Top–Down Control of Alpha Phase Adjustment in Anticipation of Temporally Predictable Visual Stimuli

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TITLE

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ABBREVIATED TITLE

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ABSTRACT
Alpha oscillations (8–14 Hz) are proposed to represent an active mechanism of functional inhibition of neuronal processing. Specifically, alpha oscillations are associated with pulses of inhibition repeating every ~100ms. Whether alpha phase, similarly to alpha power, is under top-down control remains unclear. Moreover, the sources of such putative top-down phase control are unknown. We designed a cross-modal (visual/auditory) attention study in which we used magnetoencephalography to record the brain activity from thirty-four healthy subjects. In each trial, a somatosensory cue indicated whether to attend to either the visual or auditory domain. The timing of the stimulus onset was predictable across trials. We found that when visual information was attended, anticipatory alpha power was reduced in visual areas, while the phase adjusted just prior to the stimulus onset. Performance in each modality was predicted by the phase of the alpha oscillations previous to stimulus onset. Alpha oscillations in the left prefrontal cortex appeared to lead the adjustment of alpha phase in visual areas. Finally, alpha phase modulated stimulus-induced gamma activity. Our results confirm that alpha phase can be top-down adjusted in anticipation of predictable stimuli and improve performance. Phase adjustment of the alpha rhythm might serve as a neurophysiological resource for optimizing visual processing when temporal predictions are possible and there is considerable competition between target and distracting stimuli.

INTRODUCTION

The functional role of neuronal oscillations in different frequency bands has been intensively investigated and debated during the last decades. In particular, there is a strong interest on how temporal coordination of neuronal processing across brain regions is engaged by brain oscillations (Bonnefond, Kastner, & Jensen, 2017; Buzsaki & Draguhn, 2004; Fries, 2005; Hermes, Miller, Wandell, & Winawer, 2015; Ray & Maunsell, 2010; Singer, 1999; Varela, Lachaux, Rodriguez, & Martinerie, 2001).

In that regard, alpha oscillations (8–14 Hz) have attracted considerable interest over the past few years (Foxe, Simpson, & Ahlfors, 1998; Foxe & Snyder, 2011; Jensen, Bonnefond, & VanRullen, 2012; Jensen, Gips, Bergmann, & Bonnefond, 2014; Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007; Snyder & Foxe, 2010). While prominent in the electroencephalogram (EEG), alpha oscillations have long been considered to reflect cortical idling (reviewed in Pfurtscheller et al. (1996)), but more recent work suggests that alpha oscillations reflect an active mechanism of regional specific functional inhibition (Jensen & Mazaheri, 2010; Klimesch et al., 2007). Specifically, decreases and increases of the alpha oscillations have been observed in respectively task-relevant and task-irrelevant brain regions (Bonnefond & Jensen, 2012, 2013; Capilla, Schoffelen, Paterson, Thut, & Gross, 2014; Foxe et al., 1998; Mazaheri et al., 2014; Payne, Guillory, & Sekuler, 2013; Rohenkohl & Nobre, 2011; Thut, Nietzel, Brandt, & Pascual-Leone, 2006; Worden, Foxe, Wang, & Simpson, 2000). Such modulation is observed already in anticipation of stimuli, demonstrating that the amplitude of alpha oscillation is under top-down control. Importantly, pre-stimulus alpha amplitude has been shown to predict performance in attention and working memory tasks (Bonnefond & Jensen, 2012; Frey, Ruhnau, & Weisz, 2015; Haegens, Handel, & Jensen, 2011; Myers, Stokes, Walther, & Nobre, 2014; Payne et al., 2013; Thut et al., 2006).

Not only does the amplitude of alpha oscillations reflect performance. It has been shown that perception and neuronal excitability in visual regions are also modulated by the phase of alpha oscillations (Bonnefond & Jensen, 2012; Dugue, Marque, & VanRullen, 2011; Scheeringa, Mazaheri, Bojak, Norris, & Kleinschmidt, 2011). This is in line with the idea that alpha oscillations reflect periodic ~100 ms bouts of functional inhibition (Bonnefond & Jensen, 2015; Mathewson, Gratton, Fabiani, Beck, & Ro, 2009; Spaak, Bonnefond, Maier, Leopold, & Jensen, 2012). The combination of these results raises the question of whether, in addition to amplitude, the phase of alpha oscillations is under top-down control. Several studies have shown that the alpha phase relationship between regions can be modulated in a task specific manner (Michalareas et al., 2016; Saalmann, Pinsk,

Wang, Li, & Kastner, 2012; van Kerkoerle et al., 2014; von Stein, Chiang, & Konig, 2000), and that alpha phase can be controlled through entrainment tasks (Kizuk & Mathewson, 2017). However, only three experiments have directly tested whether alpha phase is under top-down control in anticipation of upcoming stimuli. These studies have reported contradictory findings. The study of Bonnefond and Jensen (2012) was the first to report an alpha phase alignment in anticipation of distracting visual stimuli during working memory retention. Samaha et al. (2015) further showed that alpha phase was adjusted in anticipation of visual stimuli, and such alignment predicted detection and conscious perception. However, van Diepen et al. (2015) reported no evidence of phase alignment in anticipation of target or distracting stimuli in a cross-modal (visual/auditory) attention task. It is unclear which factors account for these discrepancies in findings, though we hypothesized that task complexity, in particular the level of competition between target and distracting stimuli, play a key role in alpha phase alignment. We therefore designed a cross-modal attention task which included a high level of competition between stimuli. To do so, we used a somatosensory cue (a brief electrical pulse to the hand) that indicated the modality to attend, i.e. the visual or auditory modality. The cue also represented the timestamp for predicting the onset of the visual and auditory stimuli. We chose to use a somatosensory cue such that the sensory input from the cue would not directly perturb alpha oscillations in the visual or auditory areas (Romei, Gross, & Thut, 2012; Thorne, De Vos, Viola, & Debener, 2011). In order to test whether alpha phase alignment influences stimuli processing, we analyzed its effects over both behaviour and post-stimuli gamma activity. Gamma band has indeed been strongly associated with excitability and active processing in sensory regions (Fries, Reynolds, Rorie, & Desimone, 2001; Kaiser, Buhler, & Lutzenberger, 2004).

A second core aim of our study was to identify the sources of the top-down control of the alpha phase, which remain unclear. Potential candidate areas that have been involved in cognitive control and modulation of neural activity are the dorsolateral and medial prefrontal cortex, frontal eye fields (FEF), and parietal cortex (Capotosto, Babiloni, Romani, & Corbetta, 2009; Corbetta & Shulman, 2002; Gazzaley & D'Esposito, 2007; Marshall, O'Shea, Jensen, & Bergmann, 2015; Mathewson et al., 2014; Sauseng, Feldheim, Freunberger, & Hummel, 2011).

METHODS

Participants

The study was carried out at the Donders Institute for Brain, Cognition and Behaviour. Thirty-six healthy subjects attending college (18 females) took part in the study and were recruited from Radboud University's research participation scheme. Inclusion criteria for all participants included Dutch as their mother

tongue, right-handedness according to the Edinburgh Handedness Inventory (Oldfield, 1971), normal or corrected-to-normal vision, and reported normal audition. Exclusion criteria included the presence of psychiatric or neurological diagnosis. Two participants were excluded from further data analysis due to excessive movements and muscle artifacts during the recording session. The final sample consisted of 34 subjects (17 females, mean age=23±2.5 years). The study fulfilled the Declaration of Helsinki criteria (WMA, 2013) and was conducted according to the local ethics guidelines.

Experimental paradigm

The cross-modal attention task was designed using MATLAB (MathWorks) custom scripts and Psychtoolbox (psychtoolbox.org). Each trial (~5 s duration) began with a black background and a gray central fixation cross that lasted for 1 s and were projected on an acrylic screen by an EIKI LC-XL100L projector with a resolution of 1024x768 and a refresh rate of 60 Hz (Figure 1a). Subjects were encouraged to blink or move their eyes only during this period. Afterwards, the fixation cross turned white and 1100 ms later an electro-tactile cue (2 ms) was delivered to the left or right thumb instructing the participants to allocate attention to respectively the visual (*Attend-visual* condition; 50% of trials) or auditory (*Attend-auditory* condition; 50% of trials) stimuli. This was done using two constant current high voltage stimulators (type DS7A, Digitimer, Hertfordshire, UK; mean current=3.83 mA). After a 1150 ms post-cue interval, visual and auditory stimuli were presented simultaneously for 200 ms. Three syllables with no Dutch meaning were used. They were formed by a plosive consonant and the same vowel (*Pi*, *Ti*, and *Ki*). The timing of the stimuli onset and duration was carefully controlled. For the auditory stimuli, the use of plosive consonants facilitated the mark of the trigger of the stimulus at the beginning of the sound. Moreover, the use of the same vowel (*i*) in all stimuli further allowed us to guarantee that the length of the syllables was stable.

Each syllable was delivered with the same probability in both sensory domains. Among the total number of trials (798), 75% were different between visual and auditory modality (*incongruent*). Visual stimuli were presented at the center of the screen in white. Auditory stimuli were digitally created using a male voice and delivered via ear-tubes. Each syllable was associated with either one of three buttons in a response pad. Participants were asked to respond as accurate and fast as possible to the syllable in the modality they were instructed to attend in each trial, by pressing the corresponding button using their index, middle, and ring finger. The pairing between the side of the cue and the modality to attend, and the assigned syllables to the buttons were counterbalanced across participants. All trials were randomly distributed across participants. Five breaks were introduced in

the experiment, in which participants were informed about their performance. Reaction times (RT) and response accuracy were recorded along the experiment.

Data acquisition

Ongoing brain activity was recorded using a whole-head magnetoencephalography (MEG) system with 275 axial gradiometers (VSM/CTF systems, Port Coquitlam, Canada) housed in a magnetically shielded room. MEG signals were sampled at 1200 Hz after a 300 Hz low-pass filter was applied. The data were later down-sampled to 600 Hz for off-line analysis after a 150 Hz low-pass filter was applied. All participants were recorded in the supine position. Participants' head location relative to the MEG sensors was measured during the experiment using coils placed at the nasion and the left and right ear canals. During the recordings, an Eyelink 1000 eye tracker (SR Research, Ontario, Canada) was used to monitor eye movements and blinks.

In addition to the MEG recordings, the structural magnetic resonance image (MRI) of the participants' brain was acquired (voxel size=1 mm^3) using a 3T Siemens Trio system (Erlangen, Germany). During the MRI acquisition, the same earplugs (now with a drop of Vitamin E in place of the coils) were used for co-registration of the MRI and MEG data. Additionally, a FASTRAK device (Polhemus, Vermont, USA) was used to record the head shape of participants using 300 head points relative to these three fiducial points.

Procedure

The experiment was conducted over three sessions for each participant. During the first session, inclusion criteria were confirmed, general information about the study and informed consent letters were provided, and detailed instructions about the experiment were presented. Participants then performed a practice session composed of 150 trials inside the MEG room. During the second session, the participants' head shape was digitized and the actual MEG experiment was conducted. During the third session, the MRI was obtained.

Data analysis

All data analyses were done using MATLAB custom scripts and the Fieldtrip toolbox developed at the Donders Institute for Brain, Cognition and Behaviour (Oostenveld, Fries, Maris, & Schoffelen, 2011). Epochs of the MEG recording extending 2 s before and 1 s after the onset of visual and auditory stimuli were extracted. Only epochs containing correct responses were considered. From these, those containing eye blinks or saccades, muscle artifacts or superconducting quantum interference device (SQUID) jumps were rejected using an automatic routine based on a z-score algorithm. Additional visual inspection was applied to

the remaining trials before including them in further analyses. Data was detrended before further analyses. For the sensor-level analyses, planar gradients of the MEG field distribution were calculated (Bastiaansen & Knosche, 2000). We used a nearest neighbor method where the horizontal and vertical components of the estimated planar gradients were derived, thus approximating the signal measured by MEG systems with planar gradiometers. The planar gradients representation facilitates the interpretation of the sensor-level data, since the largest signal of the planar gradient typically is located above the source (Nolte, 2003).

Time-frequency representations (TFR) for power and phase were obtained using a fast Fourier transformation (FFT) approach with an adaptive sliding time window three cycles long (ΔT=3/f; e.g. ΔT=300 ms for 10 Hz). A Hanning taper (also ΔT long) was multiplied by the data prior to the FFT. For the planar gradient, the TFR of power were estimated for the horizontal and vertical components and then summed. The power for the individual trials was averaged over conditions and log-transformed. In order to determine the amplitude of the alpha activity phase-locked in the period preceding stimuli onset, TFR of the power of averaged epochs (i.e. the event related fields; ERF) were calculated as well.

In addition, phase alignment before stimuli onset across trials was assessed using the phase locking factor (PLF) or inter-trial phase clustering (Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996). The PLF over N trials is defined as:

$$PLF(f_o, t) = \frac{1}{N}\left|\sum_{k=1}^{N} e^{i\varphi^k(f_0,t)}\right|$$

where $\varphi^k(f_0,t)$ corresponds to the estimated phase at frequency f_0 and time t resulting from the time-frequency analysis. A PLF close to 0 reflects a uniform phase distribution, whereas a PLF=1 reflects that all trials exhibit the same phase at a frequency f_0. As for the TFR analysis of power, we calculated the PLF with respect to a sliding time window three cycles long to which we applied a Hanning taper. The same number of trials for each condition within participants was included (mean=261±63), as this measure is sensitive to the number of observations (Cohen, 2014). PLF values were computed for both horizontal and vertical components of the estimated planar gradients and combined by averaging them.

Source analysis

A frequency-domain beamforming approach based on adaptive spatial filtering techniques (Dynamic imaging of coherent sources; DICS) was used to estimate the power at source level in the entire brain (Gross et al., 2001). We obtained cross-spectral density matrices by applying a multitaper FFT approach (ΔT=300 ms; 1

orthogonal Slepian taper resulting in 4 Hz smoothing) on data measured from the axial sensors. For each participant, a realistically shaped single-shell description of the brain was constructed, based on the individual anatomical MRIs and head shapes (Nolte, 2003). The brain volume of each participant was divided into a grid with a 1-cm resolution and normalized to the template MNI brain (International Consortium for Brain Mapping, Montreal Neurological Institute, Canada) using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The lead field and the cross-spectral density were used to calculate a spatial filter for each grid point (Gross et al., 2001) and the spatial distribution of power was estimated for each condition in each participant. A common filter was used for both conditions (based on the cross-spectral density matrices of the combined conditions). As for the sensor level analyses, the estimated power was averaged over trials and log-transformed. Finally, the difference between conditions for power was calculated and averaged across participants. Note that 33 subjects were included in the source reconstruction as the MRI of 1 subject was missing. All source data were estimated within the alpha range according to sensor level results (8–14 Hz, see below). The source estimates were plotted on a standard MNI brain found in SPM8.

To determine the source of the observed alpha phase adjustment (see Results section), we used a linearly constrained minimum variance (LCMV) scalar beamformer spatial filter algorithm to generate maps of source activity on a 1cm grid (Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997). The beamformer source reconstruction calculates a set of weights that maps the sensor data to time-series at the source locations, allowing to reconstruct the signal at source level. We performed time-frequency analyses on these reconstructed time series (1) subsequently averaging in the alpha band (10–12 Hz) and in the 500 ms pre-stimulus time window to get the source reconstruction of the effect observed at sensor level (see Figure 2d) and (2) in the 3–40 Hz frequency window and 1s pre-stimulus time window for the region of interest analyses (see Figure 2 e). The ERF power was averaged over trials and log-transformed.

Statistics

Behaviour

RT were analyzed using repeated measures ANOVA (RM-ANOVA) with factors condition (*Attend-visual* and *Attend-auditory*) and congruency (congruent and incongruent) as within-subject factors. Additionally, errors from the incongruent trials were classified as interference (responding to the incorrect sensory modality), ambiguous (responding to the third option in the response pad) or omission (no response). The frequency of each type of error for each condition was compared with a RM-ANOVA. For all described RM-ANOVA a Greenhouse-Geisser

correction was used in case of violation of sphericity assumption and the Bonferroni test was used for *post hoc* comparisons.

Power and phase analyses

Significant differences of total power, ERF power and PLF between conditions at both sensor and source levels were assessed using a cluster-based non-parametric randomization test (Maris & Oostenveld, 2007). This test controls for the Type I error rate in situations involving multiple comparisons over sensors, frequencies and times by clustering neighboring sensors, time points and frequency points that show the same effect. We analyzed frequencies from 3 to 40 Hz (using 1 Hz increments) with an adaptive time window long enough to include at least 3 cycles in each frequency, from -500 ms to the onset of stimuli. This time window was based on Bonnefond et al. (2012). While we kept open the frequency range for comparisons between conditions, the time window was averaged, leaving a single value for each frequency bin. Sensors for which the t value of the difference between conditions exceeded an *a priori* threshold ($p<0.05$) were selected and subsequently clustered on the basis of spatial adjacency, and the sum of the t values within a cluster was used as cluster level statistic. The cluster with the maximum sum was used as test statistic. By randomly permuting the data across the two conditions and recalculating the test statistic 1000 times, we obtained a reference distribution to evaluate the statistics significance of a given effect (Monte Carlo estimation). Additionally, for all source level analyses we also ran a false discovery rate (FDR) correction. This correction allowed us to overcome some limitations of the cluster correction approach, such as considering a set of connected smaller clusters (by chance) as one big cluster. Only clusters surviving both the cluster and the FDR corrections were reported in the text. In the main Figure (2) we showed the results of the cluster analysis as a similar approach was used at sensor level. The results of the analysis using FDR correction are shown in the Supplementary figure.

RESULTS

We used a cross-modal (visual/auditory) attentional task to quantify the modulation of alpha power and phase recorded by magnetoencephalography (MEG). A somatosensory cue delivered as an electrical pulse to the left or right hand indicated whether the subjects should attend to the visual or auditory stimuli (counter balanced over subjects; Figure 1a).

Attention related behaviour is enhanced for visual information and impaired by incongruence

Analysis of reaction time (RT) showed that subjects were faster for the *Attend-visual* compared to the *Attend-auditory* trials (834±180 vs. 919±178 ms,

respectively; $F_{(1,33)}$=83.2, p<0.001). The RTs showed a congruency effect, as they were shorter for the congruent trials for both the *Attend-visual* and *Attend-auditory* conditions ($F_{(1,33)}$=90.3, p<0.001; Figure 1b). A significant interaction between condition and congruency ($F_{(1,33)}$=14.7, p=0.001) revealed that differences between *Attend-visual* and *Attend-auditory* was stronger for incongruent trials (MD=103.9 ms) compared to congruent (MD=65.9 ms).

Consistent with the RT results, accuracy was better for *Attend-visual* compared to *Attend-auditory* trials (91% vs. 88%; $F_{(1,33)}$=5.63, p=0.02). Again, a congruency effect was observed, as congruent trials showed better accuracy compared to incongruent (95% vs. 83%; $F_{(1,33)}$=76.67, p<0.0001). A significant interaction between condition and congruency ($F_{(1,33)}$=5.38, p=0.02) revealed that accuracy differences between *Attend-visual* and *Attend-auditory* was present in incongruent trials only (MD for incongruent=5.42, p=0.02; MD for congruent=0.49, p=0.42). Within incongruent trials, interference errors (i.e. responding to the incorrect sensory modality) were significantly more frequent compared to ambiguous errors (i.e. responding to the third option in the response pad), and omissions (i.e. no response; 12.9%±8.2 vs. 1.9%±1.2 and 2.5%±5.7, respectively; $F_{(2,66)}$=35.6, p<0.001).

In summary, behavioural data showed that attention was more effective for visual attention compared to auditory, as revealed by reduced RT and larger number of correct responses. Also, congruency between sensory modalities enhanced performance in both conditions.

Alpha power is reduced in anticipation of relevant visual stimuli in occipital cortex
Next, we quantified the alpha power from the MEG data for the attended visual and attended auditory stimuli. As expected, time-frequency representations (TFR) of power revealed reduced alpha activity at occipital and parietal sensors for *Attend-visual* compared to *Attend-auditory* trials starting 600 ms before the onset of stimuli (Figure 2a). A cluster-based randomization test controlling for multiple comparisons over time, frequency and sensors revealed that this difference was significant 500 ms prior to stimulus onset in the 10 – 12 Hz band (cluster-level statistic (CS)=-30,261, p=0.04, Figure 2a). Source level analysis allowed us to localize this effect (CS=-762, p=0.005) in occipital areas bleeding into parietal cortex, with a peak in the right hemisphere of extrastriate cortex (MNI coordinates [50,-80,0], Brodmann area 19; Figure 2b). The FDR corrected analysis confirmed this effect in occipital regions (Supplementary Figure A). In conclusion, anticipatory alpha power was reduced in anticipation of relevant visual stimuli in posterior visual regions.

Alpha phase is aligned in anticipation of relevant visual stimuli in occipital and left prefrontal cortex

We then set out to determine whether alpha phase was adjusted in anticipation of the predictable visual stimuli. We did this by quantifying the TFR of the averaged trials (the event-related fields (ERF)). The logic being that a phase-reset in anticipation of a stimulus would produce an oscillatory signature in the alpha band of the ERF prior to stimulus onset. Alpha power of the ERF increased for the *Attend-visual* compared to *Attend-auditory* condition starting 500 ms before stimuli onset over occipital regions (CS=1,113; p=0.008; Figure 2c). Source analysis with cluster correction revealed alpha power increase in one cluster including occipital regions, left and right prefrontal regions, thalamus, and basal ganglia (Figure 2b, CS=670, p=0.02). Nevertheless, only the occipital cortex (t(32)=4.07, p=0.001; MNI coordinates [-14,-90,-10], Brodmann area 17), the left anterior prefrontal regions (t(32)=3.37, p=0.001; MNI coordinates [-40,36,20], Brodmann area 10), and the left thalamus (t(32)=3.11, p=0.001; MNI coordinates [-10 -30 2]) survived the FDR correction (see Supplementary figure). TFR of the ERF at occipital and prefrontal sources (derived by LCMV spatial filters) confirmed the alpha phase alignment at both regions for the *Attend-visual* vs. *Attend-auditory* conditions (Figure 2e and 2g). For the occipital cluster, a significant increase in ERF mean peak frequency from 9.3 Hz at -400 ms to 10.7 at -200 ms was observed for the *Attend-visual* condition (t(32)=-2.37, p=0.024). Changes in alpha peak frequency in anticipation to relevant stimuli onset has been described before by Samaha et al. (2015). However, the changes observed by those authors depended on the baseline frequency (frequency observed in the unpredictable condition) in each subject, i.e. increased or decreased depending on the value of this baseline. The authors interpreted this individual change as reflecting a convergence toward an ideal frequency in order to optimally adjust the phase of alpha oscillations in anticipation of predictable stimuli. In the present study, we found an increase in frequency over time in average. It is possible that increase of frequency was required in most participants in order to optimally adjust the phase of alpha oscillations before the presentation of the predictable target.

Alpha phase alignment for *Attend-visual* vs. *Attend-auditory* was reproduced when considering the PLF at both sensory (occipital CS=30.9, p=0.02) and source levels (occipital t(32)=3.33 p=0.002, prefrontal t(32)=3,3 p=0.016; data not shown). In sum, alpha phase was adjusted in anticipation of relevant visual stimuli, as revealed by the power of the ERF and PLF analyses. This effect was observed both in occipital and prefrontal regions. It should be mentioned that we did not find a significant difference when comparing post-stimulus evoked activity between conditions (P1 ERF, t(33)=-0.48, p=0.62).

Left prefrontal cortex leads alpha phase alignment in visual regions
We further determined the directional coupling between alpha oscillations in prefrontal and visual areas in order to assess which area led the other. Using a spatial filter with a LCMV beamformer, we obtained the time course from each trial at the grid points with the maximal difference of the TFR of the ERF between *Attend-visual* and *Attend-auditory* for the left-prefrontal and occipital clusters, respectively (Figure 2d). We then calculated the phase slope index (PSI), which allows determining the directional coupling based on phase lag over a limited frequency range (Catanese, Carmichael, & van der Meer, 2016; Nolte et al., 2008). The PSI is defined as:

$$\widetilde{\Psi}_{ij} = \Im\left(\sum\nolimits_{f\in \mathrm{F}} C_{ij}^{*}(f) C_{ij}(f+\delta f)\right)$$

where $C_{ij}(f)$ is the complex coherency, δf is the frequency resolution, and $\Im(.)$ denotes taking the imaginary part. *F is* the set of frequencies over which the slope is summed (Nolte et al., 2008). We chose the PSI because, unlike autoregressive methods (e.g. Granger causality), it is less sensitive to false positives due to corruption from imperfect source separation (Bastos & Schoffelen, 2015; Catanese et al., 2016). We computed the PSI for each condition from 0 to 40 Hz (1 Hz step) and calculated the PSI difference for *Attend-visual* vs. *Attend-auditory*. This revealed a clear peak in the alpha band (Figure 2f). Paired t-tests in the 10–12 Hz range (justified by the effect in Figure 2a and 2c) revealed PSI coupling from left prefrontal to occipital areas being larger for the *Attend-visual* compared to *Attend-auditory* condition (t(32)=2.3, p=0.0285, Figure 2f). These results indicate that, for visual attention, prefrontal cortex preceded occipital cortex in terms of alpha phase. This suggests that left prefrontal cortex is in charge of adjusting the occipital alpha phase.

Alpha phase is bifurcated between effective visual and auditory attention
We also explored the influence of anticipatory alpha phase over behaviour. Specifically, we hypothesized that optimal performance in each condition would be associated with different anticipatory alpha phases. According to this, we classified trials in each condition as fast or slow (in terms of a median split of RT within conditions in each participant) and averaged them (i.e. obtained the ERF) in the -500 to 0 ms window across sensors marked in Figure 2c. Then we considered each participant's peak frequency in the 8–14 Hz range (previously identified in sensors marked at Figure 2a) and compared its angle across the factors condition (*Attend-visual* and *Attend-auditory*) and RT (fast and slow) using the Harrison-Kanji test (circular analogous of ANOVA) from the CircStat toolbox (Berens, 2009). While there were no significant effects of each factor independently (χ^2 for condition=1.0, p=0.6; χ^2 for RT=0.21, p=0.9), we found a significant interaction (χ^2=4.22,

p=0.039). *Post hoc* paired Watson-Williams tests confirmed significant differences within each condition (*Attend-visual* fast vs. slow RT: F=7.92, p=0.006; *Attend-auditory* fast vs. slow RT: F=16.17, p=0.0002) and within each RT (fast RT *Attend-visual* vs. *Attend-auditory*: F=7.87, p=0.006; slow RT *Attend-visual* vs. *Attend-auditory*: F=17.24, p=0.0001), but no differences when condition and RT were opposite (*Attend-visual* fast RT vs. *Attend-auditory* slow RT: F=3.0, p=0.09; *Attend-visual* slow RT vs. *Attend-auditory* fast RT: F=0.15, p=0.69; Figure 3a). This indicates that a given phase was useful for optimal processing of visual stimuli and another for actively ignoring them. Moreover, in both conditions performance was impaired in trials where the phase corresponding to the irrelevant stimulus was present.

Alpha phase adjustment predicts interference avoidance ability

To determine whether phase alignment could be associated with individual attention ability, we classified participants as good or bad performers (median split; based on interference errors). Analysis of condition and group factors revealed that only good performers showed significant changes in the power of ERF for the *Attend-visual* condition compared to *Attend-auditory* in visual areas (condition by group effect: $F_{(1,32)}$=5.56, p=0.025, good performers MD=0.36, p<0.001; bad performers MD=0.09, p=0.21; Figure 3b). This effect was confirmed when comparing the PLF (condition by group effect: $F_{(1,32)}$=4.54, p=0.04, good performers MD=0.27, p=0.002; bad performers MD=0.03, p=0.71). In line with this result, stronger phase alignment in visual areas during the *Attend-auditory* condition was associated with more visual interference errors (i.e. answering to the visual stimuli instead of auditory) across all participants (r_s=0.46, p=0.006, Figure 3c). For the correlation between phase alignment measures in each condition and the number of visual interference errors we used PLF only because it is a normalized value (between 0 and 1), while the power of the ERF needs to be further normalized with a baseline value, which was not available in the current design. In sum, good performance ability was associated with selective alpha phase alignment when visual stimuli were relevant in corresponding (posterior) sensory areas.

Alpha phase modulates induced gamma oscillations

Finally, we set out to quantify the gamma band activity. The aim was to assess whether gamma oscillations induced by the stimuli were influenced by the anticipatory alpha phase and power (i.e. the excitability of the visual cortex prior to the onset of the stimulus). To this end, we first identified a time-frequency window of interest that showed significant increase of induced gamma power in response to all stimuli (t=150–350 ms, f=50–90 Hz) with respect to a baseline period (-200–0

ms; CS=1,131.6, p=0.0004). This gamma power increase was observed in posterior regions (see Figure 3d).

Then we estimated the mean alpha power and angle of the *Attend-visual* trials for each participant at 10 Hz (which was the mean alpha peak frequency across participants) from -500 ms to stimuli onset (0 ms) using sensor MLT57 (i.e. the one where the effect of ERF power between conditions was strongest; see Figure 3d). These mean values of power and angle were used to classify incongruent trials from both conditions as 1) containing high (≥mean power) or low (<mean power) anticipatory alpha power, and 2) falling within (mean angle±90º, i.e. optimal phase range) or outside (the remaining 180º, i.e. sub-optimal phase range) the participant's alpha mean angle range in the [-500–0 ms] time window. Then we compared induced gamma (averaged within the mentioned time-frequency window) across condition (*Attend-visual* and *Attend-auditory*), alpha power (high and low) and alpha phase (optimal and sub-optimal) factors. This analysis revealed a significant interaction of condition by phase ($F_{(1,33)}$=5.87, p=0.02). *Post hoc* comparisons showed that, for the *Attend-visual* condition, gamma was increased for trials falling under optimal alpha phase range compared with those falling under sub-optimal alpha phase (MD=0.03, p=0.01), while this result was not observed for the *Attend-auditory* condition (MD=-0.008, p=0.43; see Figure 3e). This effect over gamma remained close to significant when classifying the trials based on each participant's anticipatory peak frequency in the 8–14 Hz range instead of 10 Hz ($F_{(1,33)}$=3.28, p=0.07). In conclusion, posterior induced gamma was selectively modulated by the anticipatory alpha phase when visual stimuli were relevant.

DISCUSSION

The aim if this study was to investigate the top-down control of alpha phase adjustment in visual regions as a mechanism for improving information processing. Our main finding was that alpha phase adjusts in anticipation of predictable and relevant visual stimuli. This adjustment promotes optimal behavioural performance and modulates induced gamma oscillations. In addition, we found that left prefrontal regions led such phase adjustment.

The conditions determining when alpha phase is adjusted in a top-down manner have been discussed recently. Bonnefond and Jensen (2012) and Samaha et al. (2015) showed anticipatory alpha phase adjustment in working memory and attentional tasks, respectively. However van Diepen et al. (2015) did not find such effects in a cross-modal attentional task. The different findings might be explained by differences among the tasks. For instance, van Diepen et al. task included a considerable amount of trials (20%) that did not contain any stimuli (blank trials).

This might have reduced the chance of getting consistent alpha phase alignment. Also, reduced competition between domains and task difficulty might play a role in implementing or not phase adjustment. While in that study target/distracting features within conditions were exclusive of the corresponding sensory domain (i.e. change in orientation of Gabor patches for visual stimuli and manipulation of tone frequency for auditory stimuli), our task relied on verbal features shared by visual and auditory domains. With respect to difficulty, while van Diepen et al. reported a mean cost in RT of 24 and 31 ms for visual and auditory trials when comparing unimodal vs. bimodal trials, the cost for our task between incongruent vs. congruent trials was four-fold higher (96 and 134 ms, respectively). On this basis, we conclude that cross-modal tasks are not sufficient for producing anticipatory alpha phase adjustment (Bonnefond & Jensen, 2012; Samaha et al., 2015), unless there is sufficient competition between the stimuli in the different domains. This might explain previous discrepancies between studies exploring anticipatory alpha phase alignment. Finally, while it might be argued that van Diepen et al. (2015) results were due to the use of EEG instead of MEG, it must be noted that Samaha et al. (2015) were able to identify anticipatory phase adjustment by using the former.

While we found a clear alpha phase adjustment in anticipation of relevant visual stimuli in posterior regions, this effect was not found in parallel for inhibition of auditory distractors in superior temporal regions. Notably, we did not find either significant alpha phase alignment in visual regions (even compared to a baseline [time period between the white cross fixation onset and cue onset]) when attention was directed to auditory stimuli (and visual stimuli became distractors). Moreover, phase alignment in the auditory condition was associated with more frequent interference from visual information. Coordinated phase alignment in two sensory areas promoting opposite effects (enhanced vs. inhibited gating) might represent a high cost from a neurophysiological perspective. Thus, we hypothesize that phase alignment was prioritized for areas that were in charge of relevant stimuli, and so decreased probability of processing distractors relied on a less fine, general amplitude increase in not relevant regions. Alternatively, since visual information was predominant along the task (as revealed by RT and correct responses), it is possible that phase alignment in visual regions was automatically set up. If that was the case, effective auditory attention (implying the inhibition of visual distractors) required the suppression of this alignment, which might explain the association between visual interference errors and posterior phase alignment in the auditory condition. It must be noted that both options would require top-down modulation. These hypotheses remain to be tested, as no significant alpha modulation could be observed in the auditory cortex.

After exploring the sources of top-down alpha phase adjustment, we found that left prefrontal cortex (PFC) led visual areas. Executive control and top-down modulation exerted by PFC have been widely reported (Gazzaley & D'Esposito, 2007). Specifically, potential frontal sources of alpha activity modulation at sensory regions include the FEF and inferior and middle frontal gyri (Capotosto et al., 2009; Marshall et al., 2015; Mathewson et al., 2014; Sauseng et al., 2011; Wang, Rajagovindan, Han, & Ding, 2016; Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011). Recently, Sadaghiani and Kleinschmidt (2016) proposed that top-down alpha phase modulation across distant regions might be coordinated by the fronto-parietal (FP) network, which includes the dorsolateral PFC. Additionally, the dominance of the left prefrontal cortex might be explained by the verbal features of the stimuli. It has been consistently reported left hemisphere dominance for verbal information, compared to the right hemisphere preference for spatial features during attention and working memory tasks (Manoach et al., 2004; Walter et al., 2003). This suggests a modality-specific top-down modulation at executive areas, as reported recently by Falasca et al. (2015) and Wang et al. (2016). Notably, while the studies reporting prefrontal alpha modulation have focused on power changes, here we show PFC control of alpha phase as well during attentional performance, which is in line with recent results by Popov et al. (2017) showing right FEF modulation for a spatial attention task. Also, Bonnefond and Jensen (2012), found phase alignment in the left prefrontal area during a verbal working memory task. The structural bases by which PFC might exert control over alpha activity in sensory regions remain unclear, with evidence in favor of both cortico-cortical and cortico-subcortical connections (Marshall et al., 2015; Saalmann et al., 2012). Also, it cannot be excluded that both prefrontal and sensory oscillations could be driven by a common area but at different time lags. It must be noted that, as mentioned in the Results section, we found phase alignment for visual attention that included the basal ganglia and right PFC, but it did not survive a conservative approach to discard false positives. Further research is needed to clarify the anatomical pathways for this top-down phase adjustment.

Relevance of alpha phase adjustment for optimal processing and distraction resistance was further shown in task execution (RT). Optimal performance for each condition revealed distinct pre-stimuli alpha phases at participants' peak frequency, but phases of trials with sub-optimal performance in each condition were not different from the phases for optimal performance in the other condition. Consequently, a certain phase of the alpha cycle in sensory regions might allow enhanced gating of stimuli (e.g. visual) regardless of relevance. This implies that this phase might be useful when the stimulus from that sensory modality is relevant but would interfere with optimal processing of other stimuli (i.e. auditory) when they are attended. Moreover, alpha activity might include specific phases of excitability

that top-down influence could take advantage of, as proposed by Mathewson (2011), Palva and Palva (2007) and reviewed by Frey et al. (2015).

We also found that modulation of anticipatory phase adjustment was effective in those participants with the best “distraction resistance”. This raises the question about whether top-down modulation of alpha phase might represent a trait marker of attentional ability. Furthermore, alpha phase alignment should be explored in neurological conditions, especially those with attentional/executive deficits related to aberrant neural oscillations, like attention-deficit/hyperactivity disorder, Parkinson’s disease or schizophrenia (Mazaheri et al., 2010; Solis-Vivanco et al., 2015; ter Huurne et al., 2013; Uhlhaas & Singer, 2015).

Finally, we observed that anticipatory alpha phase modulated post-stimulus induced gamma activity at posterior regions, specifically when attending visual stimuli. Gamma oscillations have been strongly associated with active sensory processing (Kaiser et al., 2004; Lachaux et al., 2005) and can be enhanced by visual attention at corresponding sensory areas (Fries et al., 2001; Muller, Gruber, & Keil, 2000). While an amplitude-phase interaction between alpha and gamma has been reported both at rest and under top-down modulation (Bonnefond & Jensen, 2015; Osipova, Hermes, & Jensen, 2008; Roux, Wibral, Singer, Aru, & Uhlhaas, 2013; Spaak et al., 2012) and such interaction might play an interesting role for brain communication (Bonnefond et al., 2017), here we show that anticipatory alpha phase set up the excitability in a given region and as such can influence gamma power in a “distant” time window. Our results are in line with those from Mathewson et al. (2009), who reported alpha phase influence over visual awareness. Interestingly, these authors’ results derived mainly from a study in which top-down modulation of alpha was not present. The possibility that top-down modulation of alpha phase can influence gamma power and consequently sensory processing suggests that alpha phase adjustment might represent a complementary resource for attentional enhancement under high demanding tasks and when stimuli onset is predictable.

As mentioned before, one of the limitations for this study is that no evident attentional modulation of power or phase was observed in auditory cortex, unlike reported by Mazaheri et al. (2014). Since we used a supine position for our recordings, stronger signals from occipital compared to temporal regions might have blurred alpha changes in auditory areas. This leaves open the question about whether alpha phase adjustment was increased for auditory compared to visual attention at those areas, resembling what we found at visual cortex. Additionally, phase locking of slower oscillations (i.e. delta) have been shown to be involved in temporal prediction (Breska & Deouell, 2017). Though we did not find a condition

effect over slow oscillations (3-7 Hz, data not shown), whether phase adjustment of these rhythms are involved in enhanced attentional processing remains to be clarified in future experiments with longer timing.

In conclusion, our results confirm that alpha phase can be top-down adjusted in anticipation of visual predictable stimuli. This adjustment is led by the PFC and enhances related behaviour and induced gamma oscillations. We propose that phase adjustment of alpha rhythm might represent a complementary neurophysiological resource for optimal processing capabilities in the visual system when temporal predictions are possible and there is considerable competition between target and distracting stimuli. These findings also call for further research about possible changes of such adjustment in neurological disorders.

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COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

FIGURE LEGENDS
1. Cross-modal (visual/auditory) attentional task and behavioral outcome. (A) In each trial, a somatosensory cue indicated to the participants whether to attend the visual or auditory domain and ignore the simultaneous information from the other domain. (B) RT was shorter for visual attention and longer for incongruent simultaneous stimuli. Red lines represent the mean RT. I=Incongruent, C=Congruent; *p<0.001.

2. Anticipatory alpha activity is modulated by visual attention. (A) Alpha power decreased in anticipation of relevant visual stimuli at posterior regions. White dashed line indicates the time-frequency window of interest. White dots indicate the sensors with significant differences between conditions. (B) Condition (*Attend-visual* vs. *Attend-auditory*) effect for power at source level. Blue areas indicate the regions with significant differences (cluster analysis). (C) Phase alignment (ERF power) improved for *Attend-visual* at similar posterior regions as for power. White dashed line indicates the time-frequency window of interest. White asterisks indicate the sensors with significant differences between conditions. (D) Condition (*Attend-visual* vs. *Attend-auditory*) effect for ERF power at source level (cluster analysis). Left prefrontal and occipital regions showed improved phase alignment for visual attention. Red areas indicate the regions with significant differences. (E) Condition effect for ERF power at both frontal and occipital clusters at source level. The apparent disappearance of the effect about 100 ms before stimuli onset might be due to post-stimuli evoked ERF, which was common for both conditions and has important effects over phase measurements in time-frequency estimations (VanRullen, 2016). (F) Phase slope index analysis revealed increased phase lag consistency from frontal to occipital cluster for the *Attend-visual* compared to *Attend-auditory* condition. (G) ERF from *Attend-visual* condition for both frontal and occipital clusters at source level. *p<0.05.

3. Pre-stimulus alpha phase modulates performance and induced gamma oscillations. (A) Alpha phase differs for visual and auditory optimal performance (RT). Vectors represent mean direction (normalized to 1) across participants for each condition (*Attend-visual*/*Attend-auditory*) and RT (fast/slow). (B) ERF power for visual and auditory attention in good and bad performers (based on committed

interference errors). Only good performers showed changes in phase alignment between conditions; *p<0.001. (C) Increased phase alignment (PLF) in the *Attend-auditory* condition was associated with more visual interference errors (p<0.01). (D) TFR of induced gamma increase respecting pre-stimulus period (200<t<0 ms). Mean values from a time-frequency window (150<t<350 ms; 50<f<90 Hz, black dashed window) were analyzed. The white dot indicates the sensor (MLT57) at which RM-ANOVA were performed. This sensor showed the strongest ERF power effect between conditions across participants. (E) Alpha phase effect (optimal vs. sub-optimal) over induced gamma for each condition. While phase modulated induced gamma in the *Attend-visual* condition (p=0.01), no effect was observed in the *Attend-auditory* (p=0.43).

Supplementary. Condition (*Attend-visual* vs. *Attend-auditory*) effect at source level after FDR correction. (A) Total power. Blue areas indicate the regions with significant differences. (B) ERF power. Red areas indicate the regions with significant differences.

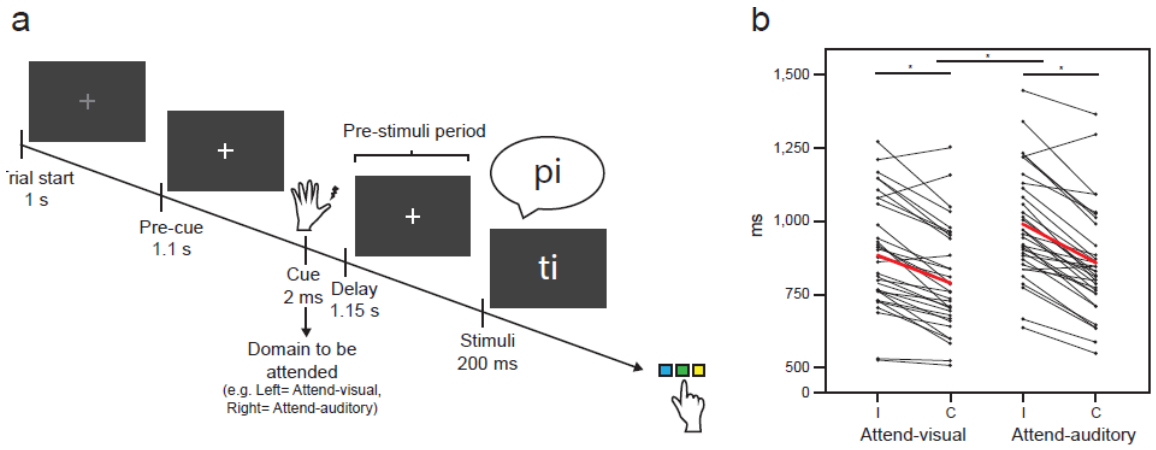

a
rial start
1 s
Pre-cue
1.1 s
Cue
2 ms
Delay
1.15 s
Pre-stimuli period
Domain to be
attended
(e.g. Left= Attend-visual,
Right= Attend-auditory)
Stimuli
200 ms
pi
ti
b
ms
1,500
1,250
1,000
750
500
0
I
C
I
C
Attend-visual
Attend-auditory

Figure 1

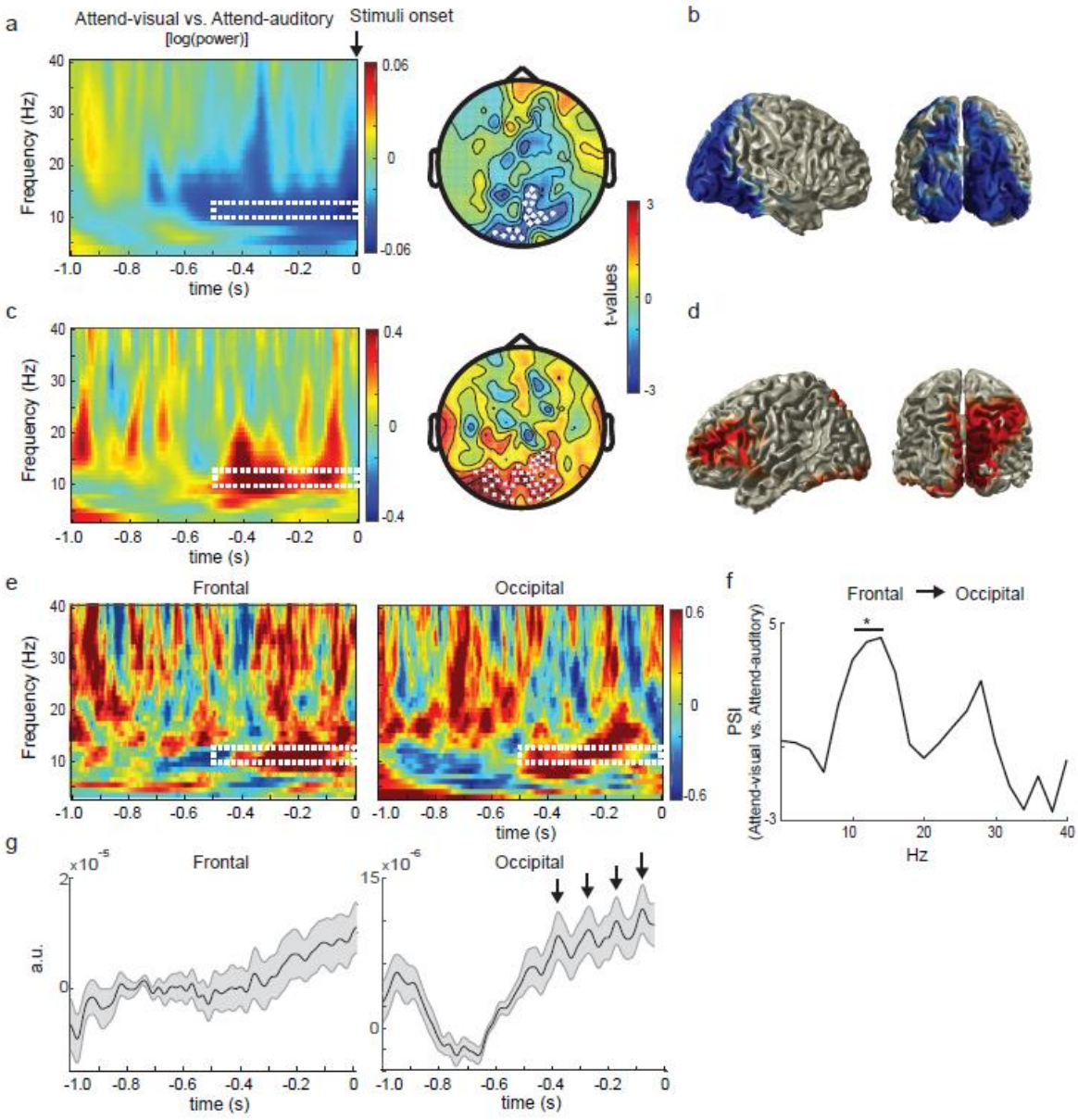

a
Attend-visual vs. Attend-auditory
[log(power)]
Stimuli onset
Frequency (Hz)
time (s)
t-values
b
c
d
e
Frontal
Occipital
f
Frontal → Occipital
PSI
(Attend-visual vs. Attend-auditory)
Hz
g
Frontal
Occipital
a.u.
time (s)

Figure 2

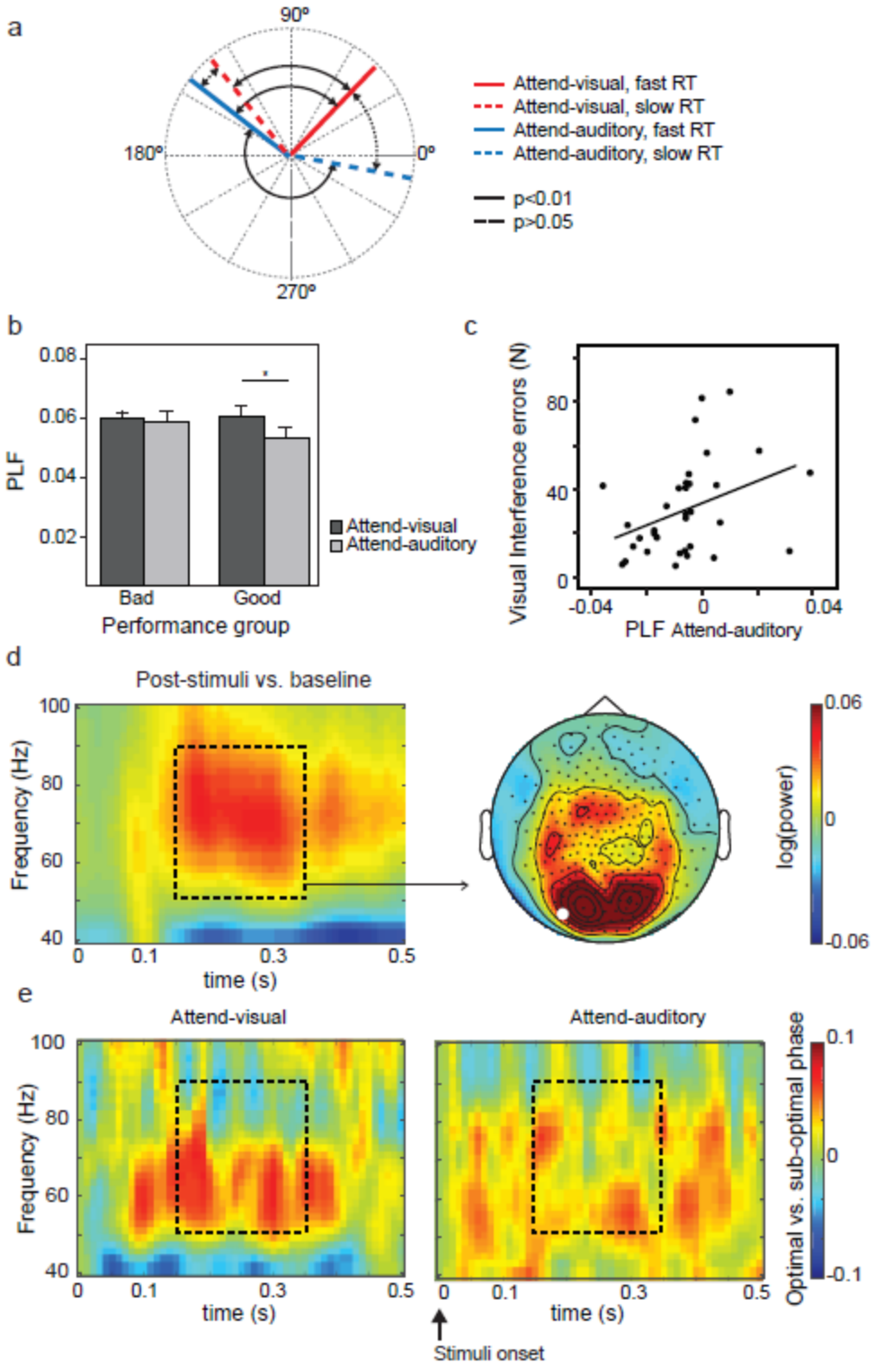
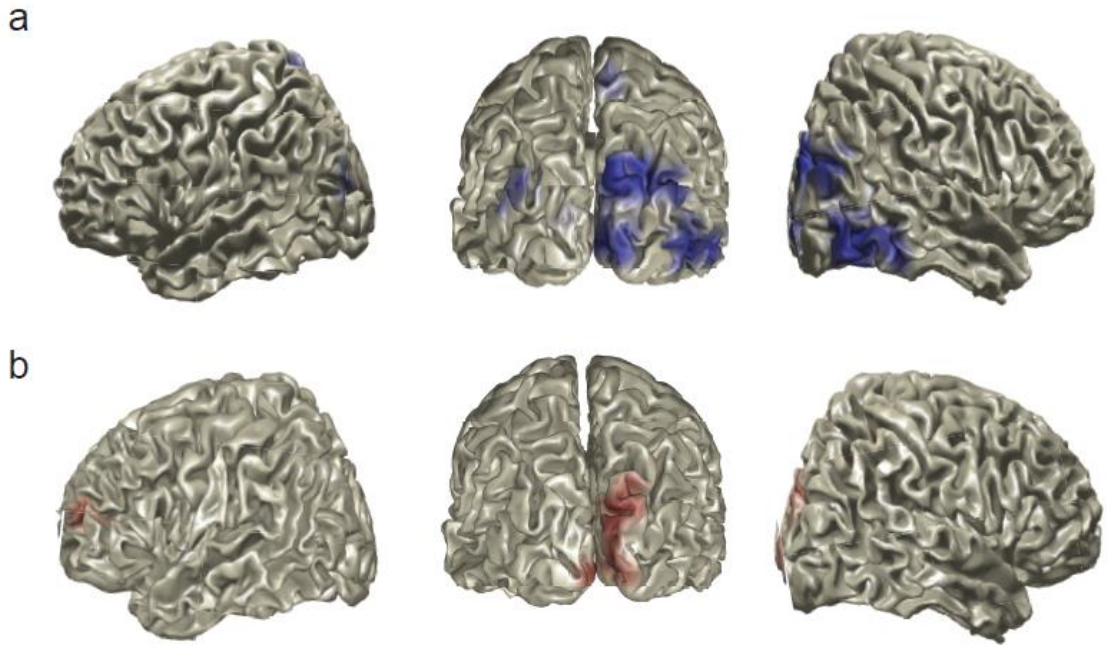

a
90°
180°
0°
270°
Attend-visual, fast RT
Attend-visual, slow RT
Attend-auditory, fast RT
Attend-auditory, slow RT
p<0.01
p>0.05
b
PLF
0.08
0.06
0.04
0.02
Attend-visual
Attend-auditory
Bad
Good
Performance group
c
Visual Interference errors (N)
80
40
0
-0.04
0
0.04
PLF Attend-auditory
d
Post-stimuli vs. baseline
Frequency (Hz)
100
80
60
40
0
0.1
0.3
0.5
time (s)
0.06
0
-0.06
log(power)
e
Attend-visual
Attend-auditory
Frequency (Hz)
100
80
60
40
0
0.1
0.3
0.5
time (s)
Stimuli onset
0.1
0
-0.1
Optimal vs. sub-optimal phase

Figure 3



Supplementary figure