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PULSE

A Monthly Update on Advances in Neuromodulation

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tDCS Found Not to Augment Cognitive Training in Randomized Clinical Trial

Tashalee R. Brown, MD PhD reviewing Hausman et al. Brain Stimulation May 2023

In the double-blind RCT known as the ACT trial, 379 older adults with age-related cognitive decline were randomized to cognitive training augmented with either active or sham tDCS; the active augmentation intervention was not found to be superior to sham.

It is estimated that roughly 35–40% of adults over the age of 65 experience some form of significant cognitive impairment. However, a large proportion of older adults experience less impairing cognitive change in the form of age-related cognitive decline. Cognitive training was developed as a means of mitigating cognitive changes of many types, consisting of guided practice of cognitive tasks aimed at improving performance in one or more domains. Studies have found evidence of improvements on trained tasks, but the transfer or

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"spillover" effects from trained into untrained domains and daily functioning has been variable. Small studies have suggested tDCS may enhance performance within both trained and untrained domains when combined with cognitive training. The current study is part 2 of an adaptive two-phase randomized clinical trial in which the first phase demonstrated cognitive training was superior to an educational training control regardless of whether tDCS was applied. The second part investigates whether tDCS augmentation of cognitive training can enhance benefits of training through improvements on a composite measure of cognitive abilities (NIH Toolbox Fluid Cognition Composite) from baseline to post-intervention and a one-year follow-up.

In this study, 334 adults between age 65–89 (mean age 71.5 +/- 5.1; 88% White) with age-related cognitive decline (and no evidence of more severe impairment or other major neurologic, medical, or psychiatric co-morbidities) across University of Florida and Arizona were randomized to cognitive training (approximately 40 hrs of computerized adaptive tasks) with either active bifrontal tDCS (n = 168, 2 mA for 20 min) or sham tDCS (n=166, received 2mA for first 30s of session to simulate habituation) administered at F3/F4 during daily cognitive training for 2 weeks, then once weekly during daily training for 10 weeks. The study revealed that, for both groups, there were improvements in NIH Toolbox Fluid Cognition Composite (FCC) from baseline to post-intervention (active group change 4.7 ± 6.5, sham group 4.5 ± 6.1) and on follow-up after one year (active group change 5.1 ± 6.6, sham group 4.3 ± 6.3). However, no inter-group difference was detected in FCC from baseline to post-intervention or from baseline to one-year follow-up. Older age and higher baseline FCC scores were associated with smaller improvements in FCC (p<0.01) regardless of treatment group. There were no significant group differences in serious adverse events.

Impact: The ACT trial was the largest sham-controlled RCT investigating augmentation of cognitive training with tDCS in age-related cognitive decline to date, though it found no significant improvement with tDCS. These results are in contrast to smaller studies demonstrating efficacy. This may be related to variability in tDCS implementation, training tasks used, or the sensitivity of the outcome measure used. While it is discouraging that this study is negative, it leaves open opportunities for further exploring the use of tDCS in subpopulations of older adults, tDCS as a means of augmenting maintenance of cognitive function, and other novel applications in this area.

Hausman, H. K., Alexander, G. E., Cohen, R., Marsiske, M., DeKosky, S. T., Hishaw, G. A., O'Shea, A., Kraft, J. N., Dai, Y., Wu, S., & Woods, A. J. (2023). Primary outcome from the augmenting cognitive training in older adults study (ACT): A tDCS and cognitive training randomized clinical trial. Brain stimulation, 16(3), 904–917. Advance online publication. https://doi.org/10.1016/j.brs.2023.05.021

Transcranial Direct Current Stimulation (tDCS) May Reduce Relapse Risk in Alcohol Use Disorder Through Functional Connectivity Changes

Frederick Burton III, MD reviewing Camchong J et al. Brain Stimul. June 2023

This double-blind RCT of 60 participants in early abstinence from alcohol found that, not only did active tDCS to left DLPFC somewhat reduce relapse risk for alcohol use disorder, but also that a decrease in risk was mediated by increases in functional connectivity between left DLPFC and the incentive salience network, suggesting efficacy of tDCS and potentially other neuromodulation modalities that can effect similar connectivity changes.

Alcohol use disorder (AUD) impacts millions of individuals worldwide, and psychosocial-based treatments have a relapse rate of roughly 64% within one year. Therefore, there is a need for more interventions that can modulate biological factors of alcohol use disorder and reduce this risk of relapse. Neural imaging studies have shown that connectivity between addiction networks and frontal regions plays a critical role in early abstinence and that higher connectivity is a protective factor against relapse. Other studies have shown variable results regarding the use of tDCS to LDLPFC for AUD, though protocols have been heterogenous. This raises the question whether noninvasive neuromodulation interventions (and tDCS in particular) should be administered in AUD to increase frontal and addiction network connectivity during the vulnerable stage of early abstinence, and that is exactly the question this study seeks to answer.

In this study, 81 participants with AUD that were in early abstinence (within two weeks of admission to a 28-day inpatient addiction treatment program) were selected, and 60 (mean age 41.7 ± 9.6, 21 female, race and ethnicity not stated) were ultimately able to enroll and be

randomized to five consecutive days of twice-daily treatment (20 minute inter-session interval) with a cognitive training task (the 4-choice reversal learning task, aimed at enhancing cognitive flexibility) during either active or sham tDCS (left to right frontal anodal to cathodal placement). Active stimulation consisted of 13 minutes of 2 mA current, while sham consisted of current application only surrounding ramp up and ramp down periods to mimic these sensations. All participants underwent pre- and post-intervention fMRI, random alcohol and drug tests during the inpatient program, and follow-up interviews at one and four months after program discharge to determine relapse/abstinence status (with one drink of alcohol consumption defining relapse). Statistical analysis was designed as strict causal discovery analysis (CDA), which is a statistical method of attempting to determine causality through comprehensive analysis of the relationships between all the parts of a theoretical model. In this case, this was done with the overarching goal of determining if tDCS would induce connectivity changes in four pre-defined addiction networks (termed causal connectivity) that would result in reduction of relapse rates. The authors defined four key relationships (and statistical tests) between treatment effects, causal connectivity, and relapse outcomes in their model to infer causation: 1) tDCS's effects on causal connectivity using general linear models 2) differences in relapse outcome based on differences in causal connectivity using general linear models, 3) tDCS's effects on relapse rates in AUD using a chi-square test, and 4) differences in relapse outcome associated with causal connectivity changes induced by tDCS using a logistic regression.

In this study of the 60 participants, 17 relapsed and 43 participants remained abstinent by one month. By the four-month followup, 25 had relapsed, 4 were not reachable, and 31 remained abstinent. Causal connectivity in two of the four networks was found to be associated with active treatment (incentive salience network F=4.31, p=0.042; negative emotionality network F=7.38, p=0.009), and increases in causal connectivity between LDLPFC and the incentive salience network were associated with abstinence at four months (F=4.72, p=0.034). Active tDCS was associated with numerically lower relapse rate compared to sham (19% active, 38% sham, p=0.11) that were statistically significant in women (9.1% active, 50% sham, p=0.038). Finally, the increased causal connectivity changes between LDLPFC and the incentive salience network induced by active tDCS were found to be associated with abstinence (OR=2.90, p=0.035), though this association became a trend when accounting for baseline connectivity and sex as covariates (OR=1.25, p=0.06). It was also found that women had higher likelihood of relapse than men using proportional hazard models (HR=2.4, p=0.03).

Impact: This study, though limited in its sample size, focus on self-report outcomes, and retention rate, showed that, not only isthe change in average strength of connectivity from LDLPFC to the incentive salience network important in reducing risk of relapse in AUD, but also that tDCS increased the strength of this connectivity. It did not conclusively demonstrate that tDCS itself is an effective treatment for AUD, but it did reveal many interesting possibilities for tDCS and other neuromodulation treatments in AUD going forward. Further prospective work with larger sample sizes, longer follow-up periods, and potential combinations with psychosocial interventions would certainly be of interest to the field.

Camchong J, Roediger D, Fiecas M, et al. Frontal tDCS reduces alcohol relapse rates by increasing connections from left dorsolateral prefrontal cortex to addiction networks [published online ahead of print, 2023 Jun 20]. Brain Stimul. 2023;16(4):1032-1040. doi:10.1016/j.brs.2023.06.011

High-frequency rTMS May Improve Poststroke Dysphagia after Infratentorial Stroke

Harinee Maiyuran, MD reviewing Dai M et al. Brain Stimulation 2023 June 9

In this prospective, sham-controlled, single-blind, randomized controlled trial of 42 patients with poststroke dysphagia (PSD) following subacute infratentorial stroke (IS), 10-Hz bilateral cerebellar rTMS was found to improve functional oral intake compared to sham.

Infratentorial strokes (IS) can be debilitating, with a high incidence of poststroke dysphagia (PSD) and a subsequent greatly elevated risk of aspiration compared to supratentorial stroke. While PSD is often a target of rehabilitation following IS, outcomes in this realm are variable, and more effective treatments for PSD would decrease mortality rate after IS. Noninvasive brain stimulation, particularly rTMS targeting the cerebellum, has been explored in other poststroke dysfunctions, with some success in gait and balance dysfunction. However, exploration of applications in PSD

have been focused on hemispheric cortex and the parameter space remains widely unexplored. It is not clear what frequency or intensity with which coil at which location is optimal. The cerebellum's role in movement coordination has made it a target for rTMS following a stroke, and it is known to play a large role in swallowing coordination as well. For these reasons, rTMS with a double-cone coil applied to the cerebellar hemispheres was examined in this study to assess its ability to improve swallowing in people with PSD after IS. 42 patients with PSD secondary to subacute unilateral IS (less than 6 months after stroke onset) without other major medical comorbidities or prior experimental PSD treatments were randomly assigned to one of three groups: bilateral cerebellar rTMS (biCRB; n=14, 3 female, mean age 61.5 ± 1.9), unilateral cerebellar rTMS (uni-CRB; n=14, 2 female, mean age 59.9 ± 3.5), and sham (coil tilted 90°) r-TMS (sham; n=14, 1 female, mean age 58.9 ± 3.1). Treatment consisted of daily sessions of 250 pulses of 10Hz stimulation at 90% MT delivered in five 50-pulse trains with a 10 second ITI to the target location with a double-cone coil. Of note, MT was determined using EMG assistance on the unaffected arm. Cerebellar placement was performed using surface landmarks from the inion, with unilateral treatment being ipsilesional active stimulation followed by contralesional sham stimulation and sham treatment being sham stimulation on both sides. Daily swallowing training was concurrently implemented over 4 weeks alongside the first two weeks of rTMS. The outcome measures used were the Functional Oral Intake Scale (FOIS), Dysphagia Outcome and Severity Scale (DOSS), and the Penetration and Aspiration Scale (PAS); FOIS changes at T1 and T2 were defined as the primary outcomes. They were assessed at baseline, T1 (day 0 after intervention), and T2 (day 14 after intervention).

All three arms demonstrated significant improvement over time on the FOIS at both timepoints. However, the biCRB-rTMS group showed the most significant improvement in FOIS scores at both time intervals and was significantly more effective than sham-rTMS. At the first time point, biCRB-rTMS had a much higher efficacy ratio than the other groups and its effect sizes were considered large (Cohen's D ≥ 1.00). By the second time point, the differences in efficacy ratio between groups diminished and were no longer statistically significant. At T1, DOSS and PAS scores generally showed marked enhancements, with the sham-rTMS group's PAS being the exception. FOIS score comparison revealed notable differences in score changes among the groups. Specifically, the biCRB-rTMS group exhibited more pronounced improvements in both scores than the sham-rTMS group. More precise numeric values regarding the described score improvements were not presented. Effect sizes were high in the biCRB-rTMS group, and medium-large in the uniCRB-rTMS group. Corticobulbar tract excitability (as determined by MEP targeting the suprahyoid muscles) also increased within the biCRB and uniCRB groups, though there was not a significant difference in these measures between the three groups. None of the participants reported adverse effects during or after the study.

Impact: This moderate-sized pilot study found that 10-Hz bilateral cerebellar rTMS with a double-cone coil may be a potential treatment for poststroke dysphagia after subacute infratentorial stroke. However, the magnitude and durability of these benefits require further study with larger samples and greater female representation. Though corticobulbar tract excitability also changed over the course of treatment, the significance of this finding is unclear. Longer term follow-up studies including video fluoroscopic swallow data and more neurophysiological results would help confirm and further this study's findings.

Dai, M., Qiao, J., Shi, Z., Wei, X., Chen, H., Shen, L., Wen, H., & Dou, Z. (2023). Effect of cerebellar transcranial magnetic stimulation with double-cone coil on dysphagia after subacute infratentorial stroke: A randomized, single-blinded, controlled trial. Brain Stimulation, 16(4), 1012–1020. https://doi.org/10.1016/j.brs.2023.05.023

Multimodal Magnetic Resonance Imaging Biomarker May Predict ECT Outcomes for Depression

Miguel Serrano-Illan, MD, PhD, reviewing Bruin WB et al. Psychological Medicine 2023 Jul 24.

This retrospective database analysis reviewed structural and functional MRIs from depressed patients who received ECT across seven different institutions. Using machine learning to analyze functional and structural MRIs, the authors found a composite biomarker of gray matter volume and functional connectivity that was predictive of remission of depression in response to ECT in test samples.

Electroconvulsive therapy is one of the most effective therapeutic modalities for severe depression, and rates of recovery are robust at approximately 50%. However, it comes with potential adverse effects that other modalities do not, including cognitive impairment and risks associated

with anesthesia. Furthermore, it is both time and resource intensive. There are no widely accepted, evidence-based predictors of ECT outcomes. However, recent functional and structural MRI studies have produced promising results, suggesting that these tools may be useful in predicting the effectiveness of ECT in some individuals. In an era in which technology plays an ever-increasing role in the delivery of healthcare at large, there has been more focus on implementing artificial intelligence and machine learning. One such potential application employs machine learning to evaluate neuroimaging and correlate findings with treatment outcomes, specifically, in this case, ECT.

The authors utilized data from the Global ECT MRI Research Collaboration (GEMRIC), an international consortium that maintains a database of neuroimaging from patients treated with ECT. They identified 189 patients who received ECT and undergone structural and resting-state functional MRI. The mean age of the sample was 51.7 ± 15.5, with 106 females, and remitters being significantly older than nonremitters (56.3 ± 14.2 vs 48.6 ± 15.5, $p<0.001$) and more likely to have psychotic features, though other demographic and diagnostic characteristics of the patients were largely not discussed. Imaging was primarily from Europe and North America. The primary outcome was defined as remission on the HDRS (HDRS score ≤7). The authors extracted structural MRI features using a common voxel-based morphometry approach and functional MRI features using the UK Biobank dataset template. They repeatedly applied machine learning to these features and their clinical data to identify features predictive of remission, randomly building their model on 80% of the data and setting aside 20% of the data to test the model each repetition.

Using this machine learning approach with a single imaging modality yielded statistically significant though clinically unreliable results in a receiver operator model (areas under the curve [AUC] of 0.51-0.67). Multimodal approaches initially yielded similar results (AUC=0.68). However, focusing on the three centers with the greatest quantity of data resulted in more helpful models on the multimodal approach (AUC up to 0.83). That model was based on structural findings in the dorsomedial prefrontal cortex, precuneus, and thalamus, in addition to functional connectivity observed in those regions. This model also held up when applied to test data (AUC of 0.70). This approach was also applied to predicting response to ECT rather than remission, though all tested models performed poorly.

Impact: This study successfully utilized machine learning to develop a potential biomarker for remission during ECT for depression that could prove quite useful going forward. However, it did not account for medication status or changes during ECT and the models used are at risk for statistical overfitting. Further work prospectively testing this marker in a controlled manner and attempting to develop markers for response or testing this marker in other treatments for depression would be of great interest and utility to the field.

Bruin WB, Oltedal L, Bartsch H, et al. Development and validation of a multimodal neuroimaging biomarker for electroconvulsive therapy outcome in depression: a multicenter machine learning analysis [published online ahead of print, 2023 Jul 24]. Psychol Med. 2023;1-12. doi:10.1017/S0033291723002040

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)