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PULSE

A Monthly Update on Advances in Neuromodulation

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Pretreatment Pupillary Reactivity is Associated with rTMS Treatment Outcome for MDD

Harinee Maiyuran, MD, reviewing Citrenbaum et al. Journal of Affective Disorders 2023 Jul 10

This observational study of patients with MDD undergoing routine rTMS found that patients had 36.2% improvement in depressive symptoms on the IDS rating scale and that the level of improvement was significantly correlated with a pre-treatment pupillometry-based biomarker: constriction amplitude.

While rTMS is an effective treatment for MDD, efforts to reliably predict response have yielded limited results. To this point, heart rate variability (HRV) has been the most studied autonomic nervous system (ANS) biomarker, with lower heart rate pre-treatment variability being linked to greater benefit from rTMS for MDD or

IN THIS ISSUE:

PTSD. However, pupillary light reflex (PLR) is another ANS biomarker that is generally faster and easier to measure than HRV, as PLR uses a handheld device—a pupillometer—that measures the reactivity of the iris in response to light. Constriction Amplitude (CA) and Maximum Constriction Velocity (MCV) are lower in patients with MDD, as both measurements correspond to the constriction or peripheral nervous system phase. Interestingly, the PLR is also regulated by prefrontal cortex regions, including the DLPFC, through the lateral habenula, which then connects the limbic system to the autonomic nuclei of the brainstem. The PLR can be a gauge of alertness, salience processing, and emotional arousal, all of which can be dysregulated in depression. If other aspects of the ANS appear predictive of clinical response, can the PLR be of clinical utility as well?

Fifty-one patients with MDD, aged 18-75 (53% females, 47% males) and with moderately severe MDD—corresponding to an average baseline score of 44.6 on the Inventory of Depressive Symptomatology Self-Report 30-Item (IDS) and 18.1 on the PHQ9—were included in this observational study. Of the 51, 46 were on at least one pharmacologic treatment for MDD.Patients underwent 30 sessions of daily rTMS over six weeks with excitatory stimulation to the left DLPFC (either 3000 pulses of 10Hz or 1800 pulses of iTBS) and parameter adjustments during treatment based on either early non-response or non-tolerability (35 of 51 patients). Percent improvement in IDS was the primary outcome, and a response was defined as at least 50% improvement by session 30. Remission was indicated by a score of 13 or less on session 30. Pre-treatment PLR was measured using a Neuroptics PLR-200. Variables measured were initial diameter (D0), maximally constricted pupil diameter (D1), latency of constriction (LAT), constriction velocity (CV), maximum constriction velocity (MCV), normalized MCV (nMCV), time to 75% pupil re-dilation (T75), and Constriction Amplitude (CA). Note that CA = D0-D1 and nMCV = MCV/D0; these variablesquantify pupillary constriction's extent (CA) and rate (nMCV). T-tests were used to examine baseline depression severity, symptom improvement was examined via a paired t-test, and differences by gender and medications for responders and non-responders were examined via Chi-squared tests. Pearson correlations were used to measure the relationships between baseline pupillary variables and treatment outcomes.

Mean percent improvement on the IDS was 32.6%, with 15 participants meeting criteria for response and eight meeting the criteria for remission. No notable differences in demographics, clinical characteristics, or medication use were identified between those who did respond and those who did not. Additionally, pre-treatment CA and percent improvement in IDS at session 30 had a significant correlation, which was still significant after correcting for the false discovery rate ($R = 0.41$, $p = 0.003$, $q = 0.028$). MCV, CV, and nMCV were not statically significantly related to treatment outcome ($R = 0.26$, $p = 0.061$, $R = 0.25$, $p = 0.080$, $R = 0.20$, $p = 0.16$, respectively).

Impact: This study demonstrated a significant positive correlation between Constriction Amplitude and symptom improvement, with greater CA being associated with more significant improvement throughout treatment. PLR constriction is generally believed to depend solely on the parasympathetic nervous system and represents a window into the PNS for any individual. Notably, the correlation between improvement in MDD and nMCV did not reach statistical significance, though this may be due to the smaller sample size or heterogeneous treatment protocols. Continuing to examine other measures of pupillary function may yield additional prognostic markers for treatment. The ease of implementing PLR as a biomarker makes it appealing for clinical use should these findings be validated in a prospective controlled manner.

Citrenbaum C, Corlier J, Ngo D, et al. Pretreatment pupillary reactivity is associated with outcome of Repetitive Transcranial Magnetic Stimulation (rTMS) treatment of Major Depressive Disorder (MDD). J Affect Disord. 2023;339:412-417. doi:10.1016/j.jad.2023.07.008

Twice Daily Inpatient rTMS for Depression Associated with Shorter Hospitalization Duration than Once Daily Treatment

Lara Tang reviewing Barnes et al. Prog Neuropsychopharmacol Biol Psychiatry 2023 July 3

This retrospective naturalistic study at a private psychiatric hospital demonstrates that, while twice-daily rTMS treatment for MDD does not impact ultimate response or remission rates, it does shorten the duration of inpatient psychiatric hospitalization by roughly 40%.

While ECT is generally considered the gold-standard inpatient neuromodulation treatment for severe major depressive disorder (MDD), rTMS is a suitable option for patients who cannot tolerate or accommodate the repeated sessions of general anesthesia ECT requires. A course of rTMS treatment for MDD traditionally consists of once daily 20- to 30-minute sessions, five days per week, for four to six weeks. This study compared the effects of daily rTMS to twice daily rTMS on remission and response rates of depression as well as length of stay of psychiatric hospitalization.

This retrospective naturalistic study of a private inpatient psychiatric hospital in Australia included 209 participants (n=162 female, mean age 46.4 ± 15.5-16.2) voluntarily admitted with a psychiatric diagnosis of MDD (unspecified severity) between 2008 and 2018. Participants deemed clinically suitable for rTMS underwent either once or twice daily rTMS, based on shared decision-making with their treating psychiatrist while undergoing routine inpatient psychiatric care in addition to rTMS.

Each rTMS session consisted of 5625 pulses (125 trains of 45 pulses and a 15s ITI) of 10Hz stimulation delivered to the left DLPFC at 120% MT. Participants in the group receiving rTMS twice daily had a 2–6-hour inter-session interval. Notably, the total sessions for each participant varied, though most had at least 15. The study's primary outcome was the clinical remission rate as defined by the HDRS. However, HDRS clinical response rate, inpatient length of stay, dropout rate before 20 sessions, and HDRS score change over time were also examined. Statistical analyses included ANOVA and ANCOVA for examining HDRS scores, Mann-Whitney tests for length of stay comparison, and chi-square tests for differences in proportions of response, remission, and dropout rates.

There were no significant differences in remission or response rates between the once-daily and twice-daily groups (remission: daily=46% vs. twice=49%; response: 60% vs. 65%; all p>0.05). However, the median length of stay for participants in the twice-daily rTMS group was significantly shorter than in the once-daily rTMS group (10 days vs. 20 days, U=1178.5, r=0.78, p<.001). There was no significant difference in dropout rates or differences in effect size between groups from pre- to post-treatment. However, a numerically greater proportion of participants stopped treatment in the once-daily group (daily=34.65% vs. twice=24.77%, relative risk=1.27, p=0.11).

Impact: Although this study demonstrated that there might not be a significant difference in the final outcome between once or twice-daily rTMS, it provided substantial clinical evidence that twice-daily rTMS may significantly shorten inpatient length of stay for depression. If replicated in multiple other settings in a controlled manner, this could reshape the inpatient treatment of depression, leading to healthcare cost savings, increased accessibility, and more widespread adoption of rTMS as a routine treatment for depression.

Barnes R, Skvarc D, Fitzgerald PB, et al. Equal remission rates and reduced length of hospital stay with twice-daily repetitive transcranial magnetic stimulation (rTMS) for major depression - A large naturalistic retrospective cohort association study [published online ahead of print, 2023 Jul 3]. Prog Neuropsychopharmacol Biol Psychiatry. 2023;127:110820. doi:10.1016/j.pnpbp.2023.110820

DepressionDC: tDCS Appears Ineffective as Augmentation Treatment for Major Depressive Disorder

Miguel Serrano-Illan, MD, PhD, reviewing Burkhardt G et al. The Lancet 2023 August 12.

This randomized controlled trial of 160 participants, known as the DepressionDC trial, investigated the efficacy of tDCS as an adjunctive treatment to SSRIs in adults with MDD across multiple academic centers in Germany. This is the largest prospective trial of tDCS for depression to date, and it found no significant difference in improvement in depressive symptoms between active and sham tDCS.

Noninvasive brain stimulation techniques have rapidly become a valuable tool for combatting treatment-resistant MDD. Though much focus has been on rTMS, tDCS has also become a strategy of great interest, given its portability, tolerability, and cost-effectiveness. While smaller trials, individual patient-level data, and meta-analyses have all supported its efficacy, there has been little study on a large multisite scale. Therefore, when we test it on a larger scale in a controlled trial, is tDCS really as effective a treatment as previously thought?

160 participants aged 18-65 (mean age 40 ± 13.3-13.6, n=89 female, 97% white) with at least moderate severity MDD (mean current episode duration 12 months) that did not respond to at least one prior medication trial were randomized to receive 24 sessions of either active or sham tDCS over six weeks in addition to continuing routine their current antidepressant. Participants received 30 minutes of bifrontal 2mA stimulation in the active group and an imitation of the

ramp-up and ramp-down phases alone in the sham group. Treatment sessions were five days per week during the first four weeks and twice weekly during the final two. Clinical assessments (including the Beck Depression Inventory-II (BDI-II), MADRS, and multiple other rating scales) were collected at baseline, weekly during treatment, and at follow-up assessments three and six months after treatment. The primary outcome was change in MADRS score from baseline to the end of treatment, with clinical response and remission rates on the MADRS and score changes on other rating scales and other timeframes defined as secondary outcomes.

The MADRS showed no significant difference in improvement between the active and sham tDCS throughtout treatment (MADRS score change active= -8.2 ± 7.2, sham= -8.0 ± 9.3, p=0.85). Secondary outcomes (clinical response, remission rates, and score changes from baseline to week 6) indicated no differences between groups during treatment or the follow-up period. There was a significantly higher incidence of mild adverse events in the active group (n=50 vs. n=33, p=0.028), which included a mixture of headaches, sleep-related problems, localized treatment site reactions (e.g., burning sensation or skin irritation), restlessness, nausea, and self-injurious behavior. There were no significant differences In moderate or severe adverse events.

Impact: This large RCT raises questions about the utility of tDCS as an augmentation treatment for MDD, particularly alongside SSRIs. It also calls into question much of the recent meta-analytic work supporting tDCS. It emphasizes the need for more research to understand the specific neurobiological effects of tDCS better so that we may know for whom to recommend this treatment modality.

Burkhardt G, et al. Transcranial direct current stimulation as an additional treatment to selective serotonin reuptake inhibitors in adults with major depressive disorder in Germany (Depression DC): a triple-blind, randomized, sham-controlled, multicentre trial. The Lancet. 2023; Vol 402 August 12. doi:10.1016/S0140-6736(23)00640-

A Greater Number of Unsuccessful Treatments is Associated with Diminished Outcomes in rTMS for Late Life Depression

Michael K. Leuchter, MD, reviewing Wathra et al. The British Journal of Psychiatry 2023 May 10

This secondary data analysis of the FOUR-D examined the effect of the number of prior medication trials on remission rates in rTMS for late-life depression and found remission rates significantly dropped from 43.9% with one or no prior medication trials to as low as 24.6% in those with three or more prior medication trials, suggesting that using rTMS earlier in the course of treatment may lead to better outcomes.

As evidence supporting the use of rTMS in late-life depression (LLD) has grown, understanding mediating factors of response and remission has become increasingly important.Prior work has shown that a greater number of unsuccessful treatments in younger adults predicts poorer response to any future treatment, including additional pharmacotherapy, ECT, and rTMS.However, this has not been as well-studied in older adults, and the question remains: does a similar pattern of diminished response exist in rTMS for LLD?

This study is a secondary data analysis of the FOUR-D trial (see our October 2022 issue for a summary of the landmark trial), which examined LLD and found that a four-minute protocol of right-sided cTBS followed by left-sided iTBS is non-inferior to one of the gold standard 48-minute protocols of right-sided 1 Hz rTMS followed by 10Hz left-sided rTMS. Remission rates on the MADRS were 28% in both treatment groups, and there were no significant differences between groups in medication trial history. However, the initial study did not examine the impact of the number of previous medication trials on remission rates. This follow-up study examined MADRS remission rate as a function of the number of prior adequate medication trials as determined using the Antidepressant Treatment History Form (ATHF), resulting in three groups for comparison: ≤1 previous medication trial, 2 previous medication trials, and ≥3 previous medication trials. Remission rates were compared between groups using a combination of Chi-square tests and Fischer's Exact test. The proportions of participants treated with specific antidepressants or classes of antidepressants were compared in a similar fashion.

The investigators found that, in the aggregate sample, remission rates were higher in participants with ≤1 previous trial (43.9%) than in participants with two previous trials (26.5%) or ≥3 previous trials (24.6%; χ^2 =6.36, p=0.04). Results were similar, though not statistically significant when examining the subgroups of those who received a TBS-based protocol (Remission rate ≤1 trial= 45.5%, 2 trials= 30.8%, ≥3 trials=19.2%; χ^2 =4.61, p=0.10) and those who received a standard rhythmic protocol (Remission rate ≤1 trial=42.4%, 2 trials=21.7, ≥3 trials=29.0%; χ^2 =0.24, p = 0.24). No differences in specific antidepressants or classes of antidepressants were described.

Impact: This secondary analysis provides significant evidence from a large RCT suggesting that medication history does appear to impact treatment outcomes in rTMS for MDD in older adults, much like in younger adults. Though the analysis does not account for the confounder of the duration of the current episode, it suggests that rTMS should be considered in LLD sooner in the course of treatment to maximize the likelihood of a positive outcome.Though the authors suggest this interpretation, the alternative hypothesis of a confounder causing those who respond less well to medications also respond less well to rTMS is another possibility. Future work exploring this confounder and validating these findings in both prospective and naturalistic data would be of great interest to the field.

Wathra, R. A., Mulsant, B. H., Daskalakis, Z. J., Downar, J., McClintock, S. M., Nestor, S. M., Rajji, T. K., Trevizol, A. P., & Blumberger, D. M. (2023). Effect of prior pharmacotherapy on remission with sequential bilateral theta-burst versus standard bilateral repetitive transcranial magnetic stimulation in treatment-resistant late-life depression. The British Journal of Psychiatry, 1–3. https://doi.org/10.1192/bjp.2023.81

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)