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Perspectives

PERSPECTIVES

Getting Excited About Learning

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'A Perspective on "Cell Type-Specific Membrane Potential Changes in Dorsolateral Striatum Accompanying Reward-Based Sensorimotor Learning"

Motor learning is thought to involve an increase in the synaptic strength of glutamatergic inputs to the dorsolateral striatum (DLS), enhancing striatal activity and invigorating specific actions.[1] However, the cell types that govern this change in synaptic strength remain unknown. The striatum comprises two principal cell types, known as direct and indirect pathway neurons (dSPNs and iSPNs), as well as multiple classes of interneurons. A "classic" model of basal ganglia function predicts that dSPNs and iSPNs oppose one another during action generation, with dSPNs invigorating actions and iSPNs opposing competing or interfering actions.[2] However, more recent models of basal ganglia function have noted that both dSPNs and iSPNs are activated during actions and action preparation,[3] leading to proposals that these cell types work together in a complementary or competitive manner to govern movement.[4] Here, with an impressive set of electrophysiological recordings in awake mice, Sippy et al. further our understanding of these models, and of how synaptic inputs onto specific striatal cell types change following motor learning.

Previously in 2015, Sippy et al.[5] used whole cell in vivo recordings to monitor membrane voltages of individual DLS neurons in a sensorimotor-association task. The authors used a magnetic coil and a small metal bead to deflect a single whisker of the mice, which signaled the availability of water. They tested this in trained mice that had learned to associate the whisker deflection with the availability of water and started licking shortly after this deflection. They found that both dSPNs and iSPNs were depolarized in response to this whisker stimulation, with dSPNs exhibiting a more rapid depolarization than iSPNs. This approach provided direct electrophysiological evidence linking this learned motor action to excitatory synaptic input to the DLS and increased our understanding of how synaptic inputs drive striatal activity and behavior. Now, an article published by Sippy et al. in this issue of Function[6] picks up where their prior paper left off, and asks the elegant and important question of how these sensorimotor reward signals evolve with learning.

Sippy et al. exposed mice to the same behavioral paradigm in which mice learned to lick for a water reward in response to a whisker stimulation. This is an ideal task to explore how brain signals evolve during learning, as mice will participate without training, allowing for comparison of neural signals in the same task in naïve and expert mice. The authors performed acute, in vivo whole cell recordings from dSPNs, iSPNs, and tonically active cholinergic interneurons (TANs), measuring membrane voltage fluctuations after the whisker deflection that signaled water availability. Critically, this experiment was performed during an initial behavioral session with "naïve" mice, and in a separate cohort of well-practiced "expert" mice, allowing the authors to compare how in vivo membrane voltage fluctuations change after learning. The experiments are impressive for both their technical skill and the insights they enable. They allow for measurements of not only changes in spiking, but also of subthreshold changes in membrane potential, which is a more sensitive measure of changes in synaptic input. In addition, this preparation allowed them to examine cellular excitability and resting membrane potentials in awake behaving mice. The authors conclude that sensorimotor learning is associated with increase in excitatory drive onto both dSPNs and iSPNs, along with the development of a hyperpolarizing response in cholinergic interneurons.

The authors replicated their prior finding that dSPNs exhibit a rapid initial depolarization, while iSPNs display a more gradual rise in membrane voltage, in response to the learned whisker deflection.[5] However, this initial depolarization was more prominent in both cell types in expert mice. Analysis of membrane voltage changes at later timepoints (up to 1.5 s after the whisker deflection) revealed that both dSPNs and iSPNs remained depolarized after the cue in expert and naïve mice. This confirms that both early learning and advanced training

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involve excitatory inputs onto DLS SPNs, with inputs onto both dSPNs and iSPNs strengthening after learning. This supports a complementary or competitive model of basal ganglia function,[4] although the rapid depolarization observed in dSPNs suggests that these changes may favor dSPNs over iSPNs early in action generation. In expert, but not naïve, mice, TANs also exhibited a long, late hyperpolarization in response to the whisker deflection. This suggests that learning is also associated with changes in inputs onto TANs, or that TANs are affected by local circuit changes. TAN hyperpolarization appeared to lag after SPN depolarization by ~100 ms, which supports prior work demonstrating a quieting of striatal TANs in response to a learned cue.[7] Thus, local plasticity mechanisms may evolve during learning to disengage TANs and gate striatal output.[8]

This study demonstrates cell-type specific changes in DLS sensory responses after the formation of sensorimotor associations. These results showcase in vivo whole cell recordings as a gold standard for exploring physiological changes during behavior, and reveal a direct link between adaptations in specific striatal neurons and learning. This work raises important questions to be addressed in future studies. First, it is unclear which striatal afferents are driving these adaptations. The DLS receives input from multiple glutamatergic structures, and future work will be needed to determine whether these adaptations are the result of a specific input structure or shared among all inputs. Additionally, as the authors point out, studies that track individual neurons over time will be needed to understand the time course of learning-induced adaptations within individual neurons. This might be facilitated with techniques such as longitudinal calcium imaging in genetically identified cell types, though the membrane potential dynamics observed in this paper would not be observable in such experiments. While those studies are forthcoming, the present study reports membrane potential dynamics in specific DLS cell types before or after motor learning, and reveals temporal differences that initially favor dSPNs, but ultimately recruit both dSPNs and iSPNs, during learned sensory driven actions. This work is a direct demonstration of how learning engages excitatory changes onto both striatal pathways, which will shape future investigations of striatal organization and function.

Conflict of Interest Statement

None declared.

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