Research shows one sleepless night can rapidly reverse depression for several days

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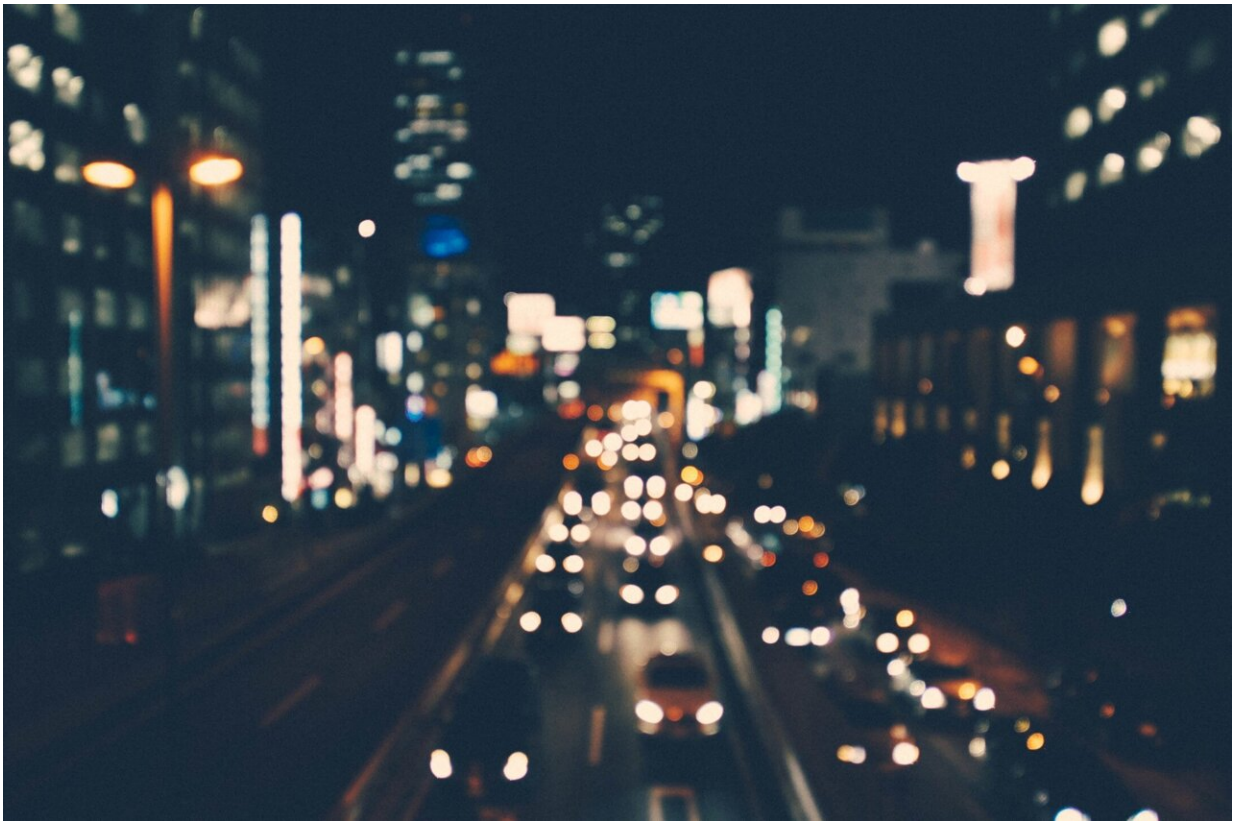

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Most people who have pulled an all-nighter are all too familiar with that "tired and wired" feeling. Although the body is physically exhausted, the brain feels slap-happy, loopy and almost giddy.

Now, Northwestern University neurobiologists are the first to uncover what produces this punch-drunk effect. In a new study, researchers induced mild, acute sleep deprivation in mice and then examined their behaviors and brain activity. Not only did dopamine release increase during the acute sleep loss period, synaptic plasticity also was enhanced—literally rewiring the brain to maintain the bubbly mood for the next few days.

These new findings could help researchers better understand how mood states transition naturally. It also could lead to a more complete understanding of how fast-acting antidepressants (like ketamine) work and help researchers identify previously unknown targets for new antidepressant medications.

The research was published online on Thursday (Nov. 2) in the journal *Neuron*The study is titled "Dopamine pathways mediating affective state transitions after sleep loss." Northwestern postdoctoral fellow Mingzheng Wu is the paper's first author, and Professor Yevgenia Kozorovitskiy is the corresponding author.

"Chronic sleep loss is well studied, and it's uniformly detrimental effects are widely documented," Kozorovitskiy said. "But brief sleep loss—like the equivalent of a student pulling an all-nighter before an exam—is less understood. We found that sleep loss induces a potent antidepressant effect and rewires the brain. This is an important reminder of how our casual activities, such as a sleepless night, can fundamentally alter the brain in as little as a few hours."

An expert in neuroplasticity, Kozorovitskiy is an associate professor of neurobiology and the Irving M. Klotz Professor at Northwestern's Weinberg College of Arts and Sciences.

Signs of sleep loss

Scientists long have known that acute perturbations in sleep are associated with altered mental states and behaviors. Alterations of sleep and circadian rhythms in patients, for example, can trigger mania or occasionally reverse depressive episodes.

"Interestingly, changes in mood state after acute sleep loss feel so real, even in healthy subjects, as experienced by myself and many others," Wu said. "But the exact mechanisms in the brain that lead to these effects have remained poorly understood."

To explore these mechanisms, Kozorovitskiy and her team developed a new experiment to induce acute sleep loss in mice that did not have genetic predispositions related to human mood disorders. The experimental setup needed to be gentle enough to avoid causing substantial stress for the animals but just uncomfortable enough to prevent the animals from falling asleep.

After a sleepless night, the animals' behavior shifted to become more aggressive, hyperactive and hypersexual, compared to controls that experienced a typical night's sleep.

Using optical and genetically encoded tools, the researchers measured the activity of dopamine neurons, which are responsible for the brain's reward response. And they found activity was higher in animals during the brief sleep loss period.

"We were curious which specific regions of the brain were responsible for the behavioral changes," Kozorovitskiy said. "We wanted to know if it was a large, broadcast signal that affected the entire brain or if it was something more specialized."

Specialized signal

Kozorovitskiy and her team examined four regions of the brain responsible for dopamine release: the prefrontal cortex, nucleus accumbens, hypothalamus and dorsal striatum. After monitoring these areas for dopamine release following acute sleep loss, the researchers discovered that three of the four areas (the prefrontal cortex, nucleus accumbens and hypothalamus) were involved.

But the team wanted to narrow down the results even further, so they systematically silenced the dopamine reactions. The antidepressant effect disappeared only when researchers silenced the dopamine response in the medial prefrontal cortex. By contrast, the nucleus accumbens and hypothalamus appeared to be most involved in the hyperactivity behaviors but were less connected to the antidepressant effect.

"The antidepressant effect persisted except when we silenced dopamine inputs in the prefrontal cortex," Kozorovitskiy said. "That means the prefrontal cortex is a clinically relevant area when searching for therapeutic targets. But it also reinforces the idea that has been building in the field recently: Dopamine neurons play very important but very different roles in the brain. They are not just this monolithic population that simply predicts rewards."

Heightened neuroplasticity

While most of the behaviors (such as hyperactivity and increased sexuality) disappeared within a few hours following acute sleep loss, the antidepressant effect lingered for a few days. This suggested that synaptic plasticity in the prefrontal cortex might be enhanced.

When Kozorovitskiy and her team examined individual neurons, they discovered just that. The neurons in the prefrontal cortex formed tiny protrusions called dendritic spines, highly plastic features that change in

response to brain activity. When the researchers used a genetically encoded tool to disassemble the synapses, it reversed the antidepressant effect.

Evolving to avoid predators?

While researchers do not fully understand why sleep loss causes this effect in the brain, Kozorovitskiy suspects evolution is at play.

"It's clear that acute sleep deprivation is somehow activating to an organism," Kozorovitskiy said. "You can imagine certain situations where there is a predator or some sort of danger where you need a combination of relatively high function with an ability to delay sleep. I think this could be something that we're seeing here. If you are losing sleep routinely, then different chronic effects set in that will be uniformly detrimental. But in a transient way, you can imagine situations where it's beneficial to be intensely alert for a period of time."

Kozorovitskiy also cautions people not to start pulling all-nighters in order to brighten a blue mood.

"The antidepressant effect is transient, and we know the importance of a good night's sleep," she said. "I would say you are better off hitting the gym or going for a nice walk. This new knowledge is more important when it comes to matching a person with the right antidepressant."

More information: Mingzheng Wu et al, Dopamine pathways mediating affective state transitions after sleep loss, *Neuron* (2023). DOI: 10.1016/j.neuron.2023.10.002. www.cell.com/neuron/fulltext/S0896-6273(23)00758-4