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Frontoparietal Networks Mediate the Behavioral Impact of Alpha Inhibition in Visual Cortex

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Abstract

Alpha oscillations are known to play a central role in the functional inhibition of visual cortices, but the mechanisms involved are poorly understood. One noninvasive method for modulating alpha activity experimentally is through the use of flickering visual stimuli that “entrain” visual cortices. Such alpha entrainment has been found to compromise visual perception and affect widespread cortical regions, but it remains unclear how the interference occurs and whether the widespread activity induced by alpha entrainment reflects a compensatory mechanism to mitigate the entrainment, or alternatively, a propagated interference signal that translates to impaired visual processing. Herein, we attempt to address these questions by integrating alpha entrainment into a modified Posner cueing paradigm, while measuring the underlying dynamics using magnetoencephalography. Our findings indicated that alpha entrainment is negatively related to task performance, such that as neural entrainment increases on the attended side (relative to the unattended side) accuracy decreases. Further, this attentional biasing is found to covary robustly with activity in the frontoparietal attention network. Critically, the observed negative entrainment effect on task accuracy was also fully mediated by activity in frontoparietal regions, signifying a propagation of the interfering alpha entrainment signal from bottom-up sensory to top-down regulatory networks.

Key words: alpha oscillations, attention, magnetoencephalography, visual entrainment

Introduction

The ability to rapidly perceive salient components of the visual environment is essential for normative cognitive function and is thought to be supported by both “bottom-up” sensory (e.g., retinotopic activation in primary visual cortices) and “top-down” regulatory (e.g., activation in frontoparietal attention networks) processes. Further, spectrally defined patterns of neural oscillatory activity have been found to play a key role in visual processing. In particular, alpha-frequency (8–13 Hz) rhythms in parietal and occipital cortices are thought to be essential for the active inhibition of irrelevant or distracting visual inputs (van Dijk et al. 2008; Jensen and Mazaheri 2010; Bonnefond and Jensen 2012; Spaak et al. 2014; Bompas et al. 2015; Gulbinaite et al. 2017). Perhaps unsurprisingly then, alpha-band oscillations, both within and outside of parieto-occipital areas, have

also been found to be essential to visual attention (Kelly et al. 2006; Capotosto et al. 2009; Foxe and Snyder 2011; Handel et al. 2011; Klimesch 2012; McDermott et al. 2017; Wiesman et al. 2017; Proskovec et al. 2018) and are a potential spectral point of mediation between bottom-up sensory mechanisms and top-down regulatory systems in the human brain.

Unfortunately, experimental manipulation of alpha-frequency activity in the human brain is difficult in healthy individuals, making causal interpretations of the role of alpha oscillations problematic. To this end, many researchers have turned to non-invasive neurostimulation (Capotosto et al. 2009; Romei et al. 2010; Zaehle et al. 2010; Sauseng et al. 2011; Herring et al. 2015; Ruhnau et al. 2016; Heinrichs-Graham et al. 2017; Wilson et al. 2018). For example, Capotosto et al. (2009) used repetitive transcranial magnetic stimulation and electroencephalography to

systematically disrupt alpha oscillations in the right parietal and frontal cortices prior to the performance of a visual target identification task. They showed that the disruption of alpha oscillations impaired the participant's ability to identify subsequently presented targets in the visual space. In addition, this impairment covaried significantly with the level of alpha-frequency disruption in parietal and occipital electrodes. These findings provide robust support for the involvement of alpha activity in frontoparietal networks in the perception of objects in the visual space. However, the experimental design precluded the authors from investigating other attention network regions that may have been involved in this process and also from examining whether signals from bottom-up systems interfered with attention networks.

Beyond neurostimulation, other studies have used flickering visual stimuli to systematically modulate endogenous rhythms in the human brain, by "entraining" activity in sensory cortices at targeted frequencies (Rohenkohl and Nobre 2011; Heinrichs-Graham and Wilson 2012; de Graaf et al. 2013; Spaak et al. 2014; Lithari et al. 2016; Gulbinaite et al. 2017). For clarity, there is also a separate literature that uses flickering visual (or auditory) stimuli, but these "steady-state" paradigms generally aim to "tag" neural responses of interest with frequency-specific information (Morgan et al. 1996; Herrmann 2001; Ding et al. 2006; Cottareau et al. 2011; Keitel et al. 2014; Norcia et al. 2015), and they often draw different conclusions from similar experimental findings (Keitel et al. 2014). However, few experiments have investigated the interaction between exogenously entrained neural oscillatory activity in primary visual cortex and the endogenous patterns of rhythmic neural activity that support visual attention and perception. Because of this void, the mechanism by which rhythmic alpha activity in visual cortex exerts its functionally inhibitory effect remains unclear. On the other hand, studies have shown that visual alpha activity covaries with target perception (van Dijk et al. 2008; Handel et al. 2011; Spaak et al. 2014; Wiesman et al. 2018), is involved in the protection of stimulus representations during working memory maintenance, and is often correlated with accuracy and load on such working memory tasks (Jensen et al. 2002; Bonnefond and Jensen 2012; Wilson et al. 2017). Alpha activity is also known to be widely distributed across the human brain (Nunez and Cutillo 1995). In fact, prior studies using flickering stimuli have reported spatially widespread effects unique to alpha range entrainment (Herrmann 2001; Ding et al. 2006; Lithari et al. 2016). Thus, it seems likely that at least some part of this alpha-related modulation is taking place in top-down regulatory networks. If this is the case, it is important to understand 1) which specific cortical regions are implicated in this modulation, 2) whether modulation at these regions affects visual perception, and 3) to what extent this modulation statistically mediates the relationship between entrained dynamics in primary visual cortex and visual perceptual abilities.

In this study, we used 10 Hz visual entrainment to modulate the endogenous alpha oscillations in occipital cortices that are known to support visual processing, mapped the resulting neural perturbations using magnetoencephalography (MEG), and delineated the effects of these neural perturbations on visual perceptual abilities. Interestingly, previous studies have found that attentional deployment enhances the neural response at corresponding retinotopic areas to entraining visual stimuli, with the notable exception of alpha-frequency entrainment, where results have been less consistent, and attention often shows either a reduced or negative effect on entrainment power (Ding et al. 2006; Kelly et al. 2006; Kim et al. 2007). Given these

data, we did not hypothesize that entrainment to the 10-Hz flicker would necessarily be enhanced by attentional cueing, but we did expect the cueing effect (i.e., the degree to which cueing biased the neural response toward or away from the entraining stimuli) to covary with visual perception of the attended stimulus, as indexed by performance metrics on the task. Further, we hypothesized that this cueing effect on the 10 Hz entrainment response would covary with activity in top-down attention networks, signifying potential interference of processing in these networks by the 10 Hz entrainment signal. Finally, we expected that the relationship between this cueing effect and task performance would be mediated by activity in the same frontoparietal regulatory networks, signifying an interfering effect of 10 Hz visual entrainment on attentional processing.

Methods

Participants

Twenty-three healthy young adults were recruited for the study ($M_{\text{age}} = 26.09$; age range: 20–33 years; 16 males; 21 right-handed). Exclusion criteria included any medical illness affecting CNS function, any neurological or psychiatric disorder, history of head trauma, current substance abuse, and any nonremovable metal implants that would adversely affect MEG data acquisition. All participants had normal or corrected-to-normal vision. The Institutional Review Board at the University of Nebraska Medical Center reviewed and approved this investigation. Written informed consent was obtained from each participant following the detailed description of the study. All participants completed the same experimental protocol.

MEG Experimental Paradigm and Behavioral Data Analysis

We used a modified version of the classic Posner cueing paradigm (Posner 1980) to engage alpha-frequency networks related to the orienting of attention (Fig. 1). Each trial began with a central fixation that was presented for a randomly varied inter-stimulus interval of 2000–2400 ms. Participants were instructed to fixate centrally on this point of the screen for the entirety of the experiment. Subsequently, the fixation was replaced with an arrow cue pointing toward the left or right. The centrally presented arrow cue remained on the screen for 2000 ms and correctly predicted the side of the to-be-presented probe stimulus on 100% of trials. On each side of the cue was an entrainment stimulus (in the form of an outline of a box) that flickered at a frequency of 10 Hz. For clarity, both sides flickered in all trials, regardless of the cue direction. At the end of the entrainment period, the boxes stopped flickering and a small break appeared on either the top or bottom side of the box (cued side only) for 1000 ms. The presentation of this probe stimulus occurred at the same time relative to flicker offset for every trial, which aligned temporally with the peak of the ongoing 10 Hz phase of the entraining visual stimuli. Prior to starting the experiment, participants were instructed to respond as quickly and accurately as possible as to whether the break appeared on the top (index finger) or bottom (middle finger) of the cued box, using their right hand on a nonmagnetic button pad. The entraining and probe stimuli occupied the same spatial areas of the visual field, so to entrain the visual cortex corresponding to the subsequently presented probe stimulus. The 200 total trials were pseudorandomized and equally split between each of the cue (left and right) and response (top and bottom) conditions. Correct responses were also pseudorandomized, such that the

Figure 1. Experimental paradigm and neurophysiological hypothesis. Each trial began with a central fixation that was presented for 2200 ms (randomized jitter of ± 100 ms). After this, a 100% predictive arrow cue pointing toward the left or right appeared centrally for 2000 ms. On each side of this cue was an entrainment stimulus (highlighted here by green dotted lines for clarity) that flickered at a frequency of 10 Hz. At the end of the entrainment period, the box stimuli ceased flickering, and a small break appeared on either the top or bottom side of the box on the cued side for 1000 ms. Participants responded as quickly and accurately as possible as to whether the break appeared on the top (index finger) or bottom (middle finger) of the cued box. The entraining and probe stimuli occupied the same spatial areas of the visual field, which ensured that the probe stimulus would be processed by entrained visual regions. The visual pathway and sine waves below reflect one of our neurophysiological hypotheses, which included a general increase in 10 Hz amplitude during the entrainment period, and either a negative or negligible effect of attention on the amplitude of this signal (red line), as has been reported in a number of previous studies. For clarity, although we did not predict a general effect of attention on entrainment across all participants, we did expect that the magnitude of attentional modulation on visual dynamics would affect task performance.

same response was never repeated more than twice. Custom visual stimuli were programmed in Matlab (Mathworks, Inc.) using “Psychophysics Toolbox Version 3” (Brainard 1997) and backprojected onto a semitranslucent nonmagnetic screen using a Panasonic PT-D7700U-K model DLP projector with a refresh rate of 60 Hz and a contrast ratio of 4000:1. Flickering stimuli were presented as a square-wave function with a frequency of 10 Hz (3 frames on/3 frames off; ~ 16.67 ms per frame), with a luminance contrast of 100% (white stimuli on a black background). Total MEG recording time was approximately 17 min. For each participant, accuracy data were computed as a percentage (correct/total trials). Reaction time data were also extracted for each individual trial, incorrect and no-response trials were removed, and outliers were then excluded based on a standard threshold of ± 2.5 standard deviations from the mean.

MEG Data Acquisition

All recordings were conducted in a one-layer magnetically shielded room with active shielding engaged for environmental noise compensation. Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1–330 Hz using a 306-sensor Elekta MEG system (Helsinki, Finland) equipped with 204 planar gradiometers and 102 magnetometers. Participants were monitored during data acquisition via real-time audio–video feeds from inside the shielded room. Each MEG dataset was individually corrected for head motion and subjected to noise reduction using the signal-space separation method with a temporal extension (Taulu and Simola 2006).

Structural MRI Processing and MEG Coregistration

Preceding MEG measurement, four coils were attached to the participant’s head and localized, together with the three fiducial points and scalp surface, using a 3D digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences). Once the participant was positioned for MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the coils. This induced a measurable magnetic field and allowed each coil to be localized in reference to the sensors throughout

the recording session. Since coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system, each participant’s MEG data were coregistered with individual structural T1-weighted MRI data ($N = 12$), when available, or alternatively were fitted to a template MRI ($N = 11$) using the scalp surface points, in BESA MRI (Version 2.0) prior to source-space analysis. Importantly, our primary neural measure of interest, the cueing effect, did not significantly differ according to whether participants data were coregistered to individual or template MRIs (two-sample *t*-test; $P = 0.48$). Structural MRI data were aligned parallel to the anterior and posterior commissures and transformed into standardized space. Following source analysis (i.e., beamforming), each participant’s $4.0 \times 4.0 \times 4.0$ mm functional images were also transformed into standardized space using the transform that was previously applied to the structural MRI volume and spatially resampled.

MEG Preprocessing, Time–Frequency Transformation, and Sensor-Level Statistics

Cardiac artifacts were removed from the data using signal-space projection, which was subsequently accounted for during source reconstruction (Uusitalo and Ilmoniemi 1997). The continuous magnetic time series was then divided into 3500-ms epochs, with the baseline extending from -2500 to -2000 ms prior to the onset of the probe stimuli, which was defined as 0 ms. Epochs containing artifacts were rejected per participant using a fixed threshold method, supplemented with visual inspection. An average amplitude threshold of 1092.39 (SD = 212.86) fT and an average gradient threshold of 107.95 (SD = 38.84) fT/s was used to reject artifacts. Across the group, an average of 160.83 (SD = 8.72) trials per participant were used for further analysis.

The artifact-free epochs were next transformed into the time–frequency domain using complex demodulation, and the resulting spectral power estimations per sensor were averaged over trials to generate time–frequency plots of mean spectral density. These sensor-level data were normalized by each respective bin’s baseline power, which was calculated as the

mean power during the -2500 to -2000 ms time period. The time–frequency windows used for subsequent source imaging of the entrainment response were determined a priori, based on the duration and frequency of the entrained stimuli. The spectral window was defined as the frequency of entrainment (i.e., 10 Hz) ± 0.2 Hz, and the time window was defined from 750 to 0 ms prior to the presentation of the probe stimulus. Although entrainment did elicit a neural synchronization beginning earlier (roughly 1500 ms prior to the onset of the probe stimulus, see below), only the time period that exhibited the strongest response (-750 to 0 ms) was used in order to maximize the signal-to-noise ratio of the subsequent source images.

MEG Source Imaging and Statistics

Cortical networks were imaged using the dynamic imaging of coherent sources beamformer (Gross et al. 2001), which applies spatial filters to time–frequency sensor data in order to calculate voxel-wise source power for the entire brain volume. The single images are derived from the cross-spectral densities of all combinations of MEG gradiometers averaged over the time–frequency range of interest, and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, we computed noise-normalized, source power per voxel in each participant using active (i.e., task) and passive (i.e., baseline) periods of equal duration and bandwidth. Such images are typically referred to as pseudo-t maps, with units (pseudo-t) that reflect noise-normalized power differences (i.e., active vs. passive) per voxel. MEG pre-processing and imaging used the Brain Electrical Source Analysis (BESA Version 6.1) software. Left and right hemisphere entrainment peak voxels were identified as the voxel in occipital cortex with the highest average pseudo-t from grand-averaged whole-brain images across all participants. These bilateral peaks were then used to compute response values separately for the attended and unattended hemifields for each trial, based on the cue direction in that trial. For example, on a left-cued trial, the entrainment peak from the right (contralateral) primary visual cortex would represent the attended hemifield, while the peak from the left (ipsilateral) primary visual cortex would represent the unattended hemifield. To investigate hypothesized covariance between cueing effects and other metrics, a cueing ratio was derived from these peak values for each participant ($[\text{attended} + 100]/[\text{unattended} + 100]$). For interpretation, higher cueing effect values indicate an increased cueing bias of neural entrainment responses toward the attended hemifield, while lower values indicate biased neural entrainment away from the attended side. Note that a constant value of 100 was added prior to the division of these data, to account for any negative amplitude values.

Statistical Analysis

Pearson product-moment correlation coefficients were computed to test hypothesized covariance between metrics, with post hoc control for multiple comparisons using Bonferroni correction unless explicitly stated otherwise. To test hypothesized mediations, relevant metrics were extracted from behavioral and neurophysiological data, and the resulting values were used in stepwise linear regressions to determine whether an indirect effect was plausible. If the effect of the independent variable was reduced to the extent of no longer being significant, a nonparametric bootstrapping analysis with at least

$10\,000$ simulations was used to test the significance of potential mediation (i.e., indirect) effects. Correlation coefficients, linear regressions, and mediation bootstrapping analyses were computed in R (Tingley et al. 2014; Team 2017). Finally, for whole-brain correlation maps, voxel-wise correlations were computed between neural activity in the participant-level whole-brain maps and relevant continuous metrics (i.e., cueing effects on entrainment). For these maps, a stringent statistical threshold of $P < 0.0005$ was used, along with a cluster threshold (k) of at least 200 contiguous voxels.

Results

Temporal–spectral Profile of 10 Hz Entrainment

Before projecting our recorded neurophysiological signals into brain space, we first needed to identify the temporal and spectral extent of the neural responses of interest. After transforming the MEG signals into time–frequency space, we observed a robust, narrow-band synchronization centered at 10 Hz over occipital sensors. This synchronization began roughly 500 ms after the onset of the entrainment stimuli and reached a maximum amplitude between 750 and 0 ms prior to the onset of the probe (Fig. 2, top). To maximize the signal-to-noise ratio of the input data, the time window with the highest amplitude (750 to 0 ms before probe onset) was used for subsequent source imaging.

Effects of Entrainment on Behavior

Consistent with previous reports, the 10 Hz entrainment response was found to originate from bilateral sources in the primary visual cortices (Fig. 2, top inset). To investigate the general effect of entrainment (i.e., regardless of attentional cueing effects), we extracted peak voxel amplitude values from the 10 Hz entrainment response in each hemisphere for each participant and averaged these values across bilateral primary visual cortices. This metric of cueing-invariant entrainment significantly correlated with accuracy on the task ($r = 0.58$, $P = 0.004$; Fig. 2, bottom left), such that as entrainment increased accuracy improved. Although of interest in itself, this relationship was not the primary focus of our investigation, as it does not account for attentional cueing and likely reflects a more general index of alertness when performing the task. To examine the effect of attentional cueing more directly, we used the same voxels described above and derived the amplitude values for 10 Hz entrainment responses corresponding to the attended and unattended hemifield separately, and then computed a ratio of these values for each participant (i.e., the “cueing ratio”; $[\text{attended} + 100]/[\text{unattended} + 100]$). For interpretation, higher cueing effect values indicate an increased cueing bias of neural entrainment responses toward the attended hemifield, while lower values indicate biased neural entrainment away from the attended side. Intriguingly, the effect of attentional cueing on the entrainment response also significantly covaried with accuracy ($r = -0.46$, $P = 0.029$; Fig. 2, bottom right). Confirming our primary hypothesis, this relationship was reversed in direction, such that greater entrainment on the attended (relative to the unattended) side was related to decreased performance on the task, indicating reduced visual perceptual abilities in that same visual space. In other words, regardless of the overall amplitude of visual entrainment, greater attentional “enhancement” of the 10 Hz entrainment in the cued hemifield (i.e., where the probe subsequently appeared) was associated with reduced performance.

Figure 2. Spectral, temporal, and spatial definitions of neural responses to entrainment, and interactions with attention and behavior. The MEG sensor spectrogram (top) displays alpha-frequency neural responses over occipital regions during the 10 Hz entrainment period, with time (in ms) denoted on the x-axis and frequency (in Hz) denoted on the y-axis. The dashed black line at -2000 ms indicates the onset of the entrainment stimuli, and the dashed black line at 0 ms indicates the onset of the probe stimulus. The color scale bar for percent change from baseline is displayed above the plot. This spectrogram represents group-averaged data from one gradiometer sensor that was a representative of the neural responses in occipital cortices. Inlaid on the far right is the source-imaged representation of this response, with the color scale bar to the right denoting response amplitude in pseudo- t units. The correlation plots below show the relationships between accuracy (on both y-axes, denoted in % correct trials) and bilaterally averaged entrainment power (denoted on the x-axis in pseudo- t) on the left, and the cueing effect (denoted on the x-axis as a ratio of attended/unattended source amplitude) on the right. Lines of best-fit, as well as the relevant covariance coefficients, are overlaid on each plot.

Frontoparietal Networks Covary with Attentional Modulation of 10 Hz Entrainment

To explore if any “higher order” cortical regions were also affected by the 10 Hz entrainment, we next computed a whole-brain correlation between each participant’s entrainment cueing ratio and voxel-wise amplitude values of neural activity during the entrainment period (-750 to 0 ms; Fig. 3, top). Using stringent statistical thresholds, activity in a widespread network of regions was found to covary with the entrainment cueing effect, including nodes in the right dorsolateral prefrontal (r-dlPFC, $r_{\max} = -0.72$), right primary motor (r-M1, $r_{\max} = -0.81$), bilateral superior parietal (r-SPC, $r_{\max} = -0.73$; l-SPC, $r_{\max} = -0.70$), and midcingulate (MCC, $r_{\max} = -0.70$) cortices (all P ’s $< 5 \times 10^{-4}$, cluster-corrected, $k = 200$). The direction of this relationship was similar across all nodes, such that as entrainment in the attended (relative to the unattended) hemifield increased, the 10 Hz response in these other regions decreased (i.e., desynchronized). Such “decreases” from baseline levels of synchrony are well supported as being indicative of active neuronal processing at this (alpha) frequency (Klimesch 1999; Goldman et al. 2002; Kelly et al. 2006; Jensen and Mazaheri 2010). Thus, this covariance should be interpreted as increased entrainment (i.e., interference) in visual cortex on the attended side leading to a

greater neural responses in frontoparietal cortices. Interestingly, the peak voxel amplitude at all five of these nodes was robustly correlated, which further supports that these regions were functioning in concert (all r ’s > 0.60 and all P ’s < 0.05 , Bonferroni-corrected; Fig. 3). Finally, we investigated the behavioral relevance of these regions by correlating amplitude values extracted from each peak voxel with task accuracy. After Bonferroni correction, only activity in the r-SPC ($r = 0.62$, $P = 0.005$, Bonferroni-corrected; Fig. 3) and l-SPC ($r = 0.55$, $P = 0.035$, Bonferroni-corrected) was found to significantly predict accuracy on the task, such that a stronger neural response in these regions (i.e., a greater decrease from baseline) was related to worse task performance (i.e., lower accuracy).

Regions of the Frontoparietal Network Mediate the Behavioral Impact of 10 Hz Entrainment

Since the above analyses indicated that the two superior parietal peaks were the most relevant nodes in this frontoparietal network for task performance, we performed a mediation analysis in which each of these regions (i.e., left and right) was the prospective mediator between the entrainment cueing ratio and task accuracy. Upon the addition of activity values from

Figure 3. Frontoparietal network covariance with cueing effects and behavior. (Top) Whole-brain covariance maps of the entrainment cueing effect and response amplitude, with significant peaks in the right dorsolateral prefrontal, right primary motor, midcingulate, and bilateral superior parietal cortices. A color scale bar depicting the statistical significance is displayed in the upper left. (Bottom left) Covariance matrix representing the intranetwork covariance of all network nodes is mentioned above. The correlation coefficient representing the amplitude relationship between each set of regional peaks is indicated by the scale bar on the right, and the individual effect size (r) for each relationship is overlaid on its appropriate square. (Bottom right) Correlation plot showing the relationship between accuracy (on the y-axis, denoted in % correct trials) and response amplitude in the right superior parietal region (denoted on the x-axis in pseudo-t). A line of best-fit and the covariance coefficient for the relationship are overlaid on the plot.

each of the superior parietal peaks, the relationship between cueing effects on entrainment and task performance became nonsignificant, indicating a full mediation. After testing each indirect effect with a statistically stringent bootstrapping procedure, activity in both the l-SPC ($b = -0.68$, $P = 0.029$, 95% CI = -1.42 , -0.07) and r-SPC ($b = -0.99$, $P = 0.008$, 95% CI = -1.80 , -0.25 ; Fig. 4) was found to significantly mediate the relationship between the entrainment cueing ratio and visual perceptual abilities (i.e., task accuracy).

Discussion

In this study, we used a modified Posner attention cueing paradigm that included a 10-Hz flicker component to perturb visual perceptual networks during task performance, while simultaneously measuring the neural dynamics underlying these perturbations. En masse, our findings support both the role of alpha oscillations in functional inhibition of visual perception, as well as a powerful interference effect on frontoparietal attention networks by 10 Hz entrainment. More specifically, we found that increased cue-biasing of neural entrainment responses toward the attended hemifield was related to reduced task accuracy. In

other words, participants with higher 10 Hz entrainment over the visual field of the to-be-presented stimulus exhibited impaired visual perception. Additionally, this cueing effect covaried robustly with activity in a network of frontoparietal regions, and activity in this network fully mediated the relationship between the entrainment cueing effect and visual impairment. In sum, these results support not only the functionally inhibitory role of 10 Hz activity in visual cortices but also the ability of interfering inhibition in these visual networks to propagate to “higher order” networks and thereby impair visual perception.

Numerous studies have suggested that alpha-frequency oscillations in visual cortices reflect a functionally inhibitory signal (Kelly et al. 2006; Rihs et al. 2007; van Dijk et al. 2008; Jensen and Mazaheri 2010; Romei et al. 2010; Foxe and Snyder 2011; Handel et al. 2011; Spaak et al. 2014; Heinrichs-Graham and Wilson 2015; Proskovec et al. 2016; Wiesman et al. 2016; Gulbinaite et al. 2017; Wilson et al. 2017), and our data clearly support this conceptualization. Namely, when entrainment was stronger in the attended hemisphere, the participant was less accurate, signifying that attentional biasing toward entrainment in the attended hemifield interfered with subsequent visual perception of the probe stimulus. Importantly, the

Figure 4. Amplitude of the right superior parietal response mediates the relationship between cueing effects and behavior. A graphical representation of one of the mediation models and results. Regression coefficients representing the statistical relationships between each measure are positioned over each arrow, and the mediated coefficient for the relationship between the cueing effect and task accuracy (accounting for the effect of right superior parietal amplitude) is presented in parentheses. This mediation effect was significant after statistically stringent bootstrapping analysis ($P = 0.008$). An identical mediation analysis using amplitude in the left superior parietal peak as the mediator found similar effects.

current framework provides a robust experimental and analytical method to test this relationship, as the normalization of the attended entrainment response to an unattended response within each participant removes the potentially confounding effects of differences in overall task engagement. Supporting this, bilaterally averaged entrainment amplitude (i.e., regardless of attentional cueing) exhibited a relationship with task accuracy in the opposite direction, suggesting that task engagement between participants also affected performance, as would be expected.

Although most studies have found visual gating by alpha inhibition to be beneficial for performance on higher order cognitive tasks (e.g., working memory), a smaller subset has shown that enhancing alpha-frequency oscillatory activity at inopportune times can also significantly impair behavior, which is in line with our findings. In particular, a number of experiments using flickering visual stimuli to entrain primary visual cortex have shown that alpha-frequency entrainment impairs visual perceptual abilities (Spaak et al. 2014; Gulbinaite et al. 2017). However, the system-level mechanism of this alpha interference effect has remained unclear until now. Although some part of this effect is likely due to a modulation of endogenous rhythmic activity in occipital cortices, our results indicate that, at least in the case of an attentional manipulation, the negative relationship between alpha entrainment and visual perception is fully mediated by activity in extravisual regions. More specifically, we found that activity in a set of frontal and parietal regions known to be involved in attention function exhibited substantial covariance with the entrainment cueing ratio, and these regions explained the entirety of the covariance between the cueing effects and task accuracy. The importance of these findings is 2-fold. First, previous studies reporting the widespread spatial distribution of alpha entrainment responses have lacked the spatial precision to identify the cortical generators of these signals reliably. Herein, we show that these generators are components of a well-established top-down regulatory system

involved in attention: the frontoparietal network. Second, the nature of this alpha-specific engagement of anterior cortices has remained elusive. Is it a compensatory mechanism to suppress the interfering effects of alpha entrainment on visual cortex, or evidence of a secondary interference effect that has “propagated” to higher order regions from visual cortices, perhaps due to the pervasive functionality of alpha oscillations across the human brain? Our data strongly support the latter, as the whole-brain analyses indicated that the increase in response amplitude within these regions was driven by attention accentuating entrainment and was a strong negative predictor of task performance. Reinforcing this interpretation and providing new insight on the functional dissociation of the frontoparietal network, our mediation analysis findings further showed that the interfering effects of entrainment on behavior were entirely due to functional disruption in the superior parietal nodes of this network.

Despite the novelty of these findings, our experiment was not without limitations. For instance, the use of a 100% predictive cue during the entrainment period precluded us from examining any potentially unique effects of 10 Hz entrainment on the process of attentional reorienting, which might provide additional insight into the mechanism of alpha entrainment interference. Further, we did not investigate the potential impact of entrainment stimulus phase on these dynamics. The relative phase of ongoing alpha-frequency entrainment has been found to influence visual perceptual abilities (Spaak et al. 2014), and thus presenting our probe stimuli at the trough rather than the peak of the entraining alpha phase might have yielded different results. Future exploration of this possibility is warranted and would help clarify the impact of each parameter. Future studies might also consider the use of complementary neuroimaging and neurostimulation modalities to expand upon these findings. For instance, it would be intriguing to see if these effects could be replicated using alpha-frequency transcranial alternating current stimulation over the occipital cortices. Finally, in light of previous findings in the field, this study investigated only the effects of 10 Hz entrainment on visual perception and attention processes, however it remains possible that other frequencies of entrainment might also interfere with higher order systems. Adding further nuance, frequency variability even “within” the alpha range might influence these effects. For instance, it appears that attention to stimuli flickering in the lower alpha-frequency range (e.g., 8–10 Hz) commonly results in a null or negative effect on the amplitude of the entrainment response (Ding et al. 2006; Kelly et al. 2006; Kim et al. 2007), while the reverse effect (i.e., an enhancement of the response by attention) appears to occur when stimuli flicker at higher alpha-frequencies (e.g., 10–14 Hz; Ding et al. 2006; Müller et al. 2006; Andersen and Müller 2010; Andersen et al. 2012). Additionally, variation in the individual alpha peak frequency between participants has been found to covary with entrainment effects on visual perception (Gulbinaite et al. 2017), which could also potentially influence the effect of visual alpha entrainment at set frequencies. Regardless of these limitations, our finding provide a new understanding of how alpha-frequency visual entrainment affects visual perception and enhance our knowledge of the functional importance of frontoparietal networks in visual attention.

Authors' Contributions

Conceptualization, A.I.W. and T.W.W.; methodology, A.I.W. and T.W.W.; formal analysis, B.R.G. and A.I.W.; resources, A.I.W. and

T.W.W.; data curation, A.I.W. and T.W.W.; writing—original draft, A.I.W.; writing—review and editing, A.I.W., B.R.G., and T.W.W.; visualization, A.I.W. and B.R.G.; supervision, T.W.W.; funding acquisition, A.I.W. and T.W.W.

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