This Week in The Journal

Stem-Cell Effects on Cortical Communication after Stroke

Claudia Green, Anuka Minassian, Stefanie Vogel, Michael Diedenhofen, Andreas Beyrau, et al.

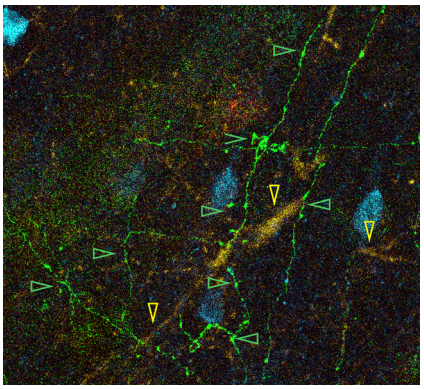
(see pages 1648–1661)

Loss of blood flow during stroke causes neuron death, first in the area normally supplied by the blocked artery (the infarct area), then in peri-infarct areas. The effects of stroke spread beyond these regions, however: because the brain is highly interconnected, neuron loss in one node reverberates throughout the network.

Neural plasticity after stroke can reorganize brain networks to produce some functional recovery, but the ability to compensate for lost neurons is limited, and most patients experience long-term functional impairment. Therefore, much effort has been focused on enhancing functional recovery. One avenue being explored is stem-cell therapy. In animal models, implanted stem cells differentiate into neurons and improve functional recovery. The benefits of stem-cell therapy extend beyond cell replacement, however: stem cell grafts also secrete molecules that reduce inflammation and/or stimulate angiogenesis and neural plasticity.

The extent to which implanted stem cells can restore network function beyond the graft area is unclear. To address this question, Green et al. monitored correlated activity fluctuations (functional connectivity) and axonal fiber density (structural connectivity) in sensorimotor networks before and for several weeks after experimental stroke was induced in mice. They then asked how implanting human neural stem cells 2 d after stroke affected connectivity measures. As expected, changes in functional and structural connectivity occurred both within and between hemispheres after stroke. Changes in structural connectivity were not obviously affected by stem cell grafts, but reductions in functional connectivity were attenuated by these grafts. Indeed, disruption of functional connectivity was relatively mild in engrafted mice during the first 4 weeks after stroke. After that, however, stem cells began to die, and connectivity strengths quickly declined in the mice that received implants. By 12 weeks after stroke, no differences were detected between engrafted and control mice.

These results suggest that stem cell grafts can attenuate loss of functional connectivity after stroke. Importantly, this effect is apparent long before engrafted stem cells are thought to differentiate into mature neurons. Moreover, the effect does not appear to result from stabilization of structural connectivity. The mechanisms by which stem cells stabilize functional connectivity and how this stabilization affects behavioral function should be investigated in future studies.



Axons from A25 (green) that terminate (arrowheads) in layer V of medial entorhinal area 28 comingle with parvalbumin-expressing (yellow) and calretinin-expressing (blue) interneurons. See Joyce and Barbas for details.

Cortical Connections of Autonomic Regulatory Area 25

Mary Kate P. Joyce and Helen Barbas

(see pages 1677–1698)

The prefrontal cortex (PFC) has diverse roles in cognitive processes, including learning, decision making, and the experience and regulation of emotion. Each of the many regions that comprise PFC is thought to have distinct functions that rely on unique patterns of afferent and efferent projections. For example, architectonic area 25 (A25), a portion of the cingulate cortex, is thought to regulate autonomic responses related to emotional experiences via dense projections to the amygdala, hypothalamus, and periaqueductal gray. Electrical stimulation of A25 alters heart and respiration rate, and it can generate feelings of sadness, well-being, or fear (Devinsky et al. Brain 118:279). Notably, A25 shows abnormal activation patterns in patients with major depressive disorder.

To deduce the role of A25 in depression and other emotional experiences, one must consider its interactions with other cortical areas. Which areas project to and receive input from A25 has not been thoroughly documented, however. Therefore, Joyce and Barbas used neural tracers to identify these projections in monkeys. They focused particularly on the laminar pattern of connections between areas, because this might provide clues regarding function. As is typical in the cortex, connections between A25 and other regions were generally reciprocal. The densest connections were with other cortical areas involved in emotion and learning, including the anterior cingulate, ventromedial PFC, and posterior orbitofrontal cortex. A25 also received projections from the medial temporal lobe and auditory association cortex. The laminar distribution of projections depended on each area's structure: projections from eulaminate cortical areas (those with a clear layer IV) typically originated in superficial layers, whereas those from agranular cortex (lacking layer IV) tended to come from deep layers. In most cases, projections from A25 terminated in superficial layers.

Knowledge of these projection patterns should guide future experiments into the role of specific interactions. Connections with the medial temporal lobe, for example, likely play roles in memory-guided behaviors, whereas those with auditory cortex might relate to emotional vocalizations. Because projections to different layers interact with different types of inhibitory neurons, they might have different roles in modulating or gating output from target regions. Future work should test these hypotheses.

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