This Week in The Journal

Hippocampal Neurogenesis Disrupts New, Not Older, Memories

Aijing Gao, Frances Xia, Axel J. Guskjolen, Adam I. Ramsaran, Adam Santoro, et al.

(see pages 3190–3198)

New neurons born in the hippocampus are thought to provide a substrate for new memories, but could they also disrupt the architecture that supports existing memories, making them harder to access? This week, Gao et al. demonstrate that hippocampal neurogenesis leads to forgetting—depending on the age of the memory.

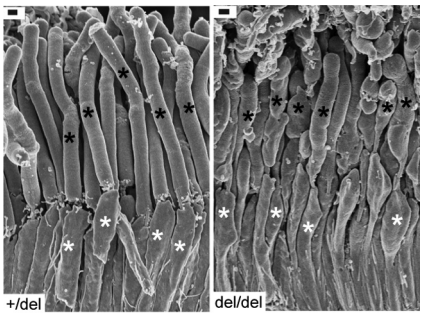
The researchers first silenced hippocampal activity using the inhibitory DREADD (designer receptor exclusively activated by designer drugs) hM4Di expressed in the dorsal hippocampus of wild-type mice. Mice underwent contextual fear conditioning in the form of foot shocks and were later tested for fear behavior back in the same chamber. Thirty minutes before testing, mice received a dose of clozapine-*N*-oxide to activate hM4Di and inhibit the dorsal hippocampus. Freezing behaviors were reduced in mice tested a day, but not a month, after conditioning, indicating that new but not established fear memories were impaired.

Next, the researchers induced neurogenesis in wild-type mice by giving them access to a running wheel, on which the animals ran ~5 km per day. Mice that exercised for 28 d after training displayed less conditioned freezing than sedentary mice. The effects of exercise on both neurogenesis and forgetting were dose-dependent, with effects emerging only after 14 d of running.

If memories do indeed "shift" out of the hippocampus over time, the authors hypothesized that established memories would be less subject to forgetting than new ones. Mice were allowed to exercise for 14 d after fear conditioning—some immediately, and some after a 14- or 28-d delay. Mice that exercised immediately showed less freezing behavior than sedentary mice, but there was no difference in mice who exercised weeks after conditioning.

In another experiment, the researchers generated mice with conditional deletion of the tumor suppressor gene p53 specifically in hippocampal neurons (iKO-p53). Deletion of p53 led to increased neurogenesis. Freezing behavior was reduced—indicating memory impairment—in iKO-p53 mice treated with tamoxifen to induce p53 deletion, thereby increasing neurogenesis, immediately after fear conditioning. Freezing behavior was unaffected in mice who were treated a month after training.

It remains unclear whether neurogenesis occurs regularly in adult humans, but the study confirms the idea that hippocampal activity is required for new memories but less important with time as they become more widely distributed to cortex. It also establishes memory age as a "boundary" marking its susceptibility to disruption by hippocampal neurogenesis.



Scanning electron microscopy of normally organized photoreceptors from a heterozygous C8orf37 $^{+/-}$ mouse (left) and photoreceptors with abnormally formed outer segments (black asterisks) from a *C8orf37*-null mouse (right).

Mystery Protein C8ORF37 Acts in Photoreceptor Morphogenesis

Ali S. Sharif, Dongmei Yu, Stuart Loertscher, Richard Austin, Kevin Nguyen, et al.

(see pages 3160–3176)

Three different retinal degeneration diseases—retinitis pigmentosa, cone-rod dystrophy, and Bardet–Biedl syndrome (BBS)—result from mutations in *C8ORF37*, a gene found on human chromosome 8 that encodes a small protein whose function remains utterly mysterious. Using CRISPR/Cas9 technology, Sharif et al. generated *C8orf37*-null mice, which displayed photoreceptor dysfunction and retinal degeneration like that seen in patients.

Photoreceptor dysfunction was apparent in the *C8orf37*-null mice at 3 weeks, the earliest time detectable with electroretinography. The outer segment (OS) of retinal photoreceptors contains tightly stacked membrane disc structures containing the molecular machinery for phototransduction. These discs must remain intact and aligned to maintain neuronal health and function. Scanning and transmission electron microscopy revealed that the OS of photoreceptors from *C8orf37*-null mice was wider, more variable, and less dense than that of heterozygous controls (see figure). The discs were severely disorganized, sometimes running perpendicular to normal and forming "abnormal membranous whirls."

Previous findings had hinted that C8ORF37 might be a ciliary protein: patients with BBS have other symptoms in addition to vision loss, thought to arise from ciliary dysfunction in other organs, and in some cells C8ORF37 localizes to the ciliary apparatus. But in *C8orf37*-null mice, cilia and other subcellular structures of the photoreceptors appeared normal, and C8ORF37 was not localized to cilia in normal mice. Instead, the protein was found throughout the photoreceptors, except in the OS, where the null phenotype was evident. That discrepancy led the authors to hypothesize that C8ORF37 plays a key role in OS morphogenesis—from outside the OS. Immunostaining of photoreceptors in *C8orf37*-null mice showed that protein levels of rhodopsin and other proteins key to OS formation were reduced by 30–70% well before OS extension. Single-cell reverse-transcription quantitative PCR indicated that protein transcription was largely unaffected, suggesting a protein-processing defect. The affected proteins were normally localized to the OS in the *C8orf37*-null, indicating that C8ORF37 is not required for targeting proteins to the OS. Based on those findings, the authors hypothesize that C8ORF37 participates in protein synthesis or processing of the proteins key to OS development, perhaps acting as a molecular chaperone.

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