Neuropsychopharmacology www.nature.com/npp

RESEARCH HIGHLIGHT

Brain reward network effects underlie septo-hippocampal control of flexible decision making

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Neuropsychopharmacology (2019) 44:2153–2154; https://doi.org/10.1038/s41386-019-0487-4

"The medial septum enhances reversal learning via opposing actions on ventral tegmental area and substantia nigra dopamine neurons"

Flexible decision making is critical for adaptive behavior in an ever-changing world. To find rewards and minimize costs, animals must rapidly update their understanding of the value and consequences of their actions to make choices based on shifting circumstances. Deficits in this process may underlie psychiatric diseases, such as schizophrenia and addiction. Therefore, understanding the neural circuits that encode and control flexible decision making is important for successful diagnosis and treatment. A common assay of decision flexibility is reversal learning, where successful reward seeking relies on learning that the spatial location of a reward has changed. Efficient reversal learning suggests cognitive flexibility, while impairments in this process are observed in animal models useful for studying disease. As such, reversal learning may be considered a translationally relevant phenomena.

Decision flexibility is often conceptualized as a "top-down", cortically driven process [1–3], but subcortical motivation and learning circuitry have important underexplored roles. In their recent paper in *Neuropsychopharmacology*, Bortz et al. [4] investigate subcortical mechanisms of reversal learning, focusing on a network including the medial septum (MS) and ventral subiculum (vSub), both of which have been implicated in spatially guided decision making [2, 5]. Bortz et al. [4] use a T-maze based task, in which rats are trained to run to a choice point leading to a left or right turn. One side is consistently baited with a food pellet reward, and rats learn to make the correct choice and receive the reward. On the test day, the location of the reward is reversed, requiring rats to inhibit the previously trained response and learn the new location. Bortz et al. [4] used a chemogenetic approach, targeting MS neurons with a viral vector coding for the designer receptor (DREADD) hM3Dq. Targeting this receptor with its ligand clozapine-N-oxide (CNO) results in increased neural activity. Activating MS neurons in this way resulted in improved reversal learning - DREADD-containing rats reached criterion faster than controls. Given that one of the primary outputs targets of the MS is the vSub, within the hippocampal complex, Bortz et al. [4] asked whether projections specifically from the MS to the vSub modulate this reversal. They examined this by expressing the excitatory DREADD in the MS, but infusing CNO directly into the vSub such that only MS terminals projecting to this region would be excited. As with activation of all MS neurons, MS-vSub activation enhanced reversal learning. In future studies, it will be important to determine whether the MS is implicated specifically in spatially guided choices [5], or has a more general role in decision flexibility, via projections to regions other than the hippocampus.

The MS-vSub circuit is embedded in a larger anatomical network that can influence a variety of key reward systems, including dopamine neurons. In a previous paper [6], Bortz et al. found that activation of MS produced opposing effects on the activity of different subpopulations of dopamine neurons, enhancing ventral tegmental area (VTA) activity, while decreasing substantia nigra (SNc) activity. Both effects were abolished when the vSub was simultaneously inhibited, leading the authors to propose that the MS can influence dopamine neuron activity via a multi-synaptic pathway from MS to vSub to the nucleus accumbens to ventral pallidum, which then projects to the VTA/SNc. As evidence for this, they showed that inactivation of the anterior ventral pallidum eliminated the increase in VTA dopamine neuron activity produced by MS stimulation. Conversely, inactivation of the posterior portion of the ventral pallidum prevented suppression of SNc dopamine neuron activity produced by MS stimulation. This suggests that there are topographically organized parallel circuits by which MS activity can bi-directionally affect dopamine neurons. To test the influence of the MS-vSub pathway on dopamine neurons more directly, Bortz et al. [4] expressed the DREADD receptor in MS neurons, and injected CNO into the vSub, to activate terminals projecting from the MS, while dopamine neuron activity was simultaneously recorded in the SNc or VTA. This circuit manipulation recapitulated the earlier effect [6] – activation of MS-vSub projections increased VTA and decreased SNc dopamine neuron activity. Taken together, these results suggest that the MS is positioned to influence dopamine signaling potentially through a hippocampal-striatal-pallidal network. It will be important to directly test this serial circuit hypothesis, given that other projections are engaged during decision making, including orbito- and prefrontal regions, which can exert parallel top-down influence on the nucleus accumbens, MS, ventral pallidum, and VTA [1–3]. Given the heterogeneous, indirect effect of MS activation on dopamine neuron activity, Bortz et al. [4] explored the role of dopamine signaling in their task, finding that systemic administration of a D1 dopamine receptor antagonist blocked the enhancement of reversal learning produced by MS activation. Although it remains unclear where in the brain dopamine's actions mediate this effect, given that dopamine neurons project directly to the MS, one interesting possibility arising from these results is that dopamine signaling

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Received: 12 August 2019 Accepted: 13 August 2019
Published online: 27 August 2019

into the MS could provide reward-related feedback that guides MS recruitment of vSub circuitry to incorporate spatial information necessary to update decisions in reversal learning.

The divergent influence of MS activation on VTA and SNc dopamine neurons described in the work of Bortz et al. highlights the importance of understanding how network effects contribute to heterogeneity in reward system activity and function. Bortz et al. [4] suggest that the decrease in SNc dopamine neuron activity accompanying MS activation may be important for allowing rats to engage in a more flexible seeking strategy during reversal, in line with a classic view of nigrostriatal dopamine in habit formation. This is an intriguing possibility to be tested in future work, to see if decreased SNc activity is explicitly required for reversal, or if enhanced VTA activity alone is sufficient to promote decision flexibility. Given the distinct roles for SNc and VTA dopamine projections in choice and reward encoding [7], it will be interesting to determine how parallel in vivo meso- and nigrostriatal activity patterns contribute to both spatial and non-spatial decision making tasks, including those that incorporate probabilistic learning rules.

The results from Bortz et al. [4] compellingly position septal-hippocampal circuitry as important for spatially guided reward seeking decisions, via network-level effects on dopamine signaling. An exciting future direction will be to determine if the MS integrates spatial information with reward, or rather recruits spatial coding regions, like the vSub, when the conditions demand it. Other recent work implicates the nucleus accumbens, via hippocampal inputs, as a key site for strengthening reward-place associations [8], and the results of Bortz et al. [4] suggest the MS plays an important role in this process. Dopamine neurons project to and receive input from the hippocampus, and these circuits also mediate reward-related behaviors [1], so there are likely multiple, presumably parallel subcortical networks for integrating reinforcement feedback with changing environmental information. A challenge for future work is to determine the extent to which different circuits within these networks contribute to temporally distinct features of decision making, such as executing choices, versus learning from their outcomes.

FUNDING AND DISCLOSURE

A.L.C. and B.T.S. are supported by NIH/NIDA grants DA007234 and DA042895. The authors declare no competing interests.

ADDITIONAL INFORMATION

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