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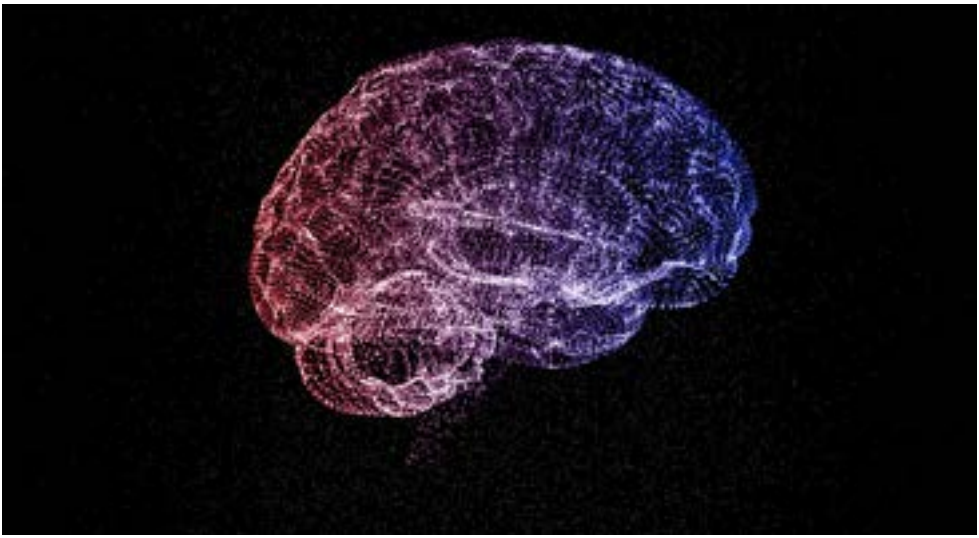
PULSE

A Monthly Update on Advances in Neuroscience



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Transcranial Direct Current Stimulation Failed to Separate from Sham in Patients with Depression

Nicole Wong Reviewing Loo et al. Brain Stimulation 2018 Jan

This international randomized controlled trial of 120 participants diagnosed with major depression found no difference between sham and transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is considered a promising treatment for major depressive disorder because of its reported efficacy, safety profile, and the potential for translation into home-based treatment. A 2016 meta-analysis of six RCTs enrolling 289 patients, mainly performed at single-centers, showed that tDCS had a small to moderate effect size in antidepressant effects relative to sham. This same meta-analysis as well as open label clinical trials suggested that tDCS may be effective for both unipolar and bipolar depression. Further, research suggests that patients with a single nucleotide

IN THIS ISSUE:

polymorphism (SNP) variation in the coding exon of brain derived neurotrophic factor (BDNF) may experience greater tDCS benefit. The present study sought to confirm prior work on the efficacy of tDCS in depression in an international, multicenter RCT, and to explore whether bipolar depression and/or BDNF genotype moderated antidepressant response to tDCS.

Using a two-arm, parallel, randomized, sham-controlled design, the researchers assigned participants to an active or sham tDCS in an initial four-week RCT phase. Leads for active and sham treatment were placed with anode over left DLPFC and cathode over right lateral frontal cortex. Active tDCS consisted of 30 minutes of 2.5 mA current, while sham stimulation consisted of an initial rapid ramp-up to 1 mA followed by a slow ramp-down to baseline over one minute and a second ramp up and down to 0.5 mA midway through the session. These relatively weak pulses were thought to mimic the scalp sensations produced in active tDCS without producing lasting changes in cortical excitability. Additionally, the tDCS device also emitted a constant current of 0.034 mA current throughout sham stimulation. Participants who did not meet remission at the end of the RCT phase were eligible to subsequently enter a four-week open label phase. tDCS was administered on consecutive weekdays for five days during both the RCT and open label phases. Participants who completed at least four weeks of the trial (either the RCT alone or the RCT followed by the open label phase) or were in remission were also eligible to enter a taper phase that consisted of four tDCS sessions delivered weekly. The primary outcome measure was change in the MADRS over the four-week RCT phase.

Of the 120 participants (52.5% female, ages 18-81 years), 84 had unipolar depression and 36 had bipolar depression. Although mood improved significantly over the four-week treatment period in both unipolar ($p = 0.001$) and bipolar groups ($p < 0.001$), the numbers of MADRS responders and remitters were modest in both groups. For the unipolar group, there was no difference in number of responders between the active (5/37, 14%) and sham (10/39, 26%) groups, though there were significantly more remitters in the sham (7/39, 18%) compared to active (1/37, 3%) groups. In the bipolar group, there was no difference in the number of responders (sham: 3/15, 20%; active: 3/18, 17%) or remitters (sham: 2/15, 13%; active: 1/18, 6%). Contrary to expectations, among participants with unipolar depression, there were more remitters in the sham group ($p = 0.03$), and there was no difference between active and sham stimulation in the bipolar sample. BDNF genotype was unrelated to treatment outcome.

Impact: Contrary to prior single-center RCTs, this international, multi-center RCT found no antidepressant difference between active and sham tDCS for unipolar or bipolar depression. Notably, the sham groups in this study had a particularly robust response. Further, BDNF genotype, previously hypothesized to moderate tDCS treatment response, did not moderate treatment response in this study. However, the researchers hypothesized that the low dose 0.034 mA current emitted during sham stimulation may have been biologically active, and additional work by the same group suggested that sham stimulation at 0.034 mA, previously considered inactive, may indeed alter neuronal function. Future studies should examine whether tDCS is truly no more effective than sham, or whether low current tDCS exhibits antidepressant effects comparable to traditional tDCS.

Loo CK, Husain MM, McDonald WM, et al. International randomized-controlled trial of transcranial Direct Current Stimulation in depression. Brain Stimul. 2018;11(1):125-133. doi:10.1016/j.brs.2017.10.011

Quantitative EEG Guided TMS May Improve Outcomes in Depression

David Lee reviewing Robertson and Mortimer Journal of Affective Disorders 2022 Jul

This open label, uncontrolled, naturalistic study suggests that quantitative EEG can help identify features guiding an individualized approach to TMS treatment for patients with major depressive disorder

Although TMS is an FDA-approved technique effective in managing depression, response rates have been limited to approximately one in three patients. This finding has prompted efforts to identify predictors of response, such as this study investigating 'bespoke' TMS therapy guided by quantitative electroencephalogram (qEEG).

The study included 210 patients with a baseline HAM-D of ≥15, with a mean HAM-D score of 21.5 corresponding to "severe" depression. Concurrent antidepressant and psychological interventions during the TMS therapy were continued or stopped based on shared decision making. EEG was obtained in eyes-open and eyes-closed conditions using a standard 10-20 configuration. Quantitative analysis of the whole-brain EEG was performed by incorporating the frequency graph, power maps, connectivity maps, and 3-D whole brain images, ultimately generating an EEG phenotype. TMS frequencies and target locations where then chosen based on the qEEG phenotypes and clinical information, though

notably the authors do not discuss how these choices were made or where the targets were. Patients were then treated daily, 5 days a week, with either rTMS (10 Hz with a total of 6,000 pulses per session, 30,000 pulses total) or theta burst (iTBS for 600 pulses followed by continuous TBS for 600 pulses, repeated about 8 times per session, for a total of roughly 50,000 pulses).

qEEG analyses revealed three distinct phenotypes: low alpha, excess beta, and excess theta. Following the treatment, the patients grossly reported a mean reduction in HAM-D score of 10.02 (95% CI: -12, -29) with no adverse effects. A 30% or greater improvement in HAM-D was noted in 158 patients (75%), and 98 patients (48%) reported a ≥50% response. In the 30% responder subgroup, the researchers observed dominance of excess beta or theta compared to the low alpha qEEG phenotypes. The researchers further noted that the 50% responder subgroup preferentially had received TBS over rTMS, with an odds ratio of 1.821 (95% CI: 1.019, 3.286, p = 0.044).

Impact: This open label, uncontrolled, naturalistic study showed that TMS therapy guided by qEEG may be effective at improving response rates in patients with severe depression. More than half of patients showed a ≥30% decrease in HAM-D scores while nearly half showed a ≥50% decrease. The results of this study are difficult to interpret, however, given the limited data which was reported on treatment allocation. More information is needed on the rationale for selection of the EEG measures used, as well as a comparison between these measures and previously reported EEG predictors of outcome including individual alpha frequency (IAF), coherence, spectral correlation coefficient (SCC), and other measures. Moving forward, large-scale controlled studies are needed to better determine the efficacy of this technique over conventional, non-qEEG guided TMS, and to better understand the relationship among distinct qEEG phenotypes.

Robertson C, Mortimer A. Quantitative EEG (qEEG) guided transcranial magnetic stimulation (TMS) treatment for depression and anxiety disorders: An open, observational cohort study of 210 patients. Journal of Affective Disorders. 2022 Jul 1;308:322-7. https://doi.org/10.1016/j.jad.2022.04.076

rTMS Proves Effective for Smoking Cessation in a Pivotal Multicenter Double-Blind RCT

Norman Spivak reviewing Zangen et al. World Psychiatry 2021 Oct

Daily rTMS of the bilateral lateral prefrontal and insular cortices with an H4 coil was effective at reducing tobacco craving and cigarette consumption in individuals with tobacco use disorder

Tobacco use disorder represents one of the most common substance use disorders, and cessation is difficult to achieve, with patients frequently making multiple unsuccessful attempts at quitting. This double blind RCT study aimed to show whether rTMS, which was shown in pilot studies to reduce cigarette craving, could be used to treat tobacco use disorder.

Researchers recruited 262 participants aged 22-70, with a smoking history of at least a half-pack per day for at least one year, and who were motivated to quit smoking. Subjects were randomized to receive either active or sham rTMS, delivered via an H4 coil which stimulated the bilateral lateral prefrontal cortex and insula. Each treatment session consisted of sixty three-second trains at a frequency of 10 Hz and intensity of 120% MT, for a total of 1800 pulses. Patients received a total of 18 sessions (5x per week for three weeks, then 1x per week for three more weeks). Prior to each treatment session, participants underwent a provocation procedure, where they imagined their smoking trigger and listened to an audio recording that asked them to handle a cigarette and lighter. The primary outcome was the four-week continuous quit rate (CQR) 18 weeks after study initiation in the ITT set, with urine cotinine verification of abstinence.

In the ITT set of participants (n=234), the CQR at week 18 was greater in the active group (19.4%) compared to the sham group (8.7%; χ^2=5.7, p=0.017). Among those who made it to study completion (n=169), the CQR at 18 weeks was greater in the active group (28.0%) compared to thesham group (11.7%; χ^2 = 7.219, p=0.007). Among those who did not quit, the active group was smoking on average 15 less cigarettes per week than the sham group by Week 6 of the study.

Impact: rTMS appears to be a safe and effective treatment modality for tobacco use disorder when administered in conjunction with cue provocation. It may be particularly useful for patients who are refractory to other smoking cessation approaches (e.g., bupropion, varenicline, or nicotine replacement therapy). It would be useful to determine whether cue exposure is a necessary component of effective treatment and examine the longer-term durability of benefit.

Zangen A, Moshe H, Martinez D, Barnea-Ygael N, Vapnik T, Bystritsky A, Duffy W, Toder D, Casuto L, Grosz ML, Nunes EV, Ward H, Tendler A, Feifel D, Morales O, Roth Y, Iosifescu DV, Winston J, Wirecki T, Stein A, Deutsch F, Li X, George MS. Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial. World Psychiatry. 2021 Oct;20(3):397-404. doi: 10.1002/wps.20905. PMID: 34505368; PMCID: PMC8429333.

A Review of Evidence Supporting "Preservation TMS" to Maintain Symptom Improvement in Depression

David M Carlson, MD reviewing Wilson et al. J Affect Disord 2022 Jan

This systematic review looks at "preservation TMS" treatments to help restore or maintain response after completing acute treatment, finding some evidence for safety and efficacy among widely varied protocols

Most studies of TMS in depression have focused on acute response, but durability and restoration of response has been less studied. This systematic review attempts to synthesize the literature to date on the safety and efficacy of maintenance or "preservation" TMS after an acute treatment series.

For this review, TMS treatments to sustain or restore acute response to treatment are called "preservation TMS." A systematic search of the TMS literature was performed using terms "maintenance," "continuation," "relapse prevention," or "rescue TMS." Exclusion criteria included papers that were commentaries, reported only outcomes from acute phase of treatment, described a case series of less than five patients, or reported no efficacy outcome.

The authors identified 30 qualifying studies, including 4 RCTs (one sham controlled), 14 open trials, and 12 case series, with a total of 1,494 participants. The majority of the studies examined maintenance TMS after an acute series of TMS (*n*=26), though two studies examined maintenance effects of TMS after ECT, one after a medication trial, and one after combined medications and TMS. Evidence quality was low but showed clear support of effectiveness and safety across a variety of protocols. There was a large degree of heterogeneity among the sampled studies, with protocols that varied in many important ways, including: when to deliver preservation TMS (fixed schedule vs. symptom-triggered); scheduling (daily sessions vs. periodic clusters of multi-treatment days); when to assess response (e.g., around treatment clusters or at fixed intervals); and the criteria for stopping the additional TMS sessions. Support for the efficacy of preservation TMS was predominantly found from open trials and case studies, with the authors identifying a high degree of potential bias in the studies reviewed.

Impact: This systematic review reported that a single acute TMS treatment course may be insufficient to yield durable benefit for some patients with depression, and found some support for safety and efficacy of preservation TMS. The conclusions available from this study are limited given the high degree of heterogeneity in the sample which precluded any quantitative findings. Though the number of studies seems to indicate a growing interest in this important aspect of depression treatment, the authors acknowledge that further systematic studies will be required to generate standard protocols and expert consensus guidelines, and to delineate whether an "acute, continuation, and maintenance" phase model is most valid for MDD.

Wilson S, Croarkin PE, Aaronson ST, Carpenter LL, Cochran M, Stultz DJ, Kozel FA. Systematic review of preservation TMS that includes continuation, maintenance, relapse-prevention and rescue TMS. J Affect Disord 2022 Jan 1;296:79-88. Epub 2021 Sep 17.

Abbrevations

DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
LIFUP (low intensity focused ultrasound pulsation)
TENS (transcutaneous electrical nerve stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tACS (transcranial alternating current stimulation)
tDCS (transcranial direct 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)

AUD (alcohol use disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BDI (Beck Depression Inventory)
HAM-D (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
PANSS (Positive and Negative Symptom Scale)
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)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)

DLPFC (dorsolateral prefrontal cortex)
M1 (primary motor cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)