

rTMS for Alcohol Cravings in Alcohol Use Disorder

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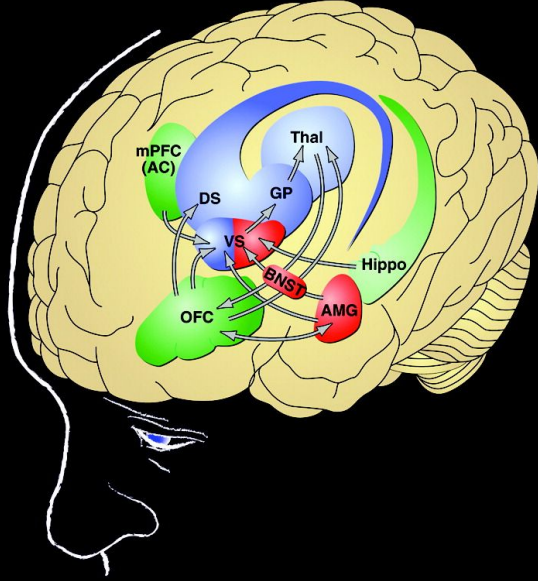
No financial disclosures

Learning Objectives

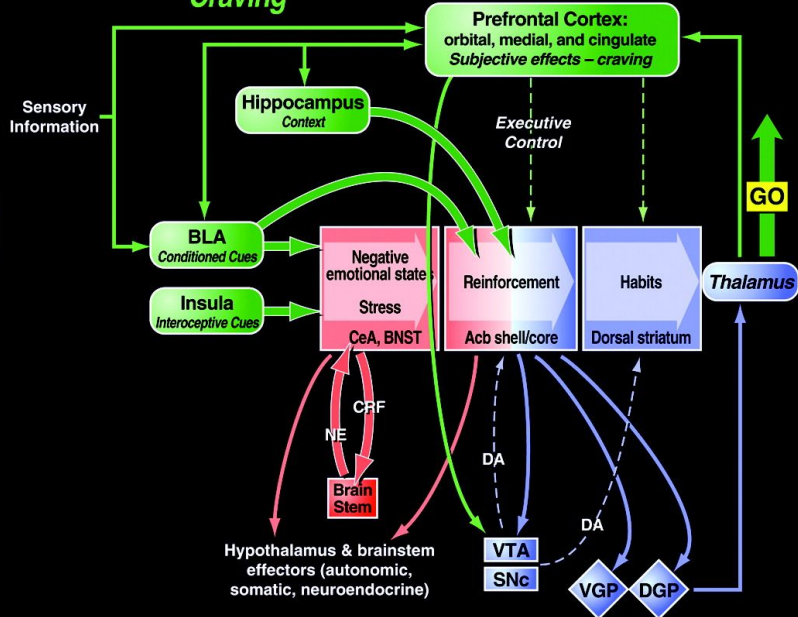
- 1) Current understanding of neuromodulation for substance use disorders.
- 2) Review of rTMS.
- 3) Review of current study looking at immediate and sustained effects of multiple rTMS sessions on alcohol cravings in AUD.

Neurobiology of Addiction

- Prolonged exposure to addictive agents results in dysfunctions in multiple circuits that maintain addiction.
- These are the consequences of neural adaptations with different time courses.
- Significant alterations can be detected in circuits implicated in reward, salience attribution, motivation, inhibitory control, learning and memory consolidation,
- Neurocircuit-based interventions might ameliorate or disrupt addiction by targeting different neuroanatomical structures that serve as 'nodes' within these circuits and that are associated with particular behavioural markers.



**Preoccupation/Anticipation
"Craving"**



Withdrawal/Negative Affect

Binge/Intoxication

Background

- Up to 50% of AUD patients may return to use within the first 2 weeks following withdrawal management.
- Noninvasive neuromodulation techniques, such as transcranial direct current stimulation (tDCS), noninvasive vagus nerve stimulation (nVNS), and repetitive transcranial magnetic stimulation (rTMS), are gaining more attention in the current research field.
- nVNS has shown promising effects. Though trials are few.¹
- Recent meta analyses showing possible benefit in tDCS and rTMS in tobacco, alcohol, stimulant, and opioid use disorder.²
Possible superiority of rTMS for AUD, TUD.
 - Possible benefit with DBS in craving, consumption and/or abstinence in alcohol, tobacco, and opioid use disorders but limited data.
- With rTMS, focus has been primarily on the IDLPFC.
- rTMS has recently gained attention as an additional treatment option in substance use disorders and has been reported to have an immediate effect on drug craving.

Background

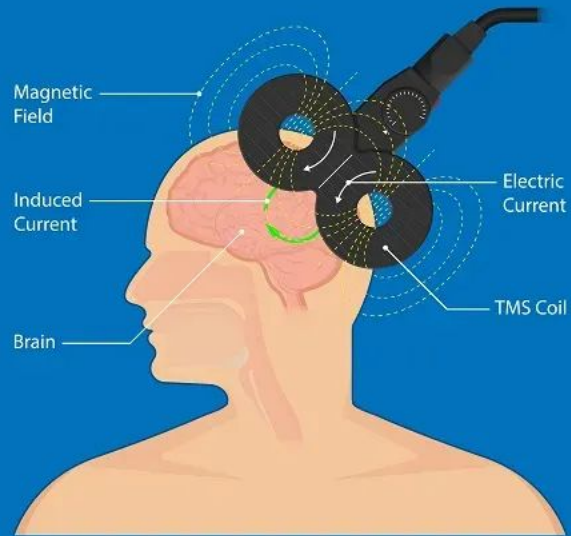
- Previous meta-analyses on craving and drug misuse have been limited because of the heterogeneity of the included studies that might have resulted from variations in treatment duration, variations of follow-up duration, rTMS brain target localization, and rTMS treatment intensity.¹
- Further studies have been published since the most recent meta-analysis.
- No meta-analysis has investigated a sustained effect of rTMS on alcohol craving in AUD.

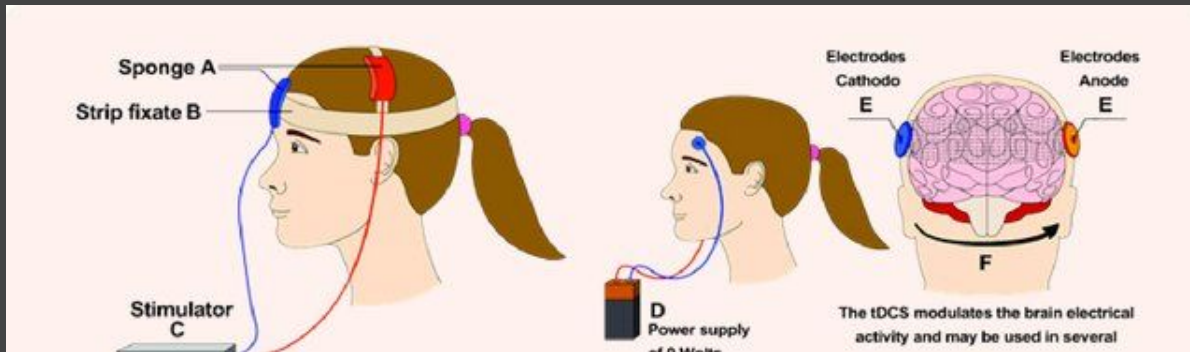
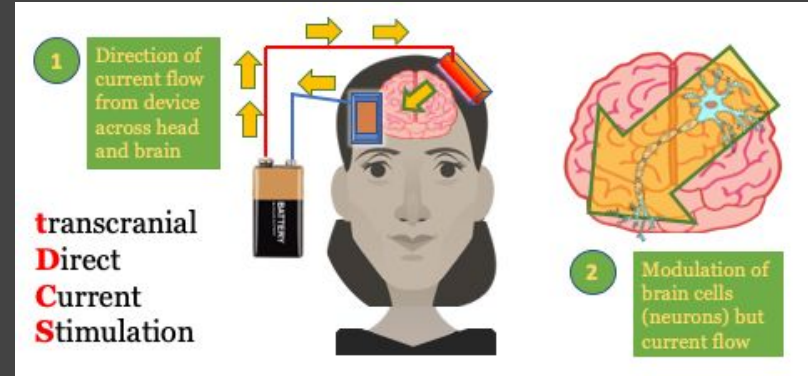
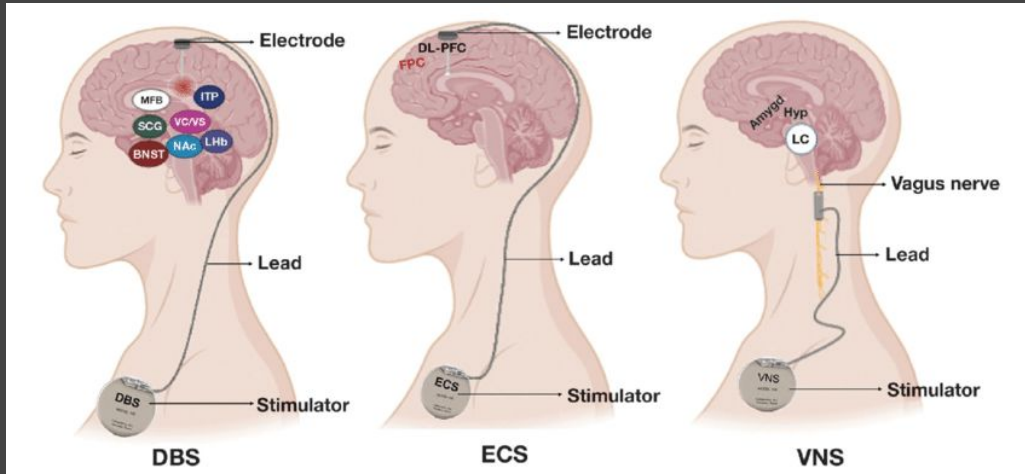
So what is TMS?

- TMS uses an electromagnetic coil placed over the skull to apply alternating magnetic fields that induce small, alternating currents in the underlying tissue of the brain.
- High-frequency rTMS (hf-rTMS) applied pulses in multiple trains stimulate the underlying brain region and have been associated with an effect that lasts beyond the duration of the treatment session.
- Whereas hf-rTMS is suggested as an excitatory stimulation, low-frequency rTMS seems to be inhibitory.
- Theta burst stimulation (TBS) is a modified paradigm of rTMS that uses burst of magnetic pulses and may elicit long-term synaptic plasticity.

TMS

Transcranial Magnetic Stimulation





Repetitive Transcranial Magnetic Stimulation for Alcohol Craving in Alcohol Use Disorders: A Meta-analysis

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Aims

- To evaluate the immediate and up to 3 months' effect of multiple-session repetitive transcranial magnetic stimulation (rTMS) on alcohol craving in AUD.

Methods

- Systematic review and random effects meta-analysis.
- Research Question:
 - Following the patient/population, intervention, comparison, and outcomes study design (PICOS) framework, the research question was defined as:
 - We want to investigate the “P” (patient/population) of individuals with AUD, the “I” (intervention) rTMS neuromodulation, the “C” (comparisons) with sham interventions, and the “O” (outcomes) craving poststimulation, as assessed by the “S” (study design) randomized controlled trials.
- Using PubMed, EMBASE, Cochrane Library, and PsycINFO databases, the study searched for original, peer-reviewed research articles based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
- The following keywords were used: “TMS” or “transcranial magnetic stimulation” or “theta burst stimulation” and “alcohol craving”.

Methods: Inclusion Criteria

- Peer-reviewed studies satisfying the following criteria were included:
 - (i) used high-frequency rTMS stimulating participants with AUD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-IV10,22,30/V20,23,31-33) or the International Classification of Diseases Version 10 (ICD-1021,34) criteria.
 - High-frequency rTMS included conventional rTMS, deep rTMS, continuous and intermittent TBS.
 - (ii) studies investigating alcohol craving as either the primary or secondary outcome via a validated or objective measurement tool (eg, scores from the Obsessive-Compulsive Drinking Scale [OCDS]).
 - (iii) employing a minimum of 10 sessions of rTMS.
 - Less than 10 sessions rTMS did not reveal any significant effect on alcohol craving demonstrated in previous meta-analyses.
 - (iv) randomized controlled trials that used sham brain stimulation
 - (v) provided means, standard deviations, t, F, or P statistics or other data that could be used to calculate the effect size. The inclusion criteria did not limit the tools used to assess clinical outcomes or the settings of the neuromodulation intervention parameters.



Dr. Oscar Morales, Medical Director of the TMS service at McLean Hospital, demonstrates how a deep TMS coil is positioned on the head during OCD treatment.

Methods: Exclusion Criteria

- (i) studies recruiting participants without alcohol use disorder (eg, heavy drinkers)
- (ii) other literature reviews, meta-analyses, dissertations, abstracts, conference presentations, and case studies
- (iii) studies assessing the neuromodulation effects but did not measure alcohol craving
- (iv) studies that used techniques other than high-frequency rTMS (eg, low-frequency rTMS)
- (v) combined neuromodulation with other intervention methods (eg, cognitive-behavioral therapy); (vi) studies lacking a well-defined sham stimulation group.

Methods

- For each included study, the following info was extracted: author information, sample characteristics, study design, type of population, number of participants, stimulation technique, rTMS stimulation target, total number of stimulation sessions (per condition), intensity (percentage resting motor threshold)/frequency (Hz), duration between the last stimulation session and follow-up evaluation, and the measures used to assess craving.
- **Primary outcome:** the relative changes in alcohol craving scores post stimulation.
- **Secondary outcomes:** relative changes in alcohol craving scores in follow-up period visits.
- The Cochrane Risk-of-Bias Tool (RoB-2) to evaluate the quality of included RCTs

Methods: Data Analysis

- All meta-analyses were performed using the statistical software “R4.0.5” with package metafor.
- A **random-effects model** was used with the underlying assumption of variability across individual study samples.
 - The outcome variables were continuous random variables assessed through different scales. So standardized mean difference (SMD) with 95% confidence intervals (CIs) was utilized to calculate the effect size of changes in alcohol craving due to rTMS ($P < 0.05$, 2-tailed).
- The I^2 statistic estimated between-trial heterogeneity.
 - An I^2 of $<40\%$ was considered low heterogeneity, $40\%–60\%$ moderate heterogeneity, and $>60\%$ high heterogeneity.
 - **A subgroup analyses was used to evaluate the effects of different stimulation areas (eg, IDLPFC, rDLPFC, mPFC).**
- A sensitivity analysis was used by serially omitting each study from the meta-analysis to assess the robustness of the results. We used funnel plots and Egger’s test ($P < 0.1$) to assess the risk of publication bias.
- 2 different effects of neuromodulation on craving were evaluated:
 - (i) the immediate effect of active rTMS versus sham stimulation (differences in post stimulation measures)
 - (ii) the maintenance effect (ie, the follow-up effects) of rTMS intervention.

Results

- A total of 12 studies were included in the final analysis.
- Across participants, 252 were randomized to active rTMS and 223 were randomized to the respective sham group.
- The included studies varied in length of intervention and follow-up period .
- The total number of sessions ranged from 10 to 20.
- 3 studies stimulated the rDLPFC. 4 studies stimulated the IDLPFC and 1 study stimulated the DLPFC bilaterally. 3 studies stimulated the mPFC and 1 study stimulated the insular cortex.
- High-frequency (>5) rTMS was employed in all studies with 3 studies administering theta-burst stimulation (50 Hz bursts at 5 Hz), 2 studies administering 20 Hz and the remaining studies administered 10 Hz.
- All studies used self-report questionnaires or scales to assess alcohol craving.
 - The assessment tools included: Alcohol Craving Questionnaire (ACQ), the Alcohol Urge Questionnaire (AUQ), the Obsessive-Compulsive Drinking Scale (OCDS), the Penn Alcohol Craving Scale (PACS), and the Visual Analogue Scale (VAS).
- Not all studies reported follow-up (FU) outcome measures.
 - 5 studies reported 1-month FU, 4 studies reported 2-month FU, 6 studies reporting 3-month FU and 2 studies reported 6-month and 12-month FU.

TABLE 1 - General characteristics of the included studies

Author(s)	Year	Diagnosis	N	Design	Outcome Measure	Stimulation Technique	Stimulation Target	No. Sessions	Frequency (Hz)	Intensity (MT%)	FU (mo)
Mishra et al	2010	AUD	45	RCT	ACQ-NOW	HF-rTMS	rDLPFC	10	10	110	1
Ceccanti et al	2015	AUD	18	RCT	VAS	dTMS	mPFC	10	20	120	1, 2, 3, 6
Addolorato et al	2017	AUD	11	RCT	OCDS	HF-rTMS	DLPFC bilateral	12	10	100	N/A
Raikwar et al	2020	AUD	60	RCT	ACQ-NOW	HF-rTMS	lDLPFC	10	10	120	N/A
Perini et al	2020	AUD	45	RCT	PACS	dTMS	insular cortex	15	10	120	1, 2, 3
Zhang et al	2022	AUD	48	RCT	VAS	HF-rTMS	lDLPFC	10	20	80–110	N/A
Harel et al	2022	AUD	46	RCT	PACS	dTMS	mPFC	15	10	100	1, 2, 3
Belgers et al	2022	AUD	32	RCT	AUQ	HF-rTMS	rDLPFC	10	10	110	3, 12
McCalley et al	2023	AUD	50	RCT	OCDS	cTBS	mPFC	10	50	110	2, 3
Hoven et al	2023	AUD	80	RCT	AUQ	HF-rTMS	rDLPFC	10	10	110	3, 6, 12
Selim et al	2023	AUD	38	RCT	PACS	dTMS	lDLPFC	20	10	<66	3
Padula et al	2024	AUD	17	RCT	OCDS	iTBS	lDLPFC	20	50	100–110	N/A

ACQ-NOW, Alcohol Craving Questionnaire; AUD, alcohol use disorder; AUQ, Alcohol Urge Questionnaire; RCT, randomized-controlled trial; VAS, visual analogue scale; PACS, Penn Alcohol Craving Scale; OCDS, Obsessive-Compulsive Drinking Scale; HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; dTMS, deep transcranial magnetic stimulation; cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; rDLPFC, right dorsolateral prefrontal cortex; lDLPFC, left dorsolateral prefrontal cortex; mPFC, middle prefrontal cortex, MT, motor threshold; FU, follow-up.

Results: Effects of rTMS on Alcohol Craving

- A total of 12 trials were combined in a quantitative meta-analysis to determine the effects of rTMS on alcohol craving.
- Immediate Effect:
 - Effect of rTMS versus sham stimulation on alcohol craving immediately after the last intervention:
 - **The meta-analysis revealed a reduction of alcohol craving after active rTMS, in comparison to sham stimulation, among individuals with AUD** (studies $n = 12$, pooled $n = 470$, active rTMS $n = 248$, sham stimulation $n = 222$; SMD = -0.79 , 95% CI: -1.53 to -0.04 , $P = 0.04$, $I^2 = 93\%$; Fig. 2).
 - The I^2 statistic represents substantial heterogeneity.
 - No change of the combined SMD was observed after removing any study from the meta-analysis.
 - So the sensitivity analysis indicated stability of the results.

Results: Effects of rTMS on Alcohol Craving

- Maintenance Effect
 - Lasting effect of rTMS on alcohol craving:
 - **1 month FU: the meta-analysis showed a tendency of reduced alcohol craving for active rTMS, compared to sham stimulation** (5 studies, active rTMS n = 92, sham stimulation n = 77, SMD = -0.55, 95% CI: -1.11 to 0.01, P = 0.052, I² = 63%).
 - **2 month FU: Did not find an effect of rTMS** (4 studies, 22,23,30,39 active rTMS n = 68, sham stimulation n = 59, SMD = -0.25, 95% CI: -0.64 to 0.15, P = 0.23, I² = 17%).
 - **3-month FU: rTMS reduced alcohol craving with a medium effect size** (6 studies, active rTMS n = 128, sham stimulation n = 118; SMD = -0.44, 95% CI: -0.77 to 0.11, P < 0.01, I² = 38%).
 - Since only 2 of the 12 included studies reported later FU, study refrained from quantitatively evaluating the SMD for this parameter. None of the studies reported any beneficial effect of rTMS intervention maintained for more than 3 months.

Results: Effects of rTMS on Alcohol Craving

- Immediate Effect by Stimulated Region
 - Effect of rTMS differed according to the stimulated brain region:
 - rTMS targeting the rDLPFC, the SMD was -1.04 (3 studies active rTMS $n = 84$, sham stimulation $n = 71$, 95% CI: -2.56 to 0.48 , $P = 0.18$, $I^2 = 96\%$).
 - Concerning stimulation of the IDLPFC, the SMD was -0.27 (4 studies, 32-34, 38 active rTMS $n = 88$, sham stimulation $n = 73$, 95% CI: -0.60 to 0.05 , $P = 0.10$, $I^2 = 0\%$). Regarding stimulation of the mPFC, the SMD was -2.12 (3 studies, active rTMS $n = 53$, sham stimulation $n = 52$, 95% CI: -4.34 to -0.09 , $P = 0.06$, $I^2 = 94\%$).
 - Identified only 1 study for each stimulation to the DLPFC bilaterally and stimulation of the insular cortex.

Conclusions

- Meta-analysis showed that rTMS, compared to sham stimulation, immediately decreased alcohol craving in individuals with AUD after the intervention when administered for at least 10 therapy sessions.
- Results on a maintenance effect varied across follow-up time points with the effect size at 1- and 3-month follow-up being clinically relevant.
 - This may be explained by the high heterogeneity of the studies included.
- Some evidence for difference between stimulation targets.
 - Neuromodulation targeting the mPFC, compared to IDLPFC and rDLPFC, might be more effective than stimulating other brain regions. Though the number of studies is limited, heterogeneity high, and more robust RCTs with sufficient follow up periods is needed for more insight.
- Suggests that rTMS, with mPFC target, can be considered a promising technique to reduce alcohol craving and could be considered for implementation into alcohol withdrawal management.

Limitations

- Small number of studies included.
- Heterogeneity between the studies.
- Lack of studies beyond 3 months.
- A subgroup analysis based on stimulated region was not done regarding the follow up periods due to limited data.
- A subgroup analysis was not done based on the number of sessions due to limited data.

Future Directions

- Meta-analyses with more studies included and that have more robust RCTs.
- Studies with longer follow up periods.
- Further analysis on different stimulated regions over different time periods.
- Further analysis on looking at the number of sessions.
- Investigate of long term variables such as relapse rate, or time to relapse.
- Studies utilizing neuroimaging data such as fMRI prior to, during and following treatment to provide better understanding of the underlying neural mechanisms mediating treatment effects.²
- Investigations with co-occurring psychiatric disorders. ²

Citation

- 1) Treiber, M., Tsapakis, E.-M., & Fountoulakis, K. (2024). Repetitive transcranial magnetic stimulation for alcohol craving in alcohol use disorders: A meta-analysis. *Journal of Addiction Medicine*, 19(2), 195–201.
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