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PULSE

A Monthly Update on Advances in Neuroscience

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Inpatient ECT is Associated with a Significantly Reduced Risk of Suicide for Patients with Severe Depression

Nicole Wong reviewing Kaster et al. The Lancet Psychiatry 2022 June

This retrospective registry study of inpatient hospitalizations showed that ECT was associated with reduced risk of death by suicide and all-cause mortality in patients experiencing a major depressive episode

ECT yields symptom remission in more than 60% of patients with depression, with a standardized effect size of 0.91. Independent of its antidepressant effects, ECT has also been associated with rapid reduction in suicidal ideation in uncontrolled studies. This population-based cohort study compared patients with depression who either received or did not receive ECT and examined the association between ECT and death by suicide at one year follow-up.

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Using the Ontario Mental Health Reporting System, researchers included all adults greater than 18 years of age who had been discharged from a designated psychiatric inpatient bed in Ontario between April 2007 and December 2017 and for whom a primary diagnosis was a major depressive episode as part of either MDD or bipolar disorder. Admissions less than 3 days were excluded due to not having enough clinical information to compare these patients with other study members, and individuals with primary psychotic disorders were excluded due to differing indications for ECT and differential risk of death by suicide in this population. To control for differences in indication and prognosis, the authors used propensity score matching, a statistical matching technique that attempts to estimate the effect of an intervention by accounting for the covariates that predict receiving the treatment. The propensity scores in this study were estimated for each hospital admission record using a logistic regression model with more than 100 potential confounders from a broad range of sociodemographic, clinical, psychiatric, and functional symptoms, as well as health service utilization characteristics. The propensity scores were then used to create a pseudo-population in which groups were balanced with respect to distributions of the observed confounders.

Of the 67,327 admissions (27,231 men and 40,096 women; mean age: 45.1 ± 16.8 years, range: 18-103 years) who met selection criteria and were eligible for propensity score weighting based on the amount of clinical information available, 4,982 (7.4%) were ECT-exposed admissions and 62,345 (92.6%) were ECT-unexposed admissions. Prior to weighting using propensity scores, the ECT-exposed admissions and ECT-unexposed admissions were significantly imbalanced with respect to a variety of clinical characteristics, suggesting that they represented clinically distinct groups. After weighting by the odds of the propensity score, however, all covariates were balanced with standardized difference < 0.10.

Within 365 days after discharge, 450 deaths by suicide occurred: 27 deaths (5.84 per 1000 person-years) in the ECT-exposed group and 423 deaths (7.26 per 1000 person-years) in the ECT-unexposed group (cause-specific Hazard Ratio [csHR] 0.80 [95% CI: 0.54-1.18]). After propensity-weighting, the csHR decreased to 0.53 [0.31-0.92] with a NNT to prevent one death by suicide of 205. The cause-specific hazard ratios for non-suicide death and all-cause mortality between the ECT-exposed and ECT-unexposed groups were 0.83 [0.61-1.12] and 0.75 [0.58-0.97], respectively.

Impact: Patients with depression who were exposed to ECT had a nearly 50% reduction in relative risk of death by suicide at one year follow-up compared to those who had not been exposed, with an NNT of 205. It is important to note that a higher NNT is expected with a rare event such as death by suicide, and the benefits of ECT may be better demonstrated in future work by choosing a different outcome variable, such as suicidal ideation. ECT was not associated with a change in risk of non-suicide death but was associated with an approximately 25% reduction in risk for all-mortality death, suggesting that ECT reduces all-cause mortality via preventing suicide.

Tyler S Kaster, Daniel M Blumberger, Tara Gomes, Rinku Sutradhar, Duminda N Wijeysundera, Simone N Vigod. Risk of suicide death following electroconvulsive therapy treatment for depression: a propensity score-weighted, retrospective cohort study in Canada, The Lancet Psychiatry, Volume 9, Issue 6, 2022, Pages 435-446, ISSN 2215-0366, https://doi.org/10.1016/S2215-0366(22)00077-3.

rTMS Appears Safe and Effective for Pregnant Women with Major Depressive Disorder

Jo Huang reviewing Kim et al. Brain Stimul 2019 January

A small, double-blinded RCT suggests that right DLPFC rTMS improves depression symptoms in pregnancy and is likely safe

About 10% of women experience depression during pregnancy, which poses a treatment challenge as both untreated depression and antidepressant use during pregnancy have been associated with adverse maternal and child outcomes. Pregnant women are also shown to prefer non-medication treatments when possible, making pregnant women with depression good candidates for rTMS. Following an open-label pilot study by the same group, this double-blinded RCT studied the effect of rTMS versus sham on depression, maternal and infant outcome, and serum biomarkers.

Twenty-two women in the 2nd and 3rd trimesters of pregnancy received 20 sessions (15 min each, 5 days per week over 4 weeks) of either eSham stimulation or active rTMS to the right DLPFC, with 11 women in each group. The eSham device replicates the noise of the rTMS device and uses a brief electrical stimulus to mimic the sensation of twitching on the scalp

and face. Active rTMS was administered at 1Hz as a single train of 900 pulses per session at 100% MT. The primary outcome was the clinician rated Hamilton Depression Rating Score (HDRS-17) and the Clinical Global Impression Scale - Severity (CGI-S) at baseline, and after sessions 10 and 20. Subjects also rated their symptoms using the BDI and Edinburgh Postnatal Depression Scale (EPDS) at these checkpoints. Cognitive assessment tasks and estradiol and progesterone levels were collected pre- and post-treatment. Vital signs were checked before and after each session. Fetal and infant health were evaluated with fetal growth ultrasound 1 week after conclusion of session 20 and by obtaining delivery records. Depression status at 6 weeks postpartum was able to be assessed using EPDS over a phone call with 16 subjects (7 sham, 6 active).

Compared to the sham group, the active group showed significantly greater reductions in HDRS-17 scores (p=0.003) and EPDS scores (p=0.008) from baseline to session 20. CGI-S score also showed a larger decline in the active group from session 10 to 20 (p=0.035). However, there was no significant difference between groups on BDI scores after session 20 and no significant difference in post-partum EPDS scores. Treatment response rate, defined by a 50% decrease from baseline HDRS-17 score, was not significantly different between groups (active: 81.8%; sham: 45.4%; p=0.088), nor was the remission rate, defined by HDRS-17 <8 and CGI <=1 (active: 27.3%; sham: 18.2%; p=0.613). Interestingly, 27.3% of sham group subjects showed response at session 10 as compared to none in the active group. There were 3 pre-term births (PTB), all in the active group, although the sample size was too small to establish a statistically different PTB rate as compared to sham. There were no otherwise significant differences in maternal and infant health, including pre- and post-treatment estradiol and progesterone levels, although more active group subjects reported headaches than sham group.

Impact: This study is the first RCT evaluating treatment outcomes and safety of rTMS in pregnancy, and has shown that a single train of 900 1 Hz pulses targeted at right DLPFC for 15 minutes each over 20 sessions produces significant improvement in depression symptoms as evaluated by HDRS-17, EPDS, and CGI-S. However, likely due to limitations posed by the small sample size, it did not show significant improvements in response or remission rates. Although this study shows that low-frequency right rTMS is relatively safe, a study of larger sample size could further confirm the safety of rTMS and interrogate any association with PTB, while potentially supporting this early signal of efficacy.

Kim DR, Wang E, McGeehan B, et al. Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder. Brain Stimul. 2019;12(1):96-102. doi:10.1016/j.brs.2018.09.005

Dorsomedial Prefrontal rTMS is Effective for Depression in Women with Borderline Personality Disorder

Norman Spivak reviewing Feffer et al, J Affect Disord 2021 December

A pilot RCT of rTMS to the dorsomedial prefrontal cortex (DMPFC) yielded significant improvements in symptoms of MDD in a group of women with borderline personality disorder (BPD)

Depression in BPD represents an area with few effective treatment options. One such treatment option is dialectical behavioral therapy which is efficacious but requires a lengthy treatment course; there also may be long wait times for therapy groups. The limited efficacy of antidepressant medications along with the limits of psychotherapy support a need for new treatment options.

Twenty adult women meeting DSM-5 criteria for both BPD and a major depressive episode were included in this randomized crossover sham-controlled rTMS trial. Patients had moderately severe depression with a score ≥18 on the HAM-D, had failed at least 1 medication trial or were unable to tolerate 2+ trials, had normal thyroid tests and blood counts, and were on stable medications and doses for four weeks prior to treatment and throughout the duration of the study. Patients received sequential sham and active rTMS treatment in counterbalanced order. Treatment was administrated using the MagPro R30 Cool-DB80 coil and consisted of 1500 pulses (first right DMPFC, then left DMPFC) delivered at 20 Hz and 120% resting MT (obtained on a lower extremity). rTMS was administered five days per week for three weeks, with a one-week break between arms, delivered as two rTMS sessions per day (with at least a one hour break between them). The primary outcome measure for the study was the HAM-D assessed by a blinded rater. EEG was obtained a week before and a week after the entire treatment course to

assess effects of treatment on brain function, using eyes open and eyes closed recordings.

Subjects who received active treatment first saw a mean HAM-D reduction of 12.1 ± 5 from baseline to end of the first treatment arm, compared to a reduction of 5.6 ± 3 in those receiving sham (p=0.0095). The subjects crossed over to sham stimulation saw a further decrease of 0.5 ± 5, while those crossed over to active treatment had a further mean decrease of 6.4 ± 2. There was no significant difference in MDD severity between the two groups at the end of the crossover, suggesting there was no significant carryover effect. With respect to EEG findings, change in theta power at the AF8 electrode between baseline to end of all treatments was correlated with reductions in MDD severity (r =0.66, p=0.0137). Exploratory evaluation of electrodes showed additional significant correlations for electrodes in prefrontal sites near AF8, including F6 and F8. All patients tolerated the treatment without dropping out or experiencing any serious adverse events.

Impact: In this randomized crossover sham-controlled study, rTMS was shown to improve symptoms of MDD in patients who have BPD, a notoriously difficult to treat population. This study was limited in generalizability due to a small sample size, and replication in larger groups is needed. Furthermore, while BPD and MDD are predominantly seen in women, future work should explore the efficacy of this treatment in men.

Feffer K, Lee HH, Wu W, et al. Dorsomedial prefrontal rTMS for depression in borderline personality disorder: A pilot randomized crossover trial. J Affect Disord. 2022;301:273-280. doi:10.1016/j.jad.2021.12.038

Meta-analysis of Noninvasive Brain Stimulation for Anxiety Disorders Shows Promising Results

David Lee reviewing Vergallito A et al. Neuroimage 2021 November

A meta-analysis of 11 RCTs suggests that Repetitive Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation may be effective for anxiety disorders and comorbid depression

Anxiety disorders are the most prevalent group of psychiatric conditions. Studies have suggested that alterations in the mesocorticolimbic pathway and imbalance between the left and right DLPFC are present in anxiety disorders. While pharmacological intervention and cognitive-behavioral therapy serve as the first-line treatments for anxiety disorders, many patients experience suboptimal responses or relapse of symptoms. Two noninvasive brain stimulation techniques - rTMS and tDCS - have been recommended by expert panels with a strong degree of evidence and approved by the FDA for multiple neurological and psychiatric applications, most notably in MDD. They also have been commonly employed in the treatment of anxiety disorders, although no specific recommendations for their use yet exists. This systemic meta-analysis examined the efficacy of rTMS and tDCS in anxiety disorders and comorbid MDD.

Among 876 peer-reviewed studies identified that were written in the English language on “rTMS” or “tDCS” and relevant anxiety disorder labels through February of 2020, the researchers identified 11 studies (8 rTMS and 3 tDCS; 6 inhibitory and 5 excitatory studies). All studies included patients with a primary diagnosis of an anxiety disorder, quantitative evaluation of anxiety disorders pre- and post-treatment, and a control or sham condition. The primary outcome included the quantitative change in the general anxiety disorder scale (Hamilton Anxiety Rating Scale [HAM-A]), specific anxiety disorder scores (e.g., Panic Disorder Severity Scale, Spider Phobia Questionnaire), and depression scale (HAM-D). Hedge’s g score was used to evaluate the effect size of quantitative change in these scores before and after the intervention, and the global effect across all 11 studies was assessed using a random-effect model.

The 11 identified studies included primary diagnoses of generalized anxiety disorder (n=6), panic disorder (n=3), or specific phobia (n=2; spiders, heights). In the six rTMS studies, four targeted the right DLPFC, one targeted the right posterior parietal cortex, and one targeted the ventromedial prefrontal cortex; four used 1 Hz stimulation, one used 10 Hz, and one used 20 Hz. The two iTBS studies targeted the left DLPFC, while in the three tDCS studies, cathodal stimulation targeted the right DLPFC in two studies and anodal stimulation targeted the left DLPFC in one study. Sham stimulation was the control in 10 of the 11 studies, while one study used CBT as a control. Nine of the studies were double-blinded, while two only blinded participants. The meta-analysis included a total of 154 patients assigned to an active neuromodulation condition and 164 to a control or sham group. Noninvasive brain stimulation yielded a significant decrease in: specific anxiety scores (standard mean difference [SMD]: -0.49

[95% CI: -0.83, -0.14]; p=0.006) across 10 of the 11 studies; general anxiety scores (SMD: -0.81 [95% CI: -1.45, -0.18]; p=0.012) across nine studies; and depression scores (SMD: −0.98 [95% CI: −1.62, −0.35]; p=0.002) across seven studies. Quantitative analyses suggested a high degree of heterogeneity between studies, and no significant publication bias was evident by inspection of funnel plots.

Impact: This systemic review and meta-analysis of 11 RCTs exploring the efficacy of noninvasive brain stimulation techniques in anxiety disorders demonstrated significant improvements in general and specific measures of anxiety with medium to large effect sizes. These results are limited by the small number of studies and heterogeneity among them, highlighting the importance of additional research in this area. Another significant limitation of this study is a lack of commentary on or analysis of the differences between rTMS and tDCS. Given the significantly larger research and regulatory support for rTMS, future work should include such comparisons.

Vergallito A, Gallucci A, Pisoni A, Punzi M, Caselli G, Ruggiero GM, Sassaroli S, Lauro LJ. Effectiveness of noninvasive brain stimulation in the treatment of anxiety disorders: a meta-analysis of sham or behaviour-controlled studies. Journal of Psychiatry and Neuroscience. 2021 Nov 9;46(6):E592-614. doi: 10.1503/jpn.210050.

Abbrevations

DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
LIFUP (low intensity focused ultrasound pulsation)
TENS (transcutaneous electrical nerve stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tACS (transcranial alternating current stimulation)
tDCS (transcranial direct 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)

AUD (alcohol use disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BDI (Beck Depression Inventory)
HAM-D (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
PANSS (Positive and Negative Symptom Scale)
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)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)

DLPFC (dorsolateral prefrontal cortex)
M1 (primary motor cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)