American College of Neuropsychopharmacology

RESEARCH HIGHLIGHT

Cell type and sex specific insights into ventral striatum deep brain stimulation for cocaine relapse

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Relapse continues to be a major problem for stimulant use disorder. Neuromodulation with tools like deep brain stimulation (DBS) is currently being explored as a potential treatment [1]. Since it was FDA-approved for the treatment of Parkinson's disease more than two decades ago, DBS has emerged as a promising approach for otherwise intractable neuropsychiatric illnesses [2]. DBS currently has a humanitarian device exemption status from the FDA for the treatment of compulsive disorders like refractory obsessive-compulsive disorder and Tourette's syndrome [2]. This suggests that DBS may also become a valuable tool in treating substance use disorders (SUDs) [1].

Preclinical studies show that DBS of the ventral striatum inhibits relapse to cocaine seeking. However, the underlying biological mechanism of this effect on drug seeking is not clear. Classical DBS involves high-frequency electrical stimulation, which is non-specific and can affect not only neuronal cell bodies near the electrode, but also glial cells and axons from distant sites passing by or terminating in the vicinity, which results in orthodromic or antidromic stimulation of distant brain areas. In the ventral striatum, DBS likely stimulates the major striatal cell types—D1 and D2 medium spiny neurons (MSNs)—as well as GABAergic and cholinergic interneurons, and various axons terminating in or passing through the ventral striatum. It is not clear whether ventral striatum DBS' effects on drug seeking are mediated by one or more cell types which are normally interconnected and together modulate the ultimate behavioral outcome. Now that DBS can be deployed to selectively affect different neuronal populations [3], and given the different roles of D1 and D2 MSNs in regulating drug-seeking behaviors, understanding the role of the different ventral striatum cell types, especially D1 and D2 MSNs, in DBS's effects on drug seeking is of high importance.

In this issue of *Neuropsychopharmacology*, Swinford-Jackson et al. use high-frequency cell-type-specific optogenetic stimulation (opto-DBS) as a surrogate for DBS to test the effects of DBS-like high-frequency stimulation of D1 and D2 MSNs in the ventral striatum on cocaine-primed relapse in male and female rats [4]. The authors used intravenous (IV) cocaine self-administration in transgenic D1-cre and D2-cre male and female rats. An adenovirus (AAV) expressing Cre-dependent channelrhodopsin was infused into the medial ventral striatum (accumbens shell) bilaterally allowing selective stimulation of D1 vs. D2 MSNs. Rats were trained to self-administer IV cocaine on FR1 and then FR5 reinforcement schedules for a total of 21 sessions, followed by extinction training. After lever pressing was extinguished, rats underwent two cocaine-primed reinstatement testing sessions during which each animal received either opto-DBS throughout the 1-h session (130 Hz, 5 ms pulse width, 1 mW) or sham stimulation (patch cable attached, but no power delivered), counterbalanced between reinstatement sessions. Given the role of D1 vs. D2 MSNs in enhancing vs. inhibiting drug-related behaviors respectively, the authors hypothesized that opto-DBS of D1 vs. D2 MSNs would enhance vs. inhibit cocaine-primed reinstatement of drug seeking. However, the results show that opto-DBS of D1 MSNs did not affect reinstatement in either male or female rats, while opto-DBS of D2 MSNs inhibited reinstatement only in male rats—no effect was observed in female rats.

The results reported by Swinford-Jackson et al. provide valuable yet incomplete insight into a potential mechanism of action of ventral striatum DBS on cocaine seeking. The relapse-inhibiting effect of opto-DBS through D2 MSNs and lack of effect through D1 MSNs stimulation is reassuring for clinical translation of ventral striatum DBS as it alleviates the concern of D1 MSNs stimulation triggering relapse. Thus, developing specific clinical DBS protocols that differentially affect D1 vs. D2 MSNs may not be necessary. However, DBS protocols that can activate D2 MSNs and inhibit D1 MSNs could be the key to superior behavioral outcomes and relapse inhibition in both sexes. Although behavioral results were obtained with stimulation at 130 Hz, the ex vivo slice electrophysiology data presented show that similar excitatory effect could be achieved at 50 Hz, suggesting that a wide range of frequencies could potentially reproduce the relapse-preventative effects of D2 MSNs opto-DBS. Previous opto-DBS research has shown that lower frequency stimulation (10–12 Hz) of D1 MSNs has beneficial effects when combined with pharmacological treatment [5]. If stimulation parameters could be determined that differentially activate vs. inhibit the D2 vs. D1 MSN populations, superior outcomes could potentially be obtained. Such an approach has been reported with DBS of the globus pallidus in Parkinson's disease models where DBS protocols were designed to selectively excite vs. inhibit two distinct cell types in the pallidum, providing better and longer-lasting relief from Parkinson's motor symptoms than traditional DBS protocols [3]. Similar selectivity between D1 and D2 MSNs in ventral striatum could prove similarly transformative for DBS treatment of SUDs.

As the authors discuss, there remain several caveats. The results suggest that DBS decreases drug priming-induced reinstatement of cocaine seeking in male but not female rats. It is possible that the male-specific effect of D2 opto-DBS is related to ovarian

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hormone fluctuations that make females resistant to this effect. It is also possible that there are sex differences in reward processing that make males more susceptible to D2 opto-DBS. Additionally, cholinergic interneurons in the ventral striatum also express D2 receptors and may therefore contribute to the effects of opto-DBS attributed here to D2 MSNs. In addition, previous studies have shown that electric and opto-DBS are not necessarily be equivalent physiologically or behaviorally [5], likely due to the non-specific electrical stimulation effects described above, which affect the interaction of the various neural and glial elements in the ventral striatum and connected brain areas. The stimulation parameters explored here (130 Hz, 5 ms pulses) exceed the kinetic capacity of channelrhodopsin, meaning that while this stimulation may enhance neuronal activity, it cannot entrain firing at this rate. This is likely different than electrical stimulation that uses much shorter stimulation pulses (60–90 µs).

Ultimately, the relevance of opto-DBS studies to DBS treatment itself must be verified by the success or failure of the DBS protocols they inspire. Nevertheless, the study by Swinford-Jackson et al. provides valuable insight into a potential mechanism for the relapse-preventative effects of ventral striatum DBS and points toward exciting directions for further research and improvement of DBS treatment for relapse prevention.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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