

Transcranial Electrical Neurostimulation as a Potential Addiction Treatment

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Joshua W. Brown, PhD¹ 

Abstract

Addiction remains difficult to treat, but non-invasive transcranial electrical and magnetic neurostimulation methods may provide promising and cost-effective treatment approaches. We provide a narrative review of recent developments and evidence of effectiveness and consider newer technology that may yield improved treatment approaches. In particular, we review temporal interference electrical neurostimulation, which allows non-invasive and focal stimulation of deep brain regions. This provides a promising new potential approach to treat addiction, because many of the brain regions that seem most important for addiction are deeper in the brain, out of reach of existing technologies such as transcranial direct current stimulation.

Keywords

addiction, transcranial electrical neurostimulation, deep brain stimulation, electroceuticals, temporal interference neural stimulation

What do we already know about this topic?

Deep brain regions such as the nucleus accumbens and insula are key to addiction, but non-invasive stimulation of the deep brain regions has been infeasible because existing technologies do not reach these deeper regions well.

How does your research contribute to the field?

We are investigating a new method of non-invasive deep brain stimulation, called temporal interference electrical neurostimulation (TINS), which holds promise to reach deep brain regions and may provide more effective treatment of addiction.

What are your research's implications toward theory, practice, or policy?

Temporal interference electrical neurostimulation may disrupt drug cravings, and if this can be demonstrated, it may be possible to mass-produce inexpensive devices that could be worn by individuals to reduce cravings.

Introduction

Drug dependence remains difficult to treat, with over 37 million in the US using illicit drugs in the last 30 days, and over 70 000 drug overdose deaths annually in the US.¹ While a number of medical treatments are available, there is an urgent need for more effective new treatments. One promising approach involves electrical neurostimulation as a means of disrupting addiction, or so-called electroceuticals as an alternative or adjuvant to behavioral and pharmacological interventions.² Electrical neurostimulation has recently been explored as a way to treat addiction. One novel device, the Bridge, has been used to minimize opioid withdrawal effects, though the stimulation is

applied to the ear, and it is unclear how it may act on the central nervous system.³ If it were possible to disrupt brain regions that underlie craving and compulsive drug use, that could provide a more effective approach.

¹Indiana University, Bloomington, IN, USA

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Corresponding Author:

Joshua W. Brown, Department of Psychological & Brain Sciences, Indiana University, 1101 E Tenth St, Bloomington, IN 47405, USA.
Email: jwmbrown@indiana.edu



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The question then becomes what brain regions, if disrupted, would provide the best treatment for addiction? Some clues in this regard come from a number of case reports in humans describing complete, permanent, and near effortless disruption of substance use disorders (SUDs). This disruption was due to direct effects on specific brain regions and circuits known to be involved in the addiction process, such as the insula, the nucleus accumbens (NAcc), the dorsolateral prefrontal cortex (DLPFC), and the amygdala.⁴ For instance, smokers have spontaneously lost all interest in cigarettes following stroke damage to the bilateral anterior insula (AI).⁵ More recent work suggests that damage to any of a larger set of brain areas which share functional connectivity with the anterior insula may also yield a loss of addiction.⁶ Similarly, Müller et al describes cases of permanent remission of alcoholism due to deep brain stimulation of the NAcc after years of 2+ liters per day of hard liquor consumption.⁷ Zhou et al report a patient who used over 1000 mg/day of heroine for over 5 years and smoked over 40 cigarettes per day. After deep brain stimulation of the bilateral NAcc, he stopped using heroine completely with no relapse during his 6-year follow-up, and he reduced his cigarette consumption to 10 per day.⁸ This has recently been extended to a series of patients across several studies.^{9,10} Other case series describe similar dramatic reductions in smoking and alcohol dependence subsequent to NAcc stimulation.¹¹⁻¹³ The amygdala also seems to play a key role in addiction relapse. In particular, error-related activation of the amygdala is greater in subjects who are more likely to fail treatment for addiction.¹⁴

The function of these brain regions has been studied extensively. The AI assists with predictions of future affective bodily states, such as satiety, pain, and craving.¹⁵ Given these findings, it is likely that the AI represents internal affective states related to drug use, such as craving, drug reward, withdrawal, adverse health effects, successful self-control and abstinence, and the anticipation of each of these states. The NAcc is associated with reward and craving, and activation may be associated with positive arousal,¹⁶ perhaps providing a visceral reward that would otherwise be sought from drugs. Thus, methods that disrupt the insula and/or activate the NAcc in particular are promising targets for treating addiction.

The potential to stimulate these brain regions non-invasively would be a boon, but current methods are mostly limited to superficial rather than deep brain areas.¹⁷ Existing non-invasive neurostimulation methods include transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial magnetic stimulation (TMS), and transcranial focused ultrasound (tFUS). The electrical methods tDCS and tACS involve passing direct electrical current or alternating current, respectively, through electrodes placed on the scalp. These methods have been used extensively for decades and involve simply applying a voltage through 2 or more electrodes placed on the scalp, such that the current is typically up to 2 mA. These methods, and especially tDCS, have been used to treat addiction

specifically.¹⁸ Some studies have also used tACS to treat addiction.¹⁹ However evidence is mixed,²⁰ and transcranial electrical stimulation is not as well established as pharmacotherapy for addiction,²¹ nor is there strong direct comparisons between electrical and pharmacological intervention.

Another potential promising method is tFUS, which involves passing ultrasound through the skull and directly into the brain. The mechanism by which it could activate neurons remains somewhat unclear, but it may work by mechanically activating ion channels, or by changing membrane capacitance.²² There is some evidence that tFUS may activate neurons in human cortex,²³ but no studies have yet investigated potential effects on addiction. Furthermore, it is challenging to focus ultrasound stimulation on deep brain regions without stimulating the overlying superficial regions, and this presents a challenge given that a number of brain regions relevant to addiction are deeper in the brain. Nevertheless, tFUS is currently being investigated as a means to treat obsessive-compulsive disorder, depression, and addiction, with modest preliminary results.²⁴

While invasive deep brain stimulation of the NAcc seems promising, it requires neurosurgery and thus presents a high bar for treatment. It would be even better if it were possible to stimulate deep regions such as the NAcc, but non-invasively. The existing methods of tDCS, tACS, and tFUS all have a common shortcoming. They are well-suited to stimulating areas toward the outside of the brain, adjacent the scalp, but they do not reach deeper areas as effectively. Increasing the stimulation intensity to reach deeper areas would necessarily involve even higher intensity stimulation in more superficial areas which could in turn cause unwanted side effects. This presents a conundrum—these existing methods do not reach well to the deeper regions that are most relevant to addiction, especially the NAcc and AI.

Fortunately, there is a new non-invasive technology that appears capable of stimulating deep regions without stimulating the superficial regions, and which involves only electrical stimulation, thus rendering it relatively less expensive than magnetic or ultrasound approaches. It is called Temporal Interference electrical Neural Stimulation (TINS), or TI for short.

Temporal Interference Electrical Neurostimulation—Theory

TI is able to stimulate deep regions of the brain, crucially without stimulating the overlying cortical areas. Grossman et al describe the approach,²⁵ which involves 2 pairs of electrodes. Each electrode pair delivers pure sinewave alternating current at slightly different frequencies. The currents are typically delivered near or above 1500 Hz. Alternating currents of this frequency are less likely by themselves to stimulate neurons, because the cell membrane acts as a low-pass filter, and it dampens the effect of the high frequency current much like

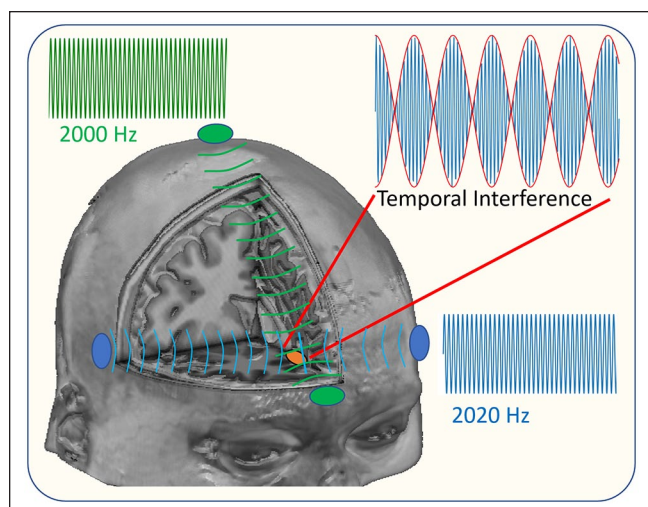


Figure 1. Temporal interference electrical neurostimulation. Two sinusoidal alternating currents of slightly different high frequencies are applied via 2 pairs of electrodes. Where the fields overlap, a lower beat frequency occurs and may stimulate neural activity.

how shock absorbers on a car smooth out sudden bumps in the road. However, when 2 alternating currents of slightly different frequencies are applied (Figure 1), the region where the currents overlap will show that the currents add to produce an electrical field whose magnitude varies at a much lower frequency, equal to the difference of the 2 frequencies. This difference of frequencies is also called the beat frequency. Intuitively, the same principle applies when plucking 2 guitar strings that are slightly out of tune with each other, and one can hear a low frequency “beat” as the strings move alternately in phase and out of phase. For an example of TI, suppose there are 2 electrical currents of 2000 and 2020 Hz. Where the electrical fields produced by the currents overlap, there will be a low frequency modulation at 20 Hz, that is, the difference between the 2 frequencies. This low frequency modulation appears able to stimulate neural activity.

The net result is that it is possible to stimulate areas deep in the brain without stimulating the overlying cortical areas. This is because if the electrodes are placed properly, the 2 currents will only overlap in a region deep in the brain. Thus, the deep region will be stimulated, but the more superficial areas adjacent the electrodes will not be stimulated, because only one high frequency current is present.

How might temporal interference patterns lead to neural activation? Cao et al investigated biophysical simulations of model neurons, in particular with Hodgkin-Huxley models as well as integrate-and-fire models and the Fitzhugh-Nagumo model. These are mathematical models of electrochemical processes associated with action potential signaling in neurons. They found that the rapid rise in the stimulation with the onset of each beat frequency cycle was sufficient to open the modeled fast voltage-gated sodium

channels, which causes the neurons to fire.²⁶ More recent work similarly suggests that nonlinearities in the ion channel responses allow the TI beat frequency to activate neurons.²⁷ These findings provide a preliminary biophysical basis for understanding how TI may cause neural activation non-invasively in deep regions.

Temporal Interference Effects

There is evidence in rodents that TI stimulation can increase neural activity. Grossman carried out a series of studies in rodents, showing that TI seemed to cause neural activation (as evidenced from histological examination), and they also found no evidence of damage to the cells. This suggests that TI may be able to activate neurons without damaging them, at least in rodents.^{25,28} A more recent study tested whether TI can cause behavioral effects. In rodents, TI with a 3 kHz carrier frequency at 350 microA per electrode pair over the sciatic nerve can elicit hindpaw dorsiflexion.²⁹ Moreover, the frequency of the dorsiflexion response matched the beat frequency of the TI stimulation. For example, when the beat frequency was 1 Hz, the hindpaw twitched at 1 Hz. This is consistent with earlier work,²⁶ which predicted that neural activity would follow the rising edge of the beat frequency envelope. This has implications more broadly for clinical interventions, as it suggests that the frequency of neural activation, in terms of burst activity if not individual action potentials, will be equal to the beat frequency of the TI stimulation.

The most recent work on TI has investigated potential clinical applications. One study investigated the possibility of using TI to reduce epileptiform activity in rodents. Specifically, the investigators first applied rapid kindling, with electrodes placed in the hippocampus, in mice to induce epilepsy. They then applied TI with a 130 Hz beat frequency (1300 and 1430 Hz frequencies) to the medial temporal lobe. Of note, they used 100 μ s duration biphasic square pulses instead of pure sinewave alternating current. The results showed that TI reduced fast ripples, a marker of epileptiform activity in the hippocampus, by over 50%, suggesting that TI may provide a promising approach to disrupting epilepsy. In human cadavers, the investigators used the same frequencies to target the anterior hippocampus, with TI at 1 and 3 mA per channel applied to the scalp, and an intracranial electrode in the target region of the hippocampus to assess the actual applied voltage. They found that the TI envelope amplitude was 8 mV in the target region, while electrodes elsewhere within the brain did not find a TI modulated signal.³⁰ Conversely, another study showed that seizure-like activity can be evoked by TI in the mouse hippocampus.³¹ The same group also investigated TI in macaque monkeys and focused on the superior colliculus performing eye movement and fixation tasks, while simultaneously recording from cells in the superior colliculus. They reported preliminary results, although it remains to be seen exactly what effects will be found on behavior in animals.³²

The clearest effect of TI on human behavior to date is found in a study of memory. When TI was delivered to the hippocampus, the BOLD activation of the hippocampus was reduced during memory encoding, and prolonged TI stimulation of the hippocampus for 30 min yielded improved recall accuracy.³³ So far in humans, the only significant side effects of TI stimulation relative to sham are increased itching on the scalp.^{33,34} Another study showed that TI applied not to the brain but rather to the throat was able to improve sleep apnea symptoms on rodents and humans.³⁵ This was done on the hypoglossal nerve, which illustrates the potential usefulness of TI applied to the peripheral nervous system.

Temporal Interference Methods

One of the current challenges to advancing TI applications is figuring out where exactly to place the electrodes. This breaks down into 2 further questions, namely which brain region to target, and where to place the electrodes to target such regions.

A key requirement is the spatial accuracy so that specific brain regions can be targeted, as missing the target by even a small margin may reduce effectiveness or cause side effects. Such is the case for deep brain stimulation of the subthalamic nucleus to treat Parkinson's disease.³⁶ Still, it has not yet been determined exactly which regions to target for maximum effect, although the literature discussed above suggests that the NAcc, or ventromedial prefrontal cortex (vmPFC), or regions functionally connected with vmPFC, may be the best candidates. Once a brain region target is identified, electrode placement can be calculated by a set of finite element simulations. This requires extensive computing power to simulate the electrical properties of the head. The simulations become more complex as more possible electrode locations are considered, so there is a tradeoff between efficient calculations versus finer spatial resolution of the electrode locations. The simulations themselves can be carried out by software such as SimNIBS, Comsol, or sim4life. Furthermore, such software can calculate the TI fields given an assumed set of electrode locations, and often many such locations must be tried to find the best set. The locations to try can be standardized by considering EEG electrode locations in the 10/10 coordinate system which is commonly used for EEG. The computations for the candidate electrode locations can be simplified somewhat by taking advantage of the assumed linearity of electrical fields. This means that in practice, one can compute the electrical fields for a smaller set of individual electrode positions and then infer the effects of an arbitrary pair of electrodes by linearly superimposing the results from individual electrode simulations. This can save considerable computational expense.

As Grossman et al point out,²⁵ it is possible to fine tune the peak of stimulation by manipulating the relative current amplitudes between the 2 electrode pairs. For example, one pair might generate 2 mA, while another might generate

1.7 mA. The tradeoff is that the peak of the TI stimulation will be weaker when the currents are different from each other, as typically safety considerations will preclude applying more than a certain maximum current per channel. In ongoing TI studies, we have applied only up to 2 mA per electrode pair to human subjects.

The question of where to place the electrodes is further complicated by the fact that everyone's head is shaped slightly differently. One approach, which we have taken, is to start with an average head shape, as produced by standard atlases such as the MNI atlas. This will not produce a perfect set of electrode locations, but it may be very close and essentially good enough, such that a more individualized set of simulations would yield the same electrode locations in the 10/10 EEG coordinate system. Alternatively, one can acquire a structural MRI of an individual subject's head and then carry out the computations specifically for the individual.

Discussion

Going forward, there is a number of promising avenues to pursue. In terms of methods, some recent work has pioneered a modified approach in which more than 2 electrode pairs can be applied in order to increase the focus and strength of the TI stimulation.³² For example, 2 electrode pairs might provide stimulation at 2000 and 2100 Hz, thus providing a 100 Hz TI envelope, while another 2 electrode pairs might target the same brain region but at different scalp electrode locations, with frequencies of 3000 and 3100 Hz. This would result in 4 electrode pairs all targeting the same region with the same beat frequency, thus increasing the strength and focality of stimulation. Recent work has shown that this technique may work at least in the peripheral nervous system.³⁵

There are still many open questions regarding potential TI treatments for addiction. The first question is where to target. Ongoing work is aimed at studying the NAcc as a potential target of TI stimulation to treat addiction, and the same group aims at validating whether TI stimulation can elicit fMRI BOLD signal increases in the targeted NAcc region. There are other likely regions that might be targeted to treat addiction as well, including the dorsal anterior cingulate cortex and AI. A second question is what beat frequencies to use. Ongoing work to stimulate the NAcc currently uses a 20 Hz beat frequency in the beta range, but other frequencies may have greater or lesser neural effects. There are further questions about how long to stimulate, with how much current, how often, and for how long the effects may last. A recent study administered currents up to 8 mA³⁵ on the hypoglossal nerve without apparent adverse effects, which is well above more common brain applications of 2 mA and suggests that it may be possible to safely increase the electrical current levels applied to the brain. A study in rats also showed that TI can even be delivered wirelessly, by using a laser to drive a photoelectric converter that delivers TI.³⁷ Beyond that, there

is a whole range of clinical disorders involving deeper brain regions, and which may benefit from TI. There are also ethical issues. Interventions that reduce craving may have side effects of altering volition and decision-making, so ethical issues will also need to be considered.³⁸ Side effects may also be a concern, as invasive deep brain stimulation may cause mania, disinhibition, and psychosis.³⁹

Contributions

JWB researched the material and wrote the manuscript.

Declaration of Conflicting Interests

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ORCID iD

Joshua W Brown  <https://orcid.org/0009-0008-3226-6360>

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