Commentary

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Modulating Morphine Context-Induced Drug Memory With Deep Brain Stimulation: More Research Questions by Lowering Stimulation Frequencies?

Meaghan Creed, Antonello Bonci, and Lorenzo Leggio

Alcohol and substance use disorders (ASUDs) are characterized by compulsive drug taking despite significant adverse consequences and represent significant medical and public health problems. According to the World Health Organization, 15.3 million people experience ASUDs, which are associated with significant disability and mortality. In the United States, the National Institute on Drug Abuse and the Centers for Disease Control and Prevention have reported a nearly threefold increase in deaths from drug overdose, including prescription opioids, in recent years, and a sixfold increase from heroin alone. Additional effective treatments are needed for individuals with ASUDs.

Relapse to a drug of abuse may occur after exposure to the drug itself (priming), by stressors or cues or both associated with the drug. Even after an extended period of abstinence, cues or contexts associated with the addictive drug induce a pathologically strong drug memory (or craving) which can drive subsequent relapse. This memory trace arises because exposure to addictive drugs induces characteristic forms of synaptic plasticity throughout the brain's reward circuitry, which is composed of dopamine neurons in the ventral tegmental area and its projection targets in the prefrontal cortex, amygdala, and ventral striatum, specifically the nucleus accumbens (NAc).

Deep brain stimulation (DBS) is a therapy in which electrodes are surgically implanted into specific brain nuclei to modulate activity of neural networks. DBS is approved by the Food and Drug Administration for essential tremor, Parkinson's disease, dystonia, and obsessive-compulsive disorder. Consistent with the key role of the NAc in the rewarding and addictive properties of alcohol and drugs of abuse, NAc DBS has been applied in preliminary clinical studies in ASUDs (1). However, most of these studies are limited by the small samples and by the lack of double-blind, sham-controlled designs. Importantly, the rationale for the stimulation target and the mechanisms by which DBS may work in addiction are only partially understood. For example, optimal stimulation parameters are not clear. This is a key question, given that behavioral effects and underlying mechanisms differ between frequencies (2). DBS protocols in patients with ASUDs have typically targeted the NAc with high-frequency (>100 Hz) stimulation, which are derived from the application of DBS for movement disorders. Preclinical studies have found that high-frequency DBS of the NAc reduces alcohol and drug seeking, preference and intake, and expression of drug sensitization (2,3).

Martínez-Rivera *et al.* (4) apply and compare two stimulation frequencies, namely 100 Hz (high) and 20 Hz (lower, beta-frequency) DBS to the ventral striatum in a morphine conditioned place preference (CPP) paradigm. They demonstrate that beta-frequency can enhance extinction of morphine-induced drug memories through activation of this reward circuitry. Mice were trained by pairing a specific context with morphine exposure, interleaving this training with sessions in which saline was paired with an alternate context. At the end of the conditioning, mice exhibited a strong preference for the morphine-paired context. This learned preference for the paired compartment represents the acquisition of the drug-associated memory. Subsequently, mice were exposed to the morphine-paired context in the absence of the drug for several days to degrade the contingency between the drug and the environment. DBS was applied during this extinction learning to determine whether DBS could facilitate extinction of the drug-associated memory (Figure 1).

High-frequency (100 Hz) DBS of the dorsal aspect of the ventral striatum impaired extinction learning; treated mice exhibited a stronger preference for the drug-paired chamber relative to control mice. This result is surprising, given the body of rodent work showing that high-frequency stimulation of the NAc prevents cue-induced reinstatement of drug seeking and suppresses context-dependent locomotor sensitization to cocaine (2). The lack of effect observed here could be related to differences in the initial drug administration paradigm and the fact that DBS is not applied during the test, but rather to enhance the extinction training. By contrast, beta-frequency (20 Hz) DBS applied to the same nucleus had the opposite behavioral effect; that is, extinction learning was enhanced. Notably, although a control group receiving stimulation outside the ventral striatum was not included in this study, the selective effects reported here support previous work suggesting that DBS does not produce nonspecific disruption of behavior.

Why could different DBS frequencies have such divergent effects on extinction of drug memories? The investigators probe the mechanisms underlying the behavioral effects by mapping DBS-induced expression of the immediate early gene, cFos. DBS at either beta- or high-frequency induced cFos expression in the infralimbic cortex, whereas beta-frequency uniquely altered expression in the amygdala, including the basolateral and central amygdaloid nuclei. No effects were observed in the striatum itself, or in the prelimbic

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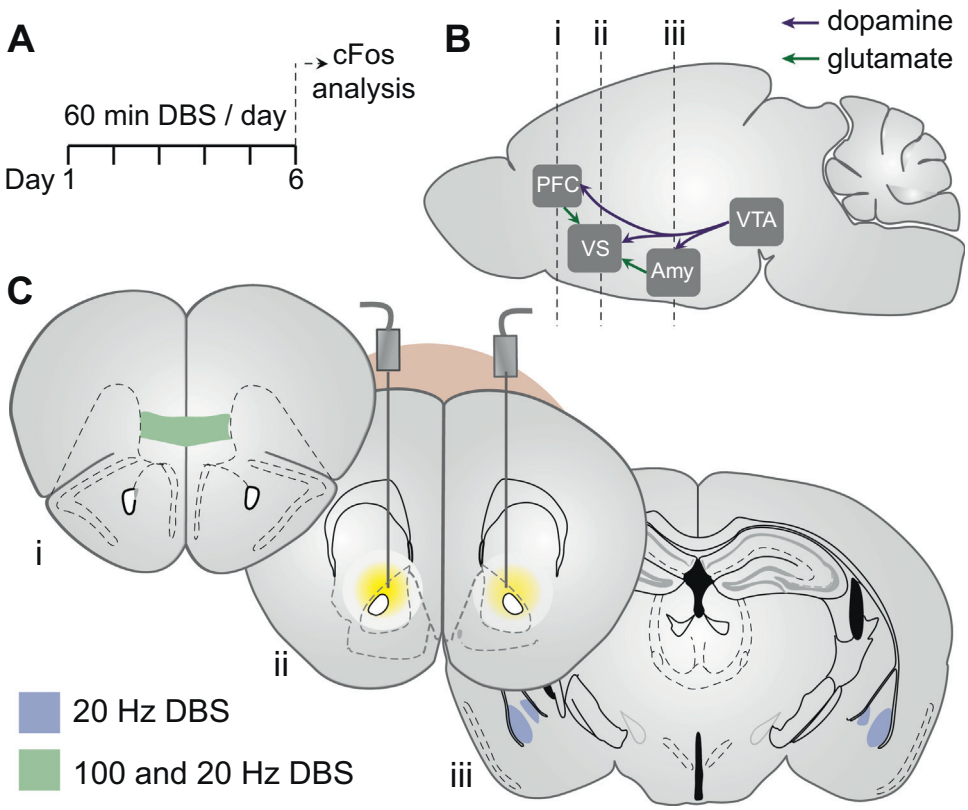

Figure 1. High (100 Hz) and beta (20 Hz) frequency deep brain stimulation (DBS) differentially modulate activity of the reward circuitry. **(A)** Timeline of experiment. **(B)** Sagittal schematic showing location of key nodes in the reward circuit, amygdala (Amy), prefrontal cortex (PFC), ventral striatum (VS), and ventral tegmental area (VTA). Dashed lines correspond to sections shown in panel **(C). (C)** Coronal schematic shows brain areas modulated by high- and beta-frequency DBS (i, iii) and stimulation site (ii).

cortex. These results are surprising, given that rodent work demonstrates that manipulations of the prelimbic cortex via repeated electrical (5) or optogenetic (6) stimulation alters adaptive behavior specifically related to drugs of abuse. In addition, preliminary clinical work suggests that stimulation of the dorsolateral prefrontal cortex (the closest human functional homologue of the rodent prelimbic cortex) may result in reduced craving for and use of alcohol and drugs of abuse [see (1) for review]. One explanation is that the measurement of cFos is not sufficiently sensitive to unequivocally resolve cell type–specific changes or to detect all decreases in activity that may be induced by DBS. For example, DBS may decrease prefrontal cortex activity through the activation of inhibitory interneurons (3) or have local inhibitory effects within the ventral striatum that would not be translated into changes in the protein level of cFos. A critical finding is that the cFos activity in the basolateral amygdala is selectively affected by behaviorally effective, beta-frequency DBS. Several lines of evidence have implicated NAc-projecting basolateral amygdala neurons in rewarding learning; neurons are excited by reward-predictive cues, optogenetic stimulation of this pathway is reinforcing, and these inputs are potentiated after learning reward-outcome associations (7). These questions may be better addressed by future electrophysiological and optogenetic studies focused on the synaptic plasticity and functional connectivity of the putative circuits involved on the mechanisms of how DBS may work in addiction. Additional questions related to the precise targeting of the electrode remain, for example, whether the laterality or selective stimulation of the shell or core NAc may result in meaningful differences.

The exact mechanisms underlying the effects of DBS in morphine context-induced CPP remain unclear. In this study by Martínez-Rivera *et al.* (4), DBS took place during this extinction learning phase. Notably, a previous study in which DBS was applied before the development of CPP indicated that high-frequency NAc DBS blocks the development of morphine-induced CPP in rats (8). This leads us to hypothesize a potential interaction between stimulation frequency and stage of the addiction disorder; that is, whereas high-frequency DBS may prevent the acquisition of CPP, once CPP is established, beta-frequency but not high-frequency DBS is able to enhance extinction learning. An interesting possibility is that different frequencies of stimulation may render neural circuits susceptible to frequency-specific forms of neuronal plasticity that underlie extinction learning. For example, 40 seconds of 50-Hz transcranial magnetic stimulation of the motor cortex induced a long-lasting depression of evoked cortical activity, whereas the same 50-Hz stimulation applied in 0.1-Hz bursts facilitated the same responses (9). The enduring effects of this stimulation were shown to be *N*-methyl-D-aspartate dependent, whereas stimulation at much higher frequencies (>100 Hz) may activate other activity-dependent synaptic mechanisms, such as metabotropic receptor-dependent plasticity (10). However, these molecular mechanisms may be both cell type and synapse type specific. Therefore, it will be important to further study the synaptic mechanisms engaged by different stimulation

frequencies, and how the choice of frequency interacts with the site of stimulation and previous drug experience, given that these factors all influence the induction and expression of synaptic plasticity (10). Furthermore, establishing a causal link between a specific form of synaptic plasticity and behavioral consequences remains a necessary and crucial step in opening novel therapeutic avenues.

This translational study takes a clinically viable therapy such as DBS and empirically determines the optimum stimulation parameters for behavioral effects, hence attempting to shed light on the network mechanisms underlying these effects. One extension is that manipulating activity within the NAc itself, or in areas upstream of the NAc such as the prefrontal cortex or amygdala, could be viable targets for neuromodulatory therapies for addiction, such as DBS, transcranial magnetic stimulation, or ultrasonic stimulation. For example, noninvasive brain stimulation techniques of cortical areas may modulate or downregulate activity of midbrain and striatum regions involved in compulsive drug-seeking behavior. However, more research is needed to better understand the potential role of DBS in addiction, to further clarify questions related to anatomical and stimulation parameters (e.g., brain area, frequency, intensity), and to optimize its clinical application.

In conclusion, studies like that by Martínez-Rivera *et al.* (4) are important because they attempt to disentangle the role of specific frequencies and neural circuits underlying behavioral effects. By using circuit dissection approaches in preclinical models, it is possible to reverse-engineer effective therapies to understand underlying mechanisms. Only by understanding these mechanisms will it be possible to optimize circuit-based therapies for addictive disorders and to translate these findings toward novel effective treatments for patients with ASUDs.

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