

# Experimental model elucidates willful starvation in anorexia nervosa

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A new study led by investigators at Beth Israel Deaconess Medical Center (BIDMC) suggests that female mice that are prone to anxiety may prefer and actively seek out a starvation-like state in response to repeated exposure to stress. The findings, published in the journal [Neuron](#), may provide a useful experimental model for investigating the neural mechanisms underlying anorexia nervosa—particularly its onset.

"While anorexia nervosa has been documented for over 300 years, its underlying causes remain unknown," said first author Hakan Kucukdereli, Ph.D., of the division of Endocrinology, Diabetes and Metabolism in the Department of Medicine at BIDMC.

"Current animal models fail to capture a key hallmark of the disorder—willful starvation. Thus, there has been the pressing need for a pre-clinical mouse model that captures the intentional seeking of a starvation state."

In healthy individuals, the state of hunger (or caloric deficit) is a mildly uncomfortable state that drives food-seeking behavior. In the lab, Kucukdereli, senior author Mark L. Andermann, and colleagues knew that precise stimulation of a few thousand neurons known as AgRP neurons will cause even a well-fed mouse to seek out another meal.

They also knew that actual food restriction—which activates these AgRP neurons—and the artificial starvation state caused by stimulating these neurons can tamp down anxiety, thereby promoting food-seeking. (Imagine a hungry mouse in your kitchen that needs to be bold enough to hunt for food, even when your cat is around.)

Based on prior associations between [stress](#), anxiety, and anorexia nervosa, Andermann and colleagues hypothesized that exposure to high

levels of stress may actually trigger individuals to willfully seek starvation as a means of reducing anxiety. The scientists trained 15 male and 17 female mice to run through a virtual reality corridor where they could choose to stop in one room associated with stimulation of their AgRP neurons or a second room associated with no stimulation.

In the absences of stress, male mice avoided AgRP stimulation; however, only a minority of female mice exhibited a strong aversion to it. Subsequent to repeated stress, however, many of these same mice behaved very differently. When the researchers exposed the mice to a five-minute period of unpredictable tail shocks, the males became, on average, less averse to AgRP stimulation. Meanwhile, female mice—on average—preferred AgRP stimulation following stress.

"Strikingly, a subset of females, but not males, began to vigorously seek this starvation-like state following stress," said Andermann, who is also a professor of Medicine and Neurobiology at Harvard Medical School.

"Surprisingly, individuals' baseline levels of anxiety-like behavior measured weeks before the experiment could predict which females will develop a preference for this starvation-like state."

Using machine learning to analyze the animals' facial expressions, the researchers found that, after exposure to stress, [female mice](#) with strong preference for AgRP [stimulation](#) also showed facial expressions that directly correlated with their behavior, potentially reflecting relief associated with a reduction in anxiety.

"Future research can link these moment-to-moment changes in [facial expressions](#) with ongoing activity of many neurons in brain regions that track physiological states or that process [negative emotions](#),"

Kucukdereli said. "Our approach lays the groundwork for future work that will identify the [neural circuits](#) that underlie the voluntary maintenance of long-term starvation in individuals with anorexia

nervosa."

**More information:** Hakan Kucukdereli et al, Repeated stress triggers seeking of a starvation-like state in anxiety-prone female mice, *Neuron* (2024). [DOI: 10.1016/j.neuron.2024.03.027](https://doi.org/10.1016/j.neuron.2024.03.027)

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