FACULTY OF MEDICINE AND HEALTH SCIENCES

What Are the Effects of Different Types of Theta Burst Stimulation on Resting-State EEG FC?

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1. PREFACE

I would like to acknowledge the contribution of my fellow researchers. Firstly, I would like to thank Dr. Ir. Deborah Klooster for her dedication in guiding my work on this thesis. Although not contractually obligated anymore, she took time out of her day for meetings and proofreading my work. Additionally, she was always open to answer any questions I had and supported me for the two years I worked on this project. Secondly, I would like to thank Prof. Dr. Kristl Vonck and Prof. Dr. Evelien Carrette for the opportunity to use their acquired data and to work on this interesting topic. Furthermore, I would like to thank one of my fellow students, Elisa Devroye, who worked under the same promotor and copromotor. She was always there to discuss the results of our findings and our next proceedings. Additionally, I could always rely on her to help me with writing the necessary Matlab code. Finally, I would like to thank my family and friends for supporting me throughout my work and proofreading this thesis.

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3. SCIENTIFIC SUMMARY

This study aims to uncover the effect of theta burst stimulation (TBS) on functional connectivity (FC) of the adult human brain. The mechanism of action of TBS remains incompletely understood, requiring further investigation. No previous studies have measured the effects of TBS on FC by utilizing the amplitude envelope correlation (AEC).

In this cross-over study, 15 participants were subjected to three experimental sessions with at least one week in between these sessions. Intermittent TBS (iTBS), continuous TBS (cTBS) or active sham stimulation were applied to the left motor cortex (M1) in a single-blinded, randomized order. Resting-state electroencephalography (rs-EEG) data were collected before and after each stimulation session, and AEC values were calculated for the alpha and beta frequency band. A Wilcoxon matched-pairs signed-rank test was applied to the AEC values to calculate changes in FC between the stimulation site and the other electrodes for each stimulation type and frequency band. Finally, a Bonferroni correction was applied to mitigate the multiple comparison problem.

Individual topoplots of AEC values showed no consistent changes between stimulation types and shifts in AEC values. Furthermore, this study was unable to identify significant changes in FC between the stimulation site and the other electrodes.

In summary, after quantifying the AEC in the alpha and beta frequency bands, TBS does not seem to induce changes in resting state FC. Future studies could focus on other measures to quantify the effect of TBS on FC.

4. SOCIETAL IMPACT

Neuromodulation is a fast-growing area of medicine. It allows us to activate different parts of brain or spinal cord. Through neuromodulation, nervous tissues can be electrically or chemically stimulated or inhibited. A form of neuromodulation is theta burst stimulation (TBS), which can be beneficial for clinical healthcare providers to treat patients with neurological (e.g., epilepsy) or psychiatric disorders (e.g., depression). The mechanism of action, or how TBS affects the brain, remains unclear. This issue prevents TBS from being integrated into current healthcare standards.

This study attempts to elucidate the mechanism of action of TBS by investigating its effects on functional connectivity (FC) in healthy individuals by studying resting state electroencephalography (rs-EEG) measurements before and after TBS sessions. FC will be studied utilizing the amplitude envelope correlation (AEC), a measure not used before to study FC. The results of this study aim to increase our understanding of how TBS affects the adult human brain, thereby supporting a better integration of TBS into clinical trials that investigate treatments for neurological or psychological disorders. Furthermore, this study attempts to demonstrate how the AEC can be utilized to study FC changes. Therefore, future research might benefit from the use of this new measure to study FC.

5. INTRODUCTION

5.1 State-of-the-art

Neuromodulation is a fast-growing area of medicine and can be used to activate different parts of the central nervous system (CNS). It can electrically or chemically inhibit, stimulate, modify, regulate or therapeutically alter activity of the autonomous or peripheral nervous system[1]. Neurostimulation has been proven to be able to help treat patients living with neurological diseases, such as Parkinson's Disease and epilepsy[2,3]. Neuromodulation can also be implemented for other applications, including treating pain syndromes such as migraine, or psychiatric disorders such as depression[3].

Different neuromodulation techniques exist that can stimulate the CNS invasively or non-invasively. Invasive brain stimulation methods, such as deep brain stimulation (DBS) and vagus nerve stimulation (VNS), require electrodes to be put in direct contact with the nerves that ought to be exited. DBS excites surrounding nerves, while VNS is able to specifically stimulate the vagus nerve. DBS requires electrodes to be implanted deep within the brain, while VNS electrodes are placed around the left vagal nerve in the patient's neck. On the other hand, examples of non-invasive brain stimulation are transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS)[2]. tDCS applies direct currents to the head of the patient, while TMS modulates brain activity through electromagnetic induction[3]. In this study, the focus will lie on TMS.

TMS utilizes a coil placed above the head of the patient to generate a magnetic field that induces electric signals in the brain through electromagnetic induction. The produced electric signals are then able to modulate cortical activity[2,3]. TMS seems to be restricted to stimulating the brain cortex, as the electrical current it produces falls off rapidly the further away it is from the TMS coil[4,5]. Different protocols exist to modulate cortical activity, single pulse TMS (spTMS) is able to evoke motor evoked potentials (MEPs) or visual sensations when performed on the motor or visual cortex, respectively. Paired pulse TMS (ppTMS) is primarily used to assess cortical excitability. Repetitive TMS (rTMS) involves usage of a train of stimuli to induce neuromodulation. While spTMS and ppTMS do not elicit long lasting effects, rTMS has been proven to elicit long lasting effects through neuromodulation. Additionally, the Food and Drug Administration (FDA) has already approved some therapies utilizing rTMS as a treatment for depression[2].

High-frequency (≥ 5 Hz) rTMS (HF-rTMS) of the left dorsolateral prefrontal cortex (DLPFC) has been widely studied and proven to have antidepressant efficacy. Furthermore, low-frequency (≤ 1 Hz) rTMS (LF-rTMS) of the right DLPFC has also been proven to have antidepressant activity[6,7]. While the effect of LF-rTMS has been proven to be optimal when applied to the right DLPFC, there is still uncertainty about whether it is best to apply HF-rTMS to the left or right DLPFC[8,9]. Additionally, not all patients suffering from depression could be treated effectively with these forms of rTMS. Therefore, other rTMS paradigms are being investigated for therapeutic efficacy in patients with depression and other disorders that do not respond to HF-rTMS or LF-rTMS. Some of the TMS modalities include accelerated rTMS (arTMS), deep TMS (dTMS) and theta burst stimulation (TBS). arTMS is used to minimize the relatively long duration of an rTMS protocol. dTMS is able to stimulate deeper and larger brain areas than HF-rTMS and has been FDA approved to treat depression[6]. TBS was developed to induce long-lasting changes in cortical excitability with low stimulation intensities[10]. It has been shown to affect synaptic plasticity more rapidly and for longer than rTMS protocols. One of the biggest advantages of utilizing TBS, is that protocols only require minutes of stimulation, while conventional rTMS protocols can last up to 40 minutes[6,11]. The remainder of this study will focus on TBS.

5.2 Theta-burst stimulation

TBS works by administering bursts of three pulses at a high frequency of 50 Hz. Between these pulses, an interburst interval is applied of approximately 200ms (5 Hz) in the theta range[12]. Two forms of TBS exist: intermittent TBS (iTBS) and continuous TBS (cTBS).

iTBS utilizes short intervals of TBS. During an iTBS protocol, 30 pulses are applied in 2 seconds, and are alternated with 8 seconds of rest. 190 seconds of stimulation is applied, for a total of 600 pulses to facilitate excitability[13,14]. iTBS has been shown to specifically affect motor cortex excitability, with effects lasting for at least 15 minutes after stimulation[13]. Additionally, iTBS has been FDA approved for Major Depressive Disorder treatment since 2019[15]. cTBS, on the other hand, has been shown to induce long-lasting inhibitory effects on cortical function by applying 300 or 600 TBS pulses, without interruption, for a total of 40 seconds[12,13,16]. cTBS has been proven to help patients who suffered from a stroke in their recovery, by applying the stimulation on the contralateral hemisphere of the lesion[17]. However, iTBS and cTBS cannot be classified as strictly excitatory and inhibitory, respectively. More recent research has shown that iTBS and cTBS have mixed effects in regard to excitation and inhibition[18]. Additionally, the general mechanism of action for TBS remains incompletely understood and therefore, further research is necessary[14]. A graphical representation of iTBS and cTBS protocols can be found in Figure 1.

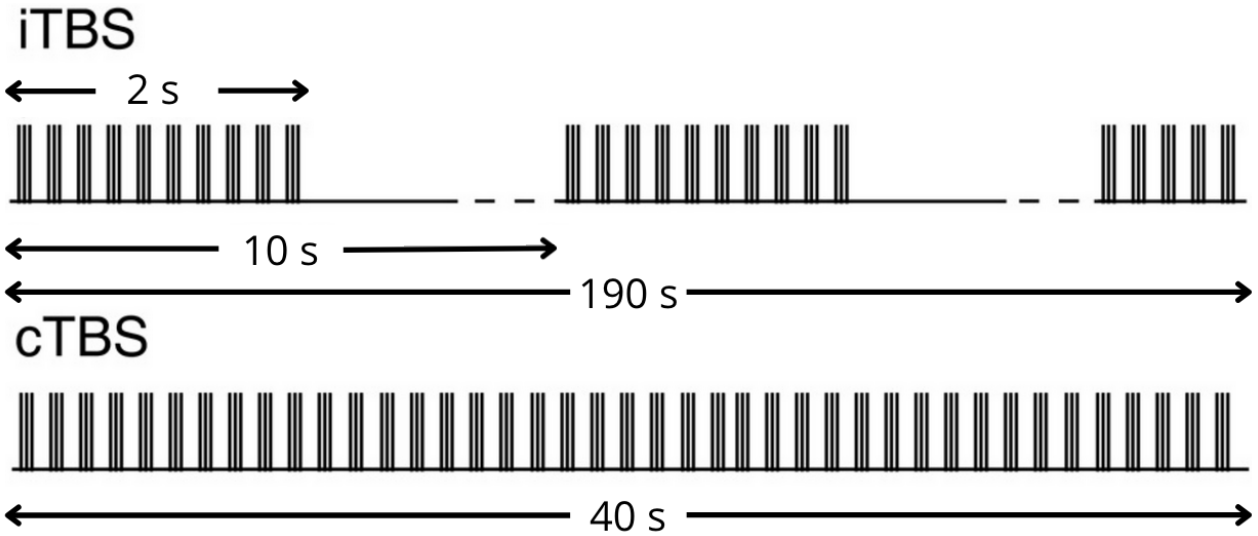

Figure 1. Graphical illustration of iTBS and cTBS stimulation protocols. iTBS applies 10 short bursts of three pulses for 2 seconds within 10 second intervals, repeating for a total of 190 seconds of stimulation. cTBS continuously applies these bursts of three pulses for 40 seconds until 300 to 600 pulses have been applied[13]. (Adapted from Huang *et al.*, 2005).
Abbreviations: cTBS = continuous theta burst stimulation, iTBS = inhibitory theta burst stimulation.

In general, TBS is able to evoke changes in cortical excitability. Therefore, the mechanism of action of TBS can be studied using electroencephalography (EEG), which can measure the brain's excitability state with high resolution. By performing a resting-state EEG (rs-EEG) directly before and after TBS sessions, functional connectivity (FC) and FC changes because of brain stimulation can be investigated[16]. EEG oscillations can be divided into five different frequency bands, containing delta (0,5-4 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (13-30 Hz) or gamma (over 30 Hz) frequencies[19,20]. The delta frequency bands are observed during deep sleep or a coma. The theta frequency bands are observed during light sleep. The alpha frequency band is

observed while a person has their eyes closed and is in a meditative state. The beta frequency band is observed in people who are awake and alert, while they actively thinking. Finally, the gamma frequency band is thought to be associated with consciousness[20].

5.3 Amplitude Envelope Correlation

Previous studies have investigated the effects of cTBS on FC through graph theoretical analysis, or how FC can be used to predict propagation of TMS evoked potentials[16,21]. For example, Shafi *et al.* (2014) have shown that cTBS of the motor cortex can induce widespread changes in cortical FC, which lead to shifts in cortical functional network topology. However, no previous study has used the amplitude envelope correlation (AEC) to study the effects of cTBS and iTBS on FC. AECs work by computing the correlation between the respective amplitude envelopes of two oscillatory brain signals. A high AEC value suggests synchrony of amplitude envelope fluctuations between oscillations and networks, while low values indicate no synchrony. This synchrony can be detected between functional brain networks, regardless of their phase coherence, within and across frequency bands[22]. The use of AECs has already been described in literature, and Bruns *et al.* (2000) have shown that AECs can be reliable and useful to detect interactions between brain regions that cannot be detected by other measures[23]. An illustration of an AEC is shown in Figure 2.

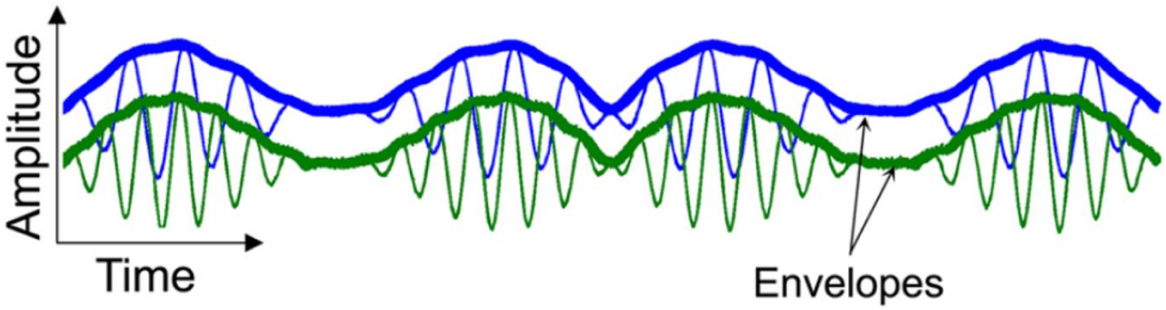

Figure 2. Amplitude Envelope Correlation over time between different brain regions after stimulation. Two envelopes are drawn in blue and green, connecting the maximal amplitudes of the corresponding oscillatory brain signal over time[24]. (Guggisberg *et al.*, 2015).

5.4 Study importance

The findings of this study could aid in increasing the understanding of the mechanism of action of TBS. Additionally, as this is the first instance of the use of AECs to investigate changes in FC, significant findings could pave the way for other researchers to also utilize this method to study changes FC. A combination of the increased understanding gained from this study and other research being done regarding which variables influence the effectiveness of TBS, could lead to the incorporation of TBS in more FDA approved clinical applications. Consequently, more patients could potentially be treated with TBS, giving hope to patients neurological or psychiatric disorders, such as those with drug-resistant epilepsy or treatment-resistant depression.

6. STUDY OBJECTIVES

A recent, yet unpublished paper by Carrette *et al.* (2024), who also works at the 4BRAIN-lab, investigated the data utilized in this study to explore the effects of cTBS and iTBS on TMS-evoked potentials (TEPs). TEP components represent a combined effect of excitatory and inhibitory postsynaptic potentials. These TEP components can be measured to investigate the mechanism of action of TBS. Unfortunately, no significant effects of TBS on these TEP components could be found [25]. Therefore, this study attempts to use another approach with this data to study the effects of TBS on FC.

The goal of this study is to investigate the effects of cTBS and iTBS on healthy participants, using AECs calculated from rs-EEG measurements before and after stimulation sessions. AECs will be calculated between electrode C3, the region TBS will be targeting, and the other 61 electrodes. The hypothesis of this project is that cTBS and iTBS induce changes in FC, while there should be no significant changes in FC after sham stimulation. This study is furthermore hypothesized to confirm if iTBS is indeed excitatory with an increase in FC and if cTBS exerts an inhibitory effect on the brain, resulting in a decrease in FC.

7. MATERIALS AND METHODS

7.1 Study design

This study utilized three stimulation sessions to investigate their effects on FC. These stimulation sessions consisted of cTBS, iTBS and active sham stimulation that were applied to the left motor cortex (M1) of the participant, targeting electrode C3. During active sham stimulation, a cTBS protocol was applied while a plastic spacer was placed between the stimulation coil and the head of the participant to negate stimulation. Before and after each stimulation session, a rs-EEG measurement was performed. These rs-EEG measurements allowed for AEC values to be calculated between each electrode and the stimulated electrode, C3. Through statistical analysis of the calculated AEC, changes in FC can be investigated between the different electrodes, a method not yet performed by other researchers.

This research took place in the 4BRAIN-lab in Ghent, Belgium, where they aim to perform translational neuroscience research to unravel the pathophysiology of neuropsychiatric disorders and develop novel therapies, more specifically they have an international renowned expertise on neuromodulation for epilepsy. At 4BRAIN many neuromodulatory therapeutic interventions have been developed, studied, and introduced to patients with drug-resistant epilepsy (both invasive and non-invasive neurostimulation techniques)[26].

7.2 Participant screening and neurostimulation procedure

After approval by the institutional Ethics Committee of Ghent University (EC 2017/0780), fifteen right-handed, male participants were selected for this cross-over study. Before being selected for the study, the participants were screened for any metallic objects that might reside in their bodies, such as medical devices. If any metallic objects were present, the magnetic forces produced by the coil during neurostimulation could displace these objects and subsequently harm the participant. Therefore, participants with metallic objects in their bodies were excluded from this study. The eligible participants were asked to sign the informed consent form and had to return to Ghent University Hospital for three sessions of neurostimulation in a period of multiple weeks: one session of cTBS, one session of iTBS and one session of sham stimulation. There was at least one week of downtime between each stimulation session for each participant. The order of these stimulation sessions was randomized to keep the participants blind to which stimulation type they were receiving. Randomization was performed through a random number generator in Excel software (Microsoft Windows, Redmond, Washington, USA).

During this study, the participants were asked to limit their caffeine intake (≤ 2 units) and get adequate amounts of sleep before every stimulation session to minimize confounding factors in the EEG recordings. When the participants were adequately prepared and deemed free of metallic objects, they were placed in an armchair, and one of the three stimulation types was applied. During the stimulation, the participants were presented with a visual target to reduce eye movement artifacts on the rs-EEG recordings. These recordings were performed directly before and after each stimulation session. A visual representation of the stimulation sessions can be found in Figure 3.

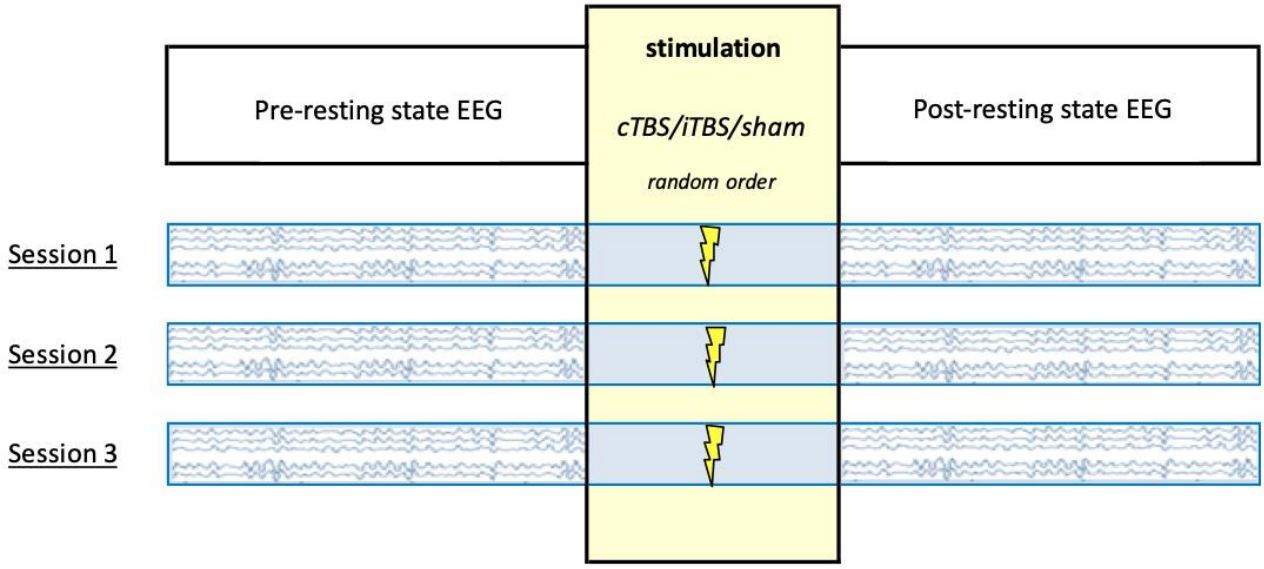

Figure 3. Visual representation of the study design, indicating the rs-EEG measurements before and after each stimulation protocol[25]. (Adapted from Carrette *et al.*, 2024).
Abbreviations: EEG = electroencephalography, cTBS = continuous theta burst stimulation, iTBS = inhibitory theta burst stimulation.

TBS was performed utilizing a MagPro X 100 stimulator, equipped with a static cooled 65 mm figure-of-eight coil. iTBS and cTBS settings previously described by Huang *et al.* (2005) were applied during the stimulation sessions[13]. In the event that the participant was exposed to active sham stimulation, a 25 mm thick plastic spacer, which minimizes effective cortical stimulation, was placed between the coil and the head of the participant. During these active sham sessions, cTBS protocols were applied.

7.3 Electroencephalography

The rs-EEG measurements were performed with a 62-channel TMS-compatible EEG cap (BrainCap TMS, Brainproducts GmbH, Gilching, Germany), combined with DC amplifiers (BrainAmp Mrplus, Brainproducts GmbH, Gilching, Germany) to ensure that the analog to digital converters do not saturate during the discharge of the TMS coil. Furthermore, A ground electrode and two electro-oculogram (EOG) electrodes were placed on the forehead of the participants. The ground electrode was used to reduce noise in the EEG recordings and the EOG electrodes were used to record horizontal and vertical eye movements during the rs-EEG sessions[25]. Figure 4 depicts a 62-channel EEG cap with electrode positions. Additionally, the stimulated brain region, electrode C3, was colored in blue[27].

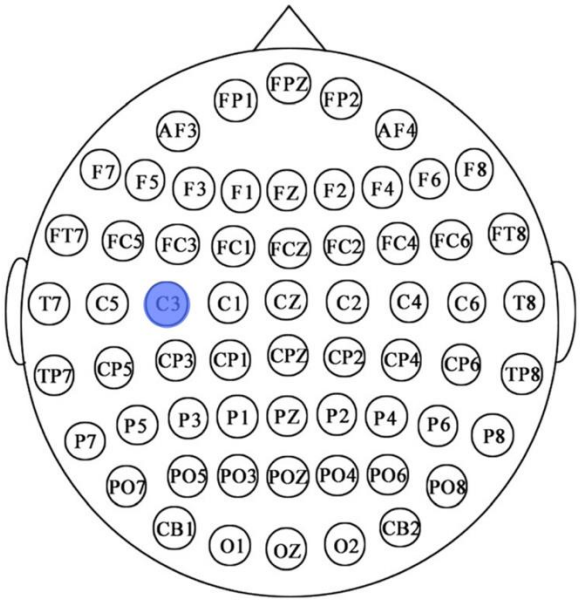

Figure 4. 62-channel EEG cap with electrode positions. The stimulation site, electrode C3, is colored in blue[27]. (Adapted from Zheng & Lu, 2015).

7.4 Neuronavigation setup

Several measures were taken to ensure reproducibility between the different stimulation protocols within each participant. Datapoints from the participants' head were saved to increase the accuracy and reproducibility of the coil positioning between stimulation sessions. This was performed utilizing a neuronavigation system for frameless stereotaxy (Localite, Bonn, Germany) with a Polaris infrared camera (Northern Digital Inc., Canada). This neuronavigation system tracked the position of the coil in relation to the stimulation target. Additionally, this target was digitized to a standard Montreal Neurological Institute (MNI) brain, which was provided by the Localite software, and co-registered on the participant's head. As a final measure, the electrode positions of the 62-channel EEG cap were digitized, saving EEG positions in relation to anatomical landmarks (e.g., nasion or the corner of the eye) for each participant. Digitization allowed near identical placement of the electrode cap between stimulation sessions[25].

7.5 Data preprocessing

After rs-EEG data was collected, offline data analysis utilized EEGLAB® (v2023.1, Delorme and Makeig) and custom-made MATLAB® scripts (R2023a, The MathWorks Inc, Natick, MA, USA). Preprocessing was done to remove noise and ensure only brain activity was analyzed. EEG measurements are prone to artifacts. Physiological artifacts are the main cause of noise that are of importance in this study, they arise due to other electrical activity of the body. Facial muscle contractions, eye movements and cardiac activity all have the potential to interfere with the measured EEG signal[28,29]. Additionally, participants sweating can create bridges between electrodes, altering electrode impedance. This change in impedance translates to low frequency artifacts[30]. Next to physiological artifacts, extrinsic artifacts can influence the EEG recording. These artifacts arise due to electrode or cable misplacement or malfunction but can also emerge due to electromagnetic interference. Artifacts can imitate cognitive or pathologic activity, making their identification and removal the most important preprocessing step[29].

First, data was down-sampled to 1000 Hz to increase the signal-to-noise ratio. Second, data was Notch filtered, removing frequencies between 47 and 53 Hz, to negate artifacts originating by

interference from the electricity-net. Third, a high pass filter of 1 Hz and a low pass filter of 50 Hz were applied, to reduce noise arising from muscle contractions or malfunctioning equipment. Fourth, all channels were visualized, and noisy channels were manually removed. Fifth, the EEG data was epoched into segments of six seconds, as previously determined by Fraschini *et al.* (2016) to be an optimal epoch length to perform AECs[31]. Sixth, epochs were visualized, and noisy epochs were manually deleted. Seventh, data was re-referenced to average by calculating the average across all EEG channels and subtracting it from the other channels, which removes noise that is present across most or all electrodes. Eight, independent component analysis was performed utilizing FastICA, from TESA software (Rogasch *et al.*, 2017), and manually examined to remove artifacts in the data, such as eye movements. The following default thresholds were applied: TMS-evoked muscle activity = 8, eye blinks = 2.5, lateral eye movements = 2, persistent muscle activity = 0.6 and electrode noise = 4. Finally, missing channels were interpolated utilizing the channels that remained at the end of the pipeline.

7.6 Amplitude Envelope Correlation

The preprocessed data was then utilized to calculate the amplitude envelopes. Data analysis was performed with Brainstorm **(Tadel *et al.* 2011)**, which is documented and freely available for download online under the GNU general public license (http://neuroimage.usc.edu/brainstorm)[32]. Customized Matlab code was used to automatically load all acquired data into Brainstorm and calculate AECs to prevent human errors in this process.

To calculate the AECs for each epoch, the 'Envelope Correlation 1XN' process was used. This process calculates AECs between the seed region, electrode C3, and N other electrodes separately. The following settings were applied during this process: the whole file was selected for the 'Time window'. C3 was selected as the 'Source channel', as this is the electrode above the stimulation site. For 'Sensor types or names', 'EEG' was selected. 'Include bad channels' was set to 'Yes', as these were already removed during preprocessing. As the 'Connectivity Metric', 'Envelope correlation (orthogonalized)' was selected to remove signals with the same phase that were measured by different electrodes. This process is necessary, as signals measured by multiple electrodes could cause our analyses to pick up on correlations that are not there[33]. For the 'Time frequency decomposition', a 'Hilbert transform' was employed. In the 'Options' menu, only alpha and beta frequencies were selected to later minimize the multiple comparison problem. Only analyzing two of the five available frequency bands allows for less statistical tests to be performed. Additionally, as stated before, the alpha and beta frequency band have been shown to be observed in people who are awake, while the delta and theta frequency band are present in unconscious people and the gamma frequency band is broadly associated with consciousness[20]. For the 'Time resolution', 'Windowed' was selected. The 'Time Window Length' and 'Time Window Overlap' were set to 6 seconds and 50%, respectively. 'Use Parallel Processing Toolbox' was set to 'No', and within the Output options, for 'Estimate & save', 'separately for each file' was selected.

This resulted in an AEC value for every epoch in every stimulation session, in each participant, for both pre- and post-stimulation data and for both alpha and beta frequency bands. Heatmaps were created to visualize the amplitude envelope data, within each session, participant and frequency band, showing the average values of each amplitude envelope within each epoch for each channel. These heatmaps were created to manually check for potential outliers in the calculated AEC values. Afterwards, AEC values were visualized in topoplots. In Matlab, separate topoplots were created for every stimulation type and frequency band, for both pre- and post-stimulation AEC values and sorted by participant. The AEC value for electrode C3 was replaced with the mean of the surrounding channels: CP1, CP3, CP5, C1, C5, FC1, FC3 and FC5.

7.7 Statistical analysis

The statistical analysis of the acquired results was performed in R (R Core Team (2024). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). AEC analyses were conducted for all three stimulation types across all participants, for every electrode and every frequency band separately. Significant changes in FC were then accessed between the stimulated electrode, C3, and the other 61 electrodes. These AEC values were checked for normality utilizing the Shapiro-Wilk test to investigate if the AEC values were normally distributed for each electrode. Additionally, quantile to quantile (Q-Q) plots were created for every Shapiro-Wilk test. The Shapiro-Wilk test and Q-Q plots indicated that the AEC values for each electrode were not normally distributed. Even after performing a logarithmic transformation of the data, the AEC values were still not normally distributed, indicating the need for a non-parametric test.

The Wilcoxon matched-pairs signed-rank test was utilized to assess significant changes in FC. For both alpha and beta frequency bands, the Wilcoxon matched-pairs signed-rank test was performed to compare pre- and post-stimulation AEC values for every stimulation type and electrode. Due to the nature of the Wilcoxon matched-pairs signed-rank test, values which did not have both a pre- and a post-stimulation measurement were excluded from the statistical test. Because of the large number of statistical tests performed, a Bonferroni correction was applied to the calculated p-values to correct for the multiple comparison problem. Due to the analyses taking into account all stimulation types, electrodes and the two frequency bands, a total of 366 statistical tests were performed. Therefore, a Bonferroni adjusted α-value of 0.0001 (0,05/366) was regarded as significant. The p-values calculated by the Wilcoxon matched-pairs signed-rank test were then utilized to create topoplots with Matlab. These topoplots visualize the calculated p-values for each electrode on a head model per stimulation session and frequency band. The p-value for electrode C3 was replaced with the mean of the surrounding channels: CP1, CP3, CP5, C1, C5, FC1, FC3 and FC5.

8. RESULTS

8.1 Data preprocessing

During preprocessing of the collected rs-EEG data, noisy channels and epochs were removed from the available rs-EEG data. A table indicating which data was available for preprocessing can be found in the supplementary materials as Tables S1 and S2. Furthermore, some independent components had to be manually adjusted. These adjustments included changing independent components that were regarded as artifacts to not be removed, or changing independent components that were regarded as normal to be seen as artifacts and subsequently removed from the data. A list of removed channels and epochs, and of the adjusted independent components can be found in Tables S3 and S4 of the supplementary materials.

8.2 AEC calculation

AEC heatmaps were manually investigated for outliers, two examples can be found in Figure 5. Some rs-EEG sessions of the beta frequency band showed epochs with elevated AEC values. These epochs were found for the pre-stimulation data in participant 12, for both session 1 and session 3, and for the pre-stimulation data in participant 9, for both session 1 and session 3. The heatmaps of these potential outliers are depicted in Figure 6. Nevertheless, as these potential outliers were few in numbers and relatively small, they were not removed from the dataset. Therefore, data from all epochs was used to compute the final AEC.

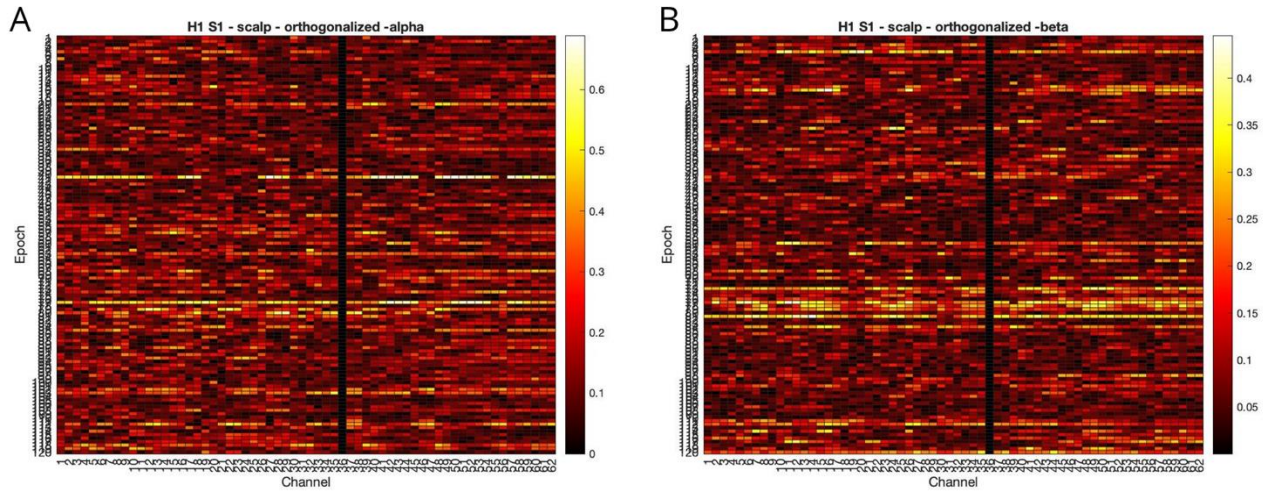

Figure 5. Heatmaps of calculated AEC values between electrode 36 (C3) and the other electrodes for pre-stimulation data of participant 1, session 1. A) Heatmap for the alpha frequency band; B) Heatmap for the beta frequency band.
Abbreviations: AEC = amplitude envelope correlation.

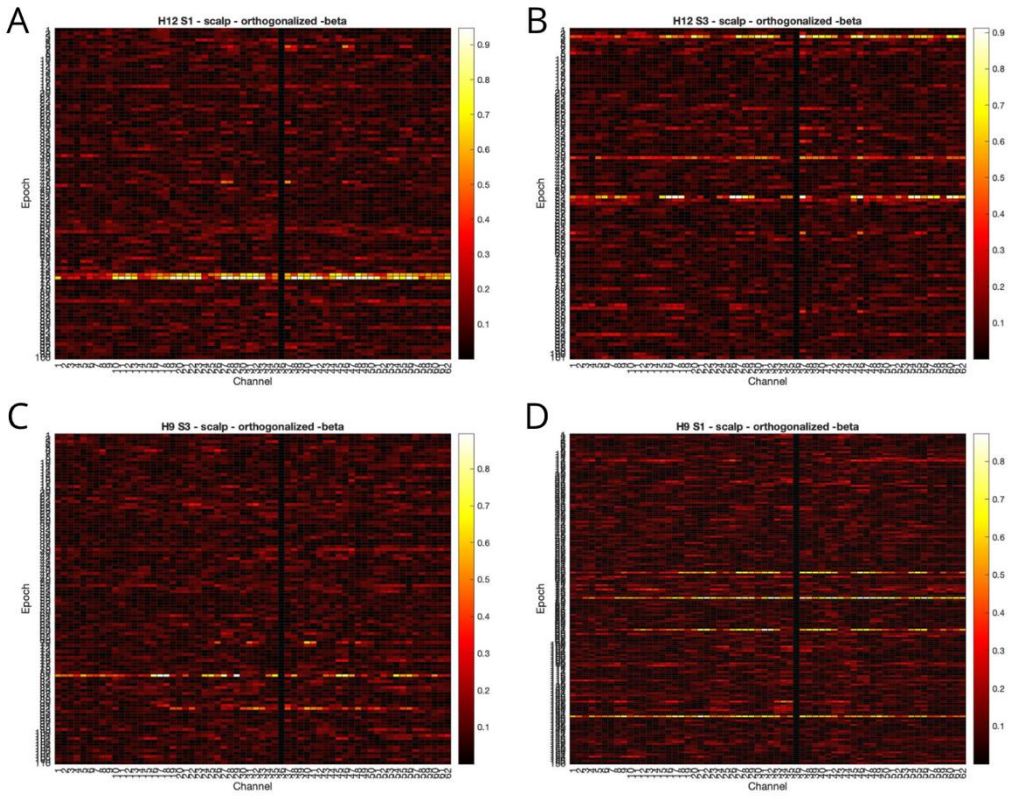

Figure 6. Heatmaps depicting potential outliers in the calculated AEC values between electrode 36 (C3) and the other electrodes for every epoch and electrode channel within a rs-EEG session. All heatmaps are of pre-stimulation data and the beta frequency band. A) Heatmap of AEC values for participant 12, session 1; B) Heatmap of AEC values for participant 12, session 3; C) Heatmap of AEC values for participant 9, session 3; D) Heatmap of AEC values for participant 9, session 1.
Abbreviations: AEC = amplitude envelope correlation.

Afterwards, the created topoplots for every stimulation session and frequency band were inspected for both pre- and post-stimulation data in every participant. These topoplots can be found in the supplementary materials, as Figures S1-S15. Both increasing and decreasing AEC values were observed after the different stimulation sessions. Some examples of increased and decreased AEC values can be seen in Figure 7. Manual investigation of these topoplots revealed that there were similar amounts of increasing and decreasing AEC values after iTBS, cTBS and sham stimulation. Some large increases and decreases were observed (Figures 7A, 7B and 7E), but in general, no stimulation type caused consistent increasing or decreasing AEC values after stimulation sessions in these participants.

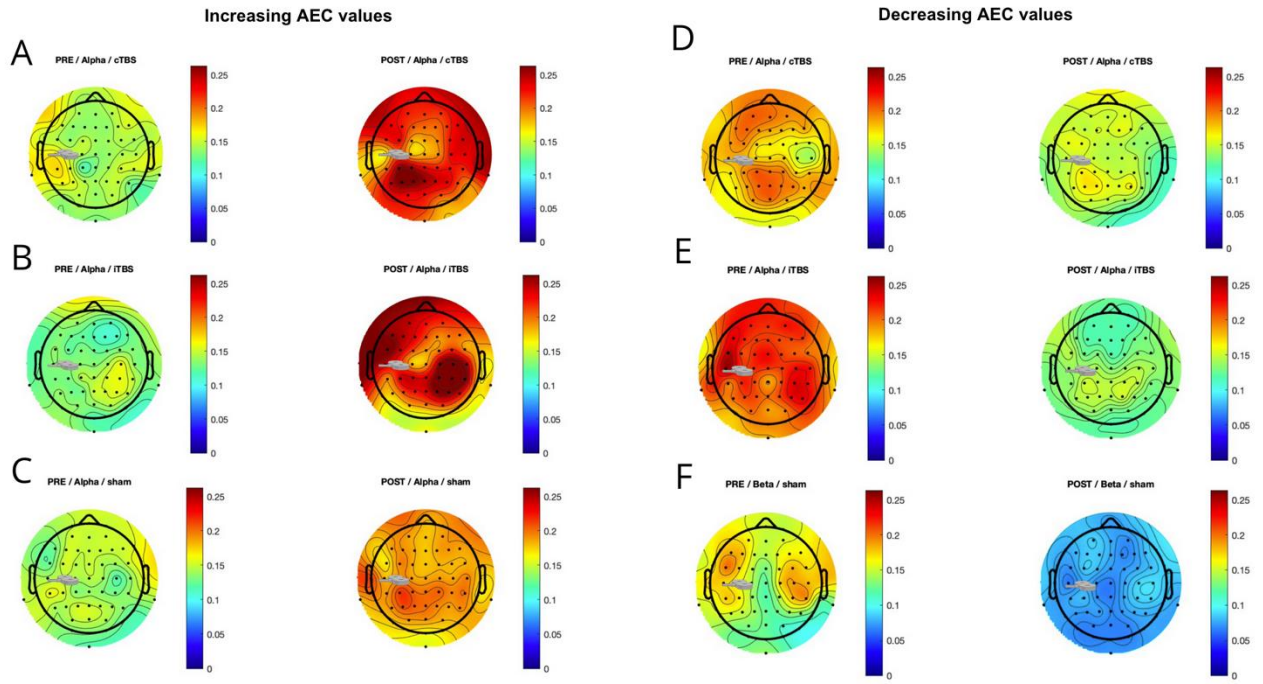

Figure 7. Topoplots of increasing (A, B and C) and decreasing (D, E and F) AEC values observed after the different stimulation sessions. The AEC value for electrode C3 was replaced with the mean of the surrounding channels: CP1, CP3, CP5, C1, C5, FC1, FC3 and FC5. A) Topoplots indicating AEC values of the alpha frequency band of participant 12, undergoing cTBS; B) Topoplots indicating AEC values of the alpha frequency band of participant 14, undergoing iTBS; C) Topoplots indicating AEC values of the alpha frequency band of participant 1, undergoing active sham stimulation. D) Topoplots indicating AEC values of the alpha frequency band of participant 2, undergoing cTBS; E) Topoplots indicating AEC values of the alpha frequency band of participant 9, undergoing iTBS; F) Topoplots indicating AEC values of the beta frequency band of participant 7, undergoing active sham stimulation. A TMS-coil is depicted in these topoplots above the stimulated brain region, electrode C3.
Abbreviations: AEC = amplitude envelope correlation, cTBS = continuous theta burst stimulation, iTBS = inhibitory theta burst stimulation.

8.3 Changes in FC

After manually concluding that there were no major outliers in the data and all AEC values could be used in further calculations, they were used to investigate changes in FC. As a consequence of the data not being normally distributed, the Wilcoxon matched-pairs signed-rank test was performed. The calculated p-values can be found in Table S5 for the alpha frequency band, and Table S6 for the beta frequency band.

61 electrodes were investigated for changes in FC. The statistical test was repeated for the three different stimulation types (cTBS, iTBS and sham) in the two different frequency bands (alpha and beta). An α-value of 0.0001 was obtained after the Bonferroni correction and applied to the results to find significant changes in FC. Before the Bonferroni correction, there were three significant p-values in the alpha frequency band. There was a significant change in functional connectivity between electrode C3 and electrode CP1 after cTBS stimulation. Furthermore, there was a significant change in functional connectivity between electrode C3 and electrodes CPz and CP3 after sham stimulation. However, after applying the Bonferroni correction, none of the calculated p-values were found to be below the α-value.

The calculated p-values are shown through topoplots in Figure 8. White crosses mark the electrodes containing p-values < 0.05, although not containing significant p-values after the Bonferroni correction. A figure of a TMS-coil was inserted in each figure above electrode C3, the region where TBS was applied. The largest p-values are shown in dark red, while p-values closest to zero are shown in dark blue. The topoplots displayed no great discrepancies, as there are no big differences in p-values between electrodes.

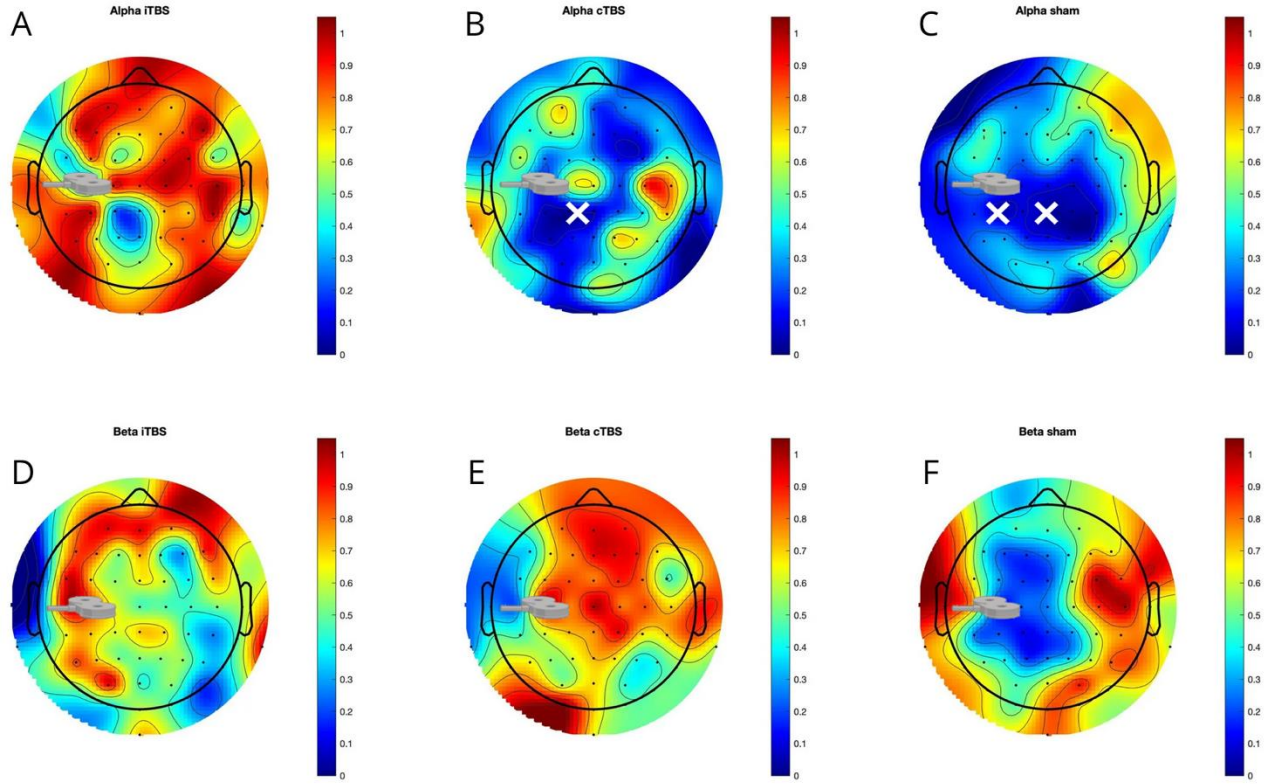

Figure 8. Topoplots created of the calculated p-values through the Wilcoxon matched-pairs signed-rank test for the three different stimulation types and two different frequency bands. The p-value for electrode C3 was replaced with the mean of the surrounding channels: CP1, CP3, CP5, C1, C5, FC1, FC3 and FC5. The p-values of each electrode were plotted onto the head models, with the legend used for each topoplot on the right of the topoplots. White crosses mark p-values < 0.05, although not significant after the Bonferroni correction. Topoplots were made for both alpha (A-C) and beta (D-F) frequency bands, and for the three stimulation types, cTBS (A, D), iTBS (B, E) and active sham (C, F). A TMS-coil is depicted in these topoplots above the stimulated brain region, electrode C3.
Abbreviations: cTBS = continuous theta burst stimulation, iTBS = inhibitory theta burst stimulation.

9. DISCUSSION

This study aimed to investigate the effects of cTBS, iTBS and active sham stimulation over the motor cortex (M1) on FC. For both the alpha and beta frequency band, pre- and post-stimulation AECs were derived from rs-EEG measurements between the stimulated electrode C3 and the other 61 electrodes. First, within each individual no clear correlations were found between stimulation type and changes in these AEC values. Next, the AEC values were used to measure changes in FC as a result of different TBS protocols. No significant differences were found between pre- and post-stimulation AECs.

9.1 Main outcomes

AEC values were calculated for every participant to create individual topoplots (Figures S1-S15). These topoplots displayed AEC values before and after each stimulation session for both the alpha and beta frequency band and the three different stimulation sessions. Important to note is that the AEC value was not accurate for electrode C3. As correlations were calculated between electrode C3 and every other electrode, the correlation between electrode C3 and itself was set to 0. The AEC value of electrode C3 was set to the mean value of the surrounding electrodes. This caused the topoplots to have smoother transitions in AEC values instead of having a value of 0 at the stimulation site. In these topoplots, AEC values increased, decreased or remained similar when comparing pre- and post-stimulation topoplots. No direct correlations between stimulation type and changes in AEC values are visible after a visual comparison of these topoplots. These findings answer the secondary objective of this study, which was to investigate if iTBS and cTBS are strictly excitatory and inhibitory, respectively. The individual topoplots indicate that iTBS and cTBS might not be strictly excitatory and inhibitory, as previously suggested by Houdayer *et al.* (2008)[18]. The lack of conclusive results might also indicate that there were unknown variables influencing the participants' response to TBS. Variables such as a participants' genetics and brain state have been shown to influence the TBS response[34].

Afterwards, changes in FC were assessed by combining AEC values across participants. Initially, there were three significant p-values in the alpha frequency band, one after cTBS and two after sham stimulation. However, after performing a Bonferroni correction, none of these p-values remained significant. The presence of the two initial significant p-values after sham stimulation, if not due to chance because of the large number of statistical tests performed, could be explained by a placebo effect. Placebo effects occur when a participant reacts positively to the context of an intervention (e.g., the expectation of brain stimulation) instead of the intervention itself[35]. Recent studies indicate that the placebo effect could modulate brain networks and neurotransmitter systems. Therefore, the expectations of the participants could have influenced the results of this study[36].

The lack of significant p-values after the Bonferroni correction indicates that iTBS or cTBS did not have an effect on FC between electrode C3 and the other electrode measurements of the participants in this study. Other researchers investigated the effect of TBS on FC through other means than AECs. Shafi *et al.* (2014) showed that cTBS altered cortical FC and shifts cortical network topology through graph theoretical analysis. Graph theoretical analysis differs from the AEC in that it utilizes clustering coefficients and path lengths between nodes, which can represent EEG electrodes, while the AEC looks at similarities between oscillatory brain signals. Graph theoretical analysis can study changes in FC through investigating information processing efficiency and information transfer. Shafi *et al.* (2014) found widespread decreases in FC in the alpha frequency band and increases in FC in the beta frequency band after cTBS[16]. Qiu *et al.* (2022) showed that cTBS modulates the motor network through a Nine-Hole Peg Test before and

after stimulation by applying an EEG microstate analysis[10]. Through EEG microstate analysis, neural signatures of cognitive processes can be studied, and it has been shown to be able to investigate EEG dynamics and link them to both cognition and disease[37]. Furthermore, EEG microstates are correlated with fMRI-based brain functional networks. Qiu *et al.* (2022) saw an increased efficiency of node C4 in microstate B, which corresponds to the visual network[10].

On another note, an investigation of MEP amplitudes by Magnuson *et al.* (2023) found iTBS and cTBS protocols to have poor reproducibility and have insignificant effects on corticospinal excitability[38]. Ozdemir *et al.* (2021) found similar results, showing low inter- and intraindividual reproducibility of cTBS and iTBS modulatory effects[14]. The lack of reproducible results and large variability after iTBS and cTBS protocols could explain the lack of significant changes in FC measured in this study.

Another explanation for the lack of significant results is the timing of the rs-EEG sessions. Huang *et al.* (2005), whose TBS protocols were applied in this study, showed long-lasting effects after iTBS and cTBS. They saw significant changes in MEPs up to 15 minutes after iTBS and up to 60 minutes after cTBS[13]. Furthermore, Chen *et al.* (2024) found that response time to rTMS can differ between individuals. These findings could indicate that the optimal time to record the rs-EEG sessions might differ between participants, as there might also be a different response time to TBS[39].

Given the acquired results, the AEC might be a poor measure for investigating changes in FC after TBS. The AEC has several advantages, such as being able to detect long-range coupling between high-frequency activities that other measures cannot detect. These high-frequency activities can be important in cognitive processing and cortical cooperativity. However, other measures, such as graph theoretical analysis, might have been able to detect changes in FC that the AEC did not identify in this study. Therefore, the lack of significant results does not strictly imply that TBS did not have an effect on FC. It might imply that the AEC was not suitable to detect these differences.

Alternatively, TBS might also have had no effects on FC. Carrette *et al.* (2024), who investigated the same dataset to uncover the effects of TBS on TMS-evoked potentials over the motor cortex, also found no significant effects of TBS on TEP components. Together, these findings imply that TBS did not significantly affect the participants of this study[25].

9.2 Limitations and future directions

This study contains some limitations regarding participant selection to increase reproducibility in the relatively small sample size. The healthy participants were all right-handed to ensure the dominant brain hemisphere was being stimulated. Furthermore, only male participants who could attend multiple sessions of brain stimulation at UZ Ghent were selected, limiting the area where patients live. Female participants were excluded from the study, as to not have their menstrual cycle potentially interfere with the results. De Bondt *et al.* (2015), have shown that the menstrual cycle can affect FC, but more research is required to uncover the relationship between hormonal changes and brain networks[40]. This limited sample size can be a disadvantage when generalizing these findings to a larger population. However, it did limit the variability between participants when studying changes in FC after TBS.

Another limitation is the single-blinded nature of this study. The researchers performing the TBS protocols on the participants could not be blinded to the stimulation types. When performing the stimulation sessions, the researcher had to know which stimulation protocol was being applied to

ensure the correct settings were used. This could introduce unconscious biases. For example, the researchers might have been more attentive when applying iTBS and cTBS. However, data preprocessing was performed blindly. Data was named after the order that stimulation sessions were performed in each participant without revealing the applied stimulation type. Only at the start of the statistical analysis of the data, were the applied stimulation protocols revealed, as this was necessary to group the data per stimulation type. Additionally, it is possible that the participants were not fully blinded. cTBS and iTBS protocols are of different durations, indicating to the participant that there were differences in stimulation type.

An issue that arose during preprocessing was that some data had been lost. Not all rs-EEG data was available to preprocess, decreasing the sample size. During the analysis of FC through the Wilcoxon matched-pairs signed-rank test, only data where the corresponding pre- or post-stimulation rs-EEG data was also available was utilized. Advantages of this approach are to maintain data integrity and simplify the interpretation of the results. Furthermore, the Wilcoxon matched-pairs signed-rank test in R required pre- and post-stimulation data to be of equal sizes, which would not be the case if all available data was included. A disadvantage of this approach was that some of the available data was lost in this way.

This study investigated changes in FC on a group level. This might cause individual variability to TBS protocols to be averaged out, as this approach can show the effects of TBS on FC in a larger population. Such findings could aid researchers in finding uses for TBS in certain conditions and diseases, as uncovering the effects in the broad population could help identify clinical applications to develop generalized treatment protocols. Furthermore, a group-level analysis would be easier to replicate and compare across studies. In spite of that, investigating individual variability would also have several advantages. Personalized findings could be investigated to study which variables affect the response to TBS. Such findings could aid in our understanding of which people respond best to TBS and what could increase the efficacy of potential TBS therapies. This study was limited to a group-level analysis as each participant underwent a single stimulation session for each stimulation type. To analyze individual variability, each participant would have to undergo multiple stimulation sessions for each stimulation type to compare changes in FC within each individual.

This study was performed on a scalp-level. FC changes were investigated based on changes in electrode data. Scalp-level data is only able to provide limited information about the underlying connections between brain regions. The main cause of this issue is volume conduction or field spread, which refers to the fact that the cortical electrical fields must pass through biological tissues before reaching the EEG electrodes. This can cause multiple electrodes to measure the same brain signal. This study performed an orthogonalization step to remove signals with the same phase, thereby attempting to limit the effect of volume conduction on our data. This step aids in ensuring final correlations are between distinct brain areas instead of between electrodes that measured the same brain signal[33]. Alternatively, changes in FC can be studied in the source space, where the source of the EEG signals is reconstructed through source localization. A source-space analysis could better approximate the network organization but suffers from the inverse problem[41,42]. Therefore, the use of source localization was outside of the scope of this study.

Future studies could overcome the limitation of reduced generalization of the data by including a larger sample size with more or other patient variables. They could include female participants and left-handed participants whose dominant brain hemisphere was confirmed through fMRI. Additionally, different ethnicities could be included to test different responses to TBS.

Researchers could also investigate changes in FC for only one type of stimulation (iTBS or cTBS) or one frequency band (alpha or beta frequency). This could cause the multiple comparison problem to be less severe, decreasing the necessary Bonferroni correction, which allows for more subtle changes in FC to be able to be detected. As a result, the likelihood of false negative changes in FC will be lower. Furthermore, future studies could delve deeper into interindividual differences by repeating each stimulation type within every participant. Such studies could aid in our understanding of interindividual variability. Additionally, the use of parametric statistical tests should be prioritized, when possible. This is because non-parametric tests, such as the one used in this study, have shown to have less statistical power[43]. The gathered knowledge such studies could aid us in determining which factors contribute to this interindividual variability and help us understand which individuals could benefit most from TBS therapies.

10. GENERAL CONCLUSION

In summary, this study applied the use of AEC on rs-EEG measurements before and after cTBS, iTBS and active sham stimulation. Changes in FC between the stimulation site, electrode C3, and 61 other electrodes were investigated within the three different stimulation types for the alpha and beta frequency bands. Individual topoplots showed no consistent changes in AEC values for the three stimulation types. The statistical analysis combined AEC values per electrode across participants and showed no significant changes in FC in any stimulation type or frequency band. As other researchers have found significant changes in FC due to TBS, future research should be performed to study the effectiveness of using AECs to study changes in FC. These future studies could focus on single forms of TBS or single frequency bands to mitigate the multiple comparison problem. Furthermore, as other researchers did find changes in FC due to TBS by applying other measures, such as graph theoretical analysis, future studies investigating the effect of TBS on FC should utilize other measures until the use of the AEC is validated and standardized.

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12. POSTER

What are the effects of different types of theta burst stimulation on resting-state EEG functional connectivity?

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Abstract | Transcranial magnetic stimulation (TMS) is a form of non-invasive brain stimulation. It is currently used as a treatment for depression and is being investigated as a possible treatment for many other neuropsychiatric diseases. Theta burst stimulation (TBS) is a type of repetitive TMS (rTMS). An important issue with TBS is the large variation in response to stimulation, the cause of which is poorly understood. This project investigates the effects of TBS on resting-state electroencephalography (rsEEG) functional connectivity (FC). Fifteen healthy, right-handed, male participants underwent three TBS protocols (600 pulses) administered to the motor cortex at 80% rMT; intermittent TBS (iTBS), continuous TBS (cTBS) and sham stimulation. Fifteen minutes of rsEEG data was recorded pre- and post-stimulation. Additionally, 150 single pulses were applied pre and post TBS while EEG was simultaneously recorded. The amplitude envelope correlation (AEC) was computed to quantify the connectivity between the stimulated region and other brain regions in the rsEEG data. The effects of different TBS protocols will be studied by comparing AECs before and after TBS. This research will contribute to our understanding of the working mechanisms of TBS. Furthermore, this increased understanding might promote the use of TBS in more clinical trials, giving rise to more therapies utilizing this form of non-invasive brain stimulation.

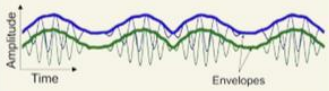
INTRODUCTION

TBS is a form of non-invasive brain stimulation that aims to induce long lasting effects in cortical excitability. Animal studies showed great promise but translation to humans demonstrated to be difficult, meaning further research regarding its effects on the human brain is required. TBS is currently only applied for treatment in depression. This study aims to elucidate the effects of TBS on the FC in the brain of healthy participants utilizing AEC on rsEEG.

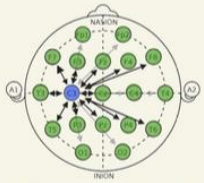
RESEARCH OBJECTIVE

Investigate the effects of different types of TBS on FC in the healthy adult human brain.

AEC

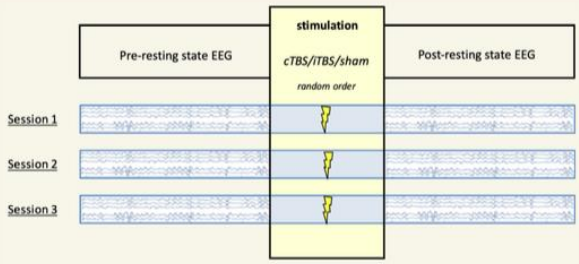


Amplitude envelope correlation | The amplitude envelope forms a curve connecting the highest amplitudes of the oscillatory brain signals that were collected by a single channel of the rsEEG. The AEC then correlates these envelopes between the different channels of a single rsEEG measurement to examine similarities between brain regions. High AEC values indicate a high synchrony between brain areas.



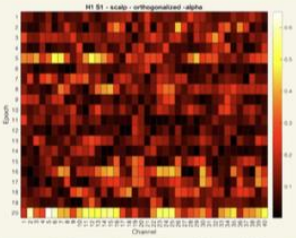
AEC to FC | AECs can then be utilized to investigate changes in FC caused by the different forms of TBS by examining the changes between AECs before and after each stimulation session in each participant. AECs will be performed between the seed region, which is the region between the stimulated motor cortex (blue), and the other electrodes (green).

STIMULATION PROTOCOL



Stimulation protocol | Visual representation of the three stimulation sessions each of the 15 right-handed, male participants underwent, undergoing a 62-channel rsEEG measurement before and after each cTBS, iTBS or sham protocol. rsEEG data was processed in Matlab, EEGLAB and Brainstorm. AECs were calculated to investigate effects on FC. (Adapted from Carrette et al., publication in preparation.)

PRELIMINARY RESULTS



AEC heatmap | Heatmap depicting amplitude envelope values of the rsEEG measured before the first stimulation session of participant 1. Epochs 20/120 and rsEEG channels 40/62 are shown to increase visibility. The heatmap displays the average value of each amplitude envelope for each channel during each epoch of 6 seconds. Amplitude envelope values were visualized to investigate if their values could be negative. These envelopes have been calculated and visualized for all pre- and post-rsEEG data.

CONCLUSION

In the following months, AECs from pre-rsEEG and post-rsEEG data will be correlated with each other. Afterwards, this study will show any measured changes in FC due to TBS in human participants. These results might then aid further incorporation of TBS in clinical trials targetting both neurological and psychological conditions. Future studies could expand on these results by including female participants, looking at delta, theta and gamma frequency-bands and increasing the sample size.

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Figure 10. Midterm poster created to showcase preliminary results.

13. APPENDIX A: LIST OF ABBREVIATIONS

AEC	Amplitude Envelope Correlation
arTMS	Accelerated Repetitive Transcranial Magnetic Stimulation
CNS	Central Nervous System
cTBS	Continuous Theta Burst Stimulation
DBS	Deep Brain Stimulation
DLPFC	Dorsolateral Prefrontal Cortex
dTMS	Deep Transcranial Magnetic Stimulation
EEG	Electroencephalography
EOG	Electro-Oculogram
FC	Functional Connectivity
FDA	Food and Drug Administration
HF-rTMS	High-Frequency Repetitive Transcranial Magnetic Stimulation
iTBS	Intermittent Theta Burst Stimulation
LF-rTMS	Low-Frequency Repetitive Transcranial Magnetic Stimulation
MEP	Motor Evoked Potential
ppTMS	Paired Pulse Transcranial Magnetic Stimulation
Q-Q Plot	Quantile to Quantile Plot
rs-EEG	Resting-State Electroencephalography
rTMS	Repetitive Transcranial Magnetic Stimulation
spTMS	Single Pulse Transcranial Magnetic Stimulation
TBS	Theta Burst Stimulation
tDCS	Transcranial Direct Current Stimulation
TEP	Transcranial Magnetic Stimulation Evoked Potential
TMS	Transcranial Magnetic Stimulation
VNS	Vagal Nerve Stimulation

14. APPENDIX B: SUPPLEMENTARY MATERIALS

14.1 Data availability

Table S1. Available pre-stimulation rs-EEG data. Table indicating which pre-stimulation rs-EEG data was available for each participant and session

Participant number	iTBS available	cTBS available	Sham available
Participant 1	Yes	No	Yes
Participant 2	Yes	Yes	Yes
Participant 3	Yes	Yes	Yes
Participant 4	Yes	Yes	No
Participant 5	No	No	No
Participant 6	Yes	Yes	Yes
Participant 7	Yes	Yes	Yes
Participant 8	Yes	Yes	Yes
Participant 9	Yes	Yes	Yes
Participant 10	Yes	Yes	No
Participant 11	Yes	Yes	Yes
Participant 12	Yes	Yes	Yes
Participant 13	Yes	Yes	Yes
Participant 14	Yes	Yes	Yes
Participant 15	Yes	Yes	Yes

Abbreviations: cTBS = continuous theta burst stimulation, iTBS = inhibitory theta burst stimulation.

Table S2. Available post-stimulation rs-EEG data. Table indicating which post-stimulation rs-EEG data was available for each participant and session

Participant number	iTBS available	cTBS available	Sham available
Participant 1	Yes	Yes	Yes
Participant 2	Yes	Yes	Yes
Participant 3	Yes	Yes	Yes
Participant 4	Yes	Yes	Yes
Participant 5	Yes	Yes	Yes
Participant 6	Yes	Yes	Yes
Participant 7	Yes	Yes	Yes
Participant 8	Yes	Yes	Yes
Participant 9	Yes	Yes	Yes
Participant 10	Yes	Yes	No
Participant 11	Yes	Yes	Yes
Participant 12	Yes	Yes	Yes
Participant 13	Yes	Yes	Yes
Participant 14	Yes	Yes	Yes
Participant 15	Yes	Yes	No

Abbreviations: cTBS = continuous theta burst stimulation, iTBS = inhibitory theta burst stimulation.

14.2 Preprocessing changes

Table S3. Modifications of pre-stimulation rs-EEG data. Table indicating how pre-stimulation rs-EEG data was modified during preprocessing for each participant and session

Participant #	Session	Channels removed	Epochs removed	ICA analysis
Participant 1	Session 1	/	/	/
	Session 2	/	IC30: changed from eye blink to electrode noise	/
	Session 3	NO DATA	NO DATA	NO DATA
Participant 2	Session 1	1, 2, 3, 21, 22, 40, 41, 60-64, 76-79	IC37: did not reject	/
	Session 2	91	/	/
	Session 3	1, 2, 10, 22, 31, 50, 98	/	/
Participant 3	Session 1	112	IC4: rejected as electrode noise, IC12: changed from eye blink to electrode noise, IC 19: changed from eye blink to electrode noise	/
	Session 2	/	/	/
	Session 3	52, 63, 64, 66, 83, 98	IC4: rejected as electrode noise, IC9: rejected as electrode noise	/
Participant 4	Session 1	NO DATA	NO DATA	NO DATA
	Session 2	/	/	/
	Session 3	/	/	/
Participant 5	Session 1	NO DATA	NO DATA	NO DATA
	Session 2	NO DATA	NO DATA	NO DATA
	Session 3	NO DATA	NO DATA	NO DATA
Participant 6	Session 1	102	/	/
	Session 2	1, 63, 67	IC10: rejected as electrode noise	/
	Session 3	1-4, 6, 7, 12, 13, 17, 23, 65, 110	/	/
Participant 7	Session 1	100	/	/
	Session 2	1, 2, 3, 4, 33, 42, 43, 52, 64, 65, 78, 79, 85, 87		
	Session 3	100	/	/
Participant 8	Session 1	1-7, 10, 11, 89	/	/
	Session 2	2-4, 25, 31, 53, 78	/	/

	Session 3	49, 50, 100-102	/	/
Participant 9	Session 1	69, 76, 89	/	/
	Session 2	1, 13, 14, 47, 62, 63, 66, 67, 77, 78, 83, 88, 92, 101, 103, 104	/	/
	Session 3	22, 54	/	/
Participant 10	Session 1	105	/	P7
	Session 2	2, 4, 5, 39, 68, 70, 82, 83, 88, 92, 99, 105	/	/
	Session 3	100-101	/	/
Participant 11	Session 1	70	IC5: rejected as electrode noise, IC9: rejected as electrode noise	/
	Session 2	1, 7, 99	/	/
	Session 3	4-6, 12, 88	/	/
Participant 12	Session 1	84	/	/
	Session 2	/	IC24: rejected as electrode noise, IC 25: rejected as electrode noise, IC28: rejected as electrode noise	/
	Session 3	1, 19, 48, 52, 63, 101	IC6: rejected as eye blinks, IC11: rejected as electrode noise, IC14: rejected as electrode noise, IC22: rejected as eye blinks	/
Participant 13	Session 1	104	IC14: rejected as electrode noise, IC16: rejected as electrode noise, IC17: rejected as electrode noise, IC35: rejected as electrode noise	/
	Session 2	3, 6, 9, 92, 124	/	/
	Session 3	99	/	/
Participant 14	Session 1	1	/	/
	Session 2	1-4, 73, 74, 92	IC5: rejected as electrode noise, IC10: rejected as electrode noise,	/

			IC12: rejected as electrode noise, IC 25: rejected as electrode noise, IC32: rejected as electrode noise	
	Session 3	97	/	/
Participant 15	Session 1	1, 20, 46, 70, 92, 93, 105	IC3: rejected as electrode noise, IC18: rejected as electrode noise, IC26: rejected as electrode noise	/
	Session 2	1, 2, 53, 99	/	/
	Session 3	5, 27, 28, 30, 62, 67, 77	/	/

Abbreviations: cTBS = continuous theta burst stimulation, iTBS = inhibitory theta burst stimulation.

Table S4. Modifications of post-stimulation rs-EEG data. Table indicating how post-stimulation rs-EEG data was modified during preprocessing for each participant and session

Participant #	Session	Channels removed	Epochs removed	ICA analysis
Participant 1	Session 1	/	2, 3	/
	Session 2	/	99	/
	Session 3	/	10, 45	/
Participant 2	Session 1	/	/	/
	Session 2	/	/	/
	Session 3	/	8	/
Participant 3	Session 1	/	10	/
	Session 2	/	68	/
	Session 3	/	6, 15	/
Participant 4	Session 1	/	/	/
	Session 2	/	/	/
	Session 3	/	/	/
Participant 5	Session 1	/	/	/
	Session 2	/	/	/
	Session 3	/	1, 2	/
Participant 6	Session 1	/	/	/
	Session 2	/	/	/
	Session 3	/	/	/
Participant 7	Session 1	/	/	/
	Session 2	/	2	/
	Session 3	/	/	/
Participant 8	Session 1	/	/	/
	Session 2	/	1	/
	Session 3	/	/	/
Participant 9	Session 1	/	/	/

	Session 2	/	/	/
	Session 3	/	/	/
Participant 10	Session 1	/	/	/
	Session 2	/	24	/
	Session 3	/	/	/
Participant 11	Session 1	/	/	/
	Session 2	/	/	/
	Session 3	/	/	/
Participant 12	Session 1	/	/	IC2: rejected as electrode noise, IC3: rejected as electrode noise
	Session 2	/	/	/
	Session 3	/	97	/
Participant 13	Session 1	/	/	/
	Session 2	/	/	/
	Session 3	/	/	/
Participant 14	Session 1	/	/	/
	Session 2	/	/	/
	Session 3	/	/	/
Participant 15	Session 1	NO DATA	NO DATA	NO DATA
	Session 2	/	/	/
	Session 3	/	/	/

Abbreviations: cTBS = continuous theta burst stimulation, iTBS = inhibitory theta burst stimulation.

14.3 Individual topoplots

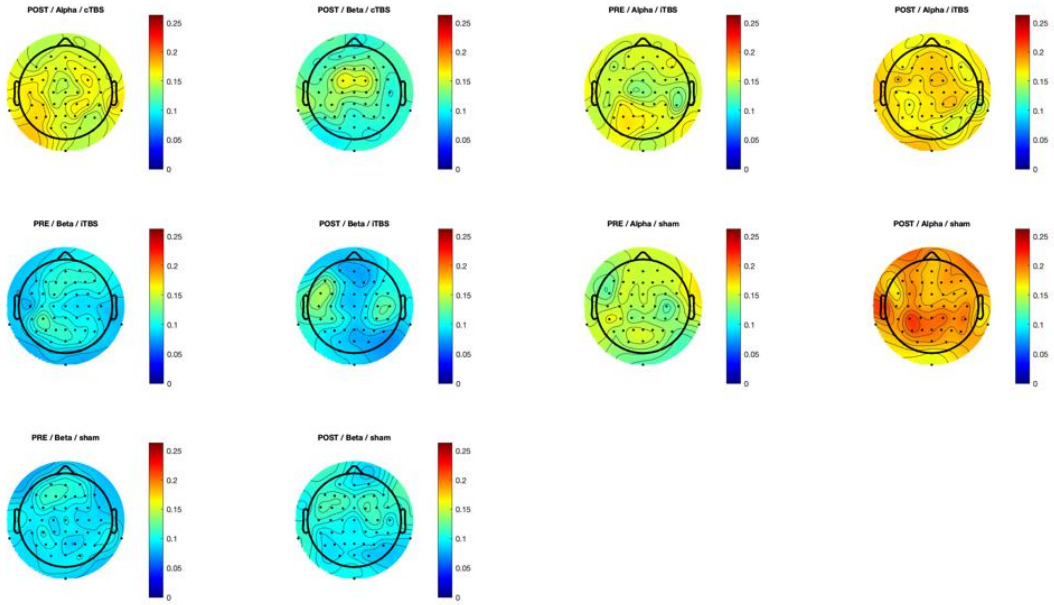

Figure S1. Topoplots visualizing AEC values for participant 1. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

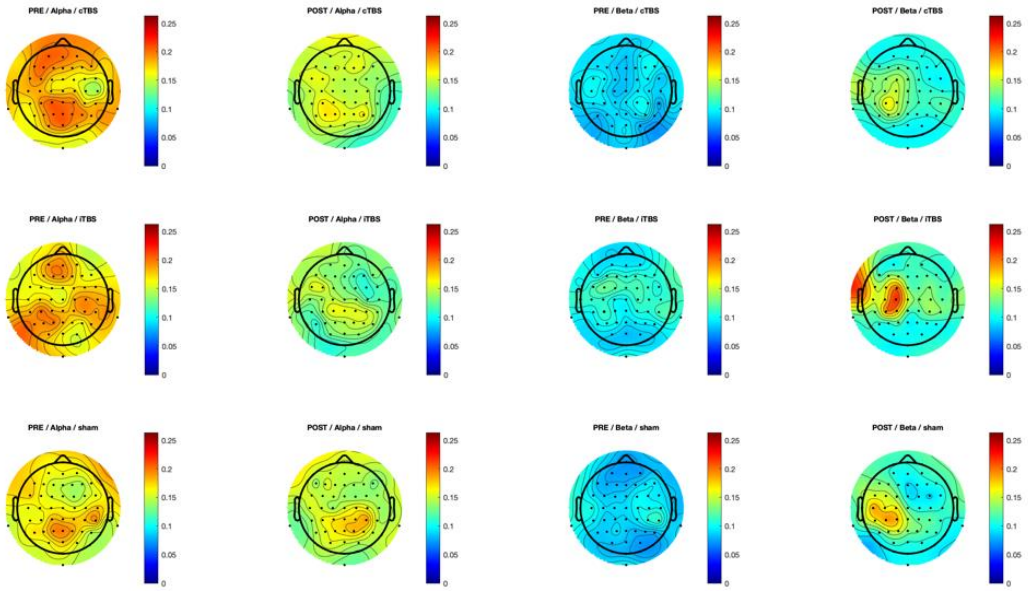

Figure S2. Topoplots visualizing AEC values for participant 2. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

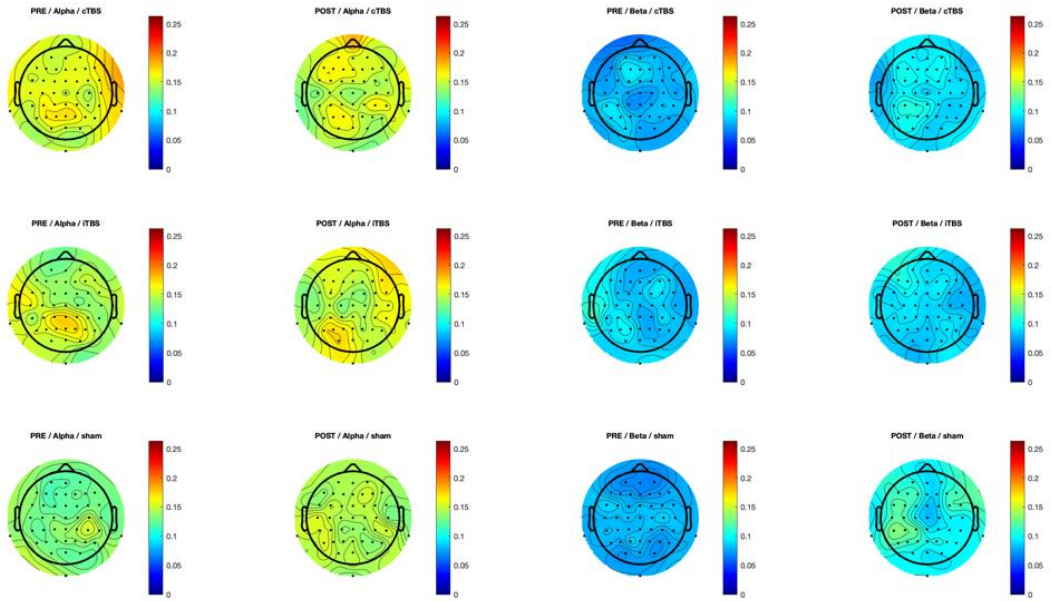

Figure S3. Topoplots visualizing AEC values for participant 3. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

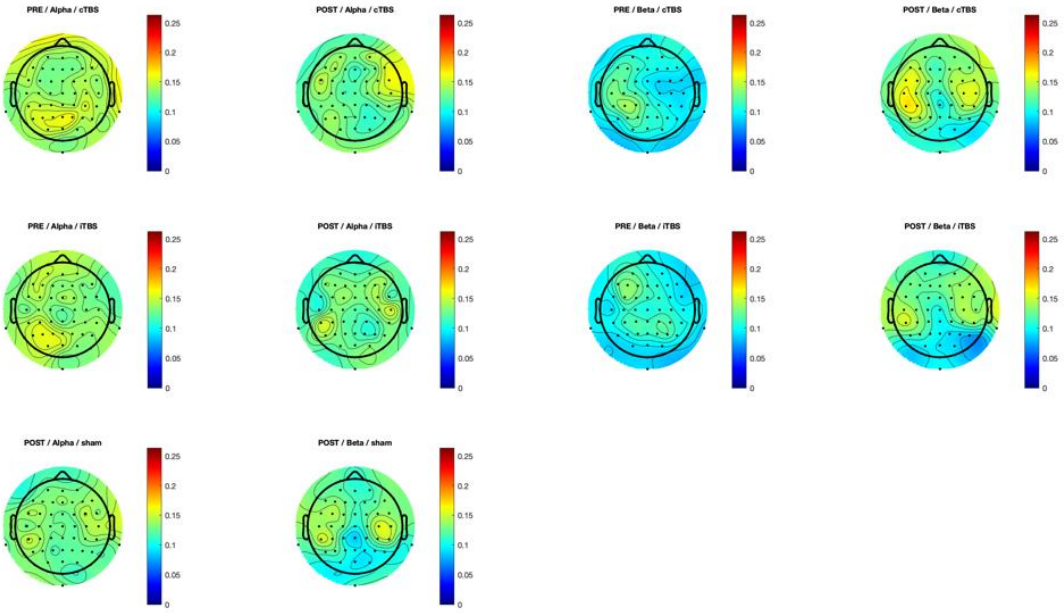

Figure S4. Topoplots visualizing AEC values for participant 4. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

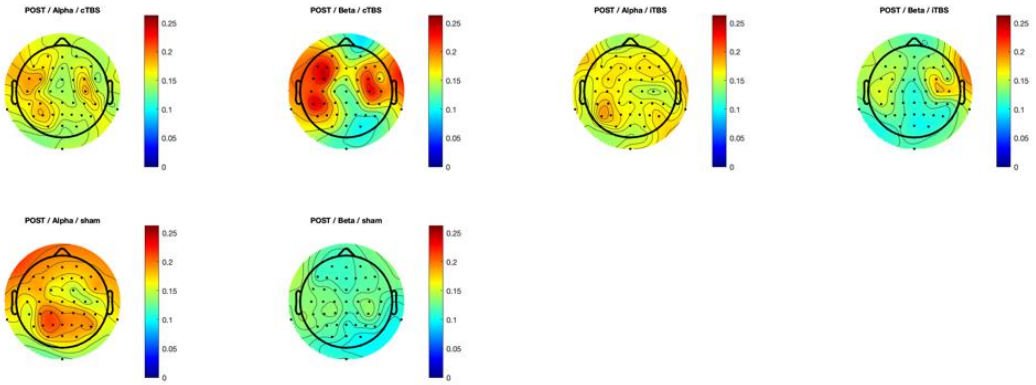

Figure S5. Topoplots visualizing AEC values for participant 5. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

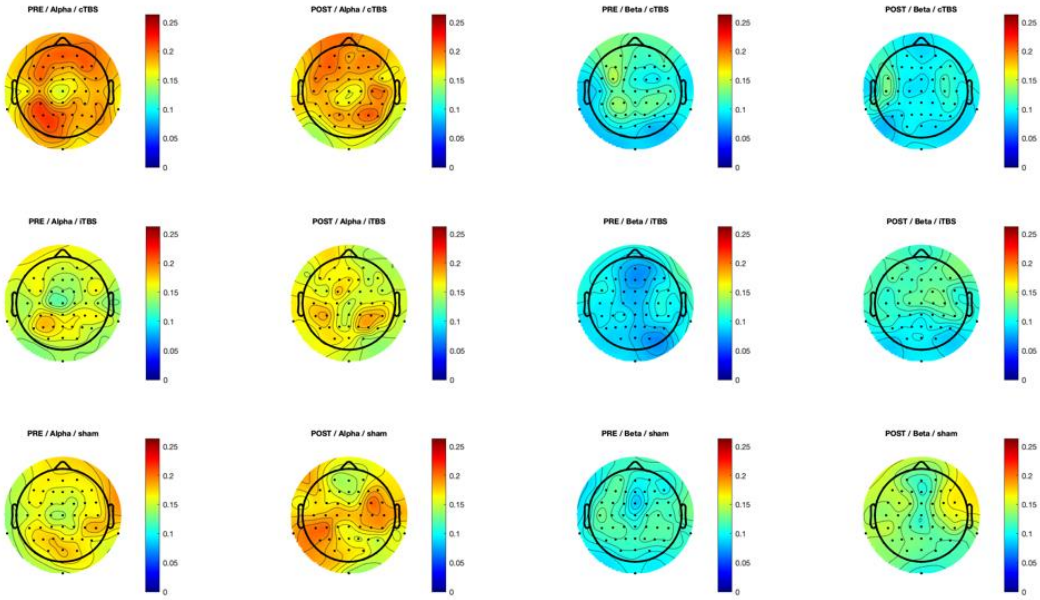

Figure S6. Topoplots visualizing AEC values for participant 6. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

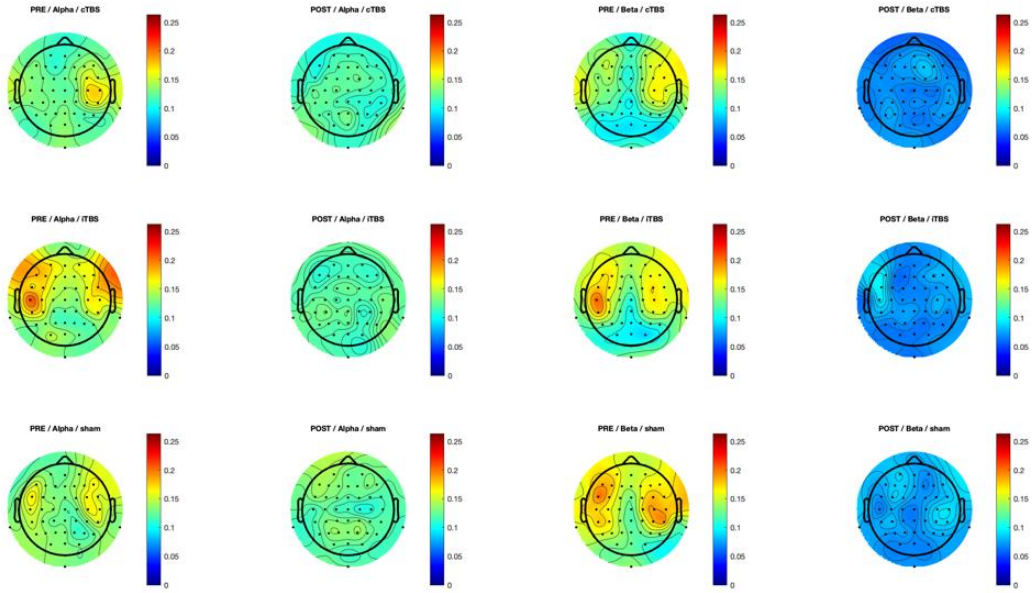

Figure S7. Topoplots visualizing AEC values for participant 7. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

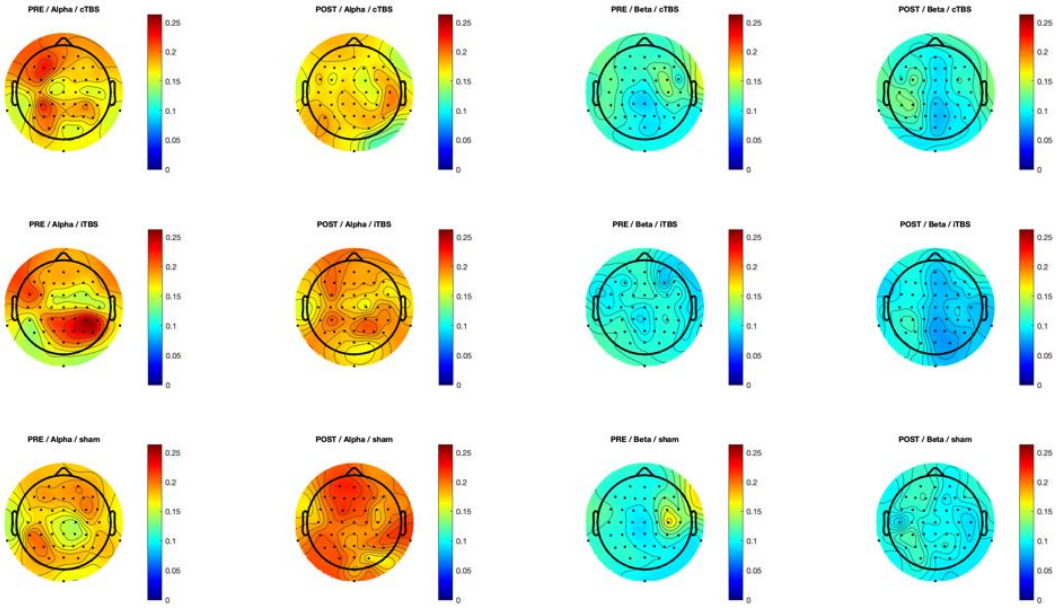

Figure S8. Topoplots visualizing AEC values for participant 8. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

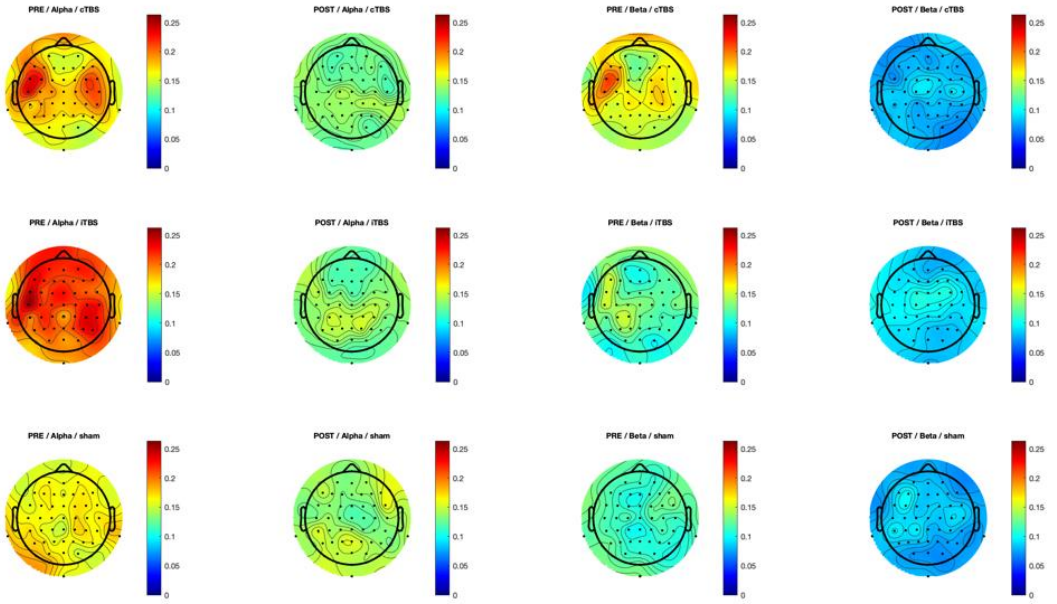

Figure S9. Topoplots visualizing AEC values for participant 9. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

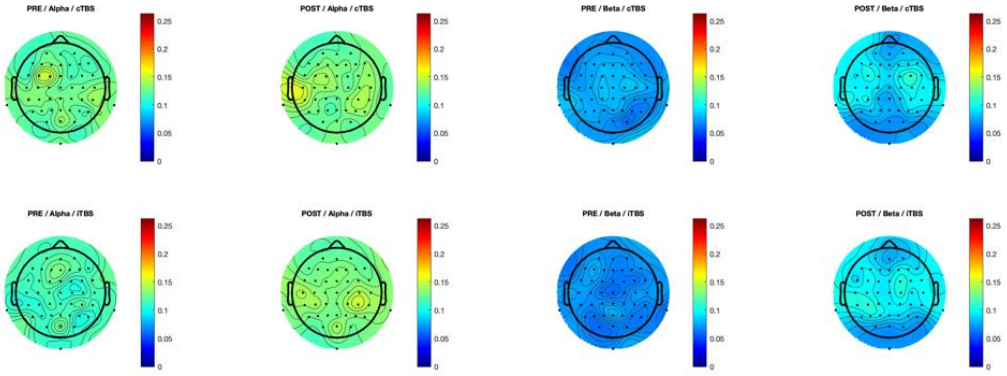

Figure S10. Topoplots visualizing AEC values for participant 10. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

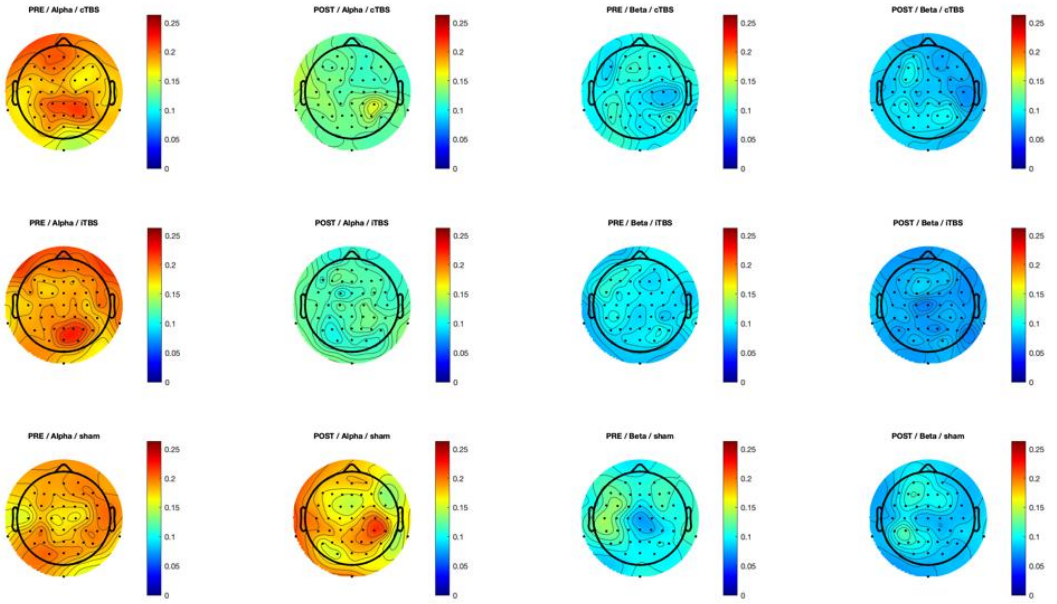

Figure S11. Topoplots visualizing AEC values for participant 11. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

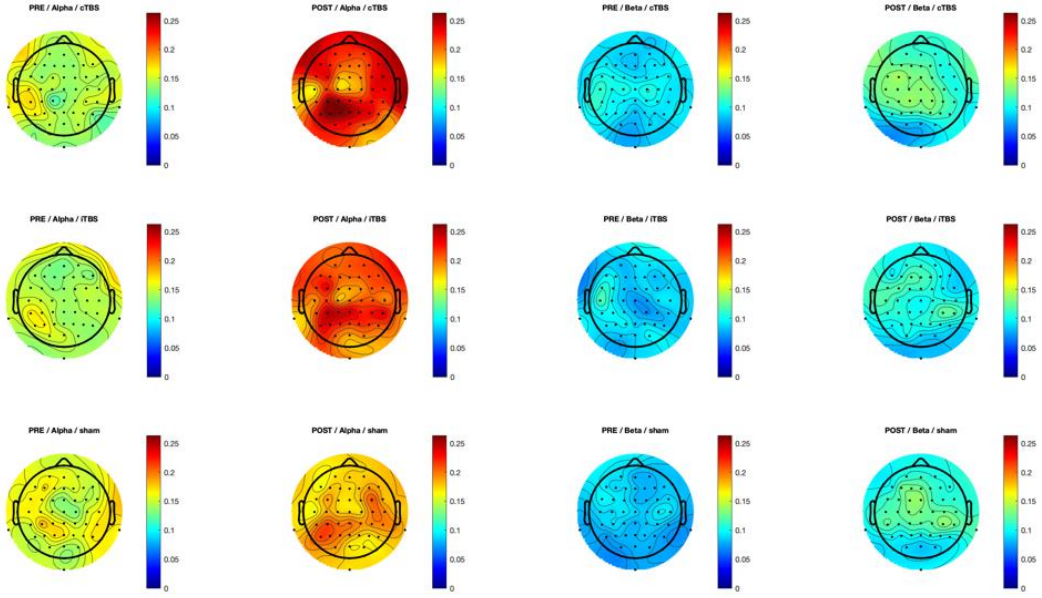

Figure S12. Topoplots visualizing AEC values for participant 12. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

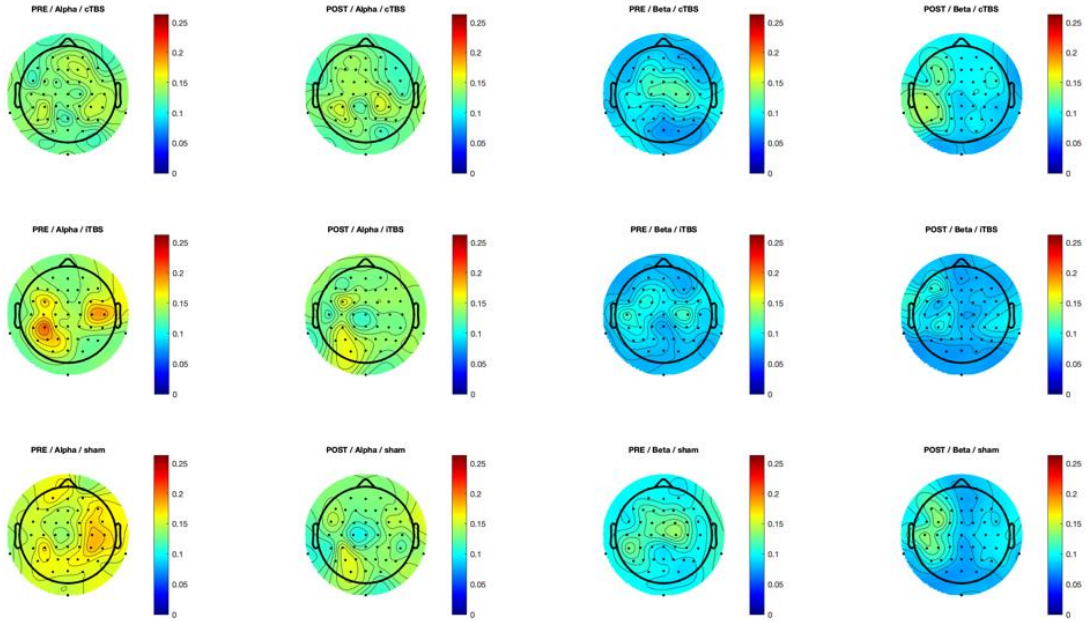

Figure S13. Topoplots visualizing AEC values for participant 13. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

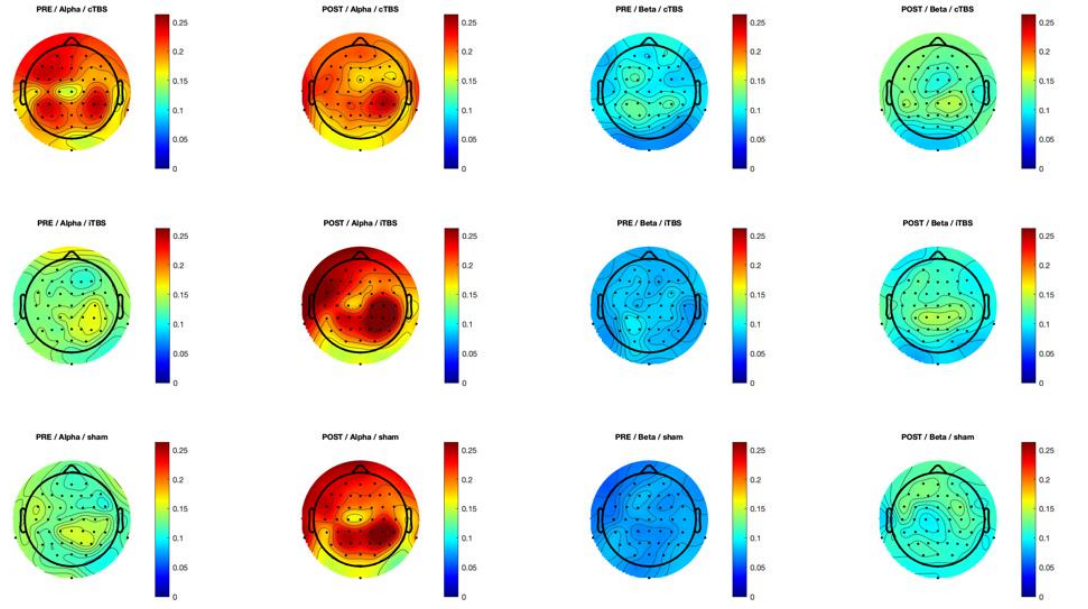

Figure S14. Topoplots visualizing AEC values for participant 14. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

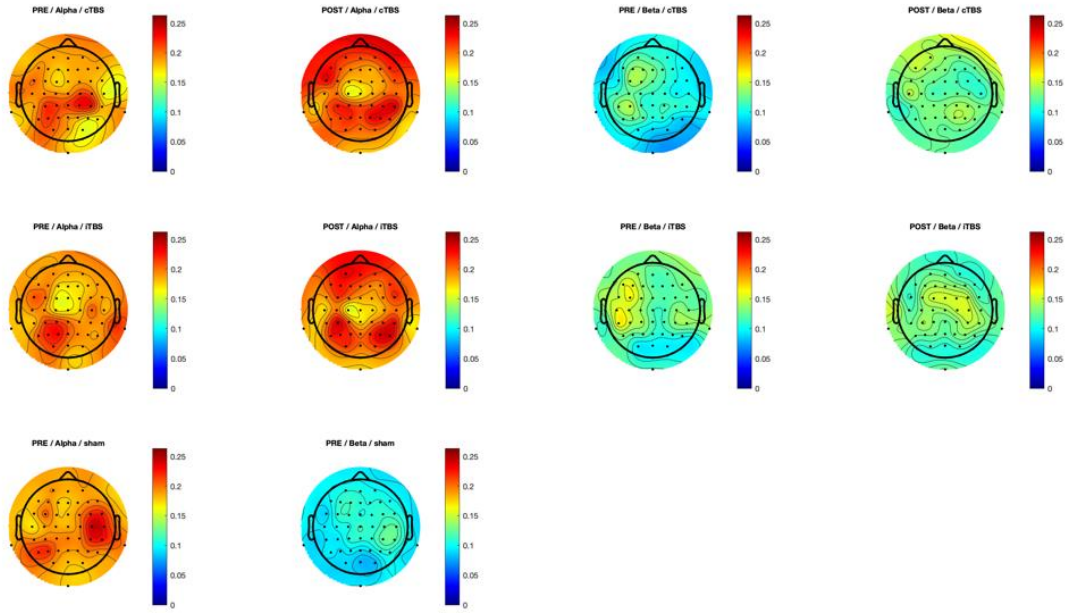

Figure S15. Topoplots visualizing AEC values for participant 15. Topoplots are titled to indicate if AEC values originate from pre- or post-stimulation data, from the alpha or beta frequency band and from cTBS, iTBS or sham stimulation.
Abbreviations: AEC = amplitude envelope correlation; cTBS = continuous theta burst stimulation; iTBS = inhibitory theta burst stimulation.

14.4 Wilcoxon matched-pairs signed-rank test results

Table S5. Wilcoxon matched-pairs signed-rank test results of the alpha frequency band. Resulting p-values of the Wilcoxon matched-pairs signed-rank test performed for AEC values of the alpha frequency band. The p-values indicate if there was a significant change in FC between the electrode in the first column and electrode C3 after each stimulation session. P-values < 0.05 are indicated in red. A Bonferroni adjusted α-value of 0.0001 was regarded as significant.

Electrode	iTBS	cTBS	Sham
Iz	0.807739258	0.068115234	0.147460938
O2	0.807739258	0.497314453	0.123046875
Oz	0.669799805	0.587890625	0.365234375
O1	0.669799805	0.127197266	0.3203125
PO8	0.951538086	0.305419922	0.700195313
PO4	0.669799805	0.454833984	0.46484375
POz	0.541625977	0.2734375	0.3203125
PO3	0.625732422	0.109863281	0.365234375
PO7	1	0.375732422	0.240234375
P8	0.71484375	0.080322266	0.46484375
P6	0.855224609	0.497314453	0.51953125
P4	0.855224609	0.635498047	0.1015625
P2	0.760864258	0.684814453	0.053710938
Pz	0.295776367	0.216308594	0.1015625
P1	0.325805664	0.146484375	0.123046875
P3	0.583007813	0.057373047	0.278320313
P5	0.951538086	0.109863281	0.278320313

P7	0.903198242	0.2734375	0.206054688
TP10	0.760864258	0.243896484	0.278320313
TP8	0.426269531	0.127197266	0.577148438
CP6	1	0.735351563	0.413085938
CP4	0.71484375	0.375732422	0.083007813
CP2	0.760864258	0.190917969	0.053710938
CPz	0.390991211	0.094238281	0.024414063
CP1	0.241210938	0.047851563	0.1015625
CP3	0.951538086	0.057373047	0.041992188
CP5	0.903198242	0.305419922	0.174804688
TP7	0.807739258	0.635498047	0.123046875
TP9	0.71484375	0.786865234	0.147460938
T8	0.807739258	0.414306641	0.637695313
C6	1	0.735351563	0.51953125
C4	0.903198242	0.892578125	0.240234375
C2	1	0.190917969	0.083007813
Cz	0.903198242	0.635498047	0.123046875
C1	0.951538086	0.587890625	0.123046875
C5	0.583007813	0.414306641	0.278320313
T7	0.855224609	0.454833984	0.174804688
FT8	0.625732422	0.2734375	0.700195313
FC6	0.501586914	0.454833984	0.46484375
FC4	0.951538086	0.146484375	0.365234375
FC2	0.903198242	0.127197266	0.206054688
AF8	0.669799805	0.2734375	0.413085938
FC1	0.501586914	0.339599609	0.240234375
FC3	0.855224609	0.243896484	0.3203125
FC5	0.357543945	0.587890625	0.46484375
FT7	0.541625977	0.2734375	0.3203125
F8	0.669799805	0.243896484	0.700195313
F6	1	0.339599609	0.700195313
F4	0.855224609	0.167724609	0.3203125
F2	0.760864258	0.109863281	0.46484375
Fz	0.71484375	0.216308594	0.46484375
F1	0.71484375	0.497314453	0.3203125
F3	0.903198242	0.541748047	0.3203125
F5	0.951538086	0.414306641	0.46484375
F7	0.426269531	0.375732422	0.1015625
AF4	0.71484375	0.2734375	0.577148438
AF7	0.855224609	0.190917969	0.3203125
AF3	0.951538086	0.684814453	0.278320313
Fp2	0.855224609	0.167724609	0.51953125
Fpz	1	0.454833984	0.278320313
Fp1	0.807739258	0.375732422	0.174804688

Abbreviations: cTBS = continuous theta burst stimulation, iTBS = inhibitory theta burst stimulation.

Table S6. Wilcoxon matched-pairs signed-rank test results of the beta frequency band. Resulting p-values of the Wilcoxon matched-pairs signed-rank test performed for AEC values of the beta frequency band. The p-values indicate if there was a significant change in FC between the electrode in the first column and electrode C3 after each stimulation session. A Bonferroni adjusted α-value of 0.0001 was regarded as significant.

Electrode	iTBS	cTBS	Sham
Iz	0.71484375	0.635498047	0.831054688
O2	0.426269531	0.497314453	0.700195313
Oz	0.583007813	0.684814453	0.831054688
O1	0.426269531	1	0.46484375
PO8	0.172607422	0.497314453	0.637695313
PO4	0.541625977	0.414306641	0.8984375
POz	0.426269531	0.684814453	0.637695313
PO3	0.951538086	0.541748047	0.46484375
PO7	0.541625977	0.839355469	0.637695313
P8	0.357543945	0.541748047	0.831054688
P6	0.357543945	0.454833984	0.831054688
P4	0.541625977	0.414306641	0.577148438
P2	0.541625977	0.684814453	0.3203125
Pz	0.541625977	0.735351563	0.240234375
P1	0.501586914	0.635498047	0.147460938
P3	0.669799805	0.541748047	0.365234375
P5	0.855224609	0.635498047	0.46484375
P7	0.669799805	0.684814453	0.637695313
TP10	1	0.587890625	0.577148438
TP8	0.501586914	0.839355469	0.764648438
CP6	0.267578125	0.735351563	0.764648438
CP4	0.390991211	0.684814453	0.637695313
CP2	0.669799805	0.946044922	0.3203125
CPz	0.71484375	0.786865234	0.206054688
CP1	0.625732422	0.735351563	0.123046875
CP3	0.71484375	0.635498047	0.206054688
CP5	0.669799805	0.454833984	0.240234375
TP7	0.325805664	0.497314453	0.637695313
TP9	0.295776367	0.2734375	0.764648438
T8	0.583007813	0.892578125	0.637695313
C6	0.541625977	0.684814453	1
C4	0.463134766	0.839355469	0.8984375
C2	0.463134766	0.786865234	0.637695313
Cz	0.463134766	1	0.278320313
C1	0.625732422	0.786865234	0.240234375
C5	0.951538086	0.243896484	0.764648438
T7	0.172607422	0.2734375	0.965820313
FT8	0.583007813	0.635498047	0.965820313
FC6	0.760864258	0.454833984	0.831054688
FC4	0.390991211	0.786865234	1
FC2	0.583007813	0.892578125	0.577148438
AF8	0.669799805	0.786865234	0.206054688
FC1	0.541625977	0.839355469	0.174804688

FC3	0.669799805	0.735351563	0.278320313
FC5	0.951538086	0.375732422	0.577148438
FT7	0.172607422	0.243896484	0.8984375
F8	0.760864258	0.735351563	0.764648438
F6	0.903198242	0.684814453	0.637695313
F4	0.325805664	0.892578125	0.700195313
F2	0.426269531	0.946044922	0.413085938
Fz	0.760864258	0.946044922	0.278320313
F1	0.541625977	0.786865234	0.206054688
F3	0.807739258	0.684814453	0.206054688
F5	0.855224609	0.375732422	0.365234375
F7	0.541625977	0.375732422	0.700195313
AF4	0.807739258	0.892578125	0.577148438
AF7	0.951538086	0.946044922	0.46484375
AF3	0.951538086	0.839355469	0.46484375
Fp2	1	0.839355469	0.577148438
Fpz	0.625732422	0.839355469	0.46484375
Fp1	0.807739258	0.839355469	0.3203125

Abbreviations: cTBS = continuous theta burst stimulation, iTBS = inhibitory theta burst stimulation.