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PULSE

A Monthly Update on Advances in Neuromodulation

Precuneus rTMS Shown Effective for Multiple Symptom Domains of Alzheimer's Disease

Michael Leuchter, MD, reviewing Jung et al. JAMA Network Open 2024 May 6

rTMS for Alzheimer's Disease (AD) treatment has been studied for almost two decades; however, most studies have targeted prefrontal brain regions yielding mixed results. This study is among the first to target the superior central parietal area using functional imaging to identify regions correlated with the hippocampus. In this double-blind, sham-controlled pilot study, the authors find daily treatment is able to substantially improve symptoms, with effects sustained for at least 4 weeks on follow-up. The improvement is substantial enough to be reflected on scales assessing global function in AD.

As previously discussed in PULSE, the use of brain stimulation techniques for Alzheimer's Disease (AD) is an expanding area of

work. Most research has focused on cognitive symptoms, yielding inconsistent benefits. While treating cognitive sequelae is important, an optimal treatment would address cognitive, functional, behavioral, and other symptom domains simultaneously. Few studies have demonstrated benefit in these domains, though recent work in rTMS of the precuneus (a region of the parietal lobe often affected early in the disease course) has shown great promise in slowing overall disease progression. The authors here use fMRI guidance to find a portion of the cortex in the precuneus region most connected to the hippocampus, followed by a treatment course of rTMS. Can rTMS of the precuneus again show promise in treating AD? Does fMRI targeting work similarly to EEG-based methods?

This double-blind, randomized, sham-controlled trial of 30 subjects (41 enrolled, 11 non-completers) age 55–90 (mean age 69.8 ± 9.1, 18 female) with mild-cognitive impairment due to AD or mild AD dementia without other major comorbidity examined the effects of 20 sessions of once-daily fMRI-guided rTMS (20 Hz, 1600 pulses per session, 40 pulses per train, unclear ITI, 100% MT) or fMRI-guided sham rTMS over the course of 4 weeks. This study was performed at a single site in Korea, and all subjects were of Korean descent. Treatment locations were determined as each subject's left parietal cortex region with the highest resting functional connectivity to the hippocampus. Cognitive assessments were

performed at baseline, 4 weeks (immediately following completion of treatment), and 8 weeks (4 weeks after completion of treatment), while fMRI was collected at baseline and week 4 only. Cognitive outcomes consisted of the Alzheimer Disease Assessment Scale–Cognitive Subscale-13 (ADAS-Cog, one of the most often used and validated measures of cognition in AD), Seoul-Instrumental Activities of Daily Living (SIADL), Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), and seven other well-validated measures. Imaging analyses focused on changes in functional connectivity between the precuneus and hippocampus. Missing or incomplete imaging data led to an n=20 for imaging analyses. Statistical analyses utilized standard tests: linear mixed-effects regression models for cognitive outcomes (potentially over-adjusted for age, sex, education, and APOE status), changes in functional connectivity were tested with one-sided t-tests, and correlation of functional connectivity changes with ADAS-Cog changes were tested with a spearman rank correlation.

The primary result of this study is a substantial improvement in ADAS-Cog based on treatment group at both week 4 (group point difference over time= -4.4 ± 1.6, p=0.007) and week 8 (group point difference over time= -5.2 ± 1.6, p=0.002). Similar results demonstrating improvement/less impairment in the active rTMS group were observed for both the CDR-SB (week 4 group point difference over time= -0.6 ± 0.3, p=0.05; week 8 group point difference over time= -0.78 ± 0.3, p=0.008) and SIADL (week 4 group

point difference over time= -1.1 ± 0.7, p=0.16; week 8 group point difference over time= -2.4 ± 0.8, p=0.002). The authors identified numeric though not statistically significant improvements on other cognitive measures. They also report increased precuneus-hippocampus functional connectivity in the active group relative to sham and significant correlation between increases in functional connectivity and improvements in ADAS-Cog (r=-0.57, p=0.005). No significant differences were found based on diagnosis (MCI vs mild AD).

> **Impact: This study provides additional evidence that rTMS of the precuneus has the potential to simultaneously treat multiple symptom domains of AD. Its use of fMRI targeting differs from prior promising work involving EEG-based targeting, indicating that these markers may overlap or there may not one specific method of personalization required for rTMS of the precuneus to be effective in treating AD. It is particularly promising the authors of this study see improvements significant to the point of seeing differences on their measure of global disease severity (the CDR-SB). Further study of rTMS of the precuneus for AD is warranted given the small sample size and sham control limitations.**

Jung YH, Jang H, Park S, et al. "Effectiveness of Personalized Hippocampal Network–Targeted Stimulation in Alzheimer Disease: A Randomized Clinical Trial." JAMA Netw Open. 2024;7(5):e249220. doi:10.1001/jamanetworkopen.2024.9220

Effect of Sex on Negative Symptoms of Schizophrenia After rTMS Treatment

Erin Hegarty reviewing Campania, M et al. Bio. Psychiatry, 2024 Mar

Data reviewing the impact of sex on rTMS treatment outcomes are limited and inconsistent. Similarly, sex differences in negative symptoms of schizophrenia after rTMS treatment have not yet been examined, the aim of this study. This secondary analysis of the RESIS (rTMS for the Treatment of Negative Symptoms in Schizophrenia) study examined response rates and degree of response in a total of 157 male and female patients with schizophrenia, as defined by changes in PANSS scores. No significant differences were found between males and females in either response rate or degree of response to 10-Hz rTMS applied to the left prefrontal cortex.

Repetitive transcranial magnetic stimulation (rTMS) to the left prefrontal cortex, now included in national and international guidelines for treatment-resistant depression, is being utilized with increasing frequency for other psychiatric conditions. rTMS to the LDLPFC has also demonstrated improvement in the negative symptoms of schizophrenia, which often appear to resemble depressive symptoms. However, data remain limited, and inconsistent. Variation in treatment parameters has been posited as the cause of inconsistent response rates. This analysis aimed to determine whether a patient's biological sex might also explain variability in response rates, as observed in a subset of the literature assessing rTMS for depression outcomes. There are well-documented differences in the clinical manifestations and functional impairment between males and females with schizophrenia, with males much more likely to meet criteria for treatment-resistance schizophrenia. Therefore, authors investigated whether there might be clear and predictable differences in response to rTMS based on biological sex.

Secondary analyses were performed utilizing data from Wobrock et al's 2015 multisite RCT, "Repetitive Transcranial Magnetic Stimulation for the Treatment of Negative Symptoms in Schizophrenia (RESIS)", which included 157 male (n=118) and female (n=39) patients with schizophrenia who were randomly assigned to receive 15 sessions of either active or sham rTMS over the course of 3 weeks. Parameters included 1,000 pulses (20 trains, 50 pulses per train, 30s ITI) of 10 Hz rTMS at 110% of resting motor threshold (RMT) per session delivered to LDLPFC. PANSS score change was the primary outcome in the original study, with outcomes showing no group differences in the improvement of negative symptoms, depression, or cognitive function. However, a small but statistically significant improvement in positive symptoms was observed in the active rTMS group. In this analysis, responders (as indicated by 25% or greater reduction in PANSS negative score) were stratified by sex to assess potential impact on response. Defined by change in the PANSS negative scale using linear mixed models, the degree of response was also

examined by sex. Lastly, authors found no significant sex differences in baseline rMT of the motor cortex. Greater reduction in PANSS positive scores was observed at later timepoints in females who received active rTMS, though authors cautioned concluding the association between time and female sex, as the sample size was small.

> **Impact: This study found that there were no differences in improvement of negative symptoms between male and female patients with schizophrenia who received 10 Hz rTMS to LDLPFC. This finding contrasts with prior reports in the treatment of depression that there is differential antidepressant efficacy of rTMS between males and females. While it may be possible that this discrepancy suggests differential effects on a symptom- or condition-specific basis, repeating this study with a larger sample size would help re-confirm (or reject) the findings.**

Campana M, Schneider-Axmann T, Wobrock T, et al. Assessing the impact of sex on high-frequency repetitive transcranial magnetic stimulation´s clinical response in schizophrenia - results from a secondary analysis. World J Biol Psychiatry. 2024;25(4):233-41.

Combined tDCS and Virtual Reality Reduces PTSD Symptoms

Harinee Maiyuran, MD reviewing Wout-Frank et al. JAMA Psychiatry 2024 Mar 6

In this double-blind, randomized clinical trial, US military veterans with a diagnosis of PTSD received active or sham tDCS treatment during virtual reality (VR) exposure therapy. Active tDCS facilitated habituation to VR and greater improvement in PTSD symptom severity when compared to sham tDCS.

Posttraumatic stress disorder (PTSD) is characterized by intrusive memories, avoidance of reminders, heightened arousal, and cognitive disturbances. It is prevalent among veterans and is often accompanied by other

medical and psychiatric issues, substance abuse, and increased suicide risk. Conventional treatments, such as trauma-focused cognitive behavioral therapies and selective serotonin reuptake inhibitors fall short, with

high dropout rates due to the distressing nature of exposure therapy and only moderate efficacy of medications.

A hypothesis for PTSD's persistence involves impaired fear

extinction and retention due to dysfunctional top-down regulation of the amygdala by the ventromedial prefrontal cortex (VMPFC). This dysfunction hinders the learning and recall of safety cues. Transcranial direct current stimulation (tDCS) is currently being explored in the treatment of PTSD, wherein treatment is hypothesized to facilitate safe memory formation and accelerate fear extinction. In the approach used in this study, tDCS was combined with VR exposure therapy. VR provides an immersive, controllable environment for exposure therapy, which can help patients confront and process trauma-related cues more effectively. An initial pilot study showed that combining tDCS with VR led to significant reductions in PTSD symptoms, encouraging further investigation. Could tDCS-augmented VR improve PTSD severity, physiological arousal, and overall functioning?

This study was conducted within the VA Providence Healthcare System, followed the CONSORT guidelines (Consolidated Standards of Reporting Trials). Patients were recruited from April 2018 through May 2023, with 65 participants consented and 54 ultimately included age 18-65. Most pertinent inclusion criteria were chronic PTSD secondary to trauma in

warzones, measured by the DSM-5. A parallel-group, double-blind design was used, with up to six sessions over ten business days. Active tDCS involved 2mA of electrical stimulation for 25 minutes, while the sham condition provided minimal stimulation. The VR used replicates environments with sensory inputs related to deployment to Iraq or Afghanistan, over 12 VR events. Primary outcomes included the PTSD-checklist (PCL-5) and quality of life, assessed at baseline, midpoint (after 3 sessions), end of treatment, and at both 1- and 3-month follow-up. Secondary outcomes included measures of depressive symptoms, clinician-assessed PTSD severity, and social and occupational functioning. Skin conductance was also measured to evaluate psychophysiological arousal.

The active tDCS plus VR group showed significant reductions in PTSD symptoms over time, with more than a 10-point reduction in symptom severity on the PTSD Checklist for DSM-5 (PCL-5) after three sessions and continuing to one-month post-treatment. The effect size was large at the one-month follow-up but not statistically significant at three months. Depressive symptoms improved in both groups without significant differences between them. Quality of life and social/occupational function improved significantly in

the active tDCS group compared to the sham group. Psychophysiological measures indicated greater habituation to VR events in the active tDCS group, with significant reductions in skin conductance reactivity across sessions.

This study found that combining tDCS with VR therapy for PTSD was more effective than VR therapy alone. Active tDCS facilitated habituation to VR cues, potentially mediating the noted improvements in PTSD symptoms, although depression severity did not improve significantly. Social and occupational functioning improved more notably at the three-month follow-up. Additionally, tDCS+VR was cost effective and thus easy to implement. Several limitations were noted, including high attrition rates during follow-up, the impact of the COVID-19 pandemic on recruitment, and participants' continuation of their prior treatments. VR scenarios were also not individualized to participants. The findings suggest that a brief course of tDCS combined with VR could be beneficial and warrant further research with longer follow-up periods and potentially more personalized VR experiences.

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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)
MST (magnetic seizure therapy)
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)
TPS (transcranial pulse 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)

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