



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

Michael K. Leuchter, MD, Managing Editor | mkleuchter@mednet.ucla.edu

Aaron Slan, MD, Editor-in-Chief | aslan@mednet.ucla.edu

Danielle Hight, Editorial Assistant | daniellehight10@gmail.com

Electrical Stimulation Aided by Use of Machine Learning Classifiers May Improve Memory Recall in Patients with Traumatic Brain Injury

Lara Tang reviewing Kahana M et al. *Brain Stimulation* 2023 July 1

This study examined using closed-loop electrical stimulation via implanted intracranial electrodes to aid memory recall in patients with refractory epilepsy and moderate-to-severe traumatic brain injury (TBI). Using machine learning classifiers to predict memory lapses and trigger electrical stimulation of the lateral temporal cortex, the authors found a 19% improvement in memory recall compared to when stimulation was off.

Patients with a history of moderate-to-severe TBI often experience cognitive impairments. Currently, memory training is the primary method of cognitive rehabilitation for these patients, though its efficacy is limited. Closed-loop electrical stimulation, a form of

IN THIS ISSUE:

Clinical Updates

- *Electrical Stimulation Aided by Use of Machine Learning Classifiers May Improve Memory Recall in Patients with Traumatic Brain Injury*
- *TMS Targeting the Right Lateral Orbitofrontal Cortex Appears Effective for Treatment of Refractory Depression*
- *Equivalent Antidepressant Effectiveness Using Beam F3 and 5.5cm-rule in rTMS*
- *Deep rTMS to Insular Cortex May Increase Rates of Abstinence in Varenicline for Smoking Cessation*

Glossary

neuromodulation involving the implantation of electrodes in the cortex to detect signals and stimulate in response, has been effectively used to treat patients with refractory epilepsy by identifying areas of neural dysfunction for surgical resection. Its ability to augment cognition with temporal stimulation is an area of great interest in those who receive these implants, and the authors of this study sought to answer if this form of invasive neuromodulation could be used to improve memory impairment in patients with TBI.

Eight participants (seven male, one female, mean age 44.5 ± 11 years) with refractory epilepsy, a history of moderate-to-severe TBI, and who were undergoing seizure monitoring and lesion localization using implanted intracranial electrodes were recruited for this study. All participants performed delayed verbal free recall tasks in which they were asked to encode and recall several lists, each consisting of twelve words. Participants performed these tasks blinded to which portions of a session did (Stim) and did not have stimulation (record-only) to areas within the lateral temporal cortex applied. Behavioral data (e.g., vocalizations) and EEG data collected during initial record-only sessions were

used to train a machine learning model to identify participant-specific classifiers (primarily based on neuronal activity) of memory recall success and failure. Then, when the model's classifiers predicted a low probability of recall during the encoding phases of the Stim portions of sessions, 200Hz stimulation with a current density of 0.081-0.099 mA/mm² (depending on geometry) was applied to the target areas within the lateral temporal cortex for 500 ms. The primary outcome examined between stimulation conditions was recall rate (proportion of total words in the list recalled), which was first normalized based on the average recall rate during record-only sessions. Differences were tested using t-tests comparing recall rates during the stimulation portions to the record-only portions of each session. Hierarchical linear mixed effects model and likelihood-ratio chi-squared tests were used to account for the effect of list position within each session, word position within each list, and stimulation of additional sites patients may have received for other clinical purposes.

Comparing recall rates between stim and record-only, a 19% improvement in recall rates (25.2% stim vs. 21.1% record-only, $t=3.36$, $p=0.012$, $d=1.18$) was observed

across the eight participants. In addition to memory improvements at the overall list level, there was a 17.5% improvement in recall at the individual item level for those on lists in the stim condition. Hierarchical models indicated stimulation benefits were specific to the lateral temporal site and occurred for all stim condition lists, regardless of the position within the session or the word order within the list. On an individual level, seven of the eight participants exhibited improved memory on stimulation lists compared to record-only lists.

Impact: This study demonstrated that neuromodulation may be effective in improving memory recall in epileptic patients with a history of TBI. Although this study is limited by its small sample size and narrow outcomes assessments, and chronic implantation of intracranial electrodes is currently primarily limited to the treatment of epilepsy and some neurodegenerative disorders, this research provides support for further development in the use of neuromodulation in patients with acquired brain injuries.

Kahana MJ, Ezzyat Y, Wanda PA, et al. Biomarker-guided neuromodulation aids memory in traumatic brain injury. *Brain Stimul.* 2023;16(4):1086-1093. doi:10.1016/j.brs.2023.07.002

TMS Targeting the Right Lateral Orbitofrontal Cortex Appears Effective for Treatment of Refractory Depression

David Carlson, MD, reviewing Tadayonnejad R et al. *Brain Stimul.* 2023 Sep 15

This open-label retrospective study of 33 patients found rTMS of the right lateral orbitofrontal cortex (rOFC) to be a safe and effective augmentation strategy in treating mood and rumination symptoms in those whose depression was unresponsive to 10Hz rTMS and iTBS priming of the left DLPFC, thus introducing a potential new treatment target for treatment-resistant patients.

High-frequency rTMS of the left DLPFC is a proven treatment for major depressive disorder not responsive to multiple medication trials or psychotherapy and is both the original and most common form of rTMS for depression. New approaches have emerged, including low-frequency right-sided

rTMS and priming stimulation. While low-frequency right DLPFC stimulation has been well-studied at this point, other right-sided targets, including the right lateral orbitofrontal cortex (rOFC), which has a known role in the circuitry of depression and rumination, have not been widely explored as treatment

targets. This retrospective open-label study examined the safety, feasibility, and efficacy of rOFC inhibitory stimulation as a novel augmentation strategy for patients who showed limited response to 20 conventional HF left DLPFC stimulation and iTBS augmentation (AKA "priming").

Thirty-three patients with moderately severe major depressive disorder were enrolled in this study. The patients were treatment resistant, having tried, on average, 7.7 ± 4 medications (antidepressants and augmentation with antipsychotics) and 1.5 ± 2 courses of psychotherapy with limited response. They initially received treatment with 10Hz rTMS administered to left DLPFC at 120% RMT, followed by the addition of augmentation with theta burst priming (600 pulses of iTBS at 80% of RMT at left DLPFC preceding the 10Hz stimulation in each treatment session) after session 10 due to limited response. After session 20, these patients received further augmentation with 1200 pulses of 1Hz stimulation over rIOFC at 120-140% RMT following priming and 10Hz at left DLPFC during each treatment session (average number of sessions including rIOFC = 15 ± 5.4).

At baseline, the average Inventory of Depression Severity – Self Report (IDS) was 44 ± 10.8 and remained unchanged at session 20 (T20) with 43 ± 10.5 ($p = 0.28$). The same lack of change was present in the IDS mood subscale (baseline = 21 ± 4.5 , T20 = 21 ± 5.0 , $p = 0.74$). Following rIOFC augmentation, patients showed significant improvement in total symptoms (total IDS post-treatment = 36 ± 14.4 , $p = 0.0004$), mood (IDS Mood subscale post-treatment = 17 ± 6.9 , $p = 0.0001$), and negative rumination (total Ruminative Response Scale [RRS]: T20 = 61 ± 14.9 , post-treatment = 54 ± 16.1 , $p = 0.001$). Further analysis showed a significant interaction between the addition of rIOFC and time on total IDS score ($p = 0.0004$), IDS mood score ($p = 0.0002$), and RRS scores ($p = 0.0006$), indicating that the rate of symptom improvement was greater after the addition of rIOFC augmentation. Twenty-four percent

of patients had a full response ($\geq 50\%$ reduction in PHQ-9), and an additional 24% had a partial response (20–50% reduction in PHQ-9) to a full course of treatment, including rIOFC augmentation.

Impact: This retrospective study is one of the first to examine inhibitory rTMS of the rIOFC as a treatment strategy and suggests it is both a safe and effective strategy for rTMS in those whose depression does not respond to more conventional approaches. Future prospective trials validating this novel approach, characterizing the differences in response, and exploring the mechanisms that differentiate it from our conventional rTMS methods are of great importance to the field.

Tadayonnejad R, Citrenbaum C, Ngo TDP, Corlier J, Wilke SA, Slan A, Distler MG, Hofman G, Adekun AE, Leuchter MK, Koek RJ, Ginder ND, Krantz D, Artin H, Strouse T, Bari, AA, Leuchter AF. Right lateral orbitofrontal cortex inhibitory transcranial magnetic stimulation for treatment of refractory mood and depression. Brain Stimul. 2023; 16:1374-1376. Published 15 Sep 2023

Equivalent Antidepressant Effectiveness Using Beam F3 and 5.5cm-rule in rTMS

Harinee Maiyuran, MD, reviewing Trapp et al. Brain Stimulation 2023 Sep 14

This prospective, randomized, double-blind comparative effectiveness trial examined dorsolateral prefrontal cortex (DLPFC) rTMS targeting via both Beam F3 and 5.5 cm-rule targeting, finding comparable antidepressant effects in both groups.

Initial landmark rTMS trials used a "5 cm" method to target the left DLPFC. This distance was later revised to a "5.5 cm-rule" or "6 cm-rule" method for more reliable targeting of the DLPFC. Other methods have been developed, such as the Beam F3 approach, which does not reference the primary motor cortex. These remain the two most common methods of targeting the left DLPFC, and current standard practice is to use one of the two. In this prospective, randomized, double-blind comparative effectiveness trial, participants with MDD were assigned to receive rTMS targeting left DLPFC using either the 5.5 cm-rule or the Beam F3 method to determine if one of

the protocols results in greater clinical effectiveness. The TMS technician placing the stimulating coil was unblinded; all others remained blinded for the duration of the study.

This study recruited 123 participants with MDD, aged 18-90, from the Interventional Psychiatry Service of the University of Iowa Hospitals and Clinics between May 2018 and May 2022. Common rTMS exclusion criteria were applied, and medications were continued during the treatment. Participants received once-daily treatment five days per week for 4-6 weeks of either 10Hz stimulation ($n=30$, 3000 pulses at 120% MT) or iTBS ($n=75$, 600 pulses at 120%

MT) depending on non-clinical factors (e.g., insurance, time/year of enrollment, and clinic practice). Clinical assessments were performed weekly for self-rated instruments (PHQ-9 and GAD-7) and every other week for the observer-rated MADRS. The primary outcome was a percent change in PHQ-9 score, and secondary outcomes included changes in GAD-7 and MADRS scores as well as response and remission rates. Additionally, imaging and cognitive outcomes were collected though published separately. Inter-group differences were assessed through a combination of T-tests and chi-squared tests of independence. Participants with 20 treatments

were ultimately part of the primary analysis, with the secondary analysis performed as a modified intent-to-treat analysis.

Of the 123 recruited, 105 participants were randomized (mean age of 43.2, 66% female) to either the Beam F3 (n=58) or 5.5 cm-rule (n=47) targeting methods. Data from 96 participants were available for the primary analysis; 9 dropped out. Drop-out rates were similar for both targeting methods (10.6% for Beam F3 and 6.9% for 5.5 cm). The average number of treatments administered was 32.7. There were no statistically significant differences in improvement by targeting method based on percent improvement in PHQ-9 (5.5 cm=36.8%, Beam F3=36.6%) or MADRS (5.5 cm=39.5%, Beam F3=37.8%), with similar results emerging from analysis of the modified intent-to-treat sample. No significant differences emerged between the

two different targeting methods when examining response (PHQ-9: 5.5 cm=36.6%, Beam F3=43.4%; MADRS: 5.5 cm=43.3%, Beam F3=43.2%) or remission (PHQ-9: 5.5 cm=22.0%, Beam F3=20.8%; MADRS: 5.5 cm=20.0%, Beam F3=18.9%) rates. Anxiety was assessed using the GAD-7, and, again, no significant differences were found in percent improvement from baseline (5.5 cm=33.6%, Beam F3=27.5%) or response rates (5.5 cm=27.3%, Beam F3=30.2%) between the two targeting groups. Notably, the 5.5 cm rule group had consistently lower GAD-7 scores at all time points after baseline. However, mixed-effects modeling found no significant effect of targeting group on GAD-7 score over time. However, an exploratory post hoc analysis that controlled for depression severity via the PHQ-9 showed a significant group-by-time interaction favoring anxiety reduction in the 5.5 cm rule group.

Impact: These results suggest clinical equivalence between the Beam F3 and 5.5 cm-rule targeting approaches, with possible minor differences in anxiolytic effects that are unlikely to be clinically meaningful. However, further investigation is warranted to explore potential differences in anxious symptom improvement, protocol-specific effects or differences, and a larger range of head sizes. Despite these limitations, the study highlights the clinical equivalence of Beam F3 and 5.5 cm targeting methods for MDD treatment and suggests avenues for future research, including individualized targeting and symptom-specific depression networks.

Trapp NT, Pace BD, Neisewander B, Ten Eyck P, Boes AD. A randomized trial comparing beam F3 and 5.5 cm targeting in rTMS treatment of depression demonstrates similar effectiveness. *Brain Stimul.* 2023;16(5):1392-1400. Doi:10.1016/j.brs.2023.09.006

Deep rTMS to Insular Cortex May Increase Rates of Abstinence in Varenicline for Smoking Cessation

Michael K. Leuchter, MD, reviewing Ibrahim et al. *Brain Stimulation* 2023 Oct 6

This double-blind, sham-controlled RCT examined the effectiveness of a four-week course of deep rTMS targeting the insula as an augmentation strategy for 12 weeks of varenicline for smoking cessation. After completing varenicline treatment, rates of abstinence were significantly higher in those who received active rTMS (82.4%) compared to sham (30.7%), supporting the promise rTMS holds for smoking cessation or other substance use disorders.

There are 1.3 billion people in the world who are smokers, and over 8 million deaths per year are linked to tobacco. While over 50% of smokers may attempt to quit or reduce their intake every year, under 10% of them succeed, and under half of those who do maintain abstinence for a significant period. While there are three medications FDA-approved for smoking cessation, relapse rates remain high, even with varenicline, generally believed to be our most effective agent. The reasons for this are unclear, but, as our understanding of the neurocircuitry

implicated in nicotine dependence has evolved, the insula has become an area of increasing interest due to its roles in interoception and reward-seeking behavior. Targeting of this area, along with the prefrontal cortex, led to pivotal studies granting FDA approval for the Brainsway H4 coil for smoking cessation. While it is known that rTMS can aid smoking cessation, it is unknown whether insular stimulation is necessary or sufficient for its benefit. It is also unknown how insular stimulation interacts with medications for smoking cessation. This study

asks: is insular stimulation helpful, and can it aid first-line pharmacotherapy for smoking cessation?

This study recruited 50 participants to receive either active or sham rTMS in addition to varenicline. Active rTMS sessions consisted of 1020 pulses of 10Hz stimulation in 34 30-pulse trains with a 26s ITI at 120% MT targeting the insula with a Brainsway H11 coil. Sham rTMS sessions used a sham stimulation coil in the same helmet. Participants received 20 sessions

of once-daily rTMS five days per week (4 weeks) while starting a standard 12-week course of varenicline. The assessment consisted of self-report abstinence, serum cotinine measurement (reflecting recent nicotine exposure), and a range of questionnaires to measure nicotine dependence, cravings, cigarette consumption, and withdrawal. The primary outcome was self-report abstinence within the past seven days. Analyses were conducted using Fisher's exact test, Mann-Whitney U tests, and mixed effects models.

Of the 50 recruited, 42 were randomized (n=24 active, mean

age 43.8 ± 12.5 , 83% male; n=18 sham, mean age 46.2 ± 12.9 , 55.6% male), with no significant differences in the characteristics of the two groups. Abstinence was significantly higher in the active rTMS group compared to sham at week 12 (active=82.4%, sham=30.7%, $p=0.013$), though not immediately on completion of rTMS at week 4 (active=66.8%, sham=64.8%) or on follow-up at week 26 (active=25.9%, sham=30.7%). Secondary outcome measures of nicotine dependence, cravings, cigarette consumption, and withdrawal showed improvement over time in both groups but showed no group effect.

Impact: This study suggests that rTMS to the insular cortex may prove to be an efficacious augmentation option for pharmacotherapy for smoking cessation. Though the study is limited by its small sample size and male-predominant sample, it supports the concept of rTMS augmenting varenicline through the notably larger abstinence rates in the active group at 12 weeks compared to sham. However, these benefits do not seem to persist for unclear reasons. Future work exploring effect durability, network-level changes, and other aspects necessary to maximize the efficacy of insular stimulation could be of great utility to the field.

Ibrahim C, Tang VM, Blumberger DM, et al. Efficacy of insula deep repetitive transcranial magnetic stimulation combined with varenicline for smoking cessation: A randomized, double-blind, sham controlled trial. *Brain Stimulation*. 2023;16(5):1501-1509. doi:10.1016/j.brs.2023.10.002

ctBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dtTMS (deep transcranial magnetic stimulation)
ECT (electroconvulsive therapy)
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)
RMT (resting MT)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
PTSD (post-traumatic stress 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)
MoCA (Montreal Cognitive Assessment)
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)
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
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)
mPFC (medial prefrontal cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)

