Neuromodulation therapies such as deep brain stimulation or transcranial magnetic stimulation have shown promise in reducing symptoms of addiction when applied to the prefrontal 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.

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Current and emerging neuromodulation therapies for addiction: insight from pre-clinical studies
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Introduction
Addiction is a brain disease characterized by compulsive drug taking despite adverse consequences, which affects 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-
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
mapping revealed decreased activation in upstream cortical, pallidal and accumbal structures and increased activity in downstream nigral subregions [24,30] (Figure 1c). These network effects likely contribute to the behavioral effects of DBS. For example, cocaine up-regulates immediate early genes in both the core and shell of the accumbens which has been causally linked to behavioral sensitization [31]; STN-DBS prevented this increase, implicating network modulation along with local inhibition in the behavioral effects of STN-DBS.

Clinical studies
Consistent with recordings in rats and non-human primates [32,33], intraoperative recording from the STN in PD patients has confirmed that STN neurons encode valence, respond to reward-related cues and track decisions during response conflict [4,34]. In PD patients, interaction between DA pathology and DA replacement therapy gives rise to a DA dysregulation syndrome (DDS), characterized by impulsive behavior, manic mood and abuse of DA medication [35]. STN-DBS reduced abuse of DA agents, attenuates impulsivity and decreases preference for reward in high effort conditions [4,36], hinting at potential in treating substance use disorders. However, the ability of STN-DBS to modify behavior relevant to addiction has not been directly tested in clinical trials; clinical results must be interpreted on the background of underlying DA dysfunction which characterizes PD. Preclinical studies are therefore useful for disentangling the specific effects of DBS on reward seeking behavior [37,38].

Novel neuromodulation paradigms to correct circuit dysfunction
There are major limitations to the use of classical (continuous, high-frequency) DBS. In movement and substance use disorders, behavioral symptoms reemerge upon DBS offset [2,3]. Another limitation is the incompletely understood mechanism(s) of action. While network-wide effects of DBS are beginning to be elucidated, whether these effects are causally related to improved behavioral symptoms of addiction are unclear. An alternative strategy is using insight from pre-clinical models to determine how addictive drugs modify reward circuit function, and leverage this insight to strategically reverse these circuit changes (Figure 2). In this regard, optogenetics (a technique which renders genetically-defined and regionally-defined populations of neurons sensitive to light), has yielded incredible insight into how addictive drugs modify circuit function [39,40]. The causal role of projections from the medial prefrontal cortex (mPFC) to the NAc in compulsive drug seeking and sensitization has been established and is providing the basis for novel neuromodulation strategies for addiction.

Optogenetically inspired DBS
Exposure to cocaine or morphine potentiates excitatory inputs from the mPFC and BLA onto the D1 receptor-expressing population of accumbal projection neurons (Figure 2a) [41,42]. This potentiation has been causally implicated in behavioral sensitization, and is driven by the synaptic insertion of calcium-permeable, GluA2-lacking AMPA receptors. Pharmacology studies in rodent models and brain slices have demonstrated that these GluA2-lacking AMPA receptors can be efficiently removed by mGluR-dependent signaling [43]. Following withdrawal from drug exposure, acute optogenetic stimulation of mPFC terminals in the NAc at 10–13 Hz reversed cocaine-evoked potentiation of this synapse through an mGluR-dependent mechanism and abolished drug sensitization and seeking during re-instatement [10**,41,42].

Since optogenetic manipulations are not immediately translated to the clinic, we sought to emulate these effects with DBS. When applied at the same frequency, DBS did not affect plasticity or sensitization. When electrical DBS was combined with pharmacological inhibition of D1-signaling (to block insertion of CP-AMPARs through DAD1 receptor signaling), the effects were similar to optogenetic-reversal: transmission at PFC to NAc synapses was normalized, and sensitization to cocaine was abolished (Figure 2b) [10**]. This optogenetically inspired DBS protocol works through a known mechanism, decreasing the likelihood of off-target effects due to non-selective mechanisms of action. Studies in nonhuman primate models of relapse are needed to determine if this protocol also affects other addiction-relevant behaviors, before it can be tested in clinical settings.

Optogenetically-inspired transcranial magnetic stimulation
Another approach that attempts to correct PFC-NAc circuit dysfunction in addiction has employed repeated transcranial magnetic stimulation (rTMS). rTMS is a noninvasive, electromagnetic-based stimulation technology which is typically applied acutely, between 1 and 15 Hz [44]. Deficits in PFC-mediated inhibitory control have been proposed to mediate compulsive drug seeking [45], and following self-administration of cocaine in rats, the excitability of NAc-projecting PFC cells is decreased [46]. This decrease in excitability is most pronounced in animals who persisted in drug taking despite punishment, a model of compulsive drug seeking [46]. A caveat is that PFC hypocactivity could be largely recapitulated by punishment alone, indicating a complicated interplay between stress, PFC-NAc circuitry and drug seeking [47]. Critically, optogenetic PFC activation decreased compulsive drug seeking in this model (Figure 2c) [46]. Based on this rationale of PFC hyperfunction, pilot studies have used rTMS to stimulate the analogous dorsolateral PFC regions in cocaine-abusing
Optogenetically inspired neuromodulation strategies. (a, b) Optogenetically inspired DBS. Schematic depicting select brain regions that have been implicated in addiction-relevant behavior. Optogenetic stimulation of PFC to NAc inputs at 12–13 Hz reversed cocaine-evoked plasticity, cocaine sensitization and reinstatement [10**,42]. (b) Cocaine potentiates excitatory transmission between mPFC and D1-MSNs, driven by insertion of GluA2-lacking AMPA receptors. Optogenetic stimulation or optogenetically inspired DBS (OiDBS) at 12 Hz reverses this plasticity by inducing a long-term depression of these excitatory mPFC to NAc synapses [10**]. (c) Optogenetic activation of the PFC suppressed compulsive cocaine seeking, while optogenetic inhibition enhanced compulsive seeking [46]. (d) On the basis of the hypothesis that driving PFC hypofunction, suppresses compulsive drug taking, rTMS was applied to the dorsolateral prefrontal cortex at 15 Hz. A pilot study reported higher rates of abstinence and decreased craving following rTMS [48*].

Patients (Figure 2d) [48*]. rTMS-treated patients exhibited lower craving scores, and abstinence rates were higher in the rTMS group one month after treatment. While larger, randomized, control studies are needed to confirm these effects, rTMS may provide a non-invasive strategy to recruit similar circuit mechanisms as DBS or optogenetic manipulations.

Conclusions and future directions
Neuromodulation strategies, such as DBS or rTMS are powerful tools for manipulating neural circuits to treat addiction. Mechanistic studies of high-frequency DBS in addiction suggest its effects are related to widespread modulation of the reward circuit, particularly to connectivity between the PFC and NAc. By establishing which
circuit changes are causally implicated in the beneficial effects of DBS, it could be possible to titrate stimulation parameters to efficiently achieve the desired network effects for symptom reduction. In the future, it is possible that functional connectivity could be assayed during DBS programming, and parameters could be tailored to each patient to optimally modulate reward circuit activity.

Recent optogenetic studies have identified specific loci of drug-evoked plasticity in the reward system that are causally implicated in maladaptive behavior [39–43]. By elucidating the precise mechanisms underlying the expression of circuit dysfunction, these studies have inspired stimulation paradigms that counter drug-evoked plasticity in the reward circuit, and have long-lasting effects on addiction symptoms [10**,48*]. These protocols work through established mechanisms, minimizing the likelihood of off-target effects arising from non-selective mechanisms of classical DBS. Closed-loop neuromodulation is another potential strategy for reducing neural adaptations or decreased efficacy that emerges with chronic DBS [49*]. In PD, closed-loop DBS uses biofeedback (EMG or electrophysiology) to trigger DBS onset exclusively during tremor. This approach improves clinical outcomes, extends battery life and reduces potential adverse effects of chronic, continuous stimulation [49*]. While there is no established signature of drug craving, this is an active area of investigation in pre-clinical studies. Validating neuronal correlates of drug craving could be used to develop closed-loop neuromodulation paradigms that could improve outcomes of DBS in addiction by modulating circuit function only during onset of maladaptive behavior. Moreover, drug-associated cues activate many areas of the reward system, including the NAc, VTA, amygdala and VP, all of which undergo drug-evoked adaptations which have been causally implicated in addiction-relevant behaviors [15,41,42,47,50,51]. To this end, targeting these brain areas may lead to more effective reductions in craving, or could treat a broader range of addiction symptoms such as negative affect emerging with drug withdrawal [50]. Pre-clinical work has demonstrated the feasibility of optogenetic, chemo-genetic or electrical modulation of the VP or VTA in suppressing drug-sensitization and seeking [50–53] which support the continued study of these targets as potential sites for neuromodulation in addiction.

Going forward, the combination of novel stimulation targets, frequencies, and less invasive stimulation technologies may allow greater flexibility in tailoring DBS for specific symptoms of addiction in individual patients. In all cases, pre-clinical studies will be needed to establish safety and efficacy of novel stimulation paradigms. Finally, insight into the nature of circuit dysfunction and mechanisms of action of neuromodulation strategies from pre-clinical studies will provide a framework for designing novel therapies for addiction.

Conflict of interest statement
Nothing declared.

References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

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This work systematically varies DBS frequency and target to determine the optimal stimulation parameters to facilitate extinction of opiate-context associations. Altering stimulation frequency in the ventral and dorsal striatum lead to profound differences in modulation of afferent and efferent structures, and suggest low-frequency DBS may render reward circuitry more susceptible to extinction training.


Based on work in pre-clinical models of compulsive drug seeking (Ref. [13], above), a pilot study was undertaken to determine if modulating prefrontal cortex with rTMS in humans could reduce behavioral symptoms of addiction. While preliminary, results indicate acute rTMS lead to sustained improvement on craving measures and abstinence rates.


The authors discuss the design and benefits of adaptive DBS, in which DBS is not applied constantly but is only applied in response to biofeedback (measuring physical tremor or electrophysiological signature of tremor). The motor improvement with adaptive DBS may be superior to classical DBS, while also reducing power consumption.


