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PULSE

A Monthly Update on Advances in Neuromodulation

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Long-Term Gray Matter Volume Decreases Associated with Electroconvulsive Therapy for Major Depressive Disorder

Harinee Maiyuran, MD, reviewing Borgers et al. Psychological Medicine 2023 Aug 17

This longitudinal cohort study of inpatients with depression found that gray matter volume increases secondary to ECT were transient, with volume decreasing years after ECT as compared to healthy controls and inpatients who did not receive ECT. These volume changes were associated with worse depression outcomes. Specifically, those with greater transient volume increase during treatment and longer-term volume loss were more likely to be depressed after 2 years.

Treatment-resistant MDD is often managed with neuromodulation treatments, including ECT, which is particularly effective for treating

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psychotic depression. As neuroimaging has become more advanced, questions about the neuroanatomical changes that accompany neuromodulation treatments have fueled studies to explore the treatments' effects on brain structures. Short-term studies of this topic have generally shown significant gray matter volume (GMV) increases during and shortly after treatment. However, these changes have not been conclusively associated with clinical outcomes or side effects. Longer-term studies have been limited in follow-up period duration (maximum 6 months) and sample size (maximum n=23 ECT patients). Though limited, this work shows transient post-ECT increases in volume and cortical thickness in the amygdala, frontal and insular cortex, and hippocampus that generally return to pre-ECT baseline within 6 months. Therefore, the authors of the study designed a longitudinal naturalistic cohort study examining inpatients with MDD who received ECT and compared them to inpatients with MDD who did not receive ECT and healthy controls.

This study of 71 participants included 21 healthy controls (HC) and 50 inpatients with MDD diagnosed via DSM-IV criteria (without other major psychiatric or neurologic comorbidity), 17 of whom received ECT and 33 of whom received treatment as usual (TAU – medication and therapy). ECT consisted of 9-12 sessions of a right unilateral protocol with further sessions depending on symptom relief, though 2 patients with insufficient response to right unilateral were transitioned to bilateral (bitemporal) stimulation.

Three time points were defined– pre-ECT/baseline (t0), after completion of ECT (t1; an equivalent time point was used for HC and TAU groups), and 2 years after baseline (t2). Structural MRIs, Beck Depression Inventory (BDI), HDRS, and a Structured Clinical Interview for the DSM-IV were performed at all time points. Medication regimens were quantified and scored in a structured manner. Those who received ECT were "treatment-resistant," with failed trials of at least 2 full antidepressant trials. Statistical analysis consisted of a series of ANOVAs examining the effects of group (TAU, HC, or ECT) and time on GMV in regions of interest while accounting for age, sex, medication load, baseline depression severity, and total brain volume as covariates.

Both the ECT and TAU groups had a significant decrease in HDRS and BDI scores. 58.8% responded to ECT (response as ≥50% decrease in HDRS score from baseline to t1), as did 48.5% to TAU. Examining GMV, there was a significant effect of group over time, with the ECT group demonstrating significant increases from t0 to t1 and significant decreases from t1 to t2. These short-term increases in GMV occurred in the hippocampus and amygdala and were linked to both immediate and delayed increases in depressive symptoms, and decreases in GMV at t2 were correlated with increases in BDI. There were no associations between GMV and changes in suicidality. Lower GMV at t2 was linked to worse outcomes in those who received ECT. In contrast, those who did not receive ECT (TAU and HC) had no notable GMV increases in the short term or decreases in GMV in the long term. Minor decreases in GMV not associated with a specific group were observed in TAU and HC from t1 to t2 when more lenient definitions of volume decrease were applied to imaging analysis.

Impact: This study provides further evidence that while ECT can induce GMV increases, these increases are transient. It also demonstrates the novel finding that GMV decreases over the course of 2 years after ECT. These volume changes are associated with worse depression rating scale outcomes immediately following ECT and longer-term. Th study is the first to examine ECT-related changes over such a time scale, and while this is a great strength, it is not without limitations. The small sample size of this study and its naturalistic, uncontrolled nature make these findings preliminary. Additionally, while there appears to be a statistical association with clinical outcome, the clinical significance is unclear, as is any association between GMV and side effects. This fi ing is certainly hypothesis-generating and warrants further study, as it may provide valuable insight into mechanisms of ECT and depression.

Borgers T, Enneking V, Klug M, et al. Long-term effects of electroconvulsive therapy on brain structure in major depression. Psychological Medicine. 2023:1-11. Doi:10.1017/S0033291723002647

Cognitive Impairment in Late Onset Depression Improved with rTMS

Frederick Burton III, MD reviewing Pan WG, Hu XY, Zhu DD, et al. Front Psychiatry. 2023 Aug 8

This randomized controlled trial of rTMS for late-onset depression examined cognition as measured by the repeatable battery for the assessment of neuropsychological status (RBANS) after completion of a 4-week course of rTMS, finding that those who received active treatment exhibited greater improvement in attention and immediate memory compared to the sham group.

Cognitive impairment is a significant issue that often complicates late-onset depression (LOD). The presence of impaired cognitive function is associated with decreased responsiveness to antidepressants. Additionally, some previous studies have suggested diminished responsiveness to rTMS in older patients, though others have observed the opposite trend. To date, no studies have been designed to primarily examine the response of cognitive impairment to rTMS in those with LOD. If we closely examine cognition in LOD, is there a significant impact of rTMS, and what does it look like?

This randomized controlled trial enrolled 58 participants over age 60 with LOD and cognitive impairment by mini mental status exam (MMSE) score (without other major neurologic or psychiatric comorbidity) in Beijing, China. Participants were randomly assigned to 4 weeks of active or sham (using an angled placement of the coil to keep the coil upright and deliver ineffective treatment) daily rTMS using 10Hz stimulation delivered in 40 pulse trains with a 56s ITI at 120% MT to the left DLPFC. After the treatment course, there was a four-week follow-up period. Assessments were administered at baseline, four weeks, and eight weeks (after follow-up). These consisted of the HAMD and a cognitive assessment, the repeatable battery for the assessment of neuropsychological status (RBANS). The RBANS tests five cognitive domains: attention, language, delayed memory, immediate memory, and visual-spatial ability. Scores range from 90 to 109, with lower scores indicative of worse cognitive function, and this was conducted 24 to 48 hours after rTMS sessions. Between-group differences over time were assessed using a series of repeated-measure ANOVAs.

Of the 58 participants initially enrolled, 51 were randomized, with 26 randomized to the active rTMS treatment (mean age 66.2 ± 4.0, 11 male, 15 female, baseline HAMD 31.2 ± 1.3) and 25 to sham (mean age 66.1 ± 4.3, 9 male, 16 female, baseline HAMD 30.1 ± 1.4). At the end of the four-week treatment phase, statistically significant inter-group differences were observed in immediate memory (active=89.7 ± 2.5, sham=81.7 ± 2.7, F=4.6, p=0.038). After the four-week follow-up period, inter-group differences were observed in both attention (active=97.3 ± 0.9, sham=93.7 ± 1.0, F=7.3, p=0.011) and immediate memory (active=95.7 ± 2.5, sham=87.6 ± 2.8, F=4.7, p=0.037). There were no significant improvements in either group related to visual-spatial function, language function, or delayed memory after treatment or follow-up phases. No significant adverse events were noted in either group. Depression outcomes were not discussed in detail.

Impact: This purpose-built study examining rTMS for cognition in LOD observed positive findings in attention and immediate memory domains. This, with the increasing evidence that rTMS is as effective for late-life depression as earlier-in-life MDD, suggests rTMS may have a unique role in the treatment of LOD. However, confirming these findings on a larger scale and with finer resolution through more timepoints would be useful for characterizing treatment response and validating these findings.

Pan WG, Hu XY, Zhu DD, et al. The cognitive effects of adjunctive repetitive transcranial magnetic stimulation for late-onset depression: a randomized controlled trial with 4 week follow-up. Front Psychiatry. 2023;14:1240261. Published 2023 Aug 8. Doi:10.3389/fpsyt.2023.1240261

Accelerated Protocols with Broad-Coil rTMS with H1 Demonstrate Effectiveness for TRD

Michael K. Leuchter, MD, reviewing Roth et al. Psychiatry Research 12 Sept 2023

This naturalistic cohort study of patients undergoing a range of accelerated rTMS protocols using the broad H1 coil found that patients undergoing these protocols experienced equivalent benefit, regardless of the number of treatment sessions per day. These outcomes were not only observed to be similar to prior trials using the same coil, but also to accelerated protocols using other coils. Additionally, durability was observed to potentially last for at least six months in those who completed followup.

As rTMS for MDD has continued to expand and undergo optimization, two parameters of recent interest have been the number of sessions per day and the necessary level of focality. Experiments with the number of sessions per day have led to the development of accelerated protocols. Meanwhile, experiments with focality and coil size have involved everything from functional imaging guiding millimeter precision and accuracy to the use of broad H and double-cone coils activating larger swaths of the cortex. While accelerated, more focal protocols have been demonstrated to work (most notably the SNT protocol), accelerated protocols involving the H-coil or other broader and deeper coils have not been systematically studied. If we examine the naturalistic data available for the H-coil, how efficacious does it appear?

This naturalistic cohort study examines 145 individuals (mean age 38.9 ± 16.8, 54.7% female, 77.9% severe depression based on at least one scale) with TRD (mean 5.2 ± 3.5 failed medication

trials) undergoing a range of accelerated rTMS treatment protocols with a Brainsway H1-coil. Stimulation was generally delivered as 1800 pulses of iTBS at 80-90% MT. A small minority of patients received 600 pulses of iTBS or standard 18Hz Deep TMS (12% combined). Protocols were divided into four categories: 2 times daily (48 patients, mean 29 treatment days), 3 times daily (8 patients, mean 8 treatment days), 5 times daily (21 patients, mean 6-7 treatment days), and 10 times daily (34 patients, mean 5 treatment days, consecutive). Clinical assessments consisted of the HDRS, BDI-II, MADRS, and PHQ9, which were measured at least at the beginning and end of treatment, with unspecified variability in collection during the study. The primary outcomes were response and remission rates 1 month after treatment (based on whichever scale a patient completed the most). This was followed by a subgroup analysis examining differences between groups based on the number of sessions per day. Response durability up to 6 months after treatment and median sessions and treatment days until response and remission were secondary outcomes.

The overall response rate of the sample was 80.2%, and the remission rate was 50.5%; this is in line with once-daily treatment using a H-coil. No significant between-group differences in response (2x/day=89.6%, 3x/day=75.0%, 5x/day=81.0%, 10x/day=67.6%, p=0.103) or remission (2x/day=56.3%, 3x/day=62.5%, 5x/day=52.4%, 10x/day=38.2%, p=0.366) at one month after treatment were detected. The median number of treatment sessions to reach both response and remission was 28, with the median number of treatment days of response or remission for 3x/day, 5x/day, and 10x/day falling in the 3-5 range. Only 2x/day had a longer median number of days of response (17) or remission (26). In terms of durability, 86.7% of responders (26/30 with data to that timepoint) demonstrated durability at 60 days, 87.0% at 90 days (20/23), and 92.9% at 6 months (13/14).

Impact: This is the first naturalistic study of accelerated protocols using the H1 coil, providing valuable insights into the effectiveness of this and other similarly broad coils for TRD in the accelerated context. The response and remission rates appear to stack up quite favorably to both the initial once-daily treatment studies of the H1 coil and other accelerated protocols (including the initial open-label trial that led to the SNT protocol).This appears to provide further evidence indicating accelerated protocols are effective in various contexts and with a range of devices. Though these findings are limited (particularly the durability findings with sample size), the questions this raises and concepts these findings support are already questions encountered on a routine clinical basis.

Roth, Y., Hanlon, C. A., Pell, G., Zibman, S., Harmelech, T., Muir, O. S., MacMillan, C., Prestley, T., Purselle, D. C., Knightly, T., & Tendler, A. (2023). Real world efficacy and safety of various accelerated deep TMS protocols for major depression. Psychiatry Research, 328, 115482. 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

Evidence of Imaging Markers of Pain-Autonomic Coupling in Complex Regional Pain Syndrome and Alleviation with rTMS of the Somatosensory Cortex

Harinee Maiyuran, MD, reviewing Delon-Martin et al. Neuromodulation 2023 Aug 16

This ancillary study of a larger clinical trial of various neuromodulation modalities for Complex Regional Pain Syndrome (CRPS) examines the effects of a five-month-long course of rTMS over the primary somatosensory cortex. The study showed activation of a region in S1 (primary somatosensory cortex), reduced pain scores and normalized skin conductance related to the affected limb. These improvements appeared to correlate with the activation of brain regions outside the motor cortex.

Complex Regional Pain Syndrome (CRPS) is a chronic pain syndrome that often presents with autonomic dysfunction, including vasomotor disturbances, edema, or sudomotor disturbances. Sudomotor function determines sweating patterns, and electrochemical skin conductance (ESC) is a frequently used measurement of sudomotor function. CRPS may present with increased (most common) or decreased sudomotor activity in an impacted limb compared to others. Changes in activity in several brain regions can impact skin conductance response, including primary cortical areas and associative areas, though this has been primarily studied in subjects without CRPS. fMRI is often used to assess this manner of activity change, and any associations with ESC are easily examined. Therefore, this ancillary study seeks to answer the question: is ESC associated with pain in

CRPS, and how linked are these to changes in cortical activity?

Eleven individuals with CRPS, aged 18-80 years old (median 56) participated in the study, with inclusion criteria of unilateral CRPS type I in either one lower or upper limb, disease for at least 1 year, intensity of pain greater than 3 out of 10, consistent medication regimen over the past month, and lack of benefit from treatment thus far. Participants completed an index treatment phase of daily rTMS for two weeks, followed by a progressive taper to twice monthly rTMS, for a total of 11 sessions. Treatment sessions consisted of 2000 pulses of 10Hz stimulation in 40 trains with a 25s ITI delivered at 80% MT to the somatosensory region corresponding to the affected limb via neuronavigation. ESC data (measured from palmar and plantar surfaces via electrode plates) and fMRI scans were collected pre-treatment and 1 month after the end of treatment. Pain assessment was done via a daily diary patients filled out at home on a visual numeric scale from 0-10. The impact of rTMS was measured on a scale from 1-7, with 1 being improved and 7 being significantly worsened. Neuroimaging analysis focused on activity changes in the sensorimotor network, examining its response to chronic pain and rTMS therapy. Changes in activity were determined through a comparison of regional activity during the completion of tasks utilizing one side of the brain at a time. Regions of significance were identified, and mean activation values were extracted for each subject and time point to distinguish baseline and post-treatment effects. Changes in these regions were assessed with paired t-tests, followed by a multiple regression model examining associations between these changes and both ESC and pain ratings.

In this study with 11 CRPS patients (mean duration 24 months, six upper limb, five lower limb), VNS pain scores were high at baseline (median 5.1), and sympathetic skin conductance (ESC) was lower in the affected limb. The median pain score was reduced to 3.4 ($p<0.05$). Though there was overall no significant change in ESC, those who demonstrated at least a 30% reduction in pain score also demonstrated a significant increase in sudomotor response as measured by ESC. This response correlated with pain reduction in these patients ($r=0.698$, $p=0.017$). Brain activation in S1 correlated with pain scores ($r=0.66$, $p=0.029$) and inversely with ESC ($r=-0.56$, $p=0.037$) values after treatment. Outside the sensorimotor network, ESC values correlated with brain activation in the middle frontal gyrus, temporoparietal junction contralateral to the painful limb, and ipsilateral precuneus ($r=0.47$-0.73, all $p<0.05$) and higher pain intensity post-treatment were linked to increased activation in the TPJ ($r=0.88$, $p<0.001$).

Impact: This exploratory study found a significant association between sudomotor function and daily pain levels in CRPS patients. Both measures improved together in those who responded to rTMS for CRPS, indicating the importance of addressing sudomotor issues for CRPS treatment. Additionally, there is some suggestion that the S1 brain region may be a promising target for rTMS therapy in CRPS and similar conditions like fibromyalgia. However, other brain regions, such as mFG and TPJ, also appear to be associated with improvement as well and warrant further exploration.

Delon-Martin C, Lefaucheur JP, Hodaj E, et al. Neural Correlates of Pain-Autonomic Coupling in Patients With Complex Regional Pain Syndrome Treated by Repetitive Transcranial Magnetic Stimulation of the Motor Cortex [published online ahead of print, 2023 Aug 16]. Neuromodulation. 2023;S1094-7159(23)00696-7. doi:10.1016/j.neurom.2023.05.005

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)