This Week in The Journal

Write Protection Expands Model of LTP

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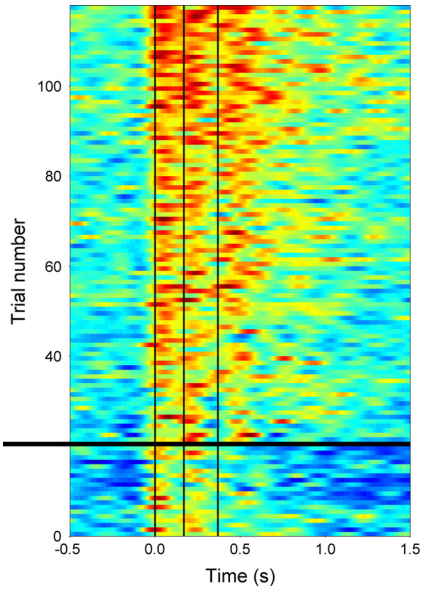
(see pages 1319–1334)

Glutamatergic activation of relatively depolarized postsynaptic neurons leads to long-term synaptic potentiation (LTP). Changes that occur early in LTP are thought to tag activated synapses, allowing them to capture newly synthesized plasticity-related products (PRPs), which include scaffolding and cytoskeletal proteins. These PRPs are required to consolidate early LTP into late LTP; without them, synaptic strength decreases to baseline within a few hours.

Ziegler et al. have developed a computational model that simulates three temporal phases of LTP, as well as the analogous stages of long-term depression (LTD). The phases are represented by three bistable, synapse-specific variables—weight, tagging, and scaffolding—which can be in "low" or "high" states. Depending on its strength and frequency, simulated synaptic activity can cause weight, tagging, and scaffolding variables to switch between low and high states with time courses characteristic of short-term potentiation, early-LTP, and late-LTP, respectively. Importantly, the model extends previous models by incorporating a two-stage write-protection mechanism that gates the transition between phases and prevents overwriting of previously stored memories. The first gate represents the molecular changes necessary for tagging; it determines whether the synaptic weight can influence the tagging variable, and its state is determined by stimulation strength. The second gate represents the molecular changes necessary for consolidation; it determines whether the tagging variable can influence the scaffolding variable and its state is determined by additional inputs that represent reward or novelty that promote the production of PRPs.

Model simulations reproduced many experimental results gathered in hippocampal slices. For example, weak tetanic stimulation produced early LTP, but strong stimulation was required to induce late-LTP. The model also replicated cross-tagging, in which strong tetanic stimulation of a subset of synapses not only produces late-LTP at those synapses, but also consolidates early-LTD that was previously produced at other synapses of the same cell. Notably, the write-protection mechanism enabled the model to replicate results not explained by previous models, such as "tag-resetting," in which the strength of a depotentiated tagged synapse spontaneously recovers, and "behavioral tagging," in which exposure to a novel environment enables a weak stimulus to induce plasticity.



SS firing pattern changes in one PC across reach trials with and without external force. In trials without perturbation (below horizontal line), firing rate (color coded) was highest around movement onset (first vertical line). The firing pattern gradually changed in the presence of external force. After adaptation (toward top of panel), firing rate increased not only at movement onset, but also at the onset of the force (middle vertical line) and, to a lesser extent, after force offset (third vertical line). See the article by Hewitt et al. for details.

Purkinje Cell Simple Spike Pattern Changes during Adaptation

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(see pages 1106–1124)

The emergence of motor deficits after cerebellar damage indicates that the cerebellum is involved in producing smooth, continuous movements. It is also thought to contribute to motor learning and adaptation in response to changing conditions, such as external forces or muscle fatigue. More specifically, the cerebellum has been hypothesized to provide forward internal models, that is, predictions about what body movements will result from motor commands. It has further been proposed that discrepancies between the predicted movement and the actual movement (as assessed by sensory feedback) produce a prediction error that can lead to modification of the internal model. How these hypothetical roles might be implemented by neuronal firing remains unclear, however.

Cerebellar Purkinje cells (PCs) exhibit two types of spiking. Simple spikes (SSs) are driven by parallel fiber inputs, and they appear to encode eye and limb position, velocity, and acceleration during movements. Complex spikes are triggered by climbing fiber input, and it has been proposed that they play a role in learning. One way to investigate cerebellar function is to examine how firing patterns change during learning. This has primarily been done during adaptation of eye movements. To investigate how modulation of PC spiking might contribute to motor learning during reaching movements, Hewitt et al. recorded PC activity as monkeys adapted such movements to counteract externally administered forces. Initially, the perturbation altered the kinematics of arm movements (i.e., the position, velocity, and acceleration of the arm over the course of the reach), but as monkeys learned to compensate for the expected perturbation over subsequent trials, the kinematic parameters became similar to those in the absence of perturbation. As this adaptation took place, the pattern of SSs changed in slightly more than half of recorded PCs, whereas complex spiking was affected in only ~10% of PCs. Unlike previous findings showing that spike timing changes alone may be sufficient for adaptation of saccade amplitude, changes in both the sensitivity and timing of SSs relative to kinematics occurred during reach adaptation. These differences were largest for position and velocity encoding. Furthermore, both increases and decreases in SSs occurred during learning, suggesting multiple plasticity mechanisms took place.

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