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Excitatory TMS Modulates Memory Representations

Wei-Chun Wang¹, Erik A. Wing¹, David L.K. Murphy¹, Bruce M. Luber^{3,5}, Sarah H. Lisanby^{3,4,5,*}, Roberto Cabeza^{1,4}, and Simon W. Davis^{1,2}

¹Center for Cognitive Neuroscience, Duke University, Durham, NC, USA

²Neurology, Duke University School of Medicine, Durham, NC, USA

³Psychiatry and Behavioral Neuroscience, Duke University School of Medicine, Durham, NC, USA

⁴Psychology & Neuroscience, Duke University, Durham, NC, USA

⁵National Institute of Mental Health, Bethesda, MD, USA

Abstract

Brain stimulation technologies have seen increasing application in basic science investigations, specifically toward the goal of improving memory function. However, proposals concerning the neural mechanisms underlying cognitive enhancement often rely on simplified notions of excitation. As a result, most applications examining the effects of transcranial magnetic stimulation (TMS) on functional neuroimaging measures have been limited to univariate analyses of brain activity. We present here analyses using representational similarity analysis (RSA) and encoding-retrieval similarity (ERS) analysis to quantify the effect of TMS on memory representations. To test whether an increase in local excitability in PFC can have measurable influences on upstream representations in earlier temporal memory regions, we compared 1Hz and 5Hz stimulation to the left dorsolateral PFC (DLPFC). We found that 5Hz rTMS, relative to 1Hz, had multiple effects on neural representations: 1) greater representational similarity during both encoding and retrieval in ventral stream regions, 2) greater ERS in the hippocampus, and, critically, 3) increasing ERS in MTL was correlated with increasing univariate activity in DLPFC, and greater functional connectivity for hits than misses between these regions. These results provide the first evidence of rTMS modulating semantic representations and strengthen the idea that rTMS may affect the reinstatement of previously experienced events in upstream regions.

Keywords

connectivity; representational similarity analysis; TMS; episodic memory

*Now at the National Institute of Mental Health. Drs. Sarah H. Lisanby and Bruce Luber contributed to this article while at Duke University, prior to joining NIMH. The views expressed are their own and do not necessarily represent the views of the National Institutes of Health or the United States Government.

Introduction

Over the past few decades, repetitive transcranial magnetic stimulation (rTMS) has developed into a powerful tool to establish causal brain-behavior relationships and improve cognition. Brain stimulation has been coupled with neuroimaging techniques in order to identify neural activity associated with enhancement of working (Mottaghy et al., 2002; Luber et al., 2007), episodic (Kohler et al., 2004), and semantic (Binney et al., 2010) memory. However, most investigations on the effects of rTMS on neural substrates of memory functioning have been limited to univariate analyses of brain activity (Bollinger et al., 2010; Lee and D'Esposito, 2012; Vidal-Pineiro et al., 2014). Here we use a combination of rTMS, representational similarity analyses (RSA), and encoding-retrieval similarity (ERS) in order to test the efficacy of this technique in eliciting changes in neural representations that are a fundamental component of memory functioning.

Many rTMS studies have sought to relate various rTMS stimulation parameters to memory-related brain processes, focusing on the underlying neural correlates, rather than a measurable difference in memory. Because the relationship between any individual measure of memory and corresponding brain function is highly complex and is often mediated by multiple brain regions and psychological processes, this approach is advantageous for targeting specific components of neural function that contribute to memory encoding and retrieval. It is generally accepted that rTMS at higher frequencies (> 5 Hz) induces local *increases* in BOLD activity during a host of different cognitive operations including motor planning (Schneider et al., 2010), working memory (Esslinger et al., 2014), and episodic memory (Vidal-Pineiro et al., 2014), *boosting* ongoing activity associated with successful performance. Conversely, 1Hz rTMS has been shown to reliably *depress* local hemodynamic activity (Muellbacher et al., 2000; de Vries et al., 2012; Plow et al., 2014). While the use of rTMS as a tool for behavioral neuroenhancement is undoubtedly informed by understanding these local effects, it remains unclear how local changes in neural activity affect large-scale system dynamics. Research combining rTMS with functional neuroimaging techniques has shown that rTMS can also have effects on distal brain regions that are functionally or structurally connected with the area targeted by stimulation (Esslinger et al., 2014; Wang and Voss, 2015). However, while the focus on “excitability” (a tenuous inference given the generality of the hemodynamic BOLD signal) in more distal regions of a circuit is becoming widespread (Fox et al., 2014), the effect of brain stimulation on the underlying representations upon which various cognitive processes operate has been almost completely unexplored.

To date, most applications examining the effects of rTMS on neuroimaging data have been limited to univariate analyses of brain activity. In contrast to standard univariate models, RSA instead asks how distributed patterns of brain activity evoked by different stimuli are related to one another, and thus provides the means to directly address questions of how mental representations are implemented in the brain as unique patterns of information. RSA methods have been used to explore how the relationship between stimuli of various dimensions—such as the visual or conceptual similarity of objects, words, or sentences—is reflected in the pattern of evoked neural responses associated with those stimuli. By comparing the similarity between each pair of stimuli in an fMRI dataset along a given

dimension, we obtain a representational dissimilarity matrix (RDM), which serves to characterize a certain computational model of stimulus properties. These model RDMs can be compared to brain RDMs reflecting the similarity in activity patterns across the same pairs of stimuli. This approach has helped identify brain regions where representational structure captures higher-level semantic meaning that is not strongly contingent on stimulus modality (Devereux et al., 2013). Regions associated with semantic representations in RSA analyses include left anterior temporal lobe (ATL), fusiform gyrus, and left angular gyrus (AG) (Clarke and Tyler, 2014; Martin et al., 2018).

In the domain of episodic memory, representational approaches have been used to test a fundamental hypothesis that retrieving information from memory produces a partial recapitulation or reactivation of brain states and representations present when information was initially experienced (Danker and Anderson, 2010). One way of testing for this reactivation has involved comparing the similarity of brain patterns between the encoding and retrieval of items, known as encoding-retrieval similarity (ERS; Ritchey et al., 2013; Wing et al., 2015). Episodic memory reactivation has been reported in posterior cortical regions, as well as in the medial temporal lobes (MTL). PFC reactivation effects in prefrontal regions (ERS and RSA) are generally less common, possibly owing to the population- and process-level heterogeneity of this region; in fact, a recent meta-analysis suggests decoding accuracy is generally lower in PFC (Bhandari et al., 2018). Nonetheless, dorsolateral PFC (DLPFC) plays an important role in controlling relational memory binding (Blumenfeld and Ranganath, 2007) and the encoding of robust representations (Clarke et al., 2014), and likely operates on such encoding operations through functionally connected pathways to subcortical memory systems (Summerfield et al., 2006; Schott et al., 2013). Furthermore, various frequencies of noninvasive brain stimulation to DLPFC has been shown to reliably affect episodic memory performance (Sandrini et al., 2003; Sole-Padulles et al., 2006; Meinzer et al., 2013), and from a practical perspective, this site provides one of the most reasonable cortical targets to access subcortical memory systems via TMS (though see Wang and Voss, 2015 for the use of a parietal target).

Whereas previous studies combining TMS with fMRI focused on univariate activity, we used multivariate RSA and ERS methods to investigate how TMS might alter the underlying stimulus representations at the time of initial learning, and the implications potential alteration might have for reactivated mnemonic information at retrieval. We turned to an existing dataset on which we originally focused on the network-level dynamics of 5Hz vs. 1Hz rTMS (Davis et al., 2017). We applied TMS to DLPFC, a region which plays an important role in controlling relational memory binding (Blumenfeld and Ranganath, 2007), before a relational memory encoding-retrieval session in which fMRI data was collected. If DLPFC-focused stimulation is to have an effect in upstream encoding locations, we expected greater connectivity from the initial stimulation site to upstream sites managing these representations. Thus, we made three predictions in the current analysis: 5Hz relative to 1Hz TMS of DLPFC would enhance (1) the quality of semantic representations (as measured by RSA), (2) the quality of episodic memory representation reinstatement (as measured by ERS), and (3) DLPFC activity and functional connectivity accounting for the effect of rTMS on representations. Answers to these questions would help to clarify the

variables that may influence the neural response to stimulation during a wide array of episodic memory paradigms.

Materials & Methods

Participants

Fourteen healthy older adults were recruited for this study (all native English speakers; 8 females; age mean \pm SD, 67.2 \pm 4.4 years; range 61–74 years); one subject was excluded due to tolerability during rTMS; two additional participants did not complete all retrieval runs and thus were included in Encoding RSA and univariate analyses, but excluded from Retrieval RSA and ERS analyses. Each older adult was screened for exclusion criteria for TMS (history of seizure, brain/head injuries) as well as psychiatric condition (MINI International Neuropsychiatric Interview, English Version 5.0.0 DSM-IV, (Sheehan et al., 1998)). None of the older participants reported subjective memory complaints in everyday life or had MMSE score below 27 (mean \pm SD = 29.1 \pm 0.8).

Stimuli & Procedure

The associative memory task was comprised of a set of 360 sentences, each of which included a concrete subject and direct object. In each sentence, both subject and direct object were capitalized to indicate to the subject which specific nouns were to be remembered (“*A SURFBOARD was on top of the TRUCK.*”). Associative strength between nouns in a sentence (as determined by the USF word association norms (Nelson et al., 2004), were normally distributed (mean = 0.025, SD = 0.038), and both the mean imageability (mean = 561.3, SD = 42.3), mean familiarity (mean = 564.4, SD = 37.9), mean concreteness (mean = 528.8, SD = 38.7) and total length of each set of sentences (mean = 6.38, range = 5–9 words) was counterbalanced across all sentences used therein.

One run of the associative task comprised an encoding block of 90 sentences presented visually for 3 seconds, separated by a jittered inter-trial interval (mean 7 seconds), with a total duration of 9 minutes for the entire encoding block. After a brief reminder of the instructions for the task (8 seconds) a subsequent retrieval block began, comprising 68 word pairs from the same previously studied sentence, and 22 new pairs composed of two words recombined from two different sentences, with a duration of 6 minutes for the entire retrieval block. Participants were asked to judge whether each word pair was intact or recombined and indicate how confident they were in their decision on a 4-point rating scale. Given the low proportion of low-confidence responses in the current data (average of 13.6% of responses to old trials, across participants), we collapsed low and high-confidence responses, and excluded encoding trials in which participants failed to indicate a response at retrieval.

Image Acquisition

An outline of all data acquisition events is depicted in Figure 1. Scanning was divided between two days, 1–4 days apart, with the first day comprised of an individualized functional DLPFC memory-success localizer for stimulation on Day 2 (Figure 2A), which comprised the same sentence encoding task described above. All procedures were completed on a GE MR 750 3-Tesla scanner (General Electric 3.0 tesla Signa Excite HD short-bore

scanner, equipped with an 8-channel head coil). Coplanar functional images were acquired with an 8-channel head coil using an inverse spiral sequence with the following imaging parameters: 64×64 matrix, flip angle = 77° , TR = 2000ms, TE = 31ms, FOV = 24.0 mm^2 , and a slice thickness of 3.8mm, for 37 slices. The anatomical MRI was acquired using a 3D T1-weighted echo-planar sequence (256×256 matrix, TR = 12 ms, TE = 5 ms, FOV = 24 cm, 68 slices, 1.9 mm slice thickness). Scanner noise was reduced with earplugs and head motion was minimized with foam pads. Behavioral responses were recorded with a four-key fiber optic response box (Resonance Technology), and when necessary, vision was corrected using MRI-compatible lenses that matched the distance prescription used by the participant.

TMS Procedure

Prior to the TMS-fMRI session, the scalp location for TMS coil position over the left DLPFC location had been found by using an infrared neuronavigation system (Brainsight: Rogue Research, Montreal, Canada). Specifically, the point of greatest activation in the left DLPFC in the fMRI memory contrast (i.e., encoding trials which were subsequently remembered versus forgotten) from the first day of scanning was chosen from the fMRI overlay on the subject's structural MRI, both of which had been uploaded into BrainSight. After co-registration of the subject's head with his MRI, the DLPFC location was marked on a tight fitting acrylic swim cap that stayed on the subject's head until TMS-fMRI interleaving was completed on the same day. At that time, participants were acclimated to the sort of TMS pulses to be delivered later in the scanner with a series of single pulses at the target site, as well as a short burst of 5Hz stimulation. The motor threshold (MT) for each subject was determined using a MagVenture R30M device located outside the scanner room, part of an MRI compatible TMS system which included a non-ferrous figure-8 coil with 12m long cable and artifact reducing counter-current charging system (MagVenture, Farum, Denmark). MTs were determined using electromyography of the right first dorsal interosseous (FDI) muscle and defined as the lowest setting of TMS device intensity at which 5 out of 10 motor evoked potentials of at least $50\mu\text{V}$ peak to peak amplitude could be elicited.

Before each functional scan, two 10-minute trains of either 1Hz or 5Hz stimulation were delivered at 120% MT immediately prior to an fMRI acquisition. The position of the TMS coil was reset to the same target site before the beginning of each rTMS session, and monitored continuously while the subject lay supine in the bed of the MR scanner. 1Hz rTMS was delivered in a continuous train of 10 minutes, while 5Hz rTMS was delivered in intermittent 6 sec trains with a 24 sec inter-train interval, also for 10 minutes. Dosage was equivalent between 1Hz and 5Hz rTMS conditions (600 total pulses), and the order of stimulation frequency was counterbalanced across participants. Immediately after the 10 minutes of TMS, participants were positioned in the scanner, and performed the encoding and subsequent retrieval portion of the sentence task while fMRI was acquired. The amount of time elapsed between the end of the rTMS train to the beginning of the functional scan was 9.4 minutes (SD = 1.7 minutes).

Data Analyses

Functional MRI preprocessing

Functional images were preprocessed using image processing tools, including FLIRT and FEAT also from FSL, in a publicly available analysis pipeline developed by the Duke Brain Imaging and Analysis Center (https://wiki.biac.duke.edu/biac:analysis:resting_pipeline). Images were corrected for slice acquisition timing, motion, and linear trend; motion correction was performed using FSL's MCFLIRT, and 6 motion parameters estimated from the step were they regressed out of each functional voxel using standard linear regression. Images were then temporally smoothed with a high-pass filter using a 190s cutoff, and normalized to the Montreal Neurological Institute (MNI) stereotaxic space. White matter and CSF signals were also removed from the data, using WM/CSF masks generated by FAST and regressed from the functional data using the same method as the motion parameters. Spatial filtering with a Gaussian kernel of full-width half-maximum (FWHM) of 6mm was applied.

To examine multivariate activity patterns, each sentence was modeled in a separate GLM using the least squares single (LSS) approach on the unsmoothed data, yielding first-level single-trial beta images for each trial in each participant (Mumford et al., 2012). This method estimates a first-level model for every trial such that the trial of interest serves as one regressor and all other trials serve as another regressor. Trials were modeled as a single stick function at the onset of a sentence (Encoding) or word pair (Retrieval) stimulus, which is then convolved hemodynamic response function (HRF); models also included six motion regressors (x-dim, y-dim, z-dim, roll, pitch, and yaw) in addition to block-wise run regressors. Group contrasts masked out white matter/CSF (SPM gray matter template values <0.1), all contrast images display effects at $p < 0.005$, and cluster-level corrections for multiple comparisons to $p < .05$ with Monte Carlo Simulations (Slotnick et al., 2003; Slotnick, 2017).

RDM Construction and RSA Analysis

Semantic similarity (RDMs) for the sentences (at encoding, Figure 3A) and the word pairs (at retrieval, Figure 3B) were constructed using the website cortical.io (Webber, 2015). Cortical.io utilizes an unsupervised machine learning algorithm to encapsulate the entirety of semantic space (trained on Wikipedia) into a vector of 16,384 co-occurring concepts, or 'semantic contexts.' To calculate semantic similarity, it extracts the semantic contexts (in the vector of 16,384) associated with the words in each sentence at encoding and each word pair at retrieval (i.e., a binary 'semantic fingerprint' that is visualized with a 128^2 matrix). To then create the RDMs, the dissimilarity (1-cosine similarity) between the semantic fingerprint for each pair of sentences or word pairs was then calculated. This 'semantic fingerprint' method is relatively new, but has been successfully used to group similar firms based on their business descriptions (Ibriyomova et al., 2017) and group academic authors based on the content of their publications (Han et al., 2017). Thus, it provides a useful tool for extracting semantic similarity beyond just single words.

For each subject, second-order correlations were computed between our semantic RDM and single-trial beta images for each participant using an in-house searchlight script (<https://github.com/brg015>) with a 5-voxel searchlight sphere, separately for the three stimulation conditions. For group analyses, these second-order correlation maps were then spatially smoothed (6-mm isotropic FWHM Gaussian filter).

ERS Analysis

ERS was calculated using an in-house searchlight script with a 5-voxel searchlight sphere (<https://github.com/brg015>) at both the item level, where encoding and retrieval trials involved the same item, and the set level, where encoding and retrieval trials belonged to the same set (i.e., stimulation condition) but involved different items. Item-ERS and set-ERS were calculated by correlating encoding and retrieval activity patterns within each searchlight sphere. For item-ERS, the encoding and retrieval activity patterns corresponding to the same trial were correlated, whereas for set-ERS, retrieval activity patterns for each trial was correlated with the encoding activity patterns for all trials in that stimulation condition (e.g., 5Hz) and then averaged to create the whole-brain similarity volume for that retrieval trial.

After ERS volumes had been calculated for each retrieval trial, fixed-effect contrasts were generated separately for item-ERS and set-ERS by averaging together all ERS volumes, yielding six mean ERS images per participant. For group analyses, these mean ERS images were then spatially smoothed (6-mm isotropic FWHM Gaussian filter). Because Baseline information was collected on a separate day, both RSA and ERS analyses are focused on the difference between RSA/ERS observed after two rTMS frequencies (5Hz, 1Hz); nonetheless, we include Baseline information here, as well as significant clusters in the Baseline condition, for descriptive purposes.

Lastly, to control for univariate activity, we also conducted confirmatory within-subject binary logistic regressions in clusters showing ERS differences as a function of stimulation condition, while still considering the influence of univariate activity at both encoding and retrieval. Such a result would help to confirm the hypothesis that TMS input specifically modulates the pattern of stimulus representations, and not merely the mean BOLD activity associated with processing the stimulus. In this regression, stimulation condition (1Hz vs 5Hz) was the dependent variable, and there were three independent variables: (1) ERS, (2) univariate encoding activity, and (3) univariate retrieval activity. A test on the parameter estimates corresponding to the ERS regressor (see Table 3, rightmost column) indicated whether similarity measures uniquely predicted stimulation condition while accounting for the effects of univariate activity. Thus, the logistic regression model represents a confirmatory test of extant results, and therefore one-tailed significance testing was used given that we expected to find an effect in the direction exhibited by the ERS.

Relationships between ERS and the DLPFC Stimulation Site

Lastly, we conducted two additional tests to examine the direct influence of left DLPFC stimulation on upstream representations. While the analyses above are focused on multivariate pattern information, estimates of univariate activity serve as useful markers of

excitation or inhibition after 5Hz or 1Hz rTMS, respectively. Thus, we examined whether the magnitude of ERS correlated with this univariate activity in the region of stimulation in DLPFC. To do so, we extracted the mean univariate activity (beta values) in the DLPFC stimulation site, and ERS (Pearson's r values) in clusters exhibiting significant effects and correlated them separately for each stimulation condition.

Second, we used task-based functional connectivity estimates to determine the degree to which these regions were coupled with DLPFC across encoding, i.e., immediately after 5Hz or 1Hz rTMS. Functional connection matrices representing task-related connection strengths were estimated using a correlational psychophysical interaction (cPPI) analysis (Fornito et al., 2012). Briefly, the model relies on the calculation of a PPI regressor for each region, based on the product of that region's timecourse and a task regressor of interest, in order to generate a term reflecting the psychophysical interaction between the seed region's activity and the specified experimental manipulation. In the current study the task regressors based on the convolved task regressors from the univariate model described above were used as the psychological regressor, which coded subsequently remembered and subsequently forgotten word pairs with positive and negative weights, respectively, of equal value. This psychological regressor was multiplied with two network timecourses for region i and j . We then computed the partial correlation $\rho_{PPI_i, PPI_j \cdot z}$, removing the variance z associated with the psychological regressor, the timecourses for regions i and j , and constituent noise regressors. We accounted for the potential effects of head motion and other confounds by assessing the 6 motion parameters and including these parameters in our partial correlation between regions.

Results

Behavioral results

As explained in the Introduction, the goal of the current analysis was to investigate the effects of TMS on mnemonic representations and their fidelity across encoding and retrieval conditions. Behavioral results for our associative memory task are summarized in Table 1. We found no significant differences between 5Hz vs. 1Hz rTMS conditions, either in Hit Rate ($t(12) = 1.18$, $p = 0.27$), False Alarm Rate ($t(12) = 1.44$, $p = 0.18$), or d' ($t(12) = 0.08$, $p = 0.94$); response times for correct trials were similarly not differentiated across stimulation conditions (all $p > 0.05$), and significance levels were unchanged when removing two participants who failed to complete retrieval runs. While rTMS order was evenly counterbalanced across participants, we nonetheless failed to see a difference in stimulation frequency order in either the post-1Hz ($t(12) = 0.76$, $p = 0.45$) or post-5Hz performance ($t(12) = 1.42$, $p = 0.18$). In order to address the possibility that 1Hz or 5Hz rTMS exhibited differential rates of decay in their effect on behavior, we examined the slope of a regression line fit to responses to all non-null-response trials, for each stimulation condition, where the x-axis described successive trials, and the y-axis represented individual trial response times. Slope values across participants (means across participants shown in Table 1) were then compared between Baseline, 5Hz, or 1Hz rTMS conditions; here we found no difference in slopes between any pairwise comparison between conditions ($t(12) < 1.0$). These null findings for behavioral differences between rTMS conditions suggest that any brain-related

differences in multivoxel pattern information (RSA/ERS) are not readily attributable to differences in task strategy or strength of encoding, and do not readily suggest evidence for differential decay rates between stimulation conditions.

Univariate Results

In order to help validate our premise that 1Hz rTMS is inhibitory and 5Hz is excitatory, we first extracted univariate activity at the stimulation site during encoding (Figure 2C). As expected, rTMS significantly modulated memory-related activity, as isolated by the subsequent memory difference in univariate activity between remembered and forgotten trials. As reported in our previous analysis of these data (Davis et al., 2017), the univariate activity for successfully remembered trials in the stimulated left DLPFC region was reduced by 1 Hz rTMS compared with Baseline ($t(12) = -2.43$, $p = 0.03$), but was increased by 5 Hz rTMS ($t(12) = 2.83$, $p = 0.015$) compared with Baseline activation for subsequently remembered encoding trials. Next, in order to test whether these univariate effects were specific to the stimulation site, we tested the contralateral right DLPFC site for each subject—we observed no univariate modulation due to subsequent memory (Figure 2C). Lastly, in order to address the possibility that 1Hz or 5Hz rTMS exhibited differential rates of decay in their effect on the BOLD response during our task, we examined the slope of a regression line fit to individual trial BOLD responses to all non-null-response trials, for each stimulation condition. Similar to the RT-slope analysis above, the x-axis represented successive trials, and the y-axis represented univariate BOLD activity during encoding trials, and slope values for all participants were compared pairwise between conditions. We found no difference in slopes for baseline (slope = 0.0014), 5Hz (slope = 0.0015), or 1Hz (slope = -0.0028) conditions ($t(12) < 1.0$), suggesting both that in our study, rTMS effects were consistent across the length of the 9 minute encoding run, and that the decay did not differ between different forms of rTMS.

RSA results

Our main goal was to examine evidence that rTMS has upstream effects on the quality of information processed in a standard memory paradigm. To test our first prediction on the effects of TMS on semantic representations, we examined the influence of rTMS on the semantic quality of representations (2nd order correlation with the semantic RDM) during the Encoding period. The searchlight RSA revealed greater second-order correlations between activity patterns and our semantic RDM for excitatory (5Hz) than inhibitory (1Hz) rTMS (inclusively masked by 5Hz effect at $p < .05$) in the left fusiform cortex (Figure 3A; Table 2, top panel). No significant clusters emerged in the reverse contrast (i.e., 1Hz > 5Hz, inclusively masked by the 1Hz effect at $p < .05$). Next, we examined the fidelity of representations during the Retrieval period, when participants were completing an associative recognition test for word pairs from the sentences read at encoding. The searchlight RSA revealed greater second-order correlations between activity patterns and our semantic RDM for 5Hz than 1Hz rTMS (inclusively masked by 5Hz effect at $p < .05$) in regions including the PHC and ATL (Figure 3B; Table 2, bottom panel). Again, no clusters emerged in the reverse contrast (1Hz > 5Hz, inclusively masked by the 1Hz effect at $p < .05$). In sum, consistent with our first prediction, we found that TMS enhanced the quality of

semantic representations (greater 2nd order correlation with semantic RDM) in typical semantic regions such as left fusiform and left ATL.

Lastly, we examine the effects of TMS stimulation regions that show RSA in the Baseline condition; we include the z-statistic for the 5Hz > 1Hz comparison within a mask derived from the cluster showing RSA effects in the Baseline condition. This value helps to provide context for the upregulation (or not) in RSA associated with the 5Hz > 1Hz difference. However, in both Encoding and Retrieval, Baseline regions (i.e., ITG) show no significant modulation associated with stimulation condition in our sample.

ERS Results

To test our second prediction, we then examined the influence of rTMS on the fidelity of memory representations measured using ERS. ERS allows us to identify the reactivation of episodic representations between encoding and retrieval by comparing activity patterns for trials belonging to the same item (i.e., item-ERS) and trials belonging to different items (i.e., set-ERS) at encoding and retrieval. We first examined whether any regions exhibited Stimulation by ERS level interactions. This contrast revealed greater item-ERS than set-ERS for 5Hz than 1Hz stimulation (inclusively masked by 5Hz effect at $p < .05$) in MTL and temporal regions (Table 3), including the left hippocampus (Figure 4). These effects were significant even when using a logistic regression model to test whether ERS predicted stimulation condition while simultaneously controlling for univariate activity at both encoding and retrieval (Table 3, rightmost column). Furthermore, they also remained significant when restricting ERS analysis to remembered trials. Memory Success did not appear to have a strong influence on these regions, such that we observed no significant Success x ERS effects in either 5Hz or 1Hz stimulation conditions (nor any Success x Stimulation interaction). Critically, we did not observe greater item-ERS than set-ERS for misses during either 5Hz or 1Hz stimulation (p 's > .70). Nonetheless, it is difficult to draw any lasting conclusions from Success-related analyses of these data given the lower proportion of misses in the current study compared to previous studies; future work focused on Success-related modulation should be mindful of these concerns in their study design.

Relationships between ERS and the DLPFC Stimulation Site

Lastly, to test our third prediction that the representational would be associated with increases in DLPFC activity and connectivity. We first extracted univariate activity at the stimulation site during encoding (see above, and Figure 2) to compare with our observed ERS values. A pairwise comparison between 1Hz and 5Hz fMRI activity for successfully remembered trials was also significant ($t(12) = 3.43, p = 0.006$). This result confirms that rTMS modulated memory-related activity at our site of stimulation and enables our two subsequent analysis of how this upregulation of univariate activity in left PFC is related to upstream effects in MTL.

We then examined whether univariate activity at the stimulation site (DLPFC) correlated, across trials, with the magnitude of our observed stimulation by ERS level interaction effects. This analysis found a significantly greater correlation ($t(10) = 2.28, p = .042$) between left DLPFC activity at encoding and the left MTL cluster for 5Hz > 1Hz

stimulation (Figure 5A). There were no significant correlations found in any other ERS regions.

Lastly, in order to link local stimulation effects in the DLPFC to representational changes as a function of memory success, we examined the functional connectivity between the DLPFC stimulation site and regions that were found to exhibit significant stimulation by ERS level interactions. We found a significant Success x Frequency interaction ($F(1,10) = 3.76, p = 0.004$), wherein connectivity at encoding between DLPFC and the left MTL cluster was greater for subsequently remembered than forgotten trials following 5Hz compared to 1Hz rTMS (Figure 5B). There were no significant correlations found in any other ERS regions. These results help to clarify the role of DLPFC in mediating upstream semantic representations that are important for successful memory functioning.

Discussion

To our knowledge, this is the first study to demonstrate that rTMS can modulate memory representations as measured by RSA and ERS. Thus, this work links brain stimulation techniques with semantic representations and episodic memory functioning using a novel multimodal paradigm. The study yielded three principal findings. First, 5Hz, relative to 1Hz, rTMS boosted the quality of semantic representation (i.e., 2nd order correlation with semantic RDM) in left fusiform gyrus. Second, 5Hz, but not 1Hz, rTMS enhanced quality of memory representations in MTL, as assessed by ERS analyses. Lastly, linking the ERS effect to the DLPFC stimulation, we found that increases in univariate activity at the stimulation site were correlated with increases in item-level ERS in MTL, and that these two sites were more functionally connected during subsequently remembered trials. We discuss each of these results and their implications below.

rTMS effects on Semantic Representations

Our result demonstrates that external manipulations of local excitability in left DLPFC impact neural pattern similarity in distinct temporal and parietal regions known to code for semantic and episodic features. Foundational to this finding is the idea that the neural and semantic similarity between individual items represents meaningful information, and that this representation in a given brain region or computational model can be characterized by the matrix of dissimilarities between the stimulus representations (Kriegeskorte and Kievit, 2013). The information encoded in our task represented complex sentences with conceptual memoranda common to everyday life. Despite its fundamental role in cognition, the informational content that is represented during reading remains elusive. To understand how semantic information is represented in the brain, we used a comprehensive database of relationships between words capturing a broad semantic space (Cortical.io). The similarity between the semantic contexts in each sentence (encoding) or word pair (retrieval) across our task can be summarized with a single representational dissimilarity matrix (or RDM), and thus presents a powerful means of describing relatively complex information patterns across multiple trials.

While no study has used TMS to examine changes in pattern similarity, a number of studies have targeted activation patterns associated with more upstream components of conceptual

encoding. Recent studies suggest that TMS, when applied early in the ventral processing stream, may strongly impact univariate estimates related to visual and mnemonic processing. 20Hz TMS applied to early visual cortex during short-term retention of visual stimuli results in a reduction in behavioral measures of working memory precision (van de Ven et al., 2012; van de Ven and Sack, 2013), supporting the notion that visual cortex stores precise representations of visual working memory contents. While most of these studies are focused on disrupting posterior regions that are thought to represent stimulus-specific information, there is also evidence that disruption of semantic processing can also occur as a consequence of 1Hz rTMS to the anterior temporal lobes (Lambon Ralph et al., 2009; Binney et al., 2010).

While our study represents an early application of work combining RSA with neuromodulation to examine semantic and episodic memories, it should be noted that a number of high-profile working memory studies have used multivariate techniques to assess how neuromodulation affects item-level representations in working memory (Rose et al., 2016; Wolff et al., 2017). While the focus of these approaches tends to focus on tagging a specific memoranda or transient “memory states”, such techniques do not speak to the modulation of an existing, model-driven assessment of a semantic system, e.g., via the semantic associations between items as assessed in our sample by Cortical.io, or feature-normed techniques as used by Tyler and colleagues (Devereux et al., 2013; Tyler et al., 2013; Clarke and Tyler, 2014). As such, these working memory memoranda serve as representations only in that they are unique neural representations, but still have no underlying psychological model of how different stimuli relate to each other.

Nonetheless, our results provide a clear step forward for the investigation of the encoding and retrieval of semantic concepts. Critically, both RSA and ERS were greater for trials after excitatory stimulation in regions typically associated with more abstract semantic representations like the fusiform gyrus and ATL (Figure 3); while the former is typically associated with representing object hierarchies or categories (Clarke and Tyler, 2014), the latter is known to play a role in stimulus-independent semantic representations (Olson et al., 2007; Patterson et al., 2007). These results suggest that conceptual information represented in temporal regions is modulated by TMS. For meaningful word stimuli, recent work has shown that representations in ATL relate to measures of true and false memory, suggesting that exogenously induced representational changes in this region might underpin aspects of memory function for similar stimuli (Chadwick et al., 2016). These convergent results therefore suggest a distinct mechanism whereby specific mnemonic representations linked to specific item information become consolidated and available for later access through the reactivation of specific neural patterns. While the frequency-specific effects observed in our study did not dissociate remembered and forgotten items (as observed by a lack of a 3-way interaction or 2-way Success x Stimulation interaction), they nonetheless demonstrate the ability of rTMS to boost the specificity of mnemonic representations, as evidenced by a significant Stimulation x ERS interaction. To date there is no evidence that brain stimulation can modulate these effects, but the current results help to shed some light on this potential mnemonic process.

Top-down influences on memory

As noted in the Introduction, one needs to consider that the region-specific effect of rTMS on memory performance might have been boosted by indirect manipulation of regions connected with the stimulation site. The current results provide preliminary evidence that excitatory influences in DLPFC can have meaningful influences on the representational information processed in more posterior cortices. We found two complimentary pieces of evidence to support the idea that PFC-mediated increases in representational similarity can be induced with rTMS. First, and most critically, the local activity increases at the site of stimulation were more strongly correlated with item-level ERS in the left MTL during excitatory relative to inhibitory stimulation (Figure 5A). Additionally, this hippocampal ERS effect was significant for remembered and but not forgotten items in our sample. Although we cannot discount this null finding due to fewer forgotten trials than previous ERS studies (Ritchey et al., 2012; Wing et al., 2015), the influence of this region in differentiating between Item > Set-level representations was clearly increased by 5Hz rTMS, and was significant even when restricted to remembered trials. Second, functional connectivity between the DLPFC stimulation site and the left MTL during encoding demonstrated a significant Stimulation x Memory Success interaction (Figure 5B), such that connectivity was greater during successfully encoded trials than subsequently forgotten trials after 5Hz (but not 1Hz) stimulation. These results suggest that representations in MTL were boosted by indirect manipulation.

While this is, to our knowledge, the first time TMS has been shown to modulate pattern similarity, it is not the first to suggest that PFC stimulation may boost the top-down activation (or controlled retrieval) of semantic knowledge (Badre and Wagner, 2007; Bunge et al., 2009). Causal links between PFC activity and the properties of visual cortical neurons has been established through intervention with TMS. Disruption of PFC activity using 1Hz rTMS causes a significant reduction in the selectivity of fMRI responses in visual cortex, and appears to inhibit top-down selective attentional modulation to specific category types in the occipitotemporal cortex, during both online perception (Higo et al., 2011), and during working memory delay phases, (Lee and D'Esposito, 2012). The principle implied here is that DLPFC inputs enhance selectivity in visual cortex; in the current study we failed to observe any significant modulation of ERS in such early visual regions (Table 3), which *did* show Baseline ERS. While it is difficult to draw lasting conclusions from such a null effect, we did find stimulation-related modulation in more downstream regions associated with amodal memory representation (Martin et al., 2018). However, given that our stimulation region was more functionally connected to MTL regions exhibiting significant ERS effects, our results are more in agreement with findings describing the importance of frontotemporal connectivity in accessing semantic and episodic memory representations (Clarke et al., 2013; Backus et al., 2016). These results therefore suggest that the amodal representational content evoked during encoding and reactivated during retrieval is fundamentally affected by stimulation in frontal control regions.

The importance of frequency

Lastly, it is key to note that both our RSA/ERS pattern similarity findings, and that success-related functional connectivity between left DLPFC and left MTL during encoding (Figure

5B) were uniquely associated with fMRI data collected after 5Hz rTMS. This result is reasonable given the importance of frontotemporal synchrony within the theta band (4–10Hz) during episodic encoding in regions functionally connected to the hippocampus, including LPFC and VPC (Osipova et al., 2006; Hsieh and Ranganath, 2014). EEG signals generated by the hippocampus are typically dominated by regular theta waves, often continuing for many seconds after being elicited by a focused event (Buzsaki, 2002, 2005).

Increased rhythmic synchrony across distant regions within a cortical network is thought to improve information processing by increasing network efficiency, an effect particularly important during demanding cognitive processing (Fries, 2009; Deco et al., 2011), such as episodic encoding and retrieval. For example, a number of scalp EEG studies have reported that frontotemporal theta rhythms are enhanced for items that are subsequently remembered more than items that are forgotten (Summerfield and Mangels, 2005; Hanslmayr et al., 2009; Nyhus and Curran, 2010). Even more recent intracranial work from Kahana and colleagues has helped to validate this observation, which suggest that widespread synchronization of theta networks predict successful encoding (Ezzyat et al., 2017; Solomon et al., 2017), and that selective modulations of theta- and high-gamma-band activity in the temporal lobes can be used to decode successful memory states and inform targeted, closed-loop brain stimulation paradigms (Ezzyat et al., 2018). Such direct applications of frequency-specific information and brain stimulation represent powerful tools for future research and clinical application.

Stimulation variables such as intensity, frequency and duration clearly have a strong influence on the psychological and neurobiological effects of rTMS. One critical aspect of offline rTMS applications like ours is the notion of decay; rTMS was delivered for 10 min, ostensibly yielding an effect that has been shown to last ~9 min (Thut et al., 2006) and hence persist during the entire encoding run (6-min). Nonetheless, some authors have suggested differential decay rates in the effect of stimulation may differ for rTMS of different frequencies. Previous studies have provided some information about the duration of behavioral (Robertson et al., 2001; Mottaghy et al., 2002) and neural (Eisenegger et al., 2008) effects after low-frequency “off-line” long-train rTMS applied to the dorsolateral prefrontal cortex (DLPFC). While the general consensus is that 1–10Hz rTMS has a sharper decay than higher-frequency theta-burst stimulation (Huang et al., 2005; Nyffeler et al., 2006), there is nonetheless still considerable debate on the duration of low- and high-frequency rTMS (Gamboa et al., 2010). Though our study was not adequately designed to elucidate these factors affecting differential decay between 1Hz and 5Hz, we cannot discount the possibility that the greater ERS after 5Hz rTMS was driven by greater decay in the behavioral and neural effects after 1Hz rTMS. Nonetheless, the lack of any difference in slopes for either RT (Table 1) or mean univariate BOLD in the stimulation site suggests no evidence for such a differential decay in our sample.

Caveats

Our study has a number of limitations. First, there are unique subjective differences between the experience of 1Hz and 5Hz rTMS. Thus, it is possible that greater RSA/ERS effects after 5Hz TMS were due to participants being cued by the greater intensity of sound produced by

a 5Hz rTMS and may have been in a state of heightened awareness. While we cannot discount this possibility, we note that 1) the memory task was not concurrent with the rTMS, so the influence of such heightened attention would have to persist through the ~10 minutes necessary to initiate the fMRI scan, 2) we observed no significant univariate effects of 1Hz stimulation compared to baseline, suggesting that the application of any TMS was not sufficient to elicit this effect, and 3) performance on the memory task did not differ as a function of stimulation frequency.

Second, our study suffers from a low sample size; a recent meta-analysis of clinical rTMS studies found that the average sample size for such studies is low (mean sample size = 18; Martin et al., 2003). Clearly this standard is not viable for the field to progress beyond qualitative observations of rTMS impact. However, our findings nonetheless provide some limited support for the conclusion that the modulatory influence of rTMS may be limited to specific frequency parameters, offer an exploratory foundation in characterizing representational changes associated with rTMS, and suggest an analytical format that may reveal important information as yet unexplored in more well-powered brain stimulation studies.

Conclusion

Overall, our findings indicate a direct link between 5Hz rTMS applied to DLPFC, and memory representations in posterior parietal and temporal cortices. Taken together, these results provide the first evidence of excitatory TMS enhancing memory representations using two different multivariate methods and suggests that rTMS may affect the reinstatement of previously experienced events in regions distal to the site of activation. By showing that stimulation impacts the neural basis of episodic memory at specific frequencies, our data provide a foundation for future work to apply stimulation when it is most likely to improve memory function.

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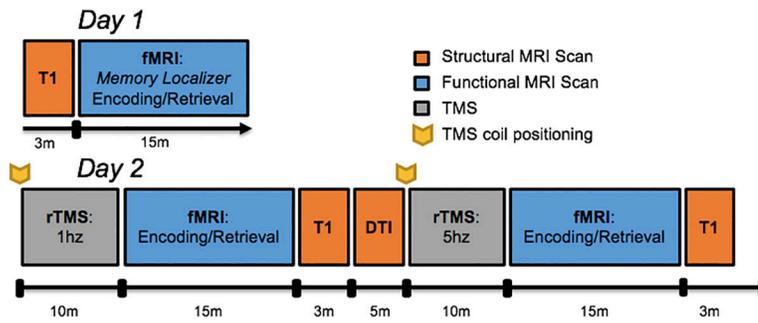
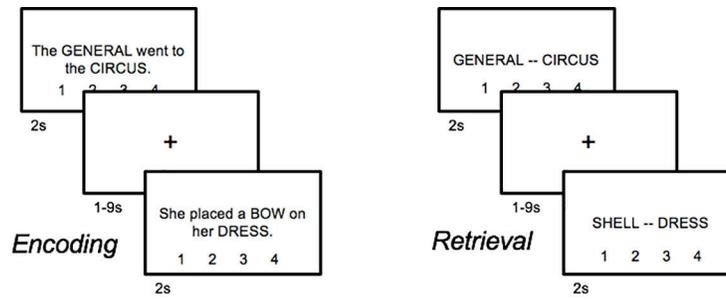


Figure 1. Timeline of imaging protocol.

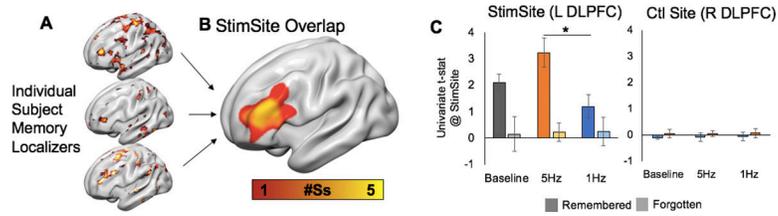


Figure 2. Localization of memory-specific rTMS targets, and univariate effects of stimulation. (A) A functional memory-success localizer collected on Day 1 in individual participants; (B) these subject specific peaks demonstrated a reasonable overlap across participants. (C) Univariate BOLD effects for subsequently Remembered and Forgotten trials during Baseline, 1Hz, and 5Hz conditions reveal a reliable excitation/suppression of the subsequent memory effect after 5Hz/1Hz rTMS. No effect was observed in the contralateral cortex.

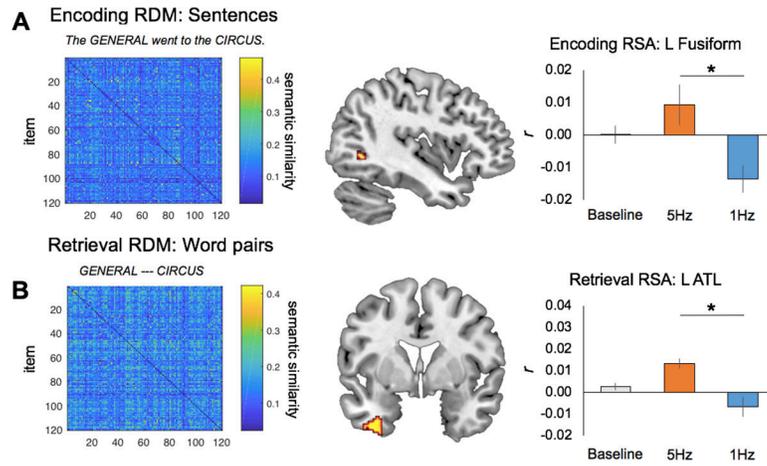


Figure 3. Regions exhibiting significant RSA effects during (A) encoding and (B) retrieval. Model RDMs based on sentential (A) or word pair similarity (B) are shown to the left, while at right are graphs representing mean 2nd order correlations between model RDMs and brain RDMs.

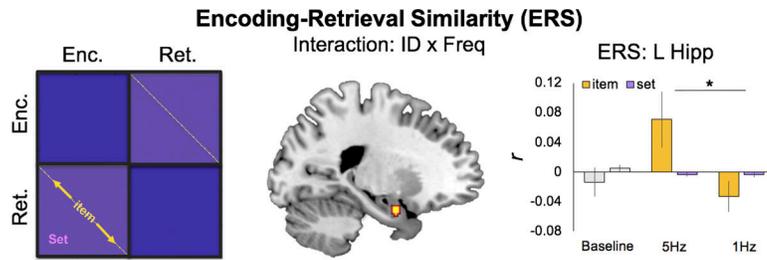


Figure 4. Encoding-Retrieval Similarity after 5Hz or 1Hz rTMS.

The schematic on the left describes encoding-retrieval items to be compared (yellow cells) versus set-level matches between unmatched pairs (light purple cells). These set-level matches serve as a reasonable comparison for ERS effects. At right, mean pattern-to-pattern similarity across stimulation conditions for item- and set-level matches.

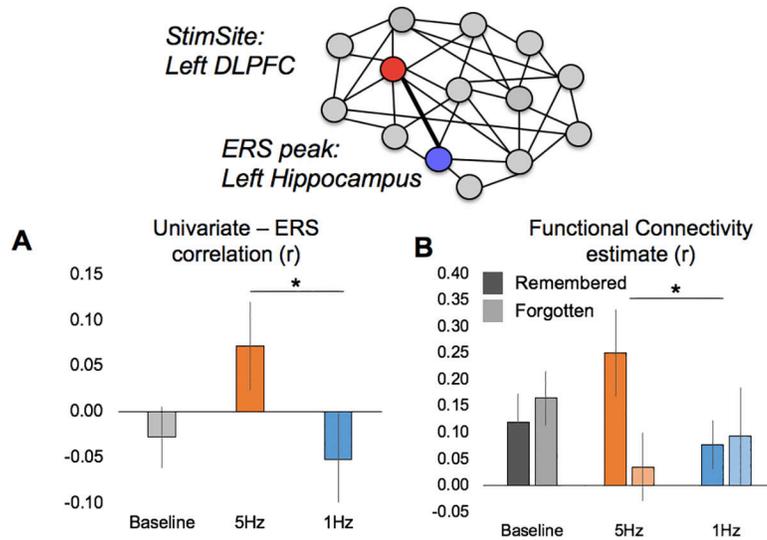


Figure 5. Relationships between Left PFC stimulation site and MTL ERS effects. (A) The increase in univariate activity associated with 5Hz rTMS (see Figure 2) served to boost ERS in left hippocampus after 5Hz rTMS. (B) Functional connectivity estimates based on the cPPI analysis during the encoding period, which demonstrate a selective increase in PFC-MTL connectivity during successfully remembered > forgotten trials, and effect present only in the 5Hz rTMS condition.

Table 1.

Behavioral performance

<i>Accuracy</i>	H (SE)		FA (SE)		d' (SE)	
Baseline	0.73	0.04	0.20	0.04	1.78	0.23
1Hz rTMS	0.80	0.05	0.10	0.03	2.36	0.20
5Hz rTMS	0.85	0.03	0.15	0.03	2.29	0.22

<i>Response Time</i>	H (SE)		FA (SE)		Slope/trial* (SE)	
Baseline	1723	101	2496	121	-0.0006	0.004
1Hz rTMS	1645	105	2424	124	-0.0018	0.002
5Hz rTMS	1576	108	2237	110	0.0031	0.006

* Note: Slope was calculated as the slope of a regression line fit to all responses during encoding for each stimulation condition. Values shown here represent a mean across participants.

Table 2.

Significant RSA clusters.

Encoding RSA						
<i>Contrast</i>	<i>Region</i>	<i>k</i>	<i>Z-score</i>	<i>x</i>	<i>y</i>	<i>z</i>
Baseline	Inferior Temporal Gyrus	27	3.09	-42	-8	-34
5Hz > 1Hz	Fusiform Gyrus	68	3.22	-36	-58	-4
	<i>Inferior Temporal Gyrus*</i>		1.03			
Retrieval RSA						
<i>Condition</i>	<i>Region</i>	<i>k</i>	<i>Z-score</i>	<i>x</i>	<i>y</i>	<i>z</i>
Baseline	Inferior Temporal Gyrus	22	2.99	48	-10	-40
5Hz > 1Hz	Left Precentral gyrus	107	3.73	-16	-24	66
	Left Anterior PHC	92	3.59	32	-22	-16
	Left ATL	137	3.30	-38	4	-44
	Posterior cingulate	24	3.01	12	-16	38
	<i>Inferior Temporal Gyrus*</i>		1.59			

Note: A mask ($p < 0.005$) for the Inferior Temporal Gyrus is included in both Encoding and Retrieval RSA contrasts for 5Hz > 1Hz in order to determine the extent of stimulation-related modulation in Baseline regions.

Table 3.

Significant ERS clusters.

ERS							
<i>Contrast</i>	<i>Region</i>	<i>k</i>	<i>Z-score</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>Reg. t</i>
Baseline	Lateral Occipital Cortex	20	3.03	42	-74	12	-
5Hz > 1Hz	Right Superior temporal gyrus	33	3.49	48	0	-18	2.71 [‡]
	Left Hippocampus/Amygdala	42	2.94	-18	0	-24	1.91 [‡]
	<i>Lateral Occipital Cortex*</i>		0.94				

Notes: Regression sig. (see methods):

[‡]p = .01 one tailed[†]p = .04 one tailed.

A mask ($p < 0.005$) for the Lateral Occipital Cortex is included in contrasts for 5Hz > 1Hz in order to determine the extent of stimulation-related modulation in Baseline regions.