AUGUST 2022 / ISSUE 18

PULSE

A Monthly Update on Advances in Neuroscience

Produced by the Neuromodulation Division of the Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

Collin M. Price, MD Managing Co-Editor | Collinprice@mednet.ucla.edu
Michael K. Leuchter, MD Managing Co-Editor | mkleuchter@mednet.ucla.edu
Andrew F. Leuchter, MD Editor-in-Chief | Aleuchter@mednet.ucla.edu

Bilateral Cerebellum rTMS Improves Cognition in Patients with Alzheimer's

Jo Huang reviewing Yao et al. Brain Stimul 2022 June

A double-blinded RCT shows that 20 sessions of daily bilateral cerebellar 5Hz rTMS improves cognitive test scores in patients with Alzheimer's Disease (AD) in a manner correlated with enhancement in cerebello-cerebral functional connectivity.

The efficacy of pharmacological treatment for Alzheimer's Disease (AD) is limited. Though the mechanism is unclear, rTMS targeting the precuneus and DLPFC have shown promise for improving some cognitive functions in those with AD. However, the multi-domain cognitive decline in AD necessitates further exploration of rTMS targets. The cerebellum is a promising target given its numerous cognitive functions (particularly processing emotion, language, and working memory) and evidence of delayed atrophy with early increases in activity during AD. The observed increases in activity of

IN THIS ISSUE:

the Crus II region are of particular interest, and are theorized to represent a compensatory mechanism in the early stages of AD. Additionally, iTBS to the cerebellum has been shown to enhance working memory and cerebellar-cortical plasticity. For these reasons, this study examines the effects of rTMS to bilateral Crus II of the cerebellum on cognitive function and cerebello-cerebral connectivity in patients with AD.

Twenty-seven patients (14 male, 13 female) ages 60-80 year with mild to moderate AD (Mini Mental State Exam [MMSE]>16) and high dependence on reliable caregivers and without significant psychiatric co-morbidities or benzodiazepine usage, received 20 sessions (five days per week over four weeks) of either sham stimulation (n=12, MagVenture sham coil) or active rTMS (n=15) to the bilateral Crus II cerebellar regions (determined using scalp coordinates physically-measured from the inion). Active rTMS consisted of 2000 pulses at 5 Hz in 20 pulse bursts delivered over 20 min at 90% MT. Outcomes measures include changes in fMRI functional connectivity between cerebellar and cerebral regions, a battery of cognitive testing scores, depression and anxiety scales, sleep scales, and ADLs. Several scales were utilized, including the MMSE, Montreal Cognitive Assessment (MoCA), Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-Cog), Rey Auditory-verbal Learning Test (RAVLT), Clock Drawing Test (CDT), Boston Naming Test (BNT), parts A and B of the Trail Making Test (TMT), and the Symbol Digit Modalities Test (SDMT). fMRIs were obtained at baseline and after completing rTMS treatment. Scales were obtained at baseline, after 20 sessions of rTMS treatment, and eight weeks after the completion of rTMS treatment.

In the active rTMS group, statistically-significant within-group improvements ($p<0.05$) were observed in global cognitive function (MMSE, MoCA, ADAS-cog), episodic memory (RAVLT), executive function (TMT-B), attention (SDMT), language (BNT), and visuospatial memory (CDT) at the end of rTMS treatment and these differences persisted eight weeks later. Other scales demonstrated no significant within-group differences. Between-group differences and measures of effect size were not reported. fMRI data demonstrated increased functional connectivity between the right Crus II and the bilateral DLPFC, and bilateral medial frontal cortex. They also demonstrated increased connectivity between the left Crus II and the right DLPFC, bilateral medial frontal cortex, and bilateral cingulate cortex. MMSE and RAVLT score improvements were respectively correlated with enhancements in functional connectivity between the right and left cerebellum Crus II with the contralateral DLPFC. SDMT improvements were positively associated with an increase in functional connectivity between the right Crus II and the contralateral medial frontal cortex.

Impact: This study evaluated and found promising results of 5Hz rTMS as a treatment for cognitive impairment in patients with AD. While the within-group improvements across multiple domains were encouraging, further work will need to focus on examining the effect size in a larger, more generalizable sample. Optimization of this novel treatment protocol or combining it with cognitive training could have broad implications in treatment of cognitive impairment in AD.

Yao Q, Tang F, Wang Y, et al. Effect of cerebellum stimulation on cognitive recovery in patients with Alzheimer disease: A randomized clinical trial. Brain Stimul. 2022;15(4):910-920. doi:10.1016/j.brs.2022.06.004

Improved Response Inhibition Correlates with EEG Biomarkers after Successful HFL rTMS for Depression

Collin M Price reviewing Yu et al. Journal of Psych Res 2022 May

In this randomized, double-blind, sham-controlled trial, HFL rTMS to DLPFC in 44 patients with MDD was clinically effective and yielded improvements in response inhibition, a measure of executive function, with improvement associated with EEG biomarkers.

Response inhibition (RI) is a component of executive function that involves inhibiting a prepared response or just-initiated action, such as rapidly hitting the breaks when a light turns from yellow to red. Deficits in RI are well known to be correlated with depression, with improvements in RI predicting antidepressant response in some studies. In this trial, researchers aimed to determine whether personalized rTMS to treat MDD would yield improvements in measures of RI and associated EEG biomarkers.

Fourty-four patients with MDD were randomized to active (n=23) or sham (n=21) rTMS delivered once daily for 15 consecutive days. Active rTMS was delivered as 3000 pulses at 10 Hz and 100% resting MT, while sham treatment was delivered with a coil that mimicked the look, sound, and sensation of active rTMS. Each subject had an individualized fMRI-guided stimulation target in left DLPFC that showed maximal positive BOLD

signal correlation with the left nucleus accumbens, with neuronavigation used to ensure accurate coil placement. RI was measured using the Stop-Signal Task (SST), in which participants were instructed to rapidly indicate the orientation of an arrow when it appeared on a screen (left or right, the Go signal) but would need to inhibit their response on 25% of the trials (indicated by the arrow turning red, the Stop signal). The Go signal appeared after 200-400ms, and the interval between the Go and Stop signals (stop signal delay, SSD) adjusted on the basis of performance to maintain accuracy at 50%. Primary SST outcome was the stop signal reaction time (SSRT), the difference between the mean SSD and the mean Go signal delay. EEG data was collected during the SST using a 64-electrode system. The primary clinical outcome was change in HAM-D, measured at baseline and end of treatment. An additional 30 healthy control (HC) participants, demographically matched to the patients, were recruited to complete the same baseline SST as a comparator group.

The active rTMS group had a significantly greater clinical response (≥50% reduction) on the HAM-D (74%) compared to the sham TMS group (29%; $\chi 2=9.0$, $p=0.003$). The pooled MDD patient group showed significantly worse RI performance at baseline compared to the HC group based on longer SSRT, with accompanying EEG biomarkers of smaller P3 amplitudes, weaker theta power, and reduced theta inter-trial coherence. After the treatment course, the active rTMS group had significantly shorter SSRT compared to baseline (CI [95%]: 6.0 - 38.8; $p=0.009$) with normalization of SSRT compared to HC (318 ms vs. 291 ms respectively at baseline, $p=0.011$; 295 ms vs. 291 ms respectively after treatment, $p=0.552$). There was no significant change in the sham group (CI [95%]: 19.1 - 15.2; $p=0.82$). The reduction in SSRT in the active group remained significant even after controlling for change in HAM-D score. There were multiple significant correlations between clinical outcomes and EEG biomarkers during successful stop trials, with greater changes in HAM-D score correlating with increased P3 amplitude and theta-band power across multiple brain regions; no such correlations were observed in the sham group.

Impact: In this randomized, double blind, sham-controlled trial, active HFL rTMS using connectivity-based targeting yielded significantly greater improvements in depression symptoms as well as response inhibition, a measure of executive function. Improvements in SSRT were significant even after controlling for change in HAM-D score, suggesting some improvements in RI may have been independent of mood changes. The most notable findings of this study were that active but not sham rTMS normalized the prolonged SSRT values associated with depression, and clinical improvements were correlated with EEG biomarkers of RI improvement. This study is consistent with prior work indicating that rTMS may have a unique benefit of improving executive function in MDD. Future studies should examine other targets (beyond left DLPFC) as well as an extended treatment course to see whether greater benefit can be obtained.

Yu F, Huang Y, Chen T, et al. Repetitive transcranial magnetic stimulation promotes response inhibition in patients with major depression during the stop-signal task. J Psychiatr Res. 2022;151:427-438. doi:10.1016/j.jpsychires.2022.05.014

tDCS May Be a Nonpharmacological Treatment Alternative for Inattention in Adults With ADHD

Tashalee R Brown MD, PhD reviewing Leffa et al. JAMA Psychiatry 2022 Aug

In the TUNED RCT, patients with ADHD not on stimulant medications showed significantly greater improvement in inattention symptoms in the tDCS group compared to sham, with no significant adverse side-effects.

Home-based tDCS is easy to use and relatively safe and may have the ability to revolutionize the delivery of neuromodulation treatment, similar to the home-based treatment of obstructive sleep apnea using continuous positive airway pressure. tDCS was used previously for the treatment of the cognitive effects of ADHD in both children and adults. However, results were conflicting, likely secondary to small sample sizes and variance in measurements.

In this randomized, double-blind, parallel, sham-controlled clinical trial, patients were assigned to either active or sham home-based tDCS in a four-week study at a single hospital in Brazil. Inclusion criteria included an inattention score of 21 or higher on the clinician-administered version of the Adult Self-report rating scale (CASRS-I), and exclusion criteria included current stimulant medication use, moderate or severe symptoms of depression or anxiety, bipolar disorder with a

manic or depressive episode in the last year, or a psychotic illness diagnosis. Active home-based tDCS participants underwent 30-minute daily sessions of tDCS at 2 mA current for 4 weeks for a total of 28 sessions. The anodal and cathodal electrodes were positioned over F4 and F3 (corresponding to the right and left DLPFC), respectively. The right DLPFC was the target of anodal stimulation based on results from a meta-analysis of fMRI studies of attention demonstrating reduced activation in this region in individuals with ADHD. The sham condition used identical devices but had only a 30-second ramp up to 2 mA followed by a 30-second ramp down to 0 mA, occurring at the beginning, middle, and end of the session; blinding was assessed with a standardized scale. The primary outcome was change in CASRS-I at 4 weeks, with secondary outcomes that included the BDI and BAI. The study did not include any remote monitoring of adherence.

Of the 64 participants who were randomized, 31 (48%) had an inattentive ADHD presentation and 33 (52%) had a combined presentation. Thirty participants (47%) were women with a mean (SD) age of 38.3 (9.6) years. Fifty-five of the 64 participants (86%) completed the 4-week follow-up. For the CASRS-I primary outcome, an ITT linear mixed-effects model revealed a statistically significant treatment by time interaction (β-interaction = −3.18; 95% CI: −4.60 to −1.75; P < .001), with decreased symptoms of inattention in the active tDCS group at week 4 compared to sham (d=1.23). Mild adverse events were more frequent in the active tDCS group, particularly skin redness, headaches, and scalp burn. There were no statistically significant differences in any secondary outcomes. The blinding assessment indicated that a significant portion of the active group correctly guessed their treatment arm, while there was no such pattern in the sham group. Further analysis showed that about 68% of treatment responders (>30% reduction in CASRS-I; n=11) correctly guessed their treatment assignment beyond rates expected by chance, while non-responders had a random distribution of guesses similar to sham.

Impact: In this double-blind, parallel arm, sham-controlled RCT, home-based tDCS was found to significantly improve symptoms of inattention in patients with ADHD who were not taking stimulant medications. The authors posit that this study yielded positive results where others failed in part because of the number of sessions. Most tDCS studies have used 1-5 sessions, whereas the mean number of sessions applied in this trial was 20-25 sessions, likely owing to the at-home nature of the treatment. The authors do note the significant rate of failed blinding in the active group, which may be consistent with unblinding due to an actual effect but could also pose a risk for a placebo effect. An additional concern about the generalizability of this study is its single-site implementation. A larger follow-up RCT study would be needed to address these concerns. The inclusion of subjects with mild depression and anxiety may confound the clinical improvement noted with tDCS, although the authors report no significant changes in depression and anxiety scores over the study period. Overall, this study provides support for the safety and efficacy of home-based tDCS for the nonpharmacological treatment of inattentive symptoms in patients with ADHD.

Leffa DT, Grevet EH, Bau CHD, et al. Transcranial Direct Current Stimulation vs Sham for the Treatment of Inattention in Adults With Attention-Deficit/Hyperactivity Disorder: The TUNED Randomized Clinical Trial. JAMA Psychiatry. Published online August 03, 2022. doi:10.1001/jamapsychiatry.2022.2055

Transcutaneous Auricular Vagus Nerve Stimulation Yields Benefits Similar to Citalopram in a Randomized Trial for Patients with MDD

Nicole Wong reviewing Li et al. Neuromodulation 2022 Apr

In a randomized 12-week, single-blind, comparative effectiveness trial, transcutaneous auricular vagus nerve stimulation resulted in depression symptom improvement similar to that of citalopram.

Implanted vagus nerve stimulation (VNS) is an FDA-approved intervention for severe MDD with known clinically significant antidepressant effects, although use is limited due to side effects, cost, and limited accessibility. Transcutaneous auricular vagus nerve stimulation (taVNS) has been proposed as a non-invasive, low-cost alternative to implanted VNS that can be self-administered. How does taVNS compare to commonly used antidepressants like citalopram?

Three hospitals in China enrolled 107 patients meeting the inclusion criteria of: 1) 18 to 65 years of age; 2) MDD as defined in DSM-V; 3) mild to moderate depression as indicated by a HAM-D score of 8-24; and 4) no psychotropic medication for three months before the study. Exclusion criteria included: 1) severe depression indicated by HAM-D score > 24 or

suicidal intent; 2) DSM-V criteria for a substance use disorder in the prior six months; 3) schizophrenia or "cognitive personality disorders" [sic]; 4) severe medical disorder such as unstable heart, kidney, or liver failure; 5) pregnancy; or 6) dementia or other cognitive disorders. Eligible patients were randomly assigned in a 1:1 ratio to the taVNS or citalopram group, with no significant differences in sex, age, major depressive episode duration, or baseline HAM-D. HAM-D scores were assessed at 2, 4, 6, 8, 10, and 12 weeks. Additionally, researchers measured peripheral blood levels of multiple neurotransmitters and neuroactive hormones. An ITT analysis was used, and researchers were blinded to what group participants had been assigned to.

Both treatment arms achieved a significant improvement in depression symptoms. There was no significant difference in response on the HAM-D (≥50% reduction in score) between the citalopram or taVNS groups at any time point. The researchers did identify a significant difference in remission rates between the citalopram and taVNS groups at week four ($p = 0.007$) and week six ($p = 0.01$), favoring taVNS. With respect to neurotransmitters, comparison between the two groups showed that there was no significant difference in peripheral blood markers before and after treatment.

Impact: In this randomized 12-week, single-blind, comparative effectiveness trial of 107 patients with mild to moderate MDD, taVNS treatment was associated with levels of symptom improvement that were similar to citalopram. The taVNS group showed significantly higher remission rates at weeks four and six; however, in the absence of a sham/placebo control treatment condition it is difficult know whether any of the symptom improvement in this study is directly attributable to the active intervention. Because this was not designed and powered as a non-inferiority study, the results must be interpreted with caution. Similarly, the data on neurotransmitter levels are difficult to interpret.

Li S, Rong P, Wang Y, Jin G, Hou X, Li S, Xiao X, Zhou W, Wu Y, Liu Y, Zhang Y, Zhao B, Huang Y, Cao J, Chen H, Hodges S, Vangel M, Kong J. Comparative Effectiveness of Transcutaneous Auricular Vagus Nerve Stimulation vs Citalopram for Major Depressive Disorder: A Randomized Trial. Neuromodulation. 2022 Apr;25(3):450-460. doi: 10.1016/j.neurom.2021.10.021. Epub 2021 Dec 18. PMID: 35088753.

Abbrevations

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
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)
TENS (transcutaneous electrical nerve 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)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive 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)
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)
SMD (standard mean difference)

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