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Alpha Synchrony and the Neurofeedback Control of Spatial Attention

Highlights

- Subjects learn to control alpha synchrony in left versus right parietal cortex
- Modulation of alpha synchrony causes a spatial bias in visual processing
- Attentional bias persists even after neurofeedback training
- Alpha synchrony plays a causal role in modulating attention and visual processing

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In Brief

During MEG neurofeedback training, subjects learned to manipulate the degree of alpha synchrony over the left versus right parietal cortex. The change in alpha synchrony was associated with a corresponding bias in visual processing and attention in the corresponding visual field.

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Alpha Synchrony and the Neurofeedback Control of Spatial Attention

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SUMMARY

Decreases in alpha synchronization are correlated with enhanced attention, whereas alpha increases are correlated with inattention. However, correlation is not causality, and synchronization may be a by-product of attention rather than a cause. To test for a causal role of alpha synchrony in attention, we used MEG neurofeedback to train subjects to manipulate the ratio of alpha power over the left versus right parietal cortex. We found that a comparable alpha asymmetry developed over the visual cortex. The alpha training led to corresponding asymmetrical changes in visually evoked responses to probes presented in the two hemifields during training. Thus, reduced alpha was associated with enhanced sensory processing. Testing after training showed a persistent bias in attention in the expected directions. The results support the proposal that alpha synchrony plays a causal role in modulating attention and visual processing, and alpha training could be used for testing hypotheses about synchrony.

INTRODUCTION

A major function of attention is to filter out distracting information. Some of the proposed mechanisms for this filtering include modulation of firing rates and synchronization of activity both within and across brain structures involved in control of attention as well as sensory processing areas. Increases in alpha synchrony in particular are associated with a decrease in neuronal excitability (Lange et al., 2013), gamma synchronization (Spaak et al., 2012; Voytek et al., 2010), and the blood-oxygen-level-dependent (BOLD) signal (Scheeringa et al., 2011). Alpha synchrony appears to influence sensory processing both during stimulus presentation as well as during the pre-stimulus interval (Herrmann and Knight, 2001). It has been proposed as a mechanism for inhibiting processing of irrelevant sensory and task information, possibly by gating the flow of information across different brain structures (Jensen and Mazaheri, 2010). In human electroencephalography (EEG) and magnetoencephalography (MEG) studies, a correlation between covert attention and lateralized parietal alpha oscillations (8–12 Hz) has long been established (Foxe et al., 1998, 2005; Worden et al., 2000; Snyder and Foxe, 2010; Banerjee et al., 2011; Zumer et al., 2014; Klimesch, 2012; Jensen and Mazaheri, 2010; Fu et al., 2001; Feng et al., 2017). Increased alpha synchrony in one hemisphere is associated with reduced attention in the contralateral visual field, whereas decreased alpha is correlated with perceptual alertness and attention in the contralateral field.

Similarly, when monkeys attend to a stimulus in the receptive field of cells in the visual cortex, these cells give enhanced responses to visual stimuli, and there is an increase in gamma synchrony accompanied by a reduction in alpha synchrony, as measured with the local field potentials (LFP) or with spike-field synchrony at the cellular level (Bollimunta et al., 2011; Fries et al., 2001). Alpha synchrony has been reported to be especially strong in the deep layers of the cortex (Buffalo et al., 2011), but it has been reported in the superficial layers as well (Bollimunta et al., 2011). Modeling shows that alpha synchrony derived from specific synaptic mechanisms may play a role in blocking unwanted information from the cortex (Vijayan and Kopell, 2012). However, correlation does not prove causality, and it is very possible that alpha synchrony plays no causal role in attention or preferential processing of attended targets versus distracters.

If the association between alpha laterality and spatial attention is mechanistically relevant, then it should be possible to experimentally manipulate spatial attention by modulating alpha laterality. In animal studies, one might attempt to test a causal role of alpha using optogenetic or electrical stimulation at alpha frequencies in animals, but direct stimulation is artificial and may synchronize population activity at far greater levels than found under normal physiological conditions. Depending on the type of genetic targeting, populations of heterogeneous types of cells will fire with short latency and little variability in response to a light pulse in optogenetic studies using CHR2, for example (Cardin et al., 2010), and it is also difficult to induce synchrony with stimulation without affecting other relevant circuit properties, including firing rates (Cardin et al., 2010). However, there has been some progress in reducing these effects using low (theta) frequencies and low-power stimulation (Nandy et al., 2019). In humans, the most direct evidence of causality of alpha in attention has been obtained from non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) (Romei et al., 2010; Thut et al., 2011) or transcranial

alternating current stimulation (Neuling et al., 2013). The results from these studies support the proposed suppressive role of alpha. However, these methods have some of the same limitations as stimulation studies in animals, including widespread effects or nonspecific synchronization in neural populations.

Although all methods for testing causality suffer from limitations, neurofeedback might potentially influence neural activity in a way that is closer to the normal state. In monkeys, neurofeedback of activity in frontal eye fields has been used to control the animal's attention in a way that resembles the normal state (Schafer and Moore, 2011). In humans, neurofeedback can be based on a measure of neural activity acquired from EEG, MEG, or fMRI, which is presented to a participant in real time through sensory feedback (for a review, see Sitaram et al., 2017; Thibault et al., 2016; Ros et al., 2014). Neurofeedback provides a unique opportunity to endogenously modulate neural activity as an independent variable and to search for variations in cognitive processes as a dependent variable (Sitaram et al., 2017). A large number of physiological phenomena have been reported that can come under voluntary control by neurofeedback, including single-neuron firing rates recorded by intracranial electrodes in epilepsy patients (Cerf et al., 2010), spike-related calcium signals recorded with two-photon imaging (Clancy et al., 2014), local field potentials (Engelhard et al., 2013), fMRI signals (deBettencourt et al., 2015), and brain oscillations recorded by EEG/MEG (Sudre et al., 2011; Vernon, 2005). Thus, it could be a promising approach to study the causality of alpha oscillations in attention.

EEG and MEG neurofeedback with high temporal resolution has been used to modify the power of brain oscillations in the frequency range of alpha (Hanslmayr et al., 2005), theta (Shoji et al., 2017), beta (Doppelmayr and Weber, 2011), and gamma (Chauvière and Singer, 2019; Merkel et al., 2018). In this study, we used MEG neurofeedback to elucidate the causal relationship between alpha synchrony and spatial attention. Alpha was recorded predominantly from the parietal cortex, which is known to play an important role in the control of attention. The parietal cortex is also a major source of alpha synchrony in EEG studies.

The most relevant study to our work is by Okazaki et al. (2015), which also used MEG neurofeedback to train participants to modulate alpha hemispheric asymmetry. However, the subjects in that study were explicitly instructed to attend to the extrafoveal stimuli presented in the left or right visual field during training, whereas alpha power was used to modulate the visibility of the attended stimuli. Given that participants practiced spatial attention during neurofeedback, it is not clear whether a bias in attention was the cause or effect of the alpha modulations during training.

In the present study, we used a task without any component of spatial attention in either the task or explicit instructions so that alpha could be manipulated independently. We developed a paradigm to train subjects to modify the relative alpha power recorded from the left versus right parietal cortex while performing a task at fixation. The task did not involve directing attention to either hemifield, and there were no explicit instructions given to the subjects regarding spatial attention. During the neurofeedback training, we tested for effects on visual processing of irrelevant probes. Finally, we asked whether there were persistent behavioral effects on attention even after training. For this, we compared performance in a classic Posner paradigm (Posner, 1980) and a free-viewing task before and after neurofeedback training.

RESULTS

Subjects (N = 20) were trained using MEG neurofeedback to manipulate relative alpha power over the parietal cortex in the left versus right hemisphere. The asymmetry in alpha power over the left versus right parietal cortex was used to modulate the contrast of stimuli used in a "match-to-sample" task presented at the center of gaze. To perform the task, the subjects learned to modulate their alpha asymmetry so that the stimuli were visible.

The subjects were divided into two groups, the left neurofeedback training (LNT) group and right neurofeedback training (RNT) group, consisting of 10 participants each. The LNT group was trained to increase alpha power in the left relative to the right parietal cortex and vice versa for the RNT. Because increased alpha is associated with inattention, the increased alpha power in the left parietal cortex compared with the right parietal cortex was hypothesized to suppress visual processing and reduce spatial attention specifically in the right (contralateral) hemifield compared with the left hemifield. Consequently, the LNT was expected to enhance visual processing and attention to the left hemifield compared with the right hemifield. The RNT group was hypothesized to have the opposite effect after training. Because the task was presented at the center of gaze, any processing bias to the right versus left hemifield was not expected to influence task performance. Any left versus right processing biases were assessed separately with probe stimuli, as described later.

The neurofeedback phase lasted 25–30 min and comprised 100 neurofeedback trials. On each trial, subjects performed an orientation match-to-sample task with foveally presented gratings. Neurofeedback was given during the sample grating presentation on each trial. Subjects were instructed to fixate on the center of the screen and use "mental effort" to increase the contrast and, hence, the visibility of the sample grating pattern after the color of the fixation cross turned to black. Therefore, the visibility of the sample grating was actually determined by alpha asymmetry (for details, see STAR Methods). Importantly, subjects were not given any instructions for covertly directing spatial attention but, rather, had to keep their focus of attention on the central stimulus. At the end of the neurofeedback period, the sample grating was removed from the screen, and after a 3-s delay period, the second test grating appeared in full contrast in an orientation that was either same or ±5° tilted away from the first grating. Participants reported whether the orientation of the test grating matched the one of the sample grating (Figure 1B).

The neurofeedback was based on MEG signals recorded on each trial, which were stored in an online buffer and divided in real time into 500-ms data segments. Each data segment was used to compute alpha power from parietal sensors and estimate an alpha asymmetry index (AAI). The AAI was calculated as the alpha power of ipsilateral minus contralateral sensors to the training direction, normalized by their sum. This AAI value

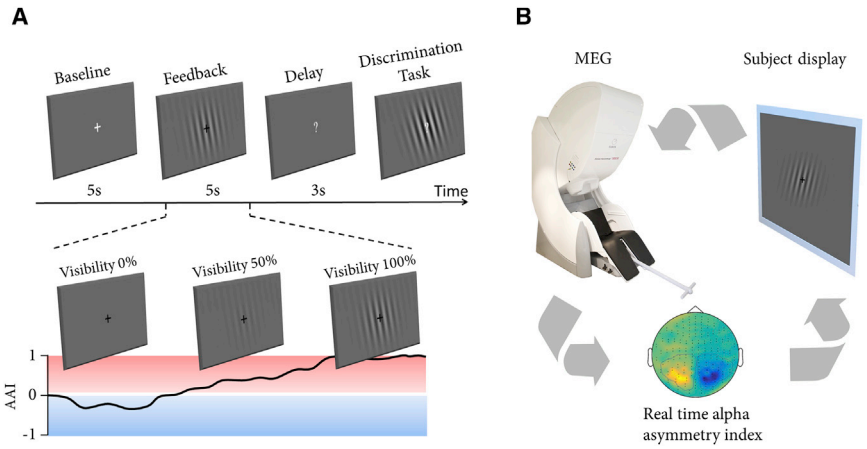

Figure 1. Neurofeedback Setup

(A) Each neurofeedback trial included a 5-s baseline followed by a 5-s neurofeedback part during which the real-time alpha asymmetry index (AAI) controlled the visibility of a grating pattern presented at the center of the screen. Negative AAI was set to 0% visibility, and positive AAI was set to linearly determine visibility from 0% to 100%. Participants were instructed to fixate on the center of the screen and use mental effort to increase the visibility of the grating pattern when the color of the fixation cross turned to black. At the end of the neurofeedback part, the grating pattern was removed from the screen, and following a 3-s delay period, a second grating pattern appeared in full visibility with orientation the same or ±5° different from the first grating pattern. Participants performed a 2-alternative forced choice task, reporting whether the orientation of the two grating patterns matched.

(B) During neurofeedback, MEG data were stored in an online buffer and divided in real time into 500-ms data segments. Each data segment was used to compute alpha power from parietal sensors and to estimate the AAI, whose value determined the visual feedback to the subject. This feedback cycle was updated every 500 ms.

determined the contrast (i.e., the visibility) of the sample grating shown to the subject. This feedback cycle was updated every 500 ms (Figure 1A). Each neurofeedback trial included a 5-s baseline followed by a 5-s neurofeedback period during which the real-time AAI controlled the visibility of a grating pattern presented at the center of the screen. Negative AAI was set to 0% visibility, and positive AAI values linearly determined visibility from 0% to 100%.

Despite the difficulty of the neurofeedback task, requiring concentration for a prolonged time, participants performed the discrimination task consistently above chance (percent correct ± SEM = 73.92% ± 4% and sensitivity index d' ± SEM = 1.7 ± 0.3).

Neurofeedback Training Enabled Online Control of Alpha Power over the Parietal Cortex

We first assessed whether subjects were able to control parietal alpha lateralization during the neurofeedback trials. MEG data from the training session were mapped onto subject-specific cortical reconstructions using a dynamic statistical parametric mapping (dSPM) approach (Dale et al., 2000; Hämäläinen and Ilmoniemi, 1994). The cortical activation maps were then transformed to time-frequency power maps in the alpha range (8–12 Hz) using complex Morlet wavelets (Tallon-Baudry and Bertrand, 1999), and the resulting power maps were averaged over trials separately for the LNT and the RNT group.

The time course of alpha power from the left and the right parietal cortex confirmed that participants could successfully modulate the laterality of alpha power in the desired direction (Figures 2A and 2B, left panels). We focused on the asymmetry of alpha power rather than the absolute magnitude because alpha power might be modulated by nonspecific influences, such as arousal. However, an examination of the individual data suggested that 45% of the participants modulated alpha by increasing their alpha in the ipsilateral hemisphere, 30% by reducing alpha in the contralateral hemisphere, and 25% with a combination of both increases and decreases. Overall, alpha power over the ipsilateral parietal cortex was stronger than contralateral alpha power, consistent with training during the neurofeedback period (two-sided permutation test, n = 10 for the LNT group and n = 10 for the RNT group, false discovery rate [FDR] corrected across time, FDR-adjusted $p < 0.05$).

To test for effects of training on the power at other frequencies, we computed the power spectral density (PSD) during the neurofeedback period (0.5–4.8 s). The PSD of the parietal cortex (Figures 2A and 2B, right panels) revealed not only alpha asymmetry but also significant gamma asymmetry (two-sided permutation test, FDR-adjusted $p < 0.05$, FDR corrected across frequencies, n = 10 for the LNT group and n = 10 for the RNT group). This gamma asymmetry was in the opposite direction as the alpha asymmetry; that is, contralateral gamma power was stronger than ipsilateral gamma power. A reciprocal relationship between alpha and gamma has also been found in animal studies of attention (Zhou et al., 2016). Although gamma asymmetry was indirectly affected by training, there was no significant correlation between gamma and alpha asymmetry across subjects ($r = -0.37$, $p = 0.1$, n = 20).

The PSD of other cortical regions in the occipital, frontal, and temporal cortex (Figure S1) confirmed that significant alpha asymmetry and gamma asymmetry were also found in the lateral occipital cortex (two-sided permutation test, FDR corrected for multiple comparisons, FDR-adjusted $p < 0.05$, n = 10 for the LNT group and n = 10 for the RNT group), consistent with the idea that synchronous feedback from the parietal cortex may have modulated synchrony in the visual system. However, there was no significant frequency asymmetry in the frontal and temporal cortices (two-sided permutation test, FDR corrected for multiple comparisons, n = 10 for the LNT group and n = 10 for the RNT group).

To probe the time course of the training effects, we tested whether alpha asymmetry was higher toward the end than the beginning of the training session. For this, we created cortical

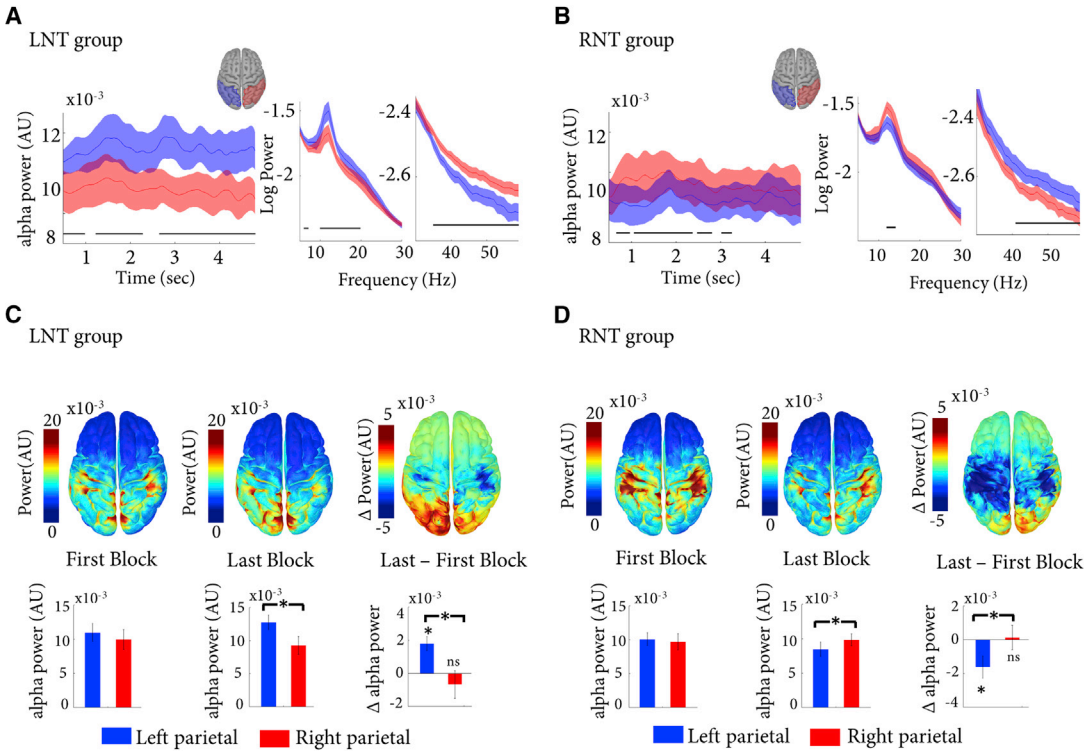

Figure 2. Modulation of Alpha Power during Neurofeedback

(A) Left panel: time course of alpha power averaged across all trials (k = 100) during neurofeedback (0.5–4.8 s) from the left (blue) and right (red) parietal cortex for the LNT group. Right panel: power spectra of the left (blue) and right (red) parietal cortex during neurofeedback averaged across all trials (k = 100) for the LNT group. Shaded regions denote SEM; lines below curves indicate time points of significant difference for the time series and frequency points of significant difference for the power spectra (n = 10 for the LNT group and n = 10 for the RNT group, two-sided permutation test, $p < 0.05$, FDR corrected for multiple comparisons).

(B) The same as (A) but for the RNT group.

(C) First row: cortical maps of alpha power averaged during neurofeedback for the first block of trials (k = 25 trials), the last block (k = 25 trials), and their difference for the LNT group. Second row: bar plots show the left (blue) and right (red) parietal alpha power for the first block and last block and their difference for the LNT group. Error bars denote SEM; asterisks above and between bars denote statistical significance (two-sided permutation test, $p < 0.05$, FDR corrected for multiple comparisons, n = 10 for the LNT group and n = 10 for the RNT group).

(D) The same as (C) but for the RNT group.

maps of alpha power separately for the first block (first 25 trials) and last block (last 25 trials) and their difference for each group separately (Figures 2C and 2D).

We found no significant alpha asymmetry for the first block of trials for both the LNT group (two-sided permutation test, p = 0.066, Cohen's d = 0.7, n = 10) and the RNT group (two-sided permutation test, p = 0.59, Cohen's d = 0.19, n = 10) (Figures 2C and 2D, left panels). In contrast, alpha power asymmetry of the last block of trials increased in both groups toward the desired direction (two-sided permutation test, p = 0.002, Cohen's d = 1.45, for the LNT group, n = 10; p = 0.008, Cohen's d = 1.44, for the RNT group, n = 10) (Figures 2C and 2D, center panels). The difference between the last and the first blocks showed that alpha asymmetry was enhanced toward the end of the neurofeedback session (two-sided permutation test, p = 0.003, Cohen's d = 1.2 for the LNT group, n = 10; p = 0.007, Cohen's d = 0.88, for the RNT group, n = 10). Interestingly, in both groups, the left parietal cortex was the primary drive for these modulations. In the LNT group, the left parietal alpha increased (p = 0.01, n = 10, two-sided permutation test), but the right parietal alpha did not change (p = 0.16, n = 10, two-sided permutation test). In the RNT group, the left parietal alpha decreased (p = 0.04, n = 10, two-sided permutation test), but the right parietal alpha did not change (p = 0.8, n = 10, two-sided permutation test).

Overall, neurofeedback training successfully modulated hemispheric alpha asymmetry over the parietal cortex in both the LNT and RNT groups in the desired direction, with the effect being stronger at the end of the training session (see Figure S2A for the distribution of AAI across all participants). In both groups, alpha asymmetry was primarily driven by modulations in the left parietal cortex, whose alpha activity increased in the LNT group and decreased in the RNT group, whereas alpha power in right parietal cortex did not change. Further, even though neurofeedback was given only for alpha asymmetry, we also observed hemispheric lateralization in the gamma band in the direction opposite to the alpha band, suggesting a mechanistic relationship between reduced alpha and enhanced gamma power.

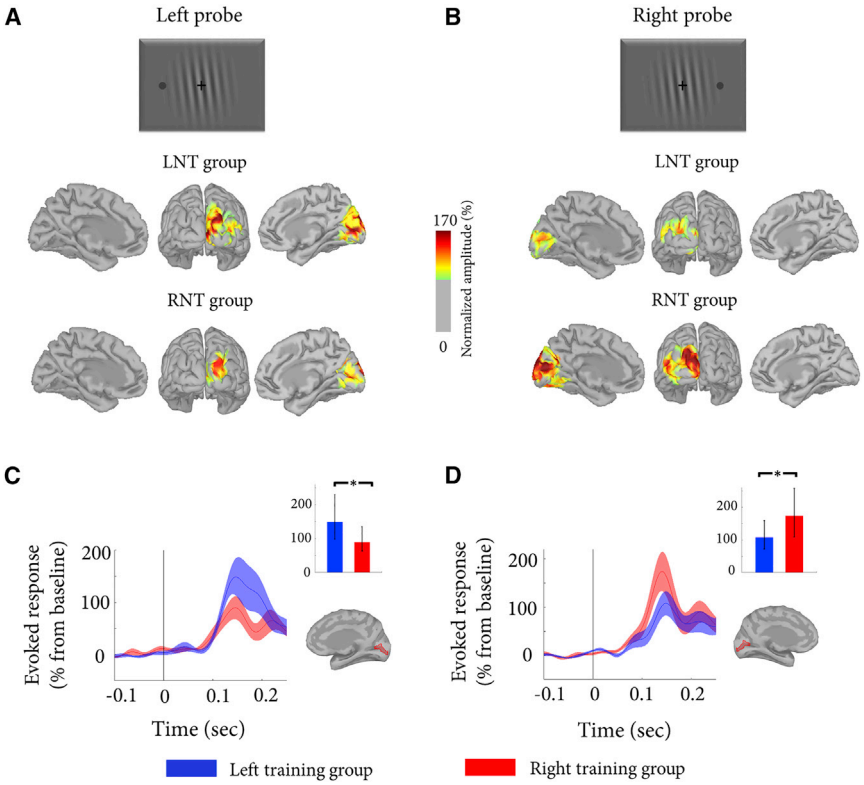

Figure 3. Probe-Related Evoked Response during Neurofeedback

(A) Cortical maps of left probe evoked response in the LNT group (top panel) and RNT group (bottom panel), averaged between 100–200 ms from probe onset.

(B) The same as (A) but for the right probe.

(C) Time course of left probe evoked response in right evoked response for the LNT (blue curve) and the RNT (red curve) groups. The inset shows the peak amplitude for the evoked responses.

(D) The same as (C) but for the right probe.

n = 10 for the LNT group and n = 10 for the RNT group; for the time series, shaded regions denote SEM; gray vertical lines indicate probe onset. The bar plots were evaluated with bootstrap tests for 95% confidence intervals and hypothesis tests using the percentile method; $p < 0.05$; error bars denote 95% confidence interval; and asterisks between bars denote statistical significance.

Last, alpha and gamma asymmetry extended beyond the parietal cortex to the occipital cortex but not to the temporal or frontal cortex, indicating that the changes did not encompass the entire hemisphere.

Neurofeedback Training Biases Online Visual Processing

To test whether the modulation of alpha power over the parietal cortex caused a spatial bias in visual processing during neurofeedback, consistent with directing attention, we intermittently presented a task-irrelevant probe stimulus in either the left or right hemifield on random trials. The probe appeared toward the end of the neurofeedback period of each trial. Subjects were instructed to ignore the probe and stay focused on the neurofeedback task. The visually evoked response elicited by the task-irrelevant probe served as an index of visual processing in each hemifield.

To test for changes in the processing of the probe, we estimated the cortical maps and the time courses of visually evoked responses elicited by the left and right probes for each training group separately (Figure 3). Consistent with the retinotopic organization of the visual cortex, the results show that the evoked responses were lateralized over the visual cortex contralateral to the hemifield containing the probe (Figures 3A and 3B).

The peak amplitude of the left probe evoked response was larger ($p = 0.0065$, percentile test, n = 10 for the LNT group and n = 10 for the RNT group) for the LNT group (mean, 148.94; 95% confidence interval, 99.59–234.58) than for the RNT group (mean, 89.85; 95% confidence interval, 63.47–134.88) (Figure 3C). In contrast, the peak amplitude of the right probe evoked response was smaller ($p = 0.03$, percentile test, n = 10 for the LNT group and n = 10 for the RNT group) for the LNT group (mean, 107.67; 95% confidence interval, 71.72–159.24) than for the RNT group (mean, 255.53; 95% confidence interval, 109.42–255.53) (Figure 3D). However, there was no significant correlation between the amount of alpha asymmetry and the asymmetry in the amplitude of the evoked responses ($r = -0.19$, $p = 0.41$, n = 20) (Figure S5A).

Overall, we found a stronger evoked response for the probe delivered ipsilateral than contralateral to the training direction (see Figure S2B for the distribution of evoked response peak asymmetry across all participants). This is consistent with a bias in visual processing in favor of the hemifield corresponding to the parietal cortex with lower alpha power.

Neurofeedback Training Causes Sustained Modulation of Spatial Attention

In the previous section, we found that alpha asymmetry over the parietal cortex caused an immediate bias in visual processing during the time participants performed the neurofeedback task, consistent with a bias in attention. Next, we explored whether the training affected alpha power and performance even after the training period.

In a subset of neurofeedback participants (n = 7 for the LNT group and n = 7 for the RNT group), we also collected MEG data in a Posner cueing paradigm (Mangun and Hillyard, 1991; Posner, 1980) both immediately before (pre-training phase) and after (post-training phase) neurofeedback training. We hypothesized that neurofeedback might cause a prolonged bias in attention and behavioral responses toward the visual field related to the hemisphere with reduced alpha power during training. The Posner cueing task is associated with an overall reduction in alpha, with a greater reduction in the hemisphere

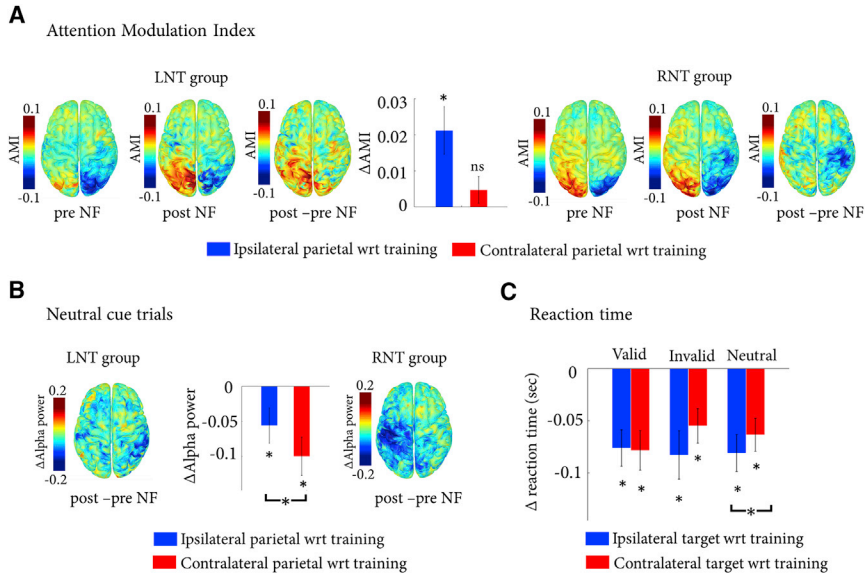

Figure 4. Effect of Neurofeedback on Neural and Behavioral Responses in the Posner Task

(A) Cortical map of the attention modulation index (AMI) pre-training and post-training and their difference for the LNT group (left panel) and the RNT group (right panel). The cortical maps were derived from the time interval from 0–1.3 s, with cue onset at time 0 s. The bar plot shows the difference in AMI post- versus pre-training in the ipsilateral and contralateral parietal cortex with respect to the neurofeedback training direction.

(B) Cortical maps of the difference in alpha power in the neutral trials post- minus pre-training in the LNT group (left panel) and the RNT group (right panel). The bar plots summarize the difference in alpha power in neutral trials post- minus pre-training in the ipsilateral and contralateral parietal cortex with respect to the neurofeedback training direction.

(C) Difference of reaction time post- minus pre-training (Δ reaction time) in the valid, invalid, and neutral Posner task conditions separately for the ipsilateral and contralateral targets with respect to the training direction.

N = 7 for the LNT and N = 7 for the RNT groups; for the bar plots, error bars denote SEM, and asterisks below and between bars denote statistical significance; $p < 0.05$, two-sided permutation test, FDR corrected for multiple comparisons.

contralateral to the attended visual hemifield (Foxe et al., 1998, 2005; Worden et al., 2000; Snyder and Foxe, 2010; Banerjee et al., 2011; Zumer et al., 2014), but we expected that potentially long-lasting effects of the neurofeedback training would interact with the cueing effects of the Posner task.

To evaluate the effects of training on alpha power in the Posner cueing task, we first defined an attention modulation index (AMI), calculated as the alpha power for left-cued minus right-cued trials, normalized by their sum: AMI = $(\alpha_{\text{leftcue}} - \alpha_{\text{rightcue}})/(\alpha_{\text{leftcue}} + \alpha_{\text{rightcue}})$. By computing the AMI for each cortical location separately, we constructed cortical maps of AMIs for both the pre-training and the post-training phase of the Posner paradigm. For both the LNT and RNT groups, and in both pre-training and post-training phases, the AMI cortical maps were positive in the left parietal cortex and negative in the right parietal cortex (Figure 4A), consistent with changes following an attentional cue found in previous Posner cueing studies (Banerjee et al., 2011; Foxe et al., 2005; Snyder and Foxe, 2010; Zumer et al., 2014).

To test whether the AMI changed because of neurofeedback, we also computed the difference Δ AMI = $\text{AMI}_{\text{post}} - \text{AMI}_{\text{pre}}$ (Figure 4A). We found that the AMI for the LNT group increased in the left parietal cortex in the post-training compared with the pre-training phase, consistent with a training effect in that hemisphere, whereas it did not change in the right parietal cortex. By contrast, the AMI for the RTN group decreased in the right parietal cortex in the post-training compared with the pre-training phase, consistent with the training in that hemisphere, whereas it did not change in the left parietal cortex. Overall, we found AMI changes only in the parietal cortex ipsilateral ($p = 0.018$) to the training direction and no changes in the parietal cortex contralateral ($p = 0.25$) to the training direction. This is summarized in the Figure 4A bar plot, which shows the averages of AMI changes within the parietal cortex ipsilateral and contralateral to the training direction (n = 14, non-parametric two-sided permutation test, FDR corrected for multiple comparisons). Thus, the effect of feedback training on alpha appears to interact with the Posner task performed after training.

To evaluate alpha effects in neutral cue trials, we estimated the changes in alpha power for the attention delay period with respect to the baseline period at each location for the post- and pre- training phases as follows: $(\alpha_{\text{attention delay}} - \alpha_{\text{baseline}})/(\alpha_{\text{attention delay}} + \alpha_{\text{baseline}})$. We compared the alpha power map in the pre-training phase with the post-training phase (Figure 4B). The results show that alpha power decreased in both hemispheres in the post- compared with the pre-training phase. Although there were no significant alpha asymmetry changes in the neutral trials in the pre-training phase ($p = 0.2$, n = 14, non-parametric two-sided permutation test), there was change in alpha asymmetry post-training compared with pre-training, in agreement with the expected training effect. Specifically, in the LNT group, alpha power decreased more in the right than in the left parietal cortex, and in the RNT group, alpha power decreased more in the left than in the right parietal cortex (Figure 4B). We summarize this effect in the Figure 4B bar plot, which shows that the contralateral parietal cortex (i.e., in the training direction) had a higher drop in alpha power than the ipsilateral parietal cortex (non-parametric two-sided permutation test, n = 14, FDR corrected for multiple comparisons, non-corrected $p = 0.006$, FDR-adjusted $p = 0.01$, Cohen's $d = 0.95$) because of training.

To assess whether the effects of neurofeedback on alpha also influenced behavior in the Posner cueing paradigm, we analyzed the reaction time (RT) of behavioral responses separately for targets ipsilateral and contralateral to the training direction. We compared RTs in the pre-training phase for the valid,

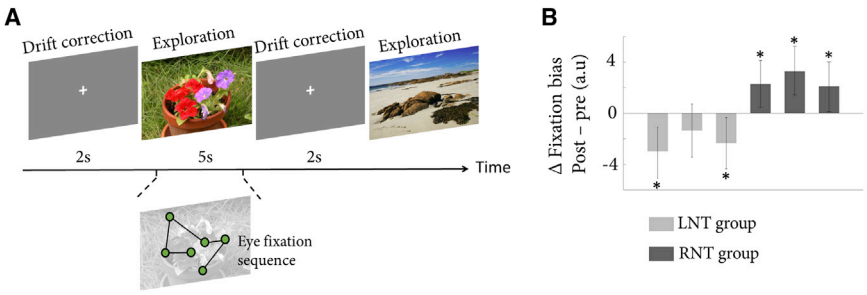

Figure 5. Effect of Neurofeedback on a Free-Viewing Task

(A) The free-viewing task required participants to explore a series of 60 static images presented for 5 s each.

(B) Difference in fixation bias post- versus pre-training for 3 LNT participants and 3 RNT participants. Negative values indicate bias to the left and positive values bias to the right. Bars denote individual participants, and error bars denote 95% confidence intervals computed with bootstrap tests. Asterisks above bars indicate significant values ($p < 0.05$, two-sided Wilcoxon rank-sum test, FDR corrected for multiple comparisons).

invalid, and neutral trials with the corresponding RTs in the post-training phase (Δ RT = $RT_{post} - RT_{pre}$) (Figure 4D). We found negative Δ RT in all cases, as expected, because of practice effects. Although there were no significant neurofeedback effects in ipsilateral versus contralateral hemifields for the valid (FDR-adjusted p = 0.7) and invalid (FDR-adjusted p = 0.1) trials, we found that RT in the neutral trials became faster for targets in the hemifield ipsilateral to the training direction (non-parametric two-sided permutation test, n = 14, FDR corrected for multiple comparisons, non-corrected p = 0.01, FDR-adjusted p = 0.04, Cohen's d = 0.82). A correlation analysis showed that participants who had the largest changes in alpha asymmetry (end – beginning) tended to have a larger reaction time difference in the neutral trials ($r = -0.58$, p = 0.02, n = 14) (Figure S5B). Thus, training caused a measurable behavioral bias on the neutral trials, which did not have any top-down spatial cue. In contrast, the training effects were apparently not sufficient to overcome the strong bias in behavioral responses caused by a spatial cue for both valid and invalid trials.

Overall, we found that neurofeedback training resulted in sustained modulation of spatial attention tested in the post-training phase. We found both neural and behavioral effects consistent with the training direction.

Neurofeedback Training Resulted in a Horizontal Bias in Free-Viewing Behavior

In the previous section, we showed that alpha training caused sustained neural and behavioral effects on covert attention, but the behavioral effects following training were only found on trials without a strong, top-down spatial cue (i.e., neutral trials). To test whether such a bias could be found in other behaviors without a top-down cue, we examined free-viewing behavior following training in a small number of subjects. For this test, a subset of neurofeedback participants who did not perform the Posner task (N = 3 for the LNT group and N = 3 for the RNT group, see Figure S4 for individual data) performed a free-viewing task both before (pre-training) and after (post-training) neurofeedback training. The free-viewing task comprised 60 trials, each beginning with a fixation cross at the center of the screen followed by presentation of a novel image for 5 s (Figure 5A). Images depicted natural outdoor scenes, urban public spaces, or computer-generated fractal shapes (Ossandón et al., 2014). Participants were instructed to carefully explore all images.

We used high-resolution eye tracking data to measure the eye fixation sequence for each image separately. We then estimated each participant's fixation bias, defined as the difference between the percentages of leftward versus rightward fixations. To evaluate whether the fixation bias was different between pre- and post-training, we subtracted the pre-training from the post-training fixation bias (Figure 5B); thus, negative values indicated leftward bias, and positive values indicated rightward bias. Of the six subjects who performed this experiment, five showed a significant bias toward the hemifield ipsilateral to the training direction ($P_1 = 0.008$, $P_2 = 0.17$, $P_3 = 0.02$, $P_4 = 0.03$, $P_5 = 0.006$, $P_6 = 0.04$; two-sided Wilcoxon rank-sum test, FDR-adjusted p values).

We found a leftward bias for the LNT group and a rightward bias for the RNT group. Thus, neurofeedback training achieved sustained modulation of spatial attention not only in covert attention in the Posner cueing paradigm but also in free-viewing behavior.

Eye Tracking Data Reveal Orientation of Spatial Attention in the Posner Task but Not Neurofeedback

Despite the desired training effects described above, it is not clear how participants learned to control their brain activity with contingent feedback, given the absence of any explicit instruction. We hypothesized that participants learned to self-regulate neural activity (that is, alpha asymmetry) relying on the feedback signal without an explicit attention-related mental strategy. However, it seems possible that participants searched for an effective mental strategy and determined that deploying covert attention in one direction or another would control the feedback signal, even though the task-related grating stimuli during training were presented at fixation. This strategy might have caused the modulation in alpha asymmetry observed in the data. To test for this, we analyzed eye tracking data from the Posner cueing task to determine any shifts in fixation caused by covert spatial attention (Engbert and Kliegl, 2003; Lowet et al., 2018) and compared the pattern of eye movements to the pattern in the neurofeedback task.

We measured horizontal fixation biases during the attention delay period of the Posner cueing task (after onset of the spatial cue and before appearance of the target) for the left cue, right cue, and neutral trials separately. We found that there was a significant leftward fixation bias (p = 0.007, n = 8) when cued for attention to the left and a significant rightward fixation bias

($p = 0.007$, $n = 8$) when cued for attention to the right but no significant bias ($p = 0.2$, $n = 8$) in neutral trials ($p < 0.05$, two-sided Wilcoxon signed-rank test) (Figure S3A). Thus, when given an explicit spatial cue to attend to the left or right hemifield, subjects tended to shift fixation slightly toward the attended direction.

To assess visual behavior during neurofeedback training, we estimated visual fixation for the LNT and the RNT groups separately. We did not find any significant horizontal fixation bias in either the LNT group ($p = 0.4$, $n = 8$) or RNT group ($p = 0.2$, $n = 7$). We also compared fixations in feedback training and the Posner task directly, using paired comparisons for each subject. Visual fixation was significantly different in the LNT group during neurofeedback versus covert attention to the left in the Posner task ($p = 0.02$, $n = 4$). Similarly, visual fixation was significantly different in the RNT group during neurofeedback versus covert attention to the right in the Posner task ($p = 0.02$, $n = 4$). Thus, fixations during feedback training and the Posner task were significantly different, supporting the idea that subjects did not attempt to shift their attention to one hemifield or the other during their neurofeedback training to influence the feedback signal (Figure S3B).

DISCUSSION

Several EEG and MEG studies have shown that modulation in the amplitude of alpha occurs consistently in relation to attention processes (Banerjee et al., 2011; Feng et al., 2017; Foxe et al., 1998, 2005; Fu et al., 2001; Jensen and Mazaheri, 2010; Klimesch, 2012; Snyder and Foxe, 2010; Worden et al., 2000; Zumer et al., 2014) and that abnormality in alpha oscillations correlates with attentional disorders (Barry et al., 2003; Foxe and Snyder, 2011; Ros et al., 2014). For example, when a stimulus modality (auditory versus visual) or a stimulus location (left versus right hemifield) is intentionally ignored rather than attended, the ignored stimulus is preceded by a relative increase in alpha power (Feng et al., 2017; Fu et al., 2001; Jensen and Mazaheri, 2010; Klimesch, 2012). Atypical alpha asymmetry during covert attention has been observed in attention deficit hyperactivity disorder (ADHD) compared with neurotypical populations (ter Huurne et al., 2013). In animal studies of the visual cortex, spatially directed attention is correlated with a reduction in alpha power and an increase in gamma power in the local field potential and spike-field coherence (Bollimunta et al., 2011; Fries et al., 2008). However, all of this evidence is correlational in nature and does not by itself establish that changes in alpha power causally modulate attention.

Here we provide more direct evidence supporting a causal relationship between alpha synchrony and attention. Subjects learned to self-regulate alpha asymmetry in the parietal cortex, which subsequently caused variations in visual processing and behavior consistent with an attentional bias toward one hemifield. Our results are consistent with previous reports (Bollimunta et al., 2011; Fries et al., 2008; Fu et al., 2001; ter Huurne et al., 2013; Jensen and Mazaheri, 2010; Klimesch, 2012) of an association between alpha asymmetry and covert spatial attention in that covertly attending to one hemifield led to increases in alpha in the ipsilateral hemisphere and decreases in alpha in the contralateral hemisphere. But here we could also establish a causal relationship between alpha activity and neural/behavioral effects in the LNT and RNT groups. Specifically, we found that higher alpha power in the left versus right parietal cortex in the LNT group led to increased visually evoked responses and attentional bias toward stimuli in the ipsilateral visual field. Exactly the opposite effects were observed in the RNT group.

A prior neurofeedback study by Okazaki et al. (2015) succeeded in training alpha in a MEG neurofeedback task, at least in the left hemisphere, and this training had a measurable effect on behavior following training. However, the subjects in that study were explicitly instructed to attend to the extrafoveal stimuli presented in the left or right visual field during training, with alpha power used to modulate the visibility of the attended stimuli. Given that participants practiced spatial attention during neurofeedback, it is not clear whether a bias in attention was the cause or effect of the alpha modulations during training. Here we separated the modulation of alpha asymmetry from spatial attention using an orthogonal, non-spatial attention task with stimuli presented at fixation. Subjects were not given any instructions to attend to extrafoveal locations, and eye position data during neurofeedback suggested that participants did not use a spatial attention strategy to perform the task. Specifically, subjects did not bias their gaze toward one hemifield during training, unlike what we observed in the spatial cueing Posner task when subjects were given an explicit attentional cue (Figure S3A). Even though our data suggest that participants did not apply a spatial attention strategy during neurofeedback, probes presented during training showed that visual processing was modulated in both hemifields according to the respective changes in lateralized alpha.

One view regarding the role of alpha oscillations is that an increase in alpha power reflects inhibition, whereas a decrease in alpha power reflects release from inhibition (Fries et al., 2001; Fu et al., 2001; Hanslmayr et al., 2011; Jensen and Mazaheri, 2010; Klimesch, 2012). The inhibitory role of alpha has been tested by Romei et al. (2008) via a combined EEG-TMS experiment. They showed that the excitability threshold for inducing visual perception (phosphine) by TMS was greater when the ongoing posterior alpha oscillation had higher power. Jones et al. (2000) have developed a computational model of the inhibitory role of alpha, based on GABAergic feedback from interneurons to excitatory neurons conveying visual information. Our results for probe-related evoked response during neurofeedback are consistent with these findings in that we show less excitability (smaller evoked response related to the probe) in the hemisphere with higher alpha than in the hemisphere with lower alpha power.

Power spectrum analysis (Figures 2A and 2B) of the visual cortex during neurofeedback showed that the hemisphere with increased alpha power also had decreased gamma power. This result supports existing evidence that alpha and gamma rhythms are often inversely coupled (Roux and Uhlhaas, 2014). One idea for the inhibitory role of alpha is that an increase in alpha synchrony is a consequence of an increase in the magnitude of inhibitory bouts, which serve to break the ongoing gamma activity (Jensen and Mazaheri, 2010). Oscillations at gamma frequencies provide a mechanism for synchronizing the input with high temporal precision relative to the time course of postsynaptic potentials (PSPs), whereas oscillations at alpha

frequencies are more temporally smeared, resulting in a less pronounced summation of PSPs (Jensen et al., 2007).

We found that parietal alpha asymmetry entrained by neurofeedback did not affect performance during trials with spatial cues, but it led to a significant attentional bias on neutral trials in a Posner task, suggesting that the attentional bias produced by training was too weak to overcome the explicit movement of attention in the time period after training. However, the bias emerged in the neutral trials, where subjects were not moving their attention in a top-down manner into either hemifield. Likewise, alpha training caused a persistent fixation bias in a free-viewing task in the post-training phase, which was also performed without any top-down attentional cues. It is possible that neurofeedback induces subtle modulations of alpha asymmetry, which may be enough to exert influence on bottom-up processes but cannot overcome the strong top-down influence of cueing. These results are reminiscent of monkey experiments in which a unilateral inactivation of the parietal cortex did not affect a direction discrimination task with attention directed into the contralateral hemifield but impaired contralateral spatial selection in a free choice task without cues (Katz et al., 2016; Lynch and McLaren, 1989). Future research is necessary to resolve whether neurofeedback can overcome top-down attentional processes.

We found that alpha asymmetry in the RNT group was smaller than in the LNT group. There is no clear explanation for this finding. Subjects were pseudo-randomly assigned to the LNT and RNT group, and there were no significant differences in alpha asymmetry between the groups before neurofeedback training. A more extreme example has been reported by Okazaki et al. (2015), who reported failure to achieve alpha asymmetry in the right hemisphere following training.

Although the neurofeedback (NF) protocol used in the present study (alpha asymmetry) may not directly have a significant therapeutic prospect in treatment of brain disorders, other than possibly unilateral neglect, it demonstrated that even naive participants could exert control of their own parietal alpha power within a single short training session. Similar effects on visual perceptual learning have been found in a decoded neurofeedback study by real-time fMRI (Shibata et al., 2011). This suggests that neurofeedback does not require special skills or extended training and, thus, may be an accessible and effective technique in a wide range of populations. The unique characteristics of neurofeedback, including endogenous control of brain synchrony, spatial specificity, persistence of the effects in the post-training phase, and safety, not only support the use of neurofeedback as a research tool but also as a possible form of treatment for attentional or psychiatric disorders. Neurofeedback might be useful to elucidate the causal basis of certain psychiatric disorders; for example, by explaining the underlying causal relationships between abnormal brain rhythms in certain networks and attentional states.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.neuron.2019.11.001.

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AUTHOR CONTRIBUTIONS

Y.B., D.B., D.P., and R.D. designed the experiments. Y.B. and D.P. conducted the experiments and analyzed the data. Y.B., D.P., and R.D. wrote the manuscript. Y.B., D.B., D.P., and R.D. edited the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited Data		
Processed data	This paper	https://www.dropbox.com/sh/bbvpoblsx4lysbt/AAApDVkqgvV5Utjxo7Wn_tAfa?dl=0
Software and Algorithms		
MATLAB (R2015 a)	MathWorks	https://www.mathworks.com/
Brainstorm(MATLAB version 13 Feb 2018)	Brainstorm	https://neuroimage.usc.edu/bst/download.php
Psychtoolbox 3	Brainard, 1997	http://psychtoolbox.org/
Maxfilter	Neuromag	http://imaging.mrc-cbu.cam.ac.uk/meg/Maxfilter
Other		
MEG	Elekta	Elekta Neuromag TRIUX, Elekta, Stockholm, Sweden
Eye tracking	Eyelink	Eyelink 1000

LEAD CONTACT AND MATERIALS AVAILABILITY

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Yasaman Bagherzadeh (yasaman@mit.edu).

EXPERIMENTAL MODEL AND SUBJECT DETAILS

A total of 20 healthy volunteers with normal or corrected to normal vision (all right-handed; age mean ± s.d. 27.8 ± 5.3 years; 12 female) participated in the study. The study was approved by the local human subjects committee at the Massachusetts Institute of Technology (MIT).

METHOD DETAILS

Experimental design

All participants completed an MEG neurofeedback phase, which trained participants to modulate the hemispheric asymmetry of alpha power over parietal sensors (25-30 min). The participants were divided into two groups, the left neurofeedback training (LNT) group (n = 10) and the right neurofeedback training (RNT) group (n = 10). The LNT group was trained to increase alpha power in the left relative to right parietal sensors. The RNT group was trained in the opposite direction.

To evaluate whether neurofeedback training resulted in sustained attentional effects, a subset of participants performed additional behavioral tests before and after neurofeedback training. In this case, the study comprised three phases completed in succession with less than 5 minutes break in-between phases. The first phase was a behavioral pre-training phase to measure the baseline performance in attention to the left and right visual fields (30 min). The second phase was MEG neurofeedback. The third phase was a behavioral post-training session, identical to the first phase (30 min), to evaluate sustained neurofeedback attentional effects relative to baseline. The behavioral phases were either a classic Posner paradigm (Posner, 1980) (n = 7 for LNT group and n = 7 for RNT group) or a free-viewing task (Ossandón et al., 2014) (n = 3 for LNT group and n = 3 for RNT group). (After recruiting the first 14 participants, we found that neurofeedback did not have any effect on the trials with top down control of attention (valid and invalid trials in Posner task) and only changed on the ''bottom-up'' trials without any spatial cue (neutral trials in the Posner task). We therefore decided to conduct the free viewing task to test for an attentional bias in another bottom up behavioral test for a limited number of remaining subjects).

Data acquisition

MEG signals were recorded using a 306-channel system (204 planar gradiometers, 102 magnetometers, Elekta Neuromag TRIUX, Elekta, Stockholm, Sweden) at a sampling rate of 1000 Hz in a magnetically shielded room. Prior to the MEG recording, we used a 3D

digitizer (Fatrak, Polhemus, Colchester, Vermont, USA) to record the position of three landmark points (nasion, left and right preauricular) and five head position indicator (HPI) coils (which were attached to the forehead and the mastoids) together with at least 100 additional points expansive over the head. The head position was measured before each recording block by electromagnetic induction to the five HPI coils (Uutela et al., 2001).

Eye movements were recorded using a MEG-compatible eye-tracking device using binocular pupil tracking at 1000 Hz (EyeLink 1000, SR Research, Ontario, Canada) following a standard 9 points calibration and validation procedure (Tatler et al., 2005).

Structural MRI data were collected for each participant to reconstruct MEG activity on the cortex. A high-resolution structural scan of each participant's brain was obtained in a 3T Trio Siemens Scanner with 32-channel head coil. T1 weighted sequences were collected with TR = 1900 ms, TE = 2.52 ms, flip angle = 9°, FOV = 256 mm^2, and 192 sagittal slices.

Neurofeedback setup

We designed a neurofeedback system that allowed us to analyze MEG data in real time and provide rapid visual feedback to participants. Real-time MEG data were segmented into 500 ms blocks using rtMEG software (Sudre et al., 2011). The segmented MEG data were corrected with the signal space separation technique to reduce the environmental noise (Taulu and Simola, 2006; Taulu et al., 2004), and then stored to a real-time buffer accessible by the stimulus computer. Alpha power (8-12 Hz) estimated for the 500-ms data segment using the short term fast Fourier transform over 60 parietal sensors (30 in each hemisphere, we used only gradiometer sensors, as the magnetometers are more sensitive to environmental noise (Hämäläinen et al., 1993),) was used to calculate the alpha asymmetry index (AAI), defined as:

$$AAI = \frac{\alpha_{IS} - \alpha_{CS}}{\alpha_{IS} + \alpha_{CS}}$$

where α_{IS} and α_{CS} are the alpha power of the ipsilateral and contralateral sensors to the training direction. The value of AAI determined the visibility of a Gabor pattern presented at the center of the screen, so that negative AAI resulted in 0% visibility and positive AAI linearly determined visibility from 0% to 100%.

Participants were instructed to fixate at the center of the screen and, after the color of the fixation cross turned to black, to use ''mental effort'' to increase the visibility of the Gabor pattern as much as possible and as long as possible. They were aware that their ongoing brain activity would determine the visibility of the Gabor pattern.

The neurofeedback phase started with a 20 s reference recording in resting state with eyes open, which was used to estimate and subsequently correct any primary bias in the alpha asymmetry between the two hemispheres. The neurofeedback phase was composed of 100 trials. Each trial included a 5 s rest period, followed by a 5 s neurofeedback period that provided a Gabor pattern visual feedback. At the end of the neurofeedback period the Gabor pattern was removed from the screen, and after a 3 s delay period a second Gabor pattern appeared in full visibility with the same orientation or ± 5° different from the original Gabor pattern. Participants performed a 2-alternative forced choice task to report whether the orientation of the two grating patterns were the same or not (Figure 1B). The task was irrelevant to the results and it was simply to keep the participants motivated to perform the task and ignore the probes.

Probe during neurofeedback

In order to test the online effect of neurofeedback training on spatial attention, we measured evoked responses to a visual transient, which was randomly flashed on the left or the right site of the screen. For this aim, on 80% of neurofeedback trials (randomly interleaved), at a random time between 3 to 4.5 s after the onset of the neurofeedback period, a small (0.25°) gray dot (named probe) was flashed for a brief 32 ms on the left or the right side of the screen at an eccentricity of 6.7°. We chose the physical properties of the probes (size, color and timing) based on pilot studies. The probes were salient enough to elicit visual evoked responses but not too bold to be perceived easily. The location of the probe (eccentricity of 6.7°) was the same as the location of the target in the Posner task. The timing of the presentation (32 ms) was based on the refresh rate of the screen. The refresh rate was 60 Hz, which corresponds to about 16.67 ms per frame. The time that it takes to display the probe (16 ms for each frame) was less than the refresh rate (16.67 ms) to avoid the vertical blanking interval. To prevent contamination of alpha power neurofeedback with the probe evoked response, the real time neurofeedback was paused for 500 ms after the onset of the probe with the contrast of the Gabor pattern remaining the same as the previous value before the task-irrelevant probe. Participants were instructed to ignore the probe, maintain fixation, and continue the task.

Posner cueing paradigm

A classic Posner cueing paradigm was used to measure spatial orienting of attention in the pre-training and post-training phase. Trials started with the central fixation cross for 1000 ms followed by a central cue. The cue was either a white triangle pointed to the left or the right side of the screen (left/right-cued trials), or a diamond-shaped cue suggesting equal attention on either side (neutral trials). After 1000 ms from the onset of the cue, a target stimulus was delivered for 32 ms on the left or right side of the screen with 6.5° eccentricity. The target was a grating pattern (0.85°) with two possible orientations: 7° or −7° from vertical.

Participants were instructed to fixate at the center of the screen and avoid any eye movements and saccades during each trial. They were requested to shift their attention covertly toward the cued direction and respond by a 2-alternative forced choice what was the orientation of the target stimulus.

The experiment consisted of 500 trials with a short break after every 100 trials. Three different cue-target combinations were used in this paradigm, namely "valid," "invalid," and "neutral" conditions. In the valid condition (70% of trials) the cue correctly indicated the location of the upcoming target. In the invalid condition (10% of trials) the target appeared on the opposite hemifield of the attended site. Finally, in the neutral condition (20% of trials) the target appeared randomly in either direction, with the diamond-shaped cue suggesting equal attention on either side. The orientation of the target was equally probable for any of these three conditions. Trials of the three conditions were randomly intermingled within each experimental run.

Free viewing task

A free viewing task was used to measure horizontal bias in free viewing behavior in the pre-training and post-training phase. We selected 120 images from natural, urban and fractal categories. The natural (50 scenes) and urban category (50 scenes) were selected from the Calibrated Color Image database(Olmos and Kingdom, 2004). The fractal category included 20 images from the Chaotic N-Space Network (http://www.cnspace.net/html/fractals.html).

In order to control for possible biases in the distribution of objects or salient features, all images were mirrored horizontally to produce two categories of original and mirrored stimuli. Each image was presented only once to each participant, in either its original or mirrored form (balanced across participants). For each participant, a random set of 60 stimuli were presented before the neurofeedback phase, and the remaining 60 stimuli after the neurofeedback phase. Images were presented in sequence, as illustrated in Figure 5a. Trials began with a central fixation cross for 2 s followed by an image presentation for 5 s. Subjects were instructed to "explore the images carefully." The images subtended 20° x 15° of visual angle. Eye fixation paths were recorded by an Eyelink 1000 eye tracker.

MEG offline analysis

Preprocessing

MEG data for all three experimental phases were cleaned from environmental noise by applying spatiotemporal filters (Taulu and Simola, 2006; Taulu et al., 2004) using the Maxfilter software from Elekta. This algorithm suppresses magnetic interference and interpolates across bad MEG sensors. We used default parameters for harmonic expansion origin in head frame defined as [0 0 40] mm and orders of spherical harmonic expansions for the inner and outer source models were 8 and 3, respectively. We used Brainstorm (Tadel et al., 2011) software to detect and remove eye blinks automatically by projecting away from the first eye blink principal component. After epoching, a 6000 fT peak-to-peak rejection threshold was set to discard artifacted trials.

Source reconstruction

To perform time-frequency analysis on the cortex and localize MEG activity on regions of interest, we mapped MEG signals on source space. Source activation maps were computed on cortical surfaces derived from Freesurfer automatic segmentation (Fischl et al., 2004) of the Colin27 default anatomy (Holmes et al., 1998). The MEG forward model was calculated using an overlapping spheres model (Huang et al., 1999). MEG signals were then mapped onto a grid of ~15000 cortical sources using a dynamic statistical parametric mapping approach (dSPM) (Dale et al., 2000; Hämäläinen and Ilmoniemi, 1994).

Neurofeedback time frequency analysis

Neurofeedback MEG data were segmented into trials from −1.0 to 5.0 s with respect to the neurofeedback onset. For each trial, the dSPM time series were transformed to TF power maps in the frequency range of alpha (8–12 Hz) band by convolving them with complex Morlet wavelets with time resolution $FWHM_t = 3$ s at central frequency f = 1 Hz. The resulting TF maps were averaged over trials and the time series were derived from parietal cortex (merging the superior parietal, inferior parietal and supramarginal sources; Desikan et al., 2006). In order to grand average the source maps across participants, the individual maps were morphed onto a default anatomy with an iterative closest point algorithm implemented in Brainstorm.

Neurofeedback power spectral analysis

The power spectral density (PSD) maps were calculated for neurofeedback period (0.5 to 4.8 s) from the left and the right parietal, lateral occipital, inferior temporal and medio-lateral frontal sources (Desikan et al., 2006) using 1 s time windows with 50% overlap. The relative power for each frequency point were calculated by dividing the spectrum over the total power.

Probe-related evoked response analysis

The preprocessed neurofeedback data were segmented into −200 ms to 300 ms trials with respect to probe onset. Evoked response maps were computed by averaging across trials and mapping on cortex using dSPM reconstruction. The resulting maps were normalized as a percent change from the average baseline. Evoked responses time series were derived from pericalcarine (Desikan et al., 2006) sources and smoothed by applying 20 Hz low pass filter. We computed the mean amplitude of the evoked response between 100 ms to 200 ms after onset of the left and the right probe, respectively. Previous studies have shown that the effect of attention on early visual cortex take place in this time range (Noesselt et al., 2002). These values were considered as an index of allocation of spatial attention and were compared between the two training groups.

Attention modulation index in Posner task

The Posner task MEG data were divided into attention left, attention right and neutral trials. The time interval for each trial was cue locked from −0.2 to 1.3 s with cue onset at time 0 s. A Morlet wavelet ($FWHM_t$ = 3.0 s and central frequency f = 1.0 Hz) was used to estimate TF of alpha power. We then calculated cortical maps of alpha modulation index (AMI) by subtracting alpha power of attention right trials from alpha power of attention left trials, and normalizing by dividing with the mean of these values:

$$AMI = \frac{\alpha_{AL} - \alpha_{AR}}{\alpha_{AL} + \alpha_{AR}}$$

where α_{AL} and α_{AR} is alpha power for the attend left and attend right conditions respectively. We compared the pre-training from the post-training AMI maps: Δ AMI = post $_{AMI}$ – pre $_{AMI}$. We also computed the mean value of Δ AMI for the ipsilateral and contralateral parietal region with respect to the training direction.

For the neutral trials we estimated the changes in alpha power for the attention delay period with respect to the baseline period at each location, for the post- and pre- training phases as follows: $(\alpha_{\text{attention delay}} - \alpha_{\text{baseline}})/(\alpha_{\text{attention delay}} + \alpha_{\text{baseline}})$. We compared the alpha power map in the pre-training phase with the post-training phase.

Behavioral analysis

Reaction time in the Posner task

Posner behavioral data were categorized into the 6 conditions (3 cues by two target-sides). Reaction times (RTs) faster than 100 ms or slower than 4 times the standard deviation of the mean were considered as outliers. Trials with wrong response or outliers were discarded from further analysis. We fit the RT distribution with an ex-Gaussian function, i.e., the convolution of a Gaussian and an exponential function. The parameters of the ex-Gaussian distribution contained a mean and standard deviation of a Gaussian component and a mean of the exponential component. We compared the RT for each condition in pre-training phase with the corresponding RTs in the post-training phase: Δ RT = post $_{RT}$ – pre $_{RT}$

Fixation bias in free viewing task

For each image, we translated the raw eye-movement data points to the fixation locations on the visual display using Brainstorm. We classified the left versus the right fixations by comparing their horizontal coordination with the center of the screen. The coordinate reference for the center was defined as the location that the participant performed the drift correction at the fixation cross at the beginning of each trial. A drift correction was used for two purposes: calibration of the eye-tracker and for confirming that participant always started the trial in the same place. We computed the fixation bias (FB) by measuring the ratio between the left and the right fixations for all images in each training phase. We subtracted the median of the FB in pre-training phase from the median of the FB in the post-training phase: Δ FB = post $_{FB}$ – pre $_{FB}$. Negative values indicated a leftward bias and positive values indicated a rightward bias. Subject level bootstrap resampling was used to assess random effects reliability. Two-sided rank-sum tests were performed to test the null hypothesis for equal medians between the pre-training and the post-training distributions.

Fixation bias in Posner task and neurofeedback

To test whether participants used covert attention strategy to perform the neurofeedback task, we analyzed eye-tracking data from the Posner task and compared the pattern of eye fixations to that obtained from the neurofeedback task. Due to acquisition limitations, eye-position coordinates were recorded as analog signal and are thus reported in arbitrary units (a.u.). Eye tracking data were analyzed from a subset of participants with good quality recordings in both eyes for both the Posner (n = 8) and neurofeedback tasks (n = 15).

The Posner eye data were divided into attention left and attention right and neutral trials. We measured the horizontal fixation bias during the attention delay by subtracting the mean horizontal coordinates of eye-position at times 300-1000 ms from the ones at time 0-300 ms with respect to cue onset (due to eye-blink contamination we excluded times before cue onset for this analysis). Negative values indicated a leftward bias and positive values indicated a rightward bias.

To assess fixation bias during neurofeedback training, we segmented the neurofeedback eye-data into trials from 0 to 3.0 s (after the onset of neurofeedback and before the appearance of the probe) for the LNT and the RNT group separately. We first measured horizontal fixation bias by subtracting the mean horizontal coordinates of eye-position at times 0.5 – 3.0 s from the ones at times 0 – 0.5 s. Negative values indicated a leftward bias and positive values indicated a rightward bias. To show the horizontal eye position during neurofeedback period we calculated the mean position of eyes for every 500 ms.

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistical analyses relied on non-parametric statistical tests that do not make assumptions about the distributions of the data and are appropriate for random-effect interface (Maris and Oostenveld, 2007; Pantazis et al., 2005).

Statistical assessment of alpha power time series and power spectral densities relied on two-sided permutation tests. The null hypothesis was that the left and right parietal cortex have equal alpha power time series and equal power spectra. In both cases, under the null hypothesis we could randomly permute the left/right labels between the two hemispheres for each participant separately. Repeating the procedure 1000 times yielded empirical distributions of the data for each time point and each frequency value, thus enabling us to convert the time series and power spectra into 1-dimensional p value maps. Finally, to control for multiple

comparisons across times or frequencies, we adjusted the p values using false discovery rate and determined significance at 0.05 adjusted level (q = 0.05).

Since evoked response peak data were too variable at the individual-subject level, to assess significance we used a bootstrap procedure that resampled with replacement across participants. For each bootstrap sample we averaged the time series of the bootstrapped subjects yielding resampled peak time series. Repeating this procedure 1000 times yielded an empirical distribution of the peak values, allowing us to estimate 95% confidence intervals for the peaks, and compare the difference of peaks for the left versus the right training group using the bootstrap percentile method.

Statistical assessment of bar plots of alpha power, alpha power difference across blocks, alpha modulation index difference across training phases, and reaction time relied on two-sided permutation tests, each time randomly permuting the corresponding data labels over participants. For alpha power bar plots we permuted the left/right parietal labels; for alpha power difference across blocks we permuted the first/last block labels; for alpha modulation index difference across training phases we permuted the ipsilateral/contralateral parietal labels with respect to training; for reaction time bar plots we permuted the ipsilateral/contralateral parietal labels with respect to training.

For fixation bias bar plots we conducted subject-specific analysis given the small number of subjects. The eye position data were bootstrapped 1000 times and the empirical distribution of the eye position was used to define 95% confidence intervals. The post-minus pre-training fixation bias differences were evaluated using two-sided Wilcoxon rank-sum tests.

In each figure, statistical significance of bar plots was adjusted using false discovery rate procedures for the number of conducted tests.

DATA AND CODE AVAILABILITY

The data presented in the manuscript are available on request.