Switching off specific brain cells protects against stress

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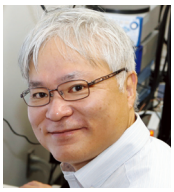

Abstract

The brain's response to stress is vital for selecting appropriate behaviors that ensure safety and survival. However, excessive or repeated stress can lead to mental health issues such as anxiety disorders. Thus, understanding the mechanisms of stress response may help reveal the onset mechanisms of mental illnesses. In our study, we used a unique whole-brain imaging system, FAST system, in conjunction with reporter mice that label activated neurons with fluorescent proteins, to closely examine the brain immediately after stress exposure. We analyzed this comprehensive brain activation maps with machine learning classification, and identified that activation of the claustrum, a thin sheet-like brain regions underneath the cerebral cortex, is characteristic of a stressed brain. Furthermore, through neuroanatomical, chemogenetic, and optogenetic techniques, we found that activation a group of cells within the claustrum elicits anxiety-related behaviors, while their inhibition can prevent anxiety and depression-like behaviors.

Background & Results

Previous research had highlighted the amygdala as center to processing negative emotions, but understanding the global impact of stress on the brain was limited. We advanced this by quantitatively mapping neuron activation throughout the entire brain following stress in a mouse model, utilizing brain-wide activation mapping and machine learning to classify the data. Our findings revealed that stress response is characterized predominantly by activation in the claustrum. Specific claustrum neurons, when chemogenetically activated, were found to induce anxiety-related behaviors. In contrast, their suppression diminished such behaviors, suggesting a pivotal role in stress-induced emotional regulation. Additionally, the claustrum receives inputs from stress-activated amygdala neurons, with targeted optogenetic activation of this circuit alone prompting anxiety behaviors, highlighting the amygdala-claustrum circuit's significance. Repeatedly suppressing claustrum activity during stress exposure also reduced depression-like behaviors, indicating its potential as a therapeutic target for mental health conditions. Prior to this, the claustrum was implicated in consciousness and brainwave modulation but its exact function in emotional response was ambiguous. This study not only opens avenues for mental illness treatment innovations but also enhances our understanding of the neural underpinnings of emotions, attention, and consciousness.

Significance of the research and Future perspective

In this study, it has been discovered that a distinct cluster of neurons in the claustrum orchestrates the manifestation of anxiety and depression-like behaviors following stress. These findings open new avenues for understanding the pathogenesis of stress-related mental illnesses and pave the way for the innovation of novel treatment strategies. This progress promises to lead to further research into understanding the intricacies of how the mind functions.

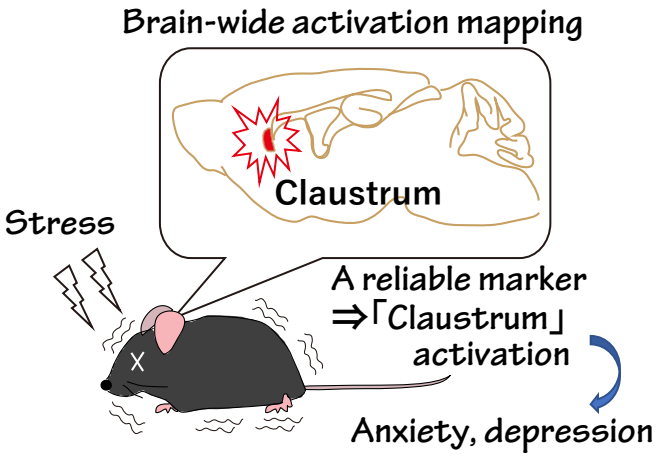

Fig 1

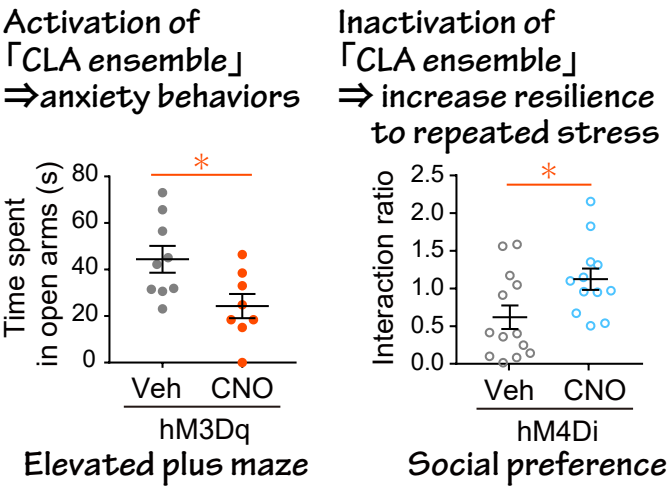

Fig 2

Patent
Treatise Niu, Misaki; Kasai, Atsushi et al. Claustrum mediates bidirectional and reversible control of stress-induced anxiety responses. Science Advances. 2022, Volume 8 (No.11), eabi6375. doi: 10.1126/sciadv.abi6375
URL
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