This Week in The Journal

Divergent Effects of Dorsomedial and Dorsolateral Striatum

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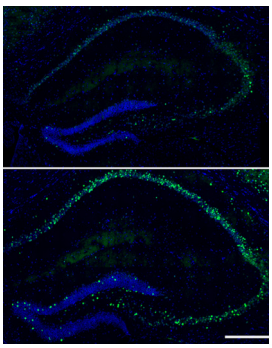
(see pages 3966–3987)

The dorsal striatum is involved in action selection and sequencing. Whereas the dorsomedial subdivision is thought to mediate goal-directed actions, the dorsolateral subdivision is thought to contribute to habitual actions. Both subdivisions have been proposed to perform these functions through divergent pathways initiated by distinct sets of spiny projection neurons (SPNs). Specifically, SPNs that express D_1 dopamine receptors predominantly promote movement via direct projections to an output nucleus of the basal ganglia, the substantia nigra pars reticulata; conversely, SPNs that express D_2 receptors are thought to inhibit movement via indirect projections to the output nuclei through the globus pallidus externus (GPe). Basal ganglia circuitry is far more complex than this model suggests, however. Indeed, some D_1-expressing SPNs send collaterals to the GPe, and Cui et al. report that direct- and indirect-pathway neurons arising in dorsomedial and dorsolateral striatum have opposite effects on movement.

Consistent with the model described above, optogenetic activation of mouse *Drd1a*-expressing (direct-pathway) SPNs in the dorsomedial striatum increased locomotor speed in mice, whereas activation of *Adora2a*-expressing (indirect-pathway) SPNs suppressed movement. Surprisingly, however, stimulation in the dorsolateral striatum had the opposite effects: activation of *Drd1a*-expressing neurons suppressed movement, whereas activation of *Adora2a*-expressing neurons increased movement. The authors hypothesized that the divergent effects of dorsomedial and dorsolateral stimulation might arise from differences in projections to the GPe. Contrary to this hypothesis, however, the extent of GPe innervation by *Drd1a*-expressing and *Adora2a*-expressing dorsomedial SPNs was similar to the innervation by *Drd1a*-expressing and *Adora2a*-expressing dorsolateral SPNs. Furthermore *Drd1a*-expressing SPNs in both mediolateral and dorsolateral striatum preferentially innervated *Npas1*-expressing neurons in the GPe, whereas *Drd2*-expressing indirect-pathway SPNs from both striatal subdivisions preferentially innervated parvalbumin-expressing GPe neurons. Notably, when dopamine neurons were killed to model Parkinson's disease, input from both dorsomedial and dorsolateral striatal SPNs to GPe *Npas1*-expressing neurons increased, whereas input from indirect-pathway SPNs was unaffected.

These results suggest that direct-pathway and indirect-pathway SPNs in the dorsomedial striatum have opposite behavioral effects from those in the dorsolateral striatum. Future work will need to determine how these opposite effects arise, given the similar projection patterns of the populations in the GPe.



The number of activated (c-Fos-labeled) cells (green) in hippocampal regions increases with exploration time: 30 s exploration (top), 1800 s exploration (bottom). See Leake et al. for details.

Hippocampal Ensemble Growth During Exploration

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(see pages 4120–4130)

When one enters an unfamiliar place, they explore the area, storing information in hippocampal circuits. When similar surroundings are encountered again, previously formed memories are partially reactivated. The amount of reactivation likely determines whether the location is deemed familiar or novel. Such judgments can be flawed, however, if insufficient information was gathered during the initial encounter. This was demonstrated in mice given footshocks in novel contexts. When shock was delivered within 30 s of the animal's arrival in a novel conditioning context, mice generalized their learned fear response (freezing) to a second context. The amount of freezing in the second context decreased as animals spent more time in the first context, peaking after ~180 s of preshock exploration. Leake et al. show how these time-dependent behavioral differences are reflected in hippocampal activity.

Consistent with previous results, mice that explored the conditioning context for 30 s before shock showed similar levels of freezing when placed in the same or a new context the next day; in contrast. mice that explored for 720 s before shock froze significantly more when returned to the conditioning context than when placed in a new context. As would be expected if more information was gathered during longer exploration times, the number of hippocampal neurons activated during a session increased with session duration, plateauing after 180–1800 s, depending on the hippocampal region. Importantly, the amount of overlap in the ensembles activated in different contexts depended on previous exploration time. In mice that explored the conditioning context for 720 s, more of the neurons activated during conditioning were reactivated when mice returned to the conditioning context than when mice were placed in the novel context. In contrast, for mice that had explored for only 30 s, the number of reactivated neurons was similar in the conditioning and new contexts.

These results support the hypothesis that longer exploration times allow more information to be encoded, enabling better discrimination of similar contexts and reducing generalization. Notably, however, no more than a small percentage of hippocampal neurons was activated regardless of exploration time, maintaining the sparse encoding that is essential for representing multiple locations in hippocampal ensembles.

This Week in The Journal was written by Teresa Esch, Ph.D.
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