Brain zap saps destructive urges

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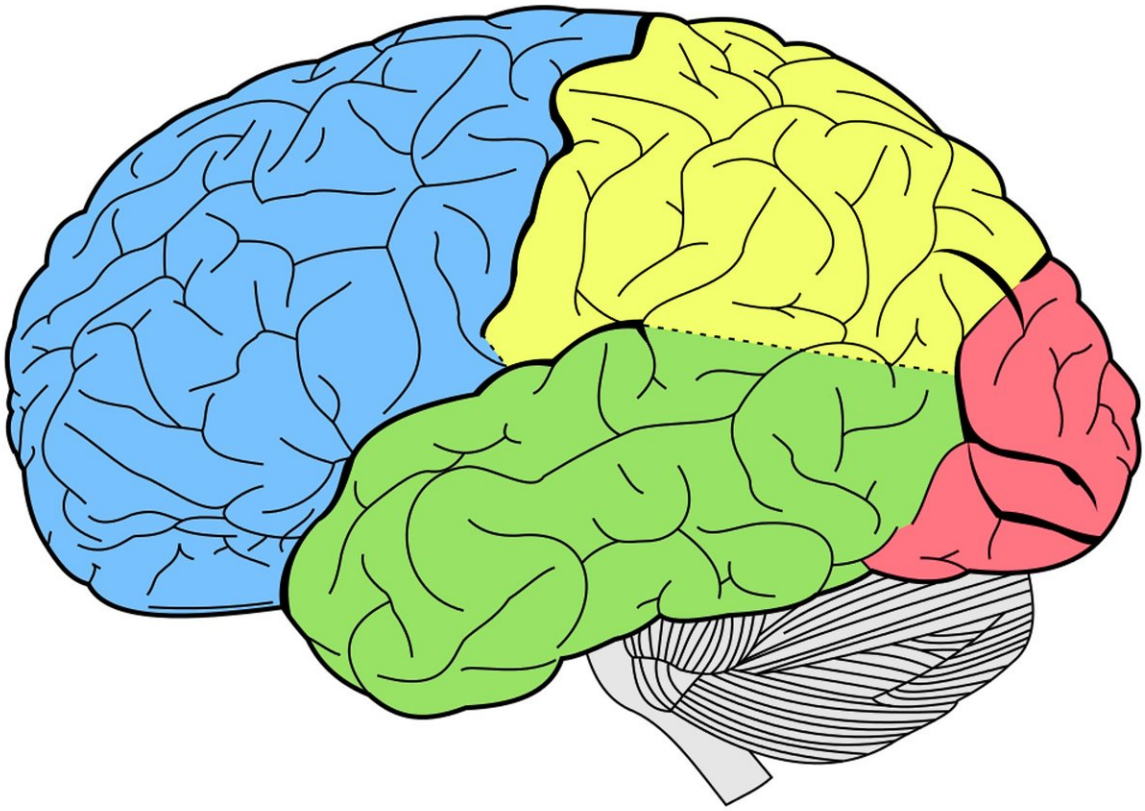

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A characteristic electrical-activity pattern in a key brain region predicts impulsive actions just before they occur. A brief electrical pulse at just the right time can prevent them, Stanford scientists have found.

Stanford University School of Medicine investigators have identified the smoking gun of a "moment of weakness": a signature pattern of electrical activity in a small, deep-brain region just a second or two before a burst of impulsive behavior.

The Stanford scientists discovered similar patterns in mice that had learned to binge eat fatty food and in a human subject anticipating a large cash reward. The researchers also showed, in mice, that supplying a small electrical pulse to the brain region in question, called the nucleus accumbens, as soon as the electrical signature manifested prevented the mice from overindulging in fatty food, while not affecting their intake of normal food, their social behavior or other physical activity.

The findings were published online Dec.18 in the *Proceedings of the National Academies of Sciences*.

"We've identified a real-time biomarker for impulsive behavior," said Casey Halpern, MD, assistant professor of neurosurgery and the study's senior author. Postdoctoral scholar Hemmings Wu, Ph.D., and neurosurgery resident Kai Miller, MD, Ph.D., share lead authorship.

Good impulses gone bad

"Impulses are normal and absolutely necessary for survival," Halpern said. "They convert our feelings about what's rewarding into concrete action to obtain food, sex, sleep and defenses against rivals or predators."

But in some contexts, impulsive behavior can be pathological, manifesting as a marked tendency to make poor decisions and act on them. One need look no further than the recent rash of reports of sexual predators perched in powerful positions in Hollywood, the media, finance and politics to see examples of a fundamentally healthy drive—sexual appetite—taken to a pathological level.

The nucleus accumbens is the hub of the brain's reward circuitry, which evolution has engineered to reinforce survival-promoting actions by inducing pleasure in anticipation or performance of those actions. The study's findings offer the promise, Halpern said, of an implantable device that monitors the nucleus accumbens for the telltale signal preceding a burst of impulsivity and immediately delivers a measured dose of electricity. This intervention may prevent impulsive and sometimes life-threatening actions by high-risk people for whom all noninvasive therapies have failed.

The findings could also lead to less invasive methods of countering obesity, substance-abuse disorders, pathological gambling, sexual addiction or intermittent explosive disorder, a psychiatric condition marked by impromptu outbursts of inappropriate ferocity.

"Imagine if you could predict and prevent a suicide attempt, a heroin injection, a burst of binge eating or alcohol intake, or a sudden bout of uncontrolled rage," said Halpern.

Clinically, Halpern focuses on deep-brain stimulation, whereby devices deliver electrical pulses to targeted brain regions in which they've been implanted. DBS is now approved by the Food and Drug Administration for treating symptoms of Parkinson's disease and essential tremor, and is currently in clinical trials for depression, obsessive-compulsive disorder and multiple other disorders of the brain.

But the tens of thousands of DBS devices in current use are inflexible in the timing, duration and intensity of the pulses they deliver; they simply fire away on a preprogrammed basis, 24/7. New-generation devices can respond to feedback from the brain region they target, or even a distant one, so pulses get delivered only when necessary and at appropriate intensities. These so-called responsive neurostimulation devices have so far been approved for partial-onset epilepsy. Because they fire only after

sensing specific electrical-activity signatures, they may actually deliver as little as five minutes per day of total stimulation, which neuroscientists such as Halpern view as greatly advantageous from the standpoint of avoiding side effects and optimizing the behavioral specificity of the treatment.

"There's no available responsive neurostimulation intervention for dangerous impulsive behavior yet, because until now no one's been able to document a characteristic signature in the brain that could be used for triggering pulse delivery by the device," he said.

From mouse to man

The Stanford scientists discovered this signature in experiments with mice. Typically, laboratory mice are fed pellets of a standard chow that's nutritious without being highly caloric. In the study, mice were given special high-fat food pellets for one hour every day for 10 days. During that hour, they were allowed to eat as much as they wanted.

The novel food took some getting used to, but by day 10 the mice became habituated to it and pretty much ate it nonstop. The researchers had implanted electrode arrays in the mice's brains in order to monitor electrical activity in the nucleus accumbens, where a pattern of heightened electrical activity—restricted to a particular low-frequency band called delta—emerged immediately prior to binge eating, peaking about one second before a mouse took a bite of the high-fat food pellet. Notably, this uptick didn't occur when that mouse was about to bite into standard lab chow. Nor was it seen in other typically rewarding activities, such as interactions with younger mice.

Halpern and his colleagues then programmed their electrode arrays to deliver 10-second pulses of electrical current—the typical regimen in approved DBS therapies—to the nucleus accumbens whenever the arrays

sensed a sizeable increase in delta intensity there. This substantially reduced the mice's high-fat binges. But it didn't affect their social lives, or their general physical behavior.

Further experiments compared responsive neurostimulation to standard DBS, random pulse delivery and manual delivery whenever an experimenter saw a mouse preparing to stuff itself. Both manual and responsive-neurostimulation pulse delivery proved superior to either random or DBS delivery, despite delivering far fewer electrical pulses daily than DBS.

Next, the Stanford researchers took advantage of a rare opportunity to perform a similar experiment on a human subject: a patient with obsessive-compulsive disorder, a condition for which DBS to the nucleus accumbens is in clinical trials. This participant was resistant to all other treatments for his OCD and had opted for surgical implantation of a DBS device.

The investigators received the participant's consent to intervene briefly once electrical leads had been introduced to the participant's nucleus accumbens but prior to their hookup with the DBS pulse generator. In the interim, the participant was asked to perform computerized tasks that generated cash rewards if completed successfully. As with the mice, once the participant got acclimated to the near-certainty of receiving a reward upon completing the task, a receiver to which the implanted electrical leads were temporarily hooked was able to detect the characteristic "high-delta" electrical signature in his nucleus accumbens just before he commenced the tasks.

"The fact that we saw a similar signal prior to two different behaviors, both intended to obtain rewards—food in the case of mice, money in the case of the human subject—to which the individuals had become hypersensitized by their repeated exposure suggests that this signal may

be common to many impulsive behaviors, making them amenable to treatment along similar lines," said Halpern.

Unlike newer parts of the brain, such as the cerebral cortex, the more deeply seated reward system's components have largely been conserved among vertebrates. So Halpern thinks the behavior-altering results his team observed in mice are likely to apply to humans, although further study will be needed to confirm these findings in a single human subject.

Halpern, Wu and study co-author Robert Malenka, MD, Ph.D., professor of psychiatry and behavioral sciences, are co-authors of a provisional patent filed by Stanford's Office of Technology Licensing on intellectual property associated with these findings.

More information: Hemmings Wu et al. Closing the loop on impulsivity via nucleus accumbens delta-band activity in mice and man, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1712214114

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