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PULSE

A Monthly Update on Advances in Neuromodulation

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EFFICACY OF TMS WITH A SHORTER INTER-TRAIN INTERVAL

Katharine Marder, MD reviewing Carpenter L et al. Brain Stimulation 2021 Jan-Feb

This large registry study found that transcranial magnetic stimulation treatment protocols employing shorter inter-train intervals demonstrated similar efficacy to treatment protocols employing the standard 26 second inter-train interval (ITI) when used for treatment of depression. Employing a shorter ITI can reduce treatment duration from 37.5 minutes to as little as 19 minutes per treatment session.

The US Food and Drug Administration (FDA) approved the first transcranial magnetic stimulation (TMS) device (NeuroStar® Advanced Therapy) for the treatment of depression in 2008. The default protocol involved delivering 3,000 pulses of 10 Hz stimulation to the left dorsolateral prefrontal cortex at an intensity of 120% of the motor threshold. The 3,000 pulses were delivered in 75 trains of 40 pulses each (4 seconds per train) separated by an “inter-train interval” (ITI) of 26 seconds, for a total stimulation time of 37.5 minutes. The ITI reflects the “rest” time between stimulation trains.

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Shorter ITIs are associated with increased seizure risk, and it is generally recommended that the ITI is at least twice as long as the stimulation train (for 10 Hz depression treatment, the train is 4 seconds). In 2016, the FDA approved the "Dash" protocol for the NeuroStar device, employing an ITI from 11-25 seconds. Does a shorter ITI impact treatment efficacy?

Researchers retrospectively analyzed stimulation parameters and treatment outcomes of patients treated on a NeuroStar device and enrolled in the NeuroStar Clinical Outcomes Registry. Included patients were over the age of 18, had MDD as a primary diagnosis, had no psychiatric comorbidities other than anxiety disorders, had a baseline Patient Health Questionnaire-9 (PHQ-9) score of at least 10 prior to TMS treatment, had at least one follow-up PHQ-9 after starting TMS treatment, and received once daily left-sided TMS treatment. Each treatment session was classified as "Standard" (>3000 pulses, 10 Hz frequency, 4s train duration, 26 second ITI), "Dash" (>3000 pulses, 10 Hz frequency, 4s train duration, 11-25 second ITI), or "Other" (fewer than 3000 pulses per session, frequencies other than 10 Hz, etc.). Patients were categorized as "Standard" or "Dash" patients if >75% of their treatment sessions involved the respective protocol type. Ultimately, the Standard protocol intent-to-treat group included 613 patients. Of these, 464 patients were classified as "Completers," having completed at least 20 treatment sessions and having completed a PHQ-9 within 4 days of the final TMS treatment. Of these, 276 patients were classified as "Fully Adherent," having completed all sessions with the specified ITI. The Dash protocol intent-to-treat group included 1493 patients, of whom 1111 were "Completers" and 354 were "Fully Adherent."

At baseline, the Standard group demonstrated higher PHQ-9 scores across all 3 samples. The Standard group also had a higher average MT across all 3 samples. There were no other significant differences between the groups. The Dash group had an average ITI of 13.4 seconds across all sessions, indicating that many sessions were performed with an 11 second ITI. ANCOVA analysis in the intent-to-treat sample revealed that patients in the Dash group had slightly but significantly higher PHQ-9 scores than those in the Standard group at the end of treatment; this was largely attributable to the higher baseline PHQ-9 scores in the Standard group. There was no significant effect of treatment group in the "Completer" and "Fully Adherent" samples. Final Clinical Global Impression Severity (CGI-S) scale scores were slightly but significantly lower in the Dash group than the Standard group in all three samples. In the "Completer" group, response rates ranged from 75% to 86%, and remission rates ranged from 53 to 66%. There were no differences in remission rates and virtually no differences in response rates by treatment group.

Impact: This study found no meaningful difference in outcomes by treatment group, despite having a large sample size. This indicates that the Standard protocol (26 second ITI) is not superior to the Dash protocol (11-25 second ITI) and more generally suggests that ITI may be shortened without reducing efficacy of treatment. This indicates that TMS treatment length may be reduced by half with no significant change in outcome. This finding may expand capacity and increase patient access to TMS.

Carpenter L, Aaronson ST, Hutton TM, et al. Comparison of clinical outcomes with two Transcranial Magnetic Stimulation treatment protocols for major depressive disorder. Brain Stimulation. 2021. 14(1):173-180. https://doi.org/10.1016/j.brs.2020.12.003.

NEUROMODULATION FOR THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER

Michael K. Leuchter, MD reviewing Kan R et al. Translational Psychiatry 2020 May 28

In this review and meta-analysis, non-invasive brain stimulation (both rTMS and tDCS) demonstrated efficacy in the treatment of Post-Traumatic Stress Disorder. This study examined the relationship between protocols and effect sizes and suggests that excitatory treatment may be the most effective strategy.

Additional treatment strategies for Post-Traumatic Stress Disorder (PTSD) are urgently needed. Both repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS) are methods of noninvasive brain stimulation that have been studied for the treatment of PTSD. These types of stimulation have primarily been studied in small individual trials that employ heterogeneous parameters and demonstrate variable results. Are these neuromodulation strategies truly effective for PTSD, and how do treatment parameters influence outcomes?

Researchers performed a meta-analysis of randomized controlled trials completed between 2000-2020 examining the use of tDCS and rTMS for the treatment of PTSD. Twenty studies were included in this review. Nine studied treatment of veterans. Seven involved co-morbid major depressive disorder in all subjects. Five relied on the self-report PTSD checklist (PCL). Two studies examined effects of tDCS, while the remaining 18 studies employed rTMS.

Of the 20 included studies, 15 compared an active form of stimulation with a sham group, and 11 were able to be included in the meta-analysis. The tDCS studies were excluded from meta-analysis due to low number (2) and heterogeneous treatment protocols. A random effects model was used for meta-analysis.

rTMS was found to be effective for the treatment of PTSD symptoms with a large effect size (Hedges' g=-0.975). Initial analyses found no significant relationship between outcome and number of sessions, number of pulses, stimulation target, or stimulation frequencies. Post-hoc meta-analyses examining each protocol classification (excitatory, inhibitory, high frequency vs. low frequency, and rTMS as augmentation vs. monotherapy) were performed. Eight studies examining excitatory stimulation found a large effect size (Hedges' g=−1.161). Five studies examining inhibitory stimulation showed a modest benefit (Hedges' g=−0.680). Three trials compared excitatory and inhibitory stimulation, and found that both reduced symptoms, with no significant difference between the two types of stimulation. Seven studies examined rTMS as monotherapy compared to augmentation therapy, and found positive effects, with a moderate effect size (Hedges' g=−0.649) when used as monotherapy, and a large effect size (Hedges' g=−1.446) when used for augmentation. Four studies with sufficient follow-up data were analyzed for durability of treatment effect, and demonstrated continued benefit 2-4 weeks after the last treatment, with a large effect size (Hedges' g=−0.909). Though all stimulation types seemed effective, excitatory stimulation used as an augmentation strategy seemed the most promising.

Impact: Both rTMS and tDCS are promising treatment approaches in PTSD. This study demonstrates that multiple rTMS treatment approaches are effective in the treatment of PTSD. While this study does not definitively answer what approach is optimal, the findings suggest that high-frequency, excitatory rTMS used as augmentation may be the most effective approach.

Kan RLD, Zhang BBB, Zhang JJQ, Kranz GS. Non-invasive brain stimulation for posttraumatic stress disorder: a systematic review and meta-analysis. Transl Psychiatry. 2020;10(1):168. doi:10.1038/s41398-020-0851-5

RAPID AND ENDURING ANTIDEPRESSANT EFFECTS OF ACCELERATED TMS: A RANDOMIZED, CONTROLLED TRIAL

Collin Price, MD reviewing Kim SJ et al., 2021 Clin Psychopharmacol Neurosci 2021 Feb 28

In this randomized controlled trial, an accelerated, 3-day course of repetitive transcranial magnetic stimulation (rTMS) was superior to sham for treatment of major depressive disorder. Accelerated treatment performed as well as a traditional, once-daily, 3-week course of rTMS.

Standard repetitive transcranial magnetic stimulation (rTMS) treatment paradigms involve once-daily sessions administered 5 days per week for a total of 3-6 weeks. These paradigms are clearly effective, but pose a significant burden to patients, including disruption to daily routines, time off work, and costs associated with travel to and from treatment centers. Accelerated rTMS paradigms administer multiple treatment sessions per day, with the goal of reducing burden to patients and speeding time to recovery. These paradigms have demonstrated efficacy in previous work, but how do accelerated rTMS paradigms perform compared to conventional, once daily rTMS paradigms?

Researchers conducted a three-arm single-blind randomized sham-controlled trial (RCT) comparing an accelerated rTMS paradigm to a conventional paradigm. Fifty-four patients diagnosed only with major depressive disorder (MDD) according to DSM-IV criteria were randomized to one of three treatment arms: accelerated rTMS (n=22 randomized, 13 completed), conventional rTMS (n=22 randomized, 15 completed), or sham rTMS (n=10 randomized, 8 completed). Active rTMS sessions administered 3,000 pulses of 10 Hz stimulation to left dorsolateral prefrontal cortex (DLPFC) at an intensity of 110% of motor threshold. The accelerated rTMS group received five sessions per day for 3 days, while the conventional rTMS group received one session per day, five days per week, for three weeks. For the sham stimulation protocol, a stimulation sound was produced but no energy was transmitted through the coil. Sham participants received the same number and frequency of sessions as the accelerated rTMS group. Assessments were performed by blinded clinicians at baseline, after the end of each treatment arm (day 3 and week 3), and at week 6. Primary outcomes were change in Korean Quick Inventory of Depression Symptomatology self-report (KQIDS-SR) and clinician-report (KQIDS-C) scores. Secondary outcomes included the Clinical Global Impression Severity (CGI-S),

the Clinical Global Impression Improvement (CGI-I), and a side-effect rating scale (FIBSER).

By day 3, the accelerated rTMS and sham groups had completed the full course of treatment, with the accelerated rTMS group showing a non-significant trend toward greater symptom improvement on the KQIDS-SR compared to the sham group. At the end of week 3, after the conventional rTMS group completed a full course of treatment, symptom improvements in the accelerated rTMS group were maintained and had become statistically significant compared to sham. The conventional TMS group showed a trend toward improvement that did not separate statistically from either the accelerated or sham groups. At the end of week 6, both the accelerated and conventional TMS groups achieved significantly greater reductions in symptoms compared to sham, with essentially identical scores when compared to each other. The clinician rating scales, including KQIDS-C, CGI-S, and CGI-I scales showed similar trends to the self-report measure, though only the accelerated TMS vs. sham comparisons reached statistical significance. Side effect profiles were similar across groups; at some time points, active rTMS was associated with lower frequency of side effects compared to sham treatment.

Impact: The results reported here provide RCT-level support for the efficacy of accelerated rTMS in the treatment of MDD. The accelerated 3-day paradigm not only showed a rapid antidepressant effect separating from sham by week 3, but also an enduring effect at week 6 that was equivalent to the effects of a once-daily 3-week course. These findings should be replicated with a larger sample size and a longer course of conventional rTMS as a comparator, but the present study provides promising evidence to support the clinical use of accelerated rTMS paradigms.

Kim SJ, Son SJ, Jang M, et al. Rapid Symptom Improvement in Major Depressive Disorder Using Accelerated Repetitive Transcranial Magnetic Stimulation. Clin Psychopharmacol Neurosci. 2021;19(1):73-83. doi:10.9758/cpn.2021.19.1.73

FROM THE ARCHIVES: DURABILITY OF TRANSCRANIAL MAGNETIC STIMULATION RESPONSE

Michael K. Leuchter, MD reviewing Dunner DL et al. Journal of Clinical Psychiatry 2014 May 13

This naturalistic observational study was the first to examine the durability of response to TMS over the course of a full year. Dunner et al. found that most patients with treatment-resistant depression who responded to TMS maintained their response over the following 12 months, while non-responder patients often showed a partial response to TMS over the same time frame. These findings confirm that TMS has durable, clinically significant benefits.

Repetitive Transcranial Magnetic Stimulation (rTMS) is established as a safe and effective treatment for Major Depressive Disorder. However, completing daily treatments over several weeks can be expensive and inconvenient for many patients. A key question for many patients and clinicians is whether the effects of rTMS last long enough to justify the burdens of undergoing treatment. This naturalistic, observational cohort study attempts to provide an answer to the important question: how long do the benefits rTMS last?

Researchers performed a longitudinal naturalistic observational cohort study examining the durability of response to rTMS treatment over the course of 12 months. At 42 sites, a total of 257 participants with medication-resistant MDD without psychotic features underwent an initial course of the standard FDA-approved rTMS treatment protocol. Participants generally received 3000 pulses per session of left-sided 10 Hz stimulation at 120% resting motor threshold (RMT) stimulation. Some modification of protocol was allowable, most often increases in pulse number, reduction of intensity for tolerability, or addition of right-sided 1 Hz stimulation. Though it was not standard protocol for subjects to undergo additional rTMS treatments or medication changes during the 12 month follow up period, all subjects maintained access to usual clinician-directed treatment. Medication changes and additional rTMS sessions were tracked and utilized as covariates in analysis. Symptom burden was scored pre-treatment, immediately post-treatment, and at 3, 6, 9, and 12 months after completion of initial rTMS treatment. Instruments scored included the Clinician-Reported Clinical Global Impressions-Severity of Illness Scale (CGI-S), the Patient Health Questionnaire (PHQ-9), the Inventory of Depressive Symptoms (IDS-SR), and its derivative the Quick Inventory of Depressive Symptoms Self-Report (QIDS-SR). Outcomes examined were based on comparisons of pre-treatment baseline scores and post-treatment baseline scores to scores from 3, 6, 9, and 12 months after treatment. At the post-treatment baseline, participants were categorized based on IDS-SR scores as non-responders (77), partial responders

(59), responders (44), and remitters (76). Response and remission rates at each timepoint (relative to pre-treatment baseline) were also examined based on IDS-SR, CGI-S, and PHQ-9 scores.

At the post-treatment baseline (immediately after treatment completion), response rates were 62.3% (CGI-S), 46.5% (IDS-SR), and 61.5% (PHQ-9). Remission rates were 41.2% (CGI-S), 29.7% (IDS-SR), and 31.1% (PHQ-9). Response and remission rates based on CGI-S scores increased over time (to 67.7% and 45.1% respectively at 12 months). Response and remission rates based on IDS-SR scores and PHQ-9 scores non-significantly decreased over time (by IDS-SR scores: 44.1% response rate and 29.3% remission rate at 12 months; by PHQ-9 scores: 60.7% response rate and 37.0% remission rate at 12 months). Among patients who responded or remitted (according to IDS-SR score) with acute treatment, 62.5% continued to meet response criteria at all follow-up time points. Multi-level statistical modeling demonstrated general patterns of sustained improvement in responders and partial responders, continued modest improvement in non-responders, and mild worsening in remitters (but remaining within the range of remission). The best predictor of long-term response was robustness of response during the initial course of treatment. No other clinical features, demographic variables, or medication changes during or after treatment were associated with significant differences in long-term outcome. In total, 36.2% patients received at least 1 additional rTMS session during the 12 month follow-up period; patients who had d achieved response or remission during their initial treatment were more likely to receive additional rTMS. The mean number of additional rTMS treatment sessions during the follow-up period was 16.2. In terms of attrition, 20.2% (52) of subjects were lost to follow-up by month 12.

Impact: This pivotal study demonstrated that nearly two-thirds of patients who responded to rTMS maintained response 12 months later (with access to clinician-directed treatment and additional rTMS, if required). These results are consistent with previous studies of durability of rTMS effects over 3 and 6 month periods, but this is the first study to demonstrate durability over a 12 month period. This study also demonstrates that long-term rTMS outcomes compare favorably to outcomes of other interventions for treatment-resistant depression. It is not possible to conclude from this observational study whether maintenance rTMS might further improve longer term outcomes, but this topic warrants further study.

Dunner DL, Aaronson ST, Sackeim HA, et al. A Multisite, Naturalistic, Observational Study of Transcranial Magnetic Stimulation for Patients With Pharmacoresistant Major Depressive Disorder. J Clin Psychiatry. 2014;75(12):1394-1401. doi:10.4088/JCP.13m08977

TRANSCRANIAL DIRECT CURRENT STIMULATION FOR THE TREATMENT OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

Andrew K Corse, MD reviewing Valiengo et al. JAMA Psychiatry 2020 Feb

In this double-blind, placebo-controlled, randomized clinical trial, tDCS (transcranial direct current stimulation) effectively ameliorated negative symptoms in patients with schizophrenia.

Negative symptoms of schizophrenia are common, disabling, and do not respond well to existing treatment options. Stimulation over the left prefrontal cortex with repetitive transcranial magnetic stimulation (rTMS) has significant positive effects in several studies, but the cost and time burden of rTMS may be prohibitive for many patients. tDCS is another noninvasive neuromodulation treatment that is safe, portable, and affordable. Is tDCS effective in treating the negative symptoms of schizophrenia?

Researchers compared tDCS to sham in a double-blind randomized clinical trial including 100 patients with schizophrenia with prominent negative symptoms (at least 20 points on the negative symptom subscale of the Positive and Negative Syndrome Scale (PANSS)). Participants were on a stable medication regimen for 4 weeks before the study period. Participants had not received recent tDCS or rTMS treatment, had no unstable medical conditions or significant psychiatric comorbidities, and had no contraindication to tDCS such as metal implants in the head. 100 participants were randomized to active or sham tDCS, and received 10 treatment sessions (2 per day over 5 consecutive days) with either active or sham tDCS. The primary outcome measure was change in the score on the negative symptoms subscale of the PANSS 6 weeks post-treatment.

At the primary endpoint, active tDCS was superior to sham tDCS (PANSS score difference, 2.65; 95% CI, 1.51-3.79; NNT, 3.18; 95% CI, 2.12-6.99; p<0.001). Significantly more participants in the active group (n=20, 40%) compared to the sham group (n=2, 4%) demonstrated response (>20% improvement) at week 6 (p<0.001) and at week 12 (38% vs 4%, p<0.001). There were no adverse effects reported in the study.

Impact: 10 sessions of tDCS significantly improved negative symptoms in schizophrenia when compared to sham. Clinical improvement was maintained over 12 weeks. While further studies are needed, and should compare tDCS directly to antipsychotics, this study provides compelling evidence that tDCS is a safe, effective, and feasible adjunctive treatment for patients with schizophrenia with predominant negative symptoms.

Valiengo LDCL, Goerigk S, Gordon PC, et al. Efficacy and Safety of Transcranial Direct Current Stimulation for Treating Negative Symptoms in Schizophrenia: A Randomized Clinical Trial. JAMA Psychiatry. 2020 Feb 1;77(2):121-129. doi: 10.1001/jamapsychiatry.2019.3199.