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PULSE

A Monthly Update on Advances in Neuromodulation

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Bifrontal tDCS in Treatment-Resistant Depression: No Significant Neurocognitive Benefits

Miguel Serrano-Illán, MD, PhD, reviewing Soldini et al. Eur Arch Psychiatry Clin Neurosci. 2024 Feb

This randomized, triple-blind, sham-controlled, multi-site clinical trial found that bifrontal tDCS did not significantly enhance neurocognitive function or predict clinical outcomes in patients with TRD.

tDCS is a noninvasive brain stimulation technique that uses electrodes on the scalp to modulate cortical excitability, most commonly targeting the left DLPFC to treat MDD. The left DLPFC is a key node in the frontoparietal network (FPN), which is involved in attention, working memory, and executive function, suggesting this node could be a useful target for neurocognitive effects of depression. However, previous studies have shown mixed results regarding the

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neurocognitive benefits of tDCS in patients with MDD, and the potential of baseline cognitive performance as a predictor of clinical response remains unexplored. This study aimed to investigate whether bifrontal tDCS could improve neurocognitive functions and if baseline cognitive testing could predict treatment response to tDCS in patients with TRD.

A cohort of 101 patients (59 females, mean age: 39 ±14 years) with TRD, who had not responded to selective serotonin reuptake inhibitors (SSRIs), were recruited from eight psychiatric centers in Germany. Patients were randomized in a triple-blind fashion to receive 24 sessions of either active or sham tDCS over six weeks. The tDCS montage placed the anode over the left DLPFC and the cathode over the right DLPFC, with active stimulation consisting of a constant 2 mA direct current for 30 minutes, while sham involved a ramp-up and ramp-down of current to mimic the sensation of tDCS without delivering sustained stimulation. The primary outcome was the change in depression severity as measured by the MADRS, and secondary outcomes included the State-Trait Anxiety Inventory (STAI). Neurocognitive performance was assessed using the EmoCogMeter, a validated digital cognitive battery that tests a variety of FPN-related neurocognitive functions, including memory span, working memory, selective attention, sustained attention, executive processes, and processing speed. The study assessed whether baseline cognitive function could predict the antidepressant effects of tDCS and the impact of tDCS on cognitive function post-treatment.

Both groups exhibited a reduction in depressive symptoms; however, the reduction in MADRS scores did not significantly differ between the active and sham tDCS groups. Active tDCS did not significantly improve neurocognitive functions related to the FPN compared to sham, and baseline neurocognitive performance did not predict changes in depression severity. Similar to the depression outcomes, there were no significant differences between the active and sham tDCS groups in reducing anxiety symptoms based on the STAI.

Impact: This triple-blind, sham-controlled, multi-site randomized clinical trial failed to show a benefit of bifrontal tDCS (compared to sham) on neurocognitive symptoms in patients with TRD. Furthermore, baseline cognitive performance does not appear to be a reliable predictor of tDCS efficacy in TRD. Future research should explore different tDCS parameters, such as varying intensities and durations, to optimize both cognitive and antidepressant effects. Additionally, combining tDCS with concurrent cognitive training could enhance its neurocognitive impact. It will also be important to identify specific patient subgroups who might benefit more from tDCS, particularly those with certain neurocognitive deficits or biomarkers. Lastly, investigating how anxiety and other comorbidities influence tDCS outcomes could lead to more tailored and effective interventions for individuals with complex clinical profiles.

Soldini A, Vogelmann U, Aust S, et al. Neurocognitive function as outcome and predictor for prefrontal transcranial direct current stimulation in major depressive disorder: an analysis from the DepressionDC trial. Eur Arch Psychiatry Clin Neurosci. Published online February 26, 2024. doi:10.1007/s00406-024-01759-2

EEG-Synchronized TMS for Depression Shows No Added Clinical Benefit

Miguel Serrano-Illán, MD, PhD, reviewing George et al. Brain Stimul 2023 Dec

This randomized, double-blind clinical trial studied the feasibility and clinical impact of EEG-synchronized rTMS in patients with TRD, finding that EEG-synchronization did not improve clinical outcomes.

Traditional rTMS typically delivers pulses at a set frequency without considering the brain's natural oscillatory rhythms. However, recent findings suggest that matching rTMS to specific brain rhythms, such as the prefrontal alpha rhythm, could enhance efficacy, similar to cardiology practices wherein synchronization with heart rhythms is crucial. Here, the authors developed an integrated fMRI/EEG/rTMS system to provide EEG-guided rTMS, hypothesizing that stimulating during the brain's more excitable phases would improve outcomes. This study compared synchronized versus non-synchronized rTMS in patients with TRD.

A cohort of 28 patients (19 female, 9 male, mean age 45±13 years) with TRD (HDRS score >20) received a 6-week course of daily rTMS for a total of 30 sessions. Prior to treatment, patients also underwent two MRI scans, including concurrent TMS/EEG/BOLD fMRI, to identify the optimal phase of the prefrontal EEG alpha rhythm for stimulation. This was accomplished by delivering TMS pulses to the left DLPFC while the patient was in the scanner, targeting various points in the EEG alpha waveform to identify the phase that corresponded to the strongest pulse-elicited BOLD activation in the dorsal ACC (dACC). Patients were then randomized into two groups: synchronized (SYNC) or non-synchronized (UNSYNC). In the SYNC group, TMS pulses were phase-locked to the individual's EEG alpha rhythm based on the initial scan, while in the UNSYNC group, pulses were delivered randomly with respect to the EEG phase. All other TMS parameters were identical between groups. The primary outcomes were response and remission on the HDRS (>50% reduction from baseline and final score <10, respectively). Changes over time were evaluated using a two-way repeated measures ANOVA, controlling for gender, age, and depression episode length. Categorical outcomes were tested using chi-square tests.

Baseline HDRS scores averaged 30.4 (SD=5.2), indicating moderate severity. These scores decreased by approximately 15 points; however, exact post-treatment numbers were not provided. The ITT analysis included 28 participants (SYNC = 15, UNSYNC = 13) who received at least one rTMS treatment session. In the SYNC group, 2 participants (13%) achieved remission, 5 (33%) were classified as responders, and 8 (53%) were non-responders. In the UNSYNC group, 6 (46%) achieved remission, 1 (7%) was a responder, and 6 (46%) were non-responders. Similar results were observed after accounting for dropouts (SYNC: 3; UNSYNC: 1). The authors found no significant difference between groups in remission rate ($\chi^2 = 0.253$, $p = 0.6$) or other clinical outcomes, though both groups showed similar improvements in HDRS scores (statistics not reported). Of note, high phase precision and consistency in EEG synchronization were associated with better clinical response in the SYNC group ($p = 0.023$), suggesting that consistent EEG-TMS synchronization, otherwise known as EEG entrainment, might predict clinical improvement.

Impact: This randomized, double-blind clinical trial demonstrated the feasibility of EEG-synchronized rTMS and suggested a potential link between EEG entrainment and clinical improvement. However, synchronizing rTMS with EEG did not confer additional clinical benefits over the non-synchronized approach. In addition to a small size, a key limitation was the assumption that the preferred synchronization phase, identified during the initial MRI session, would remain constant throughout treatment. Future studies should explore adaptive synchronization protocols that periodically reassess and adjust the preferred phase to potentially enhance treatment efficacy. Larger trials with more diverse populations and treatment arms are also necessary to validate these findings and explore the full potential of EEG-synchronized TMS in clinical practice.

George, M. S., Huffman, S., Doose, J., Sun, X., Dancy, M., Faller, J., Li, X., Yuan, H., Goldman, R. I., Sajda, P., & Brown, T. R. (2023). EEG synchronized left prefrontal transcranial magnetic stimulation (TMS) for treatment resistant depression is feasible and produces an entrainment dependent clinical response: A randomized controlled double blind clinical trial. Brain stimulation, 16(6), 1753–1763. https://doi.org/10.1016/j.brs.2023.11.010

Discrepancies in Resting Motor Threshold Measurements Using Different TMS Coils

Mohamad Shamas, PhD, reviewing Wang et al. Brain Stimul 2024 Feb

This within-subject study assessed how different TMS coils impact resting motor threshold (rMT) measurements, revealing significant discrepancies that could influence treatment dosing accuracy.

TMS is routinely employed to assess cortical excitability, and repetitive stimulation can be therapeutic for a variety of conditions. Central to these processes are the motor evoked potential (MEP) and resting motor threshold (rMT). However, variations in these measures when using different TMS coils may affect precision in research and clinical settings. This study investigated whether standardized conversion factors could be established to account for these differences, improving dosing accuracy across different TMS protocols.

The study recruited 38 healthy participants, who were divided into three groups based on the TMS system used: MagStim, MagVenture, and a Crossover group using both systems. Neuronavigation was employed to ensure consistent coil placement, with motor hotspots identified via individual T1 MRIs co-registered to a template. The rMT was defined as the minimum stimulator output required to elicit an MEP of ≥50μV in at least 5 out of 10 stimulations at the motor hotspot. Three MagStim coils (Remote, Alpha, AirFilm) and 2 MagVenture coils (C-B60, Cool-B65) were tested in a pseudo-randomized order. Post-session rMT measurements using the initial coil ruled out any incidental neuromodulation effects. Paired t-tests with Bonferroni correction were used to compare rMTs between different coils, while linear regression models explored potential conversion factors using adjusted R^2.

Significant differences in rMT values were found between different coils. In the MagStim system, the AirFilm coil produced rMTs 8.0% higher than the Alpha coil ($p < 0.0001$, Cohen's $d = 0.70$) and 9.2% higher than the Remote coil ($p < 0.0001$, $d = 0.78$). The difference between the Remote and Alpha coils was not significant ($p = 0.16$, $d = 0.13$). In the MagVenture system, rMTs with the C-B60 coil were 1.5% lower than those with the Cool-B65 coil ($p = 0.031$, $d = 0.18$). Repeated rMT measurements with the initial coil showed no significant neuromodulatory effects. Regression analysis indicated a strong correlation between coils, with adjusted R^2 values of 84% for Remote vs. AirFilm, 82% for Alpha vs. AirFilm, and 91% for C-B60 vs. Cool-B65.

Impact: This within-subject study revealed that the type of coil used in TMS can significantly affect rMT measurements. This variability is important to consider, as the use of rMT values from assessment coils for treatment could result in underdosing, potentially compromising therapeutic efficacy. The study emphasizes the importance of thoroughly documenting coil type and stimulator settings in TMS protocols to enhance the consistency and reproducibility of results. Although the study's linear regression models provided a good fit (adjusted $R^2 > 0.8$), factors such as waveform type, current direction, and individual patient differences suggest that universal conversion factors may not be feasible. Further studies with larger, more diverse cohorts are necessary to refine these conversion factors to enhance the accuracy of TMS dosing in clinical practice.

[Reference to source article in AMA format] Wang Y, Vora I, Huynh BP, et al. Coils are not created equal: Effects on TMS thresholding. Brain Stimul. 2024;17(1):1-3. doi:10.1016/j.brs.2023.11.017

Low-Frequency rTMS: Impact on Suicidal Ideation and Mood in Depression

David Lee reviewing Zhan et al. J Affect Disord, 2024 May

This open-label clinical trial demonstrated that low-frequency rTMS applied to the right DLPFC can decrease suicidal ideation and improve mood in patients with TRD, while identifying risk factors for non-response.

Suicidal ideation (SI) is the third strongest predictor of death by suicide (after prior psychiatric hospitalization and suicide attempts) and is strongly correlated with MDD. While high-frequency rTMS targeting the left DLPFC is an established treatment for MDD, low-frequency rTMS to the right DLPFC (LFR) has shown promise due to evidence of efficacy, reduced discomfort, and increased accessibility, as a result. This study aimed to investigate the distinct trajectories of SI and mood symptoms in response to LFR and to identify risk factors associated with non-improvement in these domains.

Fifty-five patients with TRD were enrolled in this open-label study. Each patient received 20 sessions of LFR (1Hz rTMS, 1200 pulses, 120% MT to the right DLPFC) over four weeks. SI was measured using the Concise Health Risk Tracking Self-Rated Version (CHRT), while mood symptoms were measured using the Inventory of Depressive Symptomatology, clinician-rated version (IDS). The authors employed latent class mixed-effect models to classify the patients' independent trajectories of SI and mood into 'improvement' and 'no improvement' groups. They then applied logistic regression to identify the risk factors for 'no improvement.'

On average, CHRT scores decreased by 32.5% after treatment, while IDS scores decreased by 29.8%. Thirty-three of the 55 (60%) patients showed improvement in SI trajectories, and 29 (53%) showed improvement in mood trajectories. While 25 (45%) of the patients demonstrated concordant improvement in both suicidal ideation and mood symptoms, 12 (22%) demonstrated discordant trajectories, with improvement in one symptom domain but not the other. Key baseline risk factors for non-improvement in SI included male sex, higher baseline anxiety, and higher baseline SI, while non-improvement in mood was associated with benzodiazepine use and higher baseline anxiety.

Impact: This open-label clinical trial demonstrates the potential efficacy of LFR rTMS in reducing suicidal ideation and improving mood in patients with TRD. It also reveals the heterogeneous nature of patient responses, identifying specific baseline

characteristics that may predict worse outcomes. However, this study is limited by a small sample size and absence of a control group. Future research should address these limitations with larger, well-controlled trials. Additional areas of interest could include investigations into the causal relationships between baseline characteristics and treatment outcomes, with the goal of refining rTMS protocols for personalized patient care.

Zhan D, Gregory EC, Humaira A, et al. Trajectories of suicidal ideation during rTMS for treatment-resistant depression. J Affect Disord. 2024;360:108-113. doi:10.1016/j.jad.2024.05.109

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)