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Parkinson's Disease: A Thalamostriatal Rebalancing Act?

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Motor impairments in Parkinson's disease are thought to result from hypoactivation of striatal projection neurons in the direct pathway. In this issue of *Neuron*, Parker et al. (2016) report that dopamine depletion selectively weakens thalamic but not cortical afferents onto these neurons, implicating the thalamus as playing a key role in Parkinsonian motor symptoms.

Parkinson's disease (PD) is a debilitating movement disorder triggered by the degeneration of dopamine-producing neurons in the substantia nigra pars compacta (SNc). Motor impairments arise in large part from dysfunction of the dorsal striatum, a forebrain area implicated in the regulation of goal-directed and habitual movements that is the major target of SNc axons.

The striatum is almost entirely composed of GABAergic spiny projection neurons (SPNs), which can be divided into two populations based on the brain areas they innervate, their responsiveness to dopamine, and their effect on motor action. Direct pathway SPNs (dSPNs) express D1 dopamine receptors and directly project to the substantia nigra, whereas indirect pathway SPNs (iSPNs) express D2 dopamine receptors and innervate the globus pallidus. These pathways are often thought to have a push-pull antagonism, with dSPNs increasing and iSPNs suppressing movement (Kravitz et al., 2010). However, it is clear that both pathways are concurrently active during movement, and subtle changes in the relative activity of one pathway over the other have the ability to exert profound effects on motor output (Tecuapetla et al., 2014).

Dopamine is believed to function as a prokinetic signaling molecule in the striatum by favoring the activation of dSPNs over iSPNs, via the complex modulation of intrinsic excitability and synaptic plasticity (Tritsch and Sabatini, 2012). A prevailing view is that the progressive loss of dopaminergic neurons disrupts this equilibrium, leading to the disproportionate strengthening of the indirect over the direct pathway and inhibition of movement in PD (Albin et al., 1989).

Previous studies have reported effects of dopamine depletion on gene expression, axonal innervation, dendritic morphology, membrane excitability, synaptic connectivity, and plasticity at SPNs (Fieblinger et al., 2014; Smith et al., 2014; Surmeier et al., 2014). However, which of these modifications (if any) underlies the suppression of motor actions in PD remains unknown. Indeed, recent findings suggest that many of these alterations represent homeostatic adaptations that compensate for the loss of dopamine, producing either minor effects in overall strength of glutamatergic afferents or yielding changes in somatic and dendritic excitability that are opposite to those predicted by the model (Fieblinger et al., 2014; Maurice et al., 2015).

In this issue of *Neuron*, Parker and colleagues identify afferents from the thalamus as playing a major role in the imbalance of the two striatal pathways in a 6-hydroxydopamine (6-OHDA) mouse model of PD, and provide compelling evidence that causally implicates the selective disruption of thalamostriatal connections in associated movement disorders (Parker et al., 2016).

SPNs in the dorsal striatum rely on strong excitation from cortical or thalamic afferents in order to depolarize from their negative resting potential and fire action potentials. In rodents, thalamostriatal inputs originate in the intralaminar complex,

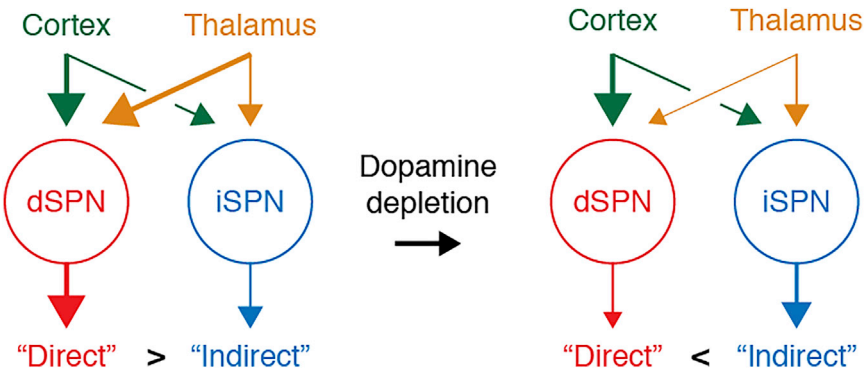

Figure 1. Synaptic Rewiring
Dopamine depletion in a PD mouse model reduces the strength of thalamic inputs (orange), but not cortical inputs (green), onto dSPNs (red) compared to iSPNs (blue) in the striatum, unbalancing the "direct" and "indirect" pathways and thereby reducing movement.

which comprise the central lateral (CL) and parafascicular (Pf) nuclei. Thalamic afferents account for at least 25% of excitatory synapses onto SPNs (Smith et al., 2014) but have been much less studied than cortical afferents. Previous work has identified differences in the presynaptic and postsynaptic properties of corticostriatal and thalamostriatal inputs (Ding et al., 2008). However, it remains unknown whether thalamic afferents are biased to one class of SPN, as observed for corticostriatal synapses (Kress et al., 2013), and whether their connectivity is altered by dopamine depletion in mouse models of PD.

To address these important questions, Parker and colleagues record from pairs of genetically identified dSPNs and iSPNs in striatal slices. They use optogenetics to selectively activate channelrhodopsin in the presynaptic terminals of cortical and thalamic afferents. Under control conditions, they find that light-evoked excitatory postsynaptic currents (EPSCs) from both cortex and thalamus are larger at dSPNs compared to iSPNs, which may allow for preferential activation of the direct pathway (Figure 1). Lesioning of dopaminergic neurons with 6-OHDA does not alter the relative strength of corticostriatal inputs, in agreement with previous findings (Fieblinger et al., 2014). However, the same manipulation significantly shifts the balance of thalamostriatal inputs toward iSPNs, consistent with a strengthening of the indirect pathway in PD (Figure 1).

The authors then perform an elegant series of synaptic physiology experiments to explore the mechanisms underlying this dramatic rewiring of neural circuitry. They find that dopamine depletion selectively weakens thalamostriatal EPSCs in dSPNs mediated by AMPA but not NMDA receptors. Moreover, this weakening occludes long-term depression at these synapses, suggesting that dopamine depletion alters thalamo-dSPN connections using a similar mechanism. Importantly, by using technically demanding paired recordings from SPNs, the authors reveal synaptic rearrangements that would have been difficult to discover with any other method.

The finding of altered connectivity raises the possibility that rebalancing of thalamic inputs from dSPNs to iSPNs contributes to motor deficits in PD. In particular, it suggests that thalamic inputs may subdue movements by preferentially activating iSPNs. To test this idea, Parker et al. (2016) also use a powerful combination of in vivo pharmacogenetics and optogenetics and find that suppressing thalamostriatal inputs selectively enhances movement in dopamine-depleted mice.

These experiments strongly suggest that thalamostriatal activity is necessary for motor impairments in this animal model. However, these in vivo manipulations involve a general reduction of thalamic afferents, and cannot distinguish the target cell type. Therefore, they cannot directly address whether a reduction of indirect pathway activity is responsible for behavioral improvements. In the future, it will be important to determine if a more focused restoration of thalamostriatal drive onto dSPNs is equally effective. These experiments will greatly benefit from knowing the precise identity of the intralaminar thalamic nuclei that are affected by dopamine depletion, as thalamic afferents from the CL and Pf have distinct presynaptic and postsynaptic properties in the striatum (Ellender et al., 2013).

In future work, it will also be interesting to investigate additional models of PD, which differ considerably in their time course and clinical manifestations. In particular, the thalamus undergoes widespread degeneration in both human patients and in primate models (Villalba et al., 2014), but not in the 6-OHDA model. Therefore, it is possible that therapeutic interventions aimed at reducing thalamostriatal activation of iSPNs might prove less effective in humans.

Overall, this elegant study uncovers an important, previously underappreciated role for the thalamus in the pathology of PD. Altered connectivity is cell-type specific, primarily occurring at dSPNs and not their neighboring iSPNs; it is also input specific, selectively involving thalamic afferents and not the well-studied cortical afferents. Notably, perturbed dopaminergic signaling has been implicated in related forms of synaptic plasticity seen throughout the striatum. For example, repeated cocaine exposure selectively weakens hippocampal inputs and enhances amygdalar inputs onto D1-expressing SPNs in the nucleus accumbens (MacAskill et al., 2014). These kinds of observations highlight the exquisite sensitivity of neuronal circuits to dopamine neuromodulation and point to challenges of dopamine restoration therapies in treating PD.

Moving forward, it will be interesting to identify the signaling pathways that underlie synaptic depression of thalamo-dSPN synapses. In particular, it will be important to determine the molecular mechanisms that render some synapses more sensitive to functional rearrangements. Ultimately, this understanding will help devise new therapeutic strategies that restore the balance of direct and indirect pathways, without resorting to systemic supplementation of dopamine.

Finally, it should be noted that dopamine depletion produces a plethora of cellular and synaptic changes at both SPNs and local interneurons. For

instance, the loss of dopamine also increases inhibitory synaptic drive from parvalbumin-positive interneurons onto iSPNs, but not dSPNs (Gittis et al., 2011). It will therefore be imperative to determine how the many modifications triggered by dopamine loss combine to influence the spiking properties of dSPNs and iSPNs. Clearly, there is much work to be done to understand the pathology of PD, and this Report by Parker et al. (2016) points to many new and exciting avenues for future investigations.

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Four to Foxtrot: How Visual Motion Is Computed in the Fly Brain

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In this issue of *Neuron*, Serbe et al. (2016) use cell-type-specific genetic tools to record and manipulate all major inputs to directionally selective neurons in *Drosophila*. Their results localize the site of motion computation and reveal unexpected complexity of temporal tuning in the underlying neural circuit.

An important task for the visual system of many animals, both vertebrate and invertebrate, is the detection of visual motion. Motion detection is essential for a range of visual functions, from maintaining gaze and guiding smooth pursuit eye movements in mammals, to detecting predators and stabilizing flight in flies. It was first hypothesized by Sigmund Exner in the late 1800s that visual motion detection is performed by specialized neural circuits—a prediction that turned out to be true. For more than a century, the challenge has been to delineate these circuits and to unravel their computational mechanisms.

The first algorithmic model for visual motion detection was devised in post-WWII Germany by Bernard Hassenstein and Werner Reichardt (Hassenstein and Reichardt, 1956). Founders of the field of biological cybernetics, Hassenstein and Reichardt applied their expertise in biology and physics to develop algorithmic descriptions of neural functions and behavior. Their studies of the turning behavior of a weevil (*Chlorophanus*), suspended from a post and walking on a Y-maze globe made of straw, led to an elegant and concise model for directional motion selectivity comprising three basic operations: temporal filtering, spatial offset, and multiplication (Figure 1A).

The Hassenstein-Reichardt model for elementary motion detection (HR-EMD) guided the development of systems neuroscience in invertebrates but was also rapidly adopted for studying the visual systems of vertebrates, following the discovery of directionally selective cells in the retina of the rabbit (Barlow and Levick, 1965). Its most significant contribution, however, is that it led to new theories of how neurons implement arithmetic operations like multiplication and subtraction and initiated the search to identify their specific neural substrates.

The search for the physical implementation of the HR-EMD model received a boost when a network of ~60 neurons in the optic lobe of the blowfly was found to respond selectively to distinct patterns of wide-field visual motion (Hausen, 1984). These neurons, the lobula plate