This Week in The Journal

Role of Cerebellum in Fear Conditioning

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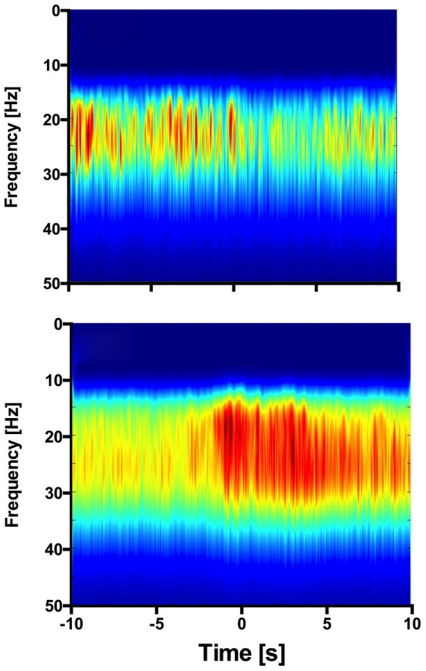
(see pages 11801–11816)

Circuits connecting the cerebellum and motor cortex are essential for motor learning and coordination. But most of the cerebellum is connected to parietal and frontal cortical areas involved in cognition, and functional imaging studies show activation of the cerebellum during cognitive tasks. Moreover, evolutionary increases in the size of the cerebellum and cerebral cortex have occurred in parallel. Together, these findings suggest that the cerebellum contributes to cognition. Cerebellar lesions that cause severe motor deficits have little effect on cognitive processes, however. Therefore, if and how the cerebellum contributes to non-motor learning remain unclear (Buckner 2013 Neuron 80:807).

To investigate cerebellar contributions to learning, Otsuka et al. examined fear conditioning in mice lacking *Cbln1*. This gene encodes the secreted protein cerebellin 1, which is expressed predominantly in the cerebellum, where it is essential for the formation and modification of synapses between parallel fibers and Purkinje cells. Consistent with previous work, *Cbln1* knockout impaired motor coordination. More relevantly, *Cbln1* knockout impaired learning during contextual and cued fear conditioning: although mutant mice responded to foot shock, they froze less often than controls in response to shock-paired cues or contexts.

Because low levels of *Cbln1* mRNA or protein were present in several areas associated with fear learning—including retrosplenial granular cortex, entorhinal cortex, and hippocampus—the authors asked whether knocking out *Cbln1* selectively in these areas or the cerebellum replicated the effect of ubiquitous knockout. Notably, acquisition of cue- and context-dependent conditioned fear was impaired in mice lacking cerebellar *Cbln1*. In contrast, mice lacking *Cbln1* selectively in forebrain neurons acquired fear responses as well as controls. Nevertheless, conditioned fear responses were reduced in these mutant mice 10 min and 24 h after conditioning.

These data suggest that normal cerebellar circuitry is required for the acquisition of conditioned fear responses. This supports the hypothesis that the cerebellum contributes to learned, non-motor behaviors in mice. Because cerebellin 1 is important for synaptic development as well as plasticity, future work should investigate whether acute cerebellar inactivation of this protein (and proteins involved more selectively in plasticity) affect the acquisition and expression of fear responses. Such experiments would help clarify the role of the cerebellum in cognitive behaviors.



Synchronization of beta-frequency oscillations in the STN decreases during movement (initiated at time = 0) in the awake state (top) and increases during movement in REM sleep (bottom). See Hackius et al. for details.

Halting Corticostriatal Communication to Speed Movement

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(see pages 11795–11800)

Parkinson's disease (PD) is characterized by slowed movement and resting tremor, which result from degeneration of dopaminergic projections from the substantia nigra to the striatum. Dopamine normally increases the excitability of direct-pathway striatal neurons, which disinhibit basal ganglia targets and thus facilitate movement, and it decreases the excitability of indirect-pathway striatal neurons, which—by disinhibiting neurons in the subthalamic nucleus (STN)—promote inhibition of thalamic targets and thus suppress movement. Therefore, loss of dopamine likely slows movement at least partly by decreasing direct-pathway activity and increasing indirect-pathway activity. But dopamine also changes firing patterns in striatal circuits. For example, increased bursting, beta-frequency (13–35 Hz) oscillations, and synchrony within and between the STN and its synaptic partners occur with dopamine loss. Such changes are thought to contribute to motor dysfunction (Galvan et al. 2015 Front Neuroanat 9:5).

Although loss of dopaminergic neurons defines PD, other neurons also degenerate in the disease. For example, loss of neurons that prevent muscle activation during REM sleep likely cause REM sleep behavior disorder (RBD), which occurs in ~50% of PD patients. These patients often speak or exhibit movements associated with fighting, eating, gesturing, and other behaviors during sleep. Intriguingly, PD symptoms are less evident during these sleep movements: the movements tend to be rapid, and tremor is absent. This suggests that basal ganglia circuits underlying motor impairment in PD do not exert such effects during REM sleep (Arnulf 2012 Mov Disord 27: 677).

To test this hypothesis, Hackius et al. recorded local field potentials and electroencephalographic activity in the STN and cortex, respectively, while PD patients with RBD slept. Surprisingly, synchronization of beta-frequency oscillations, which decreases during movements in the wake state, increased during movements in REM sleep. In contrast, synchronization between the motor cortex and STN decreased during REM sleep movements.

These results suggest that abnormal beta oscillations persist in the STN during REM sleep movements, but communication between the cortex and STN is disrupted. This suggests that cortical commands bypass the dysfunctional basal ganglia to drive movements during REM sleep. This alternative pathway might eventually be repurposed to improve voluntary movement in awake PD patients.

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