

This Week in The Journal

● Cellular/Molecular

NO Regulates Gephyrin Clustering

Borislav Dejanovic and Guenter Schwarz

(see pages 7763–7768)

Nitric oxide is produced postsynaptically at both excitatory and inhibitory synapses, and it diffuses retrogradely to regulate presynaptic transmitter release. In glutamatergic neurons, nitric oxide synthase (nNOS) binds to the scaffolding protein PSD-95, which localizes NO production to dendritic spines and near NMDA receptors. In addition to acting as a retrograde signaling molecule, NO S-nitrosylates PSD-95, which reduces levels of PSD-95—and thus the proteins it anchors—at the postsynaptic density. Dejanovic and Schwarz now report similar interactions between nNOS and gephyrin, the principal postsynaptic scaffolding protein at GABAergic synapses. nNOS was bound to gephyrin in mouse hippocampal neurons, and coexpression of gephyrin increased nNOS clustering in cell lines. Gephyrin was S-nitrosylated, and inhibiting NO synthesis increased the size of gephyrin clusters and increased synaptic expression of GABA_A receptors in neurons. Conversely, overexpressing nNOS in neurons decreased gephyrin-cluster size. These results suggest that S-nitrosylation of gephyrin regulates the size of gephyrin clusters and thus the concentration of GABA_A receptors at postsynaptic sites.

● Development/Plasticity/Repair

Resveratrol Improves Memory in Humans

A. Veronica Witte, Lucia Kerti, Daniel S. Margulies, and Agnes Flöel

(see pages 7862–7870)

Sirtuins are protein deacetylases that are activated by mild stressors. They promote cell resilience and survival, slow the aging process, and are thought to mediate the beneficial effects of exercise and caloric restriction on cognitive function. Sirtuins are also activated by resveratrol, a phytochemical found in blueberries and red grape skins. Resveratrol improves mem-

ory performance in rodents and non-human primates, and in humans it has beneficial effects in several pathological conditions associated with cognitive decline, including type-2 diabetes, impaired glucose regulation, and increases in inflammatory cytokines. Witte et al. now show that resveratrol, taken daily for 26 weeks, improved memory retention in overweight older humans. Specifically, resveratrol increased recall of words after a 30 min delay. Increased recall was associated with increased correlated activity in hippocampus and medial prefrontal cortex, suggesting connections between these structures were strengthened. Resveratrol supplements also reduced levels of body fat and increased leptin levels, suggesting it may improve cognitive function by improving energy metabolism.

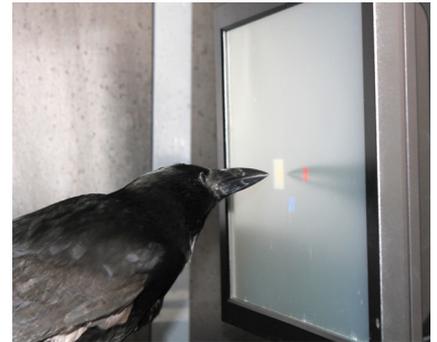
● Behavioral/Cognitive

Neurons in NCL May Underlie Working Memory in Crows

Lena Veit, Konstantin Hartmann, and Andreas Nieder

(see pages 7778–7786)

Performing complex tasks requires working memory, the ability to remember recent information and use it to guide ongoing behavior. Persistent activity in prefrontal cortical neurons is thought to underlie working memory in primates. Although birds do not have a layered cortex, some—including crows—exhibit working memory, which relies on an associative forebrain region called the nidopallium caudolaterale (NCL). To investigate the role of NCL in working memory, Veit et al. recorded from NCL neurons during a delayed match-to-sample task in which crows were shown a photograph and then, after a short delay, had to indicate which of four photographs was just seen. Approximately 19% of recorded neurons showed increased or decreased activity during the delay period after particular sample images were shown, and this image selectivity was lower on trials in which the crow made an error. Approximately 25% of these neurons had similar firing rates during sample presentation and delay periods and thus may contribute to visual working memory.



Carrion crows (*Corvus corone*) can perform a delayed match-to-sample visual working memory task. Persistent activity in NCL neurons appears to underlie this ability. See the article by Veit et al. for details.

● Neurobiology of Disease

Reducing mTOR Levels Rescues AD Phenotypes in Mice

Antonella Caccamo, Vito De Pinto, Angela Messina, Caterina Branca, and Salvatore Oddo

(see pages 7988–7998)

A large screening for natural antifungal compounds in the 1970s led to the discovery of rapamycin, produced by a bacterium present in soil from Easter Island. The beneficial effects of rapamycin extend far beyond treating fungal infections, however: because it suppresses proliferation of immune cells, it inhibits rejection of transplanted organs; and because it inhibits tumor growth, it is used in cancer chemotherapy. In fact, the mammalian target of rapamycin (mTOR) regulates growth and proliferation of all cells by regulating protein translation and degradation in response to environmental signals. But excessive mTOR activity can be detrimental, causing cognitive deficits and reducing lifespan. mTOR signaling is elevated in people with Alzheimer's disease (AD), and Caccamo et al. discovered that AD-like phenotypes were rescued in a mouse model by removing one mTOR allele, which halved mTOR levels. Specifically, reducing mTOR levels reversed changes in global gene expression patterns, decreased levels of soluble and insoluble β -amyloid peptide, and improved spatial memory in aged Tg2576 mice.