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PULSE

A Monthly Update on Advances in Neuromodulation

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Cardiovascular Biomarkers May Predict Response to Accelerated Low Frequency rTMS in MDD

David Lee reviewing Sheen et al. J Affect Disord 2022 Dec

This single-arm, open-label feasibility study suggests that autonomic nervous system cardiovascular measures are correlated with the clinical outcome of a course of accelerated low-frequency rTMS administered to right DLPFC.

Much research seeks to establish reliable biomarkers to predict rTMS treatment outcomes. One emerging set of markers is derived from autonomic nervous system measures, particularly electrocardiography (ECG) indices that are easily, safely, and accurately measured in clinical settings. Patients with MDD typically exhibit increased resting heart rate (HR) and decreased heart rate variability (HRV); these findings have been attributed to decreased parasympathetic activity. DLPFC, the most common rTMS treatment target, has been thought to also modulate parasympathetic activity

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given its connections to the thalamic nuclei involved in the regulation of parasympathetic activity, and this consequently could impact HR and HRV. Prior work has reported decreased HR and increased HRV following high-frequency rTMS applied to the left DLPFC. The authors of this study set out to investigate whether these same effects on HR and HRV are present in an accelerated low-frequency rTMS protocol to the right DLPFC.

The authors recruited 19 patients (12 female, ages 28-61) with MDD on a stable medication regimen for at least four weeks prior to enrollment and without other major medical or psychiatric comorbidities. ECG data was acquired through an electrode from the EEG system placed on the left wrist. Each rTMS session consisted of five minutes of pre-stimulation baseline rest, 10 minutes of 1 Hz rTMS (600 pulses) at 120% RMT over right DLPFC, and five minutes of post-stimulation rest. ECG data were acquired during the five minute rest periods. Each patient received a course of eight hourly sessions a day for five consecutive days for a total of 40 sessions. Clinical outcome was assessed using the BDI-II at baseline, on the last treatment day, and one and four weeks after treatment.

The authors analyzed the change in HR at each minute of the 10 minute rTMS session using a linear mixed model. HR decreased from 75.68 at baseline to 73.01 and 73.48 at two and three minutes into rTMS sessions ($p = 0.032$ and 0.007, respectively), after which no statistically significant HR differences were noted. No HRV parameters were noted to be significantly different during treatment compared to baseline. The BDI-II score improved from the baseline of 35.5 to 22.9, 21.7, and 20.9 on the last treatment day, and one and four weeks after treatment, respectively. Negative correlations were observed between the BDI-II percent improvement and: 1) pre-treatment HR (slope= -1.9%/bpm R^2 =0.396,p=0.0039 uncorrected, p=0.0117 Bonferroni-corrected); 2) HR at 3 minutes into rTMS (slope= -1.6%/bpm R^2 =0.252, p=0.0283 uncorrected, p=0.0849 Bonferroni-corrected); and 3) HR reduction between baseline and 3 minutes into rTMS (slope= -4.5%/bpm R^2 =0.263, p=0.0397 uncorrected, p=0.1191 Bonferroni-corrected).

Impact: This pilot study supports the concept that biomarkers of autonomic nervous system function may be useful in predicting rTMS treatment outcomes in MDD, particularly the electrocardiographic markers of pre-treatment HR, HR during rTMS, and HR change from pre-treatment to during treatment. However, the small sample size and exploratory nature of the analysis is limiting, especially given the loss of significance seen in two key findings when appropriate statistical corrections are applied. Additionally, the study does not report the positive and negative predictive value of these biomarkers. Still, this preliminary work suggests future work examining these markers with a larger sample may provide guidance on development and clinical implementation of ECG-related biomarkers in rTMS.

Sheen JZ, Miron JP, Mansouri F, et al. Cardiovascular biomarkers of response to accelerated low frequency repetitive transcranial magnetic stimulation in major depression. J Affect Disord. 2022;318:167-174. doi:10.1016/j.jad.2022.08.105

rTMS May Be a Safe and Effective Treatment for Children and Adolescents with MDD

Nicole Wong reviewing Qiu et al. J Affect Disord 2023 Jan

A systematic review and preliminary meta-analysis found that children and adolescents with MDD significantly benefited from rTMS.

rTMS is an approved adjunctive therapy for adults with MDD, however its efficacy and safety in children and adolescents remains unclear. Some individual trials have failed to demonstrate superiority of active over sham stimulation. The authors sought to address questions regarding safety and efficacy in one of the first meta-analyses examining rTMS in the pediatric population.

The authors identified studies before December 1, 2021 that 1) had a control group or self-controlled designs, 2) studied children and adolescents of both sexes, aged ≤ 25, with a diagnosis of MDD based on DSM-V, and 3) evaluated the HAM-D or the Children's Depression Rating Scale – Revised (CDRS-R) pre- and post-rTMS. Exclusion criteria included studies written in a language other than English or studies that used different rTMS pulse sequences from conventional rTMS (e.g., TBS and low-field synchronized TMS). The Hedges *g* was computed as a marker of effect size for each study. The withdrawal rate with 95% confidence intervals was used to evaluate the safety of each study. Risk of study bias was assessed using the Newcastle-Ottawa Scale (NOS) across the domains of Selection, Comparability, and Exposure/Outcome.

The authors included 13 studies (with 240 MDD patients, ages 10-25, 62.9% female) in their systematic review, while the

meta-analysis only included six of the 13 articles due to samples overlapping across studies (final sample included 165 patients, 61.8% female). In the systematic review sample, 12 studied left DLPFC stimulation; one studied sequential bilateral prefrontal rTMS, and the authors had shown previously that efficacy was similar between their bilateral and unilateral protocols. All studies except one employing sequential bilateral used a frequency of 10 Hz. Eight of 13 studies used 30 sessions of stimulation at 120% RMT; the remaining studies used 10-20 sessions and stimulation intensity of 80-110% RMT. Treatment duration ranged from two to eight weeks, and in 12 of 13 studies patients continued on their antidepressant or mood-stabilizing medications during treatment. According to NOS ratings, the review included one high-quality study and 12 average-quality studies. In the meta-analytic sample, rTMS significantly reduced depression in children and adolescents (Hedges *g* 1.37; 95% CI: 0.85 - 1.90; $p<0.001$) with high heterogeneity (I^2 = 99.4%). In subsequent regression analyses, they found no significant association between rTMS efficacy and study characteristics including gender ratio, mean age, sample size, RMT, session number, and study quality. With respect to safety, the combined withdrawal rate was 4% (95% CI: 2% - 9%). There was no evidence of significant heterogeneity in withdrawal rate among trials (I^2 = 0%, p = 1.00). Adverse event rate was not obtained as some studies did not report exact numbers of certain side effects, though the authors reported pain (scalp, neck, and/or eye pain) as the most common event reported in 47 patients in three studies. Nausea and vomiting were reported in 13 patients from two studies; muscle twitching and aches were reported in 18 patients from two studies. Rare adverse effects included insomnia, panic attacks and suicidal ideation (6 patients from one study).

Impact: This preliminary meta-analysis evaluating the efficacy and safety of rTMS in children and adolescents demonstrates that rTMS can benefit youth with MDD without significant safety concerns or adverse effects. These results are encouraging in light of the fact that some individual studies of rTMS therapy in children and adolescents have failed to demonstrate superiority of active treatment. More randomized controlled studies with greater power are needed to validate this finding.

Qiu H, Liang K, Lu L, Gao Y, Li H, Hu X, Xing H, Huang X, Gong Q. Efficacy and safety of repetitive transcranial magnetic stimulation in children and adolescents with depression: A systematic review and preliminary meta-analysis. J Affect Disord. 2023 Jan 1;320:305-312. doi: 10.1016/j.jad.2022.09.060. Epub 2022 Sep 27. PMID: 36174786.

Meta-Analysis Finds DBS to be Effective in Treatment Resistant OCD

Harinee Maiyuran, MD reviewing Gadot R et al. J Neurol Neurosurg Psychiatry 2022 Sep

This meta-analysis of 34 studies found that DBS in patients with treatment resistant OCD led to full response in 66% of patients with a 47% reduction in Y-BOCS, while also reducing comorbid depressive symptoms.

Treatment of OCD typically involves pharmacotherapy and cognitive behavioral therapy, with the latter involving exposure and response prevention (ERP) specifically. However, at least 10% of OCD patients have treatment resistant OCD (TROCD) in which typical therapies fail to provide significant benefit. Neurosurgical approaches have been applied in this population, including ablative surgeries and DBS. This article reported a meta-analysis of multiple studies of DBS for TROCD.

The authors searched the Pubmed and EMBASE databases following PRISMA guidelines to find studies including “OCD”, “DBS”, and related terms. Studies were included if they recruited adult subjects with a diagnosis of OCD, used DBS as the primary intervention, measured improvement in OCD using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) as the primary outcome with treatment response defined as ≥35% reduction in the Y-BOCS score, and were published in English in peer-reviewed journals. Stimulation targets most commonly included the ventral capsule/ventral striatum and the nucleus accumbens. Depression and anxiety were measured using various scales, and the authors also noted any serious adverse events (SAEs) that were reported including seizures and suicidal behavior.

The search strategy yielded 3023 records from 1986-2021, with 34 studies (published from 2005-2021) selected for further analysis, including nine RCTs (n=97) and 25 non-RCTs (n=255). Included participants had an average age of 40.8 ± 10.8 years and severe OCD based on a mean Y-BOCS of 33.5 ± 3.6. The median follow-up period of included studies was 24 months. On average, participants had failed three first line medication trials, one

adjunct medication trial, and 20 hours of ERP with a trained professional. After excluding three studies in which individual Y-BOCS scores were not available pre- and post-operatively, the Y-BOCS mean difference at last follow-up across 345 patients was 14.28 (95% CI: 12.51-16.05). After further excluding three studies with insufficient precision estimates, the meta-analytical treatment effect was a 47% decrease in Y-BOCS with 66% of patients classified as full responders at last follow-up. To assess for significance, funnel plot analysis was completed, showing that 27 of the 28 studies had statistically significant treatment effects. On depression scales, 47% of subjects were classified as full responders and an additional 16% were considered partial responders (30-49% improvement). SAEs were notable, with 31% of patients experiencing at least one SAE, including hardware complications in 8% and a pooled infection rate of 4.4%. The authors report that risk of bias (RoB) was low in all the included RCTs with respect to selection, randomization, and missing outcomes, while two thirds of studies showed a moderate-high RoB due to confounding.

Impact: In this systematic review and meta-analysis of DBS for TROCD, the authors found a significant effect of DBS with two-thirds of patients responding and an overall 47% decrease in Y-BOCS scores after roughly 24 months of follow-up. Significant limitations of the DBS approach include a high rate of SAEs and the need for highly specialized centers to perform the procedure and care for patients after implantation. There remains some risk of bias in the available literature. Still, these suggest that DBS should be considered for the most severely affected patients with TROCD.

Gadot R, Najera R, Hirani S, et al. Efficacy of deep brain stimulation for treatment-resistant obsessive-compulsive disorder: systematic review and meta-analysis [published online ahead of print, 2022 Sep 20]. J Neurol Neurosurg Psychiatry. 2022;jnnp-2021-328738. doi:10.1136/jnnp-2021-328738

Responsive DBS to Bilateral Nucleus Accumbens Improved Loss-of-control Eating in Two Patients with Refractory Binge Eating Disorder

Tashalee R. Brown, MD, PhD reviewing Shivacharan et al. Nat Med 2022 Sept

In this case study of two patients with binge eating disorder and severe obesity, the authors used DBS to identify a biomarker of loss-of-control eating in the bilateral nucleus accumbens that was used to guide a responsive neurostimulation treatment of disordered eating. Both participants had improvement in self-control of food intake and weight loss at 6 months.

Binge eating disorder (BED) is the most common eating disorder, affecting up to 3% of US adults, and is defined as consumption of large amounts of food over a short period of time. Loss-of-control (LOC) eating is associated with BED and is described as a sense that one cannot stop eating and is thought to be related to loss of inhibitory control in response to cravings or appetite cues. Recent studies have identified potential biomarkers of activity in the nucleus accumbens in mice that correlate with reward anticipation and predict behavioral responses and outcomes, which the authors sought to extend to humans in this open-label study.

In a pilot study of DBS to treat refractory BED with LOC, two adult women ages 45 and 56 years with treatment refractory BED and severe obesity despite bariatric surgery were recruited using a staggered enrollment protocol where patients went through an implantation and recording phase (6 months) then a stimulation phase (12 months). Patients underwent stereotactic implantation of bilateral depth electrodes with four contacts each at 3.5-mm electrode spacing. Two contacts were positioned in the bilateral NAc with two more proximal contacts traversing the anterior limb of the internal capsule. Responsive deep brain stimulation (rDBS) was administered using the NeuroPace Responsive Neurostimulation (RNS) system which consists of two intracranial recording and stimulating electrodes and a neurostimulator implanted in the skull. The neurostimulator monitors electrical signals and can be triggered by detection of abnormal electrophysiological activity.

Activity was recorded from the ventral and dorsal NAc. Each patient was randomized in a single blind fashion to receive a week of active (5 mA) or sham (0.5 mA) rDBS unilaterally to test tolerability and optimize parameters. NAc electrophysiological activity was recorded during both behavioral tasks (i.e., in laboratory emotion provocation followed by presentation of high calorie buffet of preferred foods) and in real world settings (patient triggered LFP activity when they had a craving and were about to eat).

Left NAc recordings showed an increase in low-frequency (1-8 Hz) power immediately before LOC eating in both patients (patient 1: 2.4 ± 1.5 dB, n = 16 bites; patient 2: 5.6 ± 3.1 dB, n = 12 bites) compared to standard meals (patient 1: 0.6 ± 1.0 dB, n=15 bites; patient 2: 0.3 ± 0.9 dB, n=11 bites;

p < 0.05). Similar findings were observed in real world settings in bilateral NAc, where an increase in low-frequency power compared with baseline was identified in 74.4% of reported LOC eating event detections in patient 1 and 76.9% in patient 2. Based on these findings, the RNS was programmed to trigger stimulation upon detection of brief increases in low-frequency activity in the bilateral ventral NAc. Patients were then exposed to 10-12 months of bilateral NAc rDBS, with stimulation delivered at 125 Hz such that it would disrupt neural communication. Following the stimulation phase, both patients reported a subjective sense of increased self-regulation and control over food intake and reported decreased LOC eating events from baseline to six months post-stimulation (patient 1 = 80% decrease; patient 2 = 87% decrease). By the end of the six-month follow-up period, patient 2 no longer met criteria for BED (<4 binge eating events per month over the prior consecutive three months, or <1 day a week on average for 3 months). Moreover, six month outcomes showed a decrease in body weight and BMI for both patients (patient 1: −5.9kg [−4.5%] and −2.2 kg/m^2 respectively; patient 2: −8.2 kg [−5.8%] and −2.9 kg/m^2, respectively). No serious adverse events were reported.

Impact: In this pilot study of responsive DBS to treat refractory binge eating disorder, the authors identified changes in NAc low-frequency power signals that were associated with loss of control eating and used this to successfully guide rDBS treatment in two patients. Both patients showed decreased frequency of LOC eating events and exhibited weight loss during the 6 month follow up period. This study successfully demonstrated the feasibility and safety of the intervention, and the encouraging results will need to be replicated in larger sample sizes with adequate controls for confounding factors such as changes in lifestyle and diet or features of the study protocol itself.

Shivacharan, R.S., Rolle, C.E., Barbosa, D.A.N. et al. Pilot study of responsive nucleus accumbens deep brain stimulation for loss-of-control eating. Nat Med 28, 1791–1796 (2022). https://doi.org/10.1038/s41591-022-01941-w

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)