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PULSE

A Monthly Update on Advances in Neuromodulation

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Functional Connectivity Mapping Between DLPFC TMS Target and sgACC Has Only a Weak Correlation with Treatment Outcome

Nicole Wong reviewing Elbau et al. Am J Psychiatry 2023 Mar

Functional connectivity mapping between the left DLPFC stimulation target and the sgACC in a sample of 295 patients with MDD accounted for only about 3% of the variance in treatment outcome, calling into question the use of this method for stimulation target selection.

rTMS to the DLPFC relieves depression symptoms in some but not all patients. One approach to improve outcomes has been to use fMRI to select rTMS stimulation targets based on functional connectivity (FC).The most common approach has been to stimulate the area in left DLPFC that has maximal negative FC with the subgenual anterior cingulate cortex (sgACC), a variable called

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sgACC-StimFC. Using the largest sample size to date, this study examined the reliability of the association between sgACC-StimFC and clinical outcomes.

Data were analyzed from 295 subjects from the THREE-D study, in which subjects with MDD were randomly assigned to receive 20 treatments of either 10 Hz rTMS or iTBS to the DLPFC. Subjects in the THREE-D study had MDD with an HDRS-17 of ≥18, were without comorbid substance use, psychotic, or personality disorders, and had failed to respond to or tolerate at least one or two antidepressants. All subjects received a structural brain scan and two 10-minute resting-state fMRI scans before and after treatment, and stimulation was targeted to a predefined stereotactic coordinate in the left DLPFC (x=-38, y=44, z=26). Importantly, all fMRI scans were rated for global signal fluctuations related to burst breathing and deep breaths by three independent raters.

The pretreatment FC of the stimulation target in the DLPFC was examined with two methods: a generic "weighted-cone" model approximating the electric field (E-field) as a 12-mm distance-weighted hemisphere (an approach that was used frequently in older studies), as well as E-field modeling performed with SimNIBS (a more individualized approach based on each subject's unique anatomy). The authors used the QIDS-SR for clinical outcomes in their model due to the slightly increased number of data points and preference for a self-rating questionnaire, given that the subjects were blinded. The present study included all participants who had two complete fMRI scans available, complete clinical outcome data for the QIDS-SR or HDRS-17, and successful cortical surface reconstruction using the two models described above.

There was no significant association between sgACC-StimFC and clinical improvement for the generic weighted-cone model, and only a weak correlation with treatment response for the SimNIBS model (r=-0.16, p=0.006), explaining roughly 3% of variance in treatment response. Because previous studies with smaller sample sizes had generally reported stronger relationships between sgACC-StimFC and treatment response, the authors tested connectivity-outcome correlations for 10,000 randomly generated subsamples of the 295 subjects with sizes ranging from 15 to 280. They found that smaller subsamples had substantially greater variance in observed effect size than large samples, with random samples of size 25-50 subjects commonly producing significant effects of r=-0.50 or greater. Lastly, the authors examined data quality as a contributor to prior variable studies, by calculating the signal variance on fMRI for each subject. They found that the subjects with the highest signal variance demonstrated variation patterns consistent with burst breathing. In subjects who demonstrated burst breathing, sgACC-StimFC was strongly correlated with clinical improvement (r=-0.49, p=0.0004).

Impact: This retrospective analysis of a large sample of patients treated with rTMS demonstrated that pretreatment functional connectivity between the left DLPFC stimulation target and sgACC had a very weak relationship to treatment outcome. The association was stronger in small subgroups of patients with a distinct respiratory pattern (burst breathing) known to be associated with depression. They also highlight many pitfalls in functional connectivity studies, including using small sample size, variability in signal processing, and methods that inaccurately approximated stimulated cortex and connectivity. These results suggest limited utility of the sgACC FC-based targeting of stimulation sites and highlight important methodological considerations for future fMRI-based biomarker work.

Elbau IG, Lynch CJ, Downar J, Vila-Rodriguez F, Power JD, Solomonov N, Daskalakis ZJ, Blumberger DM, Liston C. Functional Connectivity Mapping for rTMS Target Selection in Depression. Am J Psychiatry. 2023 Mar 1;180(3):230-240. doi: 10.1176/appi.ajp.20220306. PMID: 36855880.

Theta-Alpha Amplitude Modulation Frequency Is a Biomarker for Prolonged Intermittent Theta Burst Stimulation Efficacy in Treatment-Resistant Depression

Michelle Wu reviewing Tsai et al., Hum Brain Mapp 2022 March

In a small, double-blind sham-controlled RCT, adults with treatment-resistant major depressive disorder received 10 sessions of 10 Hz rTMS, prolonged iTBS (piTBS), or sham. piTBS patients improved relative to sham and those with enhanced theta-alpha amplitude modulation frequency showed greater response to treatment.

Two rTMS protocols, rhythmic 10 Hz stimulation and iTBS, are both effective FDA-approved non-pharmacologic therapies for treatment-resistant depression. There is no method for determining, however, which protocol will yield the best response for an individual patient.

This study examined brain network oscillations in patients receiving prolonged iTBS (piTBS), 10 Hz rhythmic rTMS, or sham. The authors applied Holo-Hilbert spectral analysis to characterize electrophysiological effects of stimulation and whether these were related to therapeutic efficacy in MDD.

Sixty-one adult patients aged 21 to 70 (M=48.8) with a diagnosis of MDD were randomly assigned to receive piTBS (n=19), rTMS (n=20), or sham stimulation (n=22). Inclusion criteria included a failure to respond to at least one antidepressant treatment in the current episode, a CGI-S score of at least 4, and a HDRS-17 score of at least 18. Exclusion criteria included those with bipolar I or II, a history of psychotic, personality, or neurological disorders, implanted medical devices, and pregnancy. The study compared resting state EEG recordings before and after a treatment phase consisting of one rTMS session per day for five consecutive days per week for two weeks, for a total of 10 sessions. Patients received either piTBS (50 Hz, 1800 pulses, 80% MT intensity), rhythmic rTMS (10Hz, 1600 pulses, 100% MT intensity), or sham stimulation (sham coil) to the left DLPFC with MRI guidance. Responders were defined as those with a greater than 50% reduction in HDRS-17 score after treatment compared to baseline.

HDRS improvement was highest for patients receiving piTBS (M = 40.9%) and was significantly larger than the sham group (M = 14.8%, $p<0.01$, $d = 1.20$). The rhythmic rTMS group also showed a numeric improvement over sham (M = 30.2%), but this did not reach statistical significance ($p = 0.13$). The response rate at 2 weeks was significantly higher in the piTBS group (42%; $p<0.01$) than the rhythmic rTMS (30%) or sham (0%) groups. Holo-Hilbert spectral analysis of EEG data revealed that piTBS responders displayed significantly increased log power in the theta-alpha range from pre- to post-treatment in the frontal and occipital regions compared to sham ($t = 2.59$, $p<0.05$). Additionally, change in log power pre- vs. post-piTBS in the frontal regions was positively correlated with percent improvement in HDRS score ($r = 0.51$, $p < 0.05$). Both rTMS responders and non-responders had an increase in average log power within alpha carrier frequency range over frontal-central regions relative to sham, but this did not correlate with clinical improvement ($r = 0.06$, $p = 0.81$).

Impact: In this double-blind sham-controlled RCT, treatment-resistant MDD patients exhibited an improvement in symptoms following two weeks of piTBS. Power changes at the theta-alpha frequency spectrum were positively correlated with improvements in HDRS-17 scores in piTBS responders. These power changes seen in responders to piTBS at session 10 warrant exploration as a predictive biomarker of treatment efficacy. Additionally, the difference in neural oscillations induced by piTBS vs. rTMS and between responders and non-responders to piTBS may lend insight into mechanisms underlying treatment response. Further work should examine whether EEG changes might be detected earlier in the course of treatment, perhaps even after a single treatment session.

Tsai YC, Li CT, Liang WK, et al. Critical role of rhythms in prefrontal transcranial magnetic stimulation for depression: A randomized sham-controlled study. Human Brain Mapping. 2022;43(5):1535-1547. doi:10.1002/hbm.25740

cTBS to Bilateral Temporo-parietal Cortex May Be Effective at Reducing Severity of Auditory Verbal Hallucinations

Harinee Maiyuran, MD reviewing Tyagi et al. Asian J Psychiatr 2022 Aug

This randomized sham-controlled study found that patients with treatment-refractory auditory verbal hallucinations in schizophrenia had a significant improvement in their symptoms after treatment with continuous theta burst stimulation of the bilateral temporoparietal cortex.

Although antipsychotics are first line treatments for auditory verbal hallucinations (AVH) in schizophrenia, they are not effective for all patients. This study examined whether cTBS could be an effective alternative treatment for AVH.

This sham controlled RCT included 59 patients with a diagnosis of schizophrenia, per ICD diagnostic criteria, a PANSS question P3 (hallucinatory behavior) score of ≥3, and a failed trial of at least one antipsychotic to treat AVH. Notable exclusion criteria included comorbid psychiatric diagnoses including a substance use disorder, and a history of ECT treatment in the past 6 months. Of 59 enrolled patients, 9 withdrew for various reasons, though no subjects left the experiment secondary to adverse consequences of cTBS. This left 50 patients for the final analysis. Patients were hospitalized, medically cleared, and received cTBS over a two-week period, with outpatient visits for follow-up after discharge. cTBS was delivered sequentially to the right and left temporoparietal cortices (TPC) at 80% resting MT with 600 pulses per hemisphere once daily each weekday for two

weeks. Sham stimulation followed the same protocol using a sham coil. Raters were blind to the randomization of subjects, and subjects were blinded to their participation as either the cTBS or sham group, though the integrity of this blinding was not fully determined. Three scales were used to measure symptoms of AVH: the PANSS, the Auditory Vocal Hallucination Rating Scale (AVHRS), and Psychiatric Symptoms Rating Scale-Auditory Hallucinations Scale (PSYRAT-AH). Additionally, the Calgary Depression Scale for Schizophrenia (CDSS), Schizophrenia Cognition Rating Scale (SCoRS), and CGI-Severity (CGI-S) were used to assess depression, cognition, and overall illness severity, respectively.

The active and sham groups were similar across all demographic and baseline clinical characteristics except for a significant difference in PANSS-General Psychopathology scores, with significantly higher scores in the sham group ($p=0.023$). In an ITT, active cTBS (compared to sham) yielded a significant group x time interaction, after controlling for several variables, on multiple outcome measures including PANSS-Positive Scale, PANSS-Total, AVHRS, PSYRAT-AH, and CGI-S (all $p<0.001$). Additionally, the active group had a 16.7% response rate in the context of AVH, compared to 3.5% in the sham group. The authors also did a supplementary per-protocol (PP) analysis to focus on the subjects who completed the study and found a significant group x time interaction remained within all clinical variables, aside from patient and informant SCoRS for cognition.

Impact: This sham-controlled RCT found two weeks of cTBS to bilateral TPC led to statistically significant improvement in treatment-refractory AVH, with improvements on positive symptom and global impression scores maintained at one month. The most significant limitations of this study are its small sample size, which likely decreased its generalizability and reliability, and lack of confirmed integrity of the subject blinding to their treatment group. Still, these results are encouraging and suggest that intensive bilateral TPC cTBS is both effective and safe in patients with AVH refractory to antipsychotic medication.

Tyagi P, Dhyani M, Khattri S, Tejan V, Tikka SK, Garg S. "Efficacy of intensive bilateral Temporo-parietal Continuous theta-burst Stimulation for Auditory Verbal hallucinations (TPC-SAVE) in schizophrenia: A randomized sham-controlled trial". Asian J Psychiatr. 2022;74:103176. doi:10.1016/j.ajp.2022.103176

tACS Improves Working and Long-Term Memory in Healthy Older Adults with Spatio-temporal Specificity

Lara Tang reviewing Grover et al. Nat Neurosci 2022 September

A series of three RCTs in healthy older adults demonstrated that tACS is an effective neuromodulation technique for improving both working and long-term memory, with dissociable effects on each domain depending on the location and frequency of stimulation.

It has been hypothesized that neuromodulation can improve memory function, specifically working (WM) and long-term memory (LTM). It remains unclear, however, which stimulation frequencies and locations are most efficacious in older adults. This study hypothesized that WM would be improved if the inferior parietal lobule (IPL) was stimulated with frequencies in the theta band and LTM would be improved if the DLPFC was stimulated with frequencies in the gamma band.

In Experiment 1 of this double-blind RCT series, 60 participants (26 females) were randomized into three tACS intervention groups (60 Hz at DLPFC, 4 Hz at IPL, and sham). The participants had a mean age of 74.6 years and baseline MOCA of 26.8. Each participant received tACS for 20 minutes/day for four consecutive days. On each day, participants performed five runs of a free recall task involving a list of 20 words. tACS was delivered with an 8x1 center-surround configuration with the anode centered over the left DLPFC or left IPL as the participants encoded the list and performed recall. Sham tACS was delivered at the same locations but involved only a 30s ramp up or down at the beginning and end. In Experiment 2, 60 additional participants (30 females; mean age: 76.7; mean baseline MOCA: 25.9) were randomized into the same three intervention groups, but this time the frequency was switched between the brain regions to serve as an active control (i.e., 4 Hz at DLPFC and 60 Hz at IPL). Experiment 3 involved 30 participants (16 females; mean age: 72.1; mean baseline MOCA: 26.3) randomized to either 60 Hz DLPFC or 4 Hz IPL stimulation and assessed using a similar paradigm except for three rather than four days of stimulation and without long term follow up. For all experiments, memory performance was evaluated prior, during the days of intervention, and one month after the intervention. Analyses included the serial position of words in the recall task, with the first four labeled “primacy,” the middle 12 labeled “middle,” and the final four labeled “recency.”

An ANOVA in Experiment 1 showed that, compared to sham, 4 Hz IPL stimulation yielded a significant day x word position x group interaction (p=0.001). Follow-up t-tests revealed significant improvements only for the recency position, correlated with WM, at days three (p=0.012, d=0.8), four (p=3.9x10-5, d=1.5), and one month (p=0.030, d=1.0). Similarly, 60 Hz DLPFC stimulation, as compared to sham, yielded a significant overall interaction (p<0.001), with further analyses showing improvements only for the primacy position (correlated with LTM) at days two (p=0.045, d=0.7), three (p=0.001, d=1.2), four (p=0.002, d=1.1), and one month (p=0.022, d=1.0). Similar analyses in Experiment 2 yielded no significant differences compared to sham in recall performance. Experiment 3 analyses revealed a significant day x word position x group (DLPFC vs. IPL) interaction (p<0.001), with follow-up analyses showing significant improvements for the primacy cluster in the DLPFC group (relative to IPL) and for the recency cluster in the IPL group (relative to DLPFC), replicating Experiment 1 findings. Additional analyses across experiments suggested the rate of memory improvements during the first four days predicted the magnitude of memory improvement at one month, and that adults with lower MoCA scores at baseline showed larger benefits from tACS, but only in the targeted domains (i.e., WM with 4 Hz IPL stimulation, LTM with 60 Hz DLPFC stimulation).

Impact: This series of three RCTs demonstrates that tACS can effectively improve memory performance in healthy older adults acutely and with durable effects at one month. A notable finding in this study was the specificity of effects, with WM improving only with low-frequency stimulation at left IPL and LTM improving only with high-frequency stimulation at left DLPFC. The results from this study highlight tACS as a cost-effective, non-invasive approach to support memory function in the elderly. This study shows promise for memory benefits in healthy older adults, however further study is needed to determine if tACS can be similarly useful for patients with neurocognitive disorders.

Grover S, Wen W, Viswanathan V, Gill CT, Reinhart RMG. Long-lasting, dissociable improvements in working memory and long-term memory in older adults with repetitive neuromodulation. Nat Neurosci. 2022;25(9):1237-1246. doi:10.1038/s41593-022-01132-3

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)