This Week in The Journal

Rubroraphe Projection Helps Restore Motor Function in Mice

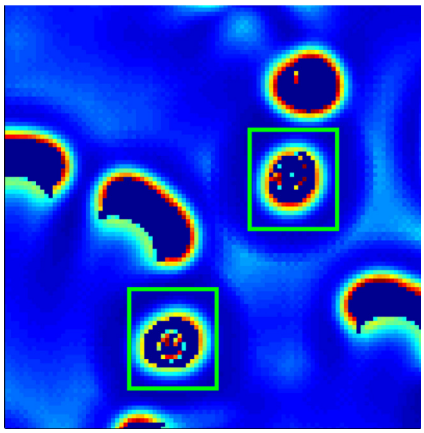
Chad S. Siegel, Kathren L. Fink, Stephen M. Strittmatter, and William B. J. Cafferty

(see pages 1443–1457)

Several factors conspire to limit axonal regeneration after spinal cord injury (SCI): growth-inhibiting molecules are present in the extracellular environment, an impenetrable glial scar forms around the lesion, and adult axons are not programmed for growth. Although these obstacles may eventually be overcome, stimulating plasticity in spared pathways might be a more expedient strategy for achieving functional recovery. SCI in humans usually spares some axons, and studies in rodents—which exhibit more spontaneous recovery than humans—suggest that motor function can be restored by increasing the role of existing latent and/or redundant pathways or by inducing spared axons to sprout and take on new roles. Sprouting can be promoted by blocking inhibitory factors such as Nogo and its receptor, NgR1.

Plasticity involving the red nucleus and its descending projections in the rubrospinal tract (RST) have a prominent role in restoring skilled movement after corticospinal tract (CST) lesions in several species. For example, corticorubral and rubrospinal axons sprout, and the RST's involvement in motor control expands. Now Siegel et al. have discovered that in mice, the red nucleus has a minor projection to the nucleus raphe magnus (NRM), which sends serotonergic projections to all spinal segments. Furthermore, they provide evidence that sprouting of this projection contributes to the recovery of skilled locomotor function after CST lesion.

Bilateral CST lesions did not affect unskilled locomotion in wild-type mice, but skilled locomotion (grid walking) was impaired. Performance significantly improved within 2 weeks, but it remained largely impaired after 5 weeks. Functional recovery was greater in NgR1-deficient mice, and this was associated with greater lesion-induced sprouting of red nucleus projections to the spinal cord, basilar pontine nuclei, and NRM. Importantly, transiently silencing NRM did not affect grid walking in uninjured mice, but it suppressed the improvements associated with lesion-induced sprouting, suggesting this projection gains a new role after CST lesion. The results demonstrate that enhancing plasticity can increase functional recovery after SCI. It should be noted, however, that the rubrospinal pathway is thought to have a limited role in humans, so promoting plasticity in this particular pathway may not benefit SCI patients.



This movie shows propagating wave patterns with complex dynamics that formed when excitation and inhibition were balanced in a network model with spatially extended coupling. Waves took the form of crescent-shaped propagating waves and wandering patches (outlined by green boxes). Colors represent membrane potential between −80 mV (blue) and spike threshold (−55 mV, red). See the article by Keane and Gong for details.

Network Model Explains Doubly Stochastic Cortical Spiking

Adam Keane and Pulin Gong

(see pages 1591–1605)

When a constant current is injected into a cortical neuron, the neuron fires a steady stream of evenly spaced action potentials. In the absence of exogenous electrical stimulation, however, spiking of cortical neurons is highly variable, even across trials in which identical sensory stimuli are presented. This variability is somewhat perplexing, because if the thousands of cortical neurons that provide input to any one cell are spiking irregularly, one might expect the total synaptic input to the cell to be relatively constant over time. The current influx over time should therefore approximate that produced by exogenous current injection and produce similarly uniform spiking.

Two hypotheses have been put forth to explain the unexpected variability in spike timing: (1) excitatory inputs are roughly balanced by inhibitory inputs so that the membrane potential fluctuates in a random walk, crossing spike threshold at variable times; and (2) although irregular, spiking sometimes occurs synchronously across presynaptic cells, providing postsynaptic neurons with synchronous synaptic input that produces sporadic above-threshold depolarization.

Cortical recordings suggest that both excitatory–inhibitory balance and synchronous spiking occur *in vivo*. In fact, evidence suggests that the two phenomena are related: balanced excitation and inhibition are required for generating cortical oscillations, which synchronize neuronal spiking. A new computational model by Keane and Gong further suggests that synchronous spiking is a natural consequence of balanced excitation and inhibition in spatially extended networks. An important feature of their model is that the strength of excitatory coupling decreases with distance between neurons, as occurs *in vivo*. When excitation and inhibition were balanced, network stimulation produced two patterns of activity, crescents and patches, that propagated in random directions through the network, moving quickly or slowly, respectively. Propagating wave fronts provided brief, synchronous input to neurons, causing irregular spiking. Moreover, the spike rate of neurons varied as activity waves or patches approached and moved on, reproducing spike rate variability found *in vivo*. Importantly, propagating waves only appeared when excitatory coupling decreased with distance, and the doubly stochastic spike pattern (variably spike timing together with slowly fluctuating spike rate) only occurred when inhibition and excitation were balanced.

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