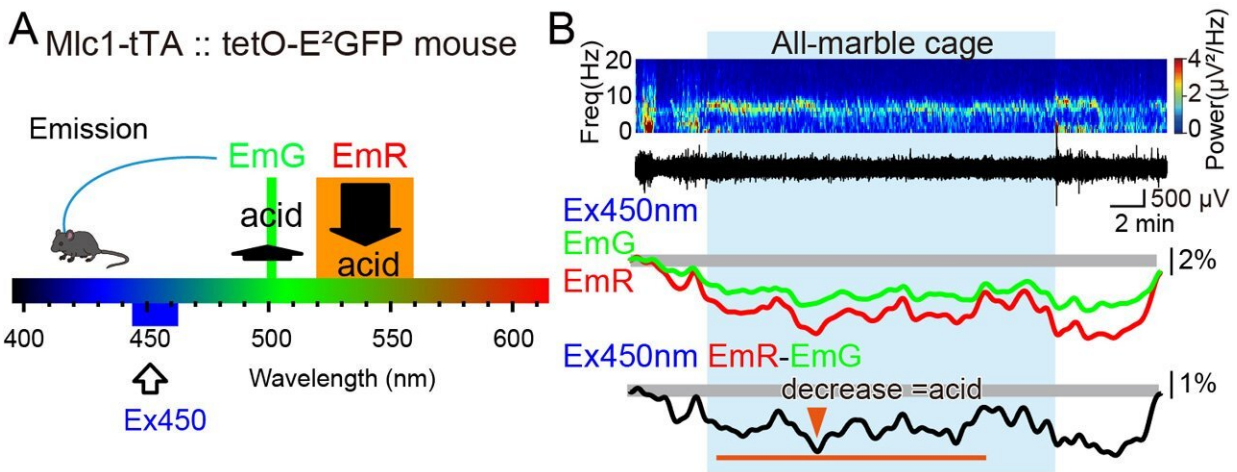


Researchers study how interactions between neurons and astrocytes may relate to anxiety

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Habenular astrocyte acidification in the anxiogenic environment. (A) The fluorescence sensor protein E²GFP is sensitive to changes in intracellular pH. The green emission in response to purple light excitation does not change much with pH changes; however, the orange emission is largely decreased with pH acidification. E²GFP was selectively expressed in astrocytes, and fluorescence fluctuation in the habenula was analyzed using the fiber-photometry method. (B) When the mouse was placed in the anxiogenic all-marble cage, ~ 8 Hz theta-band neuronal activity was detected in the local field potential recorded using a pair of electrodes placed in the habenula. With the optical fiber placed in the habenula, green emission showed a downward deflection when the mouse was placed in the all-marble cage. This indicates an increase in local brain blood volume. The expansion of the blood vessel diameter likely obstructs the emitted fluorescence from reaching the optical fiber for detection. The orange emission showed a larger downward deflection compared to the green emission. This indicates that the intracellular pH in the habenular astrocytes was acidified, and the local brain

blood volume increased when the mice were anxious. Credit: Wanqin Tan, Ko Matsui

Anxiety is often attributed to an unconscious assessment of the environment and detection of potential danger. While moderate anxiety is therefore advantageous for survival, excessive anxiety can lead to psychiatric disorders.

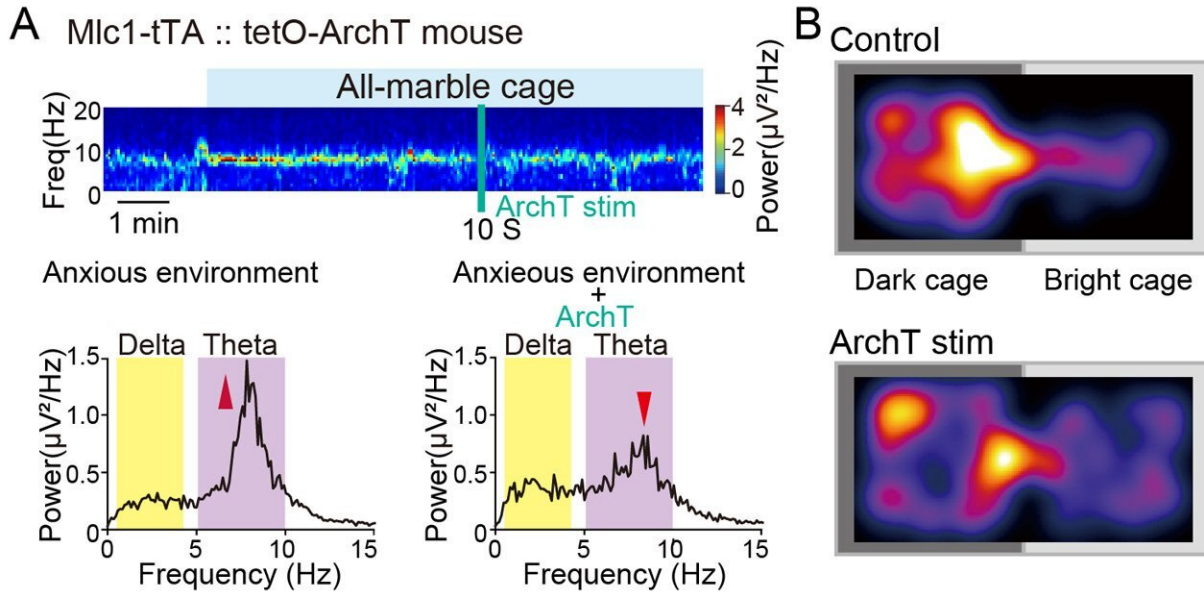
Now, researchers at Tohoku University have shed light on the intricate interactions between neurons and astrocytes within the habenula, a region of the brain associated with emotional processing. By subjecting [mice](#) to a scenario involving a floor scattered with marbles, the researchers observed behavioral responses indicative of anxiety.

[The findings](#) were detailed in the journal *Neuroscience Research* on February 10, 2024.

The habenula are a pair of small nuclei located above the thalamus. It is one of the few [brain regions](#) that controls both dopaminergic and serotonergic systems. As these neuromodulators play essential roles in a wide range of motivational and cognitive functions, habenula [neuronal circuits](#) are potentially relevant to controlling anxiety.

"Anxiety may appear to be an irrational emotion having only [negative impacts](#) on our life," says Professor Ko Matsui of the Super-network Brain Physiology lab at Tohoku University, who led the research.

"However, well-tuned anxiety is a guide provided by our unconsciousness which allows us to navigate the hidden dangers. Such tuning may be accomplished by the actions of the habenula."



Optogenetic alkalization of habenular astrocytes results in the reduction of anxiety. (A) ArchT is a light-activated outward proton pump. Photoactivation of ArchT expressed in cell membranes results in intracellular alkalization. ArchT was selectively expressed in astrocytes and the optical fiber placed in the habenula was used for photoactivation of ArchT. When the mouse was placed in an anxiogenic, all-marble cage environment, theta-band neuronal activity was detected. Photoactivation of the ArchT in the habenular astrocytes led to the reduction of the theta-band. (B) Mice normally prefer a dark room with comfortable bedding. When the mouse was placed in a two-way chamber with a dark room and a bright room with an all-marble floor, the mouse tended to stay in the dark room. However, when the ArchT in the habenular astrocytes were photoactivated, the mouse ventured to the bright room and traveled more in the bright room. These results suggest that when the acidic reaction of the habenular astrocytes is countered by optogenetic alkalization, anxiety can be reduced. Credit: Wanqin Tan, Ko Matsui

Mice perceive smooth glass marbles as potentially harmful objects due to their unfamiliarity. Mice tend to bury marbles in sawdust bedding to keep these uncomfortable objects out of sight. Here, the researchers

created a chamber filled with marbles to create an inescapable, maximum anxiety environment.

They noticed increased neuronal activity in the theta band (5 to 10 Hz) frequency, an increase in local brain blood volume, and acidification occurring in the astrocytes of the habenula when the mice were placed in the all-marble cage. When the habenular astrocytes were artificially alkalinized to counter the acidification, the theta band neuronal activity diminished.

When the mice were allowed to choose between the brightly lit all-marble cage and a dark and comfortable cage, the mice naturally chose to stay in the dark cage. However, when the habenular astrocytes were optogenetically alkalinized, the mice ventured more into the bright cage.

Astrocytes are non-neuronal cells that occupy approximately half of the brain. They have been shown to control the local ionic and metabotropic environment in the brain. Astrocytes also release transmitters that can affect neuronal activity in the vicinity. The results of this study suggest that the theta band habenular [neuronal activity](#) is regulated by the activity of astrocytes. Thus, habenular astrocytes were considered to play a role in regulating anxiety.

Lead study investigator, Wanqin Tan, says that future treatment of anxiety disorders may be realized by developing a therapeutic strategy that adjusts astrocyte activity in the habenula. "Habenular [astrocytes](#) tune the 'marble blues.' Based on this, we expect that methods to cope with [anxiety](#) could be developed," says Tan.

More information: Wanqin Tan et al, Anxiety control by astrocytes in the lateral habenula, *Neuroscience Research* (2024). [DOI: 10.1016/j.neures.2024.01.006](https://doi.org/10.1016/j.neures.2024.01.006)

Provided by Tohoku University

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