Unexpected interactions in the basal ganglia

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Abstract
The basal ganglia (BG) are a phylogenetically conserved set of subcortical nuclei necessary for coordinated motor action and reward learning. Accepted models postulate that the BG modulate cerebral cortex indirectly via an inhibitory output to thalamus, bidirectionally controlled from within the BG by direct (dSPNs) and indirect (iSPNs) pathway striatal projection neurons2-4. The BG thalamic output sculpts cortical activity by interacting with signals from sensory and motor systems5. Here we describe a direct projection from the globus pallidus externus (GP), a central nucleus of the BG, to frontal regions of the cerebral cortex (FC). Two cell types make up the GP-FC projection, distinguished by their electrophysiological properties, cortical projection patterns and expression of choline acetyltransferase (ChAT), a genetic marker for neurons that release the neurotransmitter acetylcholine (ACh). Despite these differences, ChAT+ cells, which have historically been identified as an extension of the nucleus basalis (NB), as well as ChAT− cells, release the inhibitory neurotransmitter GABA (γ-aminobutyric acid) and are inhibited by iSPNs and dSPNs of dorsal striatum. Thus GP-FC cells comprise a direct GABAergic/cholinergic projection that places frontal cortex under the inhibitory control of the striatum. Furthermore, iSPN inhibition of GP-FC cells is sensitive to dopamine 2 receptor signaling, revealing a pathway by which drugs that target dopamine receptors for the treatment of neuropsychiatric disorders can act in the BG to modulate frontal cortices.