NOVEMBER 2022 / ISSUE 21

PULSE

A Monthly Update on Advances in Neuromodulation

Produced by the Neuromodulation Division of the Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

Collin M. Price, MD Managing Co-Editor | Collinprice@mednet.ucla.edu
Michael K. Leuchter, MD Managing Co-Editor | mkleuchter@mednet.ucla.edu
Andrew F. Leuchter, MD Editor-in-Chief | Aleuchter@mednet.ucla.edu

Combination of rTMS and CBT Shows Promise for Relapse Reduction in Alcohol Dependency

Nicole Wong reviewing Liu et al. Front Psychiatry 2022 Oct

A randomized, double-blind, sham-controlled multicenter clinical trial of 263 individuals with alcohol dependency suggests that combined rTMS and cognitive behavioral therapy may reduce relapse rates

The prevalence of alcohol dependence is rising, with the World Health Organization's global status report on alcohol and health in 2018 revealing that 8.2% of the adult population in the United States struggles with alcohol dependence (AD). Up to 85% of patients with AD relapse following treatment, which includes options such as medications, rTMS to the DLPFC, and CBT. While both rTMS and CBT have been shown to reduce the risk of relapse, it is not known whether there is an increased benefit to combining rTMS and CBT.

IN THIS ISSUE:

The authors recruited 297 patients with AD from multiple hospitals across China. Inclusion criteria required participants to be 18-65 years old, meet the diagnostic criteria of AD, and have no history of neurological diseases or family history of mental disorders. Exclusion criteria were: 1) Clinical Institute Alcohol Withdrawal Symptom Scale (CIWA-Ar) indicating acute withdrawal, 2) traumatic brain injury, 3) current or prior use of psychotropic medications, 4) dependence on other substances, and 5) any contraindications to rTMS therapy. Subjects were treated with either CBT with a fixed plan (C1; an evidence-based CBT for AD lasting 60 minutes per session) or CBT without a fixed plan (C0; a brief basic interview without any form of intervention), combined with either 10Hz rTMS (delivered at 110% resting MT to left or right DLPFC) or sham rTMS (same protocol but with intensity set at 0-1%). Participants were randomized to one of six groups: sham rTMS + C0 (n=50), sham rTMS + C1 (n=37), right DLPFC rTMS + C0 (n=45), right DLPFC rTMS + C1 (n=42), left DLPFC rTMS + C0 (n=49), and left DLPFC rTMS + C1 (n=40). rTMS treatment consisted of 10 sessions over 2 weeks. The authors assessed alcohol cravings and associated symptoms at baseline and at week 24 (follow-up) using a variety of self-report and observer-rated instruments, bloodwork, physical exam, and a diary of alcohol consumption. Participants were predominantly mid to late 40s and male, and no significant between-group differences in baseline demographics, alcohol use, weight, smoking status, vitals, baseline labs, or cognition.

Of the 297 participants initially enrolled in the study, 34 terminated the study due to either severe adverse reactions or poor compliance to treatment, leaving 263 participants included in the final analysis. One-way ANOVAs revealed the sham rTMS + C0 group relapse rate (0.45) was significantly higher than that for the right rTMS + C1 (0.14, $p = 0.006$), left rTMS + C0 (0.22, $p = 0.031$), and left rTMS + C1 (0.22, $p = 0.043$) groups. The right rTMS + C0 group showed significantly higher relapse rates compared to the right rTMS + C1 group (0.14, $p = 0.046$), with no significant differences among other groups. Logistic regression revealed that smoking and quantity of alcohol consumption were independently correlated with relapse ($p < 0.05$), and Cox regression analysis demonstrated that current smoking (HR=2.31), total cholesterol (HR=1.00), and total bilirubin (HR=1.02) level were risk factors for relapse ($p < 0.05$). Of note, the authors do not comment on corrections for multiple comparisons.

Impact: This randomized, double-blind, multi-center study is the first to suggest that the combination of rTMS and CBT may be more effective than either treatment alone in preventing relapse in patients with AD. Limitations of the study included the relatively small sample size of the 6 study arms, brief 10-session rTMS course, possible inaccuracy associated with self-reported alcohol consumption, and unclear statistical methods. Future work examining single rTMS protocols with larger groups and measurements less susceptible to reporting biases would be helpful to build upon the authors' findings.

Hu X, Zhang T, Ma H, et al. Repetitive transcranial magnetic stimulation combined with cognitive behavioral therapy treatment in alcohol-dependent patients: A randomized, double-blind sham-controlled multicenter clinical trial. Front Psychiatry. 2022;13:935491. Published 2022 Oct 4. doi:10.3389/fpsyt.2022.935491

Sham Stimulation Outperforms "Deep" TMS with an H7 Coil when Combined with Brief Exposure Therapy in the Treatment of PTSD

Tashalee R. Brown, MD, PhD reviewing Isserles et al. Biol Psychiatry 2021 Nov

In this multicenter RCT, a brief exposure paradigm was combined with deep TMS (dTMS) using an H7 coil or sham stimulation to treat symptoms of PTSD. While both treatment arms improved, patients in the sham condition did significantly better than those in the active dTMS group

Exposure therapy is an effective psychotherapy for treatment of Post-traumatic Stress Disorder (PTSD) that involves the therapist and patient describing the traumatic event in detail. A small double-blind feasibility study suggested that dTMS using the H1 coil (targeting bilateral medial prefrontal cortex [mPFC]) combined with exposure therapy was superior to a control condition. The current study builds on these prior results to evaluate effectiveness and safety of mPFC dTMS stimulation using a different coil - the H7 - combined with brief exposure to patient-specific trauma narratives.

The study included 125 patients from 15 global centers (US: 11, Israel: 2, Canada: 1, and Europe: 1). Participants had a mean age of 44 years, were predominantly women (66%), and were predominantly Caucasian (85%). After screening and randomization, participants received treatment for four weeks followed by primary end point evaluation (week 5) and follow up (week 9). Participants were exposed to script driven imagery

(SDI) based on their written details of the traumatic event recorded as a 30 to 60 second audio script. Participants were then randomly assigned to receive either dTMS or sham stimulation. dTMS was administered over 4 weeks in 12 sessions using an H7 coil over mPFC, delivered at 18 Hz, for 2 second trains with 80 trains at 100% of leg resting MT. Blinding was performed using a single helmet containing H7 coil and sham. Primary outcome was change in the clinician-administered PTSD scale (CAPS-5) total score at week 5. Secondary outcomes were CAPS-5 at week 9 (response defined as > 50% improvement in CAPS-5 score) and change in Modified PTSD Symptom Scale Self-report (MPSS) at weeks 3, 5, and 9.

There were no significant baseline differences in demographics and HDRS-21 between the dTMS and sham treatment groups. At week 5, mean adjusted improvement in the CAPS-5 score was 16.32 (95% CI: 12.70–19.94) in the dTMS group and 20.52 (95% CI: 17.42–23.63) in the sham group, with the difference favoring the sham group ($p = 0.027$). At week 9, there was further improvement in both groups, with the CAPS-5 score improving 18.96 (95% CI: 14.74–23.19) in the dTMS group and 24.43 (95% CI: 20.78–28.08) in the sham group, again favoring sham ($p = 0.024$). Similar trends were found in the Intention-to-treat analysis and in MPSS measures. Assessment of the blind indicated 46% in the active group and 25% in the sham group thought they received real treatment; adding the blinding variable to the main analysis did not modify the results of the main analysis. There was no significant difference in number of adverse events between groups.

Impact: In this RCT, patients with PTSD who received brief exposure combined with either dTMS or sham showed improvements which were sustained up to 4 weeks after treatment. However, the active dTMS group had significantly less improvement than the sham group, in contrast to a prior smaller study. The authors hypothesized that differences in target specificity between the two coils might account for the difference from the prior study; the H1 coil used in the prior study is thought to be less specific in stimulating mPFC, in that it also stimulates DLPFC. These surprising and conflicting results warrant further investigation with well-designed studies, ideally with head-to-head comparison of the two dTMS coil designs.

Isserles M, Tendler A, Roth Y, et al. Deep Transcranial Magnetic Stimulation Combined With Brief Exposure for Posttraumatic Stress Disorder: A Prospective Multisite Randomized Trial. Biol Psychiatry. 2021;90(10):721-728. doi:10.1016/j.biopsych.2021.04.019

HFL-rTMS May Have Efficacy Comparable to ECT in MDD and Reduce Cognitive Adverse Effects

Lara Tang reviewing Chen et al. Front Psychiatry 2022 Oct

This retrospective study of 116 participants receiving HFL-rTMS, ECT, or both indicates that HFL-rTMS is no less effective than ECT in treating severe depression and may reduce the adverse cognitive effects of ECT

ECT was the first form of neuromodulation to prove effective in treating MDD; however, ECT often causes unwanted cognitive side effects including amnesia and impairments in verbal fluency and executive function. rTMS is a newer method of neuromodulation that has also demonstrated efficacy in treating MDD, with fewer side effects. Previous studies and metaanalyses generally have found that ECT is more efficacious than rTMS for unselected populations of patients with MDD, although HFL-rTMS may have efficacy comparable to ECT for non-psychotic MDD. This study sought to directly compare outcomes after HFL-rTMS or ECT, both in terms of depression and cognitive side effects.

This retrospective study recruited 116 inpatients with MDD at a hospital in China (aged 53.6 ± 1.2 years; 37 men). Of the 116 subjects, 26 (22%) received medication only treatment and were thus assigned as controls; 46 were administered HFL-rTMS (1150 pulses 10 Hz stimulation to the left DLPFC for 30 minutes a day) only; 22 ECT only; and 23 ECT followed by HFL-rTMS (no patients received rTMS before ECT). All subjects were maintained on the same dose and type of medication from baseline to their follow-up assessment 4 weeks after treatment administration. ECT was delivered as bilateral stimulation, with parameters determined individually on a clinical basis, performed three times a week. The authors do not comment on the presence or absence of psychotic symptoms or the number of treatment sessions received in each arm. Primary outcomes were changes in the HAMD-17 and the HAMA-14, while the Montreal Cognitive Assessment (MoCA) was used to evaluate cognitive function. All measures were collected at baseline and at 4-week follow-up.

There were no significant differences in demographic variables or HAMD-17 scores at

baseline, and no significant difference in HAMD-17 scores at 4-week follow-up among the three treatment arms. However, compared to the control group, there was a significant decline in HAMD-17 scores at 4-week follow-up in the treatment groups (control vs. HFL-rTMS, p<0.001; vs. ECT, p=0.001; vs. HFL-rTMS+ECT, p<0.001). This result was paralleled with respect to anxiety, as measured by changes in the HAMA-14 (control vs. HFL-rTMS, p=0.011; vs. ECT, p=0.035; vs. HFL-rTMS+ECT, p=0.020). In terms of cognitive impairment, there was a significant decline in MoCA scores from baseline to follow-up in the ECT group only (p<0.001), and a significant difference from controls at follow-up in the HFL-rTMS (p=0.005) and ECT (p<0.001) groups. Subjects in the ECT group scored significantly lower on the MoCA compared to subjects in the HFL-rTMS (p<0.001) and HFL-rTMS+ECT (p<0.001) groups. However, when subjects in the HFL-rTMS+ECT group were compared with those in the control group, there was no significant difference in MoCA scores, suggesting a reversal effect of HFL-rTMS on cognitive impairment evoked by ECT.

Impact: This retrospective analysis of inpatients with MDD treated with medications and clinical protocols of ECT, HFL-rTMS, or ECT then HFL-rTMS found that HFL-rTMS worked as well as ECT in treating depression and anxiety symptoms. It is difficult to compare these results to those from prior studies comparing ECT and HFL-rTMS treatment efficacy because the authors do not comment on the presence or absence of psychotic symptoms nor the total number of treatment sessions received. Intriguingly, patients who received HFL-rTMS after ECT had no significant cognitive deficits when compared to either those receiving ECT alone or control subjects. These results should be interpreted with caution, however, because the MoCA has limited sensitivity for assessment of cognitive deficits. In addition, the mean pretreatment MoCA scores for all groups of subjects were approximately 25-26, which is close to the cutoff for normal cognition in healthy individuals. These findings warrant further investigation in more rigorously controlled, prospective analyses.

Chen X, Zhang T, Shan X, et al. High-frequency repetitive transcranial magnetic stimulation alleviates the cognitive side effects of electroconvulsive therapy in major depression. Front Psychiatry. 2022;13:1002809. Published 2022 Oct 3. doi:10.3389/fpsyt.2022.1002809

Anodal tDCS to Left DLPFC Shows Promise in Enhancing Inhibitory Control in Individuals with Obesity

Nicole Wong reviewing Gluck et al. Obesity 2022 Oct

A randomized patient and rater-blinded parallel-design trial of 29 individuals with obesity suggests that anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex significantly improves inhibitory control

The DLPFC is known to regulate both eating behaviors and executive functions such as inhibitory control and goal-oriented behavior, and individuals with obesity demonstrate impaired activation of the DLPFC during a Go-No-Go (GNG) task. Furthermore, individuals with lower DLPFC activity demonstrate slower reaction times in the Stroop task, and individuals with obesity demonstrate attentional bias towards food-related stimuli in the Stroop compared to healthy-weight controls. The present study aimed to determine the effect of anodal tDCS administered to left DLPFC compared with sham on food GNG and food Stroop task performance in individuals with obesity, and to investigate associations between cognitive task performance and *ad libitum* snack food intake.

The authors enrolled adults with obesity (BMI: ≥ 30 kg/m2) who were otherwise healthy in a combined inpatient/outpatient double-blinded randomized parallel-design study of the effects of tDCS on food intake. Inclusion criteria were: 1) right-handed, 2) non-smoker, 3) stable weight (+/- 5%) for 3 months prior to recruitment, 4) tDCS naïve, 5) no history of neurological disorders, and 6) no history of medication and/or illicit drug use known to influence neurocognitive processes. While inpatient, participants received baseline assessments of food-related inhibitory control (GNG), food-related attentional bias (Stroop), and snack food taste test (SFTT) to measure *ad libitum* food intake and food preferences. They were then randomized to 15 sessions of either anodal (2mA for 40 minutes) or sham tDCS (10s of 2mA followed by no current for the remainder) to left DLPFC, with the cathode over the right supraorbital region. They received 3 sessions over 3 days while inpatient followed by 3 sessions per week during the 4 weeks of outpatient treatment (a total of 40 days). The GNG, Stroop, and SFTT were repeated on the day of inpatient discharge and at the end of the 4-week outpatient period. Throughout both the inpatient and

outpatient periods, participants were asked to adhere to a standardized diet (a weight-maintaining diet during inpatient and a 25% calorie-reduced diet during outpatient).

Of the 31 original participants recruited who met inclusion criteria, 29 (12 male; age 42 +/- 11 years; BMI 39 +/- 8 kg/m2) were included in the initial inpatient phase, and 23 completed the entire study (both inpatient and outpatient). There were no significant baseline differences between groups (anodal vs. sham) in terms of demographics, dietary adherence, and performance on GNG and food Stroop measures. GNG performance improved in the anodal group by day 31 when compared to sham ($p = 0.01$), though Stroop scores did not differ between groups. Contrary to expectation, a higher error rate in the GNG task was associated with greater snack food intake for only the sham group ($p < 0.001$). Higher food bias and palatable bias scores in the Stroop task were associated with greater snack food intake across both groups. Changes in performance on the GNG and food Stroop measures did not moderate the difference between groups in changes in snack food intake.

Impact: This RCT of 23 individuals with obesity showed that anodal tDCS was associated with greater improvement in a food GNG task as compared to sham. Although previous work demonstrated that anodal tDCS was associated with reduced snack food intake relative to sham, this study did not find evidence that improvements on the GNG task correlated with decreased intake. This study suggests that while anodal tDCS to the DLPFC may specifically improve inhibitory control that is impaired in obesity, the functional and clinical significance of this improvement is not clear. The study's small sample size may have limited the ability to detect associations between changes in inhibitory control and attentional bias with changes in snack food by group.

Stinson EJ, Travis KT, Magerowski G, Alonso-Alonso M, Krakoff J, Gluck ME. Improved food Go/No-Go scores after transcranial direct current stimulation (tDCS) to prefrontal cortex in a randomized trial. Obesity (Silver Spring). 2022 Oct;30(10):2005-2013. doi: 10.1002/oby.23529. Epub 2022 Sep 2. PMID: 36052819.

Abbrevations

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
HFL (high frequency left, 10 Hz stimulation to left DLPFC)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
TBS (theta-burst stimulation; TMS delivered as triplet burst pulses at 50 Hz, repeated at 5 Hz)
TENS (transcutaneous electrical nerve stimulation)
TMS (transcranial magnetic stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tDCS (transcranial direct current stimulation)
tACS (transcranial alternating current stimulation)

BOLD (blood oxygen level dependent)
DTI (diffusion tensor imaging)
EEG (electroencephalography)
EMG (electromyography)
fMRI (functional magnetic resonance imaging)
MRI (magnetic resonance imaging)
MT (motor threshold)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BAI (Beck Anxiety Inventory)
BDI (Beck Depression Inventory)
CGI (clinical global impression scale)
HAM-A (Hamilton Anxiety Rating Scale)
HAM-D / HDRS (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
PANSS (Positive and Negative Symptom Scale)
QIDS (Quick Inventory of Depressive Symptomatology)
YBOCS (Yale-Brown Obsessive Compulsive Scale)

ANOVA (analysis of variance)
AUC (area under the curve)
CI (confidence interval)
FDA (United States Food and Drug Administration)
ICA (independent component analysis)
ITT (intention to treat)
OR (odds ratio)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)
SMD (standard mean difference)

BA (Brodmann area)
DLPFC (dorsolateral prefrontal cortex)
DMPFC (dorsomedial prefrontal cortex)
M1 (primary motor cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)