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Choosing the Optimal Brain Target for Neuromodulation Therapies as Alcohol Addiction Progresses—Insights From Pre-Clinical Studies

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Abstract

Purpose of the Review Development of addiction involves a transition from reward-driven to habitual behavior, mediated by neuroplastic changes. Based on preclinical findings, this article article reviews the current knowledge on the use of neuromodulation therapies to target alcohol addiction and essentially reduce relapse.

Recent Findings To date, only a limited number of preclinical studies have investigated the use of neuromodulation in alcohol addiction, with the focus being on targeting the brain reward system. However, as addiction develops, additional circuits are recruited. Therefore, a differential setup may be required when seeking to alter the chronic alcohol-dependent brain, as opposed to treating earlier phases of alcohol addiction.

Summary To promote enduring relapse prevention, the choice of brain target should match the stage of the disorder. Further studies are needed to investigate which brain areas should be targeted by neuromodulating strategies, in order to sufficiently alter the behavior and pathophysiology as alcohol addiction progresses.

Keywords Alcohol addiction · Neuromodulation · Neuroplastic changes · Neuronal circuits · Brain reward system

Introduction

Alcohol use disorder is a chronic disorder, in which patients continue to engage in devastating drinking behavior despite the negative repercussions [1]. The development of addiction is thought to involve a transition from pleasure-driven consumption to a habitual behavior that includes the loss of control over drug intake and sometimes compulsive behavior. In accordance, patients with alcohol use disorder may display high impulsivity and compulsivity, paralleled with alcohol-related positive and negative reinforcements [2–6]. Initial drug use is typically characterized by positive reinforcement mechanisms, in which the drug reward reinforces actions of drug seeking (goal-directed behavior). Gradually, with repeated cycles of alcohol drinking and withdrawal episodes, there is a shift toward negative reinforcement mechanisms, whereby alcohol is consumed to alleviate the negative affect and withdrawal syndromes [7]. This may eventually lead to the establishment of habitual and to some extent compulsive alcohol seeking and consumption, as well as loss of control [4]. It is believed that Pavlovian learning is involved within this course of development. Thus, neutral cues presented with alcohol can acquire new relevance and motivational value by forming a cue-alcohol association, hence predicting the occurrence of alcohol reward. Accordingly, drug-related stimuli acquire incentive salience and induce excessive emotional and motivational response when presented [8]. Drug-related stimuli can hence trigger craving and drug-seeking behavior and eventually lead to relapse [9]. The tendency to attribute excessive motivational salience to cues varies between subjects; in both humans and animal models, it is suggested that this tendency predisposes the individual to develop addiction [10]. The tendency toward an increased incentive salience may result from drug-induced alterations in the brain reward system [11, 12].

Once addiction has been established, it tends to become chronic, with a persistent "addiction memory" being formed.

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The existence of addiction memory increases the risk of relapse even after years of abstinence and makes it difficult to treat [13–15]. Therefore, there is a clear need for interventions that would disrupt the addiction cycle and reduce relapse rates.

Currently, treatment of alcohol addiction includes a combination of psychosocial modalities and pharmacological interventions, with FDA-approved pharmacotherapies such as naltrexone, acamprosate, and disulfiram mainly being administered to reduce alcohol craving and consumption [14, 16]. Despite a combined treatment approach, therapeutic effects are often limited. Maintaining long-term abstinence remains a considerable challenge, which in part may be attributed to medical treatments lacking precision, alongside the need of continuous compliance from the patient [16–18].

Data from clinical and preclinical studies have identified addiction as a disorder of distinct neuronal circuits, in which the formation of alcohol tolerance may reflect homeostatic adjustments due to continuous exposure to the substance [2, 19••, 20–23]. Based on this view, the use of neuromodulation strategies has emerged as a mean to directly target the neuronal circuits and thereby the pathophysiology that is keeping patients in a cycle of alcohol abuse. So far, clinical trials have investigated the use of different techniques to intervene with alcohol addiction, including both deep brain stimulation (DBS) [24–26], transcranial magnetic stimulation (TMS) [27–29], and transcranial direct current stimulation (tDCS) [30–32]. To date, these intervention strategies have mainly targeted reward circuits involved in addiction manifestation. Results seem to be encouraging; however, there is a considerable knowledge gap when it comes to understanding how neuromodulation works in the brains of patients with addiction and whether neuromodulation is able to promote long-lasting relapse prevention. This necessitates a more profound comprehension of the mechanisms and effects of neuromodulation on the neurocircuitry and neurobiology and its summed/translated effects on behavior. Considering that additional circuits may be involved in the development and manifestation of addiction (i.e., circuits mediating habitual and even compulsive behavior, Pavlovian and instrumental learning, and the implementation of addiction memory), the optimal brain target and stimulation settings need to be identified and should be adjusted individually, according to patients' disease profiles.

Such in-depth investigations are often hindered in the clinic, due to the obvious ethical and regulatory limitations. Hence, preclinical research is crucial for comprehending the addiction-affected neuronal mechanisms, as well as the implications of stimulating various targets of the brain of patients with addiction. The following review focuses on preclinical research of the use of neuromodulating strategies in the treatment of alcohol use disorder.

The Neural Circuits Involved in the Development of Alcohol Addiction

The transition from controlled alcohol use to chronic alcohol drinking involves sequential alterations and recruitment of several neuronal circuits [19••, 33, 34]. It has been hypothesized that with the progression from moderate to out-of-control "compulsive" alcohol consumption, the motivational drive shifts from positive toward negative reinforcement. This progression is first reflected in the neuroplastic changes within the brain reward system, eventually proceeding to include other circuits mediating among others stress responses, habit formation, and executive functions [7, 19••, 33–35]. As such, addiction is considered a disorder of the learning and memory system, in which addictive behavior is established due to long-term plastic changes [12, 36–40]. This learned reaction plays an essential role in the recurrence of relapse, in which the encoded memory may initiate alcohol-seeking and alcohol-drinking behaviors, even following a long period of stable abstinence [36, 41].

In the development of addiction, three overall stages have been described, which include the stage of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation [7]. The initial stage of binge/intoxication is centered around the rewarding properties of a drug, alongside the development of incentive salience. The mesocorticolimbic pathway mediates the rewarding effect of a substance and translates motivation into goal-directed behavior [42, 43]. The mesocorticolimbic circuit includes dopaminergic projections from the ventral tegmental area (VTA) to the prefrontal cortex (PFC), the ventral striatum, the amygdala, and the hippocampus. Here, the nucleus accumbens (NAc) as part of the ventral striatum is considered a key player in the processing of reward [42, 44]. While early changes within the mesocorticolimbic circuit following initial alcohol intake may be transient, chronic excessive alcohol exposure typically fosters long-term alterations in the sensitivity of the circuit. Nevertheless, initial changes within the mesocorticolimbic circuit may lead to conditioned reinforcement and incentive salience, which provides the foundation for developing cue-induced drug-seeking and eventually a transition toward habitual/compulsive behavior [19••, 33].

Whereas positive reinforcement dominates the early stages of alcohol use, the importance of negative reinforcement increases as addiction develops and enters the later stage encompassing withdrawal symptoms/negative affect. Here, the neural substrates involve disruption of the same circuits implicated in positive reinforcement, yet the reinforcing value of alcohol has changed, which reflects a neuronal adaptation as a consequence of chronic alcohol exposure [19••, 45, 46]. In accordance, during the early stages, acute administration of alcohol has been shown to increase the activity of the mesocorticolimbic circuit, whereas chronic alcohol abuse decreases it [47, 48]. Activating the ventral striatum by drug

administration has been found to initially trigger neuroadaptation within this brain region, but long-term excessive drug intake also induces neuroadaptations in the dorsal striatum [40, 49–52]. As such, during the transition from controlled alcohol use to compulsive intake, the initial reinforcing effect of alcohol is found to transit from a ventral striatum reward-based phenomenon to a habitual behavior mediated by the dorsal striatum, in which the rewarding effect plays less of a role [15, 52–54]. It should be mentioned, however, that alterations in the ventral striatum are also observed in humans at the later stages of addiction, including in detoxified patients [15, 55].

The stage of withdrawal/negative affect is subsequently associated with symptoms of emotional dysregulation, which manifests due to recruitment of additional neuronal circuits outside the reward system. Such circuits include the brain stress system mediated by corticotropin-releasing factors, the extended amygdala and the lateral habenula [4, 19••, 56]. The lateral habenula inhibits signals to the VTA, when a behavior needs to be avoided. In alcohol use disorder, the lateral habenula has been found to be hyperactive during the negative emotional state following withdrawal symptoms [57, 58]. The extended amygdala is composed of the bed nucleus of stria terminalis and the medial sub-region of the amygdala. The recruitment of the extended amygdala is considered as a buffering system of the brain, in an attempt to maintain hedonic homeostasis. The extended amygdala functions as neuroanatomical structure that integrates hedonic processing and stress systems and is considered a key player in promoting negative reinforcement seen in addiction [2, 19••]. The recruitment of the extended amygdala is therefore also suggested a focal locus for the allostatic changes found in alcoholism [33]. Further, modulating the amygdala would affect neurotransmitter systems such as GABA and serotonin; the former was shown in the amygdala to be tightly involved in alcohol addiction [59], the later given its input to the amygdala and its association with compulsive impulses in other disorders [60].

The later phase of preoccupation/anticipation involves deficits in cognitive control, cravings, and the potential of relapse. Here, the exposure to specific cues associated with alcohol consumption strongly contributes to relapse long after the acute withdrawal symptoms have vanished [15, 52, 61]. Executive control over incentive salience is essential to maintain a goal-directed behavior. Patients with chronic alcohol addiction may display deficits in executive functions and cognitive control, which is considered a consequence of a dysfunction in several frontocortical areas. In patients, alcohol-associated cues have shown to activate the frontal cortex, including areas such as the dorsolateral prefrontal cortex, anterior cingulate gyrus, and orbitofrontal cortex, which subsequently have been related to increase in alcohol craving and relapse [15, 62]. Within these brain regions, GABAergic and glutamatergic interactions have been implicated in the addiction phenotypes [63–65]. Similar to the prefrontal cortex, other structures are also involved in the cue-induced cravings. These areas include the basolateral amygdala mediating the emotional memories as well as the insula that senses and integrates the information of the individual's physiological state. This information is then projected to the prefrontal cortex and ventral striatum to initiate adaptive behavior [19••,66]. Within the amygdala, the dysregulation of the serotonergic and GABAergic system are found as a neuroadaptive consequence of alcohol intake that deregulates the activity of the amygdala and results in impaired prefrontal cortical regions [59, 67]. As such, the sudden intense urge toward an addictive substance and subsequent diminished cognitive control is thought to reflect an imbalance between an increased bottom-up (subcortical) urge, in combination with a weakened top-down (prefrontal) neuronal control, which in combination leads to relapse [19••, 52, 68, 69].

Essentially, the goal of applying neuromodulating techniques is to interfere and rebalance the disturbed neurobiological processes that ultimately lead to relapse. As the development of addiction reflects a sequential neuroadaptation, this allows for deciphering which brain areas during the course of addiction should be targeted to obtain therapeutic relief. This shows the need for a personalized application of neuromodulating techniques that may range from modulating the reward system to potentially shifting the focus to also include other brain circuits involved in the later habitual or compulsive behavior. At least during the later stages, the neurobiological findings demonstrate the need of remodeling the plastic brain in order to either repress or re-imprint the addictive memory [36, 70, 71].

Modeling Alcohol Relapse

To expand treatment options and improve its outcome by targeting additional brain sites and circuits, there is a need for thorough insights into the dynamics of addiction encompassing alterations in behavior and neurobiology. Such in-depth investigations are possible in preclinical settings. As the brain changes following continuous drinking, this highlights the need for diverse animal models for the investigation of relapse behavior during the phases of the addiction cycle. Rodents are not naturally drinkers and therefore do not normally engage in drinking behavior to an extent that induces dependency [72•, 73]. Therefore, establishing an animal model that displays craving or relapse toward ethanol requires that the animal is trained toward such behavior.

The reinstatement model and the alcohol deprivation model have both been used to study relapse behavior. In the reinstatement model, animals are trained to self-administer a drug by operant conditioning. Following a period of extinction, the cue/context is reintroduced, and the ability of reinstating drug-seeking behavior is assessed [72•, 74, 75]. The re-exposure

toward cues/context has been shown to reinstate alcohol-seeking behavior in animals, which can be reintroduced in each phase of the alcohol addiction cycle [76–78].

In the alcohol deprivation effect (ADE) model, animals are exposed to long-term voluntary alcohol consumption episodes, interrupted by random deprivation periods. When animals are reintroduced to alcohol, this leads to relapse-like drinking, and the animals are then considered to be highly alcohol-dependent. The alcohol deprivation effect is considered to display the loss of control and is observed in humans as well as in both monkey, rat, and mice models of alcohol abuse [72•, 79, 80].

Invasive Neuromodulation

Given the importance of the reward circuit in the pathophysiology of addiction, this area has become the preferred target for the application of DBS in the context of addiction. DBS is an invasive yet reversible procedure, in which electrodes are implanted into brain targets considered to be involved in the pathology in question. The application of electrical stimulation alters the activity of the targeted brain region/s alongside its associated network [81, 82]. As such, DBS offers a mean to specifically target the neuronal circuit implicated in a given disorder. A few clinical studies have investigated the use of DBS applied to the NAcc in a few patients with alcoholism, with results showing a general decrease in cravings and consumption [24–26, 83]. Nevertheless, the magnitude of this effect is still unknown, including the long-term consequences of chronically stimulating a vulnerable neuronal circuit.

Only a few preclinical investigations have been published on the use of DBS in alcohol addiction. Here, the focus has mainly been on its ability to reduce alcohol consumption rather than relapse behavior. The study performed by Knapp et al. [84] was one of the first preclinical investigations into the use of NAcc-DBS as a mean to target drinking behavior in rats trained in a saccharine fading procedure. Stimulation was applied bilaterally to either the core or shell of the NAcc. Results showed a reduction in alcohol consumption, following a brief, acute stimulation of both sub-regions. Subsequently, Henderson et al. [73] applied DBS to the shell of the NAcc and found a reduction in alcohol consumption following acute stimulation in alcohol-preferring rats. Importantly, Henderson et al. measured alcohol consumption during the first 24 h after alcohol had been made available following the first deprivation period. A study by Wilden et al. [85] found that both unilateral DBS applied to the shell of the NAcc as well as pharmacological silencing of the NAcc reduced operant alcohol consumption in alcohol-preferring rats. Once stimulation was terminated, the levels of consumption returned to baseline. Collectively, these findings show that DBS applied acutely to the NAcc reduces ethanol consumption in rats genetically susceptible to alcohol intake. The study by Henderson et al. [73] was designed such that DBS was applied during reintroduction of alcohol following the first deprivation period; hence, the interpretation that acute DBS yielded an attenuating effect on "relapse-like" behavior should be cautiously considered before translating it into the clinic; it is essential as the application of DBS is directed toward severely affected patients with a high rate of relapse. Thus, to mimic the clinical situation, there is a need for further investigations into DBS applied in models displaying alcohol dependence and relapse behavior.

The study by Hadar et al. [86••] investigated the effect of chronic DBS applied bilaterally to the shell of the NAcc in a rat model displaying relapse-like drinking behavior. As opposed to the previous mentioned studies, a chronic continuous stimulation paradigm was applied in order to mimic the clinical situation. To study network effects of DBS, fMRI was performed, and effects on neurotransmitter levels were assessed. The study replicated the previous findings of Henderson et al. [73], showing that acute stimulation to the NAcc attenuated ADE in rats not yet displaying alcohol dependency. However, once animals have been repeatedly alcohol deprived and transitioned to alcohol dependency, electrical stimulation to the NAcc led to pronounced relapse, as reflected by increased alcohol consumption when alcohol was reintroduced. This relapse behavior was coupled with increased activity in the medial prefrontal cortex (mPFC) and caudate putamen (CPu) (i.e., dorsal striatum) as well as increased dopaminergic levels in the NAcc. These results show the importance of the NAcc in producing incentive salience toward ethanol, based on increase in dopamine levels and thereby the promotion of relapse [12, 86••].

Apart from the study of Hadar et al. [86••], animal models so far used to investigate the effect of DBS in alcohol addiction do not mimic progressed and severe alcohol-dependent stage. Essentially, the differential findings among the preclinical studies show that opposing effects are obtained when stimulating the brain of highly dependent versus the non-dependent subjects. This potentially reflects the shift in the circuits involved as addiction progresses. In the naïve brain, not yet exposed to chronic alcohol exposure, the reward system including the NAcc plays a substantial role in the rewarding effects of alcohol consumption. Accordingly, NAcc-DBS has positive effects on alcohol consumption in the studies by Henderson et al. [73], Knapp et al. [84], and Wilden et al. [85]. As the disease progresses, allostatic changes occur, in which additional circuits are activated and recruited and contribute to symptoms' manifestation. This is reflected in the results by Hadar et al., as NAcc-DBS applied to alcohol-dependent rats had no effect in decreasing alcohol consumption.

Non-invasive Neuromodulation Techniques

As opposed to DBS, the use of non-invasive neuromodulation procedures offers the possibility of treating a broader range of patients, including patients in an earlier stage of the addictive cycle. The use of techniques such as TMS and tDCS allows for targeting cortical areas through application of stimulation to the scalp. TMS involves the application of a magnetic field, whereas in tDCS a weak current is applied. The effect mainly revolves around an alteration in the activity of the cortical area, which is encircled by the device and considered relevant in the pathology. Both tDCS and TMS are considered safe to use, and only few mild side effects have been reported [87, 88].

The effect of tDCS and TMS is subjected to both the underlying neurobiology which displays inter-individual variability, as well as the stimulation settings [77, 78]. The clinical output is therefore determined by several interacting factors. It remains unknown how non-invasive stimulation affects the neurobiology of alcohol addiction, and there is no consensus on the appropriate stimulation protocol. In order to change the brain of patients with addiction, there is a need for remodeling the neuronal circuit. TMS and tDCS have both been employed in an attempt to alter human neuroplasticity, and indeed neuroplastic changes following stimulation have been observed in the cortex [79, 80]. In addition to this immediate effect on the cortical level, tDCS has shown the ability to also affect neuronal circuits [89–92].

Disruption of several frontocortical areas has been implicated in addiction. Disruption of cortical areas such as the orbitofrontal cortex has been linked to compulsive behavior sometimes seen in addiction [93, 94], whereas disruption of the anterior cingulate cortex has been associated with an increase in impulsivity sometimes found among patients with alcohol use disorder [93, 95]. During the later stages of the disease, the mPFC, which is involved in Pavlovian learning, is suggested to be implicated in drug reinstatement, whereas the dorsolateral prefrontal cortex is considered essential in the altered executive functions, sometimes observed in patients with alcohol addiction [96–98].

It has been hypothesized that altering the activity of the frontal cortex may improve cognitive control and thereby decrease the automatic impulses and drinking behavior frequently seen in alcohol addiction [99•]. So far clinical studies have focused mostly on the dorsolateral prefrontal cortex for both tDCS and TMS. Specifically, results show a reduction in craving and to some extent an improvement in executive functions [23–27]. However, these effects are only temporary and generally do not prevent relapse. The insula has been suggested as a potential new brain stimulation target for treating addiction, including alcohol use disorder [100]. Recently, it was reported that repeated TMS treatment (5 days a week for 3 weeks) had no effect on alcohol drinking and relapse, as compared with sham treatment [86••]. Thus, a positive effect following non-invasive stimulation of the insula in alcohol-dependent patients still remains to be demonstrated [29]. Currently, there are no preclinical studies on the effect of either TMS or tDCS in the context of alcohol addiction.

Conclusion

Due to the limited number of conducted studies, it is too early to draw firm conclusions on the use of neuromodulation in alcohol addiction from a preclinical point of view. Neuromodulation techniques offer a potentially safe and well-tolerated treatment; however, its effect on the underlying neurobiology of addiction is unknown. Preclinical and clinical investigations stress the notion that different brain sites and circuits may be relevant at different stages as addiction develops. As such, the transition from alcohol use to addiction involves initial changes in the reward system, which is followed by a shift toward habitual behavior mediated by the dorsal striatum, as well as further allostatic changes including the recruitment the stress system, extended amygdala, and dysregulation of several cortical areas. Therefore, in order to sufficiently prevent relapse, the rigid neuronal circuit of the alcohol-dependent brain may essentially require a differential setup in order to be altered, as opposed to patients in the earlier phases of alcohol addiction. Despite this shift in implicated circuits, the investigation within the field of addiction has been dominated by the neural substrates leading to positive reinforcement found in the early stages, and thus till date the reward system continues to be the main targeted area. To improve treatment options and essentially promote protracted relapse prevention, there is a need for further studies that not only thoroughly investigate the use of neuromodulation strategies in the context of alcohol addiction but also include an assessment as to which different brain targets should be selected during the progression of alcohol addiction. To this end, animal studies are indispensable, allowing scrutinizing the effect of neuromodulation to different brain areas as alcohol addiction progresses. For that, the use of animal models reflecting the different stages of alcohol addiction would promote our understanding of the precise brain areas that are involved in addiction progresses along with the direct therapeutic outcomes.

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Compliance with Ethical Standards

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