The nucleus accumbens and alcoholism: a target for deep brain stimulation

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Alcohol use disorder (AUD) is a difficult to treat condition with a significant global public health and cost burden. The nucleus accumbens (NAc) has been implicated in AUD and identified as an ideal target for deep brain stimulation (DBS). There are promising preclinical animal studies of DBS for alcohol consumption as well as some initial human clinical studies that have shown some promise at reducing alcohol-related cravings and, in some instances, achieving long-term abstinence. In this review, the authors discuss the evidence and concepts supporting the role of the NAc in AUD, summarize the findings from published NAc DBS studies in animal models and humans, and consider the challenges and propose future directions for neuromodulation of the NAc for the treatment of AUD.

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DEEP brain stimulation (DBS) has been successfully used for the treatment of movement disorders for more than 2 decades. More recently, DBS has been applied toward the treatment of a wide variety of neuropsychiatric disorders. Given the significant disease and economic burden of disorders of addiction, DBS has been proposed as a therapeutic strategy for treatment-refractory individuals.¹⁸ This is especially relevant for alcohol use disorder (AUD), in which current medical therapies and intensive treatment programs suffer from high rates of noncompliance, variable effectiveness, and serious side effects. Indeed, up to 75% of treated alcoholics relapse within 3 years.⁶⁴ The nucleus accumbens (NAc) plays a central role in the mesolimbic reward pathway, and has been the most well-studied target for neuromodulatory therapies for AUD.³⁶ In this review, we will discuss the evidence and concepts supporting the role of the NAc in AUD, summarize the findings from published NAc DBS studies in animal models and humans, and consider the challenges and propose future directions for neuromodulation of the NAc for the treatment of AUD.

Alcohol use disorder affects more than 76 million people worldwide⁵¹ and is classified by the *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)* into 3 distinct gradations: mild, moderate, and severe, with each correlating to increasing degrees of addiction or dependency.¹ However, as a drug of abuse alcohol is unique in that binge consumption of large quantities of alcohol beyond what is necessary to achieve normal intoxication is exhibited at all levels of AUD, and is the preferred method of consumption for those with the most severe AUD. In the US, binge drinking is how most young Americans are introduced to alcohol, and is responsible for 90% of the alcohol consumed by individuals under the age of 21 years.⁴⁸ Indeed, 70% of the binge drinking in the US occurs in people who are younger than 26 years,²⁶ and this behavior in early adulthood is highly predictive of alcohol dependence.⁴³ The economic burden of alcohol misuse in the US is estimated at \$250 billion dollars or more than 2% of gross domestic product (GDP), and three-quarters of this is directly related to binge-drinking behavior.⁵⁷

Conceptually, AUD can be defined as a disorder that

ABBREVIATIONS AUD = alcohol use disorder; AUQ = Alcohol Urge Questionnaire; BOLD = blood oxygen level–dependent; DBS = deep brain stimulation; fMRI = functional MRI; GABA = γ -aminobutyric acid; mPFC = medial prefrontal cortex; NAc = nucleus accumbens; VTA = ventral tegmental area.

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includes a progression from impulsivity driven by positive reinforcement in the initial states of AUD to compulsivity driven by negative reinforcement in severe AUD (Fig. 1). Negative reinforcement is defined as drug taking to relieve a negative emotional state that is derived from dysregulation of reward and stress response circuitry within basal forebrain structures including the NAc and amygdala. These pathological states are further compounded by physiological and mental withdrawal symptoms experienced by those with severe AUD.³⁷

Nucleus Accumbens and Alcohol

It was first suggested in the 1970s that drug addiction was intimately related to dysregulation of the neural reward circuitry,⁴ and since that time all drugs of abuse, including alcohol, have been demonstrated to increase dopamine levels in the brain—with the most pronounced effect occurring in the NAc, which is the primary target of the mesolimbic dopamine system and the center of the brain's reward system.⁴² There is a robust body of evidence supporting the effect of alcohol on the NAc. In murine models, increases in serum ethanol levels via direct injection have been demonstrated to increase extracellular dopamine levels measured by in vivo microdialysis and

voltammetry.²⁹ Similarly, voluntary consumption of ethanol increases accumbal dopamine levels and restores deficits in dopamine seen in withdrawal states in ethanol-dependent rats.⁴⁴ Dopamine levels in the NAc also increase in anticipation of ethanol availability, implicating the NAc in the alcohol relapse process.⁴¹ Conversely, in multiple rodent studies, blockades of dopamine receptors within the NAc have successfully reduced ethanol consumption,⁹ an effect that may be mediated via a D2 receptor mechanism.⁵⁰ Furthermore, lesioning of dopaminergic neurons or dopamine targets within the NAc increases ethanol consumption.^{21,52} More specifically, it has recently been demonstrated that the functionally and anatomically distinct subregions of the NAc—the core and the shell—are involved in alcohol-seeking behavior. Pharmacological inactivation of the NAc core reduced conditioned responses to discrete alcohol cues, implicating the NAc core in cue-induced relapse behavior. Conversely, pharmacological inactivation of the of the NAc shell reduced conditioned responses to alcohol contexts, implicating the NAc shell in context-induced relapse behavior.⁶

On a cellular level, γ -aminobutyric acidergic (GABAergic) medium spiny neurons make up the majority of the neurons of the NAc. They receive extensive glutamatergic inputs from limbic areas such as the medial prefrontal

FIG. 1. Impulse-control disorder and compulsive disorder cycles in patients with AUD. **Upper left:** Within the initial impulse-control disorder cycle, tension and arousal occur before the impulsive act, with pleasure, gratification, or relief experienced during the act, followed by regret or guilt. In compulsive disorders, obsessions (recurrent and persistent thoughts) cause marked anxiety and stress, followed by compulsions (repetitive behaviors) that are aimed at preventing or reducing distress. Positive reinforcement is associated with impulse-control disorders, and negative reinforcement is closely associated with compulsive disorders. **Upper right:** The addiction cycle can be conceptualized as consisting of 3 major components: preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect. **Lower:** Change in the relative contribution of positive and negative reinforcement constructs during the development of dependence on alcohol.³⁷ Reprinted by permission from Springer Nature: Springer. *Curr Top Behav Neurosci*. Theoretical frameworks and mechanistic aspects of alcohol addiction: alcohol addiction as a reward deficit disorder. Koob GF. © 2013.

cortex (mPFC), hippocampus, and basolateral amygdala, and they project widely to the ventral pallidum, substantia nigra, and ventral tegmental area (VTA), as well as forming interconnections within the NAc.^{63,71} Medium spiny neuron plasticity has been shown to be critical in addictive states,¹⁵ and several studies have also supported the central role of medium spiny neurons in mediating the reinforcing properties of alcohol.^{49,54} Recently, it has been revealed that mPFC projections to the medium spiny neurons of the NAc are critical for paired alcohol-cue associations and that ablation of these projections decreases the cue-induced reinstatement of previously conditioned alcohol-consumption behavior.³³ Finally, the role of the VTA-dependent dopamine release from terminal fields within the NAc in ethanol-drinking behaviors has also been elucidated. Activity of these VTA-NAc projections correlate with degree of ethanol consumption, and optogenetic stimulation of the VTA and specific VTA-NAc projections induced tonic increases in NAc dopamine-attenuated ethanol-drinking behavior in rodent models.^{2,31}

In humans, advances in neuroimaging have allowed neurochemical and functional studies of alcohol consumption that have also implicated the NAc. Alcohol consumption in human studies has enhanced extracellular dopamine levels in the NAc, and these effects were correlated with subjective feelings of euphoria and stimulation.^{53,65} Significant derangements of the dopamine system have been seen in abstinent alcoholics, in whom studies have demonstrated reduced dopamine synthesis, decreased numbers of D2/3 receptors, and reduced binding to these receptors after dopamine reuptake inhibitor challenges (methylphenidate or amphetamine) compared to normal controls.²² The opposite effects are seen in alcohol craving states or in subsequent relapse states. Similarly, in functional blood oxygen level-dependent (BOLD)-MRI studies of heavy consumers of alcohol there is increased BOLD activation within mesolimbic circuitry, including the NAc, in response to alcohol cues compared to results in light consumers. This cue-induced activity within the NAc was strongly correlated with length of alcohol use.^{7,28} In fact, in a meta-analysis of all alcohol cue-induced functional imaging studies, NAc activation correlated most strongly with degree of AUD and with AUD treatment response.⁵⁸ Taken together, the data from animal and human studies strongly support the notion that it is a reduced baseline dopamine activity within the NAc and concomitant hyperactivity in response to alcohol cues and contexts that increasingly drives alcohol consumption in the progression of AUD.

Nucleus Accumbens DBS

The history of neurosurgical treatment of AUD begins with ablative therapies. The first large series of alcohol-addicted patients treated with bilateral stereotactic cingulotomy, reported by Kanaka and Balasubramaniam in 1978, demonstrated complete abstinence in 68% of patients.³² However, there have since been neurocognitive side effects (including impaired focused attention and other executive impairments) reported from this procedure.⁷³ Based on evidence in humans and animals that blocking the NAc

response to drugs and drug-related cues may decrease cravings and relapse rates, more recent ablative therapies have focused on the NAc. A group from China published a study of 28 drug-addicted patients who underwent bilateral ablation of the NAc core, with a mean follow-up of 15 months. Complete remission was achieved in 7 patients, and 10 patients relapsed within 6 months but with less severe symptoms.¹² Long-term follow-up and expansion of this treatment cohort revealed a 47.4% total 5-year abstinence rate in the 60 individuals who completed the therapy. Several psychological indices were also improved in those who remained abstinent.¹³

Although the exact mechanism of high-frequency DBS has not been elucidated, there are several hypotheses that question whether target inhibition—in a manner similar to an ablative lesionectomy—may occur via 1) a depolarization blockade,³ 2) GABA-mediated synaptic inhibition,¹⁰ or 3) stimulation-mediated synaptic depletion.⁶⁶ Other theories suggest that DBS desynchronizes pathological neuronal network activity.²⁰ Whatever the exact mechanism of action, the rationale of applying DBS toward the NAc in the treatment of AUD is based on its role in the processing of rewards and cognitive control in the face of cue-induced cravings, and the efficacy of this therapy has been studied in both animal models and in human subjects (Fig. 2).

Animal Investigations

Details of all published animal studies of NAc DBS for AUD can be found in Table 1. The first animal study of DBS in AUD was published in 2009 by Knapp et al.

FIG. 2. NAc DBS. A T2-weighted MRI scan in the coronal view representing bilateral implantations of DBS leads in the ventral capsule/ventral striatum in the region of the NAc.¹⁸ Reprinted by permission from Springer Nature: Springer-Verlag GmbH Austria. *Acta Neurochir (Wien)*. Expanding applications of deep brain stimulation: a potential therapeutic role in obesity and addiction management. Halpern et al. © 2011.

TABLE 1. Summary of animal studies of DBS for alcoholism

Authors & Year	Animal	EtOH Procedure	DBS	Stimulation Parameters	Results
Knapp et al., 2009	Long-Evans rats, males	Continuous access to 10% EtOH, 4- to 6-wk conditioning period via saccharin fading procedure	Bilat, NAc shell or core	DBS "on" 5 min prior to EtOH access, then for 30-min consumption period: 160 Hz, 200- μ sec pulse width, escalating intensities 0, 50, 75, 100, & 150 μ A	Significantly decreased w/ increasing intensities of stimulation, no difference btwn shell or core
Henderson et al., 2010	Alcohol-preferring (P) rats, males	Continuous access to 10% EtOH, 2-wk conditioning period followed by 4- to 6-wk deprivation	Bilat, NAc	DBS "on" & "off" during 24-hr EtOH reintroduction period: 140–150 Hz, 60- μ sec pulse width, & 200 μ A	EtOH preference & consumption significantly reduced in DBS "on" vs "off" conditions
Willden et al., 2014	Alcohol-preferring (P) rats, females	Access to 15% EtOH for 1 hr/day, 4-wk conditioning period	Unilat (lt), NAc	DBS "on" for 5 days: 150 Hz, 100- μ sec pulse width, & current intensities of 100 μ A or 200 μ A	Significant decreases in EtOH consumption during DBS stim "on" that were both intensity dependent (greater effect at 200 μ A) & increased over time
Hadari et al., 2016	Wistar rats, males	Continuous access at varying concentration (5%, 10%, 20%), 8-wk conditioning followed by 2-wk deprivation cycles (initial cycle nondependent, following cycles dependent)	Bilat, NAc shell	DBS "on" 3 days prior to reinitiation of EtOH: 130 Hz, 90- μ sec pulse width, & 5.25 V	Nondependent animals significantly decreased EtOH consumption w/ DBS "on," dependent animals w/ DBS "on" increased relapse-driven EtOH consumption behavior; fMRI data revealed activation of mPFC, caudate, & putamen in DBS "on"; nondependent animals w/ dopa reduction in NAc, dependent animals w/ dopa increase in NAc

Dopa = dopamine; EtOH, EtOH consumption = ethanol, EtOH consumption.

In that study, Long-Evans rats were given access to 10% ethanol with water until intake stabilized. Bilateral DBS leads were then implanted in either the shell or the core of the NAc, and DBS was delivered for 5 minutes prior to ethanol access and then continued for 30 minutes, during which the volume of consumption was measured. Ethanol consumption was significantly reduced with increasing intensities of DBS, but there was no significant difference in consumption between those rats receiving NAc core or shell DBS.³⁵

In 2010, a second study by Henderson et al. used alcohol-preferring rats that were selectively bred to spontaneously binge ethanol in large quantities and, similar to humans, have also been shown to also increase intake after a period of deprivation. These animals underwent placement of bilateral NAc DBS, and both alcohol preference and consumption were significantly reduced in DBS "on" conditions versus sham stimulation "off" conditions.²⁵

In 2014 another study was conducted in female alcohol-preferring rats in which animals were implanted with a unilateral (left) DBS, then resumed on a drinking protocol of 1 hour a day of 15% ethanol. Subsequently, DBS was administered during ethanol exposure times for 5 days, and significant decreases were seen in ethanol consumption during the stimulation periods that were both stimulation intensity-dependent (greater effect at 200 μ A) and increased over time (drop in ethanol consumption was greater with each successive day).⁶⁸

Finally, a more recent study sought to examine the effects of NAc DBS on gating relapse-like drinking behavior in a male Wistar rat model that combined stimulation with functional MRI (fMRI) and neurotransmitter (dopamine) data. Rats were given continuous access to varying concentrations of ethanol for 8 weeks prior to a 2-week deprivation period before experimental ethanol exposure was instituted. Following the first deprivation period animals were considered nondependent on ethanol, and on successive repetitions of the protocol were considered ethanol dependent. Chronic continuous DBS was initiated during each deprivation period 3 days prior to reinstatement of ethanol. The fMRI data obtained during this period revealed activation of the mPFC, caudate, and putamen. Although initial stimulation in nondependent animals significantly decreased ethanol consumption, subsequent cycles of stimulation in so-called dependent animals actually increased relapse-driven ethanol-consumption behavior. A similar trend was seen with dopamine activity following DBS.¹⁶

Human Studies

In humans, the impact of NAc stimulation on alcohol consumption has only been reported in a handful of patients. The details of these studies are listed in Table 2. The first was a case report by Kuhn et al. published in 2007 that detailed the course of a 54-year-old man with severe anxiety, secondary depressive disorder, and severe alcohol dependency with daily alcohol consumption of more than 10 drinks/day and previous hospitalizations for withdrawal. NAc DBS was offered as a pilot intervention due to the severity of the symptoms and the refractory nature of the psychiatric disorder in this individual, the past

TABLE 2. Summary of patients treated with NAc DBS for alcoholism

Authors & Year	Case No.	Age (yrs)	Before DBS					After DBS						
			Yrs Add	EtOH Consump	Lab Results	ADS	Use Scale, Score	Side Effects	FU (mos)	Lab Results	Use Scale, Score	EtOH Consump	Relapse	MM
Kuhn et al., 2007	1	54	>10	10+ drinks/day	CDT 5.2%, GGT 185 U/L		AUDIT, 28	Acute feeling of "inner appease-ment"	12	CDT 1.5%, GGT 43 U/L	AUDIT, 1	1–2 drinks/day		
Kuhn et al., 2011	1	69	>30	0.2 L hard liquor/day	CDT 7.8%	17	AUDIT, 32		12	CDT 1.9%	AUDIT, 14	Abstinent		
Heldmann et al., 2012	1	38	>20					Hypomania, re-solved w/ parameter adjustment	35			Abstinent		
Müller et al., 2016	1	40	23	3 L hard liquor/day		34	AUQ, 37		95		AUQ, 8	Abstinent		
Voges et al., 2013	2	35	17	2 L hard liquor/day		41	AUQ, 29		Approx 84		AUQ, 8	Abstinent		
Müller et al., 2009	3	37	22			28	AUQ, 53	Hypomania, re-solved w/ parameter adjustment	Approx 90		AUQ, 8	Reported elimination of cravings	Continuous short re-lapses attributed to external stressors	Incarceration, death
	4	51	21			22	AUQ, 20		Approx 42		AUQ, 8	Abstinent for 12 mos, elimination of cravings	Continuous short re-lapses attributed to external stressors	Major depressive episode, death
	5	55	19			33	AUQ, 14		24		AUQ, 8	Abstinent for 20 mos, elimination of cravings	Continuous short re-lapses	Depression diagnosis

ADS = alcohol dependence scale; AUDIT = alcohol use disorders identification test; CDT = carbohydrate-deficient transferrin; FU = follow-up; GGT = g-glutamyltransferase; lab = laboratory; MM = morbidity and mortality; Yrs Add = years addicted.

efficacy of DBS in treating obsessive-compulsive disorder and anxiety, and the reciprocal interest of the patient.⁶² He received bilateral NAc DBS, and optimal settings that minimized adverse reactions were reached after an initial programming period of several weeks. There was no change in the severity of the patient's anxiety or depression. However, following initiation of DBS, the patient rapidly and drastically reduced his alcohol consumption, and within 1 month was consuming 1–2 drinks/day and subjectively reported having completely lost the desire to drink.⁴⁰ This same group treated another patient in 2011: a 69-year-old man with a more than 30-year history of alcohol dependence, consuming more than 200 g of vodka daily. He also received numerous detoxifications, withdrawal treatments, and psychopharmacological interventions that had all failed. Similar to the first patient, after receiving bilateral NAc DBS, the patient began to remarkably reduce his alcohol consumption and was completely abstinent after 1 year.³⁹

Because of published reports such as the Kuhn et al. 2007 study, a small clinical trial was initiated with the goal of enrolling multiple patients for NAc DBS for the treatment of severe alcoholism.^{23,47} A total of 5 patients included in this study were considered severely addicted to alcohol and on average consumed at least 200 g of ethanol per day for more than 10 years, and previous detoxifications, inpatient programs of at least 6 months, and pharmacological interventions (acamprosate and/or naltrexone) had all failed.^{23,46,67} After receiving bilateral NAc DBS, the patient in case 1 became completely abstinent without any cravings or psychological side effects, and remained abstinent 8 years after initiation of treatment. The patient in case 2 experienced a marked reduction in alcohol-related cues and cravings, and on the last long-term follow-up evaluation had been abstinent for 6 years since initiation of treatment. The patient in case 3 had both a significant drinking as well as an incarceration history, but also enjoyed a 1-year period of abstinence following initiation of NAc DBS therapy. However, he then experienced several short periods of relapse, although he reported significant reduction in alcohol-related cravings, and instead attributed his relapses to significant external life stressors. Unfortunately, 3 years after implantation he was incarcerated for 4 years, and his alcohol cravings resurfaced after his battery ran out of power while he was incarcerated. The patient died soon after of unknown causes. The patient in case 4 also enjoyed an initial abstinent period of 1 year, but then he had several short-term relapses attributed to external stressors. He developed major depressive disorder at 3 years that was treated into remission. However, he continued to relapse into the 4th year, claiming that the alcohol helped him cope with the tragic death of his brother, and he was eventually lost to follow-up. He was found dead in his home some time later of unknown causes. The patient in case 5 had nearly 20 months of abstinence before the first of several short relapses every 2–3 months. He also reported a disappearance of cravings but the continued presence of external life stressors that drove his relapses. He developed depressive symptoms 24 months after treatment that were also treated with antidepressant medication and psychotherapy.

All patients in this trial reported resolution of alcohol cravings including cue-induced cravings in everyday life, consistent with their Alcohol Urge Questionnaire (AUQ) results post-DBS. Despite a reduction in their declared urge, several patients were unable to remain completely abstinent, leaving room for the possibility that consumption of alcohol essentially shifted from goal-directed behavior to habitual behavior. The absence of craving for alcohol is consistent with the hypothesis that DBS of the NAc may be modulating the reward system of the brain, which was otherwise modulated maladaptively by alcohol.^{11,30} Two of the 5 patients died, with implications that continuous alcohol consumption contributed to their deaths. However, it is difficult to identify with certainty what was the cause of death in these patients.^{23,24,46}

Challenges and Future Directions

Modeling of AUD

Given the complexity of AUD, animal models are crude in comparison to the full spectrum of human AUD, and no single animal model can represent all the various combinations and complexities embodied in human alcoholism. However, across multiple partial paradigms it is possible to capture hallmarks of analogous physiology and behaviors. Long-term continuous access,³⁵ coupled with a period of deprivation to produce an alcohol deprivation effect⁶¹ may better mirror the long-term consequences of alcoholism and be a better vehicle with which to study the relapse and withdrawal aspects of the chronic disease,²⁵ whereas more short-term, intermittent exposure may better provoke binge patterns of heavy drinking that can reliably achieve human levels of intoxication with blood ethanol concentrations of greater than 0.08% (80 mg/dl).⁴⁸ Contrasting the positive reinforcement drivers of impulsivity with the negative reinforcement drivers (i.e., withdrawal, negative emotional states) of the compulsion that develops with long-term alcoholism, binge consumption behavior in both stages is motivated by different factors and does not represent the same underlying neurological pathology.³⁸ Heightened reward sensitivity related to loss of top-down control from the PFC and dysregulation of mesolimbic circuitry leads to impulsivity and is the primary and most specific behavioral pathology targeted in NAc stimulation.^{14,34} This picture is complicated once long-term dependence and withdrawal states are invoked, because binge behavior becomes driven not only by impulsivity that is primarily controlled by the NAc, but also under the influence of negative emotional states and limbic system deregulation.⁶⁹ Targeting of the specific impulse-driven binge behavior has been effective in ameliorating consummatory behaviors such as binge eating.¹⁷ Future studies of NAc DBS should be clear regarding the specific component of AUD being modeled and should be geared toward more reliable models of impulsivity-driven binge-drinking behaviors.^{56,59}

Mechanism of NAc DBS

Although numerous studies demonstrate a reliable treatment effect of NAc DBS on binge alcohol-drinking behaviors in animal models, a clear delineation of possible underlying mechanisms of NAc DBS remains elusive

and warrants closer study. For example, in binge eating, Halpern et al. found that D2 receptor antagonists reversed the modulatory effects of DBS in a mouse model of binge eating, suggesting that dopamine signaling specific to D2 receptors played a crucial role in the effect of NAc DBS.¹⁷ This is congruent with initial findings that D2 receptor-deficient mice had a marked aversion to ethanol compared to wild-type littermates and that there was no change in this phenotype with administration of D1 receptor antagonists.⁵⁰ Similar mechanistic studies need to be undertaken in the context of NAc DBS in models of binge ethanol consumption. As avenues for molecular and electrochemical inquiry continue to progress, more targeted and robust techniques should be considered. For example, reverse pharmacogenetic inactivation of NAc-specific neuronal firing with Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) was able to suppress alcohol consumption in a “Drinking in the Dark” (DID) binge-drinking mouse model.⁵ Another recent study used retrograde tracing, electrophysiology, optogenetics, and behavioral assays to identify region-specific subpopulations within the NAc shell that exert differential effects. Neurons in the medial shell subdivision of the NAc were revealed to exert direct inhibitory control over mesolimbic dopamine neurons within the VTA via activation of GABA receptor subtypes, whereas lateral shell neurons mainly synapsed onto VTA GABA neurons that participated in a feedback loop to the NAc.⁷² Coupling these new mechanistic experimental paradigms with NAc DBS and robust behavioral binge-drinking models will be critical for discovery of the underlying mechanism by which NAc stimulation may exert its effects.

Clinical Considerations

It is clear from the small sample size of the cases reviewed above that, although NAc DBS for the treatment of alcoholism may have some powerful effects in terms of alcohol craving and consumption reduction, this is an inherently difficult patient population that is prone to morbidity and mortality. Although craving-induced ethanol consumption may be effectively targeted with this surgical approach, there appear to be few positive ancillary effects on comorbid psychiatric conditions such as anxiety and depression,^{40,46} and external psychosocial stressors, such as incarceration or a death in the family, can lead to alcohol relapse despite lack of cravings. Although they were probably multifactorial in etiology, the two unexplained deaths from the single completed trial of NAc DBS for alcoholism underscores the overall limitations in improving the general well-being of these patients despite successful targeted intervention for reducing alcohol consumption.⁴⁶ A similar experience was seen in a recent study for NAc DBS for morbid, treatment-refractory obesity, in which 3 patients received implants—1 of whom withdrew from the study and ultimately had the leads explanted; 1 patient committed suicide; and 1 patient successfully completed the 3-year study, with an impressive BMI reduction from 55.7 to 39.3 kg/m². The study authors also concluded that it was the psychiatric comorbidities and exposure to significant psychosocial stressors that led to the poor outcomes.⁵⁵ These parallel lessons from previous studies of binge be-

havior should be well taken for future trials of this interventional paradigm. Attention should be paid not only to the adoption of stringent inclusion and exclusion criteria for enrollment, but a protocol should be established for mitigation of and building a support system for the inevitable psychosocial stressors encountered in this difficult patient population with medically refractory consumption-related addictions.

Finally, previous studies have all adopted conventional continuous “open-loop” DBS paradigms that have been successful in the treatment of movement disorders. Recent success with responsive neurostimulation systems in the treatment of epilepsy has demonstrated the effectiveness of “closed-loop” recording and intermittent stimulation systems for the treatment of episodic electrical pathology within the brain.⁴⁵ Consumption-driven disorders of impulsivity may be ideal for this type of closed-loop treatment if stimulation could be delivered during brief windows of anticipation, or so-called moments of weakness prior to the initiation of a binge.^{8,60} Wu et al. recently published a translational study validating this technique. They were able to identify a conserved local-field-potential biomarker of delta (1–4 Hz) oscillations from NAc recordings in mice prior to a food binge and in humans during a monetary incentive delay task. This local-field-potential biomarker was then used in a closed-loop responsive neurostimulator system to effectively ameliorate binge-eating behavior in mice with only targeted stimulation delivered at times of binge anticipation.⁷⁰ If analogous electrographic biomarkers of reward anticipation can be identified in binge drinking, a similar closed-loop approach may be effective for the treatment of alcoholism via the NAc and may help minimize any potential stimulation-related side effects. Indeed, a study that coupled cue-reactive fMRI BOLD signal data with resting-state electroencephalographic recording demonstrated that increased beta activity in the anterior cingulate cortex and gamma activity in the anterior cingulate cortex, ventromedial PFC, and orbitofrontal cortex revealed a hyperconnected central craving network that was disrupted with introduction of alcohol cues. Cue reactivity was correlated with increased fMRI BOLD activity in the amygdala, parahippocampal gyrus, NAc, and striatum.²⁷ This finding of coordinated neural and metabolic activity in response to alcohol stimulus would support the notion that a similar anticipatory signature may be present within the NAc and could be used as a trigger for stimulation.

Conclusions

Alcohol use disorder is a difficult to treat condition with a significant global public health and cost burden. The NAc has been implicated in AUD and identified as an ideal target for DBS. Although some initial clinical studies have shown some promise at reducing alcohol-related cravings and, in some instances, achieving long-term abstinence, patients with AUD are an inherently difficult patient population to manage. Continuing studies are necessary to establish efficacy, with a focus on mitigation of outside psychosocial stressors encountered during treatment periods. Future efforts may also clarify the underlying molecular

and electrophysiological mechanisms of NAc stimulation in AUD, and leverage newer responsive technologies to further refine and improve neuromodulatory treatments.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Halpern, Ho, Giardino. Acquisition of data: Ho, Salib. Analysis and interpretation of data: Halpern, Ho, Salib. Drafting the article: Ho, Salib. Critically revising the article: Halpern, Ho, Pendharkar, Sussman, Giardino. Reviewed submitted version of manuscript: all authors. Administrative/technical/material support: Halpern, Pendharkar, Sussman, Giardino. Study supervision: Halpern, Giardino.

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