Assessing rTMS Effects on Resting-State EEG Power and Correlation of These Effects With Cognitive Task Performance

Scholarly Report submitted in partial fulfillment of the MD Degree at Harvard Medical School

13 April 2020

Kevin Sikah, BA

Assessing rTMS Effects on Resting-State EEG Power and Correlation of these Effects with Cognitive Task Performance

Mouhsin Shafi, MD, PhD, Dept of Neurology, Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center

Recep Ozdemir, PhD, Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center

Jessica Ross, PhD, Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center

Timothy Smith, PhD, Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center

Pierre Boucher, BS, Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center

Lisa Nickerson, PhD, Applied Neuroimaging Statistics Lab, McLean Hospital

Emiliano Santarnecchi, PhD, Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center

Abstract

Title: Assessing rTMS Effects on Resting-State EEG Power and Correlation of these Effects with Cognitive Task Performance

Purpose: To assess the nature and reliability of the effects of intermittent theta burst stimulation (iTBS) vs continuous TBS (cTBS) vs sham stimulation on resting-state EEG oscillatory power in various frequency bands, determine the relationship between rTMS effects on resting-state EEG power and TMS EMG motor-evoked potentials (MEPs), and determine whether baseline neuropsychological task performance on motor and memory tasks is related to TBS plasticity at primary motor cortex (M1).

Methods: We worked with 24 healthy subjects who underwent cognitive testing at a baseline visit. These subjects would each return for three visits of TBS (where they were randomized to receive cTBS, iTBS, and Sham TBS in different orders). During each visit, corticospinal excitability was also measured through the elicitation of MEPs. Resting-state EEG was recorded before TBS administration and 15 minutes afterward. After the first three visits, subjects returned for an additional three visits in the same order as the first visits, for a total of six TBS visits. Data collected were analyzed for power in the left and bilateral frontocentral regions in the alpha and beta bands. Data were evaluated for relationships between pre/post-TBS resting-state EEG power change and cognitive testing, pre/post-TBS MEP amplitude change, and stimulation type. Pre/post EEG power changes of matched visits (e.g. cTBS visit 1 and cTBS visit 2) over the left and bilateral frontocentral regions in the alpha and beta frequencies were evaluated for test-retest reliability using Cronbach's alpha.

Results: ANCOVAs run on the acquired data did not reveal any significant relationships between stimulation type and EEG power difference scores. Internal energy (reaction time controlled for error) of the Face Memory test was modestly correlated (~0.4) with EEG power difference scores in the cTBS condition in the beta band, and MEP amplitude change had a similar correlation to EEG power difference scores in the iTBS condition in the alpha band. Sham stimulation exhibited some test-retest reliability relative to EEG power difference scores, but iTBS and cTBS did not.

Conclusion: Cognitive and motor testing may help to predict effects of TBS on brain activity, but highly predictive factors remain elusive. It is possible that other factors may exhibit a stronger link, and this analysis may benefit from linking with evaluation of TMS-EEG, rather than resting-state EEG alone.

Table of Contents

Glossary of Abbreviations

BL: Baseline

cTBS: Continuous Theta Burst Stimulation

EEG: Electroencephalogram

EMG: Electromyogram

IE: Internal Energy

iTBS: Intermittent Theta Burst Stimulation

MEP: Motor-Evoked Potential

rTMS: Repetitive Transcranial Magnetic Stimulation

spTMS: Single-Pulse Transcranial Magnetic Stimulation

SRTT: Simple Reaction Time Test

TBS: Theta Burst Stimulation

TMS: Transcranial Magnetic Stimulation

T15: 15 minutes post-TBS

T20: 20 minutes post-TBS

Section 1: Introduction

Transcranial Magnetic Stimulation (TMS) is a technique used to induce electrical signaling in cortical brain areas and modulate their excitability (21). It has been used both in research and clinical contexts. It is thought that certain frequencies of repetitive TMS (rTMS) generally have inhibitory effects (1 Hz) while others have excitatory effects (10 Hz) (22). In recent years, TMS devices have been approved by the US Food and Drug Administration for treatment of certain psychiatric and neurologic disorders such as depression, OCD, and migraine (31). It continues to be investigated for potential application in other neuropsychiatric disorders (3, 5, 12, 20). TMS is often used therapeutically in patients who have failed to improve with multiple pharmacologic interventions, and it may also be used when other modalities such as electroconvulsive therapy (ECT) are helpful but have a side effect profile that a patient is unable to tolerate.

One modality of rTMS, called theta burst stimulation (TBS), has been the subject of increasing interest in recent years, as it may have the potential to produce effects similar to traditional forms of rTMS (e.g. 1 Hz and 10 Hz) but in less time per session (13). The THREE-D trial (1) is a promising start, as it demonstrated non-inferiority of iTBS to 10 Hz rTMS for the treatment of depression. TBS is a newer modality than 1 Hz and 10 Hz rTMS and is not as well-understood as these classic protocols, so more data are required. TBS involves administering a burst of 3 pulses at 50 Hz repeated at intervals of 200 ms, and it may be administered in an intermittent (iTBS) or continuous (cTBS) fashion (**Figure 1a and 1b**). iTBS has been generally observed to have excitatory effects similar to 10 Hz rTMS, and cTBS has been observed to have inhibitory effects similar to 1 Hz rTMS (13). However, despite this general pattern, substantial within-group variability has also been observed (15), and further characterization of the reliability of rTMS effects is needed.

rTMS is thought to modulate cortical oscillations (7, 9); in motor cortex, the alpha and beta frequency bands are particularly susceptible to modulation (27). It is also proposed to exert its effects at least partly through mechanisms akin to long-term potentiation (LTP) and long-term depression (LTD) (6, 11, 19, 35). LTP and LTD are thought to be involved in memory (16), so it is possible that responses to TMS may be correlated with baseline learning prior to TMS, as greater plasticity is generally supportive of enhanced learning (8). Cognitive testing may provide an avenue through which to evaluate this.

While much research focuses on brain activity during the administration of TMS, information can be gleaned from evaluation of EEG activity at rest after TMS delivery; there have been reports of some

effects of TBS on resting-state EEG activity (30). Resting-state data may prove to be an additional source of information that could help to untangle the complicated effects of TBS.

The current study had several aims. We wanted to assess the nature and reliability of the effects of iTBS vs cTBS vs sham stimulation on resting-state EEG oscillatory power in various frequency bands, determine the relationship between rTMS effects on resting-state EEG power and TMS EMG motor-evoked potentials (MEPs), and determine whether baseline neuropsychological task performance on motor and memory tasks is related to TBS plasticity at primary motor cortex (M1). Our hypotheses are that the modulatory effects of TMS on EEG measures will show high reliability across experimental sessions, different TMS modalities will have different effects on alpha and beta frequency oscillatory power, response to TMS on EEG will correlate with TMS-EMG motor evoked potentials (MEPs), and response to TMS on EEG will correlate with neuropsychological task performance.

Section 2: Student Role

My role in the project was largely based on data analysis. The data themselves had been collected prior to my joining the lab, and the aims had been written in a way to allow for an exploratory approach to the data analysis. Some of the general ideas for the analysis were drawn out prior to my joining the lab, but I discussed the specific ways in which the data would be analyzed with my PI and other lab members. I participated in writing and editing the MATLAB scripts that were needed for the data preprocessing and analyses that I had in mind, and I also ran the analyses. The preprocessing involved removing bad channels, deleting epochs that had excessive amounts of noise or artifact, organizing the data into independent components, and selecting the components with the least amount of non-neural noise for analysis. Additionally, I wrote this report and generated the figures associated with it.

Section 3: Methods

Subject Selection

Data were collected from 24 healthy participants between the ages of 18 and 49 (mean 29.6 +/- 2.16 years old; 16 male and 8 female) who participated in research at the Berenson-Allen Center for Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center between 2017 and 2018. The study was approved by the local Institutional Review Board, and all participants provided written informed consent. All participants were right-handed per the Edinburgh Handedness Questionnaire. Exclusion criteria included history of seizures (beyond single benign seizure), history of head injury resulting in loss of consciousness, implanted medical devices or metal (unless approved by responsible MD), current history of psychiatric illness, neurological disorders, intracranial lesions, history of poorly controlled migraines (including chronic medication use for prevention), unstable medical conditions, pregnancy (by urine pregnancy test), substance abuse/dependence within the past six months, diseased or damaged skin on the face/scalp, and hair style/headdress preventing contact between electrodes and the scalp. Past medical history and medications were reviewed by the responsible MD to reach a decision about inclusion.

Cognitive Testing

In an initial session, each participant underwent cognitive testing. The Simple Reaction Time Test (SRTT) and Face Memory Test were completed at this time. No cortical activity was measured during this session. In the SRTT, participants were presented with visual cues at one of four positions on a computer screen corresponding to four keyboard buttons that they could press. Participants were asked to press a button corresponding to the visual cue presented. In the Face Memory Test, subjects were shown photos of young men in black and white with cropped hair and neutral expressions. Six faces were deemed targets while the rest were deemed distractors. During each trial, one target and two distractors were shown, with the potential for targets and distractors to appear in multiple trials. Participants were asked to indicate which of the three faces in a given trial was a target. In both tests, reaction time and accuracy were recorded. Internal Energy Scores (reaction time/(1-error), (29)) were generated for each both tests as well.

EEG and EMG

Participants underwent EEG and EMG recording on a total of six occasions after the cognitive testing session. Each session was separated from the prior session by two days to two weeks. The modality of

TBS administered during the first three visits differed such that the subject received iTBS in one visit, cTBS in another, and sham TBS in a third visit; the order of these visits was randomized for each subject (**Figure 1c**). Visits 4-6 followed the same order as visits 1-3. Identical sessions were spaced four weeks apart.

During a given session, subjects were set up with an EEG cap and EMG electrodes on the right hand for recording of MEPs. EEG was acquired using an extended version of the International 10-20 System (**Figure 2**). Ground and reference electrodes were placed on the forehead, and two electrooculography electrodes were placed near each eye to identify eye movements in a subset of participants. Most of the participants had the reference electrode placed near the left eye (**Figure 2b**); spherical interpolation was used after initial processing to unify electrode maps of the two subsets. During recording, subjects were seated in a semi-reclined armchair. Stimulation was administered with the Magpro device (MagVenture A/S, Farum, Denmark) using a figure-of-eight coil.

Assessment of Motor Threshold and TMS-MEPs

Resting motor threshold (RMT) was determined by applying single TMS pulses over M1. RMT was defined as the minimum stimulus intensity that produced a MEP of at least 50 uV in at least 50% of trials. TMS-MEPs were elicited using single pulses of 120% RMT while the hand was completely relaxed. MEPs were elicited prior to acquisition of pre-TMS resting-state EEG (see below) as well as at a number of time points after TMS administration, including 5, 10, and 20 minutes post-TMS (**Figure 1c**). Post-TMS resting state EEG acquisition was done 15 minutes after TMS administration. For this study, baseline and 20-min post-TBS MEPs (T20 MEPs) were of interest, as MEPs by definition could not be recorded during resting-state EEG recordings. MEPs were quantified using the peak-to-peak amplitude. Difference scores were made by subtracting baseline MEPs from T20 MEPs, then dividing by baseline MEP amplitude for normalization. Active motor threshold (AMT) was also determined by applying single TMS pulses over M1. AMT was defined as the minimum stimulus intensity that produced a MEP of at least 200 uV followed by an absence of background EMG activity in at least 50% of 10 trials. During determination of AMT, the tested muscles were isometrically contracted at approximately 20% of maximum voluntary contraction.

Resting State EEG

Prior to the administration of TBS, 2.5 minutes of EEG recordings were obtained. Subjects were instructed to sit in a relaxed manner with their eyes open and face muscles relaxed during this time. The

subject and EEG were monitored for signs of drowsiness. Another 2.5 minutes of EEG recordings were obtained 15 minutes after the administration of TBS.

TMS-EEG

After the first 2.5 minutes of resting-state EEG were recorded, the subject received 600 pulses of TBS over M1 of the left hemisphere. Subjects received iTBS, cTBS, or sham TBS with stimulation intensity set to 80% AMT. For subjects in whom AMT was difficult to determine, intensity was set to 70% RMT (which is within 5% of 80% AMT). iTBS was applied to M1 in 2-second trains, each with bursts of 3 TMS pulses of 50 Hz repeated at 200 ms intervals (**Figure 1a**). There was an 8 second pause between trains, such that 600 pulses were given in total. cTBS was applied to the same site in 3 pulses of stimulation at 50 Hz repeated at 200 ms intervals for 40 seconds (**Figure 1b**). 600 pulses were given in total. Subjects were randomized to receive Sham TBS in the same pattern as iTBS or cTBS due to the differences in acoustic patterns of these protocols. The Sham TBS stimulation was administered using a stimulation coil with extra shielding that reduced the magnetic field intensity to 5% of that of real TBS; a spacer was also added to the coil.

EEG Preprocessing

EEG data preprocessing was done after acquisition had been completed. A combination of the EEGLAB toolbox (4) and custom scripts in MATLAB R2019a (Mathworks, USA) were used. EEG data were downsampled to 1000 Hz. Low-pass (49 Hz) and high-pass (1 Hz) filters were applied through a fourth-order Butterworth filter. Faulty or noisy channels were removed using a script that compared subject data to known artifact-free data (10); the resulting data was spherically interpolated. A minority of visits used a different electrode map, and additional spherical spline interpolation was used on these visits' data to interpolate data from channels from the majority map (overall average +/- SD channels removed= 4.7 +/- 2.8; range = 1-13) and channels were re-referenced to the average of all channels. Data were split into 3-second epochs for visualization. Pre- and post-TBS data were concatenated, and independent components were generated using fastICA (24). Components that were highly likely to be non-neural in origin (blink, oculomotor, muscle, cardiac, or transient electrode artifacts) were rejected through an automated algorithm (33, 34) and remaining components were visualized in TESA (23) for manual rejection. Pre-TBS and post-TBS data were separated, and epochs that were contaminated by artifact that was refractory to removal via ICA were rejected prior to further analysis (average +/- SD pre-TBS epochs removed= 0.2 +/- 0.7, range= 0-5; average +/- SD post-TBS epochs removed= 0.1 +/- 0.4,

range= 0-2). This resulted in 23-72 usable pre-TBS epochs per participant with an average (+/- SD) of 50.7 (+/- 5.1) and 21-73 usable post-TBS epochs per participant with an average (+/- SD) of 49.8 (+/- 4.9).

Data Analysis/ Statistical Testing

Electroencephalography

Power spectra were generated for all electrodes (1-50 Hz, 0.5 Hz resolution) using the *spectopo* EEGLAB function (window-size= 1000 samples, window-overlap= 500 samples) (4). Power was measured in the alpha (8-13 Hz) and beta (13-30 Hz) frequency bands in the pre-TBS phase and the post-TBS phase. Two regions of interest were defined; the first was the frontocentral region of the left hemisphere (ipsilateral to stimulation), and the second combined this with the frontocentral region of the right hemisphere (bilateral). The left frontocentral region was defined as electrodes F3, F1, Fz, FC3, FC1, FCz, C3, C1, Cz on the final electrode map (**Figure 2b**), and the bilateral frontocentral region was defined as electrodes F3, F1, Fz, F2, F4, FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4. Power spectral density (PSD) in a given frequency band (e.g. alpha, beta) at each electrode was calculated by summing the power of each frequency bin (e.g. 8 Hz, 9 Hz, etc) within that band at that electrode, then dividing by the number of bins. Regional PSD in this band was calculated by averaging the band PSD of all electrodes of that region. Difference scores for each region-band were generated by subtracting the pre-TBS PSD from the post-TBS PSD, then dividing the result by the pre-TBS PSD for normalization.

Model-Building and Test-Retest Reliability

Reaction time and accuracy were recorded during the SRTT and Face Memory Test and Inverse Efficiency Scores were generated for each (29). TMS-EEG power pre- and post-TBS across protocols (iTBS, cTBS, sham) were analyzed using analysis of covariance (ANCOVA, one for each combination of alpha/beta frequencies over ipsilateral/bilateral frontocentral regions), where time between visits, age, and gender were covariates. As each model was tested with four ANCOVAs, Bonferroni correction was used. EEG PSD difference scores from the first visit of each type (i.e. visits 1-3) were used for the ANCOVA. Correlation coefficients for the relationships between EEG PSD difference scores (from the four conditions used in the ANCOVA) with SRTT IE, Face Memory IE, and TMS-MEP difference scores (peak-to-peak amplitude of MEPs elicited at 20 post-TBS minus baseline MEP amplitude, normalized to baseline MEP amplitude). Consistency of TMS-EEG power changes across sessions of the same stimulation (e.g. iTBS in sessions 1 and 4 for a given patient) was characterized using Cronbach's alpha index (25) for test-retest reliability.

This study using resting-state EEG was intended to complement a TMS-EEG study with the same participants. As the estimated change in magnitude of the TMS-evoked EEG potential in response to rTMS based on prior studies is about 30% (28), assumption of a standard deviation of the differences of 40% with an alpha of 0.05 and a power of 80% resulted in a target sample size of 24.

Section 4: Results

Four ANCOVAs (**Tables 1-4**) were run to analyze the possible relationship between stimulation type and changes in EEG power in the alpha and beta bands over a predefined frontocentral region ipsilateral to stimulation as well as a region consisting of this and its contralateral counterpart (**Figure 2b**). Since four ANCOVAs were run for this model, the Bonferroni-corrected alpha was 0.0125. None of the ANCOVAs for this model contained factors with $p<0.0125$, and further pairwise analysis was not undertaken.

Correlation analysis was undertaken using EEG PSD difference scores (from the four ANCOVA conditions-alpha PSD in the ipsilateral ROI, alpha PSD in the bilateral ROI, beta PSD in the ipsilateral ROI, and beta PSD in the bilateral ROI) (**Tables 5-7**). Specifically, the variables correlated with the EEG PSD difference scores were the SRTT IE, Face Memory IE, and MEP difference scores (between 20 min post-TBS and baseline). All of the coefficients for the SRTT IE were less than 0.2 in magnitude (**Table 5**). The Face Memory IE had coefficients close to 0.4 in magnitude for the beta band (ipsilateral and bilateral) in the cTBS condition, but all other coefficients were small (**Table 6**). The MEP difference scores had coefficients close to 0.4 in magnitude for the alpha band (ipsilateral and bilateral) in the iTBS condition, but all other coefficients were small (**Table 7**).

We investigated the test-retest reliability of the change in resting-state EEG power after delivery of TBS by calculating Cronbach's alpha (standardized, C_{as}; unstandardized, C_{au}) (**Tables 8 and 9**).

In the alpha band in the normalized model (**Table 8**), cTBS was not reliable ipsilaterally (C_{as}= 0.2018, C_{au}= 0.201) or bilaterally (C_{as}= 0.1792, C_{au}= 0.1768). iTBS was not reliable ipsilaterally (C_{as}= -1.4189, C_{au}= -1.0128) or bilaterally (C_{as}= -1.3489, C_{au}= -0.9497). Sham showed limited reliability ipsilaterally (C_{as}= 0.5132, C_{au}= 0.4739) and bilaterally (C_{as}= 0.5214, C_{au}= 0.4821).

In the beta band in the normalized model (**Table 9**), cTBS was not reliable ipsilaterally (C_{as}= -0.0095, C_{au}= -0.0093) or bilaterally (C_{as}= 0.083, C_{au}= 0.0814). iTBS was not reliable ipsilaterally (C_{as}= -0.2331, C_{au}= -0.2202) or bilaterally (C_{as}= -0.1161, C_{au}= -1.11E-01). Sham showed reliability ipsilaterally (C_{as}= 0.7544, C_{au}= 0.6338) and bilaterally (C_{as}= 0.7691, C_{au}= 0.6604).

Section 5: Discussion, Limitations, Conclusions, and Suggestions for Future Work

We sought out to determine whether cognitive testing and TMS-MEP properties could be used to predict the response to continuous, intermittent, or sham TBS, using models that also controlled for time between visits, age, and gender. However, it failed to detect any relationship between the type of TBS administered and the response to TBS. While the sample size was suitable for evaluation of active TMS effects, it is possible that resting-state effects were too small to be observed with the power of the current study. spTMS was administered for MEP measurement after the TBS but prior to the post-TBS resting-state EEG recording (5 and 10 min after TBS) in addition to the 20 min post-TBS (T20) time point. Notably, spTMS generally does not have effects lasting longer than a period on the order of seconds (17), though one of the protocols used for acute treatment of migraine does involve spTMS and is thought to work by disrupting patterns of cortical activity (14). Some of the MEP data were not sufficient to provide data for the T20 time points, weakening the contribution of this MEP term to the model.

We also investigated the relationships between the change in resting-state EEG power post-TBS and cognitive testing (SRTT, Face Memory test), in addition to the relationship between this resting-state EEG power change and MEP power change. Most of the correlation coefficients were small, but Face Memory IE had coefficients close to 0.4 in the beta band (for both the ipsilateral and bilateral frontocentral regions) with cTBS administration, while MEP power change had similar coefficients in the alpha band (ipsilateral and bilateral) with iTBS administration. One way to interpret the former relationship is that decreased internal energy (essentially reaction time multiplied by a factor representing error rate) at baseline has some relation to a smaller increase in resting-state power after cTBS administration. Notably, cTBS is generally posited to have inhibitory effects (22), so this could support a hypothesis that the putative effects of cTBS are more visible in subjects with lower internal energy on the Face Memory test. The coefficient for MEP power change in the alpha band with iTBS would imply that to some degree, a greater facilitatory response to iTBS in MEP amplitude is also reflected in resting state power in the frontocentral region.

Finally, we sought to determine whether the response to each TBS protocol was consistent. The pre- and post-TBS EEG responses from cTBS and iTBS were not reliable in the alpha or beta bands, while the response to sham stimulation seemed more consistent, with Cronbach's alpha around 0.5 for alpha and between 0.66 and 0.77 for beta. These reliability measures for the sham responses provide some support to the idea that the low reliability measures for cTBS and iTBS may have some merit. Cronbach's alpha is typically between 0 and 1, but it is possible to have negative values (26), which occurred in some

of our conditions. This can bring data quality into question, and per its formula it can occur when covariance is greater than variance.

It is interesting that we did not observe consistency in the "active" protocols (cTBS and iTBS) in our study while the THREE-D trial showed non-inferiority of iTBS to a standard rTMS depression treatment protocol (1). The THREE-D trial had a significantly greater number of participants than our study (around 500 compared to 24 in our study) and so were likely better equipped to detect this relationship. It is also possible that the participation of healthy subjects rather than subjects with depression resulted in different response patterns.

Our study had a few limitations in addition to those previously mentioned. When the TMS is administered, there is a focal area in which stimulation is greatest, but there is generally some stimulation of adjacent areas as well (2). Beyond this, stimulation of a given area often results in consequent stimulation of connected areas, such that networks are affected. This makes it difficult to attribute an effect specifically to the targeted area, though some conclusions can be drawn about the effects of TMS on networks, which may be related to cognitive/behavioral outcomes.

Additionally, TMS effects seen on EEG can come from sources beyond the direct stimulation of the brain. Stimulation of the overlying muscle, the mechanical sensation of coil activation on the skin, and the auditory signal of the sound of pulse generation can generate EEG signals. Furthermore, other sources of electricity in the room, eye movements, heartbeat, and disturbances in contact between EEG electrodes and the scalp can also act as sources of noise. These effects can generally be mitigated through data preprocessing, and as part of our preprocessing we used a toolbox that recognized noisy/artifactual components by comparing presented components with components that were labeled by experts.

It is possible that significant relationships would be found in a similar model focused on other regions or bands. The centrofrontal region was chosen due to the use of a motor task and a task that required working memory. Aside from the noted lability of alpha and beta bands in motor cortex, beta frequencies are highly represented in frontal regions; for example, increases in low beta in prefrontal areas are associated with inhibitory control (32). However, it is possible that areas most strongly related to some of the predictive measures (e.g. performance on the Face Memory test) may have signals best seen in other electrodes or that are difficult to observe via EEG (e.g. hippocampus). Given the limited

sample size, nonparametric techniques such as cluster-based permutation analysis (18) may be necessary to guide next steps in similar future studies.

We hoped that this project would contribute to the field's understanding of TBS and improve the reliability of predictions of directionality and strength of cTBS and iTBS effects. Additionally, this project was intended to provide insight into the relationship between cortical oscillations and corticospinal output, as well as whether plasticity is a general property of the brain that is preserved across outcome domains (task performance and neurophysiology). While we were not able to establish significant relationships between stimulation type and power in the centrofrontal region in the alpha and beta bands, these results have helped with guidance on next steps to take. Future work could expand the application of resting-state measures to populations beyond healthy subjects. Additionally, given the heterogeneity of effects of TBS protocols in our study and in the literature, a study directly comparing effects of TBS on resting-state EEG and TMS-EEG would help to further elucidate the workings of TBS.

Section 6: Acknowledgements

I would like to acknowledge Dr. Mouhsin Shafi for his guidance and mentorship throughout this project. He was instrumental in the brainstorming of the analysis for the project as well as in providing feedback at its various stages.

Dr. Recep Ozdemir was incredibly helpful with troubleshooting some of the coding issues that I encountered, and I appreciate his role in the collection of the data.

Dr. Jessica Ross and Dr. Timothy Smith were responsible for the base script that I edited for use in the data preprocessing stage, and they were quite helpful in troubleshooting some of the technical roadblocks that I encountered.

I am grateful to Pierre Boucher for his guidance on the minutiae of data preprocessing as well as for his role in data collection.

I appreciate Dr. Lisa Nickerson's help in guiding me through the thought process for selecting some of the statistical tests and streamlining the design of the analysis.

This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL 1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

References

1. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. The Lancet. 2018;391(10131):1683-92. doi: 10.1016/S0140-6736(18)30295-2.
2. Conde V, Tomasevic L, Akopian I, Stanek K, Saturnino GB, Thielscher A, et al. The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. NeuroImage. 2019;185:300-12. doi: 10.1016/j.neuroimage.2018.10.052.
3. Cooper YA, Pianka ST, Alotaibi NM, Babayan D, Salavati B, Weil AG, et al. Repetitive transcranial magnetic stimulation for the treatment of drug-resistant epilepsy: A systematic review and individual participant data meta-analysis of real-world evidence. Epilepsia Open. 2018;3(1):55-65. doi: 10.1002/epi4.12092.
4. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. Journal of Neuroscience Methods. 2004;134(1):9-21. doi: 10.1016/j.jneumeth.2003.10.009.
5. Feil J, Zangen A. Brain stimulation in the study and treatment of addiction. Neuroscience and Biobehavioral Reviews. 2010;34(4):559-74. doi: 10.1016/j.neubiorev.2009.11.006.
6. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning. Neuron. 2010;66(2):198-204. doi: 10.1016/j.neuron.2010.03.035.
7. Fuggetta G, Pavone EF, Fiaschi A, Manganotti P. Acute modulation of cortical oscillatory activities during short trains of high-frequency repetitive transcranial magnetic stimulation of the human motor cortex: A combined EEG and TMS study. Human Brain Mapping. 2008;29(1):1-13. doi: 10.1002/hbm.20371.
8. Galván A. Neural plasticity of development and learning. Human Brain Mapping. 2010;31(6):879-90. doi: 10.1002/hbm.21029.
9. Hamidi M, Slagter HA, Tononi G, Postle BR. Repetitive Transcranial Magnetic Stimulation Affects behavior by Biasing Endogenous Cortical Oscillations. Frontiers in integrative neuroscience. 2009;3:14. doi: 10.3389/neuro.07.014.2009.
10. Kothe CM, Makoto. Clean_rawdata EEGLAB plugin. 1.10 ed. GitHub2019.
11. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct current stimulation modulates LTP and LTD: activity dependence and dendritic effects. Brain Stimulation. 2017;10(4):e23-e4. doi: 10.1016/j.brs.2017.04.014.
12. Kumar S, Singh S, Parmar A, Verma R, Kumar N. Effect of high-frequency repetitive transcranial magnetic stimulation (rTMS) in patients with comorbid panic disorder and major depression. Australasian Psychiatry. 2018;26(4):398-400. doi: 10.1177/1039856218771517.
13. Li C-T, Chen M-H, Juan C-H, Huang H-H, Chen L-F, Hsieh J-C, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain. 2014;137(7):2088-98. doi: 10.1093/brain/awu109.
14. Lipton RB, Pearlman SH. Transcranial Magnetic Simulation in the Treatment of Migraine. Neurotherapeutics. 2010;7(2):204-12. doi: 10.1016/j.nurt.2010.03.002.
15. López-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-Del-Olmo M. Inter-individual Variability in Response to Non-invasive Brain Stimulation Paradigms. Brain Stimulation. 2014;7(3):372-80. doi: 10.1016/j.brs.2014.02.004.

16. Nabavi S, Fox R, Proulx CD, Lin JY, Tsien RY, Malinow R. Engineering a memory with LTD and LTP. Nature. 2014;511(7509):348-52. doi: 10.1038/nature13294.
17. Natalie AM, Jon BHS, Dirk De R, John NJR. Opinion: Understanding the Effects of Repetitive Transcranial Magnetic Stimulation on Neuronal Circuits. Frontiers in Neural Circuits. 2016;10. doi: 10.3389/fncir.2016.00067.
18. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: A primer with examples. Human Brain Mapping. 2002;15(1):1-25. doi: 10.1002/hbm.1058.
19. Nitsche MA, Müller-Dahlhaus F, Paulus W, Ziemann U. The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS active drugs. Oxford, UK: Blackwell Publishing Ltd; 2012. p. 4641-62.
20. Notzon S, Deppermann S, Fallgatter A, Diemer J, Kroczek A, Domschke K, et al. Psychophysiological effects of an iTBS modulated virtual reality challenge including participants with spider phobia. Biological Psychology. 2015;112:66-76. doi: 10.1016/j.biopsycho.2015.10.003.
21. Pascual-Leone A, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain : a journal of neurology. 1994;117 (Pt 4):847.
22. Pell GS, Roth Y, Zangen A. Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: Influence of timing and geometrical parameters and underlying mechanisms. Progress in Neurobiology. 2011;93(1):59-98. doi: 10.1016/j.pneurobio.2010.10.003.
23. Rogasch NC, Sullivan C, Thomson RH, Rose NS, Bailey NW, Fitzgerald PB, et al. Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: A review and introduction to the open-source TESA software. NeuroImage. 2017;147:934-51. doi: 10.1016/j.neuroimage.2016.10.031.
24. Rogasch NC, Thomson RH, Farzan F, Fitzgibbon BM, Bailey NW, Hernandez-Pavon JC, et al. Removing artefacts from TMS-EEG recordings using independent component analysis: Importance for assessing prefrontal and motor cortex network properties. NeuroImage. 2014;101(2):425-39. doi: 10.1016/j.neuroimage.2014.07.037.
25. Schlegel A. Cronbach's Alpha. MATLAB Central File Exchange 2020.
26. Thompson B. Understanding Reliability and Coefficient alpha, Really. 2003 [cited 4/13/20]. In: Score Reliability [Internet]. Thousand Oaks, California: SAGE Publications, Inc., [cited 4/13/20]; [3-30]. Available from: https://methods.sagepub.com/book/score-reliability.
27. Thut G, Miniussi C. New insights into rhythmic brain activity from TMS–EEG studies. Trends in Cognitive Sciences. 2009;13(4):182-9. doi: 10.1016/j.tics.2009.01.004.
28. Thut G, Pascual-Leone A. A Review of Combined TMS-EEG Studies to Characterize Lasting Effects of Repetitive TMS and Assess Their Usefulness in Cognitive and Clinical Neuroscience. Brain Topography. 2010;22(4):219-32. doi: 10.1007/s10548-009-0115-4.
29. Townsend JT, Ashby FG. Stochastic modeling of elementary psychological processes: CUP Archive; 1983.
30. Vernet M, Bashir S, Yoo WK, Perez JM, Najib U, Pascual-Leone A. Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS – EEG. European Journal of Neuroscience. 2013;37(4):598-606. doi: 10.1111/ejn.12069.
31. Voelker R. Brain Stimulation Approved for Obsessive-Compulsive Disorder. JAMA. 2018;320(11):1098. doi: 10.1001/jama.2018.13301.
32. Wagner J, Wessel JR, Ghahremani A, Aron AR. Establishing a Right Frontal Beta Signature for Stopping Action in Scalp EEG: Implications for Testing Inhibitory Control in Other Task Contexts. Journal of Cognitive Neuroscience. 2018;30(1):107-18. doi: 10.1162/jocn_a_01183.
33. Winkler I, Brandl S, Horn F, Waldburger E, Allefeld C, Tangermann M. Robust artifactual independent component classification for bci practitioners. Journal of Neural Engineering. 2014;11(3):035013. doi: 10.1088/1741-2560/11/3/035013.

34. Winkler I, Haufe S, Tangermann M. Automatic classification of artifactual ICA-components for artifact removal in EEG signals. Behavioral and brain functions : BBF. 2011;7:30. doi: 10.1186/1744-9081-7-30.
35. Ziemann U. Thirty years of transcranial magnetic stimulation: where do we stand?(Mini-Review)(Report). Experimental Brain Research. 2017;235(4):973. doi: 10.1007/s00221-016-4865-4.

Tables and Figures

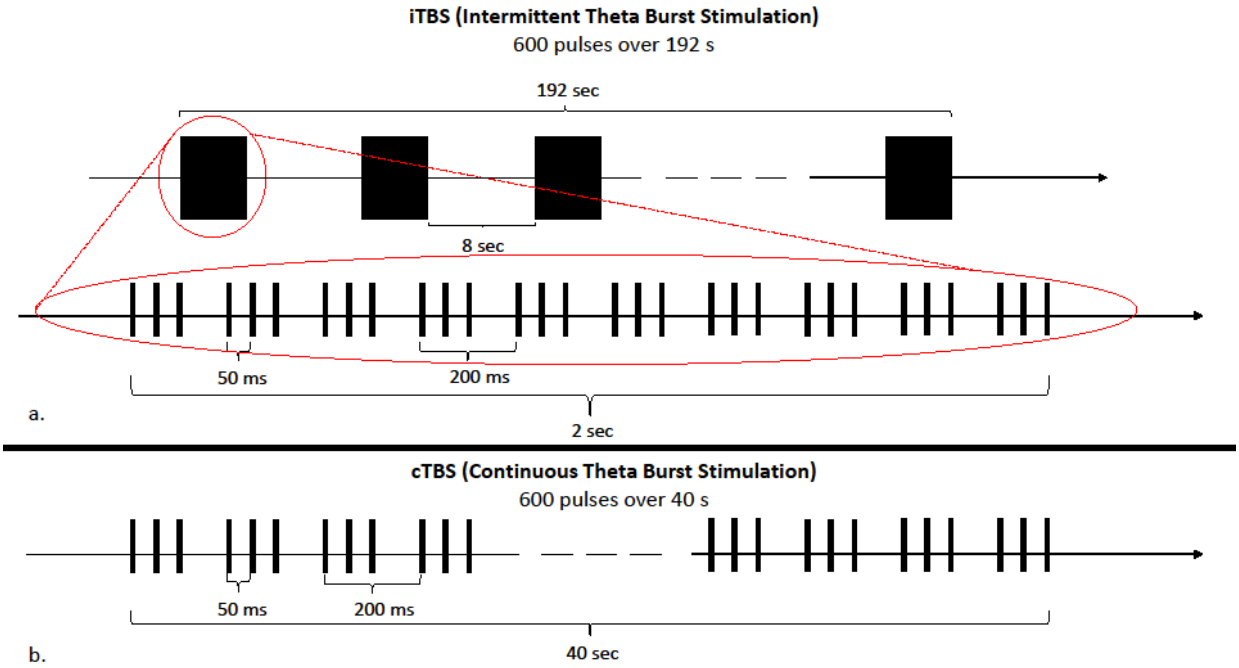

Figure 1a and 1b. iTBS and cTBS protocols. iTBS is shown in **a)**. 600 pulses are administered as bursts of 3 stimuli 50 ms apart. Each group of 3 stimuli is separated from the next by 200 ms and forms a larger block of 2 seconds duration. These 2 second bursts are separated from each other by an 8 second pause. cTBS is shown in **b)**. 600 stimuli are administered as bursts of 3 stimuli 50 ms apart, with each group separated from the next by 200 ms. Unlike iTBS, larger blocks are not formed, and the bursts are administered continuously for 40 seconds.

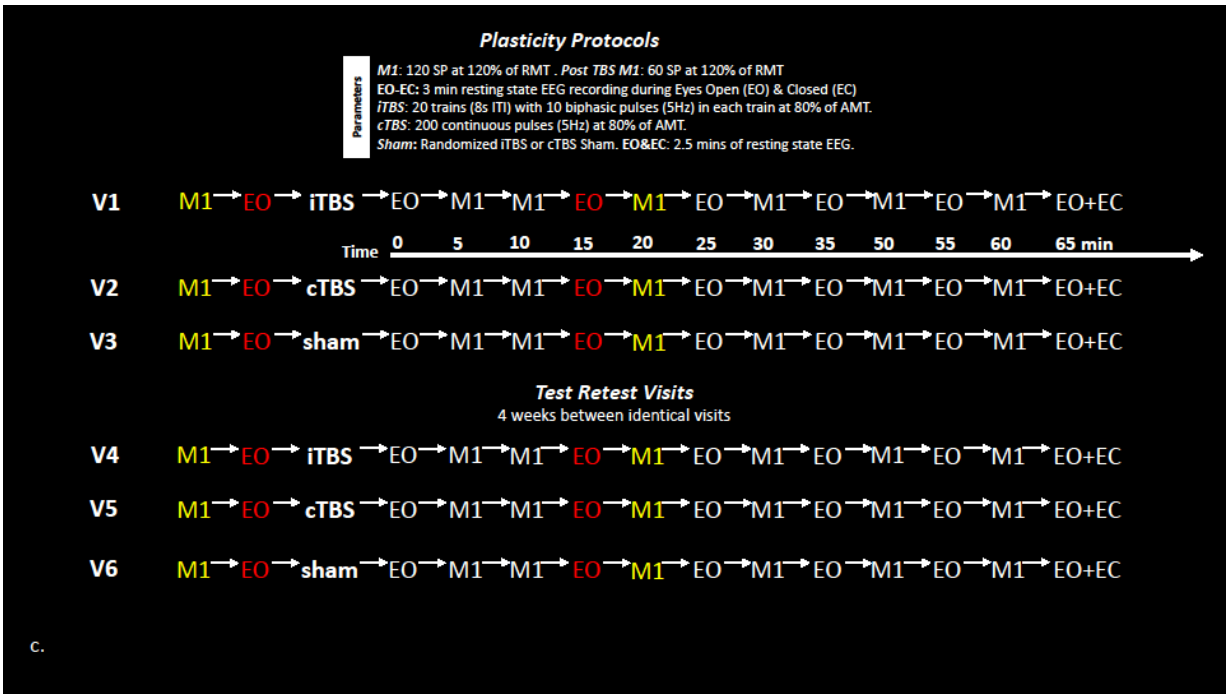

Figure 1c. Example Set of TMS Protocols. Visits 1-3 are randomized to a permutation of iTBS, cTBS, and sham for each participant. Visits 4-6 maintain this order to allow determination of test-retest reliability. An example set of visits is shown. Resting state eyes open EEG sessions of interest in red print; TMS-MEP sessions of interest in yellow print. Adapted from figure by Recep Ozdemir.

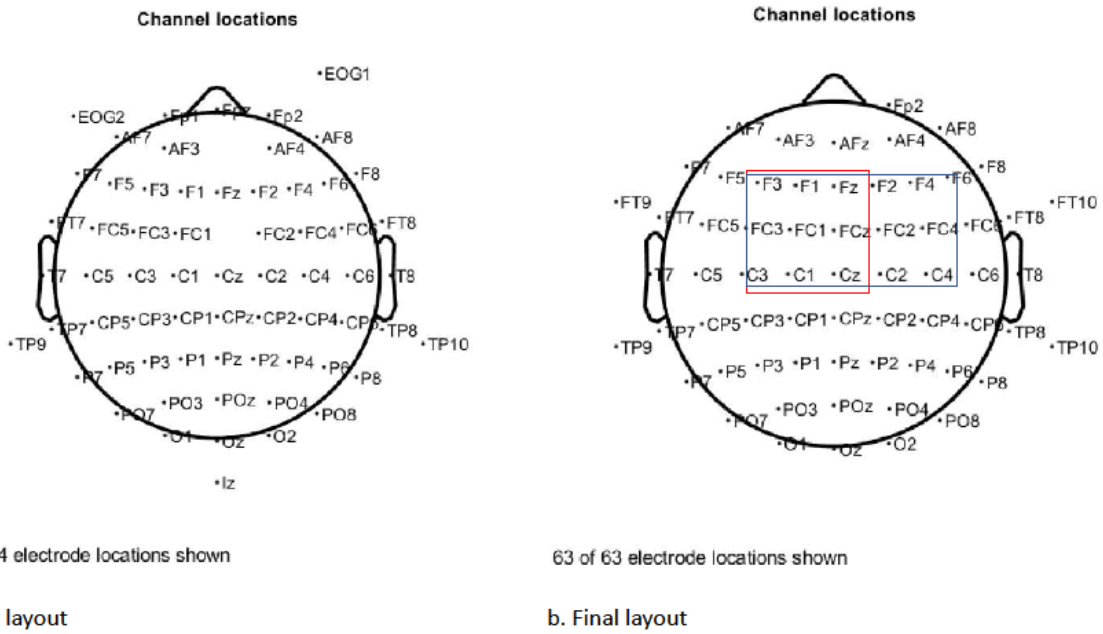

Figure 2a and 2b. Electrode maps. The first few subjects' visits were done with the electrode map in **2a**, while the majority were done with the map in **2b**. As part of preprocessing, visits with the electrode map in 1a underwent spherical interpolation to match the map in **2b** prior to power calculations. In the final layout (1b), the ipsilateral (left) frontocentral region corresponded with electrodes F3, F1, Fz, FC3, FC1, FCz, C3, C1, Cz (red box). The bilateral frontocentral region corresponded with electrodes F3, F1, Fz, F2, F4, FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4 (blue box).

ANCOVA Alpha Ipsilateral Frontocentral						
Source	Sum Sq.	d.f.	Singular?	Mean Sq.	F	Prob>F
Age	0.223551	1	0	0.223551	2.316926	0.136252
Time b/t Visits	0.208719	1	0	0.208719	2.163197	0.149583
Gender	0.255404	1	0	0.255404	2.647052	0.112007
TBS Protocol	0.222049	2	0	0.111024	1.150677	0.327202
Error	3.666477	38	0	0.096486		
Total	4.443238	43	0			

Table 1. ANCOVA table (alpha band, ipsilateral frontocentral region). One of four ANCOVAs that were run (one for each combination of alpha/beta frequency band and ipsilateral/bilateral frontocentral region). Factors included age, time since the last visit, gender, and type of stimulation (cTBS, iTBS, sham). The outcome measure of interest was change in resting-state EEG power between just prior to TBS and 15 min post-TBS. EEG difference scores were normalized to their baselines. This ANCOVA was for the alpha band over the ipsilateral frontocentral region. No variables were associated with $p<0.05$ (or the Bonferroni-corrected threshold, $p<0.0125$).

ANCOVA Alpha Bilateral Frontocentral						
Source	Sum Sq.	d.f.	Singular?	Mean Sq.	F	Prob>F
Age	0.259186	1	0	0.259186	2.662527	0.110999
Time b/t Visits	0.206427	1	0	0.206427	2.120555	0.153547
Gender	0.283216	1	0	0.283216	2.909386	0.096228
TBS Protocol	0.20672	2	0	0.10336	1.061783	0.355875
Error	3.699137	38	0	0.097346		
Total	4.488526	43	0			

Table 2. ANCOVA table (alpha band, bilateral frontocentral region). One of four ANCOVAs that were run (one for each combination of alpha/beta frequency band and ipsilateral/bilateral frontocentral region). Factors included age, time since the last visit, gender, and type of stimulation (cTBS, iTBS, sham). The outcome measure of interest was change in resting-state EEG power between just prior to TBS and 15 min post-TBS. EEG difference scores were normalized to their baselines. This ANCOVA was for the alpha band over the bilateral frontocentral region. No variables were associated with $p<0.05$ (or the Bonferroni-corrected threshold, $p<0.0125$).

ANCOVA Beta Ipsilateral Frontocentral						
Source	Sum Sq.	d.f.	Singular?	Mean Sq.	F	Prob>F
Age	0.119967	1	0	0.119967	3.021	0.090291
Time b/t Visits	0.044516	1	0	0.044516	1.121007	0.296386
Gender	0.04691	1	0	0.04691	1.18129	0.28394
TBS Protocol	0.022746	2	0	0.011373	0.2864	0.752569
Error	1.509019	38	0	0.039711		
Total	1.717719	43	0			

Table 3. ANCOVA table (beta band, ipsilateral frontocentral region). One of four ANCOVAs that were run (one for each combination of alpha/beta frequency band and ipsilateral/bilateral frontocentral region). Factors included age, time since the last visit, gender, and type of stimulation (cTBS, iTBS, sham). The outcome measure of interest was change in resting-state EEG power between just prior to TBS and 15 min post-TBS. EEG difference scores were normalized to their baselines. This ANCOVA was for the beta band over the ipsilateral frontocentral region. No variables were associated with $p<0.05$ (or the Bonferroni-corrected threshold, $p<0.0125$).

ANCOVA Beta Bilateral Frontocentral						
Source	Sum Sq.	d.f.	Singular?	Mean Sq.	F	Prob>F
Age	0.121168	1	0	0.121168	3.344906	0.07527
Time b/t Visits	0.031893	1	0	0.031893	0.880436	0.354008
Gender	0.043475	1	0	0.043475	1.200165	0.280184
TBS Protocol	0.027738	2	0	0.013869	0.382868	0.684503
Error	1.376533	38	0	0.036225		
Total	1.573962	43	0			

Table 4. ANCOVA table (beta band, bilateral frontocentral region). One of four ANCOVAs that were run (one for each combination of alpha/beta frequency band and ipsilateral/bilateral frontocentral region). Factors included age, time since the last visit, gender, and type of stimulation (cTBS, iTBS, sham). The outcome measure of interest was change in resting-state EEG power between just prior to TBS and 15 min post-TBS. EEG difference scores were normalized to their baselines. This ANCOVA was for the beta band over the bilateral frontocentral region. No variables were associated with $p<0.05$ (or the Bonferroni-corrected threshold, $p<0.0125$).

SRTT IE Correlation Table			
Band, Region	**cTBS**	**iTBS**	**Sham**
Alpha, Ipsilateral	0.062772	0.114585	-0.0988
Alpha, Bilateral	0.040321	0.140924	-0.115
Beta, Ipsilateral	0.086083	0.048227	0.05474
Beta, Bilateral	0.079974	0.068224	0.1133

Table 5 (SRTT IE Correlation Table). Correlation coefficients representing the relationship between IE of the SRTT and the normalized EEG PSD difference scores are presented here. Each row corresponds to a band and region, while each column corresponds to the TBS exposure between the pre-TBS and T15 time points. All coefficients were small, with the largest magnitude coefficient being 0.048227 (alpha, bilateral, iTBS).

Face Memory IE Correlation Table			
Band, Region	**cTBS**	**iTBS**	**Sham**
Alpha, Ipsilateral	-0.05433	-0.09315	-0.1958
Alpha, Bilateral	-0.08104	-0.08434	-0.2117
Beta, Ipsilateral	0.381817	-0.10613	0.02464
Beta, Bilateral	0.362337	-0.09129	0.04809

Table 6 (Face Memory IE Correlation Table). Correlation coefficients representing the relationship between IE of the Face Memory test and the normalized EEG PSD difference scores are presented here. Each row corresponds to a band and region, while each column corresponds to the TBS exposure between the pre-TBS and T15 time points. All coefficients were small, with the largest magnitude coefficient being 0.381817 (alpha, bilateral, cTBS).

MEP Difference Score Correlation Table			
Band, Region	**cTBS**	**iTBS**	**Sham**
Alpha, Ipsilateral	-0.11401	0.39364	-0.0608
Alpha, Bilateral	-0.10939	0.415815	-0.0367
Beta, Ipsilateral	-0.07413	0.20253	0.05134
Beta, Bilateral	-0.05483	0.208926	0.0463

Table 7 (MEP Difference Score Correlation Table). Correlation coefficients representing the relationship between normalized MEP difference scores and the normalized EEG PSD difference scores are presented here. Each row corresponds to a band and region, while each column corresponds to the TBS exposure between the pre-TBS and T15 time points. MEP difference scores were calculated by subtracting baseline MEPs from T20 MEPs and normalizing to baseline. All coefficients were small, with the largest magnitude coefficient being 0.415815 (alpha, bilateral, iTBS). Notably, iTBS correlations were greater than those of cTBS and those of Sham.

Cronbach's Alpha Statistic (Alpha Band)		
Stim, Band, Region	**as**	**au**
cTBS Alpha Ipsilateral	0.2018	0.201
iTBS Alpha Ipsilateral	-1.4189	-1.0128
Sham Alpha Ipsilateral	0.5132	0.4739
cTBS Alpha Bilateral	0.1792	0.1768
iTBS Alpha Bilateral	-1.3489	-0.9497
Sham Alpha Bilateral	0.5214	0.4821

Table 8. Cronbach's alpha statistic (alpha band). Standardized (as) and unstandardized (au) Cronbach's alpha statistics were calculated for each modality in the alpha frequency range over the ipsilateral and bilateral frontocentral regions. MEP and EEG difference scores were normalized to their baselines. No combinations of stimulation type and region were reliable in the alpha band.

Cronbach's Alpha Statistic (Beta Band)		
Stim, Band, Region	**as**	**au**
cTBS Beta Ipsilateral	-0.0095	-0.0093
iTBS Beta Ipsilateral	-0.2331	-0.2202
Sham Beta Ipsilateral	0.7544	0.6338
cTBS Beta Bilateral	0.083	0.0814
iTBS Beta Bilateral	-0.1161	-1.11E-01
Sham Beta Bilateral	0.7691	0.6604

Table 9. Cronbach's alpha statistic (beta band). Standardized (as) and unstandardized (au) Cronbach's alpha statistics were calculated for each modality in the beta frequency range over the ipsilateral and bilateral frontocentral regions. MEP and EEG difference scores were normalized to their baselines. Sham stimulation over the ipsilateral and bilateral frontocentral regions showed test-retest reliability in the beta frequency band, but no other combinations of stimulation modality and region were reliable in the beta band.