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A Monthly Update on Advances in Neuromodulation



A Special Message from our Editorial Team

In this issue, we are delighted to announce that Angela Broida, PhD, LCSW, will be joining our editorial team as an associate editor. After obtaining her PhD at the University of Washington, she completed a postdoctoral fellowship that focused on TMS-related projects at Stanford University and the Palo Alto VA. She is a member of the Clinical TMS Society and the current co-chair of its research committee. We are delighted she has joined us as the Administrative Director of the UCLA Neuromodulation Division, and even more so to announce her joining the PULSE editorial team!

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A Monthly Update on Advances in Neuromodulation



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Focal tDCS of Auditory Cortex a Potential Treatment for Chronic Tinnitus

Harinee Maiyuran, MD, reviewing Leaver et al. *Clinical Neurophysiology* 2023 Dec 16

This randomized pilot trial focused on mechanism determination of focal transcranial direct current stimulation (tDCS) of the auditory cortex, which was found to promote increases in cerebral blood flow and connectivity and reduce tinnitus loudness and intrusiveness.

Tinnitus is the perception of a ringing or buzzing sound despite lacking an external source. Chronic tinnitus often has deleterious effects on mental health and quality of life, and most treatments are of limited efficacy. Recent neuroimaging in animals and humans has suggested an involvement of not only auditory processing brain circuits but also frontal cortex and parahippocampal regions. Studies examining techniques such as rTMS have shown promise in treating

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Glossary

this debilitating condition; could tDCS also target these regions and decrease the burden of tinnitus?

This single-site randomized clinical trial included 20 participants (aged 18-75, active mean 43.5 ± 13.2 , sham mean 39.5 ± 14.0) who had been diagnosed with chronic tinnitus, defined as primary tinnitus (not secondary to another medical condition) occurring at least 50% of waking hours and felt to be intrusive at least 10% of the time spent awake, throughout the 12 months prior to screening. Five sessions of daily tDCS— active or sham — were administered (2mA current for 20 minutes with 30 s on/off ramps, placed over the auditory cortex based on standard EEG coordinates as done in prior studies). Blood oxygenation level-dependent MRI (BOLD-MRI, typical fMRI protocol) and arterial spin labeling (ASL) MRI were done before and after the first tDCS treatment. Assessments measuring tinnitus were done one week prior and one day prior to the first session, then at several time points up to four weeks after the final session. Outcomes included changes in the auditory cortex functional activity measured by BOLD and ASL MRI, as well as several self-rated symptom questionnaires (Tinnitus Functional

Index [TFI], Tinnitus Handicap Inventory [THI], Tinnitus Sample Case History Questionnaire, and Beck Depression and Anxiety inventories [BDI and BAI]).

The cortical, thalamic, basal ganglia, cerebellar, and subcortical areas of the brain were analyzed, with two primary statistical analyses: one that used linear mixed models to compare brain function changes when compared with active versus sham tDCS and another that correlated brain function changes – measured by MRI – with changes in symptoms of tinnitus after active tDCS treatment.

There were no significant differences between groups in demographics and baseline tinnitus severity. All tinnitus questionnaires improved over time in both active and sham groups, with no differences between groups. However, additional follow-up analyses showed the active group experienced a potentially greater reduction in tinnitus burden, with ongoing decreases in loudness and awareness up to four weeks after treatment. MRI analyses showed significant differences in cerebral blood flow (CBF) and functional changes (FC) between the active and sham groups, especially in the left Heschl's gyrus (CBF) and the auditory resting state network (FC). Improvements in tinnitus loudness

correlated with changes in FC of the right premotor and dorsolateral prefrontal cortex as well as the thalamus. Both regions may serve as targets for tDCS in the future. Correlations generally demonstrated good fits with $R^2 \geq 0.5$. Decreases in awareness of tinnitus were linked to changes in connectivity in the right posterior cingulate cortex and the supramarginal gyrus.

Impact: While the investigators found no significant differences between active and sham treatment, they did note modest improvements in both groups during and after treatment. Furthermore, these improvements in the active group appear to be driven by increases in fMRI activity in auditory processing networks, particularly the CBF in the left Heschl's gyrus. Despite the limitations of a small sample size and short treatment course of five sessions, these results provide valuable insight into how neuromodulation techniques, particularly tDCS, impact chronic tinnitus and modulate its mechanisms.

Leaver, Amber M., et al. "FOCAL tDCS of auditory cortex in chronic tinnitus: A randomized controlled mechanistic trial." *Clinical Neurophysiology*, vol. 158, Feb. 2024, pp. 79–91, <https://doi.org/10.1016/j.clinph.2023.11.021>.

YouTube Videos on ECT as Supportive Information for Patients

Harinee J. Maiyuran, MD, reviewing Sabra et al. *Journal of ECT* 2024 Feb 12

In this study, YouTube videos educating patients about ECT were found to be of medium quality, albeit highly reliable, when measuring clarity, comprehensibility, additional resources, objectivity, and bias.

Electroconvulsive therapy (ECT) is an important modality for addressing treatment-resistant and/or acutely life-threatening major depressive, manic, and mixed episodes; primary psychosis; and catatonia. Despite its efficacy, ECT is underutilized, with only 5.56 individuals per 100,000 with the aforementioned disorders receiving treatment, partly driven by stigma and misinformation.

Consequently, patients and caregivers seek information from other sources, including YouTube, although the accuracy and reliability of online content varies. YouTube has become an increasingly utilized source of information influencing patient decision-making, and clinician concerns about the quality and reliability of YouTube videos on ECT are understandable. Can

YouTube be a high-quality, reliable resource for patients and primary caregivers who want to learn more about ECT?

The study involved a structured search on YouTube using specific search terms related to electroconvulsive therapy and mental health diagnoses listed above, and using "and" and "or" to

help refine the search. This occurred from May 2, 2023, through August 15, 2023. Inclusion criteria included videos that were in English, focused on ECT, had effective audio and visual quality, and were between one and 20 minutes. Duplicates were excluded. These criteria narrowed the search from 500 videos to 250 videos. It is unclear if the 500 videos represented the total number of YouTube videos about ECT or a random sample of videos. Three validated measurement tools were used: the Global Quality Scale (GQS) to measure video quality (i.e. how well information flows in the video and its "ease of use") overall from 1-5, the DISCERN tool to measure reliability (i.e., accuracy and clarity of the information presented) via five questions answered 1 for yes, and 0 for no (maximum score 5, and 3 or more indicating high reliability), and a unique datasheet to assess for content, caregiver (or person delivering information in the video) appearance while watching, information presentation, source, and parameters.

The study analyzed 250 YouTube videos, examining video parameters

content, presentation methods, caregiver/presenter appearances, video sources, and overall quality and reliability. The videos showed a wide range of views and comments, with a median of 532 views and two comments. The content analysis revealed that the most frequently covered topics were the method of administration and indications of ECT, while the least discussed topic was the quality of life of patients. A slide presentation was the most common method used. Psychiatrists were the most common formal/professional caregivers featured, while family members and friends were frequently shown as informal caregivers. The primary source of these videos was educational channels, followed by personal blogs and nonprofit organizations. GQS results indicated a balanced spread across low, medium, and high-quality videos, with medium quality being the most common. The modified DISCERN tool highlighted that a significant portion of videos provided reliable information and clear objectives. Overall, the study found no significant differences in quality scores relative to video parameters or reliability scores, indicating

consistency across evaluated aspects.

Impact: Given the high prevalence of technology and social media in today's world, coupled with its high accessibility, especially when compared to clinical visits with physicians, assessing the effectiveness and reliability of sources such as YouTube in communicating clinical information is increasingly important. Unfortunately, high accessibility can also result in mixed quality, which is the case in this study and the likely reason for the medium-quality finding. However, it is encouraging that the videos presented generally reliable information even with mixed video quality. Though this study is limited by its focus solely on YouTube and limited exploration of the impact of these videos, it serves as a useful contribution guiding the creation of informational materials about ECT.

Abu MA, Mahmoud AI, Kalalideh, AlOsta MR. Is the Electroconvulsive Therapy Video on YouTube Supportive Information for Patients and Their Primary Caregivers? *PubMed*. Published online February 12, 2024. doi: <https://doi.org/10.1097/jct.0000000000000996>

rTMS as an Effective Treatment for Psychomotor Slowing in Psychosis

Harinee J. Maiyuran, MD, reviewing Walther et al. *JAMA Psychiatry* 2024 Feb 28

In this double-blind, placebo-controlled trial in Switzerland, 68% of those who received inhibitory rTMS had a significantly better outcome in decreasing psychomotor slowing compared to those who received intermittent theta burst stimulation (iTBS), sham, and no treatment.

Schizophrenia has a global prevalence of about 1% and can impact the quality of life immensely, not only due to the positive symptoms (hallucinations and delusions, in particular) but also due to negative symptoms such as psychomotor slowing, in which motor skills, speech, and facial expression are compromised. This symptom of schizophrenia has also been associated with decreased cognitive speed, increased medical

complications, and social difficulties. Psychomotor slowing has been associated with increased activity and connectivity in the supplemental motor area, an area easily targeted with rTMS. Based on prior studies indicating that rTMS can decrease psychomotor slowing in patients with Schizophrenia, this study compared inhibitory 1-Hz rTMS with iTBS, sham-rTMS, and no add-on rTMS, via a randomized,

double-blind, sham-controlled 4-arm trial involving three weeks of treatment.

Of 615 participants assessed for eligibility from March 22, 2019 – August 29, 2022, 103 were eligible, and 69 completed the intervention and follow-up assessment period. Participants were ages 18 to 60 (mean age 36.3 ± 12.4), with a diagnosis on the schizophrenia spectrum per

DSM-5 criteria and psychomotor slowing as shown by a Salpêtrière Retardation Rating Scale (SRRS) Score ≥ 15 . Treatment protocols targeted the supplemental motor area (SMA) and were 960 pulses at 110% MT in the 1Hz group, two series of 600 pulses each at 80% MT separated by 10 minutes in the iTBS group, 960 pulses of 1Hz stimulation with a sham coil in the sham group, and waiting three weeks before receiving 1Hz stimulation in the waiting group. Across all four groups, treatment was daily (on weekdays) for three weeks (15 sessions). The primary outcomes were the proportion of SRSRS responders (defined as a 30% reduction from baseline at week three) and the change in SRRS score over time. Secondary outcomes included response rates as well as changes in general illness severity, negative symptoms, catatonia, parkinsonism, dyskinesia, global functioning, social functioning, and functional capacity, all measured using a variety of scales. Nondominant wrist activity was used to represent the change in total physical activity while awake, and the coin rotation task was used to measure dexterity in both hands. Assessments were performed at baseline, week three, week nine, and week 27. Data analysis focused on comparing response rates and improvements across different treatment arms with adjustments for various covariates such as sex and medication dosage. Safety assessments and

follow-ups were conducted at specified intervals. Chi-squared tests were used for categorical outcomes, with logistic regression used to obtain odds of outcomes/response over time. Repeated-measures ANCOVAs (analysis of covariance) were generated with factors of group and time for continuous outcomes. Adverse events and blinding were assessed via chi-squared tests.

Primary outcome analysis showed that 1-Hz rTMS had a significantly higher response rate (68%) than the iTBS (36%), sham (32%), and none/waiting (18%) groups. Statistical analysis highlighted a significant reduction in psychomotor slowing for the 1-Hz rTMS group compared to others. Secondary outcome measures also showed significant improvements over time in all treatment groups, but the 1-Hz rTMS group consistently outperformed the others in reducing psychomotor slowing, as demonstrated by various scales, including PANSS, BNSS, and BFCRS. Notably, 1-Hz rTMS led to improvements in catatonia severity and other symptoms of schizophrenia when compared to the waiting and sham groups. Blinding was effective, with the majority of patients unable to correctly guess their treatment assignment. The safety profile was favorable, with no severe adverse events reported and no significant differences in minor adverse effects across groups. These findings suggest that 1-Hz rTMS is a promising treatment for psychomotor slowing in schizophrenia, offering substantial

improvements in symptoms with a good safety profile. The daily rTMS sessions were therapeutic and contributed to increased social interactions and routine activities, which may have amplified the treatment effects. Interestingly, the study highlighted the differential impacts of iTBS; despite its facilitatory intent, doubling the pulse count seemed to induce inhibitory effects in some cases. Furthermore, the trial indicated improvements in catatonia and negative symptoms, particularly anhedonia, under specific stimulation settings. However, this was inconsistent across other symptom scales, suggesting a potential limitation in statistical power.

Impact: 1Hz inhibitory rTMS of the supplementary motor area appears to be both efficacious and safe in treating psychomotor slowing and potentially other negative symptoms in patients with primary psychotic illnesses. Future research exploring a more comprehensive range of rTMS protocols, including continuous theta burst stimulation or alternative stimulation sites, to optimize treatment efficacy will greatly benefit this difficult-to-treat domain of symptoms. This trial sets the stage for further multicenter studies to replicate these findings and explore the nuanced effects of rTMS on different psychotic symptoms.

Walther S, Danai Alexaki, Weiss F, et al. Psychomotor Slowing in Psychosis and Inhibitory Repetitive Transcranial Magnetic Stimulation. *JAMA psychiatry*. Published online February 28, 2024. doi: <https://doi.org/10.1001/jamapsychiatry.2024.0026>

Transcranial Pulse Stimulation as a Promising Treatment for Neuropsychiatric Symptoms in Alzheimer's Disease

Michael Leuchter, MD, reviewing Shinzato et al. *Brain Stimulation* 2024 March 4

Transcranial Pulse Stimulation (TPS) is a novel emerging form of noninvasive brain stimulation utilizing repeated low-frequency bursts of ultrasound waves. It has been studied primarily in Alzheimer's Disease (AD), and the small open-label pilot results of this study indicate it may prove a useful tool for neuropsychiatric/behavioral symptoms in AD, which are notoriously difficult to treat.

While multiple forms of both invasive and noninvasive brain stimulation have been explored for Alzheimer's Disease (AD), modalities explored thus far have primarily demonstrated benefits for the cognitive symptoms of the disease, and these benefits have been largely inconsistent. Neuropsychiatric/behavioral symptoms are notoriously difficult to control, and a considerable need exists for effective treatments in this area. Transcranial Pulse Stimulation (TPS) is an emerging form of noninvasive brain stimulation that utilizes brief ultrasound pulses (generally lasting 3 μ s) delivered at an adjustable low repetition frequency (1-8Hz) and variable intensity (referred to as energy flux density) to generate acoustic waves that travel through the skull and up to roughly 8 cm deep (note the thalamus and multiple other deep targets of interest often lie 5-6 cm deep) in the brain. This joins tFUS as another acoustic-based form of brain stimulation, the main difference being that tFUS utilizes constant application of sonication, and TPS uses brief bursts to transmit ultrasonic waves. It is thought this transmission results in mild mechanical shifts in the cellular membrane, essentially, for lack of a better term, jiggling the membrane, thereby potentially enhancing blood flow, opening channels, releasing growth factors, or mediating any number of other effects. With its ability to target deep structures and provide a novel form of stimulation, is TPS something that might lend

itself to the treatment of Alzheimer's Disease?

This open-label study of ten subjects of unclear age (4 male, 6 female, mean age reported as 33, though inclusion criteria stated as age \geq 50) of mild-to-moderate (50% mild 50% moderate based on Functional Assessment Staging [FAST] classification) disease severity without other major comorbidity examined the effects of TPS in AD. Subjects underwent two treatments per week over five weeks for a total of ten treatments. Each treatment session consisted of 6000 pulses over the frontotemporal, parietal, and occipital regions using MRI navigation at a focus depth of 5 cm and repetition frequency of 4Hz, for a total of 26 minutes of treatment and 50 Joules of energy applied. Subjects underwent neuropsychological assessment with the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog), Neuropsychiatric Inventory (NPI), Pfeffer Functional Activities Questionnaire, and Zarit Burden Index for caregiver burden (ZBI) before treatment, as well as 30 and 90 days after treatment. Changes in these measures were assessed with a series of repeated-measures ANOVAs with time as the only noted factor variable. No other confounders or other statistical adjustments were discussed. The authors mention briefly testing whether their data was normally distributed (and therefore appropriate for their planned

analyses). However, the results of these tests are not presented, nor is anything indicating the distribution of data. Follow-up comparisons examined individual pairs of time points and did not include any form of adjustment. There is no mention of missing data (either presence or lack thereof).

The main result presented from this study is a rather large mean NPI score reduction of 23.9 points (95% CI -39.2 to -8.6) from baseline to 30 days after treatment and 18.9 points (95% CI -33.5 to -2.9) from baseline to 90 days after treatment (33 ± 22 at baseline, 9 ± 9 at 30 days, 15 ± 16 at 90 days, ANOVA $p=0.01$). They present numeric, though not statistically significant, improvements in ADAS-Cog, Pfeffer, and ZBI.

Impact: This study shows that TPS is a novel tool that warrants further study of its utility in Alzheimer's Disease. However, results from this open-label study are not clearly superior to what might be expected from a placebo for Alzheimer's Disease, and inconsistencies in the study's reporting and its incomplete reporting of methods must be reconciled. Nevertheless, should the results of this study be appropriately replicated at scale, TPS would likely become a valuable tool in the treatment of Alzheimer's Disease.

Shinzato GT, Assone T, Sandler PC, et al. "Non-invasive sound wave brain stimulation with Transcranial Pulse Stimulation (TPS) improves neuropsychiatric symptoms in Alzheimer's disease." *Brain Stimulation*. 2024;17(2):413-415. doi:10.1016/j.brs.2024.03.007

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)
MST (magnetic seizure therapy)
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)
TPS (transcranial pulse 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)

