Journal Club

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Shared Motivational Functions of Ventral Striatum D1 and D2 Medium Spiny Neurons

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Review of Natsubori et al.

The striatum is an essential structure influencing behavioral action selection in processes relevant to reward and motivation. Abnormalities in striatal function are associated with several psychiatric and neurological disorders, including addiction, depression, schizophrenia, Parkinson's disease, and Huntington's disease (Kreitzer and Malenka, 2008). The striatum comprises the dorsal striatum, which regulates motor output and decision-making, and the ventral striatum, which predominantly regulates reward and hedonic states. Both regions receive excitatory inputs from cortical and thalamic regions, as well as receiving dense innervation from midbrain dopaminergic nuclei.

The striatum lacks glutamatergic neurons; instead, nearly all striatal neurons are GABAergic. These GABAergic neurons include a large population of principal projection neurons called medium spiny neurons (MSNs) and a much smaller population comprising multiple classes of interneurons (Kreitzer and Malenka, 2008). MSNs can be further divided by their expression of Type 1 (D1) or Type 2 (D2) dopamine receptors. These classes play largely divergent roles in motor control and goal-directed behavior. Whereas D1 MSNs have primarily been shown to promote motor output and goal-directed behavior, D2 MSNs have been shown to inhibit these behaviors (Kravitz et al., 2010, 2012; Durieux et al., 2012; Freeze et al., 2013). These opposing behavioral functions are attributed to the distinct projection targets of D1 and D2 MSNs within the basal ganglia. Dorsal striatal D1 MSNs directly disinhibit the dopaminergic ventral mesencephalon to promote motivation, whereas D2 MSNs indirectly inhibit the dopaminergic mesencephalon by way of the globus pallidus to reduce motivation. With respect to their projections to basal ganglia nuclei, the dorsal and ventral striatum have traditionally been considered anatomically analogous; D1 MSNs in the ventral striatum project directly to the ventral mesencephalon, and D2 MSNs in the ventral striatum project indirectly to the ventral mesencephalon by way of the ventral pallidum (Kreitzer and Malenka, 2008). However, recent evidence suggests that, unlike the dorsal striatum, ventral striatal MSN output projections do not segregate exclusively based on D1/D2 subtype or by the direct/indirect pathway. For example, approximately half of the neurons in the ventral pallidum receive input from ventral striatal D1 MSNs, suggesting that there is some anatomical overlap in D1 and D2 MSN projection targets (Kupchik et al., 2015). In addition, the ventral pallidum itself projects to multiple limbic and cortical regions in addition to the ventral mesencephalon (Smith et al., 2009). These findings bring into question whether the traditional anatomical, and more importantly, behavioral distinctions between D1 and D2 MSNs are appropriate for the ventral striatum.

D1 and D2 MSNs in the ventral striatum are oppositely modulated by cocaine, with cocaine increasing D1 MSN activity and decreasing D2 MSN activity (Calipari et al., 2016). Consistent with this, inhibition of D1 MSNs in the ventral striatum using designer receptors exclusively activated by designer drugs reduces conditioned preference for a cocaine-paired context (Calipari et al., 2016). Moreover, optogenetic activation of D1 MSNs in the ventral striatum promotes conditioned preference for a cocaine-pared context, whereas optogenetic activation of D2 MSNs reduces it (Lobo et al., 2010). It remains unclear, however, whether ventral striatal D1 and D2 MSNs play similarly opposing roles in mediating motivation for natural rewards. Although not formally distinguished from each other, it is also not known whether the medial versus lateral subdivisions of the ventral striatum differ in their contributions to motivated behaviors.

To address these questions, Natsubori et al. (2017) used fiber photometry and optogenetics to either record from or manipulate D1 or D2 MSNs in the ventrolat-

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eral striatum during precise epochs of a food reinforcement task. D1 and D2 MSNs in the ventrolateral striatum displayed remarkably similar activity patterns during several phases of the operant task, with transient activation upon trial start (lever presentation) and reward delivery, indicating that both neuron types might be driving the observed behavior. D1 and D2 MSN activity patterns were remarkably similar throughout the phases of the task. Averaged traces showed that both MSN types increased their activity at the trial start, gradually increased until the first lever press, and sharply peaked immediately following reward delivery. Upon visual inspection of representative traces, it appears that D2 MSNs showed sustained increases in activity at the first lever press that did not terminate until the last lever press, while D1 MSNs showed a narrow peak that quickly returned to baseline after the first lever press. However, these particular activity patterns were not analyzed statistically. The researchers also found that D2 MSN activity was higher in trials where the latency from trial start to first lever press was shorter, indicating that D2 MSN activity is positively correlated with motivational state. Contrary to the authors' hypothesis, D1 MSN activity was not statistically different between short and long latency groups. To investigate the contributions of D1 and D2 MSNs in the ventrolateral striatum to motivation for food reward, Natsubori et al. (2017) used a progressive-ratio task and optogenetically inhibited D1 or D2 MSNs at various epochs of the task. Progressive ratio tests the level of effort (lever presses) animals will exert to receive a single reward by systematically increasing the ratio of lever presses to rewards during the session. The maximum number of lever presses that an animal will perform to receive a single reward is referred to as the breakpoint. Brief optogenetic inhibition of either D1 or D2 neurons at the trial start reduced breakpoint, increased latency to the first lever press, and increased the time taken to complete the progressive-ratio task. However, delivering inhibition at the first lever press only affected behavior when it was delivered to D1 MSNs, in which case it reduced breakpoint and the rate of active lever pressing. Together, these findings may suggest that both MSN subtypes in the ventrolateral striatum motivate aspects of food-seeking behavior, with D1 MSNs driving both the initiation and sustainment of motivated responding and D2 MSNs influencing only the initiation of motivated responding. Alternatively, these results could indicate that D2 MSNs in the ventrolateral striatum are required to suppress alternative behavioral responses to promote goal-directed behavior.

Importantly, the results of this study extend the findings of an earlier investigation by the same research group (Tsutsui-Kimura et al., 2017). In this previous report, Dr. Kenji Tanaka's group expressed diphtheria toxin receptors selectively in D2 MSNs in the ventrolateral striatum of mice. After administration of diphtheria toxin, the neurons were initially hypofunctioning and displayed decreased output to the ventral pallidum. These neurons eventually died as a consequence of the repeated diphtheria toxin administration. During the period when D2 MSNs were hypo-functioning, animals tested in a food-incentive task showed deficits in goal-directed behavior that persisted after ventrolateral striatal D2 MSN death. Specifically, these mice displayed reduced overall responding for food rewards, increased omission of responses when food availability was signaled, and decreased breakpoint in a progressive-ratio task. Echoing the findings of Natsubori et al. (2017), acute optogenetic inhibition of these neurons immediately following lever presentation in the progressive-ratio task decreased breakpoint while increasing latency to the first lever press, indicating that these neurons are important for this task at the initiation of the trial. Importantly, the above manipulations of ventrolateral striatal D2 MSNs did not alter the preference for a methamphetamine-paired context in a conditioned-place preference paradigm, suggesting that the rewarding properties of drugs are not affected by ventrolateral striatum D2 MSN hypo-function or ablation. Together, these two reports from the Tanaka group advance our understanding of VS D2 MSN function in reward and motivation and suggest that, at least within the ventrolateral striatum, D2 MSNs may positively drive goal-directed responding for natural food rewards.

Recent studies investigating ventral striatal MSN subtype contributions to motivation for drugs suggest that the classical distinction between D1 MSNs (promoting motivation) and D2 MSNs (inhibiting motivation) is accurate (Lobo et al., 2010; Calipari et al., 2016). However, the results of Natsubori et al. (2017) suggest that both ventral striatal MSN subtypes can positively drive motivation. There are several possible explanations for these seemingly disparate findings. First, it is possible that the ventromedial striatum and the ventrolateral striatum display different connectivity with basal ganglia nuclei such that the proportion of neurons sending overlapping D1 and D2 inputs to ventral pallidal neurons is greater in the ventrolateral striatum than in the ventromedial striatum. Notably, the above studies investigating the role of the ventral striatum in motivation for drugs focused on the ventromedial striatum; the present investigation specifically targeted the ventrolateral striatum. Data from Kupchik et al. (2015) demonstrate that the ventromedial striatal projection to the ventral pallidum consists of both D1 and D2 MSNs, with ~50% of ventral pallidal neurons receiving D1 MSN input and 89% of ventral pallidal neurons receiving D2 MSN input. These findings specifically describe the projection patterns of the ventromedial striatum and not the entire ventral striatum; therefore, it is possible that D2 MSNs in the ventrolateral striatum can uniquely promote motivation via a more prominent overlap of inputs with D1 MSNs in the ventral pallidum. This possibility should be evaluated in future investigations. A second possible explanation is that D2 MSNs may specifically promote motivation for natural rewards in a manner that does not extend to drug rewards. Although substances, such as cocaine, produce extremely robust increases in ventral striatal dopamine, ethologically relevant rewards, such as food, produce much weaker, but more physiological, release of dopamine in the ventral striatum. Perhaps high levels of dopamine produce opposing activation patterns of ventral striatal D1 and D2 MSNs, whereas lower levels, possibly through an unknown ventral striatal microcircuit, promote activation of both D1 and D2 MSNs. In support of this specific role for D2 ventral striatal neurons in regulating motivation for natural rewards, a recent study by Soares-Cunha et al. (2016) found that optogenetic stimulation of D2 MSNs in the ventral striatum increased lever pressing for food rewards in a reinforcement task, whereas optogenetic inhibition reduced it. Importantly, this optogenetic activation and inhibition of ventral striatal D2 MSNs increased and decreased the firing rate of dopaminergic neurons in the ventral mesencephalon, respectively, suggesting that D2 MSNs in the ventral striatum can drive the activation of dopamine target neurons. This would also suggest that inhibition of D2 MSNs in the ventral striatum does not block the suppression of alternative behavioral responses, but rather directly decreases the motivation for food. Overall, the study by Natsubori et al. (2017) enhances our current understanding of how D1 and D2 MSNs in the ventral striatum influence motivation, and paves the way for interesting follow-up investigations.

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