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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

A Special Message to End the Academic Year

This issue we would like to give a special thank you to Dr. Andrew Leuchter, Distinguished Professor of Psychiatry and Director of the Neuromodulation Division at UCLA, who has served as our Editor-in-Chief since our first issue in March 2021. The PULSE newsletter has grown nationally under his leadership, currently reaching more than 1,000 subscribers each month. Starting in July 2023, he will be handing over the editorial reins to Dr. Aaron Slan, who joined the faculty of the Neuromodulation Division in 2022 after completing his psychiatry residency at Columbia Presbyterian Medical Center in New York. Dr. Slan is an expert clinician-educator who will serve as Editor-in-Chief as part of his leadership of our overall educational programs, including UCLA's Intensive TMS Training Course.

We also wish to thank and congratulate Dr. Collin Price, who has served as our lead Managing Editor since August 2021 and is completing his residency training at this month. He will go on to pursue advanced training in research through the VA MIRECC and mood disorders through the UCLA Mood Disorders Fellowship. He has been integral to the success of this newsletter. Starting next month, Dr. Michael Leuchter will serve as the lead Managing Editor of PULSE. Dr. Leuchter is a Research Track resident entering his PG4 year, and has special interests in neuromodulation and geropsychiatry.

Our new editorial team looks forward to continuing to bring you the latest developments in neuromodulation research and treatment each month!

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Meta-analysis Suggests tACS Improves Cognition Across Populations

David M Carlson, MD reviewing Grover S et al. Sci Transl Med 2023 May

This meta-analysis of 102 studies found that tACS improved cognition across multiple domains with effect sizes of 0.20-0.56, suggesting a role for tACS as both an investigative tool and treatment option

Transcranial alternating current stimulation (tACS) has emerged as a potential strategy for modulating cognitive function using frequency-specific entrainment of cortical activity.

This analysis examined 102 randomized, sham-controlled studies comprising 2893 patients (1290 male, 1603 female) with a mean age of 30.82±15.9, including 333 older adults and 177 adults with a psychiatric disorder (including ADHD, MDD, schizophrenia, and MCI, among others). The studies examined multiple cognitive domains, including visual attention, working memory, long-term memory,

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executive control, fluid intelligence, learning, decision-making, motor learning, and motor memory. These domains were also separately broken down into performance-based (e.g., accuracy, sensitivity, task score) and reaction time (RT)-based component measures. Across the studies, the most common modulation frequency was theta (41%), with alpha, beta, gamma and slow frequencies each used in at least 10% of studies. Most of the tACS protocols also used a standardized (as opposed to individualized) modulation frequency (81% vs 19%), a passive sham control instead of active sham (94% vs 6%), assessed cognition “offline” or after treatment instead of “online” or during (58% vs 42%), and generally took 20-25 minutes to complete. Analyses examined effects of modulation intensity, assessment timing (during vs. after tACS treatment) and multi-region current modeling protocols (in-phase or anti-phase simultaneous stimulation of two cortical regions) on cognitive measures across the whole population and within the population subgroups. Hedges’ g effect size (ES) and 95% CI were calculated for each outcome.

The authors found moderate improvements with tACS compared to sham treatment across all cognitive domains (ES 0.29; 95% CI [0.21,0.37]). On individual measures, moderate improvements were found in working memory (0.20; [0.11,0.29]), long-term memory (0.26;[0.13, 0.38]), attention (0.32;[0.15, 0.49], and fluid intelligence (0.38;[0.18,0.59]). Larger improvements were seen in studies testing executive control (0.56;[0.32,0.81]). Meta-regression analysis examining the effect of assessment timing found greater improvements for offline vs. online task performance (0.39 vs 0.17, respectively; p = 0.010) for performance measures, though not RT-based measures or combined measures. A similar analysis showed an inverse relationship between modulation intensity and executive control effect sizes across combined (β=-0.72; p=0.036), performance (β=-0.81; p=0.043), and RT measures (β=-0.97; p=0.03). When electrode placement was guided by pre-treatment current flow simulations of the electric fields in tACS, this enhanced effectiveness for offline effects (0.54 with vs 0.3 without) and weakened effectiveness for online effects (0.07 with vs 0.29 without). In older adults, a significant effect of tACS on cognitive function was found across combined measures (0.37; [0.12,0.62]) and increased for performance measures. Amongst those with psychiatric illness, tACS also had a significant effect on combined measures (0.48; [0.14,0.81]). Multi-site bidirectional stimulation synchronized in-phase appeared to improve cognition on combined measures (0.32; [0.10, 0.53]), and anti-phase synchronization significantly impaired cognition (0.31, [0.08,0.55]).

Impact: This meta-analysis of 102 studies finds that tACS improved cognition across multiple domains in all three population groups examined. While this study is limited by the heterogeneity and publication bias of the underlying studies, it does suggest that tACS has the potential for a broad role in cognitive enhancement in the future. It is possible that with more consistent prospective rigorous replication studies and examination of the factors like the parameters space and effect durability, tACS will become a mainstay treatment for cognitive enhancement.

Grover S, Fayzullina R, Bullard BM, Levina V, Reinhart RMG. A meta-analysis suggests that tACS improves cognition in healthy, aging, and psychiatric populations. Science Translational Medicine. 2023:15(697). Published May 24 2023

Systematic Review Confirms Safety Profile of rTMS

David Lee reviewing Wang et al. J Affect Disord, 2022 Jan

This meta-analysis of 53 randomized sham-controlled trials indicated that rTMS was a safe and well-tolerated treatment for TRD.

Since the FDA approval of rTMS for TRD in 2008, there have been many systemic reviews and meta-analyses to demonstrate the efficacy of TMS in patients with depression, though those assessing safety have been lacking. Therefore, the authors of the study aimed to perform a systematic review and meta-analysis on randomized sham-controlled trials evaluating the safety of TMS in patients with MDD.

The authors selected 53 original full-text articles from PubMed, Embase, Clinical Key, and Cochrane Library. These randomized sham-controlled studies aimed to investigate the safety of rTMS in patients with primary unipolar MDD using the odds ratio of adverse effects, or the dropout rate due to adverse events between active rTMS and sham groups. Across the included studies, rTMS interventions included standard, accelerated, priming, deep, synchronized, and iTBS, as mono or augmentation therapy. For the primary outcomes, the authors evaluated the odds ratio of 1) dropout due to adverse events and 2) serious adverse events including death, life-threatening experience, new or prolonged hospitalization, persistent disability, congenital anomaly, or other important medical event such as seizure,

suicide attempt, and syncope. As secondary outcomes, the authors assessed the odds ratio of non-serious adverse effects, including mood switch to hypomania or mania, headache, discomfort or pain at the stimulation site, dizziness, anxiety, insomnia, muscle twitching, or tinnitus.

The authors found that the dropout rate due to an adverse effect was not significantly elevated in the active rTMS versus sham groups (3.3% vs 2.3%, odds ratio (OR) 1.30, confidence interval (CI) = 0.78-2.16, p = 0.31). The serious adverse events were also not significantly elevated (0.98% vs 1.5%, OR = 0.59, CI = 0.25-1.42, p = 0.24). The incidences of seizure, suicide attempt, or syncope as specific serious adverse effects of TMS were low, and their odds ratios compared to the sham group were not significantly elevated. The incidences of some non-serious adverse events were significantly elevated in the active rTMS vs sham groups, including headache (22.6% vs 16.2%, OR = 1.48, CI = 1.15-1.91, p = 0.002), and discomfort (10.9% vs 5.0%, OR = 1.98, CI = 1.22-3.21, p = 0.006) or pain (23.8% vs 5.2%, OR = 8.09, CI = 4.71-13.90, p < 0.001) at the stimulation site. There was no significantly elevated risk of other non-serious adverse effects including mood switch from depression to hypomania, dizziness, anxiety, insomnia, muscle twitching, or tinnitus. Across all the studies and measures, there were low or unclear risks of bias, low heterogeneity, and low risks of publication bias.

Impact: This meta-analysis of 53 randomized sham-trolled studies on the safety of rTMS in patients with TRD validated previous findings that rTMS poses no significantly elevated risk of serious adverse effects, including seizures, suicide attempts, or switch to mania. Although there was elevated risk for some non-serious adverse effects such as headache or discomfort at the stimulation site, these were transient and mild.

Wang WL, Wang SY, Hung HY, Chen MH, Juan CH, Li CT. Safety of transcranial magnetic stimulation in unipolar depression: A systematic review and meta-analysis of randomized-controlled trials. J Affect Disord. 2022;301:400-425. doi:10.1016/j.jad.2022.01.047

Spatiotemporal Biomarker of TRD Found to Normalize with Successful Accelerated iTBS

Jo Huang reviewing Mitra et al. Proc Natl Acad Sci 2023 May

Analysis of resting-state fMRI directional-signaling patterns in TRD patients pre-and post- treatment identified a spatiotemporal biomarker of symptom severity and treatment response in the anterior cingulate cortex, with responders showing a normalized temporal pattern similar to that observed in healthy controls.

Neuroimaging studies in patients with depression have provided evidence for dysregulated signaling between the anterior cingulate cortex (ACC) and other brain areas involved in emotional processing. rTMS may improve depressive symptoms by modulating ACC signaling via stimulation of the left DLPFC. Recent work in resting-state fMRI (rs-fMRI) has examined directional-signaling patterns between functionally connected regions across the human brain in patients with depression. This study investigates the relationship between an FDA-cleared neuromodulation approach, the Stanford neuromodulation therapy (SNT), and brain-wide directional-signaling in patients with TRD and healthy controls (HC).

Directional signaling patterns in rs-fMRI were acquired and analyzed in the following settings: 1) immediately before and after SNT clinical trials (one randomized double-blind sham-controlled clinical trial and one open label trial), and 2) in two cohorts of HC. The sample included 14 subjects receiving active SNT, 6 receiving sham, and 54 HC. The SNT intervention involves daily administration of 10 iTBS sessions (one per hour) for 5 consecutive days targeting an individualized left DLPFC target based on the point of maximal anticorrelation with the subgenual ACC.

Active SNT resulted in a statistically significant temporal shift between the left DLPFC and ACC in patients with MDD, with the left DLPFC shifting earlier and the bilateral ACC shifting later with respect to the rest of the brain. Further analysis showed that later shift of ACC relative to DLPFC contributed strongly to the increased “earliness” of the left DLPFC. Additionally, there was a statistically significant earlier shift of several other brain regions relative to the ACC, including anterior insula, lateral prefrontal cortex, and temporoparietal junction. The anterior insula and lateral prefrontal cortex specifically showed reversal of their temporal relationship to the ACC after active SNT – from being active later than ACC to before ACC. Notably, this temporal order (with rs-fMRI activity in insula and prefrontal cortex preceding that of ACC) strikingly resembled rs-fMRI in HC. Symptom improvement, as measured by MADRS scores, significantly correlated in a

logarithmic manner with the extent of late shift of ACC. However, improvement in MADRS scores was not corrected with the extent of early shift of left DLPFC.

Comparison of SNT "high response" (>90% reduction in MADRS score, N = 6) and "nonresponse" groups (<50% reduction in MADRS score, N = 6) showed that the "high response" group has an ACC-seeded lag map similar to the TRD group average at baseline, while the "nonresponse" group's lag map was similar to that of HC. The study then further quantified the relationship between treatment responsiveness and ACC-seeded lag map at baseline and found that lag of ACC relative to other areas was significantly correlated with treatment response. Finally, the study found that both being in the "high-response" group and having higher ACC lag at baseline were correlated with higher baseline MADRS scores compared to the "nonresponse" group.

Impact: This study characterized directional signaling patterns in rs-fMRI based on temporal delay of activity between regions before and after SNT treatment. A shift of the ACC-salience network delay towards a temporal profile similar to that observed in HC after SNT was correlated with treatment response. The temporal relationship between ACC and other areas in the salience network - anterior insula, lateral prefrontal cortex, and temporoparietal junction - was correlated with symptom severity at baseline. These findings in a small number of subjects suggest that aberrant directed signaling between ACC as a potential biomarker for a subpopulation of TRD and potentially a marker of treatment response to SNT. These findings should be interpreted in light of recent findings that have raised questions regarding the reliability and clinical significance of the ACC-DLPFC functional connection in patients with TRD (see our April 2023 issue for more information).

Mitra A, Raichle ME, Geoly AD, Kratter IH, Williams NR. Targeted neurostimulation reverses a spatiotemporal biomarker of treatment-resistant depression. Proc Natl Acad Sci U S A. 2023 May 23;120(21):e2218958120. doi: 10.1073/pnas.2218958120. Epub 2023 May 15. PMID: 37186863; PMCID: PMC10214160.

From the Archives: Twice Daily rTMS is Safe and Effective for TRD

Michael Leuchter reviewing Loo et al. Psychological Medicine 2006 Dec

This sham-controlled trial of 38 patients with TRD finds twice daily rTMS treatment is both safe and efficacious for symptom relief.

Before its FDA approval in 2008, there was a great deal of work in optimizing the antidepressant effects of rTMS. The parameter space was (and still is) large, and a number of studies have examined stimulation parameters such as frequency, intensity, pulse number, and site. These studies primarily examined once-daily treatment. However, the authors of this study asked a different question: can multiple rTMS treatments per day be administered safely and efficaciously?

The authors recruited 38 participants (mean age 45.7±15.0 sham, 49.8±2.5 active; 42% female sham, 52% female active) with TRD (mean MADRS 32.6±4.3 sham, 29.5±3.9 active; f=5.5, p=0.03) and administered two weeks of twice daily treatment with 2 hours between sessions with either an active coil (n=19) or sham coil (n=21). Active stimulation consisted of 1500 pulses of 10Hz stimulation at 110% RMT administered in 30 trains of 5 second duration with a 25 second ITI. Following completion of the two-week blinded period, participants were offered open-label once daily treatment to complete a full six-week course of rTMS (4 weeks for active, 6 weeks for sham). The primary outcome examined was change in MADRS score, however, multiple other mood (HDRS, BDI, Affect Underpinned by Severity and Social Impairment [AUSSI] scale, CORE measure of psychomotor disturbance) and cognition scales were examined as well.

Over the course of the blinded two-week period, participants demonstrated improvement in all mood scores (range of f=8.8-43.6, range of p=<0.001-0.005). Those receiving active treatment demonstrated greater improvement on the MADRS (f=4.2, p=0.047) relative to sham, though this was not observed on other scales. All participants also demonstrated improvement on three of the several cognitive tests: Trail Making Test B, Rey Auditory-Verbal Learning Test both immediate and delayed recall, and Weschler Adult Intelligence Scale forward digit span (f=8.2-13.0, p=0.001-0.007). During active treatment, participants experienced scalp discomfort (n=15), headache (n=8), tearfulness (n=4), brow twitching (n=3), nausea (n=1), anxiety (n=1), agitation (n=1), and "feeling high" (n=1). During sham treatment, one participant experienced nausea.No serious adverse events occurred in either arm. All participants continued to improve over the course of open-label once-daily treatment following

the blinded phase, and between-group differences after the blinded phase were not discussed in depth.

Impact: rTMS continues to be used primarily as a once-daily treatment for TRD. This study was the first sham-controlled trial to examine the efficacy and safety of administering multiple rTMS treatments in a single day and provided a basis for expanding work in the realm of accelerated rTMS protocols. Though the active group did have less severe depression at baseline, the findings that twice-daily treatment was both effective for symptoms relief led to development of protocols examining as many as 15 treatments in a single day. Multiple accelerated protocols appear to be safe and effective. It remains unclear what is the optimal number of treatments per day, how far apart they should be spaced, and whether the benefits of accelerated treatment are as durable as those of standard daily treatment. Optimization of accelerated parameters is important to ensuring greatest benefit for patients.

Loo, C. K., Mitchell, P. B., McFarquhar, T. F., Malhi, G. S., & Sachdev, P. S. (2007). A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. Psychological Medicine, 37(3), 341–349. https://doi.org/10.1017/S0033291706009597

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (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)