, it has become apparent that there are significant differences in the intrinsic excitability of these two types of neuron as measured with somatic current injection, glutamatergic stimulation, or by measuring spike invasion into the dendrites [11–14]. Using either somatic current injection or spike invasion of dendrites to assess excitability, iSPNs are more excitable in *ex vivo* brain slices than dSPNs. But why? One obvious possibility is that this difference in intrinsic excitability counterbalances the neuromodulatory effects of dopamine.