This Week in The Journal

Parkin Stabilizes Hippocampal Postsynaptic AMPA Receptors

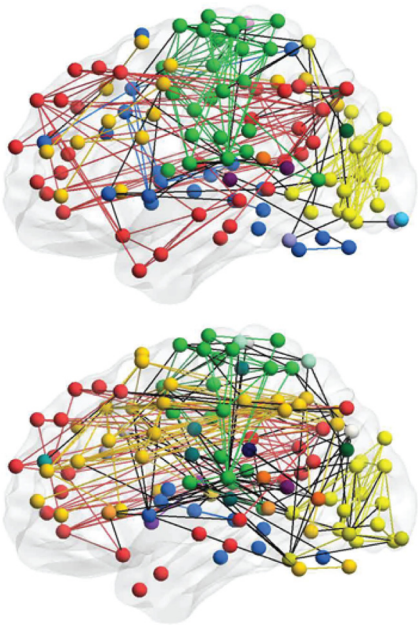
Giuseppe P. Cortese, Mei Zhu, Damian Williams, Sarah Heath, Clarissa L. Waites

(see pages 12243–12258)

Parkinson's disease (PD) is a neurodegenerative disease characterized by rigidity, bradykinesia, and cognitive disruptions. PD ravages the dopaminergic neurons of the midbrain, accounting for disordered movement, but changes in other areas are less well studied. The causes of PD are only beginning to emerge, but genetics plays a role. Cases of PD caused by monogenic mutations in one of a handful of identified genes make up an estimated 3–5% of all PD. An autosomal recessive loss-of-function mutation in *PARK2*, a gene that encodes Parkin, an E3 ubiquitinase, causes a rare, severe type of juvenile-onset PD. Previous research had indicated that loss of Parkin affected glutamatergic signaling in hippocampal neurons, but it was unclear how.

To find out how Parkin affects hippocampal signaling, Cortese et al. used lentiviral transfection with an shRNA to knock down Parkin expression by ~60% (sh Parkin) in dissociated, cultured rat hippocampal neurons. Control neurons were transfected with green fluorescent protein (GFP), human Parkin tagged with GFP, or shParkin and GFP-tagged human Parkin as a rescue construct. In whole-cell patch clamp recordings, shParkin cells displayed significantly smaller miniature EPSCs compared to their Parkin-containing counterparts, suggesting reduced glutamatergic transmission; miniature EPSC frequency was not affected, however.

In neurons cultured on glial microislands, postsynaptic Parkin-deficient neurons contacted by presynaptic untransfected neurons also showed smaller evoked EPSCs, and AMPA receptor-mediated currents in Parkin-deficient neurons were half the size of those in control neurons. Consistent with this, surface expression of AMPA receptors was dramatically reduced in Parkin-deficient neurons. The density of glutamatergic synapses was unaffected by Parkin knockdown, although staining was reduced for Homer1, an adapter protein involved in signal transduction and plasticity. Overexpression of Homer1 in Parkin-deficient neurons completely rescued surface expression of the AMPA subunit GluA1, suggesting that Parkin stabilizes Homer1 at the postsynaptic density. The authors determined that endocytic zones required for removal of AMPA receptors from the membrane were reduced in Parkin-deficient neurons. Measurements of AMPA receptor recycling revealed that with the loss of Homer1 at endocytic zones, receptors were not endocytosed, eventually leading to a deficit in membrane AMPA receptors. The findings account for disrupted signaling with reduced Parkin, which may underlie some PD symptoms.



Network assignment for rest (top) and n-back task (bottom) for the functional atlas. Each color represents a network, each colored line represents a within-network edge, and each black line represents a between-network edge. Each circle corresponds to the coordinates of the center of an ROI. See Cohen and D'Esposito for details.

Whole-Brain Functional Networks Dynamically Respond to Demands

Jessica R. Cohen and Mark D'Esposito

(see pages 12083–12094)

Neuroplasticity gives the brain the capability to adapt to changing environments throughout our lifetimes, but the brain's ability to make dynamic changes on a moment-to-moment basis is perhaps even more fundamental. While researchers have made tremendous gains in understanding how individual neurons communicate with one another, a great gap remains in our grasp of how dynamic network communications give rise to thought and emotion. Some tasks likely require integration of brain networks, whereas others probably require segregation.

Cohen and D'Esposito used theoretical graph analysis of functional magnetic resonance imaging (fMRI) scans to examine functional connectivity during two different tasks. A sequence-tapping motor execution task is thought to depend on a single brain network, whereas an n-back test of working memory likely engages multiple networks. By examining whole-brain connectivity in individuals performing both tasks, the authors were able to compare functional connectivity patterns in the two tasks.

Thirty healthy volunteers were trained to tap out a particular sequence with their right and left fingers before performing the task in the scanner. For the n-back test, subjects were presented with a series of letters and asked whether each letter was the same as the letter presented previously (one-back), or two or three presentations back. For example, in the sequence R-D-T-R-S, "R" meets the qualifications for a 3-back letter. Resting state scans were collected before and between the tasks. The authors used identified regions of interest (ROIs) from two brain atlases to determine functional connectivity. By quantifying the relative difference between within-network connectivity and between-network connectivity during the tasks, the authors determined that the motor task led to greater network segregation compared to the n-back test. In contrast, global efficiency—a measure of inter-connectedness across the whole brain—was higher during the n-back task than the tapping task. Functional connectivity was also linked to task performance. During the n-back test, increased global efficiency was associated with accuracy. The study contributes to an understanding of how the brain dynamically recruits within- or between-network activity depending on immediate demand.

This Week in The Journal is written by Stephani Sutherland, Ph.D.