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Transcranial Magnetic Stimulation and Deep Brain Stimulation in the treatment of alcohol dependence

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Abstract

Alcohol dependence is a major social, economic, and public health problem. Alcoholism can lead to damage of the gastrointestinal, nervous, cardiovascular, and respiratory systems and it can be lethal, costing hundreds of billions to the health care system. Despite the existence of cognitive-behavioral therapy, psychosocial interventions, and spiritually integrated treatment to treat it, alcohol dependence has a high relapse rate and poor prognosis, albeit with high interindividual variability. In this review, we discuss the use of two neuromodulation techniques, namely repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS), and their advantages and disadvantages compared to first-line pharmacological treatment for alcohol dependence. We also discuss rTMS and DBS targets for alcohol dependence treatment, considering experimental animal and human evidence, with careful consideration of methodological issues preventing the identification of feasible targets for neuromodulation treatments, as well as inter-individual variability factors influencing alcoholism prognosis. Lastly, we anticipate future research aiming to tailor the treatment to each individual patient by combining neurofunctional, neuroanatomical and neurodisruptive techniques optimizing the outcome.

Keywords

rTMS; DBS; addiction; alcoholism; habenula; nucleus accumbens; liver transplant

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Introduction

The World Health Organization estimates that there are 140 million people with alcoholism worldwide. Alcohol dependence and alcohol abuse or harmful use cause substantial morbidity and mortality (1), have significant neurologic and psychiatric comorbidity (including suicide) and complicate the assessment and treatment of other medical and psychiatric problems (1). Of all chronic heavy drinkers, 15–20% develop hepatitis or cirrhosis, which can occur concomitantly or in succession (2). Treatment for liver cirrhosis requires liver transplantation, but only a fraction of patients are ever selected to receive one because of medical or psychiatric contraindications, ongoing use of alcohol or death (3) and 21% of those receiving a transplant relapse on alcohol use after transplantation (3) leading to excess mortality (4). Early liver transplantation has been advocated for patients with severe alcoholic hepatitis not responding to medical therapy as well (5), and these patients have an 8 % relapse rate. Taken together, excessive alcohol consumption, including binge drinking, and high average daily alcohol consumption are responsible for an average of 79,000 deaths in the United States each year (6).

According to the Centers for Disease Control and Prevention the cost of excessive alcohol consumption in the United States surpasses \$200 billion dollars (7), largely resulting from losses in workplace productivity, health care expenses for problems caused by excessive drinking, law enforcement and other criminal justice expenses related to excessive alcohol consumption, as well as motor vehicle crash costs from impaired driving. Clinical management of these patients is complicated as their adhesion to the treatment often fails. Benzodiazepines are often prescribed to ameliorate the psychomotor agitation that most patients experience during withdrawal, and to prevent progression from minor withdrawal symptoms to major ones. Unfortunately, as many as a third of alcoholics also abuse benzodiazepines, which may complicate the pharmacological management of these patients (8). Short-term treatment of alcoholics with the opiate antagonist naltrexone decreases the chance of alcohol relapses for about a third of the subjects, and the chance of returning to drinking for half of that number (9), but its effects do not appear to be sustained (9).

The first drug to reach clinical use with a specific indication to treat alcoholism was acamprosate, a GABA receptor agonist which competes with alcohol to bind to GABA-A receptors, albeit its precise mechanism of clinical action still remains somewhat controversial (10-12). Yet, even though acamprosate has a moderate effect reducing the risk of alcohol relapse and it increases the cumulative duration of abstinence (13), it does not decrease binge drinking (11) and does not reduce pharmacologically induced alcohol cravings (14), even though it can reduce self-reported (15) and cue-induced cravings (16). Interestingly, the efficacy of acamprosate to reduce self-reported cravings is modified by a functional polymorphism in the GABA receptor gene (16). Likewise, a meta-analysis suggested that the effect of naltrexone in patients with alcohol dependence may also be moderated by genetic factors (17). In particular, the possession of the μ -opioid receptor gene predicts better outcomes in naltrexone-treated patients with alcohol dependence (17). Thus, there seems to be strong support for the importance of matching treatments to the patient's genetic make up to improve therapeutic outcome. Indeed, in the United States, ethnic differences in alcoholism onset, persistence, and recurrence rates are

increased risk in minority groups (18), a finding that may reflect genetic or cultural differences, or both.

In any case, the cumulative evidence of pharmacological trials (19) and psychosocial interventions (20,21) suggests that current treatment of alcohol related disorders have at best modest efficacy, and there is a real need for more effective interventions particularly at the high end of the severity spectrum when patients have significant medical morbidity and significant mortality.

Molecular and Synaptic Effects of Chronic Alcohol

Limited knowledge about the mechanisms of action of drugs used to treat alcohol dependence has prevented the progress of pharmacotherapies for this addiction. It is also implicit that to reveal such mechanism of action, a clear model of the neural pathways underpinning alcohol dependence should be demonstrated. The neural circuits underlying addiction have been largely elucidated (22), and we recently summarized how they can be approached by neuromodulation therapies (23). The molecular mechanism of alcohol's effects on the brain is complex and its target proteins include, but are not limited to, ion channels, neurotransmitter receptors, and intracellular signaling proteins. The most common alcohol action on "cys-loop" ligand-gated ion channels is to potentiate channel opening in the presence of a low concentration of agonist by increasing the probability of channel opening, and/or increasing agonist affinity; this potentiating effect can influence both synaptic and extrasynaptic receptors. For example, alcohol increases the amplitude and/or duration of GABA-A and Glycine receptor-mediated inhibitory postsynaptic currents (IPSCs) (24).

The ionotropic glutamate receptors (iGluRs) constitute a second class of neurotransmitter-activated ligand-gated ion channels modulated by alcohol. All three of the major classes of iGluRs (AMPA receptors, NMDA receptors, and kainate receptors) are consistently inhibited by alcohol, but inhibition of NMDARs is the best characterized of these effects and is associated with intoxication (24). The synaptic responses mediated by NMDARs are also reduced by alcohol, and this inhibitory action is thought to contribute to cognitive impairment produced by its consumption (24). In addition, alcohol acutely increases adenosine levels in the brain contributing to cerebellar dysfunction during intoxication, and downregulates adenosine tone during chronic administration, contributing to insomnia during withdrawal (25). Both of these effects are mediated in part through several adenosine receptors and regulation of glutamate levels acting on glutamate transport (25). Lastly, alcohol facilitates synaptic release of GABA and either has no effect or inhibits release of glutamate, suggesting a fundamental difference between GABAergic and glutamatergic terminals in most brain regions that may contribute to the net effects of alcohol (24). The postsynaptic effects on neurotransmitter receptors appear to occur within the receptor molecules themselves. The sum result of the effects of alcohol on neurotransmission appears to dampen synaptic excitation and reduce most forms of synaptic plasticity.

The effects of chronic exposure to alcohol are, however, significantly different from those of acute intoxication; indeed, chronic alcohol results in facilitation of NMDARs function and

increased glutamate release, resulting in a hyperexcitable state of the brain during withdrawal that contributes to withdrawal symptoms and relapse, and possibly in excitotoxicity (24). Paradoxically, the acute effects of alcohol during intoxication remain unchanged at the synaptic level, indicating that the behavioral tolerance observed in chronic alcoholics cannot be explained on the basis of synaptic changes (24). The effects of chronic exposure to alcohol on GABA neurotransmission also differ from the acute effects, but the exact result varies regionally in the brain and depends on the final receptor configuration resulting from the exposure to alcohol (24). Lastly, alcohol affects the modulatory effects of neuropeptides, particularly those implicated in stress responses, which appear to contribute to drinking and relapse (24).

Given the complexity of the molecular effects of alcohol it seems unlikely that a single molecular target may be effective in reversing its effects on the brain. Rather, modulating the altered circuits in the brain to restore them to pre-exposure function (if that were possible) appears as a more promising strategy. Alcohol, and drugs of abuse in general, are self-administered by humans laboratory animals because of their rewarding effect; yet, most people use it without losing control (26). Human studies with neurophysiological and imaging techniques have illuminated the impact of molecular changes on brain function and are reviewed next.

Brain Functional Changes with Chronic Alcohol

The nature of the changes in reward circuits during development of addictions has become increasingly clear in recent years (23). In animal models, addictive drugs share the property of voluntary self-administration correlated with enhancement in the functioning of the reward circuitry of the brain, encompassing dopaminergic projections from the ventral tegmental area to nucleus accumbens and ventral pallidum via the medial forebrain bundle (24,27). Neuronal activity in this circuitry encodes elements of hedonic tone, attention to and expectancy of reward, as well as responses to expectancy errors and incentive motivation (anticipatory responses), and all drugs of abuse enhance (directly, indirectly or even trans-synaptically) dopaminergic synaptic function in the nucleus accumbens. Indeed, self-administration is regulated by nucleus accumbens dopamine levels, and aims to maintain synaptic dopamine levels elevated to maintain a desired hedonic level; yet, adaptive changes during addiction lead eventually to a hypodopaminergic dysfunctional state within the circuitry (22). In addition, the brain circuits mediating alcohol craving and relapse are anatomically, neurophysiologically and neurochemically different from the circuit just described (24), implicating serotonergic, opioid, endocannabinoid, GABAergic and glutamatergic mechanisms as suggested before and leading to a transition from reward-driven to habit-driven drug-seeking behaviors (24). In anatomical terms this transition corresponds to a change from primary encoding by the nucleus accumbens, to encoding by the dorsal striatum, and relapse after a period of abstinence appears to involve the amygdala, hippocampus, the bed nucleus of the stria terminalis, and the lateral tegmental noradrenergic nuclei of the brain stem (24,28).

In addition to subcortical pathways, acute alcohol administration (and ensuing intoxication) affects prefrontal cortical function in an experience-related fashion. Indeed, alcoholics (and

controls) respond to acute alcohol administration with a variable decrease in brain glucose metabolism (26). Surface recordings of brain activity with electroencephalography (EEG) have shown that low alcohol doses uniformly increase slow activity (in the theta and lower alpha frequency bands), whereas higher frequencies may or may not change depending on the individual's drinking history (26). Indeed, activity in the beta band (associated with arousal) is decreased in alcoholics and reliably differentiates between 'low' and 'moderate' alcohol drinkers (determined by pattern of alcohol consumption), as well as familial history of alcoholism (26). When the recording is time-locked to auditory stimuli that need to be attended to, acute alcohol consumption attenuates the amplitude of event related potentials linked to attentional processes (N100 and P200), while increasing the latency and decreasing the amplitude of cognitive suppression (P300 in a go-nogo task) amplitudes have also been reported in response to alcohol intoxication (26). When alcohol is used repeatedly, its effects are modulated by experience (including previous effects of use) and contextual factors (e.g., places, people, or objects) which become motivation to use through operant or classical conditioning giving rise to the subjective craving. Studies of this subjective experience have revealed orbitofrontal cortex and nucleus accumbens activation when it occurs. For instance, EEG dimensional complexity (an indicator of activation of underlying cortex), as well as increased amplitude of cognitive processing (P300) evoked potentials occur when chronic alcoholics are exposed to a use cue (26). The severity and pattern of physiological changes can accurately predict relapse (26). Taken together these data suggest that in chronic problem consumers alcohol-related cues evoke more brain activation than in controls, which has been interpreted as incentive salience and arousal when stimuli related to alcohol use are encountered (26).

Another feature of addiction is that one drink will unleash excessive consumption and disruption of self-control, thought to result from a compromised inhibitory function of the prefrontal cortex. Impaired top-down control of behavior would lead or contribute to bingeing. Interestingly, unlike what was described regarding the acute effects of alcohol on occasional users, binge drinkers showed larger N200 and smaller P300 as compared to controls in tasks requiring sustained attention or pattern recognition, suggesting exaggerated motivation or salience rather than loss of control (26). In support of this explanation is the finding that alcoholics have significant reductions in dopamine D2 receptor availability in the striatum and decreased metabolic activity in the prefrontal cortex, neither of which can be fully accounted for by impairments in behavioral responses or motivation (26). An additional consequence of distorted attentional processes in alcoholism is the decrease of self-awareness, which correlates with changes in metabolic activity in the insula and medial prefrontal cortex regions (26). During early withdrawal of alcohol, metabolic activity is reduced throughout the striatal-thalamo-orbitofrontal cortex circuit, and as time goes on the changes become more circumscribed to the cortex (26).

Thus, it is clear that regardless of the specific molecular changes induced by drugs of abuse (including alcohol), they induce over time specific changes in brain function which could be addressed at the level of circuits. Transcranial magnetic stimulation (TMS) and DBS may be able to selectively target brain circuits involved in the successive stages of addiction, providing a window to efficacy were pharmacological treatment is not effective.

rTMS for the treatment of alcohol dependence

Transcranial magnetic stimulation (TMS) takes advantage of electromagnetic induction to generate targeted electrical fields in the surface of the brain; an ability that has attracted considerable interest as a tool to modify brain activity in humans in a relatively non-invasive fashion. Direct modification of brain activity has been used as a probe for the role of specific brain structures on behavior (29), and as a therapeutic option for various psychiatric and neurological disorders (23). Standard TMS devices induce neuronal stimulation in cortical regions lying superficially under the coil in the vicinity of the scalp surface (29) because the field decays quickly with increasing distance from the coil (30).

Although scientific research on TMS-based treatments for addictions is still in its infancy, some promising studies have shown moderate success. To the best of our knowledge, there have been so far only five original articles assessing repetitive TMS (rTMS) as a treatment for alcohol dependence (31-35). Two of the cited articles targeted the (right) dorsolateral prefrontal cortex (DLPFC) (33,34). The first did not find a significant treatment effect of a single session of TMS on craving. Instead, Mishra and colleagues applied ten sessions of rTMS after which they found a significant reduction of craving in the experimental group compared to the sham stimulation group, which persisted up to a month after treatment. A different study targeted the DLPFC but only on the left hemisphere (35). Their protocol consisted in ten sessions of rTMS, and found no changes in cravings when compared to sham stimulation (35). However, the rationale behind choosing the DLPFC as a target for alcohol dependence is far from clear, and one is forced to ponder if the main reason to focus on this structure was its accessibility with standard figure-8 TMS coils.

In a case report on a patient with alcohol dependence, rTMS of the dorsal anterior cingulate cortex (dACC) was used to treat alcohol cravings (31). Because of its proximity to the orbitofrontal cortex and its connectivity with the amygdala and nucleus accumbens (both of which form part of the reward circuit) it was proposed that stimulation of the dACC could reduce cravings, and indeed the patient did not experience withdrawal symptoms or cravings for 3 months after treatment, at which time she suffered a relapse (31). Interestingly, this study assessed resting state quantitative electroencephalography combined with source localization during the patient's craving as well as after successful TMS treatment. During craving, the patient presented beta activity in the ACC and posterior cingulate cortex which was not present after rTMS (31). Finally, successful treatment of alcohol dependence was reported with a protocol of 10 sessions of rTMS on the temporo-occipital area, but the target was vaguely defined encumbering the interpretation of the results (32).

TMS methods have certain limitations. Traditional TMS performed with round coils or figure-8 coils cannot stimulate farther than 2 centimeters from the skull, limiting possible targets to superficial cortex (36). Coil arrays designed to reach deeper structures may overcome this particular problem (37). However, to the best of our knowledge, no deep TMS treatment specific to alcohol dependence has been reported.

Deep Brain Stimulation for the treatment of alcoholism

A surgical alternative to directly stimulate subcortical structures is deep brain stimulation (DBS), which uses implanted electrodes to deliver electrical pulses to stereotactically targeted areas of the brain. DBS targeting the nucleus accumbens has been shown to reduce drug seeking behavior and drug consumption (28), as well as alcohol dependence (38-42). Initial studies in alcohol-preferring rats resulted in decreased alcohol seeking behavior in comparison to rats receiving sham DBS (42), suggesting that even a single session of DBS may suppress alcohol intake and also reduce the salient effect of alcohol in a forced abstinence condition in alcohol-preferring rats. A single case study reported an alcohol dependence patient who experienced suppression of cravings and consequently reduction of alcohol intake after DBS in the nucleus accumbens (38). Moreover, the cited study proposed a mechanism for reduction of cravings; namely normalization of the aberrant activity of the nucleus accumbens and anterior mid-cingulate cortex cognitive control network, as reflected by correction of the error related negativity on electroencephalography (38). Since this pioneer intervention, more cases of DBS in the nucleus accumbens for alcohol dependence have been published. Recently, five more cases have been reported of which two have fully recovered and the other three had shorter and milder relapses (39).

No other structures have been targeted to date by DBS in patients with alcoholism. Regardless of the proposed central role of the accumbens in addictive behavior (43), several caveats should suggest the need for alternative targets. First, a significant fraction of alcoholic subjects with nucleus accumbens DBS experienced poor concentration, poor short-term memory, anorexia, or loss of sexual desire (44). In addition, in patients with nucleus accumbens DBS for obsessive compulsive disorders (45), Tourette syndrome (46) or depression (47), similar side effects have been reported. The side effects of nucleus accumbens DBS suggest that its partial efficacy for alcohol dependence may be the result of a general decrease in the value of reward, which may not yield optimal quality of life. Furthermore, the nucleus accumbens can be differentiated anatomically between the shell (medial) subregion implicated in motivation, and the core (dorsolateral) subregion implicated in cognitive control (48,49), and current DBS literature does not specify optimal location within the nucleus. For comparisons between studies see table 1.

One of the arguments used to select the nucleus accumbens as a DBS target for alcohol dependence arises from fMRI data showing activation during alcohol related cue tasks in alcoholics (50-53). Unfortunately, in the current literature, most of functional imaging studies are correlative in nature. Imaging studies indicate brain regions which may plausibly be involved (either directly or coincidentally) in certain symptom or disease, although those regions may not be necessary for such manifestation (54). In fact, inconsistencies in brain regions supporting the same function between correlational (neuroimaging) and causational (neurodisruptive) techniques have been reported in the literature (55,56).

In our view, a target that has not been given due consideration is the lateral habenula, which has been shown to reduce addictive behavior in animal models (57,58). Lateral habenula releases GABA onto dopaminergic cells of the rostral-medial tegmental nucleus resulting in inhibition of ventral tegmental area and substantia nigra dopaminergic cell activity (59,60).

In animal models, midbrain dopamine levels rise with unexpected rewards and decrease with the omission of expected rewards, which is the exact anti-correlated pattern of the neuronal activity in the lateral habenula (61). Such findings have been later extended to the human brain (62). Yet, lateral habenula DBS has not been attempted in alcohol dependence (although a case report has been published of its use to treat depression) (63). A few technical notes have been recently published, encouraging high resolution MRI and manual tracing of its boundaries in conjunction with a stereotactic atlas of the human brain in T1 images (64). Moreover, new paradigms using, for example, noxious heat have been tested for fMRI settings (65) aiming to functionally localize it. The cited study performed functional and structural connectivity analysis of the habenula, demonstrating that despite the limitations of functional resolution, unclear landmarks and difficulties in the spatial registration of functional with structural images, the habenula can be functionally localized, and functional as well structural connectivity analyses are plausible (65).

As already mentioned, the lateral habenula has efferent connections to the ventral tegmental area and the substantia nigra, and receives afferent connections from the caudate and putamen, the nucleus accumbens and the medial prefrontal cortex. Functional connectivity findings have shown a correlated physiological activity fluctuation between the habenula and the medial prefrontal cortex (extending towards the ACC), and the striatum, and anticorrelated between habenula and the midbrain dopaminergic nuclei (65).

A curious susceptibility of habenula neurons to manganese toxicity deserves mention here (66). Excessive accumulation of manganese in the brain causes early psychotic symptoms usually followed by a syndrome similar to idiopathic Parkinson's disease, associated with neuronal loss and gliosis in the globus pallidus, the substantia nigra pars reticulata and the striatum (67). Since on the one hand manganese is the sole trace element to accumulate in the brain of alcoholics (68), and on the other hand manganese deposition in the habenula provides an ideal contrast signal in T1 weighted MRI images (69,70), the habenula may be clearly visible (and therefore amenable to direct targeting) in the context of deep brain stimulation for alcoholism.. Further neuroimaging studies in alcohol patients should investigate the impact of manganese on T1 quality images.

Imaging and physiological outcome measures for alcohol-dependence treatment

A crucial methodological problem in substance abuse literature is that outcomes are too often measured by self-reported scales and therefore affected by sources of variability very different from the primary brain dysfunctions underlying addiction. For instance, in alcohol dependence research, the sensitive nature of the data collected and the patient's denial of their addiction may lead them to misreport their alcohol use. Conversely, relying on blood screens alone may miss alcohol intake events occurring too further back in time to be identified (71). Thus, if the efficacy of neuromodulation therapies is to be tied to the primary neurobiological changes following transition from occasional use to addiction, it is essential to develop direct measures of functional or structural brain changes. Both MRI and electrophysiological tools can now complement the traditional outcome measures by offering objective and quantitative evidence of brain repair in alcohol related disorders.

Alcoholic patients have smaller hippocampal volumes than healthy controls (72), and this finding is more prominent in adult alcoholic patients with adolescent-onset use compared to the controls and the late-onset group (73). Indeed, age at onset seems a key determinant of the severity of the anatomical changes. Adolescent alcohol users had more hippocampal asymmetry and reduced left hippocampal volume compared to either users of combined marijuana and alcohol or non-using controls (74), and the severity of the morphological abnormality correlated with the severity of abuse (74). Amygdala volume reduction is also observed in some alcohol-dependent subjects, along with hippocampus, and ventral striatum volumes, but interestingly only amygdala volumes correlate with alcohol craving and predict risk of relapse (75). These changes seem to be reversible, since in long-term abstinent alcoholics subcortical volumes are unaffected except when significant psychiatric comorbidities are present (76).

Reinforcement of behavioral responses involves, besides those brain structures directly responsible for hedonic reward, networks responsible for oversight systems affiliated with emotion, memory, judgment, and decision making. As one would perhaps predict, transition from occasional use to abuse or dependence of alcohol is reflected by widespread changes in brain structures related to those networks. Indeed, volume reductions have been reported in right dorsolateral-prefrontal cortex, right anterior insula, and right nucleus accumbens of alcoholic subjects, and at least some of these changes are reversible with abstinence (43,77). Chronic alcohol consumption is also associated with smaller volumes in orbitofrontal cortex (78) and this finding predicts likelihood of relapse after rehabilitation (79,80).

Remarkably, the reversibility of anatomical changes after alcohol abstinence seems to occur rapidly for white matter (81), and somewhat more slowly and perhaps less completely for gray matter structures, particularly in the prefrontal cortex (81). A recent study validated a formula predicting the trajectory of the gray and white matter volume regeneration in recovering alcoholics. By using MRI-measured volumetric data, they estimated the individual's gray and white matter volume of the frontal, parietal and temporal lobes at different time points of abstinence with high accuracy (82).

A caveat emptor is in order. Even though group effects reach clear statistical significance, individual variability is prominent in the data (81,82). One source of variation that has become increasingly more apparent is the genome. Indeed, both gray and white matter restoration in abstinent patients recovering for alcoholism is affected by brain derived neurotrophic factor (*BDNF*) genetic variants. Specifically, by dividing patients in two *BDNF* genotypes (valine/methionine (Val66Met (rs6265)) heterozygotes or valine homozygotes) and scan them at different time points of abstinence, the authors demonstrated that the homozygote group increased in gray matter volume, contrary to the heterozygote group which increased in white matter volume (83). Likewise, several genes of the dopaminergic and glutamatergic neurotransmitter systems have been found to be associated with alcohol disease and related intermediate phenotypes. Hippocampal volumes were found to be associated with epistatic effects of the catechol-O-methyltransferase - metabotropic glutamate receptor 3 genes in alcohol-dependent patients but not in controls (84).

Taken together, these neuroimaging techniques have the potential to be employed for measuring effectiveness of the treatment and for monitoring the patient's progress, and genetic markers might be helpful to predict the optimal therapy for each patient.

Future directions

To date, pharmacological and cognitive behavioral treatments for alcohol dependence have achieved limited success. Alternatively, rTMS has shown moderate success, even though it has limited ability to reach several of the key elements in the brain circuit underpinning alcohol addiction. DBS offers the possibility to target deep brain structures causally related to this addiction. However, because of its invasive nature, such procedure should be considered only after careful evaluation of the costs and benefits this intervention may have in each patient. We believe that DBS treatment would be of great value in patients undergoing liver transplant due to cirrhosis caused by alcohol addiction. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), up to 70 percent of all alcoholic hepatitis patients may eventually develop cirrhosis, which is considered a major cause of death in the United States. Liver transplant is the only definitive treatment for severe liver failure. For the transplant to be successful, it is essential that alcoholic patients remain abstinent after surgery. Because of the shortage of donated organs, transplant to patients with alcoholic liver disease remains controversial, out of concerns that patients may resume drinking, thereby harming the transplanted organ (85). DBS treatment seems justified in alcohol dependence patients undergoing liver transplant, as the danger of losing the new organ urges to adopt the potentially most effective although still speculative measure. We predict flourishing research on the topic in the coming years.

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Table 1

Neurostimulation treatment in alcoholism.

Study	N	Target	Technique	Findings
de Ridder et al., 2011	1	dACC	TMS	temporary abstinence
Heldmann et al., 2012	1	NAc	DBS	improved beahvioral control
Henderson et al., 2010	9 (rats)	NAc	DBS	reduce alcohol use
Herremans et al., 2012	36	right DLPFC	TMS	negative results
Hoppner et al., 2011	19	left DLPFC	TMS	negative results
Kuhn et al., 2011	1	NAc	DBS	reduced alcohol use and craving
Mishra et al., 2010	45	right DLPFC	TMS	reduced craving
Staroverov et al. 2009	54	Temporoccipital area	TMS	improvement in cognitive functions
Voges et al., 2012	5	NAc	DBS	3 patients succesfully treated.

Summary of published studies on the use of neurostimulation in alcohol dependent subjects. dACC: dorsal anterior cingulate cortex, NAc: nucleus accumbens, DLPFC: dorsolateral prefrontal cortex.