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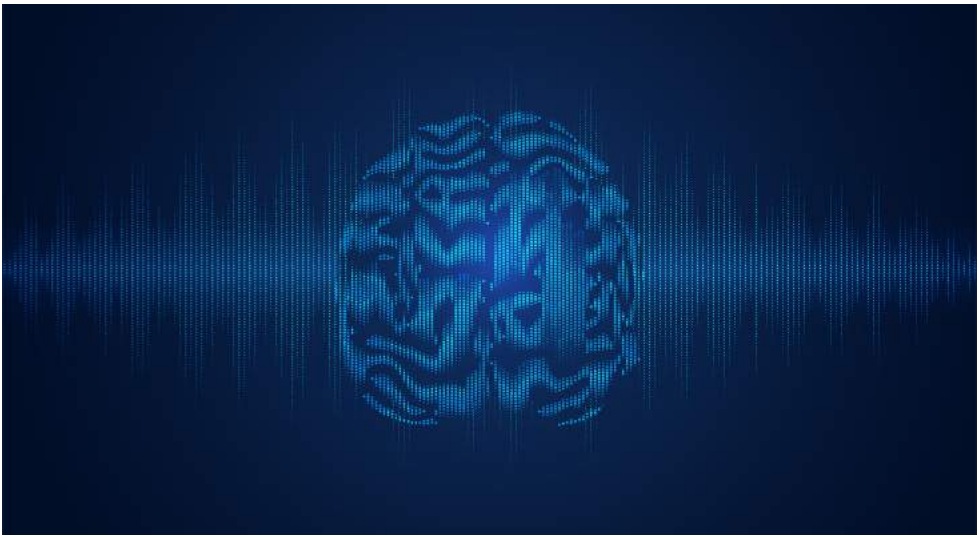
PULSE

A Monthly Update on Advances in Neuroscience



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Modulation of Evoked Potentials by Initial 10 Hz rTMS Session Predicts Clinical Outcomes of a Six-Week Treatment Course

Collin M Price reviewing Hinchman et al. J Affect Disorder 2022 Apr 15

Clinical response to a six-week course of 10 Hz rTMS to left DLPFC in patients with TRD was predicted by the extent of modulation of corticomotor excitability from a single rTMS session. However, outcomes were predicted only by modulation with 10 Hz rTMS, not iTBS.

Despite many efforts to determine predictors of response to left DLPFC rTMS in patients with TRD, the field still lacks reliable prognostic markers. One potential avenue for predicting response is in measurement of cortical excitability and plasticity using TMS-evoked motor potentials. This study compared the degree to which two rTMS protocols (10 Hz vs. iTBS) modulated cortical excitability and the extent to which this predicted clinical outcomes.

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Thirteen patients with TRD aged 18-80 years were recruited to participate. All participants underwent a six-week course of rTMS delivered in daily sessions, five days a week, of 3000 pulses at 10 Hz and 120% resting MT targeting the left DLPFC. Prior to their treatment course, each participant underwent two cortical plasticity assessments using single-pulse TMS to generate motor-evoked potentials (MEP) before and after an initial rTMS session of either 3000 pulses of 10 Hz rTMS at 90% resting MT or 600 pulses of iTBS at 80% active MT; the order of 10 Hz vs. iTBS was randomized between patients. Plasticity assessments were delivered in blocks of 30 pulses to M1 applied before (x3 blocks) and after (x6 blocks; 5 min intervals) rTMS. Clinical outcomes were assessed using the BDI-II and HAM-D obtained at baseline and the end of treatment, with the primary clinical outcome the percent change at end of treatment on the BDI-II.

Baseline resting MT and MEP amplitudes showed no significant difference between the initial rTMS protocols (10 Hz vs. iTBS). Plasticity assessments revealed no consistent effect of either protocol on MEP amplitudes and no difference between the protocols with respect to effects on MEP amplitudes. Clinically, the group responded well to a course of 10 Hz rTMS, with 46% showing response (≥50% reduction) on the BDI-II and 46% showing remission (score ≤12). Although neither initial rTMS stimulation had a significant effect on MEP amplitudes overall, ANOVAs revealed that greater increases in MEP amplitudes from initial 10 Hz stimulation were significantly associated with percent-improvement on the BDI-II ($p<0.001$) and HAM-D ($p=0.022$). In contrast, MEP changes from the iTBS condition were not a significant predictor of percent-improvement on either the BDI-II ($p=0.10$) or HAM-D ($p=0.77$). Post-hoc analysis of the 10 Hz data using non-parametric Spearman correlations showed that a decline in BDI-II scores was associated with significantly higher changes in MEP amplitudes at 20 min, 30 min, and the collective 5-30 min period after stimulation (all $p<0.05$). For the 10 Hz Post-20 min MEP values, a threshold of ≥68% change could correctly classify BDI-II response in 92% of patients with an AUC ROC = 0.91.

Impact: This analysis of M1 MEP in patients with TRD provides evidence that cortical plasticity in response to one rTMS session may have predictive value for overall clinical outcomes with 10 Hz rTMS to the left DLPFC. Changes in MEP after 10 Hz rTMS, but not iTBS, were predictive of improvement, with MEP changes 20 minutes after 10 Hz stimulation showing the strongest association with improvement. This study is one of the first to demonstrate a frequency-specific predictor of outcome: acute changes induced by an initial stimulation session were associated with the outcome of treatment with the same form of stimulation (10 Hz), but changes from initial stimulation with a different frequency (iTBS) were not. Future studies should examine whether plasticity changes with iTBS are also associated with iTBS treatment outcome. Limitations of this study include a small sample size, choice of target for MEP (M1 rather than DLPFC), and lower stimulation intensities for MEP than those used clinically. Further studies investigating predictive utility of MEPs at the treatment target and with clinical-level stimulation intensities are warranted given these findings.

Hinchman CA, Fried PJ, Jannati A, Press DZ, Pascual-Leone A, Stern AP. Corticomotor plasticity as a predictor of response to high frequency transcranial magnetic stimulation treatment for major depressive disorder. J Affect Disord. 2022;303:114-122. doi:10.1016/j.jad.2022.02.005

Large-Scale Structural Network Changes Correlate with Clinical Response to rTMS in Depression

David M Carlson, MD reviewing Nestor et al. Neuropsychopharm 2022 Feb

A randomized controlled trial examining structural covariance networks found a cortical network profile associated with depression and identified a post-treatment change in cortical thickness that correlated with clinical response in depressed patients who responded to rTMS.

Despite the emerging recognition of rTMS as a first-line treatment for MDD, it remains a time-intensive process with a still-unexplained mechanism of action. rTMS is thought to work by targeting disrupted brain network connectivity, but to date, no network-based biomarkers have been found to correlate with rTMS treatment response in MDD.

This study of 266 patients with MDD from a larger multi-center study examined structural covariance networks (SCNs), which consider cortical gray matter thickness, volume, and surface area maps from T1-weighted MRI and may represent a marker of network connectivity. MRIs for participants were obtained at baseline and one week after completion of treatment, for which subjects were randomized to receive either 10 Hz rTMS or iTBS administered to the left DLPFC (133 in each group) for a total of 20-30 treatments. Response was defined as a ≥50% reduction in the HAM-D. From baseline MRIs, the authors

identified an "MDD signature network" that distinguished depressed participants from a groupof 70 healthy controls. This global network was co-located with the default mode and salience networks. They also examined the DLPFC region targeted by rTMS, which is anatomically distinct from the MDD signature network.

In both 10 Hz rTMS and iTBS groups, change in thickness of the DLPFC target region SCN was positively correlated with percent change in HAM-D score, but only for TMS responders; no such correlation was found for non-responders. Also notable was that, while thickness and volume of the DLPFC target SCN correlated with HAM-D scores at baseline, no association was found between pre-treatment values and treatment response. Additionally, there was no correlation between changes in the MDD signature network SCN and treatment response.

Impact: This first-of-its-kind analysis of structural covariance networks demonstrates that a change in thickness of the DLPFC region targeted by rTMS correlates with response in both 10Hz rTMS and iTBS treatments for depression. Although limited to anatomical markers that do not directly reflect network activity, this work nonetheless is an encouraging finding in the search for biomarkers of TMS response.

Nestor SM, Mir-Moghtadael A, Vila-Rodriguez F, Giacobbe P, Daskalakis ZJ, Blumberger DM, Downar J. Large-scale structural network change correlates with clinical response to rTMS in depression. Neuropsychopharm. 2022; 47(5):1096-1105 PublishedFeb 2, 2022

rTMS Shows Promise for Treatment of Tardive Syndromes

David M Carlson, MD reviewing Khedr et al. J Neural Transm 2019 Feb

In this randomized controlled trial, patients with tardive syndromes treated with rTMS demonstrated a significant reduction in dyskinesia symptoms compared to those receiving sham procedures or no treatment.

Tardive syndromes (TDS), a group of potentially irreversible movement disorders caused by dopamine receptor-blocking agents, are most often associated with antipsychotic medication use. It is defined by the onset of oro-buccal-lingual dyskinesia and/or Parkinsonian tremors and rigidity after three or more months of cumulative exposure to dopamine-blocking agents (one month in patients older than 60), which can persist for years after discontinuation of the offending agent. TDS is typically refractory to dopaminergic, anticholinergic, or GABAergic therapies traditionally used for other movement disorders. Though selective VMAT2 inhibitors and deep brain stimulation have shown promise, these options can be costly and/or invasive; thus, this study sought to investigate the utility of non-invasive rTMS in the management of TDS.

This study evaluated 26 patients with drug-resistant TDS from Aswan University Hospital in Egypt. All participants had received standard-of-care medications such as baclofen, benztropine, and dopaminergic drugs with unsatisfactory results. They were randomized into two groups: 13 to active rTMS and 13 to a sham procedure. The treatment protocol used 20 Hz rTMS at 100% resting MT, provided bilaterally to M1 for 1000 pulses per hemisphere and 10 consecutive days of treatment. Results were measured using the Abnormal Involuntary Movement Scale (AIMS), which was performed at baseline and after completion.

Both active and sham groups saw a significant reduction in AIMS scores, with the active rTMS group achieving a reduction of 8.3 ± 1.7 (p=0.0001) while the sham group showed a reduction of 1.2 ± 3.3 (p=0.03). A repeated measures ANOVA yielded a significant time x group interaction indicating significantly greater improvement in the active group compared to the sham group. This trend was observed in all subscales (overall severity, incapacitation, and awareness). There were no significant changes in cortical excitability measures in any group.

Impact: This trial provides evidence for bilateral 20 Hz rTMS of M1 as a treatment option for drug-related tardive syndromes in patients unresponsive to "first-line" medication treatments. Limitations of the study include the lack of comparison with the emerging first-line options of VMAT2 inhibitors and a lack of longer-term follow-up beyond the immediate post-treatment assessment. Nonetheless, these results provide promising evidence for a new treatment of this feared complication of antipsychotic therapy.

Khedr EM, Al Fawal B, Abdelwarith A, Saber M, Rothwell JC. Repetitive transcranial magnetic stimulation for treatment of tardive syndromes: double blind randomized clinical trial. J Neural Trans. 2019;126:183-191. Published Online 13 October 2018

iTBS to Left DLPFC Significantly Modulates TMS-Evoked Cortical Potentials in a Dose-Independent Manner

Collin M Price reviewing Desforges et al. Clin Neurophysiol 2022 Apr

In a group of neurotypical healthy controls, concurrent TMS-EEG before and after iTBS to the left DLPFC showed significant modulation of cortical evoked potentials. However, iTBS pulse number (600, 1200, or 1800) had no effect on the magnitude of prefrontal activity modulation.

Initial iTBS protocols targeting the DLPFC to treat MDD used 600 pulses, with more recent clinical trials commonly using higher pulse counts. Although higher pulse count has been shown to enhance efficacy, the effects of pulse number have not been extensively studied, and prior work has shown that larger iTBS pulse counts over motor cortex may actually attenuate or even reverse effects of stimulation. In this study, the authors set out to assess the cortical effects in healthy volunteers of three different doses of iTBS – 600, 1200, and 1800 pulses – by comparing TMS-evoked potentials before and after each iTBS dose.

The study utilized a crossover design in which each participant received three doses of iTBS (600, 1200, or 1800) at three different randomized, counterbalanced visits, each separated by at least 7 days. The participants were 14 right-handed volunteers (F: 7) aged 18-40 years without lifetime history of neuropsychiatric disorder or six-month history of SUD. Theta-burst TMS was delivered using a Magstim Super Rapid2 coil at an intensity of 80% active MT, with the left DLPFC targeted using neuronavigation to ensure consistent placement. Immediately before and after each iTBS session, TMS-evoked potentials (TEP) and event related spectral perturbations (ERSPs) were recorded using a TMS-EEG system delivering single pulse and paired-pulse stimulations. EEG signals were recorded from five electrodes surrounding the stimulation target (AF3, F1, F3, FC1, and FC3). TEP amplitudes were compared within standard latency windows: P30 (20-35 ms), N45 (40-50 ms), P60 (55-65 ms), N100 (85-125 ms), and P200 (170-220 ms); ERSP were investigated within canonical EEG bands. Statistical analyses included a linear mixed model for the amplitudes of each TEP component and ERSP EEG band, with dose and time-point as within-subject factors, for single- and paired-pulse probes.

For the single-pulse TMS probe, no significant interaction was observed between dose and time-point for either TEP or ERSP. Single-pulse TEP revealed that all doses of iTBS decreased the amplitude of the P30, P60, and P200 components, and increased the amplitude of the N45 component (all $p<0.001$). Single-pulse ERSP showed that all iTBS doses reduced theta band power ($p=0.002$). Similar to the single-pulse data, the paired-pulse TMS probes showed no significant interaction between dose and time-point for either TEP or ERSP. Paired-pulse TEP revealed that all doses of iTBS significantly decreased the short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI) ratios of the P30 and P200 components and increased the SICI ratio of the N45 component (all $p<0.02$). Paired-pulse ERSP showed no significant pre-post change for any iTBS dose in any frequency band for the SICI ratio, while the LICI ratio showed a reduction in the theta band post-iTBS ($p=0.022$).

Impact: In this randomized crossover study of healthy controls, three doses of iTBS (600, 1200, and 1800) were all found to have similar effects on DLPFC activity. These effects included a general decrease in cortical activity as measured by TEP and a decrease in TMS-induced theta power. This study was limited by a small sample size and no control condition. Additionally, patients with neuropsychiatric illness likely have different baseline levels of cortical activity which may limit applicability of these findings to clinical populations. Because this study was performed in healthy subjects, it also is unclear whether the lack of a dose-response relationship on EEG activity has any relevance to clinical outcome. Replication of these findings in a larger, clinical population with a sham control iTBS condition, along with examining treatment outcome, could have significant clinical implications.

Desforges M, Hadas I, Mihov B, et al. Dose-response of intermittent theta burst stimulation of the prefrontal cortex: A TMS-EEG study. Clin Neurophysiol. 2022;136:158-172. doi:10.1016/j.clinph.2021.12.018

Abbrevations

DBS (Deep Brain Stimulation)
dTMS (deep Transcranial Magnetic Stimulation)
EEG (electroencephalography)
EMG (electromyography)
HF-rTMS (high frequency repetitive Transcranial Magnetic Stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent Theta Burst Stimulation)
MT (motor threshold)
rTMS (repetitive Transcranial Magnetic Stimulation)
tACS (transcranial Alternating Current Stimulation)
tDCS (transcranial Direct Current Stimulation)

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

AUD (Alcohol Use Disorder)
MDD (Major Depressive Disorder)
OCD (Obsessive Compulsive Disorder)
SUD (Substance Use Disorder)
TRD (treatment resistant depression)

BDI-II (Beck Depression Inventory)
HAM-D (Hamilton Depression Rating Scale; 17-item version unless otherwise specified)
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)
ICA (independent component analysis)
ITT (intent to treat)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)