Controlling a single brain chemical may help expand window for learning language and music

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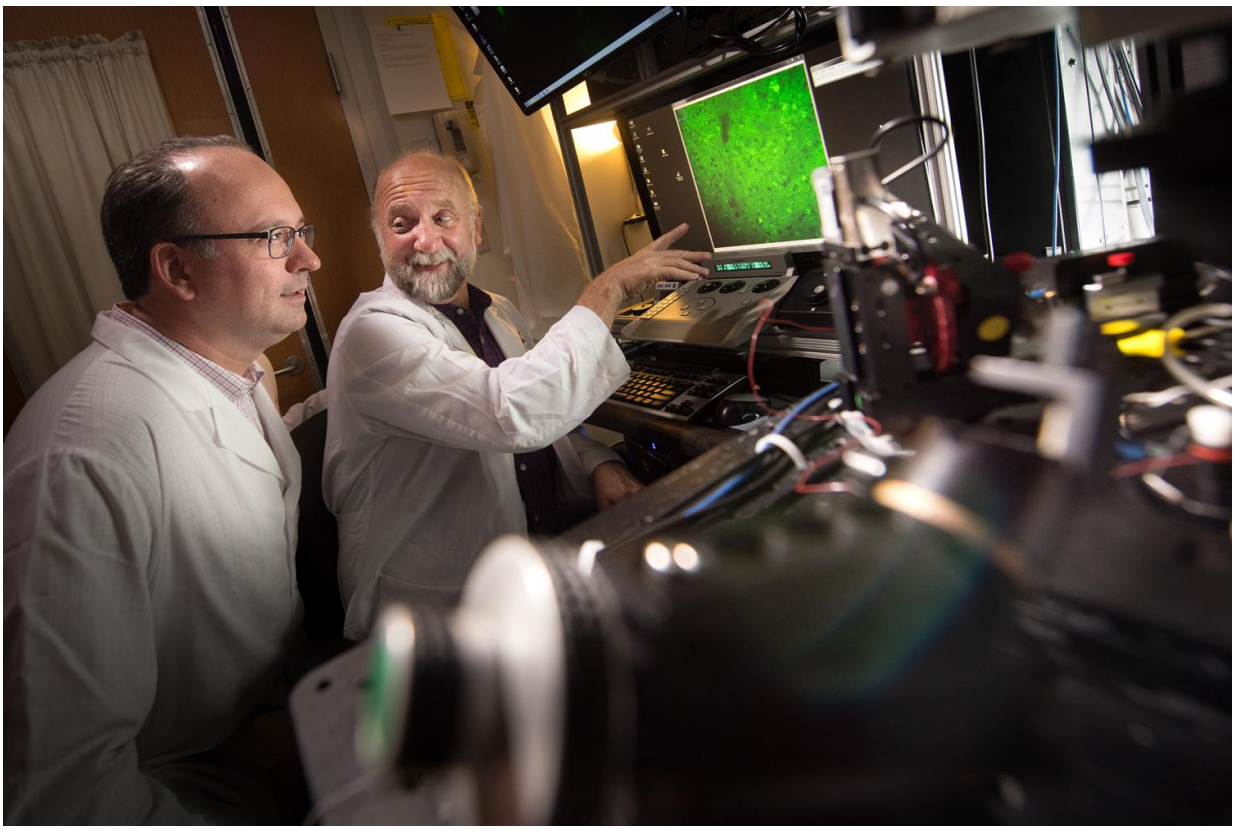


(from left) Noah Roy, Ph.D., a postdoctoral research associate in Dr. Zakharenko's lab, and first author Jay Blundon, Ph.D., an associate scientist in Dr. Zakharenko's lab. Credit: Seth Dixon / St. Jude Children's Research Hospital

Learning language or music is usually a breeze for children, but as even young adults know, that capacity declines dramatically with age. St. Jude Children's Research Hospital scientists have evidence from mice that restricting a key chemical messenger in the brain helps extend efficient auditory learning much later in life.

Researchers showed that limiting the supply or the function of the neuromodulator adenosine in a brain structure called the auditory thalamus preserved the ability of adult mice to learn from passive exposure to sound much as young children learn from the soundscape of their world. The study appears June 30 in the journal *Science*.

"By disrupting adenosine signaling in the auditory thalamus, we have extended the window for auditory learning for the longest period yet reported, well into adulthood and far beyond the usual critical period in mice," said corresponding author Stanislav Zakharenko, M.D., Ph.D., a member of the St. Jude Department of Developmental Neurobiology. "These results offer a promising strategy to extend the same window in humans to acquire language or musical ability by restoring plasticity in critical regions of the brain, possibly by developing drugs that selectively block adenosine activity."

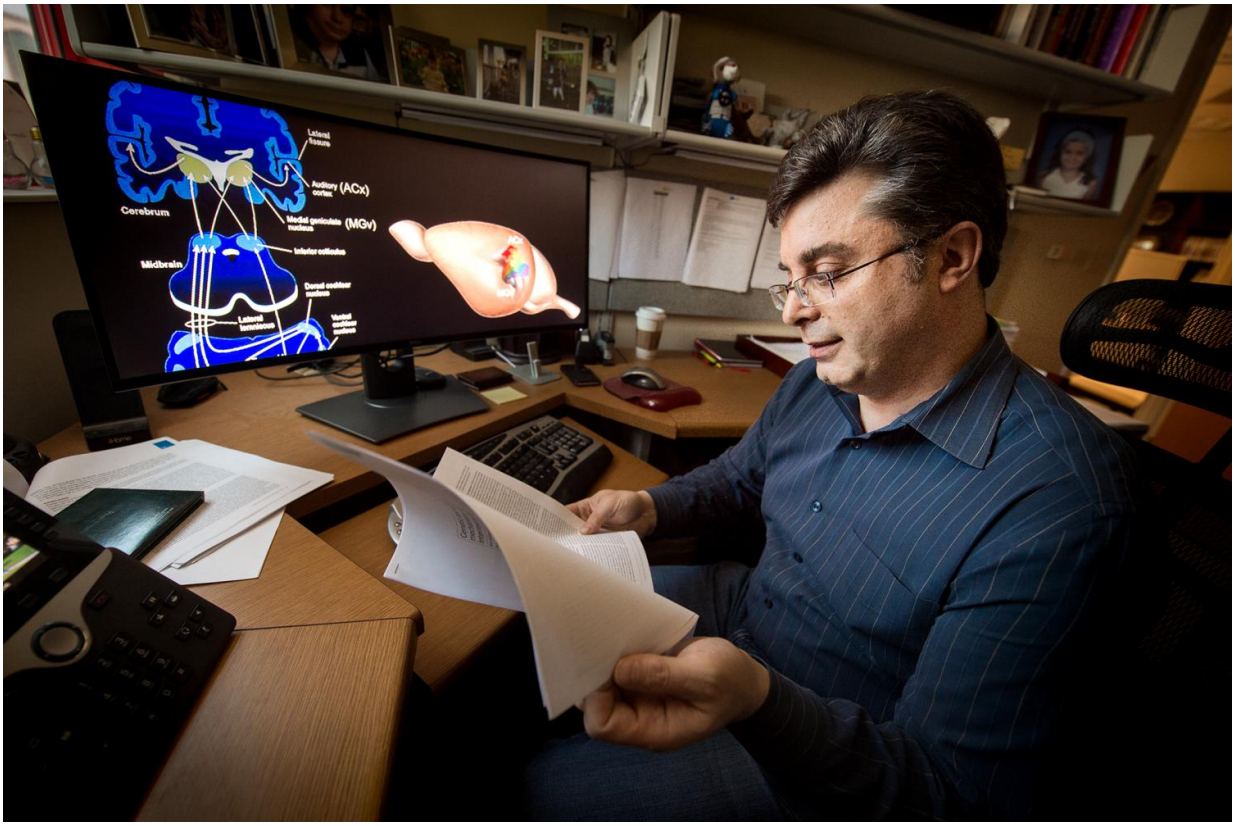
The auditory thalamus is the brain's relay station where sound is collected and sent to the auditory cortex for processing. The auditory thalamus and cortex rely on the neurotransmitter glutamate to communicate. Adenosine was known to reduce glutamate levels by inhibiting this neurotransmitter's release. This study also linked adenosine inhibition to reduced brain plasticity and the end of efficient auditory learning.

Researchers used a variety of methods to demonstrate that reducing adenosine or blocking the A1 adenosine receptor that is essential to the chemical messenger's function changed how adult mice responded to

sound.

Much as young children pick up language simply by hearing it spoken, researchers showed that when adenosine was reduced or the A1 receptor blocked in the auditory thalamus, adult mice passively exposed to a tone responded to the same tone stronger when it was played weeks or months later. These adult mice also gained an ability to distinguish between very close tones (or tones with similar frequencies). Mice usually lack this "perfect pitch" ability.

Researchers also showed that the experimental mice retained the improved tone discrimination for weeks.



Corresponding author Stas Zakharenko, M.D., Ph.D., is a member of the Department of Developmental Neurobiology. Credit: Seth Dixon / St. Jude

"Taken together, the results demonstrated that the window for effective auditory learning re-opened in the mice and that they retained the information," Zakharenko said.

Among the strategies researchers used to inhibit adenosine activity was the experimental compound FR194921, which selectively blocks the A1 receptor. If paired with sound exposure, the compound rejuvenated auditory learning in adult mice. "That suggests it might be possible to extend the window in humans by targeting the A1 receptor for drug development," Zakharenko said.

Zakharenko and his colleagues also linked the age-related decline in ease of auditory learning to an age-related increase in an enzyme (ecto-5'-nucleotidase) involved in adenosine production in the auditory thalamus. Researchers reported that mature mice had higher levels than newborn mice of the enzyme and adenosine in the auditory thalamus. Deletion of this enzyme returned the adenosine level in adult mice to the level of newborn mice. Therefore, researchers are currently looking for compounds that target ecto-5'-nucleotidase as an alternative approach for extending the window of auditory learning.

More information: J.A. Blundon el al., "Restoring auditory cortex plasticity in adult mice by restricting thalamic adenosine signaling," *Science* (2017). science.sciencemag.org/cgi/doi … 1126/science.aaf4612

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