Different serotonergic pathways to the amygdala could underpin distinct anxious behavioral patterns

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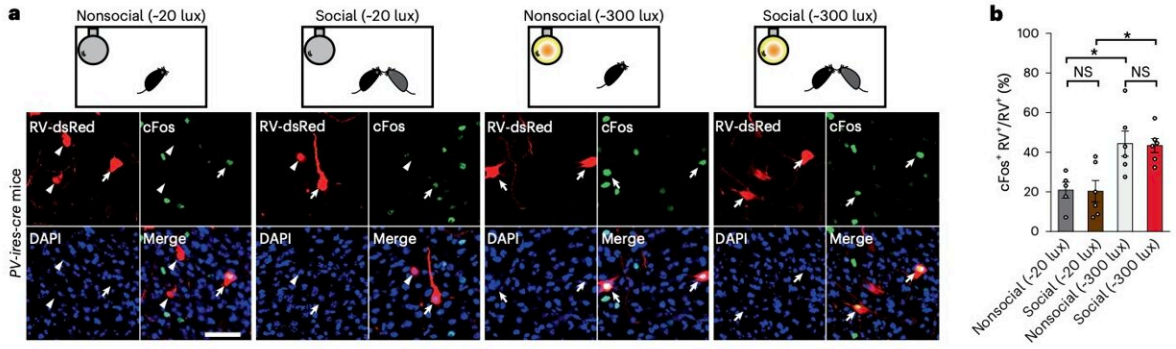

a,b, Anxiogenic/social stimuli (a, top), representative images (a, bottom) and statistics (b; mean ± s.e.m, n = 5, 6, 6 and 6 mice, one-way ANOVA, $F(3, 26) = 7.057$, $P = 0.0022$; nonsocial, 20 lux versus 300 lux, $t(26) = 3.194$, *$P = 0.019$; social, 20 lux versus 300 lux, $t(26) = 3.292$, *$P = 0.019$) of cFos expression in DRNvGluT3∩5-HT-BAPV neurons. Arrows, cFos+ dsRed+ ,; triangles, cFos− dsRed+ ; scale bar, 50 μm. Credit: Yu et al

Anxiety disorders are widespread mental health conditions that affect approximately one in five people. They are characterized by varying degrees of nervousness, apprehension and fear, typically associated with catastrophic thoughts about imagined or potential threats.

Anxiety is not only limited to humans, as researchers have observed similar behavioral patterns in many animal species. These behaviors are now known to have an evolutionary function, as they can help animals to avoid harm and dangerous situations, ultimately promoting their survival.

In humans, however, when these behavioral patterns become dysregulated, they can be very disruptive, significantly impacting their quality of life and everyday experiences. Gaining a better understanding of anxiety and its neural underpinnings could thus have incredibly valuable implications. Most notably, it might help to devise more effective treatment strategies that could improve the lives of the countless individuals with anxiety disorders.

Researchers at Zhejiang University and other universities in China have recently carried out a study on rats aimed at better understanding the serotonergic pathways associated with distinct anxious behaviors. Their findings, published in *Nature Neuroscience*, suggest that different behavioral features of anxiety could be supported by different serotonergic pathways leading to the amygdala, the brain region known to be associated with fear and emotional behavior.

When under stress, mice often display two key anxiety-like behavioral patterns, namely that of avoiding interactions with other mice and hiding in the dark or avoiding light. In their experiments, the researchers examined what behaviors mice engaged in when different serotonergic pathways were activated.

"We demonstrate that in mice, social and anxiogenic stimuli, respectively, increase and decrease serotonin (5-HT) levels in basal amygdala (BA)," Xiao-Dan Yu, Yu Zhu and their colleagues write in their paper. "In dorsal raphe nucleus (DRN), 5-HT∩vGluT3 neurons projecting to BA parvalbumin (DRN5-HT∩vGluT3-BAPV) and

pyramidal (DRN5-HT∩vGluT3-BAPyr) neurons have distinct intrinsic properties and gene expression and respond to anxiogenic and social stimuli, respectively.

"Activation of DRN5-HT∩vGluT3→BAPV inhibits 5-HT release via GABAB receptors on serotonergic terminals in BA, inducing social avoidance and avoidance of bright spaces. Activation of DRN5-HT∩vGluT3→BA neurons inhibits two subsets of BAPyr neurons via 5-HT1A receptors (HTR1A) and 5-HT1B receptors (HTR1B). Pharmacological inhibition of HTR1A and HTR1B in BA induces avoidance of bright spaces and social avoidance, respectively."

Essentially, the researchers found that when they activated different serotonergic pathways, both male and female mice displayed slightly different anxiety-like behavioral patterns. Their results highlight the importance of specific serotonergic pathways to the amygdala in the regulation of separate anxiety-related behaviors.

In the future, more studies on this topic could explore potential gender differences in the expression of these serotonergic pathways further, as past findings suggest that hormones associated with the ovarian cycle can affect anxiety in females. In addition, the recent work by Yu, Zhu and their colleagues could pave the way for more research into the serotonergic pathways they examined, which might confirm or further unpack these findings.

More information: Xiao-Dan Yu et al, Distinct serotonergic pathways to the amygdala underlie separate behavioral features of anxiety, *Nature Neuroscience* (2022). DOI: 10.1038/s41593-022-01200-8