Revealing how the mouse brain's reward center responds to deep-brain stimulation

By Tony Liu

Eating disorders are a serious societal challenge, even more so now that close to 10% of the American population has been diagnosed with severe obesity [1]. Many such individuals also struggle with overeating and binge-eating disorders, which can be difficult to manage even with behavioral and pharmacological therapy.

In recent years, deep brain stimulation (DBS) has emerged as a promising treatment for intractable psychiatric conditions, including obsessive compulsive disorder and treatment-resistant depression. In DBS, an electrode is lowered into the patient's brain to deliver pulses of current directly to a specific brain region.

The promise of deep brain stimulation is that one can modulate activity in spatially-specific brain regions and dysfunctional neural circuits. However, deep brain stimulation's efficacy is constrained by our limited understandings of both neural circuit function and the neural effects of brain stimulation.

The study in *Proceedings of the National Academies of Science*, authored by a team led by Dr. Robert Malenka and Dr. Boris Heifets in Stanford's Departments of Neurosurgery and Psychiatry, and Dr. Casey Halpern, now of the University of Pennsylvania, begins to address these shortcomings by recording how brain activity in mice's "reward center" changes in response to deep brain stimulation [2].

The specific region of interest in this study is the nucleus accumbens (NAc), a region nestled about 4 millimeters under the mouse's brain surface which lies at the nexus of many of reward pathways. In mice, the NAc has been shown to be a critical node in integrating inputs carrying information about motivation, emotion, and planning. In humans, pilot deep brain stimulation studies have shown that NAc stimulation can attenuate binge-like alcohol drinking.

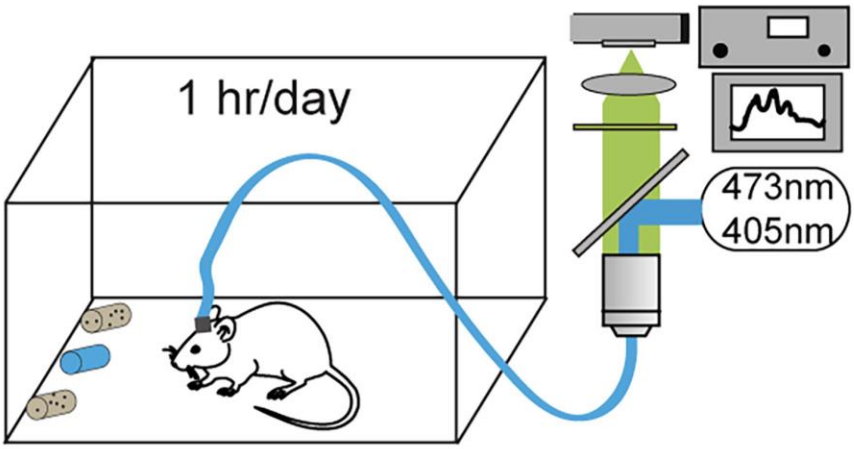
"Deep brain stimulation has inspiring clinical effects that benefit patients with movement disorders every day," said Halpern. "It's effects on psychiatric disease and related disorders are less pronounced." By using novel recording tools to better understand mechanisms of DBS in mice, Halpern said, the team aimed to shed light on how to better strategize and implement DBS in humans for novel indications.

Measuring neural activity while electrically stimulating is challenging, due to the recording artifacts that arise with each pulse of stimulation. Consequently, the team recorded neural activity using an *optical* technique called fiber photometry, which involves recording the fluorescent signal from neurons which have been genetically engineered to change their fluorescence in response to calcium influxes associated with neural activity.

While using this approach to record calcium signals in the left NAc, the team introduced the mice to the overfeeding behavioral paradigm. For 1 hour each day, a high-fat food pellet was placed into each mouse's cage, while the mice were already sated. Although the mice initially ignored the high-fat food, over the course of 10 days, the mice ate increasingly more of it. This paradigm aimed to model hedonic binge-eating behavior.

Over the course of 10 days, the fluorescent calcium signal in the NAc began to ramp up in magnitude as the mice approached the high fat food. By recording from different dopamine neuron subpopulations in the NAc with genetic engineering techniques, the team found that this ramping effect was specific to a population of neurons known as D1 medium spiny neurons, which have been implicated in previous studies to form a recurrent loop with the lateral hypothalamus, possibly to regulate and override a satiated state.

Having established the neural signatures of hedonic feeding behavior, the team investigated the behavioral and neural impacts of deep brain stimulation. When stimulating the NAc continuously at 130 Hz, the team observed a dramatic attenuation of the mice's consumption of high fat food. However, low frequency, 3 Hz DBS had little effect on the mice's behavior.



Mice develop binge-eating behavior upon daily exposure to a high-fat food pellet (blue pellet), while neural activity recordings are conducted from their nucleus accumbens (Wu et al, 2022) https://doi.org/10.1073/pnas.2109269118

Further, the 130 Hz DBS – but not the 3 Hz DBS – effectively abolished the neural signature of increased NAc calcium signal prior to consuming high fat food. This points towards the NAc ramping signal as a neural biomarker whose decrease reflects the effectiveness of the stimulation in attenuating binge-eating behavior.

One issue oft raised with continuous DBS is its potential decay in efficacy over time. To probe this issue, the authors compared the effectiveness of stimulation applied only during the 1-hour high fat exposure, to the effectiveness when stimulation was turned on for an additional 2 hours prior to the exposure.

Though both stimulation paradigms decreased the mice's high fat intake, the longer stimulation paradigm was somewhat less effective. Moreover, the 3-hour continuous DBS paradigm was less able to suppress the NAc calcium signal ramp, compared to the 1-hour continuous paradigm. These results point to a decay in continuous DBS's effect over time.

One emerging paradigm to improve the efficacy duration of DBS is to use a closed-loop stimulation approach, also known as responsive DBS (rDBS). In rDBS, stimulation only occurs in short bursts in response to a biomarker, and the underlying neural circuit may thus have less time to adapt to the stimulation.

In this study, the rDBS was set up to trigger 10 second bursts of stimulation upon the detection of a 20% increase in the amplitude of NAc low frequency oscillations. The authors again compared activating rDBS only during the 1-hour high fat exposure, versus for an additional preceding 2 hours before the high fat exposure.

From Left to Right: Professor Robert Malenka, Professor Boris Dov Heifets, Professor Casey Halpern

The authors found that across six mice, there was no statistically significant difference between the high-fat intake reduction from the 1-hour and 3-hour stimulation paradigms. Importantly, the responsive DBS paradigm led to less overall stimulation compared to the continuous DBS paradigm – stimulation was active only about 15% of the time, when averaged over the 3-hour period.

Overall, this study combines optical imaging and deep brain stimulation to reveal insights into the neural bases of binge-eating and therapeutic neuromodulation. By directly comparing continuous and responsive DBS paradigms of different durations, the authors present the

provocative finding that rDBS approaches may be critical to avoiding the attenuation of the therapeutic efficacy which occurs with continuous DBS.

Closed-loop DBS approaches are being increasingly trialed in non-human and human primates [3, 4]. However, while it is challenging to study the effects of stimulation on specific cell types and at fast time scales in primates, genetic and optical toolboxes are available in rodents to make these questions more tractable. As such, rodent studies, including this work, will remain critical for understanding and refining the efficacy of deep brain stimulation.

Source Article: Wu, H., Kakusa, B., Neuner, S., Christoffel, D. J., Heifets, B. D., Malenka, R. C., & Halpern, C. H. (2022). Local accumbens in vivo imaging during deep brain stimulation reveals a strategy-dependent amelioration of hedonic feeding. *Proceedings of the National Academy of Sciences*, *119*(1).

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