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The Efficacy of Neurofeedback for Alcohol Dependence-A Systematic Review

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ABSTRACT

Objective: The aim of this systematic review is to look into the published studies that reported effectiveness of non-pharmacological neurofeedback interventions in patients with alcohol dependence.

Data sources: PubMed, Google Scholar, The Cochrane Library, Science Direct and Clinicaltrial. gov were searched until April 04, 2022. 20 research articles (including 618 participants) were retrieved and included for qualitative analysis. The sample size ranged from one (case report) to eighty, with years of publication ranging from 1977 to 2022.

Study selection: Original articles of any design reporting on the use of neurofeedback approaches in the treatment of alcohol addiction were included.

Data extraction: Information related to study design, participants, control group, neuromodulation therapy, number of sessions and key findings of study were extracted.

Results: Out of the 20 studies included, 8 (40%) had a moderate risk of bias, while the other *i.e.,* 60% had a low risk of bias. The effectiveness of various neurological treatments in the treatment of alcohol dependence was established in these 20 studies. There have been 11 studies on EEG neurofeedback training, three studies on real-time FMRI neurofeedback, two studies each on transcranial direct current stimulation and transcranial magnetic stimulation and one study each on deep brain stimulation and theta burst stimulation.

Conclusion: The use of various neuromodulation approaches to the treatment of alcohol use disorder shows promise. However, more research with a larger sample size is required.

Keywords: Feedback ; Alcohol dependence; Efficacy; Temozolomide; Epigenomics

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INTRODUCTION

Alcohol Use Disorder (AUD) is a major public health issue that affects millions of people throughout the world, with prevalence varying widely between nations and being highly impacted by drinking cultures and social norms. Alcohol use disorders affect an estimated 237 million men and 46 million women worldwide, with high-income nations having the highest prevalence. Alcohol is responsible for 5.3% fatalities (3 million) and 132.6 million Disability-Adjusted Life Years (DALYs), accounting for 5.1% of all DALYs. Alcohol has been related to more than 200 disease and injury states, including mental and behavioral problems, liver disease, cardiovascular disease and unintentional and intentional harm (traffic accidents, suicide, etc.).

Despite significant advances in understanding the central mechanisms underlying alcohol addiction and identifying related risk factors, alcoholism continues to be a serious medical and social concern. Only 19.8% of individuals with lifelong AUD are ever treated, and 45%-75% of those that are treated relapse a year later. Psychotherapies and pharmacological options such as naltrexone, disulfiram and acamprosate are now approved as recommended treatments, however they are usually ineffective. These medications have only a moderate level of effectiveness and are intended to treat the acute symptoms of alcoholism rather than the addiction itself. As a result, improved or adjuvant therapies that may enhance or facilitate alcoholism therapy are urgently needed.

Neurofeedback (NF) technique, a form of operant conditioning, for restructuring and regulating brain wave patterns is being used as an adjuvant therapy for the treatment of AUD. It is a therapeutic learning process in which an individual receives visual and auditory feedback regarding his or her brainwaves in able to train them how to self-regulate their brain activity. Participants use this information to alter their behavior and as a result, their brain activity in order to attain the desired result. Inattention, impulsivity, hyperactivity, tension, depressive symptoms and anxiety are all reduced. Neurofeedback can potentially prevent relapses through its calming effect on the central nervous system.

There is presently no comprehensive review of study investigating the use of neurofeedback approaches in the treatment of alcohol dependence. As a result, we performed a thorough evaluation of the current literature to determine the efficacy of various neurofeedback therapies in people with alcohol dependence.

Methods

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist guidelines will be followed.

Search Strategy

Five different databases (PubMed, The Cochrane Library, Science Direct, Clinicaltrial.gov and Google scholar) were used to conduct a comprehensive literature search.

There were no constraints on the country, time or language of publication during the literature search. Letters to the editor, conference proceedings and practice guidelines were not included in the study.

The broad key terms used for database searches were (neurofeedback therapy or neuromodulation or EEG biofeedback or brainwave biofeedback or neurotherapy) and (alcohol dependence disorder) and only research articles were retrieved and evaluated.

Study Selection

Titles and abstracts were reviewed for eligibility criteria after duplicates were removed. Abstracts and full-text papers of identified studies were independently reviewed.

Criteria for Considering Studies

The inclusion criteria included published studies of any design (including case reports) reporting on efficacy or effectiveness of neurofeedback therapy for alcohol dependence disorder. The exclusion criteria were:

- Studies not related to alcohol dependence disorder
- Studies not providing sufficient data or without results
- Studies in languages other than English
- Commentaries, guidelines, editorials, book chapters, letter to editor, reviews and metanalysis
- Animal studies
- Protocols

The reference lists of previous systematic reviews/metanalysis will also be screened for relevant studies.

Data Extraction and Synthesis

The two independent reviewers extracted data from selected studies. Any disagreements were resolved through discussion. The data was extracted using a standard excel spreadsheet. The overview and characteristics of the studies that were included are presented [1]. Authors, year of publication, country, study design, participants, control group, neuromodulation therapy, number of sessions and major findings of study were collected for each included study. Meta-analysis was not conducted due to the heterogeneity of the interventions, populations and outcome measurement.

Study Quality Assessment

To assess the risk of bias in the included studies, the quality of the selected studies was evaluated using the Joanna Briggs Institute's (JBI) critical appraisal checklists for studies. If the "yes" score in a study was % or below, the probability of bias was considered high. Studies with a score of 50% to 69% were considered at moderate risk, while those with a score of 70% or more had low risk of bias. Disagreements between the two reviewers were addressed by discussion and consensus.

Identification and Description of Studies

There were a total of 12,894 citations, with 7,355 from PubMed, 4,210 from Google Scholar, 1,301 from Science Direct, 15 from Clinical trial.gov and 13 from The Cochrane Library and among these 7,697 duplicate studies were removed [2]. A total of 7,529 studies were eliminated after the titles and abstracts of 7,697 articles were evaluated. The remaining 167 articles fulfilled the full-text review criteria. After applying exclusion criteria, 147 full texts were excluded and remaining 20 articles were included for final qualitative analysis. In the flow diagram, the study selection process is illustrated (**Figure 1**). There were 14 randomized control trials, three non-randomized studies and three case reports among the 20 articles.

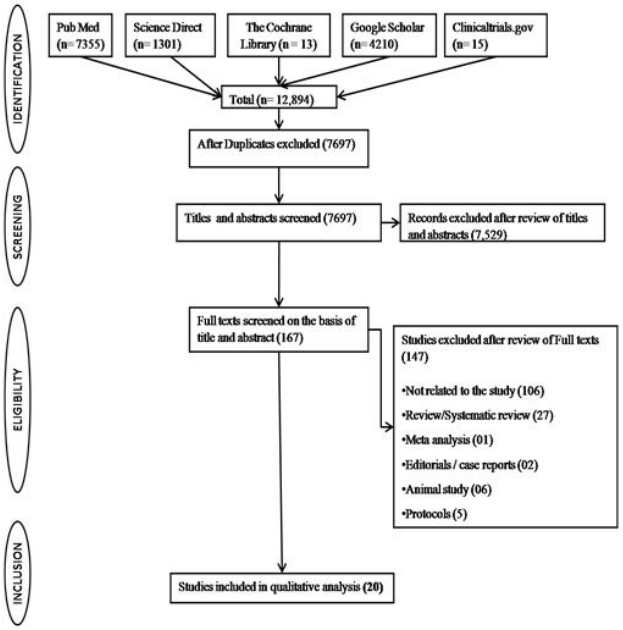

Figure 1: Flow chart showing the process of selecting or rejecting articles for inclusion in the study.

Characteristics of the Included Studies

There were 618 patients in all that participated in the studies. The sample size ranged from one to eighty and the years of publication spanned from 1977 to 2022. From 1977 to 2000, there were seven studies, and from 2000 to 2022, there were thirteen. Out of a total of 20 studies published nine studies were conducted in the United States, four in Germany, three in the United Kingdom, two in India and one each in the Netherlands and South Korea.

Study Quality Assessment

Two reviewers independently assessed the quality of all of the studies that were included. The majority of the studies in this analysis had a low to moderate risk of bias. 07 (50%) of the 14 RCTs had a moderate risk of bias, while the other 50% had a low risk of bias. For three of the case reports that were included, the risk of bias was low. One of the three non-randomized trials had a moderate risk of bias, whereas the other two had a low risk of bias.

Efficacy of Neurofeedback Interventions in AUD

Among the 20 studies included, EEG neurofeedback training, transcranial Direct Current Stimulation (tDCS), Transcranial Magnetic Stimulation (TMS), Deep Brain Stimulation (DBS), real time FMRI neurofeedback (rtfMRI-NF) and Theta Burst Stimulation (TBS) were all used to treat AUD.

Electroencephalogram-Neurofeedback (EEG-NF)

Eleven EEG-based neurofeedback studies (six randomized controlled trials, three non-randomized studies and two case reports) have been included, investigating the efficacy in AUD and including a wide range of neurofeedback training sessions (Range: 4 -40 sessions). The Peniston protocol (modulation of alpha-theta frequencies), developed by has been adopted in the majority of these studies.

LITERATURE REVIEW

DeGood, et al., included 40 subjects that were randomized into users of alcohol (n=21) and non-users of alcohol (n=19) and underwent four, 40-min eyes-closed occipital alpha (8-13 Hz, 10 μV) biofeedback sessions over a 4-week period. The self-regulation of occipital alpha density was found to be superior in non-users of alcohol compared to users of alcohol. Ghosh, et al., reported a case of 39-year-old man with alcohol dependency syndrome was given EEG neurofeedback training. The patient's cognitive deficiencies, anxiety and sadness were significantly reduced after ten sessions of EEG neurofeedback training. The therapeutic effectiveness of alpha-wave biofeedback therapy for alcoholics was also studied by Passini, et al. Twenty-five participants were compared to a matched control group before and after a 3-week alpha-wave biofeedback regimen. The experimental group underwent ten hour-long alpha training sessions and demonstrated significant improvement in long-term therapeutic benefits on anxiety than the control group. However, there were no discernible effects on drinking behavior [3].

In 36 Korean patients with alcohol use disorder Ko and Park, investigated into whether neurofeedback may help to normalise abnormally high beta and low alpha waves. The participants were divided into two groups: An experimental group (n=17) and a control group (n=19). When it comes to lowering brain hyperarousal, there was no significant difference between the two groups. The hyperarousal state, on the other hand, was maintained in the experimental group but worsened in the control group. The experimental group showed a significant increase in fundamental psychological need satisfaction, alcohol abstinence self-efficacy and self-regulation when compared to the control group.

Seven studies reported effectiveness of EEG-alpha-theta brainwave training using Peniston protocol. Fahrion, et al., investigated the effects of EEG alpha and theta brainwave training on a recovered 39-year-old alcoholic patient who exhibited desire and fear of relapse after 18 months of sobriety in a controlled case study. Following therapy, there were signs of more relaxed CNS functioning under stress and

lower autonomic activation during both relaxation and stress. The patient appears to behave in a calmer manner under the influence of stress four months after therapy and he claims no longer having an alcohol craving [4]. After alpha-theta training, Kelley et al. showed increases in coping skills and sobriety in 19 alcoholic individuals. The BDI depression score also decreased significantly. According to Saxby and Peniston, the experimentally treated alcoholics with depressive syndrome demonstrated dramatic decreases in self-assessed depression, decreased stress-related personality characteristics and sustained relapse prevention.

Dalkner, et al. and Lackner, et al. observed that after 12 sessions of alpha-theta training of 13 patients in the experimental group, there was increased control of their brain activity during the course of neurofeedback. Reduction in avoidant and stress-related personality traits were also observed. Peniston and Kulkosky, reported that 15 sessions of alpha-theta training in alcoholic patients (n=10), decreased relapse and reduced depressive symptoms and prevented elevation of serum β-endorphin levels. Another study by Twemlow and Bowen observed promotion of insight and attitude change in 67 alcoholic patients after 20 sessions of alpha-theta training.

Transcranial Direct Current Stimulation (tDCS)

Two randomized controlled studies explored tDCS induced behavioral and neuro-physiological modulation in subjects with AUD. These studies have reported that tDCS reduces craving and cue-reactivity for alcohol by modulating cortical excitability in the prefrontal cortex. da Silva investigated into the use of repetitive unilateral tDCS in alcoholic patients to reduce craving and relapse. Thirteen subjects with AUD, 18 to 75 years of age, were enrolled in the study [5]. Six of the thirteen subjects were assigned to the tDCS treatment group, while the other seven were assigned to the simulation or sham group.

Depressive symptoms and craving were reduced to a larger extent in the tDCS group compared to the sham group (p=0.005 and p=0.015, respectively). The study reported an increased change in executive function in the tDCS group compared to the sham-tDCS group (p=0.082). However, the repetitive unilateral tDCS was reported to increase relapses in AUD patients. More relapses were observed in the tDCS group compared to sham tDCS (four alcoholic subjects (66.7%) *vs.* one (14.3%), p=0.053).

Holla and colleagues, studied the effects of prefrontal tDCS on resting-state functional magnetic resonance imaging in individuals with AUDs, as well as the connections between impulsivity and time to first lapse. For a five-day treatment, patients with AUD were administered either verum-tDCS (n=12) or sham-tDCS (n=12). Active-tDCS substantially improved whole-brain network efficiency and inter-regional connectivity within a local prefrontal sub-network (p0.001). There was also a considerable reduction in the chance of relapse.

Real-Time Functional Magnetic Resonance Imaging Neurofeedback (RTFMRI-NF)

Three randomized clinical trials looked into using rtfMRI-based neurofeedback therapy to prevent relapse and evaluate changes in craving-related neural responses in individuals with alcohol dependence. In exploratory pilot investigations, Karch, et al. and Kirsch, et al., evaluated the possibility of neurofeedback training to modulate brain activity linked with alcohol craving. Both studies included German participants, with treatment-seeking patients with alcohol use disorder and heavy-drinking college students being compared to healthy controls.

Kirsch, et al. enrolled 38 heavy drinkers and randomly assigned them to one of three groups: Real feedback (rFB, n=13), yoke Feedback (yFB, n=13) or passive control (noFB, n=12). Neurofeedback was found to be effective in reducing striatal activity in response to alcohol cues, with a substantial down regulation of striatal areas in the rFB group [6]. Furthermore, through engaging executive control mechanisms, it promotes self-efficacy in down regulating subjective craving.

Karch, et al. recruited 13 patients with alcohol addiction (AUD nf group) and 14 healthy controls from a specialized therapeutic programme for alcohol-addiction. The AUD nf group had lower brain activity and greater connection between frontal and sub-cortical regions after neurofeedback training, but healthy people had no significant reduction. The decreases in craving seen following neurofeedback training were attributed to lower insular activity in alcohol patients.

Subramanian, et al. included 52 alcohol-dependent individuals and randomly assigned them to one of two groups: treatment (rtfMRI NFT in addition to regular therapy; n=25) or control (standard care only; n=27). Over the course of four months, the treatment group received six neurofeedback training sessions. Both groups had relatively low recurrence rates, according to primary outcome measures [7]. The majority of patients adjusted the salience system in the intended directions, decreasing activity in reaction to alcohol cues and increasing activation in response to positive goals.

Transcranial Magnetic Stimulation (rTMS)

Two randomized controlled studies included investigated the effect of high frequency rTMS on craving and mood in alcohol dependent subjects. Hoppner, et al. Conducted a sham-controlled trial in 19 alcohol-dependent women who were randomly allocated to receive either ten daily active (20 Hz, high frequency; n=10) or sham (n=9) stimulation sessions to see if rTMS had any effect on mood and craving. Following stimulation, there were no significant alterations in mood or craving, as assessed by the hamilton depression rating scale and the obsessive compulsive drinking scale. Schluter, et al. investigated the effect of 10 high frequency rTMS sessions on impulsivity in 80 alcohol dependent patients.

Subjects were randomly allocated in active high frequency rTMS group (n=40) and sham high frequency rTMS group (n=40). This intervention had no further effect on impulsive measures, and there was no significant difference in task performance scores [8]. However, there was a significant influence of age on the Go-NoGo task, with higher age being related with better performance.

Theta Burst Stimulation (TBS)

McCalley and colleagues conducted a randomized double-blind sham-controlled study to assess how effective continuous TBS is at lowering drinking behavior and brain responses to alcohol cues in people with AUD. Fifty people with AUD were engaged in an intensive outpatient programme and received ten sessions of continuous TBS (left frontal pole; 1 session/10 days; 110 percent RMT, 3600 pulse/session, cue-provocation before and during session) [9]. The patients were divided into two groups: Real (n=26) and sham (n=24). 10 days of medial prefrontal cortex TBS was well tolerated, reduced drinking and lowered brain responsiveness to alcohol cues for up to three months after treatment initiation.

Deep Brain Stimulation (DBS)

This is the first case study to show that DBS can be used to treat AUD. Found that an alcohol-dependent patient who had bilateral nucleus accumbens DBS consumed less alcohol. The patient was 69-year old male suffering from alcohol dependence for more than 30 years. Following the initiation of DBS, the patient's drinking behavior improved significantly. After eight months on DBS, the patient only drank alcohol on rare occasions and after a year, he no longer drank alcohol at all. Both addictive behavior and cravings were normalized by DBS.

DISCUSSION

Alcoholism is one of the primary causes of morbidity and mortality across the world. AUD treatment options are still limited in terms of efficacy and accessibility. Treatments for alcohol use disorder, both pharmacological and cognitive behavioral have had varying degrees of success to far. Several recent studies have suggested that noninvasive brain stimulation methods might be useful in the treatment of addiction problems. There has been a surge in interest in using brain stimulation to treat AUDs in this context. Researchers have been able to better understand brain systems associated in addiction, such as those involved in positive and negative reinforcement, decision making, and cognitive control, due to better in neuroimaging methods [10]. Neurological therapies such as EEG-neurofeedback training, real-time functional magnetic resonance imaging neurofeedback, transcranial direct current stimulation, transcranial magnetic stimulation, deep brain stimulation and electroconvulsive therapy, which aim to reverse the neuroplastic alterations caused by chronic alcohol consumption, are desperately needed. Eugene Peniston established the Neurofeedback (NF) technique for restructuring and regulating brain wave patterns for the treatment of AUD.

Participants use this feedback to change their behaviour and brain activation in order to attain a desired outcome. For instance, the individual is asked to adjust feedback information using mental methods such as envisioning certain events (e.g., thinking about the negative consequences of alcohol consumption), and the expected changes are positively rewarded. Neurofeedback can potentially prevent relapses through its calming effect on the central nervous system.

Neurofeedback therapy is now being used to treat a variety of mental diseases, with promising results. In recent years, the influence of EEG frequency biofeedback as a therapy technique for psychiatric problems has been extensively studied. Neurofeedback improves self-efficacy and has a positive impact on the brain's self-control capabilities. Furthermore, increased alpha activity is thought to assist the patient in remaining calm and better coping with stress. Participants are likely to acquire increased self-confidence and minimize emotional stress, feelings of inadequacy, insecurity and fear as a result of increasing control over physiological processes. Vernon, et al. conducted a study in which volunteers participated in a series of neurofeedback sessions. They found that individuals who received neurofeedback improved their recall from 70.6% to 81.6%, whereas those who did not get neurofeedback only improved their recall from 72.5% to 75.1%.

Alcohol is one of the drugs of abuse that have been increasingly burdening our society. Chronic alcohol drinking causes brain damage, which increases activity in the autonomic nervous system, resulting in physical and psychological stress as well as withdrawal symptoms such as anxiety and sleep disturbances [11]. Alcohol can cause highly addictive effects by meditating brain reward system, particularly prefrontal cortex areas and impairing frontal functions. Impaired inhibitory control is often seen in individuals with addictive behaviors, and has been associated with substance use frequency in some groups. Found that decreased neuronal activity in addiction-related brain regions is associated with decreased craving. High beta waves, which indicate anxiety and excitement, are increased during hyperarousal, while alpha waves, which indicate calmness, are lowered, according to studies. Furthermore, increased high beta waves are clinically significant since they are linked to the severity and recurrence of AUD.

The brain regions most typically impacted by alcohol cues include the Medial Prefrontal Cortex (MPFC), ventral and dorsal striatum, Anterior Cingulate Cortex (ACC) and anterior insula. There has recently been growing interest in using non-invasive neuromodulation of these brain areas as a unique therapeutic approach for AUD. In healthy populations, neurofeedback interventions have been used to regulate inhibitory control, with inconsistent results. Canterberry and colleagues, investigated neurofeedback as a method for helping nicotine-dependent cigarette smokers self-regulate their cravings. Patients with AUD are said to benefit from neurofeedback therapy because it improves their autonomy, competence, and relatedness.

We reviewed the existing literature and included studies that reported effectiveness of neurofeedback interventions on AUD. The purpose of this study is to explore if neurofeedback training may help patients with alcohol dependence avoid relapse, reduce anxiety and despair, and minimize alcohol cravings and consumption. A total of 20 studies, mostly RCTs, using a number of neurofeedback methods for patients with alcohol dependence were included. The non-pharmacological interventions include EEG neurofeedback training (11 studies), real time FMRI neurofeedback (03 studies), transcranial direct current stimulation (02 studies), transcranial magnetic stimulation (02 studies), deep brain stimulation (01 study) and Theta burst stimulation (01 study).

Eleven EEG-based neurofeedback studies have been included in our study. Ghosh, et al. reported that after ten sessions of EEG neurofeedback training the patient's cognitive deficiencies, anxiety and sadness were significantly reduced. Passini, et al. study the therapeutic effectiveness of alpha-wave biofeedback therapy for alcoholics and reported that ten hour-long alpha training sessions had significant improvement in long-term therapeutic benefits on anxiety than the control group. DeGood, et al. reported that the self-regulation of occipital alpha density was found to be superior in non-users of alcohol compared to users of alcohol after alpha biofeedback sessions [12]. Ko and Park, investigated whether neurofeedback training can normalise the excessive high beta and low alpha waves. They found no significant difference between the two experimental and control group when it came to reducing brain hyperarousal. The experiment group that received neurofeedback training, on the other hand, had a significant rise in fundamental psychological need satisfaction, alcohol abstinence self-efficacy and self-regulation.

Seven studies reported effectiveness of EEG-alpha-theta brainwave training in patients with AUD. Studied the effects of EEG alpha and theta brainwave training in a 39-year-old alcoholic patient, finding that after therapy, the patient seems to behave in a more calm manner under stress and no longer has alcohol cravings. Saxby and Peniston, reported sharp reduction in self-assessed depression and stress-related personality traits and prolonged prevention of relapse in subjects undergone alpha-theta brainwave training. Kelley, et al. reported improvements in the ability to cope and significant reduction in BDI depression score after alpha-theta training. Dalkner, et al. and Lackner, et al. observed that after 12 sessions of alpha-theta training, there was increased control of their brain activity during the course of neurofeedback. Peniston and Kulkosky, reported that alpha-theta training decreased relapse and reduced depressive symptoms and prevented elevation of serum β-endorphin levels. Another study by Twemlow and Bowen observed promotion of insight and attitude change after 20 sessions of alpha-theta training.

Two randomized controlled studies explored tDCS induced behavioral and neuro-physiological modulation in subjects with AUD. These studies have reported that tDCS reduces craving and cue-reactivity for alcohol by modulating cortical excitability in the prefrontal cortex.

Da Silva, et al. reported that use of repetitive unilateral tDCS in alcoholic patients reduce craving and depression as compared to the sham group. Holla and colleagues observed that active-tDCS increased the whole-brain network efficiency as well as inter-regional connectivity within a particular local prefrontal sub-network significantly and the likelihood of relapse was also significantly reduced.

Three randomized clinical trials looked into using rtfMRI-based neurofeedback therapy to prevent relapse and evaluate changes in craving-related neural responses in individuals with alcohol dependence. Karch, et al. and Kirsch, et al. investigated the feasibility of neurofeedback training to modify brain activity associated to alcohol craving in exploratory pilot studies. Kirsch, et al. reported that neurofeedback reduced striatal activation to alcohol cues and Karch, et al. observed that brain activation was decreased across neurofeedback training in the AUD neurofeedback group. Subramanian, et al. observed that the salience system was modulated in the desired directions by the majority of patients, who decreased activity in response to alcohol cues and increased activation in response to positive goals.

Two randomized controlled studies included investigated the effect of high frequency rTMS on craving and mood in alcohol dependent subjects. Hoppner, et al. found no significant alterations in mood or craving following stimulation. Schluter, et al. also observed no additional effect of intervention on impulsivity measures and no significant difference between scores of task performance as well. McCalley, et al. observed that 10 days of medial prefrontal cortex TBS reduced drinking and decreased brain reactivity to alcohol cues. Kuhn, et al. reported that DBS decreased alcohol consumption and normalization of both cravings and addictive behavior in an alcohol dependent patient

CONCLUSION

There are various pharmaceutical interventions for alcoholism, but they frequently fail to manage the addictive aspects of alcoholism, particularly the craving to consume alcohol. Novel therapeutic strategies like non-invasive brain stimulation methods are required to remedy this poor scenario, as they may reduce alcohol cravings and risky behaviors in people with AUDs. Neurofeedback interventions as a non-pharmacological therapy or as an adjunct to pharmacological treatment in patients with AUD may have a significant impact, but they need to be investigated further in studies with a larger sample size.

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