Baby neurons in adult brains are needed to maintain memory: Study

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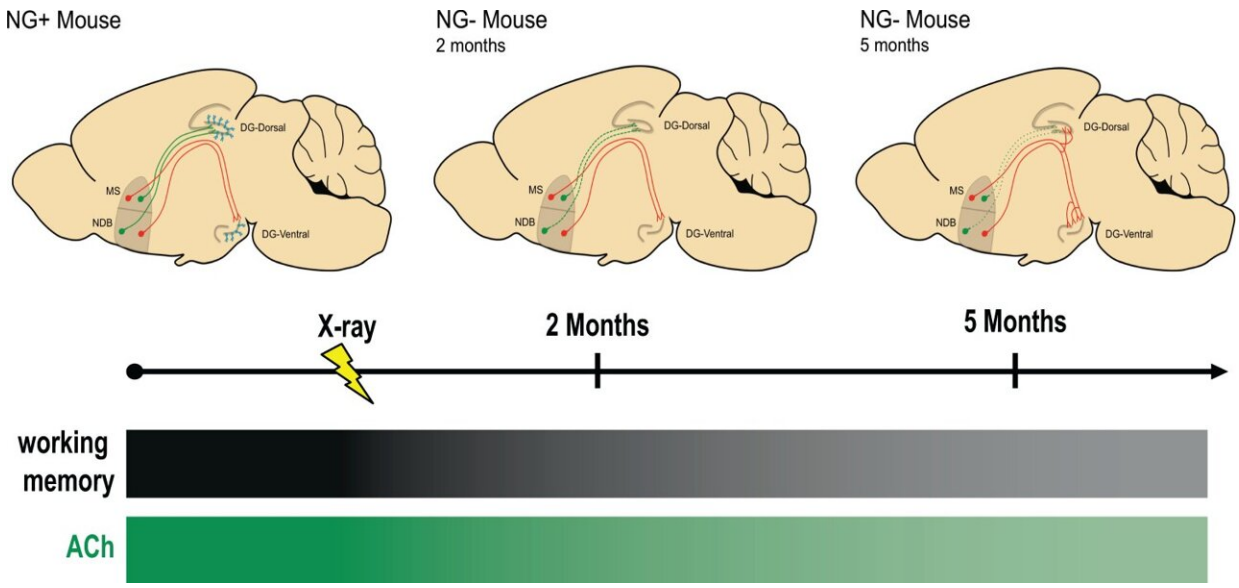

Structural and functional reorganization of the septohippocampal circuit in NG– mice. NG+ mice show acetylcholine release that supports working memory and cholinergic afferent organization within the septohippocampal projection. NG– mice without neurogenesis for 2 months show an emerging deficit in acetylcholine release in the hippocampus but maintain cholinergic afferent organization within the septohippocampal projection. NG– mice without neurogenesis for 5 months show significant reductions in hippocampal acetylcholine release and rewiring of cholinergic septohippocampal inputs with septal neurons that normally project to the ventral hilus innervating the dorsal hilus and increased local arborization of MS-NDB cholinergic neurons within the ventral hilus. Credit: *Molecular Psychiatry* (2023). DOI: 10.1038/s41380-023-02167-z

A quarter-century ago, researchers discovered that adults, not just developing infants, can generate new brain cells, a process called neurogenesis. But it's still not clear what role these new neurons play in health or disease.

In a new mouse study, Columbia University researchers found that neurogenesis in adults is critical for maintaining brain circuits that support working memory across the lifespan and chronic loss of adult neurogenesis causes progressive memory loss, like that seen in age-related cognitive decline and Alzheimer's disease in humans.

The study, "Adult-born neurons maintain hippocampal cholinergic inputs and support working memory during aging," was published in July in the journal *Molecular Psychiatry*.

"The encouraging news is that these memory deficits were completely reversible in mice, raising the possibility that we can prevent or treat memory loss related to aging or dementia in humans," says study leader Alex Dranovsky, MD, Ph.D., associate professor of psychiatry at Columbia University Vagelos College of Physicians and Surgeons.

Researchers estimate that the brain's hippocampus—which plays a key role in memory, learning, and emotion—makes about a thousand new neurons each day throughout adulthood.

"Considering that the brain contains about 100 billion neurons, it's reasonable to question whether this level of neurogenesis could have any impact on brain function," says Dranovsky. "But over the life of the animal, the effects of these new cells can add up as they make connections with other neurons and other parts of the brain."

To test whether adult neurogenesis is vital to brain health over the long term, Dranovsky's team stopped the process in adult mice by irradiating

the birthplace of new neurons or with genetic engineering.

Over time, the mice produced less and less of the neurotransmitter acetylcholine in the hippocampus, leading to a profound rewiring of a brain circuit critical for memory. The mice also experienced a slow but progressive decline in working memory (temporary "sticky notes" for carrying out mental tasks).

Remarkably, while neurogenesis was suppressed immediately after treatment, the memory, anatomic, and biochemical changes took five months (about a quarter of the mouse life span) to emerge.

Even though the brain circuit changed in a way that impaired memory, the circuit did form new, but dysfunctional, connections that could be recruited to improve memory.

"It was as if existing neurons were trying, but failing, to compensate for the loss of neurogenesis and what started out as a subtle defect in acetylcholine," Dranovsky says, "and they just needed a little nudge."

The researchers suspected that the remodeled circuit had sufficient reserves of acetylcholine but couldn't release it when needed. Using a drug, the researchers nudged the circuit to release more acetylcholine and completely rescued the memory deficits even in aged mice.

"The results suggest that we have to revisit old notions about the aging brain," says Dranovsky. "It seems to be more plastic than we've thought."

Cholinesterase inhibitors have been used to treat patients with Alzheimer's disease, with little success. "We think this drug, and many others, have failed because they're focused on one type of cell or molecule. What our findings tell us is that we probably need to address the fact that the whole memory circuit is compromised in aging and

dementia."

More information: Greer S. Kirshenbaum et al, Adult-born neurons maintain hippocampal cholinergic inputs and support working memory during aging, *Molecular Psychiatry* (2023). DOI: 10.1038/s41380-023-02167-z

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