



## A Monthly Update on Advances in Neuromodulation



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### The Impact of ECT on a common causal circuit in depression

Harinee Maiyuran, MD, reviewing Argyelan M et al. *Molecular Psychiatry* 2023 Nov 20

**Building on findings in recent years of a neural network that is both involved in depression and linked to changes secondary to TMS and DBS, the authors of this study examined the same causal depression network (CDN) in ECT. They found brain volume changes in areas linked to the same CDN and correlated with clinical outcomes.**

Recent work has indicated the existence of a possible common causal network in which changes have been associated with improvement in treatment-resistant depression after both TMS and DBS. This network, which involves the subgenual cingulate cortex, DLPFC, vmPFC, inferior frontal cortex, frontal eye fields, and intraparietal sulcus, has been implicated in depression and other conditions, including multiple sclerosis and post-stroke depression.

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##### Glossary

The study of changes in this network during ECT has thus far been limited by insufficiently sensitive analytic methods. With a larger sample size and more sophisticated multivariate methods (specifically a principal component analysis [PCA]) applied to the electrical field and structural data, could there be a convergence towards a CDN? If so, how might it align with that of prior work?

This database study examined 386 participants (233 female) with a mean age of 54 recruited from 19 sites, all of whom received ECT for depression (mean  $12.5 \pm 5.4$  sessions of ECT). Volume changes were measured via MRI before and after ECT treatment and processed in a standardized manner with imaging software to eliminate bias in volumetric change estimates. Electric field (EF) software modeling was based on tissue conductivity and electrode placement. Electrode placement was in one of 3 locations: right unilateral (246), bitemporal (79), and mixed (61). Clinical assessment of depressive symptom burden was performed using the MADRS (mean baseline score of 25.5). Principal Component Analysis (PCA) was

used for the multivariate analysis, comparing the antidepressant-linked CDN changes between electrode placements for both the structural data and electric fields, with age and number of sessions as covariates.

Following completion of ECT, participants experienced an average 59% decrease in MADRS score. Most brain regions exhibited increased volume up to 6.7% following treatment, with greater increases in the BT (bitemporal) and MIX (right unilateral, then switch to bitemporal) groups. Both groups also had higher EF amplitudes. There was a strong relationship between volume change and average EF in all three groups (Right unilateral [RUL]  $r=0.39$ , BT  $r=0.56$ , MIX  $r=0.47$ , all  $p<0.001$ ). Moreover, volume change in regions similar to the prior CDN correlated with clinical outcome in all three groups. Of all the volumetric change components studied, only changes in this network correlated significantly with clinical improvement. The direct relationship between the volumetric impact of ECT in most brain regions (particularly those outside of this CDN) and the number of

ECT sessions indicates a likely dose-response relationship unrelated to clinical response.

**Impact:** This study sheds immense light on the relationship between ECT, electrical field, brain volume changes, and improvement of depressive symptoms. This study provides further evidence supporting a CDN that can be acted upon through neuromodulation and reliably alleviates symptoms. However, many questions remain regarding the impacts of electrical field strength, electrode placement, seizure patterns, and dose. Additionally, looking at the relationship between CDN-related volume changes and symptom improvement in a prospective manner would be invaluable. Regardless, it is notable that the same neural network involved with symptom management and clinical improvement with DBS and TMS is also seen in ECT.

Argyelan M, Deng ZD, Ousdal OT, et al. Electroconvulsive therapy-induced volumetric brain changes converge on a common causal circuit in depression. *Mol Psychiatry*. Published online November 20, 2023. doi:10.1038/s41380-023-02318-2

## Baseline Pupillary Reactivity as a Differential Biomarker for Early rTMS Efficacy in MDD

Lara Tang reviewing Citrenbaum et al. *Brain Stimulation*, 2023 Oct 18

**This cohort study of individuals with MDD who received an initial course of rTMS at either 10 Hz or intermittent theta burst stimulation (iTBS) provides evidence for the use of baseline pupillary light reflex (PLR) as a differential biomarker for identifying which rTMS protocol may have the most clinical efficacy for an individual patient. Normalized maximum constriction velocity (nMCV), a measure used to quantify PLR, was positively associated with improvement of MDD symptoms when a 10 Hz protocol was used and negatively associated with an iTBS protocol. Furthermore, among subjects with a reduced baseline PLR, as measured by a low nMCV, the iTBS group had a 2.6 times greater symptom improvement in the first ten sessions compared to the 10 Hz group.**

It has been well established that rTMS is highly effective in treating patients with MDD. Less clear, however, is whether certain mainstay protocols are more effective than others, with 10 Hz and iTBS delivered to left DLPFC

showing comparable efficacy for MDD symptoms. That said, there remains significant variability in clinical response, which has not yet been characterized. Changes to the autonomic nervous system appear to be one of the clearest physiologic

indicators impacted by MDD and treatment with TMS, with heart rate variability being the primary indicator studied to date. With PLR being a sensitive indicator of autonomic dysfunction, could it also be a reliable biomarker for

predicting if one stimulation protocol would elicit a more significant clinical improvement than another?

Fifty-two subjects diagnosed with MDD received ten sessions of rTMS administered to the left DLPFC, following either the 10 Hz or iTBS protocol ( $n=35$ ,  $n=17$ , respectively). Protocols were selected based on the treating physician's clinical judgment and patient preference. Most subjects were on concomitant psychotropic medication, while all subjects were naïve to TMS treatment before the first session. PLR, characterized by pupil constriction amplitude (CA) and maximum constriction velocity (MCV and its normalized/corrected form of nMCV), was recorded for each subject before their first session. The study's primary outcome was the percent improvement in clinical symptoms of MDD from session 1 to session 10 as measured by the Inventory of Depressive Symptoms Self-Report 30-item (IDS-SR). Symptom improvement was analyzed using paired t-tests of

IDS-SR scores from session one to session ten. A two-way ANOVA test assessed the interaction between rTMS protocol and PLR parameters (nMCV and CA), with the percentage of clinical improvement as the dependent variable. Unpaired t-tests were used to identify whether having a high or low nMCV at baseline was associated with greater clinical improvements in either protocol.

Overall, subjects showed significant improvements of 20-25% in IDS-SR scores from session one to session ten with no significant difference between protocol groups. Within the 10 Hz group, pre-treatment nMCV and CA were positively associated with clinical improvement (nMCV  $r=0.48$ ,  $p=0.004$ ; CA  $r=0.44$ ,  $p=0.008$ ). Meanwhile, within the iTBS group, pre-treatment nMCV was negatively associated with clinical improvement ( $r=-0.52$ ,  $p=0.03$ ). Analyses revealed a significant association between pre-treatment nMCV and rTMS protocol, indicating differential outcomes

based on this interaction ( $F=12.0$ ,  $p=0.001$ ). Subjects were stratified into low or high nMCV statistical groups, split across the median. On average, those with a low baseline nMCV who received iTBS had a 2.6 times greater improvement in IDS-SR scores than those with a low baseline nMCV who received 10 Hz stimulation ( $p=0.01$ ).

**Impact:** Prior studies suggest that indicators of autonomic nervous system function, such as heart rate variability, help guide rTMS treatment. This is the first study investigating the utility of pupillary light reflex as a biomarker in differentiating the clinical efficacy of two rTMS protocols in MDD. This study's findings are significant, as they establish PLR as a potential non-invasive and cost-effective tool for clinical decision-making with rTMS protocols in MDD.

Citrenbaum C, Corlier J, Ngo D, et al. Pretreatment pupillary reactivity is associated with differential early response to 10 Hz and intermittent theta-burst repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder (MDD). *Brain Stimulation*. 2023;16(6):1566-1571. Doi: [10.1016/j.brs.2023.10.006](https://doi.org/10.1016/j.brs.2023.10.006)

## Low-Frequency Right DLPFC rTMS does not Impact Functional Connectivity Marker Examined for Left-sided Treatment in MDD.

Miguel Serrano-Illán, MD, PhD, reviewing Tan V, et al. *Brain Stimul*. 2023 Aug 3

**This observational study investigated the effects of low-frequency right dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation on functional connectivity with the subgenual anterior cingulate cortex (sgACC), a biomarker of interest in recent years in rTMS for TRD. Though functional connectivity changes between sgACC and parietal and ventral attention networks occurred, there was no significant association between connectivity changes and clinical outcomes. This suggests a low-frequency right DLPFC rTMS may utilize a different mechanism of action compared to high-frequency left DLPFC rTMS.**

In rTMS for MDD, two of the most widely used stimulation protocols are low-frequency (typically 1Hz) right DLPFC stimulation and high-frequency (typically 10Hz) left DLPFC stimulation. A proposed mechanism of rTMS's antidepressant effects is the modulation of connectivity between specific regions of the DLPFC and subgenual anterior cingulate cortex (sgACC). This hypothesis was partly developed based on observations resulting from left

DLPFC stimulation. However, it has not been examined in the context of low-frequency rTMS administered to the right DLPFC. This study explored how low-frequency right DLPFC rTMS affects sgACC-DLPFC connectivity and whether this can predict treatment outcomes using concurrent TMS-fMRI and personalized e-field simulations.

Thirty-four subjects with TRD underwent a resting-state fMRI

(rs-fMRI) and concurrent TMS-fMRI session followed by four weeks of daily treatment with 1800 pulses of 1Hz stimulation at 120% MT delivered to the right DLPFC using structural neuronavigation. Baseline DLPFC-sgACC connectivity and its response to TMS were assessed based on rs-fMRI and TMS-fMRI data. These data were also used to generate a map for electric-field modeling. The mean age of 34 subjects was 41.44

$\pm 16.18$ , with 26 females and 23 Caucasian subjects vs eight who self-classified as "other" in terms of race. Clinical assessment with the MADRS was performed before and after treatment; the baseline mean MADRS was  $29.59 \pm 6.93$ , suggesting severe TRD. Though the primary and secondary outcomes were not clearly stated, this study grounded most analyses in MADRS score improvement. Two pairs of hierarchical linear regressions were performed: one based on assessing the correlation between the degree of DLPFC-sgACC connectivity (both resting state and TMS-fMRI) in the e-field region and MADRS improvement, and the other assessing MADRS

correlation with functional connectivity changes (both resting state and TMS-fMRI) between sgACC and a specific sub-region near the stimulated DLPFC region.

The authors found that low-frequency right DLPFC rTMS both improved depressive symptom burden (mean post-treatment MADRS score  $18.27 \pm 9.53$ ; approximately 38% improvement) and increased left sgACC functional connectivity to parietal regions within the ventral attention network, but this increased connectivity did not correlate with clinical improvement using either hierarchical approach. However, other covariates, such as motion

during fMRI and baseline MADRS, were significantly predictive of depression outcomes for rTMS in all models.

**Impact:** This study showed that, while low-frequency right DLPFC rTMS alters left sgACC connectivity, it does so differently (and in relation to different areas) than observed for high-frequency left DLPFC rTMS. These results provide valuable insights into possible alternate pathways mediating rTMS's effects in depression and warrant further prospective study.

Tan V, Jayachandra J, Ge R, et al. Subgenual cingulate connectivity as a treatment predictor during low-frequency right dorsolateral prefrontal rTMS: A concurrent TMS-fMRI study. *Brain Stimulation*. 2023;16(4):1165-1172. doi:10.1016/j.brs.2023.07.051

## Additional rTMS Sessions in Depression Treatment Course are Associated with Better Outcomes

Michael K. Leuchter, MD, reviewing Hutton et al. *Brain Stimul*. 2023 11 Oct

***This naturalistic observational study of the NeuroStar® database reports outcomes in a sample of over 7000 patients and, in particular, examines differences in outcomes based on the total number of sessions in an individual's treatment course. The authors found that those who received fewer than 30 sessions in their treatment course exhibited poorer outcomes than those who received 30 or 36, and that those with more than 36 sessions demonstrated ongoing significant steady improvement with no evidence of a plateau effect.***

As is the case for most therapeutics, the "real-world" implementation of rTMS for depression looks quite different compared to clinical trials. One of the more notable differences is the higher rates of response and remission in clinical practice; response can be as high as 60% and remission as high as 30%. We also see variability in the length of courses of TMS in clinical practice; insurance companies will generally cover 36 sessions, but many patients will have greater or fewer than the standard 36. Naturally, there is variability in the stimulation protocol used (e.g., 10Hz, iTBS, 1Hz). With such heterogeneity in clinical practice, it can be difficult to discern the impact of these myriad parameters. The authors of this study seek to leverage the large naturalistic NeuroStar® outcomes

registry to determine the effect of treatment course length on treatment outcomes.

The authors extracted data for 7,215 patients over the age of 18 with MDD from their registry of 13,732 patients (mean age  $46.6 \pm 16.1$ , 64.0% female) spread over 110 sites. Clinical assessments were performed using the PHQ-9 and CGI-Severity (CGI-S) scales at fixed intervals (pre-treatment and sessions 10, 20, 30, 36, and post-treatment). Though the mean number of treatment sessions was 33, patients were divided into six groups based on how many sessions they received in their course: 1-19 sessions, 20-29 sessions, 30-35 sessions, 36 sessions, 37-41 sessions, and >41 sessions. The PHQ-9 score was the primary outcome, with

response/remission rates and CGI-S as secondary outcomes. There were notable differences in treatment protocols between groups (e.g. those with prolonged courses were more likely to receive sequential bilateral treatment). The analysis consisted of six different components to compare outcomes between the groups and account for alternate explanations of observed differences.

The initial analysis with one-way ANOVA revealed the presence of between-group differences, and subsequent analysis found that those who received fewer than 30 sessions had less reduction in post-treatment PHQ-9 scores ( $F=84.81$ ,  $p<0.001$ ) and lower response (1-19=26.4%, 20-29=47.6%, 30-35 and 36 both

>60%;  $p < 0.001$ ) and remission (1-19=8.5%, 20-29=20.6%, 30-35 and 36 both >30%;  $p < 0.001$ ) rates. Over the course of treatment, all groups except those who received more than 36 sessions improved at the same rate based on mixed effects models ( $F=465.04$ ,  $< 0.0001$ ); those with >36 sessions (37-41 and >41) improved significantly more slowly. However, the entire time they continued

treatment, they continued to improve. It was also noted that during the first ten sessions, those in the 36-session group averaged a 3.0% improvement in score per session (30% at session ten), which slowed to roughly 1.0% per session over time thereafter. By the end of treatment, those with prolonged courses achieved similar levels of improvement as those with standard courses.

**Impact:** This naturalistic study provides valuable outcomes data to guide clinicians, and demonstrates the potential impact of continuing TMS when treatment goals have not yet been reached. This encouraging finding warrants further study in a prospective manner using additional rating instruments, and if replicated, could significantly impact clinical practice.

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Hutton TM, Aaronson ST, Carpenter LL, et al. Dosing transcranial magnetic stimulation in major depressive disorder: Relations between number of treatment sessions and effectiveness in a large patient registry. *Brain Stimulation*. 2023;16(5):1510-1521. doi:[10.1016/j.brs.2023.10.001](https://doi.org/10.1016/j.brs.2023.10.001)

*ctBS (continuous theta burst stimulation)*  
*DBS (deep brain stimulation)*  
*dtTMS (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)*

