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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 2 neuromodulation techniques, namely repetitive transcranial magnetic stimulation and deep brain stimulation, and their advantages and disadvantages compared with first-line pharmacological treatment for alcohol dependence. We also discuss repetitive transcranial magnetic stimulation and deep brain stimulation 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 interindividual variability factors influencing alcoholism prognosis. Finally, we anticipate future research aiming to tailor the treatment to each individual patient by combining neurofunctional, neuroanatomic, and neurodisruptive techniques optimizing the outcome.

Key Words: rTMS, DBS, addiction, alcoholism, habenula, nucleus accumbens, liver transplant

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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 neurological and psychiatric comorbidity (including suicide) and complicate the assessment and treatment of other medical and psychiatric problems.[1] Of all chronic heavy drinkers, 15% to 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

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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 a polymorphism 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.[24]

The ionotropic glutamate receptors constitute a second class of neurotransmitter-activated ligand-gated ion channels modulated by alcohol. All 3 of the major classes of ionotropic glutamate receptors (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] Finally, 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]

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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] Finally, 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 preexposure 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 the 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 by 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 transsynaptically) 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 anatomic 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 manner. Indeed, alcoholics (and controls) respond to acute alcohol administration with a variable decrease in brain glucose metabolism.[26] Surface recordings of brain activity with electroencephalograhy 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 needs to be attended to, acute alcohol consumption attenuates the amplitude of event-related potentials liked to attentional processes (N100 and P200), whereas 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 (eg, places, people, or objects) which become motivation to use through operant or classic 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, electroencephalograhy 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 1 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 with 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 deep brain stimulation (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.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) FOR THE TREATMENT OF ALCOHOL DEPENDENCE

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 noninvasive manner. 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

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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 5 original articles assessing 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 10 sessions of rTMS after which they found a significant reduction of craving in the experimental group compared with 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 10 sessions of rTMS, and found no changes in cravings when compared with 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 (ACC) 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 dorsal ACC 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 temporooccipital 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 cm 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.

DBS FOR THE TREATMENT OF ALCOHOLISM

A surgical alternative to directly stimulate subcortical structures is 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 with 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-dependent 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 midcingulate cortex cognitive control network, as reflected by correction of the error related negativity on electroencephalograpy.[38] Since this pioneer intervention, more cases of DBS in the nucleus accumbens for alcohol dependence have been published. Recently, 5 more cases have been reported of which 2 have fully recovered and the other 3 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, aconuresis, 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 coincidently) 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 rostromedial tegmental nucleus resulting in inhibition of ventral tegmental area and substantial 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 anticorrelated 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 magnetic resonance imaging (MRI) and manual tracing of its boundaries in conjunction with a stereotactic atlas of the human brain in T1 images.[64]

TABLE 1. Neurostimulation Treatment in Alcoholism

Study	N	Target	Technique	Findings
De Ridder et al[31]	1	dACC	TMS	Temporary abstinence
Heldmann et al[41]	1	NAc	DBS	Improved behavioral control
Henderson et al[42]	9 (rats)	NAc	DBS	Reduce alcohol use
Herremans et al[34]	36	Right DLPFC	TMS	Negative results
Hoppner et al, 2011[35]	19	Left DLPFC	TMS	Negative results
Kuhn et al[38]	1	NAc	DBS	Reduced alcohol use and craving
Mishra et al[33]	45	Right DLPFC	TMS	Reduced craving
Staroverov et al[32]	54	Temporoccipital area	TMS	Improvement in cognitive functions
Voges et al[39]	5	NAc	DBS	3 patients successfully treated

Summary of published studies on the use of neurostimulation in alcohol-dependent subjects.
dACC indicates dorsal anterior cingulate cortex; DBS, deep brain stimulation; DLPFC, dorsolateral prefrontal cortex; NAc, nucleus accumbens; TMS, transcranial magnetic stimulation.

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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 disease, associated with neuronal loss and gliosis in the globus pallidus, the substantia nigra pars reticulate, and the striatum.[67] As 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 DBS for alcoholism. Further, neuroimaging studies in alcohol patients should investigate the impact of manganism 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 with the controls and the late-onset group.[73] Indeed, age at onset seems a key determinant of the severity of the anatomic changes. Adolescent alcohol users had more hippocampal asymmetry and reduced left hippocampal volume compared with either users of combined marijuana and alcohol or nonusing controls,[74] and the severity of the morphologic 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, as 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 the likelihood of relapse after rehabilitation.[79,80]

Remarkably, the reversibility of anatomic 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 neurotropic factor genetic variants. Specifically, by dividing patients in 2 brain-derived neurotropic factor genotypes [valine/methionine (Val66Met (rs6265)) heterozygotes or valine homozygotes] and scanning 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 because of cirrhosis caused by alcohol addiction. According to the National Institute on Alcohol Abuse and Alcoholism, up to 70% 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-dependent 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.

REFERENCES

1. Schuckit MA. Alcohol-use disorders. *Lancet*. 2009;373:492–501.

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2. Menon KV, Gores GJ, Shah VH. Pathogenesis, diagnosis, and treatment of alcoholic liver disease. *Mayo Clin Proc*. 2001;76:1021–1029.
3. Karman JF, Sileri P, Kamuda D, et al. Risk factors for failure to meet listing requirements in liver transplant candidates with alcoholic cirrhosis. *Transplantation*. 2001;71:1210–1213.
4. Faure S, Herrero A, Jung B, et al. Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. *J Hepatol*. 2012;57:306–312.
5. Mathurin P, Moreno C, Samuel D, et al. Early Liver Transplantation for Severe Alcoholic Hepatitis. *N Engl J Med*. 2011;365:1790–1800.
6. Mokdad AH, Marks JS, Stroup DF, et al. Actual causes of death in the United States, 2000. *JAMA*. 2004; 291:1238–1245.
7. Bouchery EE, Harwood HJ, Sacks JJ, et al. Economic costs of excessive alcohol consumption in the US, 2006. *Am J Prev Med*. 2011;41:516–524.
8. Johansson BA, Berglund M, Hanson M, et al. Dependence on legal psychotropic drugs among alcoholics. *Alcohol Alcohol*. 2003;38:613–618.
9. Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev*. 2005;CD001867.
10. Pierce RC, O'Brien CP, Kenny PJ, et al. Rational development of addiction pharmacotherapies: successes, failures, and prospects. *Cold Spring Harb Perspect Med*. 2012;2:a012880.
11. Witkiewitz K, Saville K, Hamreus K. Acamprosate for treatment of alcohol dependence: mechanisms, efficacy, and clinical utility. *Ther Clin Risk Manag*. 2012;8:45–53.
12. Mason BJ, Heyser CJ. The neurobiology, clinical efficacy and safety of acamprosate in the treatment of alcohol dependence. *Expert Opin Drug Saf*. 2010;9:177–188.
13. Rösner S, Hackl-Herrwerth A, Leucht S, et al. Acamprosate for alcohol dependence. *Cochrane Database Syst Rev*. 2010;CD004332.
14. Umhau JC, Schwandt ML, Usala J, et al. Pharmacologically induced alcohol craving in treatment seeking alcoholics correlates with alcoholism severity, but is insensitive to acamprosate. *Neuropsychopharmacology*. 2011;36:1178–1186.
15. Hammarberg A, Nylander I, Zhou Q, et al. The effect of acamprosate on alcohol craving and correlation with hypothalamic pituitary adrenal (HPA) axis hormones and beta-endorphin. *Brain Res*. 2009;1305: (suppl):S2–S6.
16. Ooteman W, Naassila M, Koeter MWJ, et al. Predicting the effect of naltrexone and acamprosate in alcohol-dependent patients using genetic indicators. *Addict Biol*. 2009;14:328–337.
17. Chamorro A-J, Marcos M, Mirón-Canelo J-A, et al. Association of μ-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis. *Addict Biol*. 2012;17:505–512.
18. Grant JD, Vergés A, Jackson KM, et al. Age and ethnic differences in the onset, persistence and recurrence of alcohol use disorder. *Addiction*. 2012;107: 756–765.
19. Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. *Int J Psychiatry Med*. 2011;42:227–266.
20. Jaehne A, Loessl B, Frick K, et al. The efficacy of stepped care models involving psychosocial treatment of alcohol use disorders and nicotine dependence: a systematic review of the literature. *Curr Drug Abuse Rev*. 2012;5:41–51.
21. Weiss RD, Kueppenbender KD. Combining psychosocial treatment with pharmacotherapy for alcohol dependence. *J Clin Psychopharmacol*. 2006;26: (suppl 1):S37–S42.
22. Volkow ND, Wang G-J, Fowler JS, et al. Addiction circuitry in the human brain. *Annu Rev Pharmacol Toxicol*. 2012;52:321–336.
23. Alba-Ferrara LM, Fernandez F, de Erausquin GA. The use of neuromodulation in the treatment of cocaine dependence. *Addict Disord Treat*. 2012. [Epub ahead of print].
24. Lovinger DM, Roberto M. Synaptic effects induced by alcohol. *Curr Top Behav Neurosci*. 2013;13: 31–86.
25. Nam HW, McIver SR, Hinton DJ, et al. Adenosine and glutamate signaling in neuron-glial interactions: implications in alcoholism and sleep disorders. *Alcohol Clin Exp Res*. 2012;36:1117–1125.
26. Parvaz MA, Alia-Klein N, Woicik PA, et al. Neuroimaging for drug addiction and related behaviors. *Rev Neurosci*. 2011;22:609–624.
27. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci*. 2006;29: 565–598.
28. Luigjes J, van den Brink W, Feenstra M, et al. Deep brain stimulation in addiction: a review of potential brain targets. *Mol Psychiatry*. 2012;17:572–583.
29. Pascual-Leone A, Walsh V, Rothwell J. Transcranial magnetic stimulation in cognitive neuroscience—virtual lesion, chronometry, and functional connectivity. *Curr Opin Neurobiol*. 2000;10:232–237.
30. Esser SK, Hill SL, Tononi G. Modeling the effects of transcranial magnetic stimulation on cortical circuits. *J Neurophysiol*. 2005;94:622–639.
31. De Ridder D, Vanneste S, Kovacs S, et al. Transient alcohol craving suppression by rTMS of dorsal anterior cingulate: an fMRI and LORETA EEG study. *Neurosci Lett*. 2011;496:5–10.
32. Staroverov AT, Zhukov OB, Raigorodskii YM. Efficacy of transcranial magnetotherapy in the complex treatment of alcohol withdrawal syndrome. *Neurosci Behav Physiol*. 2009;39:891–895.
33. Mishra BR, Nizamie SH, Das B, et al. Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: a sham-controlled study. *Addiction*. 2010;105:49–55.
34. Herremans SC, Baeken C, Vanderbruggen N, et al. No influence of one right-sided prefrontal HF-rTMS session on alcohol craving in recently detoxified alcohol-dependent patients: results of a naturalistic study. *Drug Alcohol Depend*. 2012;120:209–213.
35. Höppner J, Broese T, Wendler L, et al. Repetitive transcranial magnetic stimulation (rTMS) for treatment of alcohol dependence. *World J Biol Psychiatry*. 2011;12:(suppl 1):57–62.
36. Rossi S, Hallett M, Rossini PM, et al. ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120: 2008–2039.
37. Bersani FS, Minichino A, Enticott PG, et al. Deep transcranial magnetic stimulation as a treatment for psychiatric disorders: a comprehensive review. *Eur Psychiatry*. 2013;28:30–39.
38. Kuhn J, Gründler TOJ, Bauer R, et al. Successful deep brain stimulation of the nucleus accumbens in severe alcohol dependence is associated with changed performance monitoring. *Addict Biol*. 2011; 16:620–623.

39. Voges J, Müller U, Bogerts B, et al. Deep brain stimulation surgery for alcohol addiction. *World Neurosurg*. 2012. [Epub ahead of print].
40. Münte TF, Heinze H-J, Visser-Vandewalle V. Deep brain stimulation as a therapy for alcohol addiction. *Curr Top Behav Neurosci*. 2013;13:709–727.
41. Heldmann M, Berding G, Voges J, et al. Deep brain stimulation of nucleus accumbens region in alcoholism affects reward processing. *PLoS ONE*. 2012;7: e36572.
42. Henderson MB, Green AI, Bradford PS, et al. Deep brain stimulation of the nucleus accumbens reduces alcohol intake in alcohol-preferring rats. *Neurosurg Focus*. 2010;29:E12.
43. Makris N, Oscar-Berman M, Jaffin SK, et al. Decreased volume of the brain reward system in alcoholism. *Biol Psychiatry*. 2008;64:192–202.
44. Li N, Wang J, Wang X-L, et al. Nucleus accumbens surgery for addiction. *World Neurosurg*. 2012. [Epub ahead of print].
45. Sachdev PS, Cannon E, Coyne TJ, et al. Bilateral deep brain stimulation of the nucleus accumbens for comorbid obsessive compulsive disorder and Tourette's syndrome. *BMJ Case Rep*. 2012. [Online].
46. Viswanathan A, Jimenez-Shahed J, Baizabal Carvallo JF, et al. Deep brain stimulation for Tourette syndrome: target selection. *Stereotact Funct Neurosurg*. 2012;90:213–224.
47. Bewernick BH, Kayser S, Sturm V, et al. Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. *Neuropsychopharmacology*. 2012; 37:1975–1985.
48. Pothuizen HHJ, Jongen-Rêlo AL, Feldon J, et al. Double dissociation of the effects of selective nucleus accumbens core and shell lesions on impulsive-choice behaviour and salience learning in rats. *Eur J Neurosci*. 2005;22:2605–2616.
49. Van der Plasse G, Schrama R, van Seters SP, et al. Deep brain stimulation reveals a dissociation of consummatory and motivated behaviour in the medial and lateral nucleus accumbens shell of the rat. *PLoS ONE*. 2012;7:e33455.
50. Claus ED, Ewing SWF, Filbey FM, et al. Identifying neurobiological phenotypes associated with alcohol use disorder severity. *Neuropsychopharmacology*. 2011;36:2086–2096.
51. Bragulat V, Dzemidzic M, Talavage T, et al. Alcohol sensitizes cerebral responses to the odors of alcoholic drinks: an fMRI study. *Alcohol Clin Exp Res*. 2008;32:1124–1134.
52. Kareken DA, Claus ED, Sabri M, et al. Alcohol-related olfactory cues activate the nucleus accumbens and ventral tegmental area in high-risk drinkers: preliminary findings. *Alcohol Clin Exp Res*. 2004;28: 550–557.
53. Myrick H, Anton RF, Li X, et al. Differential brain activity in alcoholics and social drinkers to alcohol cues: relationship to craving. *Neuropsychopharmacology*. 2004;29:393–402.
54. Price CJ, Mummery CJ, Moore CJ, et al. Delineating necessary and sufficient neural systems with functional imaging studies of neuropsychological patients. *J Cogn Neurosci*. 1999;11:371–382.
55. Alba-Ferrara L, Ellison A, Mitchell RLC. Decoding emotional prosody: resolving differences in functional neuroanatomy from fMRI and lesion studies using TMS. *Brain Stimul*. 2012;5:347–353.
56. Alba-Ferrara L, Hausmann M, Mitchell RL, et al. The neural correlates of emotional prosody comprehension: disentangling simple from complex emotion. *PLoS ONE*. 2011;6:e28701.
57. Friedman A, Lax E, Dikshtein Y, et al. Electrical stimulation of the lateral habenula produces enduring inhibitory effect on cocaine seeking behavior. *Neuropharmacology*. 2010;59:452–459.
58. Friedman A, Lax E, Dikshtein Y, et al. Electrical stimulation of the lateral habenula produces an inhibitory effect on sucrose self-administration. *Neuropharmacology*. 2011;60:381–387.
59. Baldwin PR, Alanis R, Salas R. The role of the habenula in nicotine addiction. *J Addict Res Ther*. 2011;S1.
60. Jhou TC, Fields HL, Baxter MG, et al. The rostromedial tegmental nucleus (RMTg), a GABAergic afferent to midbrain dopamine neurons, encodes aversive stimuli and inhibits motor responses. *Neuron*. 2009;61:786–800.
61. Matsumoto M, Hikosaka O. Lateral habenula as a source of negative reward signals in dopamine neurons. *Nature*. 2007;447:1111–1115.
62. Salas R, Baldwin P, de Biasi M, et al. BOLD responses to negative reward prediction errors in human habenula. *Front Hum Neurosci*. 2010;4:36.
63. Sartorius A, Kiening KL, Kirsch P, et al. Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. *Biol Psychiatry*. 2010;67:e9–e11.
64. Lawson RP, Drevets WC, Roiser JP. Defining the habenula in human neuroimaging studies. *Neuroimage*. 2013;64:722–727.
65. Shelton L, Pendse G, Maleki N, et al. Mapping pain activation and connectivity of the human habenula. *J Neurophysiol*. 2012;107:2633–2648.
66. Finkelstein Y, Zhang N, Fitsanakis VA, et al. Differential deposition of manganese in the rat brain following subchronic exposure to manganese: a T1-weighted magnetic resonance imaging study. *Isr Med Assoc J*. 2008;10:793–798.
67. Sidoryk-Wegrzynowicz M, Aschner M. Manganese toxicity in the CNS: the glutamine/glutamate-γ-aminobutyric acid cycle. *J Intern Med*. 2013;273:466–477.
68. Khan MM, Ho BT, Davis CM, et al. Trace element levels in human alcoholic brain. *Alcohol*. 1984;1: 397–401.
69. Saito M, Sawayama T. Neurological picture. Visualised manganese ion within the basal ganglia and long axonal tracts. *J Neurol Neurosurg Psychiatr*. 2009;80:695.
70. Mok SI, Munasinghe JP, Young WS. Infusion-based manganese-enhanced MRI: a new imaging technique to visualize the mouse brain. *Brain Struct Funct*. 2012;217:107–114.
71. Korte JE, Magruder KM, Chiuzan CC, et al. Assessing drug use during follow-up: direct comparison of candidate outcome definitions in pooled analyses of addiction treatment studies. *Am J Drug Alcohol Abuse*. 2011;37:358–366.
72. Beresford TP, Arciniegas DB, Alfers J, et al. Hippocampus volume loss due to chronic heavy drinking. *Alcohol Clin Exp Res*. 2006;30:1866–1870.
73. Ozsoy S, Durak AC, Esel E. Hippocampal volumes and cognitive functions in adult alcoholic patients with adolescent-onset. *Alcohol*. 2013;47:9–14.
74. Medina KL, Schweinsburg AD, Cohen-Zion M, et al. Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicol Teratol*. 2007;29:141–152.
75. Wrase J, Makris N, Braus DF, et al. Amygdala volume associated with alcohol abuse relapse and craving. *Am J Psychiatry*. 2008;165:1179–1184.
76. Sameti M, Smith S, Patenaude B, et al. Subcortical volumes in long-term abstinent alcoholics:

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associations with psychiatric comorbidity. *Alcohol Clin Exp Res*. 2011;35:1067–1080.

77. Chanraud S, Martelli C, Delain F, et al. Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning. *Neuropsychopharmacology*. 2007;32:429–438.
78. Le Berre A-P, Rauchs G, La Joie R, et al. Impaired decision-making and brain shrinkage in alcoholism. *Eur Psychiatry [Internet]*. 2012. [Epub ahead of print]. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0924933812001368. Accessed February 28, 2013.
79. Durazzo TC, Tosun D, Buckley S, et al. Cortical thickness, surface area, and volume of the brain reward system in alcohol dependence: relationships to relapse and extended abstinence. *Alcohol Clin Exp Res*. 2011;35:1187–1200.
80. Cardenas VA, Durazzo TC, Gazdzinski S, et al. Brain morphology at entry into treatment for alcohol dependence is related to relapse propensity. *Biol Psychiatry*. 2011;70:561–567.
81. Gazdzinski S, Durazzo TC, Mon A, et al. Cerebral white matter recovery in abstinent alcoholics—a multimodality magnetic resonance study. *Brain*. 2010;133:1043–1053.
82. Mon A, Delucchi K, Durazzo TC, et al. A mathematical formula for prediction of gray and white matter volume recovery in abstinent alcohol dependent individuals. *Psychiatry Res Neuroimag*. 2011;194:198–204.
83. Mon A, Durazzo TC, Gazdzinski S, et al. Brain-derived neurotrophic factor genotype is associated with brain gray and white matter tissue volumes recovery in abstinent alcohol-dependent individuals. *Genes Brain Behav*. 2013;12:98–107.
84. Puls I, Mohr J, Wrase J, et al. Synergistic effects of the dopaminergic and glutamatergic system on hippocampal volume in alcohol-dependent patients. *Biol Psychol*. 2008;79:126–136.
85. Anantharaju A, Van Thiel DH. Liver transplantation for alcoholic liver disease. *Alcohol Res Health*. 2003;27:257–268.