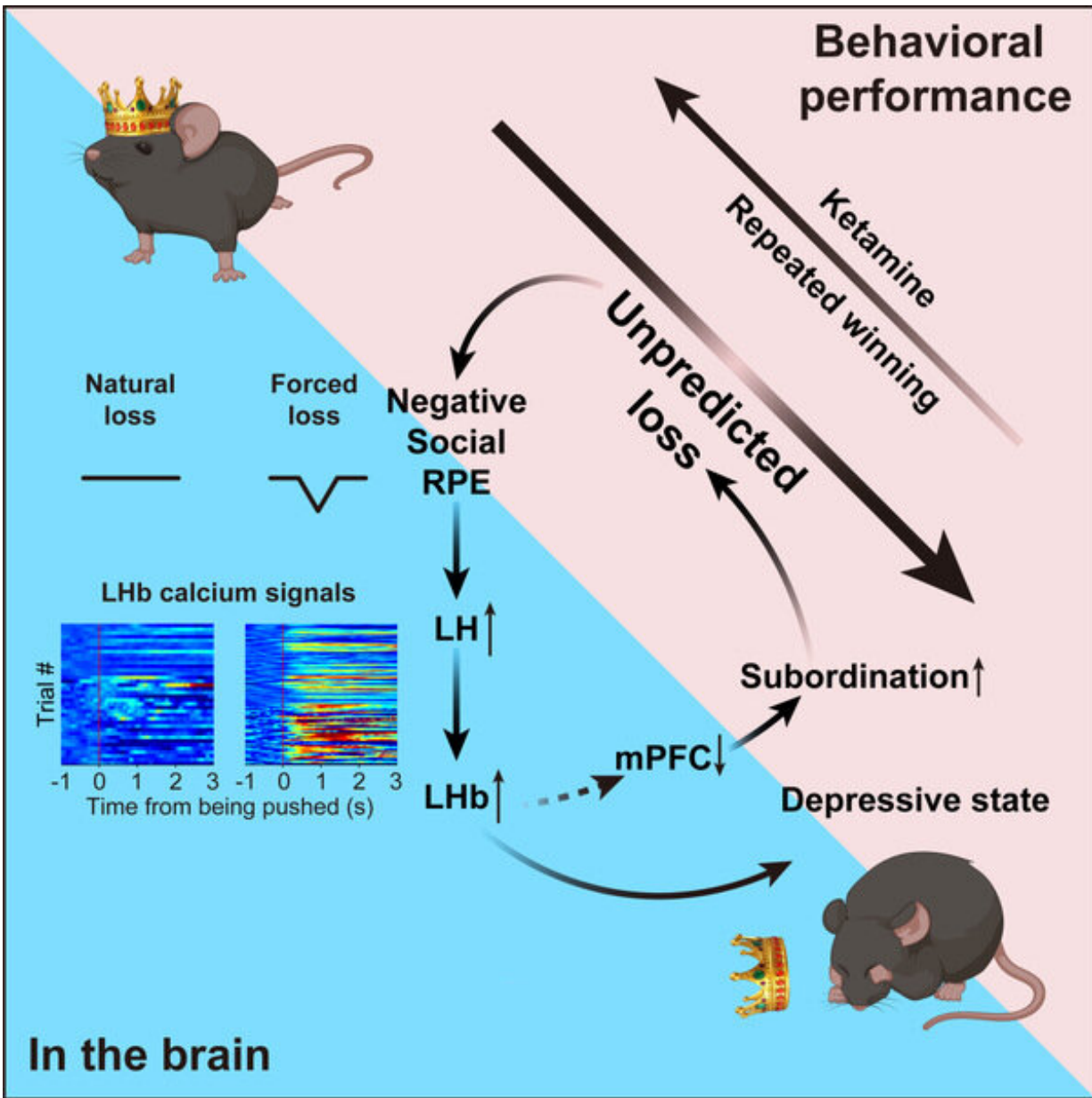


Are people with high social status more prone to depression?

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Credit: *Cell* (2023). DOI: 10.1016/j.cell.2022.12.033

The Alpha is the "king" of a horde of mice. While meeting another mouse in the pipeline, Alpha can scare it away with merely a glance. But one day the situation changes. With unexpected courage, the little "mouse brother" pushes Alpha out of the way directly after confronting the "king" for several seconds. After experiencing this Waterloo for several successive days, Alpha becomes depressed and loses his previous dominance.

This reversal was orchestrated by a cohort of brain scientists who witnessed the whole process of Alpha's "crown loss" and recorded its [neural activity](#) in the brain. After six years of experiments, the team led by Prof. Hu Hailan has established a mouse model of depression to explore the key neural mechanism behind this process.

Their findings were published in an article titled "Neural mechanism underlying depressive-like state associated with social status loss" in the journal *Cell* on January 23.

Social hierarchy is pervasive in humans and animals. To measure [social hierarchy](#) in mice, HU's team developed the tube test by which the social rank of each mouse could be determined by the number of wins it gained when competing against other mice.

In both humans and animals, social status has a significant impact on their physical and mental health. A study of immigrants in the United States reveals that immigrants with status decline are nearly three times as prone to depression as other people.

Prof. Hu Hailan was intrigued by the neural mechanism behind these

phenomena. "90% of the human depression cases are triggered by social factors." For scientists, the first step is to build animal models that could simulate the process in the lab. Thus, Alpha becomes the "chosen" mouse because it is the "king" of the tube test.

A new day comes. The little "mouse brother" is about to go through a new round of competition in the tube. This time, the researchers quietly block the passage behind the little "mouse brother." Soon, it finds that the only way out is to charge forward. It thus braces itself to push Alpha hard. After several back-and-forth shoves, Alpha is pushed out of the way.

After several consecutive days of "forced defeat," Alpha loses its dominance. Even in the absence of human intervention, the "king" begins to yield to the little "mouse brother" spontaneously. "This shows that it has lost its dominant position," says Fan Zhengxiao, the leading author of the study.

Subsequent forced swimming tests or sucrose preference tests suggest that Alpha shows conspicuous depressive-like behaviors. "Alpha's experience, to some extent, mimics depression induced by the decline in dominance in the human world," says Fan Zhengxiao. The researchers can perform a series of experiments on this new animal model to explore the neural mechanism behind it.

According to Fan Zhengxiao, they rule out the effect of loss per se. The lower-ranking mice won't get depressed even if they suffer from continuous losses to those higher-ranking mice. Depressive-like behaviors are triggered only in those higher-ranking mice which have a rapid decline in social status. This suggests that depression may be related to the discrepancy between the expectation of winning and the reality of losing.

Through a series of experiments, Hu's team hypothesizes that the negative reward prediction error may act as a catalyst for neural changes, which mediate depressive-like behaviors induced by social status loss. "In a forced loss scenario, the higher-ranking mouse tends to have a higher expectation of winning. The forced loss will generate a negative prediction error. In contrast, the lower-ranking mouse, more often than not, has a lower expectation of winning. Therefore, their loss won't bring any psychological disparity," says Fan Zhengxiao.

In the study, Hu's team repeatedly "replays" the "crown loss" scenario and tracks calcium activity and neuroelectric activity signals in specific brain areas via fiber photometry. After a series of experiments, the underlying neural mechanism gradually becomes clear. The [lateral habenula](#) (LHb) functions as an anti-reward center and it can be activated by a variety of aversive stimuli.

When the high-ranking mouse suffers from a "forced loss," the reward prediction error signal will activate the LHb, thereby inducing depressive-like behaviors. Meanwhile, in the [medial prefrontal cortex](#) (mPFC) where social competition is encoded, the activity of excitatory neurons will also be reduced, leading the high-ranking mouse to "retreating" and "self-degrading" behavior. "The activation of the LHb mediated by the negative reward prediction error is the neural mechanism behind the depressive-like state associated with [social status](#) loss," says Fan Zhengxiao.

Interestingly enough, if neuronal activity in the LHb is inhibited by optogenetics, the higher-ranking mouse displays less depressive-like behaviors after a "forced loss."

The tube test is a non-violent social competition. Alpha's experience to some extent simulates the dynamics of competition in human society, thus promising to help understand and intervene this type of socially-

induced depression.

Moreover, HU's team discovers the close interaction between the "social brain" and the "emotional brain." The activation of the mPFC can rekindle the "fighting spirit" of the mouse. With this spirit, it can reverse the situation. After several successive victories like this, the mouse will show less depression-like behaviors. In the end, Alpha—the [mouse](#) that has gone through several "forced losses"—regains its past glory. "This discovery provides insights into interventive therapy for depression," Fan Zhengxiao says.

Compared with low-ranking mice, high-ranking mice, which are accustomed to winning, can be more fragile and vulnerable to losses. Prof. Hu Hailan thinks that this phenomenon may illustrate the necessity of "frustration education."

More information: Zhengxiao Fan et al, Neural mechanism underlying depressive-like state associated with social status loss, *Cell* (2023). [DOI: 10.1016/j.cell.2022.12.033](https://doi.org/10.1016/j.cell.2022.12.033)

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