DRUG & ALCOHOL FINDINGS *Review analysis*

This entry is our analysis of a review or synthesis of research findings considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original review was not published by Findings; click Title to order a copy. Free reprints may be available from the authors – click prepared e-mail. The summary conveys the findings and views expressed in the review. Below is a commentary from Drug and Alcohol Findings.





## A review of brain stimulation methods to treat substance use disorders.

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*Already used to treat various neurological and psychiatric disorders, a review investigates the utility of brain stimulation techniques for drug and alcohol problems.*

**SUMMARY** While different types of treatments are available for substance use disorders, recovery can be a long process involving set-backs and relapses, and existing treatments may not be effective for all patients. Among other things, this suggests a need for further research to develop novel and more effective treatments.

Brain stimulation (or 'neuromodulation') techniques such as repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation have been investigated as possible treatments for substance use disorders and, research shows, may have promise in comparison to conventional pharmacotherapy and behavioural interventions (1 2 3). The purpose of the featured review was to provide a broad and critical review of currently available brain stimulation techniques as treatments for substance use disorders, including a comparison of the magnitude of effect (the 'effect size') across different diagnoses.

**Key points**
**From summary and commentary**

While several types of pharmacological and behavioural interventions are available for substance use disorders, these may not be effective for all patients. The featured review investigated the therapeutic potential of brain stimulation techniques as a novel and emerging way to treat drug and alcohol problems.

The results revealed that short-term treatment with repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) may be beneficial for drug craving and consumption.

With research still in its infancy, future studies should focus on extending the therapeutic benefits by increasing the frequency of stimulation and duration of treatment.

### Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method used to treat various neurological and psychiatric disorders, including Parkinson's disease, schizophrenia, obsessive compulsive disorder, and chronic pain. It involves the use of an electromagnetic coil held against the scalp, producing repetitive trains of magnetic pulses, resulting in a temporary magnetic field pulse in the coil that can be targeted to specific brain regions (1 2). Studies have demonstrated its ability to produce clinically significant and lasting changes in targeted brain regions (1 2).

This treatment method has minor side effects (ie, headache, dizziness) and is pain free, making it well-tolerated by most patients. Additionally, rTMS is a cost-effective alternative to other more expensive treatment methods such as electroconvulsive therapy. Research into the applicability of rTMS to substance use disorders is in its preliminary stages. Twenty-eight studies were identified for this review, all using rTMS as a potential treatment for substance use disorders, with a total of 788 participants randomly allocated to active rTMS treatment or 'sham' rTMS treatment – sham treatment involving clinicians going through the same motions as they would for delivering rTMS, but without actually following through with the treatment.

### Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is another non-invasive brain stimulation method involving two or more electrodes being placed on the scalp, which deliver a low-intensity direct current at a constant rate to a targeted area of the brain. It is a low-cost and pain-free stimulation method with minor side effects (such as scalp irritation and itchiness) and no requirement for recovery time, making it a well-tolerated treatment. Similar to rTMS, tDCS has been used to treat various neurological and psychiatric conditions such as Parkinson's disease, chronic pain, and clinical depression.

The review identified 23 studies in which tDCS was explored as a treatment option for substance use disorders, with 677 participants exposed to tDCS or 'sham' stimulation.

### Deep brain stimulation

Deep brain stimulation (DBS) has been used to treat disorders such as Alzheimer's disease, obsessive-compulsive disorder, and chronic pain. Unlike rTMS and tDCS, DBS involves a surgical procedure, where varying numbers of electrodes are implanted directly into the brain.

Due to its invasive nature, DBS may cause serious side effects such as infection, seizure, and stroke. However, once a patient has recovered from the original surgical procedure, DBS seems to be well-tolerated.

The exact mechanisms by which DBS exerts its clinical effects remain unclear, though the ability of DBS to directly manipulate neural circuits in reward pathways may target addictive behaviours. Nine studies investigating the use of DBS as treatment for substance use disorders were identified, with 25 participants randomised to receive active or 'sham' stimulation.

## Main findings

With respect to the effects of brain stimulation, there were commonalities between rTMS and tDCS:
• Studies of rTMS had promising findings, showing a significant effect in the majority of studies on craving and/or consumption among participants dependent on nicotine (10/11 studies), stimulants such as cocaine and methamphetamine (5/7 studies), and alcohol (6/9 studies).
• The magnitude of the effect of rTMS on measures of alcohol, nicotine, methamphetamine, and cocaine dependence was promising but highly variable, consistent with the methodological diversity of published studies.
• tDCS demonstrated comparable efficacy to rTMS in the treatment of nicotine (5/8 studies), stimulants (3/6 studies), and alcohol dependence (5/7 studies). The magnitude of the effect on cocaine was highly variable. Large effect sizes were observed in one study of opioids and one study of cannabis, and one study recorded a small effect size for methamphetamine.

There were positive results across all nine studies of DBS, which tested the technique among samples of people dependent on alcohol, nicotine, stimulants, and opioids. However, determining the effect of the intervention was limited by small sample sizes (1–10 participants, averaging 3.3 participants per study), and findings being limited to 'case series', a type of medical research method without a control group whereby individuals receiving the same intervention are observed before and after an intervention.

Presented below by type of treatment and type of substance (not including nicotine), the findings summarise Tables 1, 2 and 3 in the featured paper.

### Repetitive transcranial magnetic stimulation

**Alcohol.** Five studies found a significant reduction in craving, and two studies found a significant reduction in consumption. Of the two studies that examined both consumption and craving, in one there was a significant reduction in alcohol consumption, but no significant difference in craving, and in the other there was a significant decrease in both craving and consumption.

**Cocaine.** Three studies found a significant reduction in cocaine craving, while the remaining study found no significant change in craving.

**Methamphetamine.** Two out of three studies investigating effects on methamphetamine dependence found a significant reduction in cue-induced craving. Another study found that the treatment actually increased self-reported craving.

**Cannabis.** A single study found no significant reduction in craving.

### Transcranial direct current stimulation

**Alcohol.** Four studies found a significant decrease in craving, and another three found no significant difference between the treatment and control groups in term of craving. In one where craving was positively impacted, there was conversely a significant increase in the rate of relapse.

**Cocaine.** Two studies found that the treatment significantly decreased craving, and in one study this was maintained after exposure to cocaine cues (the other study did not measure that outcome).

**Methamphetamine.** A single study found a significant reduction in acute craving, however, there was an increase in cue-induced craving 20 minutes after treatment.

**Opioids.** A single study found a significant decline in heroin craving which was maintained in the presence of heroin-related cues.

**Cannabis.** A single study found a significant reduction in cannabis-related craving.

### Deep brain stimulation

[*The statistical significance of the findings was not reported because all studies were case reports involving as few as one patient and as many as five.]*

**Alcohol.** One study found that two patients remained abstinent one year later, while the other patient decreased their number of drinking days.

**Cocaine.** In one patient, a decrease in craving and consumption was observed.

**Opioids.** One study found a decrease in heroin use, another a decrease in desire to use and consumption, and in the third, the patient became abstinent for five years without relapse.

## The authors' conclusions

Findings were mixed across all three types of brain stimulation method, which may be accounted for at least in part by variation in the parameters of the methods (ie, frequency, intensity, duration of treatment, brain regions stimulated), target substances, as well as diversity in the study samples, including the presence of co-occurring psychiatric disorders.

The use of brain stimulation techniques may be a promising treatment option for people with substance use disorders. However, there is a need for further research in this emerging field.

FINDINGS **COMMENTARY** Neuromodulation techniques such as repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation target unwanted nervous system responses (free version of paper available). In respect of people with substance use disorders, the scientific interest is in whether these techniques would be effective at targeting responses to external and internal stimuli such as craving and impulsivity, and ultimately whether the treatments impact consumption. In the featured review very few studies measured consumption, opting instead for craving as a primary outcome in 21 of 39 studies on alcohol and illicit drugs, and craving as a secondary outcome in 12 studies (including in two studies where the primary outcome was craving and the secondary outcomes were cue-induced craving and craving after additional sessions of treatment). Consumption was a primary outcome in only four studies and a secondary outcome in two. In addition, abstinence was the primary measure in two

studies.

In the roughly two thirds of studies examining the effect on craving, there was a significant decrease in groups receiving the treatment compared with control groups. In two studies a statistically significant positive effect was observed on consumption. Overall, this does not constitute strong evidence of the utility of brain stimulation techniques for drug and alcohol problems. However, the application of this family of treatments to substance use disorders is admittedly in its infancy.

Two out of three of the methods studied were compared with 'sham' treatments – a form of control group whereby clinicians take patients through the same motions as they would if they were delivering the treatment (in this case brain stimulation), but without actually following through with the treatment. Understandably, this would not be possible to act out with deep brain stimulation, which involves an invasive surgical procedure where electrodes are implanted directly into the brain.

The argument for conducting so-called sham-controlled trials is that the performance of 'doing' the treatment may be an active ingredient – exerting an effect – and should be isolated from the effect of the treatment itself. However, critics have argued that until the efficacy of a given procedure is established, it doesn't make sense to examine which aspects of a procedure are responsible for its benefit:

> *"The idea that controlling for the placebo effect is necessary for a quality efficacy study is, in part, based on outdated concepts that psychological factors are generic and non-unique. This has never been proven and, in fact, more recent studies are suggesting the contrary. Therefore, it is of no benefit in efficacy trials to try to control for any effects that can potentially only be achieved through the particular procedure being examined.*

Among the full range of brain stimulation treatments, the most notorious is electroconvulsive therapy, described by the mental health charity Mind as a treatment which "involves sending an electric current through your brain, causing a brief surge of electrical activity within your brain (also known as a seizure)". This method was not included in the featured review, however, it is possible that it could colour people's perceptions of brain stimulation techniques in general. The controversy surrounding electroconvulsive therapy largely comes from the abuse and misuse of it in the past (1 2), embedded in the public consciousness through films such as *One Flew Over the Cuckoo's Nest* and *Girl, Interrupted*:

> *"Many depictions of [electroconvulsivetherapy] in film and television have portrayed the therapy as an abusive form of control. Most famous is the film 'One Flew Over the Cuckoo's Nest,' in which an unruly patient is subjected to the procedure as a punishment. There is probably no fictional story that so haunts our consciousness of a medical treatment."*

Electroconvulsive therapy is now only approved for use in certain circumstances, not including for treatment of substance use problems, and only if all other options have been considered.

As with the application of invasive and non-invasive brain stimulation techniques to other medical problems, there are ethical considerations beyond whether they are efficacious for substance use problems. Explored in the context of eating disorders, these considerations include:
• The avoidance of side effects: While the risks associated with participating in certain brain stimulation techniques may be low, the lack of evidence for their long-term effects and efficacy makes the risk–benefit ratio difficult to assess. Issues of safety also need to be balanced with the desire to help a group of patients not helped by other methods.
• Respect for the autonomy of patients: Protecting the informed consent process of patients is a key way of demonstrating respect for their autonomy. However, this is not always straightforward. In cases where brain stimulation methods are seen as a 'last resort' for patients who do not respond to other treatments, patients may be "desperate" for a solution, and as such be "overly motivated" to participate in exploratory research or treatments and expose themselves to risks. Whether patients can fully understand the nature of interventions and implications of participation in this context becomes an important consideration.
• Respect for the authenticity of patients: Where the medical problem is seen as part of the patient's identity or core to their sense of self, or the treatment goes against their worldview, patients may resist treatment on the grounds that it threatens their authenticity. An ethical approach to treatment requires respecting patients' concerns with authenticity, while understanding that these views can change over time, and the need to jointly determine treatment goals.

Synthesising a body of literature about the effect of brain stimulation techniques on drug and alcohol dependence, the featured review assumed a neurophysiological or biological underpinning of addiction and recovery (known as the 'brain disease model'), and as such was predicated on a highly contested view of the nature of addiction. One of the implications for framing acute drug and alcohol problems in this way is that it "may help to moderate some of the moral judgment attached to addictive behaviors and foster more scientific and public health-oriented approaches to prevention and treatment". However, it should not preclude the discussion of genetic, environmental, developmental, and social factors that render some people vulnerable to developing and continuing to live with drug and alcohol problems, including family history, early exposure to drug use, and exposure to high-risk environments.

*Thanks for their comments on this entry in draft to Dr Avinash De Sousa, consultant psychiatrist and psychotherapist. Commentators bear no responsibility for the text including the interpretations and any remaining errors.*

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