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**Review**

# Brain Stimulation in Addiction

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Localized stimulation of the human brain to treat neuropsychiatric disorders has been in place for over 20 years. Although these methods have been used to a greater extent for mood and movement disorders, recent work has explored brain stimulation methods as potential treatments for addiction. The rationale behind stimulation therapy in addiction involves reestablishing normal brain function in target regions in an effort to dampen addictive behaviors. In this review, we present the rationale and studies investigating brain stimulation in addiction, including transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation. Overall, these studies indicate that brain stimulation has an acute effect on craving for drugs and alcohol, but few studies have investigated the effect of brain stimulation on actual drug and alcohol use or relapse. Stimulation therapies may achieve their effect through direct or indirect modulation of brain regions involved in addiction, either acutely or through plastic changes in neuronal transmission. Although these mechanisms are not well understood, further identification of the underlying neurobiology of addiction and rigorous evaluation of brain stimulation methods has the potential for unlocking an effective, long-term treatment of addiction.
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## INTRODUCTION

There are four main procedures developed to stimulate specific brain regions. These include: (i) transcranial electrical stimulation; (ii) transcranial magnetic stimulation (TMS); (iii) transcranial direct current stimulation (tDCS); and (iv) deep brain stimulation (DBS). Transcranial electrical stimulation delivers an electrical current to the brain across electrodes, and it provided much of the early data on the neurophysiological effects of stimulating cortical regions and the propagation of the stimulus in the central nervous system (Rossini *et al*, 2015). However, because transcranial electrical stimulation requires a current of several hundred volts, transcranial electrical stimulation was largely replaced by TMS, which uses magnetic pulse to induce an electrical current in the brain. TDCS delivers a very low intensity electrical current (1–2 mA), which is likely too low to initiate action potentials in neurons, but may modulate firing rates by changing the membrane potential of neurons. DBS is currently the only method available to directly stimulate deeper brain regions, but a disadvantage of DBS is the need for surgery and the maintenance of implanted hardware. The purpose of this review is to condense experimental findings from the large and growing literature of brain stimulation and addiction, draw conclusions, and offer our perspective on how to improve its evaluation. We refer the reader to other recently published reviews for additional perspectives of its safety and efficacy (see (Gorelick *et al*, 2014b; Hadar and Zangen, 2015)).

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## TRANSCRANIAL MAGNETIC STIMULATION (TMS)

TMS uses electromagnetic induction to generate an electrical current in the brain. The device consists of a conducting coil to produce the current, which induces a brief magnetic field orthogonal to the plane of the coil, which in turn generates an electrical current in the brain. Early TMS coils were circular, and the stimulation delivered was greatest around the circle edge but low in the center. The figure 8 coil was designed to produce a field with the highest intensity at the juncture of the two circles (Rossini *et al*, 2015).

An issue with TMS is the limited depth of brain tissue that can be reached (Figure 1b). The rapid attenuation of the electrical field results in TMS being largely restricted to superficial cortical targets (Deng *et al*, 2014). As a result, most TMS studies of psychiatric disorders, including addiction, have stimulated the dorsolateral prefrontal cortex (DLPFC). However, given the need to investigate the stimulation of deeper brain regions as therapeutic targets (Figure 1a), there is a demand to develop coils that can reach these targets. Among these is the H coil, designed to stimulate deeper brain structures using spatial summation to reduce attenuation (Roth *et al*, 2002), although this comes at the cost of reduced focality (Zangen *et al*, 2005; Huang *et al*, 2009), so that larger brain regions are stimulated. There are a number of different types of H coils that target different brain regions, and these have been tested clinically in psychiatric and neurologic disorders (Deng *et al*, 2014).

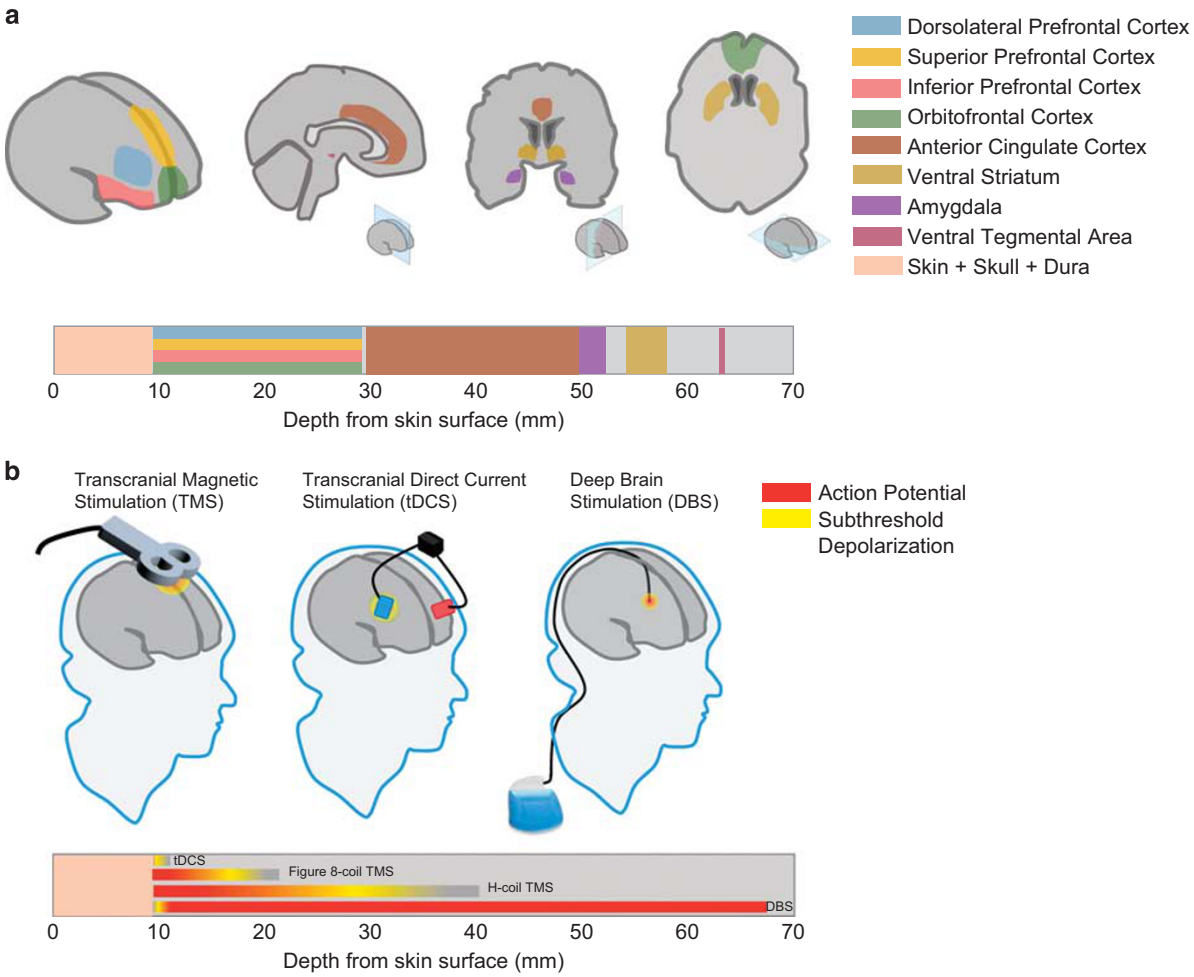


**Figure 1** Overlap of brain regions to target in addiction with brain stimulation methods. (a) Human brain regions implicated in addiction. *Top*. Illustration of the major areas of the brain implicated in addiction based on imaging studies. Perspectives are from (left to right) cortical surface, sagittal, coronal, and horizontal perspectives (inset shows approximate view) *Bottom*. Approximate distances of implicated brain regions from skin surface above frontal and parietal bones. (b) Methods of brain stimulation. *Top*. Illustrations depicting methods of brain stimulation used in human from left: repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS) with theoretical range of depolarization and action potential level of stimulation from current delivered. *Bottom*: Theoretical range of direct stimulation shown in distance from skin surface above frontal and parietal bones. Both tDCS and rTMS can stimulate cortical regions, while can DBS reach deeper subcortical structures.

TMS applied to the motor cortex provides a method for investigating the neurophysiology of cortico-spinal connections, because changes in activation can be determined by measuring alterations in the motor evoked potential (MEP). In clinical studies, the intensity of the TMS stimulus is determined by the minimum stimulation required to elicit a reliable MEP in the targeted muscle group. This is assessed using the motor threshold (MT), identified as the intensity delivered to the MT that elicits the contraction of a muscle (such as the hand or calf muscle). The MT is used to determine the intensity of the TMS pulse that will be delivered to the target brain region, such as the DLPFC.

Generally, repetitive TMS (rTMS), in which a series of consecutive stimuli are delivered within a session, is used in clinical research. The frequency of the delivered stimuli can be low frequency (LF, 1 Hz or below) or high frequency (HF, between 5 and 20 Hz), where LF stimulation is inhibitory and HF stimulation increases cortical excitability (Gorelick *et al*, 2014a). This theory is largely based on studies of cortico-spinal motor output, where HF TMS to the motor cortex increases cortical excitability, whereas LF stimulation reduces the measured MEP, although there are exceptions to this observation (Gorelick *et al*, 2014a). An additional variation in stimulation frequency, based on observations made using *in vitro* electrophysiology is called theta burst stimulation (TBS) where 3 pulses at 50 Hz is repeated at 5 Hz. When applied to the cortex, low amplitude continuous TBS (cTBS) produces an inhibitory-like effect, similar to LF continuous stimulation, whereas intermittent TBS (2 s TBS every 10 s) produces a facilitatory effect similar to HF stimulation (Huang *et al*, 2005; Hanlon *et al*, 2015b).

Repetitive TMS has been shown to cause lasting effects on physiology and behavior. These actions are believed to follow or approximate traditional phenomena of Hebbian forms of synaptic plasticity including long-term potentiation and long-term depression (Hoogendam *et al*, 2010). For instance, LF rTMS (~1 Hz) of the human motor cortex can decrease the MEP for over an hour following cessation (Chen *et al*, 1997; Iyer *et al*, 2003). HF stimulation with rTMS (10 Hz) can increase the MEP for up to 2 h post cessation

**Table 1** Transcranial Magnetic Stimulation (TMS)

| Drug | Treatments | *n* | Target | Stimulation | Outcome measures | Effect | Citation |
|---|---|---|---|---|---|---|---|
| Nicotine | 1 | 11 | L DLPFC | 10,20 Hz, 90,100% MT | Craving | ↓ | Johann *et al*, 2003 |
| | 1 | 16 | L DLPFC | 10 Hz, 100% MT | Cue-induced craving | ↓ | Li *et al*, 2013a, b |
| | 2 | 14 | L DLPFC | 20 Hz, 90% MT | Craving<br>Ad libitum smoking | No effect<br>↓ | Eichhammer *et al*, 2003 |
| | 1 | 14 | L DLPFC | 10 Hz, 90% MT | Cue-induced craving<br>EEG delta | ↓<br>↓ | Pripfl *et al*, 2014 |
| | 1 | 10 | L DLPFC | 1 Hz, 110% MT | Cue-induced craving<br>fMRI: ACC, OFC, VS | ↓<br>↓ | Hayashi *et al*, 2013 |
| | 1 | 15 | SFG<br>SFG<br>MOC | 1 Hz, 90% MT<br>10 Hz, 90% MT<br>1, 10 Hz, 90% MT | Cue-induced craving<br>Cue-induced craving<br>Cue-induced craving | No effect<br>↓<br>No effect | Rose *et al*, 2011 |
| | 10 | 48 | L DLPFC | 10 Hz, 100% MT | Cue-induced craving<br>Cigarette consumption | ↓<br>↓ | Amiaz *et al*, 2009 |
| | 20, w therapy | 15 | L,R DLPFC | 20 Hz, 90% MT | Craving<br>Smoking | ↓<br>No effect | Wing *et al*, 2012 |
| | 15 | 35 | L DLPFC | 10 Hz, 110% MT | Smoking | ↓ | Prikryl *et al*, 2014 |
| | 13, h-coil, w/cues | 115 | PFC, insula<br>PFC, insula | 1 Hz, 120% MT<br>10 Hz, 120% MT | Cigarette consumption<br>Cigarette consumption | No effect<br>↓ | Dinur-Klein *et al*, 2014 |
| Alcohol | 10 | 45 | R DLPFC | 10, Hz, 110% MT | Craving | ↓ | Mishra *et al*, 2010 |
| | 10 | 20 | R and L DLPFC | 10, Hz, 110% MT | Craving | ↓ | Mishra *et al*, 2015 |
| | 1 | 31 | R DLPFC | 20 Hz, 110% MT | Craving (lab)<br>Craving (home) | No effect<br>No effect | Herremans *et al*, 2012 |
| | 1 | 29 | R DLPFC | 20 Hz, 110% MT | Craving<br>Response inhibition | No effect<br>↑ | Herremans *et al*, 2013 |
| | 1 | 19 | L DLPFC | 20 Hz, 90% MT | Craving<br>Depressive symptoms<br>Alcohol cue attention | No effect<br>No effect<br>↓ | Hoppner *et al*, 2011 |
| | 20, h-coil | 11 | MPFC<br>LPFC | 20 Hz, 120% MT | Craving | ↓ | Rapinesi *et al*, 2015 |
| | 10 | 18 | MPFC | 20 Hz, 120% MT | Craving<br>Depressive symptoms | ↓<br>↓ | Ceccanti *et al*, 2015 |
| Cocaine | 1 | 6<br>6 | R DLPFC<br>L DLPFC | 10 Hz, 90% MT<br>10 Hz, 90% MT | Craving<br>Craving | ↓<br>No effect | Camprodon *et al*, 2007 |
| | 10 | 36 | L DLPFC | 15 Hz, 100% MT | Craving | ↓ | Politi *et al*, 2008 |
| | 1 | 11 | MPFC | cTBS, 110% MT | Craving | ↓ | Hanlon *et al*, 2015a, b |
| Methamph. | 1 | 10 | L DLPFC | 1 Hz, 100% MT | Craving | ↑ | Li *et al*, 2013a, b |

Abbreviations: L, left; R, right; cTBS, theta burst simulation; DLPFC, dorsolateral prefrontal cortex; MOC, motor cortex; MT, motor threshold; MPFC, medial prefrontal cortex; PFC, prefrontal cortex; SFG, superior frontal gyrus; VS, ventral striatum.

(Jung *et al*, 2008). Interestingly, the persistent effects of HF stimulation can be blocked by NMDA receptor antagonists indicating that a glutamatergic mechanism similar to long-term potentiation is involved (Huang *et al*, 2008). Imaging studies have supported these findings and demonstrate that cortical stimulation can achieve lasting effects in brain regions that receive efferent connections from the targeted region including the anterior insula (Hanlon *et al*, 2015b) and the striatum (Cho *et al*, 2015; Hanlon *et al*, 2015b) when the PFC is stimulated.

## rTMS Studies in Addiction

There have been a series of studies investigating the effect of rTMS in addiction, and these are summarized in Table 1. Most studies used a limited number of sessions (usually 1–2), to investigate acute effects such as craving. Fewer studies used more sessions (10 or more), which are needed to assess rTMS as a potential intervention for drug or alcohol consumption.

*Nicotine*. Among the substance use disorders, nicotine (tobacco) dependence has been the most studied with both acute (1–2 sessions) and repeated (>10 sessions) of rTMS.

*Acute effects of rTMS on craving*. Six studies have investigated the effect of 1–2 sessions of rTMS, and craving was the primary behavioral measure. Five of these targeted the left DLPFC, and one study stimulated the superior frontal gyrus (see Table 1). Of the studies targeting the left DLPFC, most (4/5) used HF rTMS at 90–110% of MT.

The first study, by Johann *et al* (2003), compared HF rTMS with sham and showed a reduction in craving for cigarettes. Similar results were reported by Li *et al* (2013a), who compared a single session of HF rTMS with the left DLPFC (*vs* sham) on cue-induced craving (smoking *vs* neutral pictures) and showed that active rTMS reduced craving for cigarettes under both cue conditions. A third study looked at both craving and cigarette smoking and showed that HF rTMS to the left DLPFC had no effect on craving, but did decrease smoking during an *ad libitum* smoking period following the delivery of rTMS (Eichhammer *et al*, 2003).

Two of the studies targeting the DLPFC investigated brain function in addition to craving. Pripfl *et al* (2014) showed that HF rTMS reduced cigarette craving in nicotine-deprived smokers and reduced EEG delta power, a measure of wakefulness that has been implicated in nicotine dependence (Pripfl *et al*, 2014). The second study delivered LF (1 Hz), in contrast to the other studies, to inhibit the left DLPFC and used fMRI to investigate changes in brain activation (Hayashi *et al*, 2013). The results showed that one session of LF rTMS reduced craving for cigarettes and reduced the response to craving-related signals in the ventral striatum, medial orbitofrontal cortex, and anterior cingulate (Hayashi *et al*, 2013).

Of the studies delivering short-term rTMS, one targeted the superior frontal gyrus, and compared high and LF stimulation (Rose *et al*, 2011). The results showed that craving, elicited by cigarette smoke, was increased following 10 Hz stimulation (compared with the 1 Hz), although cigarette craving was reduced following the neutral cues in the 10 Hz condition (Rose *et al*, 2011).

*Repeated sessions of rTMS.* Four studies have investigated the effect of multiple sessions of rTMS as an intervention for cigarette smoking. The first was a randomized, sham-controlled study ($n=48$) performed with the figure 8 coil targeting the left DLPFC using 10 HF rTMS sessions and a maintenance phase (Amiaz *et al*, 2009). Craving for cigarettes was elicited with smoking *vs* neutral cues and cigarette consumption was measured by self-report and urine cotinine levels. Both craving and cigarette smoking were reduced in the active rTMS group, but there was significant subject drop out and a dissipation of the effect during the maintenance phase, suggesting that longer stimulation may be needed.

Studies in smokers with schizophrenia show split results. A significant decrease in cigarette smoking was not seen in a 10-week, randomized, double-blind, sham-controlled trial of 20 sessions of HF rTMS to the DLPFC (with the figure 8 coil) in schizophrenic smokers (Wing *et al*, 2012). The rTMS was delivered as an adjunctive treatment to transdermal nicotine and group therapy, and whereas the active rTMS group reported a decrease in craving compared with the sham group, no difference in smoking was seen between the two groups. However, another study in smokers with schizophrenia showed that HF rTMS to the DLPFC (figure 8 coil) for 21 sessions reported a reduction in cigarette smoking. Craving was not assessed, and the amount of cigarettes consumed was measured only by subjects' self-report (Prikryl *et al*, 2014).

Only one study has been published using an H coil to stimulate the insula, ventrolateral prefrontal cortex and the DLPFC bilaterally (Dinur-Klein *et al*, 2014). This study was a large randomized sham-controlled study ($n=115$) that compared sham, high and LF stimulation administered for 10 days over 2 weeks followed by three non-consecutive treatments for an additional week. The rTMS was delivered in the context of smoking cues, and smoking was measured by urine cotinine levels and subjects' self-report. The results showed that HF rTMS combined with exposure to smoking cues led to a reduction in smoking of 44% at 3 months (Dinur-Klein *et al*, 2014).

Overall, the studies of nicotine use disorders show that acute rTMS directed at the DLPFC reduces craving for nicotine. However, some of this work shows that there is a mismatch between craving and actual smoking, indicating that studies investigating cigarette consumption are crucial. Of the studies investigating this, the largest (115 subjects) showed that HF, but not LF, stimulation with the H coil directed at the bilateral insula, ventrolateral prefrontal cortex, and the DLPFC reduced smoking (Dinur-Klein *et al*, 2014). Similar results were shown in the study using the figure 8 coil delivering HF stimulation to the left DPLFC (Amiaz *et al*, 2009). Together, these studies indicate that HF rTMS, directed at the structures of the prefrontal cortex, may serve as an effective intervention for nicotine use disorders.

*Alcohol.* In alcohol use disorders, the majority of studies have investigated craving only, with no randomized controlled trials investigating alcohol intake. These studies have used both the figure 8 coil to target the DLPFC and H coil to stimulate broader regions of the prefrontal cortex.

Five studies targeted the DLPFC with HF rTMS, to investigate craving for alcohol. Mishra *et al* (2010) performed a single-blind, sham-controlled study of 10 sessions of HF rTMS to the right DLPFC in alcohol-dependent subjects who were abstinent $>10$ days before starting rTMS. The results showed a greater reduction in craving for alcohol in the active group over the sham condition. In a subsequent study, this same group compared 10 sessions of HF rTMS with the right and left DLPFC and showed that both right and left rTMS reduced craving for alcohol (Mishra *et al*, 2015).

However, other studies targeting the DLPFC have not shown that rTMS reduces craving in alcohol dependence. Herremans *et al* (2012) investigated a single session of HF rTMS to the right DLPFC (*vs* sham), and did not report a difference in craving, measured immediately after the session nor in subjects' regular home environment during the days following rTMS (Herremans *et al*, 2012). In a second study by this group, using similar methods, active rTMS was shown to improve cognitive performance on the Go-NoGo task, indicating improved response inhibition, though again no change was seen in craving for alcohol (Herremans *et al*, 2013). Similarly, in alcohol-dependent women, one session of HF rTMS (20 Hz at 90% MT), *vs* sham, did not produce changes in craving or depressed mood, although this group reported a decrease in attention to alcohol-related cues, measured as attentional eye blink (Hoppner *et al*, 2011).

Two studies have investigated the H coil, directed at medial and lateral prefrontal cortex. Rapinesi *et al* (2015) performed a 6-month study in subjects with comorbid

dysthymic disorder/alcohol use disorder using bilateral rTMS to stimulate the medial and lateral prefrontal regions (including the orbitofrontal cortex), with a left preference (Roth *et al*, 2007). The rTMS was used as an adjunctive treatment to pharmacotherapy. The results showed an improvement in depressive symptoms and a reduction in craving for alcohol. Similar results were reported in a pilot study using the H coil directed at the medial prefrontal cortex *vs* sham, where HF rTMS was shown to decrease craving for alcohol and reported alcohol intake (mean number of drinks per day and drinks on days of maximum alcohol intake) (Ceccanti *et al*, 2015).

Overall, the data in alcohol dependence are less cohesive than that reported for nicotine use disorders, but there are fewer studies. In addition, most of the studies targeted the right DLPFC, whereas the nicotine studies targeted the left DLPFC. Nonetheless, the studies targeting the DLPFC and craving are more split than those investigating nicotine. Small studies using the H coil, which stimulates broader prefrontal regions, show some promise for using rTMS in this disorder. Indicating that specific stimulation may not be necessary to achieve a therapeutic outcome.

*Cocaine and methamphetamine*. Three studies have been performed using TMS with the figure 8 coil in cocaine dependence. The first study used two sessions of HF rTMS and showed that craving for cocaine was reduced by rTMS applied to the right, but not the left, DLPFC (Camprodon *et al*, 2007). In a second larger study, HF rTMS applied to the left DLPFC did reduce cocaine craving in 10 daily sessions (Politi *et al*, 2008). A sham-controlled, crossover study investigated the effect of low amplitude TBS directed at the mPFC on craving and brain activation using fMRI (Hanlon *et al*, 2015b). The results showed that TBS to inhibit stimulus evoked brain activity in the medial PFC reduced craving and decreased activity in the striatum and anterior insula (Hanlon *et al*, 2015b).

Only one study has been performed in methamphetamine dependence comparing a single session of LF (1 Hz) *vs* sham (Li *et al*, 2013b). rTMS was delivered to the DLPFC in the presence of drug-related and neutral cues, and the results showed that the LF rTMS *increased* craving for methamphetamine compared to sham.

*Cannabis*. The only study we found investigating TMS in cannabis abuse used single and paired pulse TMS to investigate differences in cortical excitability, and did not investigate craving or other measures of drug use (Fitzgerald *et al*, 2009). Two groups of cannabis users, heavy and light, were compared with controls and both groups showed short interval cortical inhibition, but no difference in other measures of cortical inhibition or cortical excitability.

Other studies have investigated changes in cortical inhibition and excitability in addiction, and these have been recently reviewed (Bunse *et al*, 2014). Overall, these findings indicate that alcohol dependence is associated with alterations in cortical excitation and inhibition, depending on the duration of abstinence (Bunse *et al*, 2014). Cocaine abuse is associated with a higher resting MTs and higher intracortical facilitation compared with controls (Bunse *et al*, 2014; Hanlon *et al*, 2015a). Given that cortical inhibition and excitability can serve as surrogates for GABA and glutamate signaling, these studies provide some insight into potential alteration in these neurotransmitters (Bunse *et al*, 2014; Hanlon *et al*, 2015a).

*Considerations*. Overall, a number of studies indicate that 1–2 sessions of HF rTMS may be effective in reducing craving in addiction compared with sham, and the strongest evidence for this is in nicotine use disorders. However, most of the short-term rTMS studies in addiction included small numbers of subjects, and there is a degree of variability in the subjects' clinical characteristics, brain regions targeted, and methods for assessing and eliciting craving. In addition, some of these studies are inconsistent for drug or alcohol craving, indicating that studies investigating the effect of rTMS on the consumption of substances are needed.

Randomized controlled studies on cigarette smoking have been performed in nicotine dependence. These studies indicate that HF rTMS reduces smoking, and there is evidence that pairing rTMS with smoking cues may increase the efficacy of rTMS. In addition, these studies indicate that multiple sessions are required, and that maintenance dosing may be needed to sustain the effect.

## TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)

Transcranial direct current stimulation (tDCS) delivers a low voltage, relatively weak current across an anode and cathode placed on the scalp. The electrical current penetrates the skull to a degree, and there are two mechanisms by which tDCS has been proposed to modulate brain activity: (i) by changing the resting membrane potential of the neurons, where the neurons proximal to the anode are depolarized and those at the cathode are hyperpolarized; and (ii) by modulating synaptic activity in a manner similar to long-term potentiation (at the anode) and long-term depression (at the cathode) (Stagg and Nitsche, 2011). Thus, the modulatory effects are thought to be dependent on the intensity, duration, and direction of the current, where excitability is increased with anodal tDCS and that cathodal tDCS contributes to hyperpolarization and inhibition.

### tDCS Studies in Addiction

TDCS has been tested for the treatment for addictive behaviors and the results of these studies are summarized in Table 2.

*Nicotine*. Studies investigating the effects of tDCS on nicotine dependence have focused on craving and nicotine cues, and the results suggest that tDCS may reduce craving for nicotine, though they are not completely consistent. Fregni *et al* (2008) performed a randomized, crossover study of smokers using three conditions: sham, anodal tDCS to the left DLPFC, and anodal tDCS to the right DLPFC. Both types of active tDCS reduced craving for nicotine, following cues, compared with sham. A subsequent study by this same group showed that repeated tDCS with the anode positioned at the left DLPFC resulted in a self-reported decrease in craving and smoking, in the active group *vs* sham (Boggio *et al*, 2009). In

**Table 2** Transcranial Direct Current Stimulation (tDCS)

| Drug | Treatments | *n* | Target | Stimulation | Outcome measures | Effect | Citation |
|---|---|---|---|---|---|---|---|
| Nicotine | 1, 20 min | 24 | R DLPFC | Anodal. 2 mA | Cue induced craving | ↓ | Fregni *et al*, 2008 |
| | | | L DLPFC | Anodal, 2 mA | Cue induced craving | ↓ | |
| | 5, 20 min | 23 | L DLPFC | Anodal, 2 mA | Craving | ↓ | Boggio *et al*, 2009 |
| | | | | | Smoking, self-report | ↓ | |
| | 5, 30 min | 12 | R DLPFC | Anodal, 2 mA | Craving, intent to smoke | No effect | Fecteau *et al*, 2014 |
| | | | | | Craving, desire to smoke | ↓ | |
| | | | | | Smoking, self-report | ↓ | |
| | | | | | Carbon monoxide monitor | No effect | |
| | 1, 20 min | 24 | L DLPFC | Anodal, 2 mA | Craving | No effect | Xu *et al*, 2013 |
| | | | | | Negative affect | ↓ | |
| Alcohol | 1, 20 min | 13 | R DLPFC | Anodal, 2 mA | Cue induced craving | ↓ | Boggio *et al*, 2008 |
| | | | L DLPFC | Anodal, 2 mA | Cue induced craving | ↓ | |
| | 5, 26 min | 33 | R DLPFC | Anodal, 2 mA | Cue induced craving | No effect | Klauss *et al*, 2014 |
| | | | | | Anxiety/Depressive sympt | No effect | |
| | | | | | Quality of life percept. | ↑ | |
| | 5, repetitive 20 min | 13 | L DLPFC | Anodal, 2 mA | Cue induced craving | ↓ | da Silva *et al*, 2013 |
| | | | | | Anxiety/Depressive sympt | ↓ | |
| | | | | | Relapse | ↑ | |
| | 1, 10 min. | 41 | L DLPFC | Anodal, 1 mA | Craving | ↓ | den Uyl *et al*, 2015 |
| | | | R IFG | Anodal, 1 mA | Craving | No effect | |
| Cocaine | 1, 20 min | 36 | R DLPFC | Anodal, 1.5 mA | Risk taking | ↓ | Gorini *et al*, 2014 |
| | | | L DLPFC | Anodal, 1.5 mA | Risk taking | ↑ | |
| | 5 repetitive, 20 min | 13 | R DLPFC | Anodal, 2 mA | Cortical excit. to drug cues | ↓ | Conti *et al*, 2014a |
| | | | R DLPFC | Anodal, 2 mA | | | |
| | 1, 20 min | 13 | R DLPFC | Anodal, 2 mA | Ant Cingulate excit | ↓ | Conti *et al*, 2014a |
| | 5, 20 min | 36 | R DLPFC | Anodal, 2 mA | Craving | ↓ | Batista *et al*, 2015 |
| Cannabis | 1, 15 min | 25 | R DLPFC | Anodal, 2 mA | Risk taking | ↑ | Boggio *et al*, 2010 |
| | | | L DLPFC | Anodal, 2 mA | Craving | ↓ | |
| | | | | | Risk taking | ↑ | |
| | | | | | Craving | No effect | |

Abbreviations: L: left; R, Right; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus.

a third study by this group, Fecteau *et al* (2014), investigated two tDCS conditions (active or sham), where the active condition consisted of the anode at the right DLPFC and cathode at the left DLPFC. This group reported that active tDCS reduced craving on the 'desire to smoke' scale but not on other measures. Cigarette smoking was decreased when measured as subjects' self-report in a smoking diary, but not when using a carbon monoxide monitor (obtained before stimulation and at day 5 after stimulation). Only one other group has performed a study of anodal stimulation over the left DLPFC (Xu *et al*, 2013). The results showed improvement in smoking-related negative affect compared with sham, but no effect on cigarette craving.

*Alcohol*. In alcohol dependence, tDCS shows a less consistent effect on craving. Boggio *et al* (2008) performed a sham-controlled study in alcohol-dependent subjects (abstinent 10 days) comparing three types of tDCS: (i) sham, (ii) anode at the left DLPFC/cathode right DLPFC, and (ii) anode at the right DLPFC/cathode left DLPFC. Craving was elicited with alcohol-related cues, and the results showed that both types of active tDCS reduced craving compared with sham. However, another study investigated craving for alcohol using a similar type of tDCS (left cathodal/right anodal over the DLPFC), in alcohol-dependent subjects showed no difference in alcohol craving or depression/anxiety symptoms compared with sham (Klauss *et al*, 2014).

In a third study, da Silva *et al* (2013) investigated active tDCS (anode over the left DLPFC) *vs* sham in alcohol-dependent subjects receiving outpatient clinical treatment. Measures of craving, depression/anxiety, and cue response were also obtained. The results showed that active tDCS was associated with a trend toward greater relapse, although depressive symptoms, response to cues, and craving improved with tDCS *vs* sham.

Finally, a study of tDCS to the DLPFC was compared using tDCS directed at the right inferior frontal gyrus and sham in heavy drinkers that measured craving for alcohol and response bias toward alcohol (den Uyl *et al*, 2015). The results showed that craving was reduced with tDCS to the DLPFC, but not the inferior frontal gyrus, and that tDCS did not have an effect on bias for alcohol, assessed with an implicit association test.

*Cocaine*. The tDCS studies in cocaine abuse have mostly focused on cognitive function. Gorini *et al* (2014) investigated the effect of tDCS in risky choices in cocaine abusers

and controls under three conditions: (i) sham; (ii) left anodal/right cathodal stimulation of the DLPFC; (iii) a right anodal/left cathodal stimulation of the DLPFC. The results showed that activation of the DLPFC (both conditions) reduced risky choices on the balloon analog risk task. However, another measure of risk-taking, the game of dice task, showed that right DLPFC anodal stimulation increased safe behavior, while risk-taking behavior increased after left DLPFC anodal stimulation in the cocaine abusers (Gorini *et al*, 2014).

Conti *et al* (2014a) investigated the effect on tDCS on cortical excitability using event-related potentials, under neutral and drug cue exposure in cocaine abusers, using bilateral (left cathodal/right anodal) tDCS to the DLPFC *vs* sham. The results showed that single session tDCS increased current density in response to cues the P3 segment, though the methods for obtaining current density were not explicit. Craving was measured in this study, and no significant change was seen following active tDCS. In a similar study, Conti and Nakamura-Palacios (2014b) administered left cathodal/right anodal or sham stimulation over the DLPFC to cocaine abusers and recorded event-related potentials during drug-related *vs* neutral cues. Active TDCS was found to decrease activity in N2 EEG component in response to a cocaine cue, whereas activity increased in the sham group.

Most recently, a double-blind randomized clinical trial in cocaine abusers was performed with five sessions of tDCS to the left cathodal/right anodal DLPFC *vs* sham (Batista *et al*, 2015). The results showed that craving for cocaine was significantly reduced in the tDCS group after treatment when compared with sham.

*Cannabis*. One study has looked at tDCS in chronic marijuana smokers comparing: (i) sham; (ii) left anodal/right cathodal tDCS of the DLPFC; and (iii) right anodal/left cathodal tDCS of the DLPFC (Boggio *et al*, 2010). Craving for marijuana was assessed in addition to risk taking with a task. The results showed that sham was associated with less risky choices compared with the active tDCS but that craving for marijuana was reduced after right anodal/left cathodal DLPFC stimulation compared with sham stimulation.

*Considerations*. Taken together, the studies investigating the effect of tDCS on substance use disorders are unclear. The studies using craving as an outcome measure are split, with some studies showing an effect while others do not. In addition, whereas tDCS at the anode is thought to increase excitability, while the cathode is inhibitory, many of these studies show the same effect with the anode and cathode switched.

Only three studies measured actual drug or alcohol intake, and these did not show a beneficial effect. One of these investigated alcohol intake, and reported a trend toward greater relapse in the active tDCS group. The other two studies investigated cigarette smoking, and found a decrease in smoking based on the subjects' self-report (smoking diary). However, when objective measures were used (one study, breath carbon monoxide), no effect was seen from active tDCS over sham.

An issue with both tDCS and TMS in treating psychiatric disorders is that of reliability and reproducibility. As described above, many of the studies in addiction include small numbers of subjects, and use different methods with varying outcome measures. However, it should be noted that this process is similar to that establishing rTMS as a treatment for depression (George *et al*, 2009). The early studies in depression consisted of investigator-initiated studies with small numbers of subjects and variations in methodology, which eventually led to a consensus on rTMS and depression (George *et al*, 2009).

## DEEP BRAIN STIMULATION (DBS)

Deep brain stimulation (DBS) is a surgical procedure where bipolar electrodes are placed into specific brain regions and stimulated through implanted pulse generators. Stimulation parameters are programmable and depend on targeted brain region, disorder, and patient response. Stimulation induces an electric field up to 1 cm depending on specific neural tissue density (Hardesty and Sackeim, 2007). The mechanism of action is somewhat unclear as stimulation has variable actions on cellular physiology; each neural process may be depolarized or hyperpolarized depending on distance from the electrode (McIntyre *et al*, 2004). In addition, many stimulation variables including brain region, frequency, intensity, and state of neuronal synchronization can influence the direction and duration of its effects on neuronal activity. Although the specific neuronal effect of DBS remain largely debated, it is likely that DBS acts through multiple concurrent mechanisms (reviewed by (Herrington *et al*, 2016)). Macroscopic theories based on clinical data posit that HF stimulation results in an ablative effect of synchronized neural circuits, but a stimulatory effect in unsynchronized neural circuits (Murrow, 2014).

### DBS Studies in Addiction

DBS is currently in use in humans for some neurologic and psychiatric disorders. DBS has not been used extensively in addiction, but there are some preliminary studies. In humans, previous case studies in which patients received DBS for other indications, such as anxiety or mood disorders, have reported that stimulation to the ventral striatum/nucleus accumbens reduced the consumption of substances of abuse, such as alcohol, nicotine, and heroin (Kravitz *et al*, 2015). There have been some studies and case reports evaluating DBS in addictive disorders (summarized in Table 3).

*Alcohol*. Small studies have been conducted specifically using DBS to treat refractory alcohol dependence. Five severe alcohol dependent subjects have been reported in the literature, where bilateral DBS was performed to the ventral striatum (nucleus accumbens) (Muller *et al*, 2009; Heldmann *et al*, 2012; Voges *et al*, 2013). These studies showed that all subjects experienced a reduction in craving and two achieved complete abstinent from alcohol. In another case report of one subject, similar results were reported where the subject improved error processing on cognitive testing and reduced addictive behaviors (Kuhn *et al*, 2011).

**Table 3** Deep Brain Stimulation (DBS)

| Drug | Treatments | *n* | Target | Stimulation | Outcome measures | Effect | Citation |
|---|---|---|---|---|---|---|---|
| Nicotine | Chronic for other disorders | 10 | B VS | Range: 130–145 Hz; 90–180 μs, 3–6.5 V | Cessation | 3/10 | Kuhn *et al*, 2009 |
| Alcohol | Chronic | 5 | B VS | 130 Hz; 90 μS, 4.5 V | Craving<br>Abstinence | ↓<br>2/5 | Voges *et al*, 2013 |
| | Chronic | 1 | B VS | 130 Hz; 120 μS, 5.5 V | Alcohol consumption<br>Cognitive control | ↓<br>↓ | Kuhn *et al*, 2011 |
| Heroin | Chronic | 2 | B VS | Range: 130–140 Hz; 90, 120 μs; 0–5 V | Drug use<br>Anxiety/Depressive sympt | ↓<br>↓ | Kuhn *et al*, 2014 |

Abbreviations: L, left; R, right; B, bilateral; VS, ventral striatum.

*Heroin*. A case report of two heroin-dependent subjects who received bilateral DBS to the ventral striatum reported that the subjects experienced an improvement in depressive symptoms and anxiety, and a reduction, though not cessation, in their drug use (Kuhn *et al*, 2014). This group also reported that 3 of 10 nicotine-dependent subjects who had received DBS to the ventral striatum for the treatment of other disorders were able to quit smoking despite previous failed attempts (Kuhn *et al*, 2009).

Preclinical work has supported the use of DBS in addictive behaviors. Studies in rodents have shown that brain stimulation of the NAc reduces alcohol self-administration, morphine seeking, and cocaine-seeking and relapse-like behavior (Liu *et al*, 2008; Vassoler *et al*, 2008; Knapp *et al*, 2009; Henderson *et al*, 2010; Vassoler *et al*, 2013; Wilden *et al*, 2014) (further reviewed in (Luigjes *et al*, 2012) and summarized in Table 4). These studies have also shown effects on addictive behaviors when the prefrontal cortex, lateral hypothalamus, subthalamic nucleus, and lateral habenula have been targeted (Levy *et al*, 2007; Friedman *et al*, 2010; Rouaud *et al*, 2010). A major limitation of these studies are that the electrode and brain structures are difficult to scale from human to rodent, which makes it surprising that nonhuman primate studies have not been attempted.

*Considerations*. The data using DBS in addiction are limited, and shows uneven results, with some subjects, but not the majority, reducing or stopping their addictive behaviors. However, these studies are small, and owing to invasive nature, the implantation of stimulation devices is only performed in the most refractory of patients. Preclinical work supports the use of DBS in modulating addictive behaviors and provides a chance to better understand its therapeutic mechanisms.

### Comparison of Stimulation Techniques

Currently, there are no existing clinical or preclinical studies that directly compare the effectiveness of brain stimulation methods; however, it is clear that each method has practical advantages and disadvantages. For instance, there are many brain regions implicated in addiction such as the nucleus accumbens and amygdala that are not accessible to direct stimulation from tDCS or rTMS (Figure 1). It is also unknown whether continuous stimulation, not yet feasible with rTMS, would be required to achieve a long-term therapeutic effect. Finally, it is unclear whether focal stimulation as provided by DBS is more effective than widespread stimulation by rTMS. In practice, these questions may be answered on an individual basis where noninvasive stimulation therapies like rTMS and tDCS would be initially attempted and that if there is no response, DBS could be a last resort step to treat addictive disorders in resistant patients.

## TARGETING PLASTIC MECHANISMS IN ADDICTION

The progression to addiction is thought to be driven by maladaptive changes in the neural circuitry of reward learning and response inhibition (Kelley, 2004). Such changes have been identified in animal models and occur as a result of the repeated pharmacological effects of abused substances in the context of drug administration (Luscher, 2013). It is believed that chronic, excessive drug use causes an overlearning of the environmental and internal cues associated with drug use as compared with natural rewards (Di Chiara and Imperato, 1988; Hyman *et al*, 2006). Additional studies have shown that the cortical circuitry that regulates behavioral flexibility and the inhibition of drug-seeking behavior can undergo adaptations as well (Kalivas *et al*, 2005; Everitt, 2014). The motivation for drugs following extended drug exposure is believed to driven by a shift from positive to negative reinforcement (Koob and Le Moal, 1997) and as a result, drug-associated cues become increasingly salient and can drive drug-seeking behaviors despite negative consequences (Schultz, 2011). The potentiation of drug reward systems and an attenuation of brain systems underlying response inhibition are thought to be mediated by long-term changes in synaptic plasticity and intrinsic excitability of neurons (Kauer and Malenka, 2007; Stuber *et al*, 2010; Kourrich *et al*, 2015).

If addictive disorders are mediated by adaptations that are truly plastic, then it should be possible to reverse them if affected circuits can be correctly identified and targeted. Evidence from animal models suggests this may be possible. Physiological measurements of synaptic strengthening including long-term potentiation and its surrogate, an increase in glutamate receptor AMPA/NMDA receptor ratio can be induced in the rodent ventral tegmental area by acute exposures to many drugs of abuse including cocaine, alcohol, nicotine, morphine, and benzodiazepines indicating

**Table 4** DBS in Animal Models

| Drug | Treatment | Species | *n* | Target | Stimulation | Behavioral model | Effect | Citation |
|---|---|---|---|---|---|---|---|---|
| Alcohol | DBS, during session | LE Rat | 4 | NAc shell | 160 Hz; 200 μS; 150 μA | 2BC EtOH consumption (30 min.) | ↓ | Knapp *et al*, 2009 |
| | | | 5 | NAc core | | 2BC EtOH consumption (30 min.) | ↓ | |
| | DBS, 1 h during session | P Rat | 9 | NAc shell | 140–150 Hz; 60 μS; 200 μA | 2BC EtOH consumption (1 h) | No Effect | Henderson *et al*, 2010 |
| | 24 h doing session | | 6 | NAc shell | | 2BC EtOH preference (1 h) | ↓ | |
| | | | | | | 2BC EtOH consumption (24 h) | ↓ | |
| | | | | | | 2BC EtOH preference (24 h) | ↓ | |
| | DBS, during session | P Rat | 4 | NAc shell | 150 Hz; 100 μS; 200 μA | 2BC EtOH consumption (1 h.) | ↓ | Wilden *et al*, 2014 |
| Cocaine | DBS, during session | SD Rat | 14 | LH | 20–100 Hz; 100 μS; 200–400 μA | Seeking i.v. cocaine | ↓ | Levy *et al*, 2007 |
| | | | 9 | mPFC | | PR i.v. cocaine | No effect | |
| | | | 7 | | | Seeking, PR sucrose | No effect | |
| | | | 8 | | | Seeking i.v. cocaine | ↓ | |
| | | | 8 | | | PR i.v. cocaine | ↓ | |
| | | | 7 | | | Seeking, PR sucrose | No effect | |
| | DBS, during session | SD Rat | 7 | NAc shell | 160 Hz; 60 μS; 150 μA | Priming induced reinstatement | ↓ | Vassoler *et al*, 2008 |
| | | | 8 | DS | | Priming induced reinstatement | No effect | |
| | | | 8 | | | Food seeking | No effect | |
| | DBS, during session | LE Rat | 9 | STN | 130 Hz; 60 μS; 50–130 μA | SA, PR i.v. cocaine | ↓ | Rouaud *et al*, 2010 |
| | | | 14 | STN | | SA, PR food | ↑ | |
| | DBS, 15 min during session | SD Rat | 10 | R LHb | Low: 10 Hz;; 200 μA | SA cocaine | ↑ | Friedman *et al*, 2010 |
| | | | 12 | | High: 100 Hz; 200 μA | SA cocaine | No effect | |
| | | | 30 | | Combined High and Low | SA cocaine, Extinction, Reinstatement | ↓ | |
| | DBS, during session | SD Rat | 5 | NAc shell | 160 Hz; 60 μS; 150 μA | Cocaine Reinstatement | ↓ | Vassoler *et al*, 2013 |
| | | | 8 | NAc core | | | No effect | |
| | DBS, during session | Mouse | 7 | NAc shell | 130 Hz; 90 μS; 50 μA | Locomotor sensitization | ↓ | Creed *et al*, 2015 |
| | DBS, 1, 7 days prior to session | | 7 | NAc core | 2–130 Hz; 90 μS; 50 μA | Locomotor sensitization | No effect | |
| | | | 4–6 | mPFC | 2–130 Hz; 90 μS; 50 μA | Locomotor sensitization | No effect | |
| | | | 8, 12 | NAc shell | 12 Hz; 90 μS; 50 μA w/ D1 antagonist | Locomotor sensitization | ↓ | |
| Morphine | DBS, intermittent | SD Rat | 10 | L NAc core | Range: 130 Hz; 210 μs; 200–500 μA | CPP | ↓ | Liu *et al*, 2008 |

Abbreviations: L, Left, R, right, LE, Long–Evans; P, alcohol preferring; SD, Sprague-Dawley; LH, lateral hypothalamus; LHb, lateral habenula; NAc, nucleus accumbens; mPFC, medial prefrontal cortex; STN, subthalamic nucleus; 2BC, 2-bottle choice; EtOH, ethanol; i.v., intravenous; i.p., intraperitoneal; PR, progressive ratio; CPP, conditioned place preference.

common neural substrates (Ungless *et al*, 2001; Saal *et al*, 2003; Tan *et al*, 2010). Long-term glutamatergic adaptations can be observed in the NAc following chronic cocaine, alcohol, and nicotine exposure (Mameli *et al*, 2009; Gipson *et al*, 2013; Wang *et al*, 2015). Behavioral data from drug-exposed mice has further supported a role of glutamate neurotransmission in the NAc in addictive behaviors. For example, cue-induced seeking of nicotine, cocaine, and alcohol can be blocked by genetic and pharmacological inhibition of glutamate receptors in the NAc (Anderson *et al*, 2008; Conrad *et al*, 2008; Schroeder *et al*, 2008; Gipson *et al*, 2013). Intriguingly, increased AMPA/NMDA ratio in VTA and NAc neurons observed during withdrawal from cocaine can be reversed through the induction of metabotropic glutamate receptor-long-term depression which results in a redistribution of AMPAR subunits in the synapse (Mameli *et al*, 2007; Creed *et al*, 2015). The ability to block or reverse potentiated circuitry that regulates addictive behaviors demonstrates the therapeutic potential of targeting plastic mechanisms in addiction.

In recent years, emerging strategies like optogenetics that can bi-directionally modulate specifically targeted neural circuits have advanced our understanding of the circuits underlying addictive behaviors (Aston-Jones and Deisseroth, 2013). These techniques have also demonstrated the potential to reverse drug-induced neuroadaptations and subsequent drug-seeking behavior. For instance, Chen *et al* (2013) demonstrated that the intrinsic excitability of the prefrontal cortex in compulsive drug-seeking animals is profoundly reduced, and that this effect could be reversed with optogenetic stimulation of prelimbic neurons. Similarly, Pascoli *et al* showed that increased AMPA/NMDA ratio in the NAc that underlies cocaine sensitization can be reversed by low-frequency optogenetic stimulation of corticostriatal circuitry through a depotentiation of cortical inputs on NAc neurons (Pascoli *et al*, 2012; Pascoli *et al*, 2014). As optogenetics is not available for human use, recent work has focused on the use of DBS to mimic the effects of optogenetic manipulation, and a recent study showed that LF DBS, in the presence of a dopamine receptor 1 antagonist, reversed the cocaine-induced physiological changes in NAc neurons and blocked locomotor sensitization 1 week after treatment (Creed *et al*, 2015). These data highlight the translatable potential of findings from emerging technologies like optogenetics into stimulation therapies as well as the capability to combine pharmacological treatment with brain stimulation to reverse drug-induced plasticity and addictive behavior (Luscher *et al*, 2015).

In summary, brain stimulation modalities are being explored as treatments for addiction as pharmacological treatments have not been as successful as previously hoped. Whereas brain stimulation techniques have proven to be effective in treating a variety of neurological and psychiatric disorders, there are few randomized controlled clinical

trials in addiction. The studies described above indicate that brain stimulation, may have an effect on craving, but more studies that measure drug or alcohol intake are needed. Furthermore, optimization of stimulation strategies based on the known biology of the disorder will help realize the potential of stimulation therapies for addictive disorders.

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