Complementary Motivational Roles of Nigroaccumbens and Nigrostriatal Dopaminergic Pathways

Saunders BT, Richard JM, Margolis EB, Janak PH. *Dopamine neurons create Pavlovian conditioned stimuli with circuit-defined motivational properties*. Nat Neurosci 2018;121:1072-1083.

Processes associated with striatal complex dopaminergic neurotransmission include reinforcement learning, habit formation, motivational processes, and vigor modulation. Prior experimental work usually focused on one of these aspects of striatal complex dopaminergic signaling. Saunders and colleagues present an elegant study suggesting that different populations of midbrain dopaminergic neurons mediate distinct but complementary functions.[1]

Saunders et al used a modification of the oldest reinforcement learning paradigm — Pavlovian conditioning. They employed a conventional conditioned stimulus (CS; light and tone cue) and optogenetic stimulation of midbrain dopaminergic neurons to replace the natural rewards used as unconditioned stimuli (US). Optogenetic activation was designed to mimic the phasic (burst) generation of dopaminergic neuron action potentials accompanying reward presentation. Using locomotion as the conditioned response (CR), Saunders et al demonstrate that pairing of CS with optogenetic mimicry of phasic midbrain dopamine neuron activity reproduces all features of conventional Pavlovian conditioning. Phasic midbrain dopamine neuron activity appears both necessary and sufficient to induce Pavlovian conditioning — an impressive finding.

Targeting optogenetic activation at either substantia nigra pars compacta (SNc) neurons projecting to the dorsal striatum or ventral tegmental area (VTA) neurons projecting to the nucleus accumbens, Saunders et al identified distinct functional contributions to the locomotion CR. Pairing CS presentation with VTA neuron activation induced CS-evoked approach behavior toward the CS light. This approach behavior was absent in animals pairing CS presentation with SNc activation. These animals experienced general locomotion activation with CS cue presentation. The implication is that the VTA-accumbens projection subserves learning of cue values, whereas the SNc-striatal projection modulates movement vigor. Both these functions are necessary for appropriate responses to an environmental cue signaling reward.

This functional differentiation of the VTA-accumbens and SNc-striatal projections is consistent with common clinical phenomena. The VTA-accumbens projection is relatively spared in Parkinson's disease. Ventral striatal neurons also express higher levels of dopamine D3 receptors than dorsal striatal neurons. Dopamine replacement medications, particularly D2/D3-preferring dopamine agonists, will mimic robust activation of VTA-accumbens dopaminergic neurons, even in the face of poor motor performance secondary to advanced degeneration of the SNc-dorsal striatal projection. This is a situation analogous to selective optogenetic activation of VTA neurons. Treatment-related complications such as punding and impulse control disorders are plausible analogues of the enhanced CS presentation approach behavior described by Saunders et al and may represent distorted learning of cue or action values.

Saunders et al imply that functional differentiation is from different properties of these dopaminergic neuron populations. However, these results may reflect the functional differentiation of the striatal complex based on differing corticostriate inputs. That identical optogenetic excitation of VTA and SNc neurons produced different behavioral consequences suggests that functional specificity resides in the highly differentiated striatal complex.

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1. Saunders BT, Richard JM, Margolis EB, Janak PH. Dopamine neurons create Pavlovian conditioned stimuli with circuit-defined motivational properties. Nat Neurosci 2018;121: 1072-1083.

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