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TMS-evoked oscillations in human cortical circuits: A search for natural frequencies

Abbreviated Title: TMS-evoked oscillations and natural frequencies

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Abstract

Previous evidence suggests different cortical areas naturally oscillate at distinct frequencies, reflecting tuning properties of each region. The concurrent use of transcranial magnetic stimulation (TMS) and electroencephalography (EEG) has been used to perturb cortical regions, resulting in an observed post-stimulation response that is maximal at the natural frequency (Rosanova et al., 2009; Ferrarelli et al., 2012). These frequencies were reported to progress from high-to-low in a rostro-caudal gradient across the cortex, such that a consistently evoked dominant α-band oscillations (8–12 Hz) occurred in the occipital cortex (BA 19), β-band oscillations (13–20 Hz) in the parietal cortex (BA 7), and fast β/γ-band oscillations (21–50 Hz) in the frontal cortex (BA 6). Thus far, literature investigating natural frequencies in cortical circuits with TMS-EEG have only been demonstrated in the left hemisphere. Here, we attempted to replicate these previous findings in the right hemisphere by employing TMS-EEG to directly perturb approximately homologous cortical areas in human subjects during a passive state (N=12) and during an active task (N=12) in both sexes. Contrary to previous reports, we found limited evidence of differences in fundamental frequency between stimulation sites; while frequency-specific responses differed between sites, the same features displayed in previous studies were not replicated, such as the rostro-caudal gradient. Instead, each site possessed its own complex pattern of global and local changes in response to stimulation, with the pattern differing per subject. These findings suggest that cortical regions exhibit complex frequency-specific profiles that cannot be described by a hierarchical progression alone.

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Introduction

Over the past 20 years, a large body of research has focused on oscillatory signatures arising from macro- and micro-scale neural recordings. Among these studies has arisen the concept of natural frequencies of human cortical modules, suggesting that distinct regions of the cortex naturally oscillate at distinct frequencies (Niedermeyer, 1999). Of great interest is an expansion of the natural frequencies concept, reporting that evoked dominant oscillations consistently follow a rostro-caudal gradient with α-band (8–12Hz) in occipital (BA 19), β-band (13–20Hz) in parietal (BA 7), and fast β/γ-band (21–50 Hz) in frontal cortex (BA 6). However, primary evidence for this progression comes from a single study (Rosanova et al., 2009), in which single-pulse transcranial magnetic stimulation (TMS) was applied to perturb cortical regions while simultaneously recording electroencephalography (EEG), measuring the resultant changes in maximal evoked frequency. This and a follow-up study (Ferrarelli et al., 2012) by the same group support the notion of a hierarchical progression across the brain of oscillatory frequency. Yet, to our knowledge, the effects they report have not been replicated elsewhere.

In the follow-up study (Ferrarelli et al., 2012), four cortical areas (parietal, motor, pre-motor, prefrontal) in the left hemisphere were stimulated at an electric field strength of 120 V/m while concurrently recording EEG. Compared to age-matched healthy control subjects (N=20; 13 males, *M*=31.7 years), patients with schizophrenia (N=20; 16 males, *M*=32.8 years) showed intrinsic slowing in natural frequency of frontal/prefrontal regions (~2-Hz decrease in motor area, and approximately 10-Hz decrease in prefrontal area), but not in the parietal area. The authors claim these findings suggest the prefrontal natural frequency of an individual can predict some symptoms and cognitive dysfunctions of schizophrenia. Furthermore, they reported that in patients with schizophrenia, the frequency of prefrontal cortex oscillations was inversely related to the level

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of positive symptoms on the Positive and Negative Syndrome Scale (PANSS), including reaction time of correct responses on a word memory task. However, some questions remain, for instance whether the prefrontal natural frequency slowing in patients with schizophrenia was due to a medication effect, and why the rostro-caudal gradient appeared for some subjects but not others, showing that frequency-specific responses can differ per subject regardless of group type.

While the above studies highlight the fundamental nature of a rostro-caudal gradient in cortical frequency, evidence to the contrary exists. Schomer (2007) reported the prominence of alpha-rhythms over the posterior region of the cortex, yet they were widely distributed and incorporated in parietal and posterior temporal regions in approximately one-third of healthy adults. Furthermore, magnetoencephalography (MEG) data show that each cortical area engages in different characteristic oscillatory patterns, or spectral profiles, for individual areas; thus, each brain area engages in several spectral *modes* consisting of varying oscillatory bands that change based on whether a subject is resting or engaged in a task (Keitel and Gross, 2016). Given the importance of understanding oscillatory mechanisms, as well as the implications for potential diagnostic purposes of natural frequency and mental illness (Rosanova et al., 2009; Ferrarelli et al., 2012), we therefore sought to replicate and extend these findings.

In the present study, we tested two groups of subjects (N=12 each) while simultaneously applying single-pulse TMS and recording resultant EEG responses. We thus doubled the initial sample size of the original study (N=6; Rosanova et al., 2009); further, prior studies only stimulated subjects at sites in the left hemisphere. As such, in our study we stimulated subjects at the same sites but in the opposite hemisphere, in order to verify the extendibility of these findings. One group was tested while subjects were at rest, similar to the previous reports, while a second group was tested while actively engaged in a simple sensorimotor task. We precisely repeated the

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methods and analysis regimes of the prior studies, wherein TMS was administered and frequency spectra data were obtained to measure the maximum evoked frequency at each stimulation site.

Materials and Methods

Subjects. Twenty-four right-handed subjects (12 females, age 19–36 years) with normal or corrected-to-normal visual acuity participated in this study, and were randomized into one of two groups: twelve subjects participated in the passive experiment (7 females, mean age 22.5 years), while the other twelve subjects participated in the active experiment (5 females, mean age 25.2 years). Following the Rossi et al. (2009) safety and ethical guidelines, all subjects were eligible to receive TMS. All subjects provided informed consent and all protocols were approved by the George Mason University Institutional Review Board.

TMS. A focal figure-of-eight air-cooled coil with 70mm wing diameter driven by a Magstim Rapid^2 biphasic stimulator (Magstim Inc., Wales, UK) was used to non-invasively stimulate the subjects' cortex. On the right hemisphere of the scalp, three cortical sites were selected over the EEG electrodes P4 (occipital), C4 (parietal), and F4 (frontal), as they were homologous to the regions stimulated in the Rosanova study (2009). To verify anatomical locations of the cortical stimulation sites a T1-weighted MRI of one subject was used and targeted using MNI coordinates in the Brainsight neuronavigation system (Rogue Research Inc., Montreal, Canada).

High-density EEG recording during TMS. TMS-evoked potentials (TMS-EP) were recorded using an actiCHamp 64-channel amplifier (Brain Products GmbH, Germany) and TMS-compatible actiCAP slim active electrodes (international 10-20 system), with FCz as the online reference. BrainVision Recorder (v. 1.20.0801) was used to digitize the EEG at a sampling frequency of 5000 Hz. Electrode impedances were kept <5 kΩ. To minimize contamination of

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auditory potentials evoked by the click associated with the TMS coil discharge (ter Braack et al., 2015), subjects underwent a TMS-click auditory perception (TMS-CAP) test prior to beginning the experiment. During the test, subjects wore inserted wired silicone-tipped earplug headphones with a Noise Reduction Rating (NRR) of 26 dB, while a masking noise with the same spectral profile of the TMS coil click was continuously played. Recordings of the TMS coil click emitted by the Magstim coil were used to create the masking noise and scrambled into a continuous sound file with the same spectral properties, thus, capturing the specific time-varying frequency components of the TMS click. For the TMS-CAP test, subjects listened to the masking noise while a brief TMS burst was administered on top of the FCz (average reference) electrode. Subjects were instructed to notify the experimenter if they could hear the TMS coil click. If a subject reported hearing the click, the volume of the masking noise was raised to a level still comfortable for the subject and/or the stimulator intensity output percentage was lowered until the click was as imperceptible as possible without lowering the stimulator output to an ineffective intensity (<40 V/m; Rosanova et al., 2009). Once the TMS-CAP was complete, subjects were required to continue wearing the earplug headphones for the duration of the experiment while listening to the masking noise at their individualized fixed volume. All TMS-induced artifacts were attended to during offline analysis.

TMS protocol. During this experiment, subjects in both groups received a single-pulse TMS protocol. This consisted of a series of TMS pulses that were administered one-at-a-time over a part of the brain on the right hemisphere of the scalp, approximately over electrodes P4, C4, and F4 (see Figure 1). At each of the three electrode sites, a total of 100 pulses were administered repetitively at each site, separated by a short period of time based on randomized experimental group assignment (passive or active), resulting in a total of 300 pulses overall. Based on their

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individual TMS-CAP results, subjects in the passive experimental group received single pulse stimulation at a fixed intensity of between 30–50% of maximum stimulator output (MSO; range 44.7–74.5%), while subjects in the active experimental group received single pulse stimulation at a fixed intensity of between 35–50% of MSO (range 52.1–74.5%,); both groups received an average of 42.5% MSO (± 7.23 for passive and ± 5.84 for active, respectively). According to an independent samples t-test, MSO values were not different between the two groups; $t(22) = 0$, $p = 1$.

We additionally calculated the modeled electrical field of our TMS stimulator across the different MSO intensities employed. To that end, we conducted electrical field modeling using SimNIBS software (v. 2.1.2; Thielscher et al., 2015), on a standardized MNI template with a modeled Magstim TMS coil matching our own. Similar to MSO values, we observed no differences between groups (Passive: average 63.3±10.77 V/m; Active: average 63.3±8.71 V/m). Additionally, we note that the lowest intensity in our tested sample (44.7 V/m) did not exceed the minimal intensity reported by Rosanova and colleagues (2009) for eliciting rostro-caudal gradients.

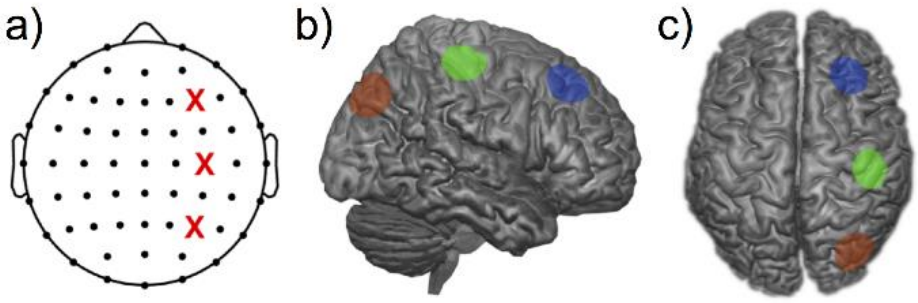

Figure 1. Stimulation sites. a) represents electrode stimulation sites, indicated by red X mark; top X is F4, middle X is C4, and bottom X is P4. Images b) and c) represent stimulation sites on a rendered brain as determined by Brainsight localization of the TMS coil on a sample subject.

General experimental procedures for both experimental groups. During the experiment, subjects sat in an ergonomic chair, relaxed, and with eyes open looking at a fixation cross on a

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screen. Once the selected electrode site was targeted, we stimulated it at an intensity that was set by the subject's TMS-CAP results.

Passive group experimental procedures. Subjects in the passive experimental group did not perform a sensorimotor task; instead, they were instructed to rest with their eyes open during the experiment. Subjects viewed an LCD monitor with a 120 Hz refresh rate (Cambridge Research Systems, United Kingdom) approximately 70-cm away with a black background, and were instructed to keep their eyes fixed on a 5x5 cm black fixation cross that appeared in the center of the screen. Each of the three electrode sites were stimulated in a counterbalanced block design and received 100 stimuli per block at a randomized inter-stimulation-interval (ISI) between 4–6 seconds.

Active group experimental procedures and task. Subjects in the active experimental group performed a sensorimotor luminance detection task that relied on gradual signal detection, and was programmed in PsychoPy (v. 1.85.6; Peirce, 2009). Subjects viewed a screen approximately 70-cm away with a grey background and a 5x5 cm fixation cross with a white outline in the center of the screen that gradually changed from a solid black center to solid white, achieving full luminance (see Figure 2). Once the subject perceived the fixation cross to reach full luminance, they pressed a key with their right hand, upon which a single-pulse stimulation was delivered before the next trial automatically began. A white outline of a fixation cross was presented to each subject at the start of each trial, during which the interior gradually increased in luminance at a rate of 0.0025 value/frame (in HSV units). Each of the three electrode sites were stimulated in a counterbalanced block design and received 100 stimuli per block.

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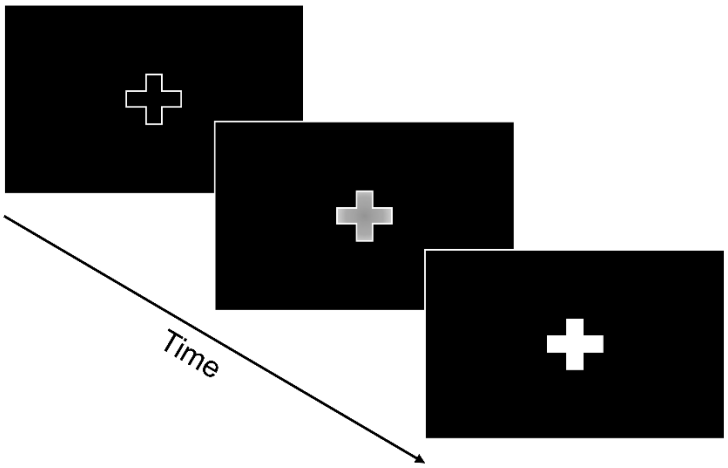

Figure 2. Schematic of the sensorimotor luminance detection task for the active experimental group. Subjects viewed a fixation point that gradually became illuminated in the center, and were required to press a button when they judged the luminance to be fully saturated, thus initiating the next trial.

Analysis. Offline data analysis was conducted using the EEGLAB MATLAB Toolbox (Delorme and Makeig, 2004) in MATLAB R2017b (The MathWorks Inc., Natick, MA). Continuous data were downsampled to 500 Hz and subsequently analyzed via the *clean_rawdata* plugin (v. 0.34; Kothe, 2014) to clean continuous data following the Artifact Subspace Reconstruction (ASR) method (Mullen et al., 2013) to remove bad EEG channels. To prevent result biases from potentially removing excessive datapoints, *clean_rawdata* provided us with controlled, objective rejection criteria to eliminate noisy channels for such artifacts as eye blinks and face/neck muscle activity. Following this, all data were re-referenced to the grand average of all electrodes and then epoched for all three stimulation sites from -1000 to +1000 ms around the TMS pulse; the data for each epoch was baseline-corrected to the mean of the entire epoch span.

TMS-artifact removal. Given the emergence of concurrent TMS and EEG as an important tool for assessing cortical properties, Rogasch and colleagues (2017) created TESA, an open-source extension for EEGLAB, with the purpose of improving and standardizing analysis across the field of TMS-EEG research. We applied the TESA toolbox to all three stimulation site epochs to remove artifacts; all steps adhered to the TESA pipeline as outlined by Rogasch and colleagues

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(2017). This process involved 1) removing all data around the TMS pulse from -10 to +10 ms, 2) interpolating removed data within the TMS pulse, 3) removing noisy trials via EEGLAB's built-in joint probability detection, 4) running a first round of independent component analysis (ICA) using the FastICA algorithm, 5) removing artifact components via visual inspection, 6) applying a first-order Butterworth filter with a bandpass of 1–100 Hz, as well as a notch filter to remove 60 Hz electrical line interference, 7) running a second round of FastICA with subsequent artifact component rejection. Following the above steps, data were again filtered between 1 and 50 Hz and segregated into separate, site-specific epochs.

Time/frequency analysis. To analyze time-frequency domain responses we calculated the event-related spectral perturbation (ERSP) values based on Morlet wavelets, via the EEGLAB *newtimef* function, by convolving a mother wavelet at 100 linearly-spaced frequencies spanning 5 to 50 Hz, with 3.5 cycle wavelets and a 0.5 scaling factor. Baseline correction was applied to the average power across trials by subtracting the mean baseline power. Analysis of time/frequency data thus proceeded at both the "local" and "global" levels, following the convention of Rosanova and colleagues (2009). Accordingly, global effects were determined by averaging, for each subject, the time/frequency spectrogram across all electrodes to form a single representation of the ERSP across the scalp. In contrast, local effects were determined by examining the ERSP underneath each stimulation electrode across all three sites of stimulation. To minimize the effect of possible artifacts occurring at the time of stimulation, natural frequencies were calculated by averaging the ERSP values in a time window between 20 and 200 ms (see below).

The above parameters were chosen to replicate the results of prior work; yet, we also included an additional analysis in which ERSPs were baseline-corrected at the single-trial level, rather than the average, via single-trial normalization, which has been shown to decrease

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sensitivity to noise artifacts (Grandchamp and Delorme, 2011). All of the calculations outlined below were also calculated on this secondary data set.

Global field power. In addition to the analysis of ERSP data, we also calculated global field power (GFP), defined as the reference-independent response strength, and calculated as the standard deviation across all electrodes at each timepoint (Murray et al., 2008). GFP data were analyzed across all three sites of stimulation, separately for passive and active groups, in order to determine if there were any differences in evoked activity following TMS at any site.

Natural frequencies. Our analysis of natural frequencies proceeded initially according to the description from previous reports (Rosanova et al., 2009; Ferrarelli et al., 2012). To determine the natural frequency for each subject at each stimulation site, the global ERSP (gERSP) response was analyzed by calculating the sum of power values for each frequency within the 20–200 ms time window, and then determining which frequency had the highest value. In this way, the max frequency would not be driven alone by a single frequency with a very high peak, but could instead be provided by a frequency with a moderate yet sustained response that was larger than at other frequency bands. Natural frequencies were calculated for each stimulation site for each subject in both groups.

In addition to the above description, we explored several additional methods of calculating natural frequencies, so as to ensure that our results were not driven by our choice of analysis method. We thus included three additional measurements of natural frequencies. In the first, instead of calculating the sum of power values for each frequency, we instead determined the natural frequency as the one containing the largest response at any timepoint within our window. In this way, the natural frequency *could* be driven by a very large peak and not by a longer yet lower sustained response. In the second additional method, we first transformed all ERSP power

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values at the global level into absolute power, before calculating natural frequency using the original method of the largest sustained response. This analysis method was chosen out of concern that the largest response may be a *decrease* in power at a particular frequency band. In the third additional method, we calculated natural frequency as the band with the largest cumulative integral, using the *trapz* command in MATLAB; this choice was driven so as to maintain the original, non-rectified ERSP data but still calculate an absolute measure of change that could account for zero-crossings.

As an additional possibility that might lead to discrepancies between our findings and the original work, we implemented one additional analysis for the calculation of natural frequencies. In the original work, Rosanova and colleagues (2009) used a threshold for individual electrode data within each subject at $p < 0.01$ using a bootstrap method from baseline data called from the *newtimef* function; this step was conducted before calculating the global average and natural frequency. We replicated this analysis and extracted the natural frequency as outlined above in the original method.

Statistical analysis. All statistical analysis of behavioral data and natural frequencies were carried out in SPSS (v. 19, IBM Corporation). For the analysis of global and local effects, we employed cluster-level corrections for significance ($p < 0.05$), using the method outlined by Maris and Oostenveld (2007) and implemented via Fieldtrip using the *statcondfieldtrip* command in EEGLAB. For both local and global effects, we determined regions of significant deviation from baseline for each of the sites, for each of the two groups. In addition, we compared the gERSP between groups, by averaging across all three sites within each group and comparing the overall responses.

Results

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Global response to TMS

Our initial analyses set out to attempt to replicate the findings of Rosanova et al. (2009) and Ferrarelli et al. (2012). In these studies, an increase in power is observed following TMS that is maximal at a particular frequency band, dependent on the site of stimulation. These changes reflect the spectral properties of the TMS-evoked oscillations, which consists of a number of repeated positive and negative deflections (Lioumis et al., 2009). When examining the gERSP response, averaged across all electrodes, we observed a combination of increases and decreases in power following TMS. Notably, only the *decreases* in power survived our cluster-corrected significance threshold, in contrast to the original findings. This finding was observed across both passive and active groups.

Notable differences were also observed between passive and active groups, as well as between the different sites of stimulation. For the passive group, we observed decreases in power that were synchronous with the TMS pulse in the gamma frequency band (40–50 Hz) across all three sites. Across stimulation sites, the gamma desynchronization became longer lasting from posterior to frontal regions, and was further accompanied at the frontal site by a significant decrease in the high beta range (20–30 Hz) approximately 100–300 ms after the TMS pulse. In contrast, the active group exhibited a larger desynchronization response across all three sites, extending from the beta to gamma range (see Figure 3).

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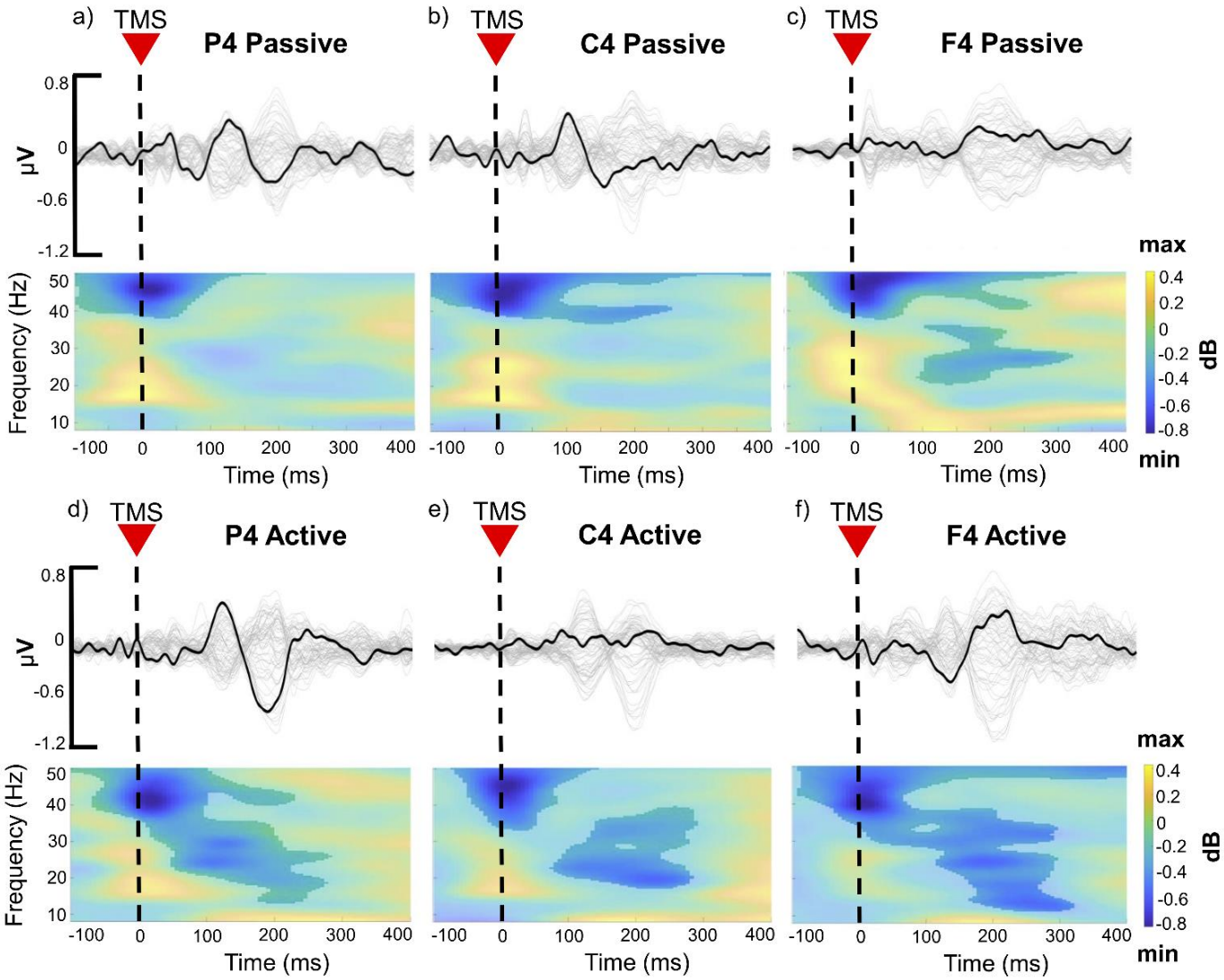

Figure 3. Global plots for all subjects illustrating the three cortical sites targeted by TMS. Butterfly plots (top panels) of all electrode time courses with the black trace line highlighting the electrode directly underlying the stimulator. ERSP plots (bottom panels) display saturated color areas representing significant frequency (Hz) activation compared to baseline. (a) P4 for passive group, (b) C4 for passive group, (c) F4 for passive group. (d) P4 for active group, (e) C4 for active group, (f) F4 for active group. Significance was determined via cluster-based permutation testing.

In addition to the spectral response, we also calculated and measured the GFP. Here, as well, we observed no differences between site in the evoked response, nor was there any difference between passive and active groups (Figure 4). As a secondary measure, we wanted to determine if differences in stimulation intensity influenced the size of the response. To that end, we calculated running Pearson correlations between GFP and MSO values for each group for each site. At no

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point for any site or group did we observe a significant correlation (all $r < 0.532$), suggesting that stimulation intensity did not influence the evoked response.

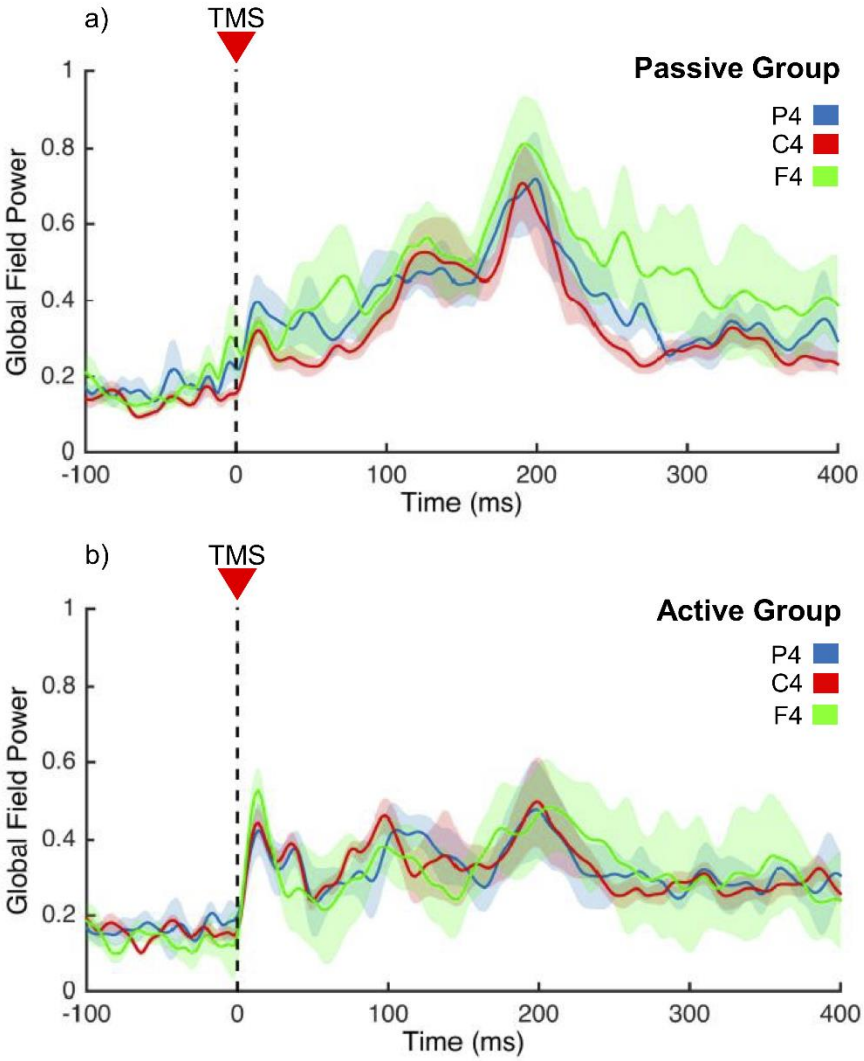

Figure 4. Global field power (GFP) across stimulation sites and groups. Shaded regions display standard error. No differences between stimulation site or group were detected.

Natural frequencies

The major finding of the previous work was that the so-called "natural frequency," characterized as the frequency band with the largest sustained response to TMS, increases in a rostro-caudal gradient. Calculating the natural frequency using the same method outlined by the previous authors yielded a range of values across all three sites. Though the individual maximum frequencies showed a large oscillatory range, there were no outliers. Yet, no linear effects were

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observed in these values across all three sites, for either the passive or active groups. To determine if this null finding was due to the method, we used for calculating the natural frequency, we also employed three other methods for calculating (see Figure 5). None of these methods provided data that exhibited a linear relationship between stimulation site and natural frequency. However, along with the gERSP responses, we observed that the active task group exhibited significantly higher natural frequencies evoked by TMS than the passive group. A two-way ANOVA revealed that group type had a significant effect on mean activation in Hz ($F(1, 88) = 7.456$, $p = 0.008$, $\eta p^2 = 0.078$), with higher frequencies reported during the active experimental group ($M = 20.42$, $SD = 1.073$) compared to the passive experimental group ($M = 16.28$, $SD = 1.073$).

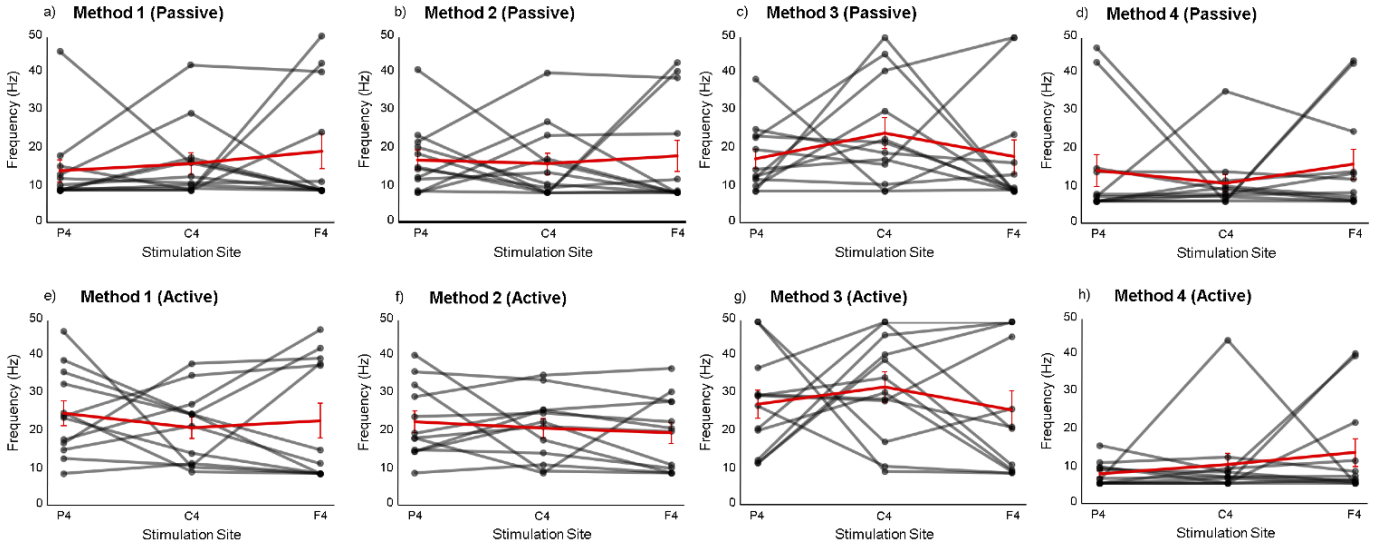

Figure 5. Natural frequencies, as determined by four different methods. Red trace lines indicate mean frequency based on electrode site, with SE bars; black traces represent individual subjects. Panels (a) through (h) display the results of each method for each group. None of these methods provided data that exhibited a significant linear relationship between stimulation site and natural frequency.

Local response to TMS

Passive group. During P4 stimulation, observations for the P4 site showed significantly evoked activations in the gamma-band that were recorded from stimulation onset to 100 ms post-stimulation, in addition to beta-band activations from 100 ms to 200 ms. No significantly evoked activations were observed for the C4 site during C4 stimulation. During F4 stimulation,

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observations for the F4 site showed significantly evoked activations in the gamma-band that were recorded from stimulation onset to 300 ms post-stimulation.

Active group. Though similar to the observations made in the P4 for the passive group, the significantly evoked activations in the active group, during active task engagement, showed a longer post-stimulation effect. At the P4 site, significantly evoked activations in the gamma-band that were recorded from stimulation onset to 250 ms post-stimulation, with an overlap of beta-band activations from 50 ms post-stimulation until 300 ms. No significantly evoked activations were observed for the C4 site during C4 stimulation, nor for the F4 site during F4 stimulation (see Figure 6 for both groups).

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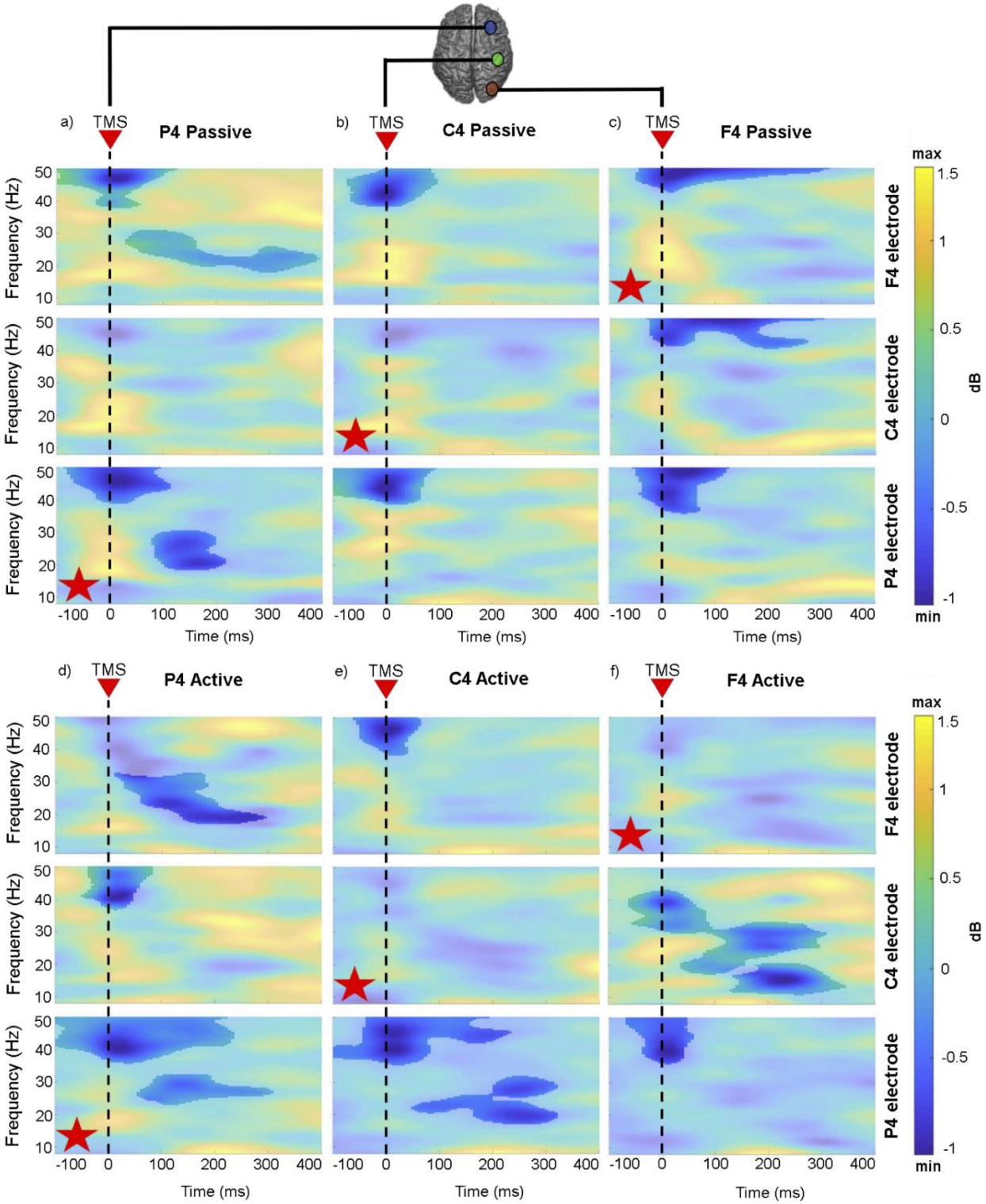

Figure 6. Local responses to stimulation. ERSP plots of local responses (under each electrode) to TMS stimulation at each site under each condition. Panels (a-c) represent Passive group and (d-f) represent Active group. A red star at the lower left corner of a panel indicates the ERSP plot under the electrode that was stimulated. Saturated color areas represent significant frequency (Hz) activation compared to baseline.

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Active group response times. Response times (RTs) were calculated in seconds (s) for the active group, which performed the illumination detection task; P4 (2.20±1.24), C4 (2.44±1.27), F4 (2.26±1.26) (see Figure 7). A nonparametric Friedman test showed a significant difference in RTs between stimulation sites; $\chi^2(2, 12) = 8.667$, $p = 0.013$. Post hoc analysis with Wilcoxon signed-rank tests were conducted with a Bonferroni correction applied, resulting in a significance level set at $p < 0.05$. Median (IQR) RTs based on stimulation sites were 2.13 s (1.19 to 2.74) for P4, 2.05 s (1.52 to 2.92) for C4, and 2.06 s (1.17 to 2.76) for F4, respectively. There were no significant differences between RTs for P4 and F4 ($Z = -0.784$, $p = 0.433$) or between RTs for C4 and F4 ($Z = -1.412$, $p = 0.158$). However, there was a significant difference between RTs for C4 compared to P4, with slower RTs overall for C4 ($Z = -1.961$, $p = 0.05$).

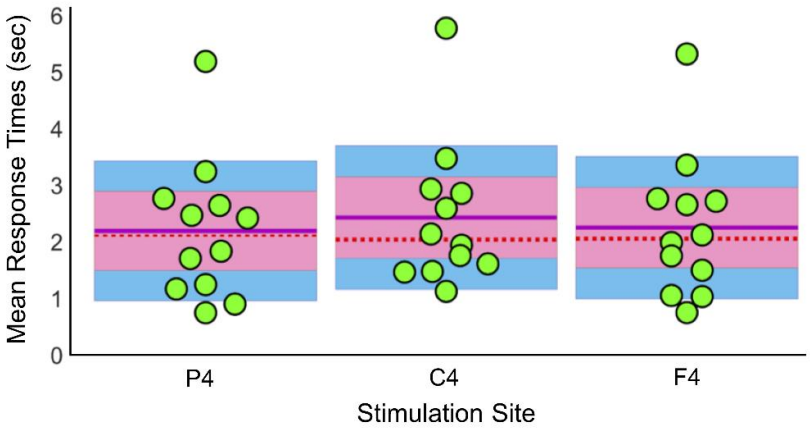

Figure 7. Active group task response times (RTs) in seconds, based on electrode stimulation site. Green circles represent for mean RTs for each active task subject, per stimulation site. Based on electrode site, the purple lines indicate mean RTs, while dashed red lines indicate median RTs. Shaded pink regions represent 95% confidence intervals, whereas blue regions indicate standard deviation. Subjects were moderately slower in responding following single-pulse stimulation over C4.

Discussion

In the current study, we attempted to replicate findings from Rosanova and colleagues (2009), specifically a rostro-caudal gradient of natural frequencies. This and a follow-up study (Ferrarelli et al., 2012) by the same group support the notion of a hierarchical progression across the brain of oscillatory frequency. However, our findings markedly differed from those of

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Rosanova and colleagues (2009), as we found no evidence in either group (passive or active) for natural or differing dominant frequencies evoked at different stimulation sites, nor a rostro-caudal gradient in evoked frequency. Rather, our results revealed the complexity of patterns in global and local changes that occur in response to stimulation, in addition to conspicuously broader and distinct patterns between the passive and active states. These findings suggest cortical regions exhibit complex frequency-specific profiles that cannot be described by a hierarchical progression alone. Our findings therefore raise an important caveat to studies of oscillatory mechanisms in humans, by failing to replicate an important and influential finding. Furthermore, our findings suggest that oscillatory mechanisms are characterized by more complex, state-dependent patterns than have previously been appreciated.

Despite our staunch effort to employ the methods and analyses reported by Rosanova and colleagues (2009), we failed to replicate their findings. Furthermore, we explored alternative methods of calculating the natural frequencies. However, no significant outcome differences appeared between stimulation site, and any method employed, to include the reported effect from either the original or follow-up study. Instead, we found a variety of effects at different electrodes, but critically no rostro-caudal gradient. Specifically, our findings suggest that TMS-evoked maximum frequencies are more complex and differ based on individual activation patterns.

The explanation of a hierarchical progression proposed by Rosanova and colleagues (2009), may be too general. For instance, though different source-localization algorithms were used, three additional relevant studies have shown a more complex pattern of global EEG activation; Hillebrand and colleagues (2016) found gamma-band frequencies distributed across frontal cortex, while Keitel and Gross (2016) and Mellem and colleagues (2017) found elevated gamma power in the frontal *and* inferior temporal regions. Furthermore, though Groppe and

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colleagues (2013) found variability in dominant frequencies of cortical regions using electrocorticogram (ECoG) to examine frequency distributions in the resting brain, they did not observe a rostro-caudal gradient, instead reporting substantial overlap of dominant frequencies across the lateral central, temporal, and frontal areas.

An attempt to explain the complexity of varying oscillatory bands, Mellem and colleagues (2017) further investigated whether timescales of different frequency bands might correlate with a sensory-to-higher processing hierarchy. However, their results did not yield strong biases toward particular timescales across all cortical regions nor did they find exclusivity of lower areas biased toward faster frequencies or higher areas biased toward slower frequencies. Thus, these authors contend that dominant higher-frequency bands that have been observed in the frontal cortex during concurrent TMS-EEG studies may be a result of that brain region's involvement in higher level cognition. This explanation has potential to elucidate our findings of higher frequency evoked power across the brain during sensorimotor task engagement. Furthermore, Hillebrand and colleagues (2016) suggest that frequency bands may serve as channels of communication across brain regions, though dependent on the activation in multiple bands within each region.

Perhaps the most notable aspect of our findings is the difference in evoked frequency between the experimental groups. While performing the sensorimotor task, evoked responses became more widespread in both frequency and time; additionally, when comparing the natural frequency between experimental groups, the sensorimotor task was observed to evoke a consistently higher frequency than in the resting state group. This difference suggests that cognitive engagement incorporates higher frequency oscillations, consistent with several other known findings of brain function (Crone et al., 1998; Canolty et al., 2006; Voytek et al., 2010;

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Crone et al., 2011; Groppe et al., 2013). A state-dependent TMS effect might account for these findings. State-dependency is defined as response changes according to the state of the cortex when the stimulus, such as a TMS pulse, is applied (Siebner et al., 2009). Moreover, the state of activation has been shown to influence the response (Thut et al., 2003; Massimini et al., 2005; Silvanto et al., 2007; Romei et al.,2008; Silvanto and Pascual-Leone, 2008; Massimini et al., 2010; Miniussi and Thut, 2010; Romei et al., 2016; Petrichella et al., 2017). Matthews (1999) suggests the effect of small TMS pulses might be facilitated if the cortex is already active; thus, it would be reasonable to presume that single pulse stimulation may well enhance cortical activation while a subject is actively engaged in a task. Previous studies have shown evidence of the effect of TMS pulses varying as a function of the state of the brain. For example, when comparing neuronal activation during resting/baseline states to active task engagement, researchers found TMS over the motor cortex enhanced activation during motor execution and motor imagery (Kasai et al., 1997; Fadiga et al., 1999; Hashimoto and Rothwell, 1999), while others found greater ease of inducing phosphenes with TMS over the occipital region during visual mental imagery (Sparing et al., 2002). The latter finding suggests distinct operational modes for the brain between resting state and task-based networks. Consistent with this view, previous investigations comparing resting-state and task-based network activity in functional magnetic resonance imaging (fMRI) have revealed network reorganization between these states (Spadone et al., 2015; Gonzalez-Castillo and Bandettini, 2018); in particular, the frequency profile of fMRI inter-connectivity shifts between resting and task-based activity, with lower frequencies dominating the former and more broadband representation during tasks (Ciuciu et al., 2014). Although these fluctuations operate on an order of magnitude below those measured by EEG in the present study (0.01-0.1Hz), they reveal a similar pattern to our findings, suggesting a correspondence (Bridwell et al., 2013).

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Notably, for the current study, the higher evoked frequencies did not depend on the stimulation site, suggesting a global change in brain functioning, independent of the local changes. Additionally, our findings suggest that TMS can be a useful tool for evoking latent oscillations in the brain. Previous reports have advocated for the detection of natural frequency, namely the rostro-caudal gradient, using concurrent TMS-EEG as a diagnostic tool for neuropsychiatric conditions, such as depression, epilepsy, and disorders of consciousness (Rosanova et al., 2009; Ferrarelli et al., 2012). However, due to the current study's failure to replicate the rostro-caudal gradient, and the observed complexity of frequency-specific response patterns, it is important that investigation into understanding these oscillatory mechanisms continue.

Limitations

In the current study, there are two possible limitations that should be noted. First, we note that the stimulation levels in our study are lower, on average, than used in both previous reports. This was done to avoid auditory-evoked artifacts in the EEG response. Yet, we note that TMS intensity was above 40 V/m, which Rosanova and colleagues (2009) specified as minimal for evoking dominant frequencies. Further, no correlation between TMS intensity and global response was observed; consequently, lower TMS intensity may not provide a clear explanation for the lack of rostro-caudal gradient replication. The other possible limitation could be a lateralization of the rostro-caudal gradient, as both previous studies stimulated cortical areas in the left hemisphere (Rosanova et al., 2009; Ferrarelli et al., 2012), whereas the current study stimulated homologous cortical areas in the right hemisphere. However, to our knowledge, no evidence for lateralization in hemispheric dominance of frequency distributions has been reported, and so it is unlikely to explain the lack of such a finding in our data.

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Conclusion

We attempted to replicate previous findings of a rostro-caudal gradient of natural frequencies by employing concurrent TMS-EEG while at rest (passive group) and during task engagement (active group). However, no rostro-caudal gradient was observed in either group, with limited evidence of differences in fundamental frequencies of cortical areas. The observed complex patterns of global and local changes, in response to stimulation, suggests cortical regions exhibit complex frequency-specific profiles. Thus, the explanation of a hierarchical progression may be too general. Additionally, the differences in evoked responses between the two experimental groups suggests that oscillatory mechanisms are characterized by complex, state-dependent patterns, with an overall higher mode of frequency during active engagement.

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