Review

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Brain Stimulation in Alcohol Use Disorders: Investigational and Therapeutic Tools

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ABSTRACT

Alcohol use disorders (AUDs) are a major health and social problem worldwide. Brain stimulation holds great promise as an investigational tool to help us understand the pathophysiology of alcohol dependence and as a therapeutic tool to treat AUDs. Numerous studies suggest that glutamatergic, gamma-aminobutyric acidergic, and dopaminergic neurotransmission are altered by alcohol consumption and among patients with AUDs. Alcohol's disruption of neurotransmission is likely to play an important role in its detrimental effects on neuroplasticity, which, in turn, may contribute to the pathophysiology of alcohol dependence. Specifically, aberrant neuroplasticity in the brain reward circuitry is a potential mechanism underlying the pathophysiology of alcohol dependence. The dorsolateral prefrontal cortex (DLPFC), a part of the brain's reward circuitry, is directly accessible to noninvasive brain stimulation and may represent a potential target for the treatment of AUDs. While the literature suggests that impairments in neuroplasticity are likely to be present in the DLPFC and brain reward circuitry in alcohol-dependent patients, this is yet to be directly evaluated in humans. Findings from numerous neuromodulatory brain stimulation studies demonstrate that altering neuroplasticity in the DLPFC in alcohol-dependent patients holds promise as a treatment for alcohol dependence, but the optimal neuromodulatory parameters are yet to be identified. Gaining a better understanding of alcohol dependence vis à vis neuroplasticity in the DLPFC and brain reward circuitry can help us optimize the treatment of alcohol dependence using neuromodulatory brain stimulation in the DLPFC.

Keywords: Addiction, Alcohol, Alcohol use disorders, Brain stimulation, Plasticity, Transcranial magnetic stimulation

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Alcohol is an addictive substance. Some regular drinkers develop alcohol use disorders (AUDs), which include alcohol abuse and alcohol dependence. AUDs have emerged as a major health and social problem worldwide (1). Alcohol-attributable deaths account for 3% to 8% of all global deaths, and alcohol accounts for 4% to 6% of global disability-adjusted life years lost (2). Alcohol contributes to increased rates of mortality and morbidity through increased occurrence of diseases, such as liver cirrhosis, cancers, cardiovascular disorders, and alcoholic encephalopathy, and increased rates of motor vehicle accidents, violence, and homicides (3–6).

The transition from alcohol use to AUDs involves neurochemical and neurophysiological changes in the brain. Alcohol acts on multiple neurotransmitter systems, and therefore its neurophysiological effects are widespread. The known primary targets of alcohol are *N*-methyl-D-aspartate (NMDA), gamma-aminobutyric acid (GABA) type A ($GABA_A$), glycine, 5-hydroxytryptamine 3 (serotonin), and nicotinic acetylcholine receptors, as well as L-type calcium ion channels and G-protein-activated inwardly rectifying potassium ion channels [for review, see (7)].

Alcohol's action on glutamatergic and GABAergic neurotransmission are of particular interest owing to their 80% contribution to the neuronal connections in the brain (8). Alcohol's effect on glutamatergic and GABAergic neurotransmission may play a role in mediating its effect on neuroplasticity, as neuroplasticity is dependent, in part, on $GABA_A$ and NMDA receptor activities (9–11). Additionally, dopaminergic neurotransmission, which is also altered by acute alcohol consumption and dependence (12–14), may also be an important mediator of alcohol's effect on neuroplasticity (15). Alcohol's effect on neuroplasticity may, in turn, have important consequences among patients with AUDs (16,17). Accumulation of evidence suggests that drugs of abuse can act on mechanisms of neuroplasticity in the brain regions implicated in drug reward and reinforcement (18). This has contributed to the hypothesis that addiction may be a harmful but powerful form of learning and memory (19–24).

Brain stimulation shows great promise as a tool in alcohol research and treatment for several reasons. First, transcranial magnetic stimulation (TMS) can index the effects of alcohol and alcohol dependence on glutamatergic and GABAergic neurotransmission. Second, brain stimulation techniques can be used to study how neuroplasticity is altered following acute alcohol consumption and in the addicted brain. Work in this area will help elucidate the role of neuroplasticity in the pathogenesis of alcohol dependence. Last, neuromodulatory techniques specifically targeting the dorsolateral prefrontal

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cortex (DLPFC), part of the brain's reward circuitry, are demonstrating value as therapeutic tools for the treatment of alcohol dependence (25–27). Here, we review the literature demonstrating that 1) brain stimulation can be used to understand aberrancies in neurotransmission caused by acute alcohol consumption and alcohol dependence; 2) brain stimulation protocols can be employed to index alcohol's effects on neuroplasticity; and 3) neuromodulatory brain stimulation can be used as a potential treatment for AUDs. Furthermore, we explore the possible mechanisms of action of neuromodulatory strategies for the treatment for AUDs. Findings from our review reveal gaps in the current knowledge on alcohol's effect on neuroplasticity in the DLPFC. While the literature suggests that impairments in neuroplasticity are likely to be present in the DLPFC and brain reward circuitry, this is yet to be evaluated in humans. Recent brain stimulation techniques may provide further evidence for aberrant neuroplasticity in patients with AUDs. Additionally, studies using brain stimulation suggest that neuromodulation of the DLPFC has potential as a treatment for AUDs. However, the optimal parameters for brain stimulation treatment still need to be identified. Understanding how plasticity is altered in the DLPFC of alcohol-dependent patients can help us optimize neuromodulatory brain stimulation for the treatment of AUDs.

TRANSCRANIAL MAGNETIC STIMULATION TO MEASURE THE EFFECT OF ALCOHOL ON CORTICAL EXCITABILITY

Inhibitory neurotransmission in the brain is mainly mediated by GABA (28), whereas excitatory neurotransmission is primarily mediated by glutamate (29). TMS is a noninvasive experimental technique that can be used to index cortical inhibition and excitability. Cortical inhibition can be measured using long-interval cortical inhibition, an index of GABA type B ($GABA_B$) receptor-mediated neurotransmission, and short-interval cortical inhibition (SICI), an index of $GABA_A$ receptor-mediated neurotransmission (30–33). The cortical silent period (CSP) is another TMS measure that reflects inhibitory neural mechanisms. The early component of the CSP is controlled by spinal mechanisms (34,35), while the late long-lasting portion is believed to be controlled by $GABA_B$ (36). Cortical excitability can be measured using intracortical facilitation (ICF), an index of NMDA receptor mediated neurotransmission (37,38).

TMS has been used to index the acute and chronic effects of alcohol on cortical inhibition and excitation. Ziemann *et al.* (39) examined the effect of alcohol on TMS measures of cortical inhibition and excitability. In a study using six healthy subjects, this group demonstrated that alcohol consumption enhances SICI and suppresses ICF, suggesting an increase in $GABA_A$ receptor mediated neurotransmission and a decrease in NMDA receptor mediated neurotransmission, respectively. Additionally, acute alcohol administration resulted in an increase in the CSP duration, suggesting an increase in $GABA_B$ receptor mediated neurotransmission (39).

In addition to indexing the acute effects of alcohol on cortical inhibition and excitability, TMS is a valuable tool to index any imbalances in these forms of neurotransmission in alcohol-dependent individuals. Nardone *et al.* (40) used SICI, ICF, and CSP to examine changes in cortical excitability during alcohol withdrawal. The group tested 13 subjects with alcohol withdrawal syndrome, 12 chronic alcoholics, and 15 control subjects. They found that ICF was increased during withdrawal compared with alcohol-dependent individuals and healthy control subjects. While there was a trend toward reduced SICI in alcohol-dependent individuals, there was no significant difference in SICI and CSP duration between patients experiencing alcohol withdrawal and control subjects (40).

Taken together, the findings from both of these TMS studies suggest that while acute alcohol consumption results in an increase in $GABA_A$ and $GABA_B$ receptor-mediated neurotransmission and a decrease in NMDA receptor-mediated neurotransmission, withdrawal in alcohol-dependent individuals results in a potentially compensatory increase in NMDA receptor activity. Aberrancies in NMDA receptor-mediated neurotransmission in alcohol-dependent individuals are likely to be paralleled by aberrancies in neuroplasticity, particularly NMDA receptor-dependent long-term potentiation (LTP). Such aberrant neuroplasticity may represent one potential mechanism underlying the pathophysiology of alcohol dependence.

ABERRANT NEUROPLASTICITY IN ALCOHOL DEPENDENCE

Aberrancies in NMDA and GABA receptor-mediated neurotransmission are likely to impact neuroplasticity, as these processes are thought to be related to LTP, an important form of neuroplasticity. LTP involves stable and long-lasting enhancement of synaptic efficacy (41).

Studies from slice preparations of the rat motor cortex have demonstrated that the induction of LTP is dependent on disinhibition produced by application of a $GABA_A$ receptor antagonist and is disrupted by NMDA receptor blockade (9–11). Interestingly, it has been argued that aberrancies in neuroplasticity related to modifications in the efficacy of glutamatergic neurotransmission may be a key underlying factor in alcohol dependence (42,43). There are multiple lines of evidence from animal and in vitro studies that suggest that neuroplasticity in the reward brain circuitry can be affected by drugs of abuse [for review, see (18)]. It is hypothesized that mechanisms of learning and memory play at least a partial role in the development of drug dependence (44). Specifically, the molecular and cellular mechanisms, such as LTP, that underlie associative memories in forebrain circuits that receive input from midbrain dopamine neurons are hypothesized to be major substrates of the compulsive drug use seen in drug dependence (21). A key aspect of drug dependence is the transition from recreational drug use to compulsive drug taking. Neuroplasticity is thought to play a key role in this transition to dependence (45). Additionally, certain genes can produce aberrancies in neuroplasticity that predispose individuals to be susceptible to addiction (46). These genetic predispositions can contribute to an unfortunate cycle in which aberrant neuroplasticity makes individuals susceptible to AUDs, which then further exacerbates such aberrancies.

Excessive neuroplasticity or hyperplasticity may be implicated in the transition to alcohol dependence. Enhanced NMDA receptor-mediated neurotransmission in alcohol