Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Current and emerging neuromodulation therapies for addiction: insight from pre-clinical studies

Meaghan Creed

Neuromodulation therapies such as deep brain stimulation or transcranial magnetic stimulation have shown promise in reducing symptoms of addiction when applied to the prefontal cortex, nucleus accumbens or subthalamic nucleus. Pre-clinical investigations implicate modulation of the cortico-basal ganglia network in these therapeutic effects, and this mechanistic understanding is necessary to optimize stimulation paradigms. Recently, the principle that neuromodulation can reverse drug-evoked synaptic plasticity and reduce behavioral symptoms of addiction has inspired novel stimulation paradigms that have long-term effects in animal models. Pre-clinical studies have also raised the possibility that tailoring neuromodulation protocols can modulate distinct symptoms of addiction. Combining mechanistic knowledge of circuit dysfunction with emerging technologies for non-invasive neuromodulation holds promise for developing therapies for addiction and related disorders.

Address
University of Maryland School of Medicine, Department of Pharmacology, 655 West Baltimore Street, Bressler Research Building, 4-021, Baltimore, MD 21201, USA

Corresponding author: Creed, Meaghan (mcreed@som.umaryland.edu)

Current Opinion in Neurobiology 2018, **49**:168–174

This review comes from a themed issue on **Neurobiology of behavior**

Edited by **Kay Tye** and **Nao Uchida**

https://doi.org/10.1016/j.conb.2018.02.015

Introduction

Addiction is a brain disease characterized by compulsive drug taking despite adverse consequences, which afflicts an estimated 15.3 million people worldwide [1]. Currently, there are few effective treatments for addiction. In this context, neuromodulation therapies which alter neural activity through targeted electrical or magnetic stimulation, hold promise. Deep brain stimulation (DBS) is one such neuromodulation therapy, where current is passed through electrodes implanted into discrete brain nuclei. Since its inception over 30 years ago [2], DBS has been used to treat over 120 000 patients with movement disorders, and is increasingly being applied for other neurological and psychiatric indications. DBS is one of the few therapeutic strategies to target specific neural circuits, although non-invasive stimulation modalities such as repeated transcranial magnetic stimulation (rTMS) or focused ultrasound (FUS) are also being investigated. We propose that by understanding neural circuit dysfunction in addiction and concurrently elucidating mechanisms of action of neuromodulation therapies, it becomes possible to design novel stimulation paradigms that effectively restore circuit function and reduce symptoms of addiction.

Classical deep brain stimulation paradigms

Investigations of DBS in addictive disorders have focused on two main targets: the nucleus accumbens (NAc) and the subthalamic nucleus (STN). To date, the NAc is the only brain site to be tested in clinical trials of DBS for addiction [3]. Because of its role in motor control, the STN has been a DBS target for movement disorders [1]. However, the STN is involved in emotionally guided action selection, and results from patients with movement disorders suggest that STN-DBS may reduce compulsive and impulsive behaviors relevant to addiction [4].

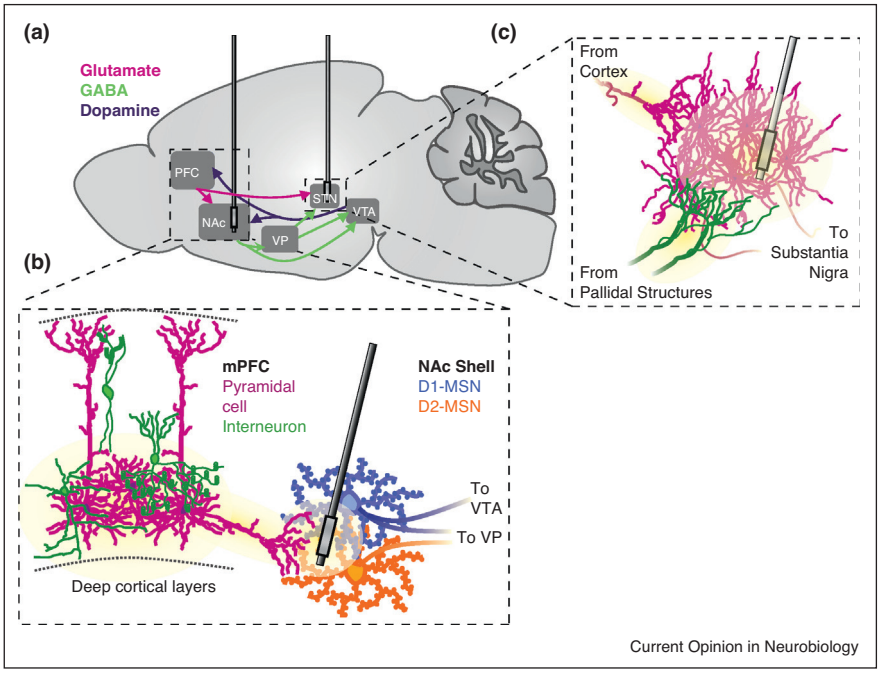
Pre-clinical models are critical for studying the mechanisms underlying the effects of NAc-DBS or STN-DBS in addiction. Many experimental paradigms are used to model features of addiction [5,6]. For example, behavioral sensitization, in which the locomotor response to a drug increases with repeated administrations and persists following drug withdrawal, models behavioral plasticity [5]. In re-instatement paradigms, rodents self-administer the addictive drug before a period of forced abstinence. Exposure to the drug, to stress, or to drug-associated cues are then presented in the drug-taking context and subsequent drug seeking is measured as a model of relapse behavior [6]. In the majority of pre-clinical studies, DBS is applied to targets (NAc or STN) and at frequencies (>100 Hz), to recapitulate DBS applied in the clinic.

NAc-DBS in addictive disorders

Pre-clinical studies

The NAc is a reward system structure, critical for integrating inputs from cortical, thalamic, amygdala and hippocampal sub-regions to guide motivationally relevant behavior. NAc function is modulated by dopamine (DA) inputs arising from the ventral tegmental area (VTA; Figure 1a) and all addictive drugs share the property of increasing DA levels in the NAc [7]. Pre-clinical investigations support the feasibility of high-frequency NAc-

Figure 1



Studies of deep brain stimulation in rodent models. **(a)** Schematic depicting key nodes in the reward circuitry that have been implicated in the effects of NAc-DBS and STN-DBS. **(b)** Hypothesized mechanism of NAc-DBS. High frequency sitmulation of the NAc shell induces local inactivaiton of medium-spiny neurons (MSNs) and antidromic activation of prefrontal cortex (PFC). Collateral activation of PFC interneurons may paradoxically decrease cortical activity. **(c)** High frequency stimulation of the subthalamic nucleus decreases excitability and ultimately output of the STN without a complete depolarization block. STN-DBS also induces network activity at upstream structures such as the pallidum, accumbens and cortex, although the causal role of this network modulation on the behavioral effects of STN-DBS has not been established.

DBS in reducing addiction-related behavior. NAc-DBS suppresses sensitization to ethanol and cocaine [8,9,10••], and reduces on-going consumption and seeking of ethanol, psychostimulants and opiates [11–14]. Extensive evidence implicates antidromic activation of PFC afferents in the behavioral effects of NAc-DBS. Immediate early gene and MRI mapping reveals NAc-DBS activates the prefrontal cortex [15,16•], particularly inhibitory interneurons [17]. In addition, the behavioral effects of DBS are attenuated by inactivation of accumbal fibers of passage with lidocaine [17]. Pharmacological inactivation of PFC subregions, but not NAc cell bodies alone, emulated the reduction of reinstatement of drug seeking by NAc-DBS [17,18]. Despite this apparent involvement of the mPFC, DBS of the mPFC itself does not suppress drug sensitization or consumption [10••,17], indicating the unique role of mPFC-NAc projections in suppressing addiction-related behavior (Figure 1b).

Clinical studies

In the clinic, NAc-DBS was initially applied for OCD and depression, although observations of spontaneous cessation of addictive drug use led to the testing of NAc-DBS in the context of addiction [19,20]. In a series of case reports to directly test its effects in alcohol-dependent patients, NAC-DBS decreased subjective report of craving and increased proportion of abstinent patients relative to controls at two-month follow-up [3,21]. Mechanistically, NAc-DBS increased cingulate cortex activity [3], and decreased functional connectivity between the PFC and NAc measured with fMRI [22]. These results are consistent with pre-clinical studies implicating PFC-NAc connectivity in the effects of NAc-DBS on addiction-relevant behavior, and have been interpreted as NAc-DBS enhancing inhibitory control [3,22].

STN-DBS modulates reward-seeking behavior

Pre-clinical studies

The STN is a nucleus in the basal ganglia output pathways that plays a critical role in action selection. In rats, STN-DBS decreases motivation for cocaine, reduces cocaine-primed reinstatement, and prevents escalation of heroin taking without affecting consumption of non-drug rewards [23–25,26••]. Mechanistically, STN-DBS reduces excitability and firing rate of STN neurons without inducing a complete depolarization block in brain slices [27], and decreases firing rates of STN neurons *in vivo* [28]. Moreover, reduced demand for drug following STN-DBS can be mimicked with local inactivation, further suggesting inactivation as a causal mechanism [29]. However, STN-DBS exerts complicated effects in the larger basal ganglia network: immediate early gene