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Original Article

Trans-cranial Magnetic Stimulation in Treatment of Alcohol Use Disorder: A Meta-analysis

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Abstract

Background and objective: In the US, about 14.5 million people ages 12 and older suffered from alcohol use disorder (AUD) in 2019. AUD affects multiple systems and is a major cause of disability and morbidity, severely reducing quality of life. With currently available pharmacotherapy and psychotherapy (including behavioral therapy) relapse rates remain high due to poor patient acceptability as well as the added factor of craving and impulsivity in addiction disorders. This points to the development of therapies that also act on functional areas of brain responsible for craving and impulsivity. Transcranial magnetic stimulation (TMS) is one type of neuromodulation under study for the treatment of AUD. Here, we review the work done on TMS as a treatment for AUD.

Methods: We searched PubMed and Cochrane databases for relevant articles with the main search terms of "transcranial magnetic stimulation" and "alcoholism".

Results: Most studies involve stimulation of right dorsolateral prefrontal cortex. Majority demonstrate a decrease in craving but only over time, not between groups. Overall, studies using TMS for the treatment of AUD show mixed results in changes in craving, impulsivity, and alcohol intake.

Conclusion: Mainly, the studies are limited by sample size and lack of uniformity in outcomes measured. Significance of TMS for treatment of AUD is still not clear. A standardized protocol of investigation is needed to allow for a meta-analysis to calculate the overall effect.

Introduction

Alcohol use disorder (AUD) is a medical condition characterized by an impaired ability to stop or control alcohol use leading to clinically significant impairment or distress.[1] According to the 2019 National Survey on Drug Use and Health (NSDUH), 85.6 percent of people 18 years or older drank alcohol at some point in their life.[2] the 2020 NSDUH reports about 14.5 million people ages 12 and older suffered from AUD in 2019, men forming greater proportion compared to women.[3] Alcohol-related causes lead to approximately 140,000 deaths annually.[4] Alcohol consumption adds to loss of quality of life of the patient as well as social and financial burden on the society.[5,6] The consequences of alcohol dependence are multisystemic. There is also constant difficulty in achieving as well as maintaining abstinence,[7,8] which have been challenging tasks for the treating physician as well as the patient. Furthermore, alcohol use disorder can co-present with neuropsychiatric disorders. A mechanism-based advancement in treatment to reduce dependence on pharmacotherapy or increase adherence to currently used medications for AUD is needed.[9]

There is abundance of literature on mechanism of alcohol dependence. Ceccanti *et al*. add evidence to Solomon's opponent system that alcohol dependence occurs through sequential changes in the neurons.[10–12] In earlier stages of alcohol dependence , positive reinforcement by dopamine opposes the stress system which would otherwise lead to negative behavioral symptoms. In later stages an imbalance occurs in dopaminergic and opposing system and dominance of latter system results in negative behavioral

Keywords: Transcranial magnetic stimulation; Alcohol use disorder; Craving; Impulsivity.

Abbreviations: ACQ, alcohol craving questionnaire; AUD, alcohol use disorder; AUQ, alcohol usage questionnaire; DBS, deep brain stimulation; DLPFC, dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; OCDS, obsessive compulsive drinking scale; PACS, penn alcohol craving scale; TMS, transcranial magnetic stimulation; VAS, craving visual analog scale.

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symptoms, leading to relapse. Furthermore, one of the mechanisms of craving, withdrawal and impulsivity is decreased dopamine activity in mesolimbic areas and Nucleus Accumbens (NAc) leading to hypo-frontality, measured through serum prolactin levels, which are indirect indicators of dopaminergic activity.[10] Dopamine functionality in the brain is affected by various mechanisms which include alteration in levels of dopamine, dopamine receptors and dopamine transporter. All of these mechanisms point to decreased activity of dopamine in AUD.[13]

In a neural connectivity perspective, fronto-striatal pathways modulate limbic and executive control systems. The connections between medial prefrontal cortex (MPFC) and ventral striatum form the limbic circuit whereas projections between dorsolateral prefrontal cortex (DLPFC) and dorsal striatum make up executive control circuit. Mechanisms which make the alcohol use disorder patients prone to drug related cues could possibly be enhanced limbic circuit activity during an appropriate stimulus (drug cue) and reduced activity in executive control circuit to oppose the limbic drive for drug.[14,15] These form a potential basis of neuromodulation, which could be direct (targeting MPFC) or indirect (targeting DLPFC).[16] For DLPFC, dopamine release in nucleus accumbens (NAc) mediates its modulatory effects.[17] Therefore idea of altering excitability of DLPFC noninvasively, by an electric or a magnetic field, emerged to reduce craving.[18] Such modulation of neural circuits has already been significantly studied for major depressive disorder (MDD) and obsessive compulsive disorder (OCD).[19]

Current pharmacotherapy to treat alcoholism includes disulfiram, naltrexone and acamprosate.[20] These drugs have been proven effective: Disulfiram works by causing nausea however fails to reduce craving. On the other hand naltrexone and acamprosate (effective for relapse prevention) may not cause nausea, but nonadherence to their oral formuations is a significant barrier to optimized care for many patients.[21] Promising advancement in medical treatment with drugs such as topiramate, gabapentin and baclofen for AUD along with neuromodulation may play an important role in future.[22] With current pharmacotherapy and psychotherapy, the abstinence rate by the end of 1st year of treatment is less than 40%.[7,8,23] Keeping in view the adverse effects and high motivation needed to complete treatment, newer techniques have been sought to deal with AUD. Non-invasive neuromodulation has been one of the studied treatment modalities. Transcranial magnetic stimulation (TMS) and transcranial electric stimulation (TES) are two major types. TMS is a method of applying varying levels of magnetic field to the brain non-invasively (transcranial: through the scalp) to modulate neuronal excitability.[24] We discuss TMS in treatment of AUD. TMS was initially used as an investigative technique, where the method of application is pulse application. With time, it found a therapeutic role as well.[25,26] TMS is thought to work by long term potentiation (LTP) or long term depression (LTD) of neural activity depending on the frequency, type of stimulation and stimulated area.[16]

In this perspective, efforts have been directed at exploration of a non-invasive method of treatment for AUD to decrease the relapse rate as discussed above. For this purpose, TMS can be applied for the treatment of AUD which has previously been approved for depression and OCD. TMS is a safe procedure, with a common side effect being headache and a severe (but low risk) side effect being seizure.[27,28] Apart from proven safety, the major advantages of TMS are that it is a non-invasive procedure compared to deep brain stimulation (DBS) and while it may produce twitching, the patient does not have to experience the annoying sensations when compared to TES.[29] In near future it is already projected to become affordable like pharmacotherapy.[30] However, disadvantages of TMS include that it cannot penetrate to deeper structures as DBS can and it is not as precise as DBS.[31] Furthermore, the treatment duration is long, requiring 10 to 30 visits making it difficult for patients to follow. TMS is also being questioned, like other neuromodulation techniques, for its ability to affect patient autonomy and alter decision making capacity.[32]

Here, we review different original studies done to date to investigate the use of TMS in reducing subjective aspects of craving and/or impulsivity in AUD patients.

Methods

A thorough search on this topic was done in PubMed and Cochrane databases through March 2022. The search terms used were: "alcoholism", "alcohol" AND "disorder", "dependence ", "addiction", "alcohol use disorder" AND "stim*", "magnetic", "magnetic stimulation, transcranial".

There was no restriction applied on age, gender, publication type or period of study. Studies identified through database searches were initially screened by their title. Articles with titles different from our interest were excluded, rest of the articles were reviewed by reading through abstracts and were finalized to be discussed in our review. Studies that targeted AUD (irrespective of presence of a comorbid disorder all types of studies whether randomized or open label, with or without any level of blinding, with or without control, and for any duration of follow up were considered for inclusion. However, studies that were only case studies did not describe the protocol for transcranial magnetic stimulation, or were only exploratory in purpose were excluded. A Flowchart demonstrating PRISMA exclusion strategy is shown in Figure 1.

Results

Our review comprises of 19 studies. A good range of target sites have been stimulated. 9 studies stimulated Right Dorsolateral Prefrontal Cortex, 5 Medial Prefrontal Cortex, 2 Left Dorsolateral Prefrontal Cortex, 2 Bilateral DLPFC, 1 Right vs Left DLPFC and 1 study stimulated Insular Cortex. Maximum number of sessions performed was 20 excluding a case study of De Ridder (1Hz stimulation of dorsal Anterior Cingulate Cortex, not included in the table because it involves only one subject) where it was 21. Most studies used a frequency of 10 Hz for stimulation. 13 studies used a figure of 8 coil, 5 studies used an H coil, and one study used a double cone coil.

Types of assessments used include craving scales as Alcohol Craving Questionnaire (ACQ), craving Visual Analog Scale (VAS), Obsessive Compulsive Drinking Scale (OCDS), Penn Alcohol Craving Scale (PACS), and Alcohol Usage Questionnaire (AUQ). Impulsivity scales include Go-no-go task, Delay Discounting Time (DDT), Stop Signal Task (SST). Alcohol intake and consumption scales include Days of Maximum Alcohol Intake (DMAI), percentage Heavy Drinking Days (pHDD) and daily consumption. Some studies also measured relapse rate.

It is interesting to note the differences on a subgroup level of assessment methods. Two studies, from the same group utilized ACQ, which measures the level of alcohol craving, and did not show any significant difference between the active and sham groups. 7 studies utilized OCDS to measure obsessive compulsivity and craving towards alcohol. Overall, there was no significant between the groups in 4 studies while 3 demonstrated a significant effect, real group scores better than sham group scores. In VAS and AUQ measurements only one out of 4 respective studies showed a significant difference in scores between real and sham groups.

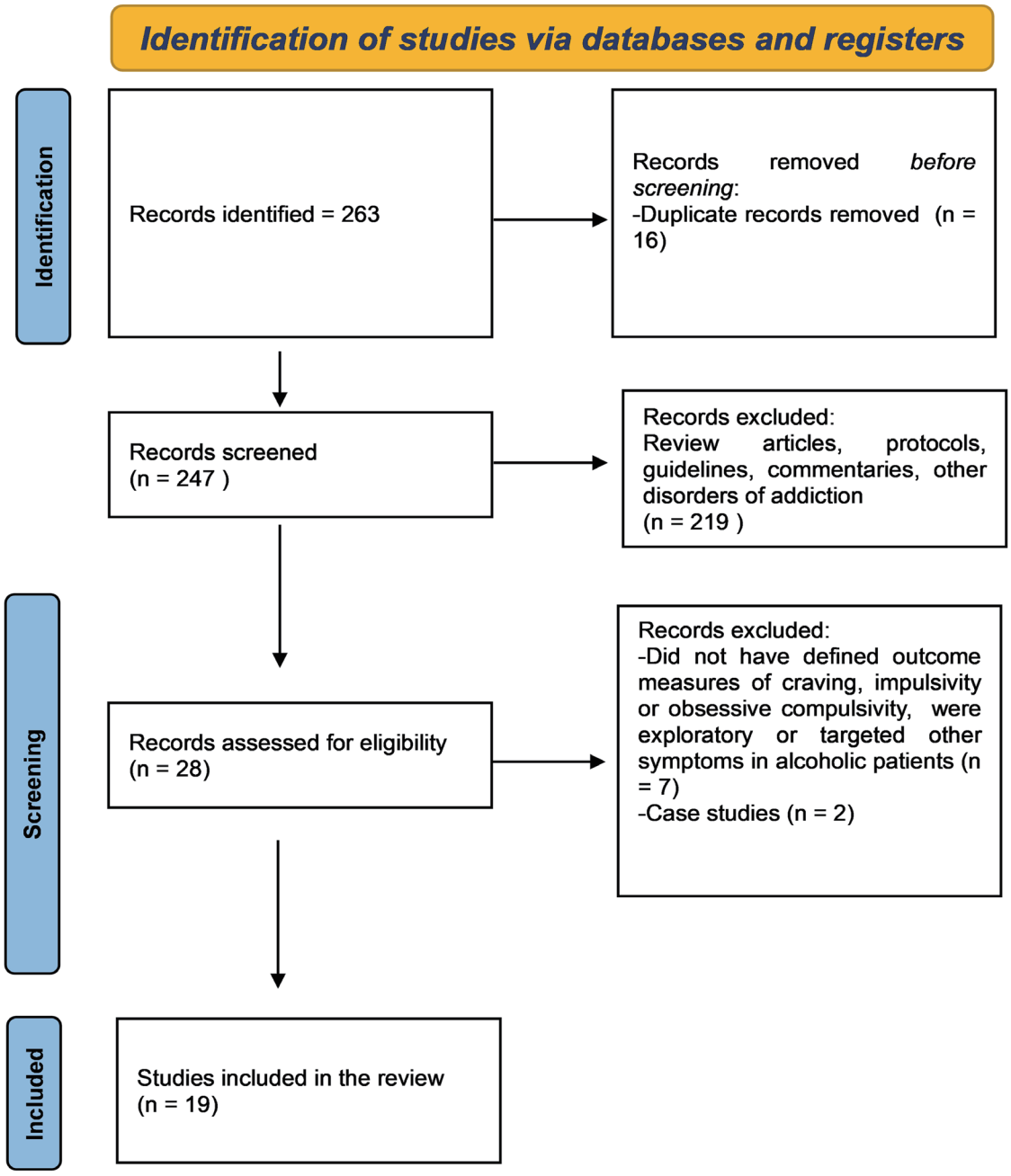

Fig. 1. Identification of studies via databases and registers.

However, there have been improvements within the groups. Other factors such as years of education have a positive correlation while the age of onset of alcohol use has a negative correlation with outcome scores. The results are summarized in Table 1.[10,13,33–49]

Discussion

The aim of this review is to highlight the studies done on TMS therapy for AUD, their promising features and limitations. Non-invasive neuromodulation therapies, such as transcranial magnetic stimulation and transcranial electrical stimulation, are rapidly gaining interest in the treatment of addiction and psychiatric disorders. Treating these disorders will ameliorate the multisystemic deteriorating effects on the patient and society. TMS was approved by FDA as a treatment modality for major depressive disorder in 2008[50] and obsessive compulsive disorder in 2018.[51] The effect of TMS on craving in AUD has been studied in some combination of open label, single blind and sham controlled, but very few randomized sham-controlled double-blind trials. Most of the studies have measured outcomes/endpoint from 1 to 6 months. There are very few studies which follow patients beyond the 6-month period.[38,49] The outcomes measured include craving, impulsivity,

Table 1. Characteristics and outcomes of studies included in this meta-analysis

Study	Study design	Inclusion criteria	Frequency of stimulation, Coil shape	Target location	# of TMS sessions	1) Severity of alcohol abuse (years of drinking or by scale); 2) Alcohol use status on starting TMS; 3) Co morbid psychiatric disorders	Number of participants	Outcome
Mishra 2010[33]	Randomized single blind sham controlled, 1 month follow-up	Age:18–60 years, CIWA-Ar score 10 or less	10 Hz; Figure-of-8 coil; 110% MT	Right DLPFC	10	1)15.3 years in active 13.5 years in sham	Sham 15 + Active 30 = 45	Significant effect of treatment over time for ACQ-NOW($p < 0.0005$).
Hoppner 2011[34]	Randomized sham controlled, 10 days follow-up	Mean age(years): Real: 43.1; Sham: 48; Females only	20 Hz; 90% MT	Left DLPFC	10	1) 8 years in real; 6.7 years in sham; 2) 14 days after detoxification	Sham 9 + Active 10 = 19	OCDS: No significant difference in craving between real and sham groups.
Herremans 2012[35]	Randomized single blind sham controlled, between subjects, 3 days follow up	Age: 18–65 years	20 Hz; Figure of 8 coil; 110 % of MT	Right DLPFC	1	2) Detoxified (Substitution phase completed in mean duration of 12 days)	Sham 16 + Active 15 = 31	OCDS: Significant main effect of time ($p = 0.02$). However, no significant main effect for group. In delayed effects of one stimulation session, no main effects for test moment (Saturday, Sunday, Monday) or for Group.
Herremans 2013[36]	Randomized single blind sham controlled, crossover design	Age: 18–65 years	20 Hz; Figure of 8 coil; 110% MT	Right DLPFC	1	2) Detoxified (Diazepam substitution completed in mean duration = 14 days and then benzodiazepine-free period 7 days)	29 patients, crossover design	OCDS: A significant main effect for time ($p = 0.03$).
Mishra 2015[37]	Single-blind, active-comparator. 10 days follow up	Age: 18–60 years, Male CIWA = Ar score 10 or less	10 Hz; Figure of 8 coil; 110% MT	Right vs Left DLPFC	10	1) 16.9 years in Right, 17.7 years in Left; 2) 3 days of detoxification	10 Right + 10 Left = 20	ACQ-NOW: No main effect of group (right & left DLPFC) but significant main effect of time ($p < 0.0001$). The interaction effect between group and time was not significant. GCI:No main effect of group (right & left DLPFC) but significant main effect of time ($p < 0.0001$). The interaction effect between group and time was not significant.

(continued)

Table 1. *(continued)*

Study	Study design	Inclusion criteria	Frequency of stimulation, Coil shape	Target location	# of TMS sessions	1) Severity of alcohol abuse (years of drinking or by scale); 2) Alcohol use status on starting TMS; 3) Co morbid psychiatric disorders	Number of participants	Outcome
Girardi 2015[38]	Open label add-on compared to standard treatment, 6 months follow up	Age: 16–65 years >5-year duration of illness	20 Hz; H1 coil; Deep TMS; 120% MT	Bilateral DLPFC	20	1) 9.6 years in add-on 12.6 years in standard; 2) Detoxified for 1 month; 3) Dysthymic disorder	Add-on dTMS 10 + standard treatment 10 = 20	Add-on deep TMS to standard leads to significant reduction in craving, OCDS. Reduction of OCDS from baseline was significantly larger in the experimental than in the control group at all time-points($p < 0.01$).
Ceccanti 2015[10]	Randomized double blind placebo controlled, 6 months follow up	Mean age(yeats): Real: 43; Sham: 47; Males only	20 Hz; H coil; Deep TMS; 120% MT	Medial PFC	10	1) 26 years in real, 25 years in sham; 2) 10 days of residential withdrawal for benzodiazepines flush out. TMS only therapy provided.	Sham 9 + Real 9 = 18	Daily alcohol consumption(drinks/day): Real vs sham not significantly different. DMAI: Real vs sham not significantly different. VAS: Real vs sham not significantly different.
Herremans 2015[39]	2-part study: Experimental part: single blind sham controlled between subjects; Treatment part: open label	Age: 18–65 years	20 Hz; figure-of 8 coil; 110% MT	Right DLPFC	15 (in 4 days)	1) Mean 12 years, # of days patients drank more than 5units/day: 19.6; 2) No alcohol for at least 7 days, 2 weeks washout period for those on anti-craving medications	Experimental part:13 Sham + 13 Active = 26 in 1 rTMS session; reatment part: All 23 subjects in Accelerated HF-rTMS treatment part	Experimental part: TLS (ten-point Likert scales): Active v sham (1 rTMS session) No significant effect on TLS-scores for the active stimulation and the sham stimulation. No significant difference in TLS between both (active vs sham) stimulation groups. Accelerated HF-rTMS treatment part: Significant decrease for both the OCDS ($p = 0.02$) and the AUQ ($p = 0.02$) after HF-rTMS treatment. A significant effect between all TLS of the first scan compared with all TLS of the last scan (all $p < 0.05$). However, all other TLS comparisons were not significant.

(continued)

Table 1. *(continued)*

Study	Study design	Inclusion criteria	Frequency of stimulation, Coil shape	Target location	# of TMS sessions	1) Severity of alcohol abuse (years of drinking or by scale); 2) Alcohol use status on starting TMS; 3) Co morbid psychiatric disorders	Number of participants	Outcome
Herremans 2016[40]	Open label; 4 weeks follow up	Age: 18–65 years	20 Hz; Figure of 8 coil; 110% MT	Right DLPFC	15 (in 4 days)	1) 14.5 years in relapsers, 9.8 years abstainers# of days patients drank more than 5units/ day: Relapsers; 17.7. Abstainers: 20 2) At least 1 week diazepam free before stimulation	19	Relapse rate of 68% (13/19) at 1 month with no significant difference in characteristics of relapsers and abstainers.
Del Felice 2016[41]	Add-on rTMS with disulfiram, Single blind, randomized sham controlled1 month Follow up	Age: 18–65 years	10 Hz; Figure of 8 coil; 100% MT	Left DLPFC	4	2) Abstained for more than 6 days before the beginning of the rTMS sessions	Sham 10 + Active 10 = 20	Alcohol intake: No significant modifications over time or group Craving (VAS): No significant modifications over time or group. Attentional bias (Mean Numeric Stroop scores): Improved from 0.311 to 0.901 at 1 month ($p = 0.004$). Go/ No-Go task: Improved from 0.450 to 0.966 at 1 month ($p = 0.0.015$)
Addolorato 2017[13]	Double blind, randomized sham controlled trial	Age: 39–64 years Alcohol withdrawal CIWA-AW score 10 or less.	H coil, 10Hz (deep rTMS); 100% MT	BilateralDLPFC	12	1) 17 years; ADS:13.8 ± 7.5	Sham 6 + active 5 = 11	OCDS: Craving did not significantly change in the real and sham group. Alcohol intake (Abstinence days, number of drinking days number of drinks per drinking days and total drinks): Significantly reduced alcohol intake($p = 0.008$) in real group only, with time.
Hanlon 2017[42]	Single blind sham controlled crossover study	Mean age in years: 27	cTBS; 5Hz; Figure of 8 coil; 110% MT	Left Frontal pole(MPFC)	1	1) Duration of use:13.2 ± 12; AUDIT:14.2; TLFB:11.7; 2) Allowed to drink but undetectable blood alcohol levels in the lab.	24	Self-reported craving (VAS): Significant main effect of time ($F(2,132) = 3.62$), but no interaction nor effect of condition (real versus sham).

(continued)

Table 1. *(continued)*

Study	Study design	Inclusion criteria	Frequency of stimulation, Coil shape	Target location	# of TMS sessions	1) Severity of alcohol abuse (years of drinking or by scale); 2) Alcohol use status on starting TMS; 3) Co morbid psychiatric disorders	Number of participants	Outcome
McNeill 2018[43]	Counterbalanced, within-participants, controlled stimulation	Age: 18 - 27 years	cTBS, 50 Hz; Figure of 8 coil; 80% MT	Right DLPFC	1	1) AUDIT: 11.75 ± 4.4; TLFB:39.6 units; 2) Actively consuming	20	Alcohol consumption: Participants consumed significantly more beer following active stimulation compared with control stimulation ($p < 0.001$).
Kearney-Ramos 2018[44]	Single blind, active-sham controlled	Age: 21–54 years	5Hz; cTBS; Figure of 8 coil; 110% MT	Left Ventral MPFC	1	1) Years of alcohol use: 10 ± 5.1, AUDIT:14.2 ± 4.8; 2) Time since last alcohol use:2.8 ± 2.6 days	Sham 12 + active 12 = 24	Self-reported alcohol craving: No significant main or interaction effects of time (pre/post) or treatment (real/sham) on self-reported alcohol craving ($p \geq .05$).
Schluter 2019[45]	Single blind Randomized Controlled Trial	Age: 20- 65 years; Less than 4 months after detoxification	10 Hz; Figure of 8 coil; 110% MT	Right DLPFC	10	1) 11 years in active, 10 years in sham; 3) Active group taking antidepressants significantly	Sham 40 + active 40 = 80	DDT: No significant main effects of session, or treatment group; GNGT:No significant main effects of session or treatment group. SST: No significant main effects of session, or treatment group.
Jansen 2019[46]	Single blind, sham controlled	Mean age in years: AUD: 42; HC: 44	10 Hz; Figure of 8 coil; 110% MT	Right DLPFC	1	1) Mean AUDIT of all participants: 22.11; 2) Sober for at least 3 weeks	Sham 18 + active 20 = 38 (AUD; n = 39) and healthy controls (HC; n = 36)	AUQ: No differential effect on change in craving over time (pre and post) for AUD patients and/or HC.
Irene 2020[47]	Double-blind, randomized, sham-controlled, clinical trial. 12 weeks follow up	25–64 years, postmenopausal or negative UPT females	10 Hz; H8 coil; 120%; MT	Insular cortex, bilaterally, excluding prefrontal areas	15	1) ADS: 19.3 in rTMS group, 16.7 in sham group, Peth 0.9–1.1, TLFB 39–48%. 3) Mild cognitive impairment (MMSE not less than 24)	Sham 22 + active 23 = 45	AUQ: Significant main effect of time during treatment, for both ($p < 0.001$). PACS: Significant main effect of time during treatment ($p = 0.01$). However, no between group effect.

(continued)

Table 1. *(continued)*

Study	Study design	Inclusion criteria	Frequency of stimulation, Coil shape	Target location	# of TMS sessions	1) Severity of alcohol abuse (years of drinking or by scale); 2) Alcohol use status on starting TMS; 3) Co morbid psychiatric disorders	Number of participants	Outcome
Maayan Harel 2021[48]	Randomized double blind, sham controlled, 12 weeks Follow up	Mean age in years: Active: 43.7; Sham: 42.5	10 Hz; H7 coil; Deep TMS; 100% of MT	MPFC and ACC	20	AUDIT active 24.5 (7.2); 26.1 (6.3); ADS 16.5 (7.5); 17.8 (6.2); TLFB, HDD, % 36.8% (32%); 37.6% (27%); 2) Abstinent from alcohol for at least 5 days (but no more than 1 month)	Sham 24 + active 27 = 51	pHDD: Significantly lower in the active group than the sham group ($p = 0.037$). PACS: During follow up craving levels increased in the sham group but less so in the active group.
Maarten Belgers 2022[49]	Single blind randomized sham controlled12 months Follow up	Age: 20 to 65years	Figure of 8 coil; 10 Hz; 110% MT	Right DLPFC	10	1) Years of problematic use add on tms 16.4 (6.5) years; 14.3 (7.4) years; 2) Detoxification less than 6 weeks; 3) Some patients with PTSD	Sham 16 + active 14 = 30	VAS, OCDS-5, and AUQ: In the follow-up period, from after rTMS, increased craving over time for all participants but less increased craving over time in the rTMS group versus sham ($p < 0.05$ for main effect of time and group and interaction effect of group by time). Alcohol use (alcohol use per day and the total amount of alcohol): Decreased alcohol use in the rtms group vs sham $p = 0.001$. Percentage abstinence: The percentage abstinence at the endpoint did not differ between groups.

ACC, Anterior cingulate cortex; ACQ-NOW, Alcohol craving questionnaire; ADS, Alcohol dependence scale; AUD Alcohol use disorder; AUDIT, Alcohol use disorders identification test; AUQ, Alcohol usage questionnaire; CIWA-AR, Clinical Institute withdrawal assessment alcohol scale revised; cTBS, continuous theta burst stimulation; DDT, Delay discounted task; DLPFC, Dorsolateral prefrontal cortex; DMAI, Days of maximum alcohol intake; dTMS, deep TMS; GCI, General craving index; GNGT, Go-no-go task; HC, Healthy controls; HDD, Heavy drinking days; HFrTMS, High frequency repetitive TMS; MMSE, mini mental state examination; MPFC, Medial prefrontal cortex; MT, Motor threshold; OCDS, Obsessive compulsive drinking scale; PACS, Penn alcohol craving scale; pHDD, percentage heavy drinking days; PTSD, Post traumatic stress disorder; SST, Stop signal task; TLFB, Timeline followback; UPT, Urine pregnancy test; VAS, Visual analog scale.

alcohol consumption and blood alcohol levels. There is consistency in measuring craving in most of the studies. However other outcomes such as impulsivity or consumption are not measured as consistently. Mishra *et al*. initially demonstrated decrease in craving using rTMS.[33] His study was based on randomized single blind sham-controlled design with one month follow-up. This was followed in 2015 by Girardi *et al*. who performed an open label study to prove significant effect of add on TMS therapy compared to standard treatment.[38] Studies gained pace afterwards, most finding decrease in craving or alcohol intake with time, but not significantly different from non-treatment (control) group.[10,47]

AUD often coexists with other psychiatric diagnoses. This has two-pronged significance. With TMS treatment, the coexisting psychiatric condition may improve together with craving in AUD,[52] or the medication used for the psychiatric condition may confound the results of TMS. Similarly consumption of other substances of abuse and severity of abuse of each of these, including alcohol, can determine effect of treatment.[45] The severity of AUD can affect the outcomes after TMS therapy. Chronic alcohol use causes cortical atrophy which implies that intensity of stimulation that reaches the cortex and sub-cortex of these subjects will also vary by the severity of disease.[53,54] Thus, patients must be classified accordingly to determine their respective dosage regimens.

There is a need to find out possible duration for which maintenance treatment can be administered like depression where authors have recommended it for up-to several years.[55,56] It is also important to know whether this will have any possible side effects for example headache, seizures in the long term and also whether altering one reward function affects other daily activities possibly resulting in a general lack of motivation.

Most of the studies have been conducted only on a relatively smaller sample size. To measure the effect of TMS, which is statistically significant in treatment of AUD, multi-centric larger sample studies should be under taken.[38] The context in which a study is conducted can also impact the results. This includes measuring craving in a subject's natural environment compared to a testing environment where a subject is given a cue and impulsivity is measured. However in trying to measure effect of TMS in a patient's natural environment rather than in a clinical setting, accurate cues and controls are difficult to set up.[35]

Depth of stimulation is also important as the distance from scalp to cortex is variable in the population.[42] The depth of stimulation is determined by the coil shape (*e.g.* flat vs bent, figure of 8 vs H- coil design) which is further compounded by the shrinkage of cortex in alcoholics and aged groups.[31,57] The shape of TMS coil also determines regional precision and cortical surface area affected.[54] Modelling techniques have revealed that H-coil designs affected greater cortical area and depth compared to figure of 8 coil and circular coil designs. Other than affecting the depth of stimulation, age is also a clinical factor in predicting the efficacy of TMS.[58] TMS therapy benefit appears later in the older patients than in the younger patients and this has implications for setting treatment guidelines and insurance based health systems.[59] However, the age factor may be confounded by the years of alcohol abuse which in itself is an independent prognostic factor.

Majority of studies have investigated Right DLPFC. Others have worked on MPFC, Left DLPFC, dorsal Anterior Cingulate Cortex and insula. When comparing effect of rTMS on right with rTMS on left DLPFC,[37] craving was reduced in both right and left stimulation groups but without any significant difference between the side stimulated. rTMS over left side had a positive correlation between severity of alcohol dependence and reduction in craving scores. Right sided rTMS was more effective in mild to moderate cases, authors thus postulating that right sided rTMS affected indirectly through transcallosal suppression of left DLPFC. VMPFC has also shown promising results with respect to cue reactivity however not as successful with reduction in craving. It provides an insight into other possible target areas for stimulation.[44] One study is based on the role of insula in craving.[47,60] Although it shows no significant effect, but wider connections of insula to several other areas have been proved.

The behavioral state of subjects when they are undergoing TMS is also very important. Emphasis has been placed on this by Mahoney *et al*.,[54] who build on the work of Ramos *et al*.[61] The operating state of a synapse during TMS application determines the degree to which it can be modulated.[61–63] This operating state further depends on prior activation of the circuit, therefore leading to the concept of behavioral priming for stimulation.

Future direction

TMS is gaining popularity as a therapy for addiction including alcohol addiction, psychiatric and cognitive disorders. In the case of TMS for AUD, it is most important for the scientific community to develop a consensus on how the outcomes will be measured and also to collaborate towards a larger, multicenter study. Furthermore, many studies have missed out on the value of control and all future studies should include a control group. Any protocol that may be formed for multicenter studies must include daily alcohol consumption as an outcome measure as it is the final goal of any type of therapy combatting AUD. Moreover, a standardized cue exposure for behavioral priming during TMS therapy session for AUD should also be developed and documented as a variable in future studies. This is significant because cue exposure is a requirement during TMS for OCD and has been studied in a similar context for PTSD and smoking, enhancing efficacy of TMS in these subjects.[54,64,65] Recently Maayn Harel *et al.* have inducted this concept into their study by allowing the subjects to hold and smell alcohol before undergoing TMS procedure.[48]

Conclusion

Pharmacotherapy for the treatment of AUD works in the short term and requires strict patient compliance. This management strategy may be further strengthened by adding on TMS, to reduce craving and relapse. Although multiple studies have been conducted on TMS to prove it an effective treatment modality as in the case of depression and OCD, the results of these studies are mixed and still not directing to a definite conclusion. Future studies should be multicentric and based on a standardized protocol.

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Author contributions

The authors contributed equally to this work.

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