

Repetitive Transcranial Magnetic Stimulation in Alcohol Dependence: A Randomized, Double-Blind, Sham-Controlled Proof-of-Concept Trial Targeting the Medial Prefrontal and Anterior Cingulate Cortices

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ABSTRACT

BACKGROUND: Alcohol addiction is associated with a high disease burden, and treatment options are limited. In a proof-of-concept study, we used deep repetitive transcranial magnetic stimulation (dTMS) to target circuitry associated with the pathophysiology of alcohol addiction. We evaluated clinical outcomes and explored associated neural signatures using functional magnetic resonance imaging.

METHODS: This was a double-blind, randomized, sham-controlled trial. A total of 51 recently abstinent treatment-seeking patients with alcohol use disorder (moderate to severe) were randomized to sham or active dTMS, using an H7 coil targeting midline frontocortical areas, including the medial prefrontal and anterior cingulate cortices. Treatment included 15 sessions over 3 weeks, followed by five sessions over 3 months of follow-up. Each session delivered 100 trains of 30 pulses at 10 Hz. The primary predefined outcome was reduction in percentage of heavy drinking days, obtained using timeline follow-back interviews. Secondary analyses included self-reports of craving, ethyl glucuronide in urine, and brain imaging measures.

RESULTS: Both craving after treatment and percentage of heavy drinking days during follow-up were significantly lower in the active versus sham control group (percentage of heavy drinking days = $2.9 \pm 0.8\%$ vs. $10.6 \pm 1.9\%$, $p = .037$). Active dTMS was associated with decreased resting-state functional connectivity of the dorsal anterior cingulate cortex with the caudate nucleus and decreased connectivity of the medial prefrontal cortex to the subgenual anterior cingulate cortex.

CONCLUSIONS: We provide initial proof-of-concept for dTMS targeting midline frontocortical structures as a treatment for alcohol addiction. These data strongly support a rationale for a full-scale confirmatory multicenter trial. Therapeutic benefits of dTMS appear to be associated with persistent changes in brain network activity.

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Excessive alcohol use accounts for approximately 5% of global disease burden and close to 6% of all deaths (1). Only about 25% of people with alcohol addiction [hereafter equated with moderate to severe alcohol use disorder or alcohol dependence (2)] ever receive treatment (3). This gap is caused, in part, by a lack of effective treatments with good patient acceptance. Behavioral treatments with support for efficacy exist, but their effect sizes are modest. Approved pharmacotherapies for alcoholism are few and have limited efficacy and patient acceptance, and their uptake in clinical practice is minimal (1,4).

Despite major advances in the neuroscience of alcohol addiction, no mechanistically novel treatments have been approved in the past 15 years. This may be related, in part, to the complexity of alcohol actions. Alcohol acts on multiple

molecular targets, including ionotropic and metabotropic neurotransmitter receptors, ion channels, and multiple neurotransmitters and neuromodulators. It is presently unclear which among these underlie the initiation, progression, and maintenance of alcohol addiction (5). An involvement of multiple neurotransmitter mechanisms represents a challenge for efforts to develop novel pharmacotherapies. An attractive alternative or complementary strategy may therefore be offered by methods that noninvasively target pathology of brain circuit activity, rather than individual neurochemical systems.

Repetitive transcranial magnetic stimulation (rTMS) may offer opportunities for this type of noninvasive, network-targeting intervention. rTMS can be delivered using protocols that differ in a multitude of variables, such as the choice of brain target and stimulation parameters, and no clearly

efficacious protocol has emerged to date (6). Prior rTMS studies in alcohol addiction typically have targeted the dorsolateral prefrontal cortex (PFC) and have not provided robust support for clinical efficacy (7–13). Similarly, the findings of our recent study targeting the insular cortex were negative (14). This prompts the question whether other stimulation targets have a better potential to yield clinical benefits in alcohol addiction.

The anterior cingulate cortex (ACC) and medial PFC (mPFC) may offer mechanistically attractive candidate treatment targets for rTMS. The ACC and mPFC and their interactions with cortical and subcortical areas subserve craving, reward-related decision making, and top-down control of drug seeking (15–20). Neural responses of the ACC to alcohol-related cues are associated with self-reported craving, addiction severity, and relapse (19,21,22). Finally, a meta-analysis of functional neuroimaging studies found that foci within the ACC are among those whose activity is associated with the efficacy of interventions (23).

Collectively, these data provide a mechanistic rationale for evaluating whether targeting the mPFC and ACC has the potential to produce clinical benefits in patients with alcohol addiction. An H7 deep rTMS (dTMS) coil that allows for targeting of these structures has recently been developed and has demonstrated efficacy in obsessive-compulsive disorder (24,25). In this condition, clinical response correlated with treatment-induced changes associated with ACC activity (24). Here, we report clinical and neuronal results of a randomized, sham-controlled trial of dTMS using the H7 coil over the mPFC and ACC in short-term abstinent participants with alcohol addiction. We assessed clinical efficacy using established measures of heavy drinking as the primary measure and evaluated craving as a potential mediating secondary outcome. To determine whether active treatment measurably influenced brain circuit function, we also examined seed-based resting-state connectivity, i.e., the temporal correlation of blood oxygen level-dependent signal between mPFC and ACC seeds and their respective targets.

METHODS AND MATERIALS

Study Overview

This was a double-blind, sham-controlled, randomized clinical trial performed at the Ben-Gurion University and the Soroka Medical Center, Be'er Sheva, Israel. Recruitment occurred between July 2016 and December 2019. The study was approved by the local Institutional Review Board (0404-15) and the Israeli Ministry of Health and was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT02691390). For detailed methods, see [Supplemental Methods](#).

Participants

Participants were recruited via social media and local newspaper advertisements. Recruitment targeted individuals who had a current DSM-5 diagnosis of moderate to severe alcohol dependence, as established by an independent psychiatrist, and who were treatment seeking. Additional inclusion criteria included age 18 to 65 years and alcohol use in the past month but not in the 5 days before the first magnetic resonance

imaging (MRI) scan and/or the first treatment session. Exclusion criteria included those commonly used in rTMS studies [see [Supplemental Methods](#) and (26)]. A total of 62 participants were included. After inclusion, participants completed standard alcohol withdrawal treatment (if needed) and thus were not intoxicated or in severe withdrawal when treatment was initiated. Participants provided written informed consent and were asked to abstain for 5 days to maintain safety, and those arriving sober to the first treatment session ($n = 51$) were randomized to either an active or a sham dTMS group (1:1 ratio), using the minimization method to reduce baseline group differences in age and alcohol consumption reported during the past 90 days (27,28). All randomized participants who had at least one postbaseline assessment (relevant to the primary outcome) formed the modified intention-to-treat cohort and were included in the primary analysis set ($n = 46$).

Overall Design

An overview of the study design is presented in [Figure 1](#). During the baseline phase (up to 2 weeks), all questionnaires were administered. Baseline MRI scans were also collected and included a structural scan and a functional MRI (fMRI) resting-state scan. During the acute treatment phase, which lasted 3 weeks, active or sham sessions were delivered five times per week, each session lasting 30 minutes. dTMS was always preceded by craving induction, as previously described (14). Briefly, this involved 3 minutes of holding and smelling, but not consuming, the alcoholic beverage of choice for each participant. Symptom provocation was aimed to activate brain circuitry associated with craving, which theoretically makes it more liable for modulation (29), and has promoted response to dTMS in prior studies (30,31). The second posttreatment MRI session was collected at the end of the 3-week acute treatment phase. During the follow-up (FU) phase, maintenance treatment sessions and clinical assessments were conducted at five visits at 1, 2, 4, 8, and 12 weeks (FU1–5) after conclusion of the acute treatment phase.

Assessments

Severity of alcohol problems and dependence were assessed using the Alcohol Use Disorder Identification Test (32) and the Alcohol Dependence Scale (33). Alcohol consumption was assessed using timeline follow-back (34), and alcohol craving was assessed using the Penn Alcohol Craving Scale [craving “in the wild” (35)]. Urine samples were collected for detection of 10 common drugs (Innovacon Inc.), and the alcohol (ethanol) metabolite ethyl glucuronide was detected using a DrugCheck Rapid EtG dip test kit (Express Diagnostics International).

Treatment

Active and sham dTMS was administered using a Magstim Rapid2 TMS stimulator (Magstim Co. Ltd.) equipped with an H7 coil (BrainsWay) (24,25). Electric field distribution is provided in [Figure S1](#). In each session, the optimal spot on the scalp for stimulation of the leg motor cortex was localized, and resting motor threshold was defined as previously described (36). Then, the coil was moved 4 cm anterior to the motor spot, aligned symmetrically (over the mPFC), and tightened as

rTMS Targeting mPFC and ACC for Alcohol Use Disorder

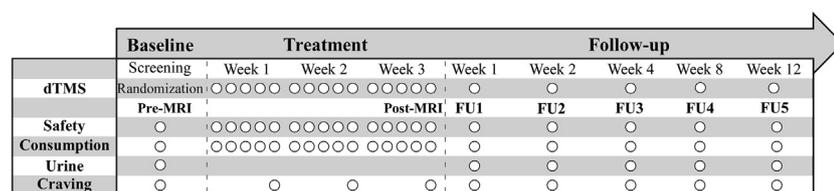


Figure 1. Study timeline and assessments. Symptom severity at baseline was assessed using the Alcohol Use Disorder Identification Test and Alcohol Dependence Scale. Alcohol consumption was assessed using timeline follow-back and alcohol craving levels using the Penn Alcohol Craving Scale. Urine samples were collected for detection of 10 common drugs and as an objective validation of

alcohol consumption (using the ethyl glucuronide detection kit). During the acute treatment phase, urine samples were collected daily for ethyl glucuronide, and the Penn Alcohol Craving Scale was measured weekly. During follow-up (FU), alcohol consumption was assessed using timeline follow-back and urine samples, and alcohol craving levels were assessed using the Penn Alcohol Craving Scale. dTMS, deep repetitive transcranial magnetic stimulation; MRI, magnetic resonance imaging.

previously described (25). After symptom provocation described above, active or sham stimulation was delivered for 30 minutes. The stimulation protocol was based on parameters that have yielded a positive efficacy signal in nicotine addiction (30), recently replicated in a large multicenter study (37). Each session included 100 trains of 30 pulses at 10 Hz (3 s) with a 15-s intertrain interval, for a total of 3000 pulses. Stimulation intensity was at 100% of the individual's leg resting motor threshold. Sham stimulation was delivered using a different coil located within the same helmet and producing similar acoustic and scalp sensations without effective field penetration into the brain (24,25). Participants, operators, and raters were all blinded to the type of coil (active or sham) used. Blinding was achieved through the use, for each participant, of a masked personal magnetic card that determined which coil within the helmet would be activated (24,25).

Outcome Measures

The predefined primary outcome was reduction in the percentage of heavy drinking days (pHDD) (≥ 4 alcohol units for women and ≥ 5 for men within 1 day) during the FU period. All randomized participants who had at least one postbaseline assessment relevant to this primary outcome (modified intention-to-treat cohort, $n = 46$) were included in the primary analysis. The secondary outcome was the change in craving levels, measured by the Penn Alcohol Craving Scale. Exploratory outcomes included posttreatment differences in functional connectivity of brain areas implicated in the pathophysiology of alcohol addiction. To obtain an objective validation of reported abstinence, urine samples were collected during baseline, before each treatment, and at each FU visit and determined as positive or negative according to the kit instructions immediately after collection. Missing samples were considered positive.

Magnetic Resonance Imaging

Imaging protocols were coordinated with the SyBil-AA (Systems Biology of Alcohol Addiction) Horizon 2020 Consortium. MRI data acquisition and fMRI data preprocessing and analysis have been previously described (14) and are presented in detail in Supplemental Methods. Baseline brain measures included structural MRI and resting-state fMRI. The same imaging protocols were repeated after the acute treatment phase, 3 weeks after baseline.

Preprocessing and analysis of fMRI data were performed with the AFNI software v.18.3.16 (38). For resting-state functional connectivity analysis, two seeds were defined: one in the

mPFC (Montreal Neurological Institute [MNI] coordinates = 0, 58, 7; 8-mm radius sphere), corresponding to the anterior default mode network node, and one in the dorsal ACC (dACC) (MNI = 6, 28, 22; 8-mm radius sphere), corresponding to the salience network (SN) node (Table S1).

We obtained minimum cluster size for multiple comparison correction using the latest AFNI approach (39), in which spatial group smoothness parameters are calculated from the residuals and subsequently used to estimate cluster size threshold (14). For the resting-state functional connectivity analysis, the statistical testing was performed on a gray matter default mode network mask and on a gray matter SN mask (Supplemental Methods and Figure S2). Clusters surviving a per-voxel p value of .001 and a cluster alpha of 0.05 were considered significant, and multiple comparisons corrected. FU analyses on beta correlation coefficients' resting state were performed using JASP (version 0.11.1.0.0).

Statistical Analysis

Power analysis assuming medium to large ($f = 0.35$) effect size (25) indicated a required sample size of 68 participants to detect a between-group effect in a 2×2 mixed analysis of variance with a statistical power of 0.9. The number of participants for enrollment was set to 84, taking into consideration an expected dropout rate of 25% before and during treatment initiation, given the requirement of being sober for at least 1 week before the first dTMS treatment, and during the first 3 weeks of acute treatment. While we aimed to recruit 84 patients (passing both initial phone screening and the final screening), recruitment was terminated after 62 patients owing to changes in staffing and budget limitation.

All analyses were performed for the modified intention-to-treat set as defined above. Group differences in baseline measures were investigated using independent-sample t tests or Mann-Whitney U tests, depending on normality of the data. Treatment influence on the primary and secondary outcome measures was tested using mixed-effects linear repeated models with time, group (active and sham), and time \times group interaction as fixed effects and a random intercept. If the time \times group interaction term was found nonsignificant, it was removed from the final model to preserve statistical power. The number of time levels in each model was determined by the number of assessments per measure. The categorical outcome measure of the urine tests was investigated in a similar manner but using a generalized linear mixed-effects model for repeated measures with logit as linking function (similar to logistic regression). Discrete behavioral measures

were analyzed using χ^2 tests. Outliers were defined as ± 2.5 SDs or more out from the group mean and were removed. All behavioral measures were analyzed using JASP (version 0.11.1.0.0) or MATLAB (R2020a; The MathWorks, Inc.).

RESULTS

Participants

A total of 62 treatment-seeking participants abstinent from alcohol for at least 5 days (but no more than 1 month) were enrolled in the study. Eleven participants dropped out before the first treatment session and were not included in the analyses; 51 participants initiated treatment. During the 3-week acute treatment phase, relapse to alcohol use was exclusionary for safety reasons, due to a potential for seizures; 5 participants (4 in the active condition and 1 in the sham condition) relapsed during this phase and dropped out of the study. Among the remaining 46 participants who entered the FU phase, an additional 5 participants (3 in the active condition and 2 in the sham condition) dropped out before completing the FU (Figure 2 and Table S2).

The reasons for dropout during the acute treatment and FU phases were resumption of alcohol use or unwillingness to participate or adhere to the study schedules. For the purpose of assessing relapse, dropouts and participants lost to FU

were classified as nonabstinent. No difference was observed between the active and sham groups in baseline demographics and clinical characteristics (Table 1). In addition, the groups did not differ in the average leg motor threshold or in the percentage of correct guesses on the question assessing the integrity of the blinding procedure.

Primary Outcome: Reduction of Heavy Drinking

pHDD during the FU phase was significantly lower in the active group than the sham group (pHDD mean \pm SEM = $2.9 \pm 0.8\%$ vs. $10.6 \pm 1.9\%$; $p = .037$). Specifically, pHDD was very low in both active and sham groups after the treatment phase but increased during the FU phase in the sham group while remaining low in the active group (Figure 3A; see Figure S3 for individual data). This was supported by a significant group difference in weekly amounts of alcohol consumption (Figure 3B; see Figure S3 for individual data) and by a trend-level group difference in the percentage of alcohol-positive urine samples (Figure 3C).

Secondary Outcome: Craving

During the acute treatment phase, Penn Alcohol Craving Scale scores decreased in both groups but did so more steeply in the active group than the sham group (Figure 3D; see Figure S4 for individual data). During the FU phase, craving levels began to increase in the sham group but less so in the active group (Figure 3E; see Figure S4 for individual data). Of note, the observed differences in craving preceded those in heavy drinking.

Other Clinical Outcomes

Mood and Anxiety Symptoms. Although participants did not meet diagnostic criteria for depression or had clinically significant depression or anxiety symptom ratings at baseline (Beck Depression Inventory, Comprehensive Psychopathological Rating Scale depression and anxiety scores; Table 1), there was an overall reduction in symptoms over time on all these measures (Supplemental Results and Figure S5), regardless of group.

Safety and Tolerability. No serious adverse events occurred in the course of the study. The only adverse events observed were moderate to severe headaches, which resolved spontaneously in all cases and did not differ in frequency between randomization groups (Table 1).

Resting-State Functional Connectivity

We first established that randomization had not introduced any group differences at baseline and focused the initial analysis on the posttreatment data. This analysis found that the active group had significantly decreased connectivity between the mPFC seed and a cluster in the subgenual ACC (MNI = $-2, 37, -8$; cluster size = 7 voxels, corrected; $F_{1,30} = 9.19$, $p < .005$, $\eta_p^2 = 0.24$) and decreased connectivity between the dACC seed and the caudate that was nominally significant and on the threshold of cluster size required for multiple correction (MNI = $13, 16, -5$; cluster size = 5; 5.6 needed for correction; $F_{1,30} = 12.23$, $p < .002$, $\eta_p^2 = 0.29$). We then carried out an FU analysis by applying a two-way analysis of variance to the β

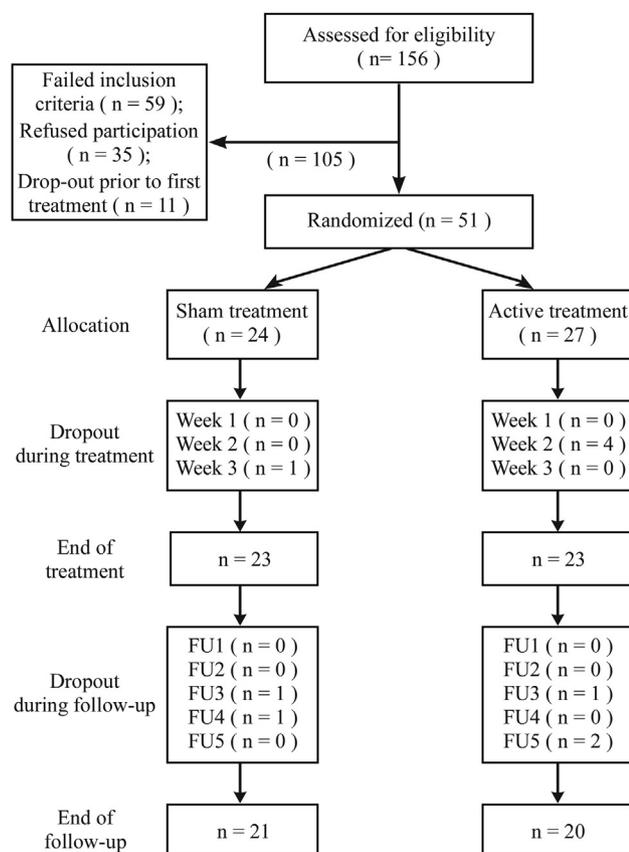


Figure 2. Enrollment and disposition of participants. FU, follow-up.

Table 1. Demographic and Clinical Characteristics of Patients Who Entered Follow-up Evaluation (mITT Set)

Characteristics	Active, <i>n</i> = 23	Sham, <i>n</i> = 23	<i>p</i> Value ^a
Baseline Demographic Characteristics			
Females, <i>n</i>	8	8	–
Age, years	43.7 (8.7)	42.5 (9.8)	.81
Education, years	12.5 (1.7)	12.18 (1.6)	.71
Baseline Clinical Characteristics			
MoCA	28.1 (1.6)	27.6 (1.6)	.29
AUDIT	24.5 (7.2)	26.1 (6.3)	.56
ADS	16.5 (7.5)	17.8 (6.2)	.59
TLFB, HDD, %	36.8% (32%)	37.6% (27%)	.92
Consumption, average g/day	58.5 (51.8)	66.3 (60.6)	.63
PACS	14.6 (6.3)	15.9 (6.8)	.51
BDI	15.2 (9.8)	12.6 (7.8)	.9
SETS	21.9 (8)	25 (7.4)	.18
CPRS			
Depression	5.9 (4.3)	6.1 (3.9)	.84
Anxiety	6.7 (5.1)	8.1 (4.7)	.35
NEO-FFI			
Neuroticism	2.02 (0.81)	1.86 (0.87)	.53
Extraversion	2.22 (0.64)	2.17 (0.69)	.79
Openness	2.1 (0.43)	2.13 (0.45)	.8
Agreeableness	2.6 (0.59)	2.56 (0.59)	.8
Conscientiousness	2.63 (0.62)	2.69 (0.54)	.71
Other Clinical Characteristics			
RMT, stimulator power output, %	66.6% (1.55%)	66.5% (1.54%)	.96
Blinding assessment, patients who correctly guessed their treatment arm at the end of follow-up, % (<i>n</i>)	47% (10/21)	50% ^b (9/18)	.85 ^c
Adverse events, headache, moderate to severe, <i>n</i>	4	3	.68 ^d

Values are presented as mean (SD) unless otherwise indicated.

ADS, Alcohol Dependence Scale; AUDIT, Alcohol Use Disorder Identification Test (scores of >20 indicate high-likelihood of dependence); BDI, Beck Depression Inventory; CPRS, Comprehensive Psychopathological Rating Scale; HDD, heavy drinking days; mITT, modified intention-to-treat; MoCA, Montreal Cognitive Assessment; NEO-FFI, abbreviated five factor personality assessment; PACS, Penn Alcohol Craving Scale; RMT, resting motor threshold; SETS, Stanford Expectations of Treatment Scale; TLFB, timeline follow-back.

^aTwo-tailed *p* value using independent-samples *t* test.

^bData missing for 2 participants.

^c χ^2 test.

^dZ test.

coefficients extracted from the clusters identified by the analysis, with time as the within-subject factor and group as the between-subject factor. This analysis found that connectivity was reduced in the active group but enhanced in the sham group compared with baseline in both networks (Figure 4 and Figure S6).

DISCUSSION

In a randomized, double-blind, sham-controlled proof-of-concept trial, we found that dTMS with a midline prefrontal

target significantly reduced alcohol craving and heavy drinking. After an acute treatment phase of five weekly treatment sessions for 3 weeks that induced reduction in craving, heavy drinking was reduced throughout a 12-week FU, and these reductions were accompanied by changes in functional connectivity of the mPFC, ACC subregions, and caudate. Treatment was safe and well tolerated. There were no serious adverse events, with only a small proportion of participants reporting transient headaches, a common complaint in rTMS studies (26).

rTMS has attracted considerable interest as a potential treatment for addictive disorders (40). However, with exception of nicotine addiction (30,41), studies to date (7–13,42,43) have yet to provide robust support for its efficacy in addiction by established standards of evidence-based medicine, i.e., through adequately powered double-blind, randomized, sham-controlled trials. Available studies have used a variety of protocols and targets and have not established persistent effects of TMS on brain activity. It has therefore remained unclear what rTMS-based strategy, if any, may hold promise as an alcohol addiction treatment. Of note, however, a small, randomized, sham-controlled pilot study has previously used a high-frequency protocol and an H coil to target the mPFC (7). The primary outcomes of that study were neuroendocrine (prolactin and cortisol), but alcohol craving and use were assessed as secondary measures and were reduced.

Based on the pilot finding and a literature implying an involvement of the mPFC and ACC in alcohol use, craving, and treatment outcomes, this study targeted a midline frontal location with the objective to modulate circuit activity within these structures. Based on efficacy in prior nicotine addiction trials (30,41), we used a stimulation protocol that delivered 3 weeks of high-frequency (10 Hz) stimulation. We found a consistent signal for efficacy across both primary (heavy drinking) and secondary (craving) outcomes. This was accompanied by neural signatures supporting altered activity of networks that include the targeted structures. Our study does not allow inferences about a causal role of the observed brain activity changes for clinical outcomes. However, the brain findings do provide a biomarker of target engagement and are at a minimum consistent with such a role.

The signals for efficacy of dTMS in our study were obtained despite a pronounced placebo effect. Large placebo effects are routinely observed in clinical alcohol treatment trials and have the potential to mask specific treatment effects (44). In this study, the placebo effect was likely amplified by the high frequency of clinic visits, demanding nature of the procedure (45), and daily craving provocations, which follow principles of cue exposure therapy, a clinical alcoholism treatment (46). The magnitude and time course of the placebo effect in this study was very similar to those observed in our recent dTMS study that used the same basic design and targeted the insular cortex (14). Detection of a specific treatment effect despite the pronounced placebo response supports the robustness of the findings.

Abstinence has historically been considered the only valid regulatory end point in studies of alcohol addiction treatments, but this landscape is changing. A recent analysis by the Alcohol Clinical Trials Initiative indicated that a reduction of drinking risk levels, as defined by the World Health

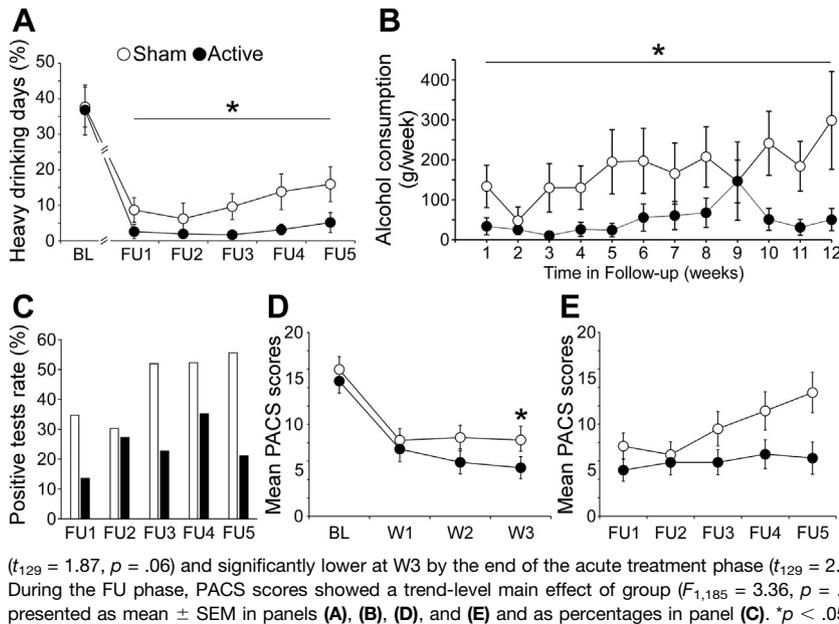


Figure 3. Alcohol consumption and craving. **(A)** Percentage of heavy drinking days (measured by timeline follow-back during the follow-up [FU] phase) showed significant main effects of group ($F_{1,208} = 4.40, p = .037$, mean difference = 7.7%, Cohen's $d = 0.50$). **(B)** Alcohol consumption during FU. Mean \pm SEM of weekly alcohol consumption in grams of ethanol, as reported using timeline follow-back during the FU phase. A mixed-effects linear repeated model, with group (active and sham) and week (W) (1–12) as fixed effects and a random intercept, indicated a significant main effect of group ($F_{1,486} = 5.21, p = .02$, mean difference = 121.78 g, Cohen's $d = 0.47$). **(C)** Percentages of positive urine ethyl glucuronide samples during the FU visits. A generalized linear mixed model analyzing percentages of positive urine samples indicated a trend-level effect of group ($F_{1,4} = 3.32, p = .069$). **(D)** During the acute phase of treatment, Penn Alcohol Craving Scale (PACS) scores showed a significant group \times time interaction ($F_{2,129} = 3.37, p = .04$). Model coefficients indicated that craving levels of the active group were lower than those of the sham group by W2 at trend level ($t_{129} = 1.87, p = .06$) and significantly lower at W3 by the end of the acute treatment phase ($t_{129} = 2.48, p = .01$; mean difference = 3, Cohen's $d = 0.48$). **(E)** During the FU phase, PACS scores showed a trend-level main effect of group ($F_{1,185} = 3.36, p = .07$, mean difference = 3.7, Cohen's $d = 0.52$). Data are presented as mean \pm SEM in panels **(A)**, **(B)**, **(D)**, and **(E)** and as percentages in panel **(C)**. * $p < .05$. BL, baseline.

Organization, is a worthwhile indicator of treatment outcome. This outcome has been found to capture clinically meaningful improvements that were experienced by more patients than either abstinence or no heavy drinking days and also aligned better with the treatment goals of many patients (47). The

potential for reductions in heavy drinking to confer a meaningful clinical benefit is in line with observations that lowering alcohol consumption for several weeks is sufficient to initiate recovery of executive and general cognitive functioning, as well as underlying brain changes (48).

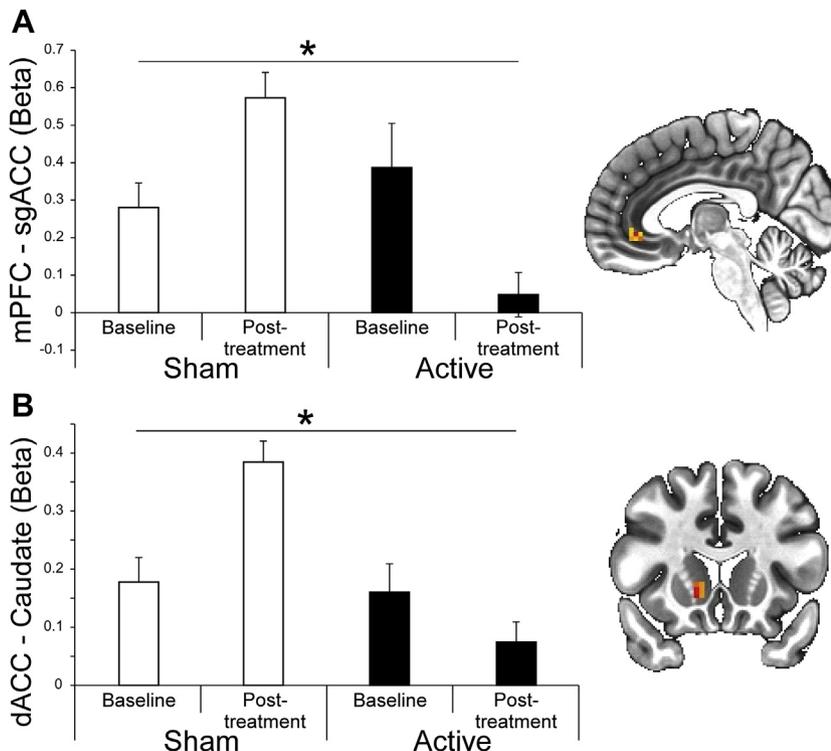


Figure 4. Brain imaging results. Seed-based resting-state functional connectivity findings at baseline and after treatment. Bars represent β coefficients extracted from regions with between-group difference in connectivity to the respective seed. Two-way analysis of variance indicated significant time \times group interaction for **(A)** medial prefrontal cortex (mPFC)–subgenual anterior cingulate cortex (sgACC) connectivity ($F_{1,63} = 15.68, p < .001, \eta_p^2 = 0.2$) and **(B)** dorsal anterior cingulate cortex (dACC)–caudate connectivity ($F_{1,63} = 13.08, p < .001, \eta_p^2 = 0.14$). Main effects for group were also found significant for mPFC–dACC connectivity ($F_{1,63} = 6.9, p < .05, \eta_p^2 = 0.1$) and dACC–caudate connectivity ($F_{1,63} = 16.43, p < .001, \eta_p^2 = 0.17$). Main effect for time was not significant (mPFC–dACC: $F_{1,63} = 0.09, p = .77, \eta_p^2 = 0.001$; dACC–caudate: $F_{1,63} = 2.25, p = .14, \eta_p^2 = 0.02$). Data are presented as mean \pm SEM, * $p < .05$ between the active and sham groups.

rTMS Targeting mPFC and ACC for Alcohol Use Disorder

We found that reduction of heavy drinking in the active dTMS group was associated with decreased functional connectivity between the dACC and caudate nucleus and between the subgenual ACC and mPFC. Overall, this pattern is opposite to that reported in heavy alcohol users and in alcohol addiction (15,16,49). Our neuroimaging findings should be interpreted with caution owing to the small size of the clusters for which altered connectivity was found but are appealing in a mechanistic context. The dACC, a key node of the SN, is implicated in the detection of salient stimuli, switching from self-directed default mode network activity to externally directed activity of the central executive network, and goal-directed behavior (50–52). The ventral striatum, including the caudate, is involved in incentive motivation and shows the highest degree of activation in response to alcohol-associated cues in people with heavy drinking or alcohol addiction (19,53). It can therefore be speculated that a weakened connectivity between the dACC and the caudate reflects a weakened ability of alcohol-associated incentive motivation signals to gain control over SN activity and motor action. Attenuated connectivity between the subgenual ACC, a structure involved in mood regulation (54,55), and the mPFC, which exerts top-down control over drug seeking (18,56), may indicate a weakened influence of mood states over alcohol seeking.

Our study has several limitations. It is a proof-of-concept trial with a sample size that compares favorably with prior trials of TMS in addiction but is small by normal standards of treatment trials in addiction. A larger confirmatory multicenter trial will be needed before efficacy of this intervention can be considered established. It is also possible that the treatment protocol may benefit from optimization. Most importantly, a longer duration of initial treatment may improve efficacy. For example, the Food and Drug Administration–cleared dTMS protocol used for obsessive-compulsive disorder treatment with the H7 coil includes 6 weeks of daily sessions (25). However, determining the optimal duration is likely to represent a trade-off. Although increasing treatment duration may result in more robust efficacy, it may also increase dropout rates in a population with alcohol addiction owing to the requirement for daily clinic visits. Moreover, despite a low rate of reported headaches in this study, discomfort or pain during treatment (given the average resting motor threshold, which was 66%), particularly in the first sessions, was quite often noticed by operators. Finally, our results were obtained in a population with a high level of functioning and alcohol addiction that on average was of moderate severity, as assessed by the Alcohol Dependence Scale. It remains to be determined whether feasibility and efficacy will generalize to patients with higher severity.

Despite these limitations, we believe that the findings presented here represent an important advance. dTMS targeting the mPFC and ACC appears to be a safe and well-tolerated intervention, with promising initial evidence for efficacy in alcohol addiction. A full-scale multicenter study to confirm the efficacy of this intervention appears warranted.

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AZ is an inventor of deep TMS coils and has financial interest in BrainsWay, which produces and markets these coils. MHe has received consulting fees, research support, or other compensation from Indivior, Camurus, BrainsWay, Aelis Farma, and Janssen Pharmaceuticals. UA is an electroencephalography consultant for BrainsWay. All other authors report no biomedical financial interests or potential conflicts of interest.

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rTMS Targeting mPFC and ACC for Alcohol Use Disorder

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