

## COGNITIVE NEUROSCIENCE

# The strength of anticipatory spatial biasing predicts target discrimination at attended locations: a high-density EEG study

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## Abstract

Cueing relevant spatial locations in advance of a visual target results in modulated processing of that target as a consequence of anticipatory attentional deployment, the neural signatures of which remain to be fully elucidated. A set of electrophysiological processes has been established as candidate markers of the invocation and maintenance of attentional bias in humans. These include spatially-selective event-related potential (ERP) components over the lateral parietal (around 200–300 ms post-cue), frontal (300–500 ms) and ventral visual (> 500 ms) cortex, as well as oscillatory amplitude changes in the alpha band (8–14 Hz). Here, we interrogated the roles played by these anticipatory processes in attentional orienting by testing for links with subsequent behavioral performance. We found that both target discriminability ( $d'$ ) and reaction times were significantly predicted on a trial-by-trial basis by lateralization of alpha-band amplitude in the 500 ms preceding the target, with improved speed and accuracy resulting from a greater relative decrease in alpha over the contralateral visual cortex. Reaction time was also predicted by a late posterior contralateral positivity in the broad-band ERP in the same time period, but this did not influence  $d'$ . In a further analysis we sought to identify the control signals involved in generating the anticipatory bias, by testing earlier broad-band ERP amplitude for covariation with alpha lateralization. We found that stronger alpha biasing was associated with a greater bilateral frontal positivity at ~390 ms but not with differential amplitude across hemispheres in any time period. Thus, during the establishment of an anticipatory spatial bias, while the expected target location is strongly encoded in lateralized activity in parietal and frontal areas, a distinct non-spatial control process seems to regulate the strength of the bias.

## Introduction

Designating the probable or relevant location of an upcoming visual target through the use of a directional cue (such as an arrow) results in enhanced detection and discrimination of stimuli at that location (Posner, 1980). Although the neural signatures of modulated target processing have historically been the principal focus of experimental research (e.g. Hillyard *et al.*, 1998), many recent neurophysiological studies have turned to the preparatory processes involved in the deployment of spatial attention prior to target presentation (e.g. Hopfinger *et al.*, 2000; Nobre *et al.*, 2000; Worden *et al.*, 2000;

Simpson *et al.*, 2006). Neuroimaging studies have demonstrated the concerted involvement of the prefrontal and posterior parietal cortices in the control of attention shifts (Hopfinger *et al.*, 2001; Corbetta & Shulman, 2002; Yantis & Serences, 2003; Ruff *et al.*, 2008), whereas preparatory activity has been observed in location-specific low-level visual areas, purportedly reflecting the maintenance of attentional bias leading up to the expected target (Kastner *et al.*, 1999; Woldorff *et al.*, 2004; Silver *et al.*, 2007).

Although neuroimaging experiments have enabled the localization of the implicated brain areas, electroencephalographic (EEG) and event-related potential (ERP) experiments have been informative with regard to the timing and sequencing of discrete attention-directing processes. The most consistently reported effects have been characterized by comparing responses to leftward- and rightward-pointing central arrow cues. In the standard ERP, it is typical to observe: (i) a relative negativity occurring at ~200–300 ms post-cue over parietal areas contralateral to the cued location [early directing-attention negativity (EDAN)] (Harter *et al.*, 1989; Yamaguchi *et al.*, 1994; Nobre *et al.*, 2000), (ii) a relative negativity over the contralateral frontal cortex occurring at 300–500 ms post-cue [anterior directing-

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attention negativity (ADAN)] (Eimer *et al.*, 2002; Praamstra *et al.*, 2005; Green & McDonald, 2006) and (iii) a sustained process typically beginning at ~500 ms distributed over the posterior visual areas, most often taking the form of a relative contralateral positivity [late directing-attention positivity (LDAP)] (Harter *et al.*, 1989; Hopf & Mangun, 2000). Thus, ERP findings would seem to parallel the abovementioned neuroimaging work, implicating the parietal and frontal cortices as well as lower-tier visual areas. Preparatory biasing during the late 'pre-target' period is typically also reflected in oscillatory activity in the alpha band (8–14 Hz) over parieto-occipital areas. A decrease in alpha power contralateral to the attended visual hemifield is believed to reflect enhanced excitability in retinotopic areas (Worden *et al.*, 2000; Sauseng *et al.*, 2005; Thut *et al.*, 2006; Rihs *et al.*, 2007), whereas an ipsilateral increase (i.e. over cortical regions processing unattended stimuli) has been associated with active suppression (Worden *et al.*, 2000; Kelly *et al.*, 2006).

Despite the prevalence of lateralized ERP effects in spatial cueing studies, there is a lack of consensus regarding the nature and extent of their involvement in attention deployment. Complications have variously arisen from arguments of bottom-up cue-feature contributions (van Velzen & Eimer, 2003), null findings under particular task conditions (Green & McDonald, 2006; Green *et al.*, 2008) and the observation that fronto-parietal functional magnetic resonance imaging (fMRI) activations associated with the control of attentional deployments following symbolic cues have been predominantly bilateral and largely independent of cue direction (Hopfinger *et al.*, 2000; Corbetta & Shulman, 2002; Corbetta *et al.*, 2002, 2005; Woldorff *et al.*, 2004; see Praamstra *et al.*, 2005). Moreover, little is known regarding the relationship between these ERP effects and the biasing of alpha power during attentional deployment, as few studies have measured all processes in the same experiment (Jongen *et al.*, 2006; Dale *et al.*, 2008).

One powerful approach to identifying processes critical to attention shifting entails the establishment of links with behavioral performance. Recent fMRI work has made significant progress on this front, in particular in linking pre-stimulus preparatory 'baseline shifts' in the early visual cortex to detection performance (e.g. Ress *et al.*, 2000; Sylvester *et al.*, 2006, 2007, 2008). In comparison, accounts of such links in human electrophysiology remain relatively sparse. In particular, spatially-specific baseline shifts in the broad-band (we use the term 'broad-band' to refer to activity measured from standard ERP waveforms, which have not been decomposed into frequency bands) ERP have not yet been demonstrated to bring about spatially-specific behavioral benefits (see Jongen *et al.*, 2006; Talsma *et al.*, 2007). In one spatial cueing study, such a relationship was demonstrated for alpha-band activity (Thut *et al.*, 2006). Using a trial-by-trial prediction analysis Thut *et al.* (2006) showed that reaction time (RT) decreased as a function of alpha lateralization to the left hemisphere (LH) on attend-left trials and to the right hemisphere (RH) on attend-right trials. Analogous effects on detection accuracy or sensitivity were not found, however, and broad-band biasing indices were not examined.

Our main goal in the present study was to establish the functional relevance of cue-evoked electrophysiological processes recorded during an instructionally-cued spatial attention task by testing for links with behavior. First, we sought to determine whether discrimination sensitivity ( $d'$ ) and/or RT could be predicted by purported markers of anticipatory attentional deployment observed during the cue-target interval on a trial-by-trial basis. Second, we investigated the role played by relatively early cue-evoked ERP processes in the control and invocation of anticipatory bias by testing for a relationship between alpha lateralization and preceding broad-band amplitude.

## Materials and methods

### Participants

Sixteen (five female) neurologically normal, paid volunteers, aged between 21 and 40 years (mean 27.5 years) participated in the study. All subjects provided written informed consent and the Institutional Review Board of the Nathan Kline Institute approved the experimental procedures, which were in accordance with the Declaration of Helsinki. All subjects reported normal or corrected-to-normal vision. Four subjects were left-handed as assessed by the Edinburgh handedness inventory (Oldfield, 1971).

### Task and procedure

Subjects were instructed to maintain fixation at all times on a central white cross on a cathode-ray tube (CRT) monitor placed 150 cm away with a mid-gray background. The trial sequence is depicted in Fig. 1. A red/green arrow cue of 100 ms duration was first presented at fixation, with equal probability pointing leftward or rightward toward one of two bilateral locations. These locations were centered at a horizontal distance of  $4.2^\circ$  from the fixation cross and  $1.2^\circ$  above the horizontal meridian, each marked by four small white dots outlining a  $2.4^\circ \times 2.4^\circ$  square. The cue consisted of a red or green disc of  $1^\circ$  diameter with an embedded arrow of the opposite color. The arrow and disc colors were red on green for half of the experimental runs and green on red for the other half, with the order counterbalanced across subjects and days of testing. Red and green values were pre-calibrated for each subject to be approximately isoluminant by flicker photometry. This was intended to minimize sensory effects related to luminance differences between the left and right cues. An imperative target stimulus (100 ms duration) was presented 933 ms after cue onset at the left or right marked location (valid or invalid with respect to cue direction) with equal probability. Targets consisted of either a white 'x' or '+' (both arms spanning  $0.75^\circ$ ) embedded in a circular array of eight small white circles (see Fig. 1) such that the overall stimulus diameter was  $1.95^\circ$ . At the beginning of each experimental run, either the 'x' or '+' was randomly chosen as the 'Go' target stimulus and the other as the 'No-Go'. This assignment was then fixed for that run, with Go and No-Go stimuli occurring with equal probability on each trial. Subjects were instructed to shift their attention covertly to the location indicated by the cue and respond by pressing a mouse button with the index finger of their right hand only when a Go target appeared on that side, and to ignore stimuli

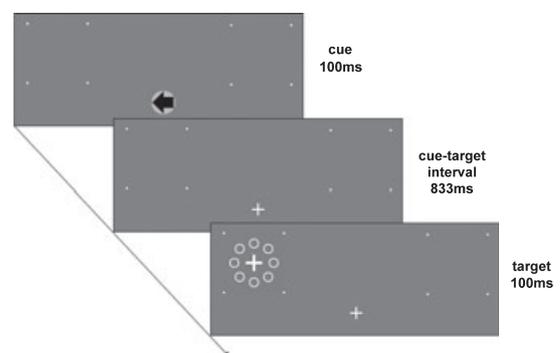


FIG. 1. Stimuli and task. Green/red arrow cues (here depicted in black and gray) indicated the location to be attended prior to an imperative target. Subjects responded only to a 'Go' target (a '+' or 'x' symbol designated the beginning of each run) appearing on the cued side 50% of the time and ignored uncued stimuli.

appearing on the invalid side entirely. This design, involving fully instructional cues (where a left cue instructs to attend to the left and ignore the right), contrasts with the traditional Posner paradigm, which instead uses probabilistic cues (where a left cue means that the target is ~80% likely to appear on the left and ~20% on the right but is relevant either way). Whereas the latter has been used extensively in behavioral studies of spatial attention examining costs and benefits in RT (e.g. Posner, 1980), many ERP studies have used the former, as modulations of target processing tend to be stronger (Eimer, 1994) and the number of sweeps for valid and invalid trials are equated. Trials were separated by a 1633 ms interval. A total of 100 trials were presented per run, resulting in a block duration of approximately 4.5 min. Subjects completed 20 runs on each of 4 days of testing. The data were collected as part of a 4 day study on the effects of compounds found in tea on visuospatial attention orienting. On each day subjects were administered either a placebo (water), 100 mg of theanine, 50 mg of caffeine or both, with the order counterbalanced across subjects. Treatments exerted effects only on background activity and not phasic cue-related processes, and have been reported separately (Kelly *et al.*, 2008). To ensure that small treatment effects not detected in that study could not influence our results here, we conducted our prediction analyses on each day separately and treatment was separated out as a factor in the statistical tests (see below).

#### Data acquisition

Continuous EEG data were acquired at a sample rate of 512 Hz from 164 scalp electrodes and four electro-oculographic (EOG) electrodes (placed on the nasion, supranasion and at the outer canthi of the eyes) using the BioSemi ActiveTwo system (<http://www.biosemi.com>). Off-line, the data were low-pass filtered with a 45 Hz cutoff and re-referenced to the nasion. Channels displaying large lower-frequency noise fluctuations (usually resulting from defective electrodes or unreliable conductivity to the scalp) were identified automatically by comparing the SD of amplitude over 50-s data segments at each channel to that of the six closest surrounding channels. If the SD of a channel was more than twice that of at least three of the six neighboring channels, the channel was interpolated. On average, this criterion led to interpolation of two channels for each run. Given the high-density electrode coverage over the scalp (average inter-electrode spacing of ~1.5 cm), this interpolation step should result in minimal distortion of the data. Horizontal EOG recordings allowed measurement of eye movements during testing. In order to map EOG amplitude to visual angle, preliminary calibration runs were carried out, wherein subjects performed 10 brief, randomly cued eye movements to each of 16 locations spread across the screen at eccentricities of 4° and 2° relative to the fixation cross. Trials were rejected off-line if eye gaze deviated by more than 0.5° during the cue-target interval. Three subjects for whom eye movements were detected on more than 25% of trials based on this criterion were excluded from further analysis. For the remaining subjects eye movements were detected on  $8.8 \pm 6\%$  of trials.

#### Data analysis

Behavioral performance was assessed via the discriminability index ( $d'$ ) of signal detection theory and by measuring RTs.  $d'$  purely indexes sensitivity to imperative stimulus identity (here 'x' or '+'), independent of inter- or intra-individual variations in response criteria, by taking into account the accuracy of responding on No-Go

imperative stimuli as well as on Go stimuli (Green & Swets, 1966).  $d'$  was derived from the hit rate (proportion of all valid Go stimuli that were responded to) and false alarm rate (proportion of all valid No-Go stimuli that were incorrectly responded to), calculated only from trials containing no eye movements or artifacts. Ceiling effects on hit rate were corrected in the standard way by assuming 0.5 misses and similarly a floor effect of zero false alarms was corrected to 0.5. The average RT to correctly executed target detections was measured from the onset of the target.

#### Overall effects of cue

In a first analysis, we established the presence of the alpha-band cueing effect in the pre-target interval and tested for the typically observed lateralized ERP effects that have been associated with the shifting of spatial attention. The latter comprised an early posterior contralateral negativity, a mid-latency frontal contralateral negativity and a late sustained posterior contralateral positivity, which we respectively label the EDAN, ADAN and LDAP following the convention in previous studies (see Harter *et al.*, 1989; Hopf & Mangun, 2000). (The reader should note that by our adoption of the common acronyms EDAN, ADAN and LDAP we are not necessarily supporting the notion that each is a unitary process that is invariable across studies. We apply the terms here mainly for convenience and consistency.) Cue-evoked ERPs were derived for leftward ('cue-L') and rightward ('cue-R') cues at all electrodes. For consistency with our prediction analysis, only valid trials were included and the ERPs were derived separately for each day of testing. Electroencephalographic data were epoched from -150 ms before to 1000 ms after cue onset and baseline-corrected with respect to the interval -100 to 0 ms, with an artifact rejection threshold of  $\pm 90 \mu\text{V}$  applied. For visualization of the time-course of alpha amplitude we used the temporal spectral evolution (TSE) technique (Salmelin & Hari, 1994), which is carried out simply by filtering each epoch with a passband of 8–14 Hz, followed by full-wave rectification and averaging across trials. The averaged TSE waveforms were then smoothed by averaging data points within a sliding 100-ms window. For statistical testing we used the same alpha amplitude measure as in our prediction analysis detailed below, integrating across the 8–14 Hz band of the spectrum derived using the fast Fourier transform.

We tested for the occurrence of the EDAN, ADAN, LDAP and alpha cueing effect by conducting a  $2 \times 2 \times 4$  ANOVA for each, with factors of Cue direction, Hemisphere and Treatment. The ERP/TSE amplitude was integrated over typical time intervals and averaged across clusters of five neighboring electrodes over typical regions for each process, guided by previous observations (Hopf & Mangun, 2000; Nobre *et al.*, 2000; Jongen *et al.*, 2006; Kelly *et al.*, 2006). The time intervals and equivalent sites in the 10–20 system were: EDAN, 240–280 ms, symmetrical clusters centered on P5 and P6; ADAN, 370–410 ms, symmetrical clusters surrounding F3 and FC3 over the LH and F4 and FC4 over the RH; LDAP, 420–920 ms, symmetrical clusters surrounding P7 and PO7 over the LH and P8 and PO8 over the RH; and alpha, 420–920 ms, symmetrical clusters bounded by P3, P5 and PO3 over the LH and P4, P6 and PO4 over the RH.

#### Prediction of performance based on pre-target spatially-selective processes

To test for predictive links between each of the four spatially-selective preparatory processes and task performance, we derived single-trial measures of each by taking the differential across hemispheres. Only valid trials where the target appeared on the cued side were included in this analysis. The same parameters for epoching, baseline correction

and trial rejection were applied as above. The EDAN, ADAN and LDAP were each measured simply by subtracting the RH from the LH amplitude, using the same time intervals and electrode clusters as above. For alpha, we derived a normalized lateralization measure by subtracting the RH from the LH amplitude and dividing by the sum, following Thut *et al.* (2006). Alpha amplitude was measured by computing the fast Fourier transform over the interval 420–920 ms and integrating across the 8–14 Hz frequency band, a robust measure that has previously been utilized successfully in the single-trial classification of leftward- vs. rightward-directed attention (see Kelly *et al.*, 2005).

For each of the four lateralized amplitude indices, the prediction analysis began by sorting trials from each individual, each day of testing and each cue direction into five equally sized bins (i.e. quintiles) according to the value of the index. Thus, bin 1 comprised the 20% of trials with the most negative indices and bin 5 the most positive 20%. Extreme values were first discarded by rejecting the top and bottom 2.5% of sorted trials before binning. Binning separately for each day ensured that any variation across the days of testing in the lateralized amplitude indices and performance (including systematic differences resulting from either treatment or practice) could not bias the binning procedure and drive effects involving Quintile. A repeated-measures ANOVA with factors of Cue (Left, Right), Quintile (five levels from most negative to most positive) and Treatment (Placebo, Theanine, Caffeine, Theanine + Caffeine) was conducted for each of the indices, separately testing for effects on  $d'$  and RT. The same trial bins were used for the RT prediction analysis as for the  $d'$  analysis but, in the case of the former, only the correct target trials within each bin were used to calculate average RT. Cue  $\times$  Quintile interactions, indicating a spatially-specific predictive relationship between the lateralized amplitude index and the behavioral-dependent measure, were followed up with polynomial linear contrast analyses for each cue direction.

#### *Covariation of preceding event-related potential amplitude with alpha biasing*

It is possible that shorter-latency processes (such as the EDAN and ADAN) do not directly influence a given trial's behavioral outcome but do determine the efficacy of the intervening biasing activity preceding the target stimuli and thus have a mediating effect on behavior. Moreover, such a role in the generation of anticipatory biasing activity need not be played by a spatially-selective process but rather may be provided by non-spatially-selective, bilateral processes, consistent with the bilateral activations observed within regions of the fronto-parietal network in fMRI studies (see Corbetta & Shulman, 2002). To investigate this, we tested for predictive links between ERP activity in the earlier time range ( $< 420$  ms) and pre-target alpha lateralization using a similar trial-by-trial 'prediction' analysis. Because alpha amplitude measures, being narrowly band-limited, are the most resilient to noise on a single-trial level, we took alpha lateralization as the independent variable in this analysis, i.e. trials were sorted into quintiles according to the alpha lateralization index as in the previous analysis but this time the dependent measures consisted of amplitude values in the cue-evoked ERP prior to the development of the alpha biasing effect.

As we lack a strong basis for predicting the implication of any one component over another, we conducted statistical cluster plot analyses, providing a complete spatio-temporal map of significant effects. This exploratory analysis approach has been employed in many previous studies mainly to inform further hypotheses (see e.g. Dockree *et al.*, 2005). As mentioned above, it is just as plausible that the source of alpha biasing is expressed in the coactivation of regions in both

hemispheres as in the differential activation across hemispheres. Thus, we tested for each of these two possibilities in a separate cluster plot.

For each of the five bins of trials sorted on the basis of alpha lateralization for each cue direction, an average cue-locked ERP was derived using an epoch window of  $-100$  to  $420$  ms with respect to cue onset. We derived 'coactivation' and 'differential' dependent measures by pairing each left-hemisphere electrode in the montage with the symmetrically located electrode over the RH and taking the sum and difference of amplitude, respectively. For each timepoint and electrode pair, we fitted a regression line to the coactivation/differential amplitude values across the five trial bins and recorded the slope.

In the 'coactivation' (LH + RH) cluster plot, timepoints were marked only if all of the following criteria were met: (i) the difference of the slopes in the cue-L and cue-R conditions was significantly different from zero at the 0.05 level (i.e. a Cue  $\times$  Quintile interaction); (ii) the slope in each of the respective cue conditions was significantly different from zero and in opposite directions (one-tailed t-tests in the direction of the underlying amplitude); and (iii) criteria (i) and (ii) were satisfied for at least 11 consecutive sample points ( $\sim 21$  ms). The values represented in color (Fig. 4) are the t-values resulting from the test of criterion (i). Because the cue-R slope is subtracted from the cue-L slope, positive t-values shown in green represent bilateral coactivity that is more positive the more alpha is biased in the direction appropriate for the cue, i.e. toward the left for leftward cues and toward the right for rightward cues. Conversely, negative t-values marked in orange represent points where the amplitude is more negative the stronger the cue-dependent biasing.

The 'differential' (LH – RH) cluster plot maps the points where the difference in amplitude between symmetrically opposite electrode sites is linearly dependent on the magnitude of alpha biasing. The equivalent criteria for representation in color in this case were: (i) that the sum of the slopes in the cue-L and cue-R conditions was significantly different from zero (i.e. a linear main effect of Quintile); (ii) the slope in each of the respective cue conditions was significantly different from zero and in the same direction; and (iii) criteria (i) and (ii) were satisfied for at least 11 consecutive sample points ( $\sim 21$  ms). The values represented in color are the t-values resulting from the test of criterion (i). This captures activity that is spatially selective, i.e. defined by the differential across hemispheres, which may vary with the alpha differential for either cue direction. Because the alpha biasing effect, EDAN and ADAN are all expressed as relatively negative amplitude contralateral to the cue direction, a relationship with the EDAN and/or ADAN would result in positive t-values, marked in green.

## Results

### *Behavior*

The hit rate was significantly lower for left visual field (83.6%) than for right visual field (90.2%;  $t_{12} = 3.03$ ,  $P < 0.02$ ) targets, as was  $d'$  (2.04 vs. 2.56;  $t_{12} = 3.26$ ,  $P < 0.01$ ). Also, RT was slower for left visual field than right visual field targets (622 vs. 593 ms;  $t_{12} = 3.64$ ,  $P < 0.005$ ). This behavioral asymmetry may be due to the fact that all responses were right-handed, as has been suggested previously (Jongen *et al.*, 2006, 2007). However, it should be noted that a similar asymmetry has been found even when the response hand was counterbalanced (Nobre *et al.*, 2000). Whatever the cause, we took account of this performance asymmetry in our prediction analysis by testing for effects of quintile separately for each cue direction where appropriate. Responses were made on  $< 0.7\%$  of invalid trials on

average, demonstrating that subjects followed instructions to ignore these.

### *Effects of cue direction on broad-band event-related potential and alpha-band activity*

Figure 2A shows ERP waveforms derived over the left and right frontal and occipito-temporal cortices (upper panels), and TSE waveforms over parieto-occipital sites (lower panels), collapsed over cue validity and day of testing. The typical lateralized components EDAN, ADAN and LDAP are readily observed in the difference waveforms (gray traces) superimposed on the broad-band ERP plots. The scalp topographic maps show the progression of components from ~200 ms up until the time of target presentation (Fig. 2B). In the upper row the data are collapsed across leftward and rightward cues to highlight activity common to both directions. A set of bilaterally-distributed components can be identified in the time interval between the EDAN and ADAN, which we labeled roughly according to the order in which they occur, their polarity and scalp topography. Two bilateral parietal positivities, one medial and one more lateral, can be seen at ~250 ms (P2m) and ~310 ms (P2l), respectively, whereas a bilateral frontal positivity at ~390 ms (P3f) followed very closely by a parietal positivity (P3p) are evident just prior to the biasing effect. A contingent negative variation (Walter *et al.*, 1964) component can also be seen, building in amplitude leading up to the target. In the lower row of scalp maps, the difference topographies are depicted (cue-L – cue-R). A left-hemisphere asymmetry is evident in the EDAN at ~250 ms. This is a typical feature of the EDAN that has been observed previously and attributed to right-hemisphere dominance of attention (Hopf & Mangun, 2000; Nobre *et al.*, 2000; Foxe *et al.*, 2003; Ruff *et al.*, 2009). The ADAN can be seen to gradually develop as the contralateral negativity shifts anteriorly to frontal sites, reaching a maximum in the time frame of the fronto-parietal positivities P3f and P3p. The LDAP appears shortly after and is sustained up until target presentation. The typical alpha biasing effect can clearly be seen in the TSE waveforms, where the alpha amplitude over each hemisphere is relatively decreased on deployment of attention to the contralateral side.

In the EDAN time interval (240–280 ms), the  $2 \times 2 \times 4$  ANOVA revealed main effects of Cue ( $F_{1,12} = 14.59$ ,  $P < 0.002$ ) and Hemisphere ( $F_{1,12} = 5.53$ ,  $P < 0.05$ ), and a Hemisphere  $\times$  Cue interaction ( $F_{1,12} = 15.86$ ,  $P < 0.002$ ). There was a Hemisphere  $\times$  Cue interaction ( $F_{1,12} = 61.33$ ,  $P < 0.001$ ) in the ADAN interval (370–410 ms). There was also a Hemisphere  $\times$  Cue interaction ( $F_{1,12} = 27.42$ ,  $P < 0.001$ ) in the LDAP interval (420–920 ms). Finally, for alpha amplitude in the pre-target interval there was a main effect of Hemisphere ( $F_{1,12} = 10.44$ ,  $P < 0.01$ ), with larger alpha over the LH, and there was a Hemisphere  $\times$  Cue interaction ( $F_{1,12} = 30.30$ ,  $P < 0.001$ ). Although there were no effects involving Treatment on the broad-band indices (all  $P > 0.1$ ), there was a main effect of Treatment on alpha ( $F_{3,36} = 3.50$ ,  $P < 0.05$ ), reflecting the reduction of tonic alpha, but not spatially-selective alpha biasing, on ingestion of both theanine and caffeine as described previously (Kelly *et al.*, 2008).

### *Predictive relationships between spatially-selective preparatory processes and performance*

Figure 3 plots  $d'$  and RT as a function of the binned index level of each of the spatially-selective 'attention-directing' processes, i.e. EDAN, ADAN, LDAP and alpha lateralization. The  $2 \times 5 \times 4$  ANOVAs with factors of Cue, Quintile and Treatment were conducted to test for significant relationships between pre-target indices and

performance. A main effect of Cue was found for both  $d'$  and RT for all predictor variables (all  $P$ -values  $< 0.01$ ), reflecting the hemifield asymmetry in performance.

### *Effects on reaction time*

There were no effects on RT with either EDAN or ADAN as the predictor variable ( $P > 0.1$ ). There was a significant interaction between cue direction and LDAP index level (Cue  $\times$  Quintile,  $F_{4,48} = 2.87$ ,  $P < 0.05$ ). Polynomial linear contrasts revealed a linear trend for cue-L trials ( $F_{1,12} = 14.49$ ,  $P < 0.005$ ) with RT decreasing with decreasing LDAP index (stronger leftward bias). Although it appears that Fig. 3 promises the opposite trend for cue-R trials, linear contrasts did not reach significance ( $P = 0.18$ ). With the alpha lateralization index as the predictor variable, there was a Cue  $\times$  Quintile interaction ( $F_{4,48} = 2.78$ ,  $P < 0.05$ ). Polynomial linear contrasts revealed a linear trend for cue-R trials ( $F_{1,12} = 11.33$ ,  $P < 0.01$ ) with RT decreasing with decreasing alpha index (stronger rightward bias). However, the opposite trend for cue-L trials did not reach significance ( $P = 0.23$ ). No effects involving Treatment reached significance (all  $P > 0.1$ ).

### *Effects on discriminability $d'$*

No effects on  $d'$  were found with EDAN, ADAN or LDAP as the predictor variable (all  $P > 0.1$ ). With the alpha lateralization index as the predictor, there was a significant Cue  $\times$  Quintile interaction ( $F_{4,48} = 3.76$ ,  $P < 0.01$ ). Polynomial linear contrasts revealed a linear trend for both cue-L ( $F_{1,12} = 9.16$ ,  $P < 0.02$ ) and cue-R ( $F_{1,12} = 9.00$ ,  $P < 0.02$ ) trials, with  $d'$  increasing with stronger leftward bias in cue-L trials and with stronger rightward bias in cue-R trials. No effects involving Treatment reached significance (all  $P > 0.1$ ).

Given that the alpha and LDAP indices were both found to have predictive power for performance, it was of interest to test for links between them. To this end, we conducted a  $2 \times 5 \times 4$  ANOVA with the same factors but with the alpha lateralization index as the independent variable and the LDAP index as the dependent variable. A main effect of Quintile was found ( $F_{4,48} = 3.05$ ,  $P < 0.05$ ), driven by an inverse relationship between the indices (linear contrast,  $P < 0.02$ ), i.e. the greater the relative contralateral decrease in alpha, the greater the relative contralateral positivity in the broad-band ERP (i.e. the greater the LDAP). It should be noted that this relationship does not arise automatically due to the overlap in time and scalp distribution of the alpha effect and LDAP; the LDAP is measured over an integer multiple of alpha cycles and so should contain negligible contributions from the alpha band.

### *Relationship between pre-target alpha biasing and preceding event-related potential activity*

Figure 4 shows the statistical cluster plots marking significant linear relationships between the alpha biasing level and cue-evoked ERP amplitude both when combined across hemispheres ('coactivation' LH + RH map, Fig. 4A) and when subtracted ('differential' LH – RH map, Fig. 4B). The electrode pairs represented on the  $y$ -axis are ordered from the most posterior regions at the bottom of the maps to the most anterior at the top, with horizontal gridlines marking pairs lying within standard regions designated in the 10–20 system. No reliable covariation with alpha biasing was found for differential amplitude at any time in the cue-evoked ERP, most notably during the EDAN and ADAN timeframes where parietal and frontal clusters of positive  $t$ -values would be expected (see Fig. 4B). In contrast, a strong relationship was found in the interval 370–400 ms at frontal sites for the coactivation measure (Fig. 4A). This indicates that, on cue-L trials,

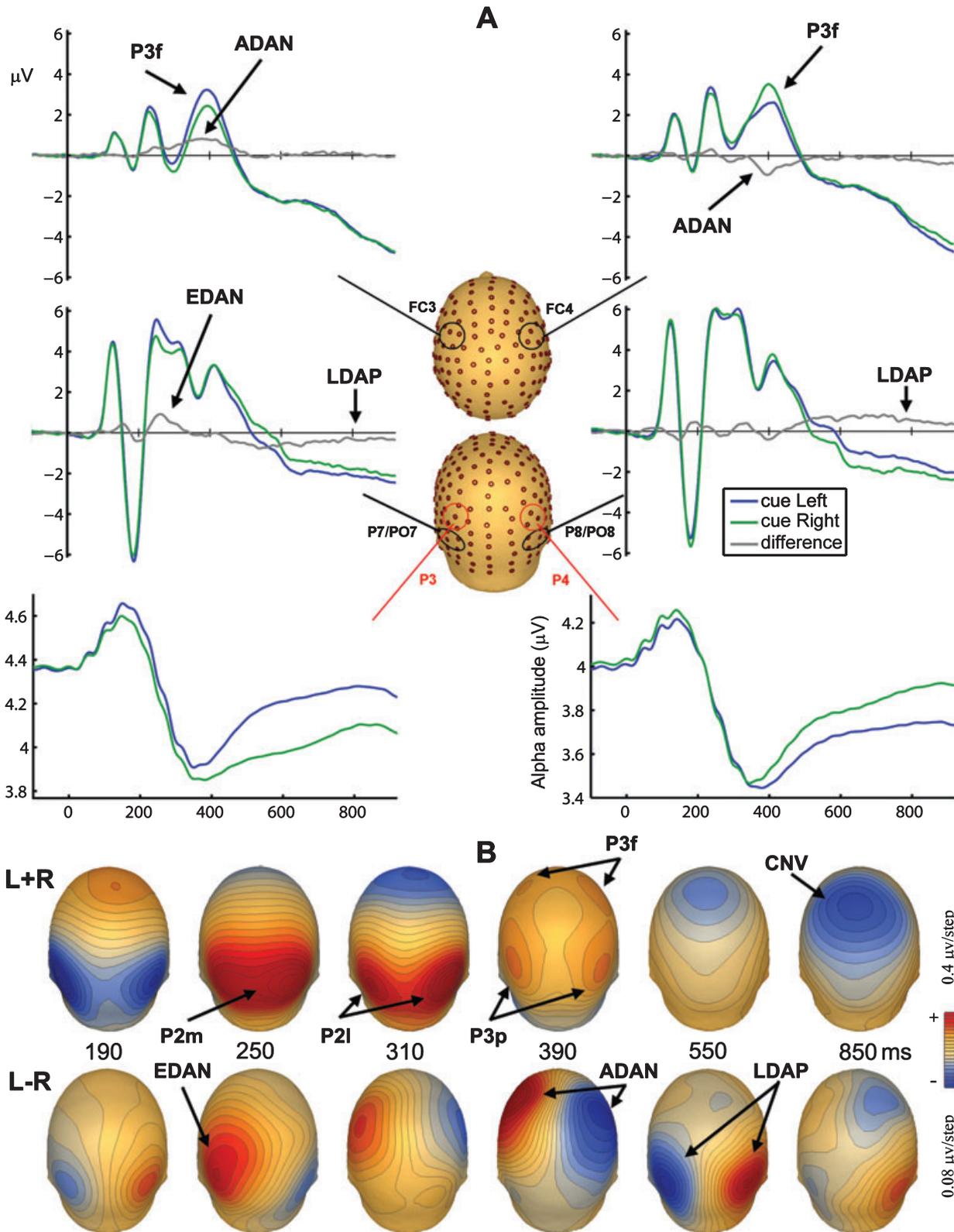


FIG. 2. (A) Broad-band ERPs to left and right cue stimuli over the left and right fronto-central and occipito-temporal scalp, along with timecourses of alpha amplitude measured from parieto-occipital sites. The typical spatially-selective lateralized processes associated with attentional deployment are marked in the gray difference waveforms. These are labeled EDAN (240–280 ms), ADAN (370–410 ms) and LDAP (420–920 ms). Posterior waveforms are plotted at the sites used to test for the LDAP component. Time zero marks the onset of the cue stimulus. Waveforms are plotted up until the onset of the target. (B) Scalp topographic maps of amplitude at selected post-cue timepoints. The upper row shows the distribution of non-spatially-selective activity (i.e. the cue-L and cue-R conditions are collapsed) and the lower row shows the spatially-selective activity (i.e. cue-R is subtracted from cue-L). The timepoints were chosen mostly to coincide with peak latencies in the collapsed L + R data, as these components were less broad than the difference wave components.

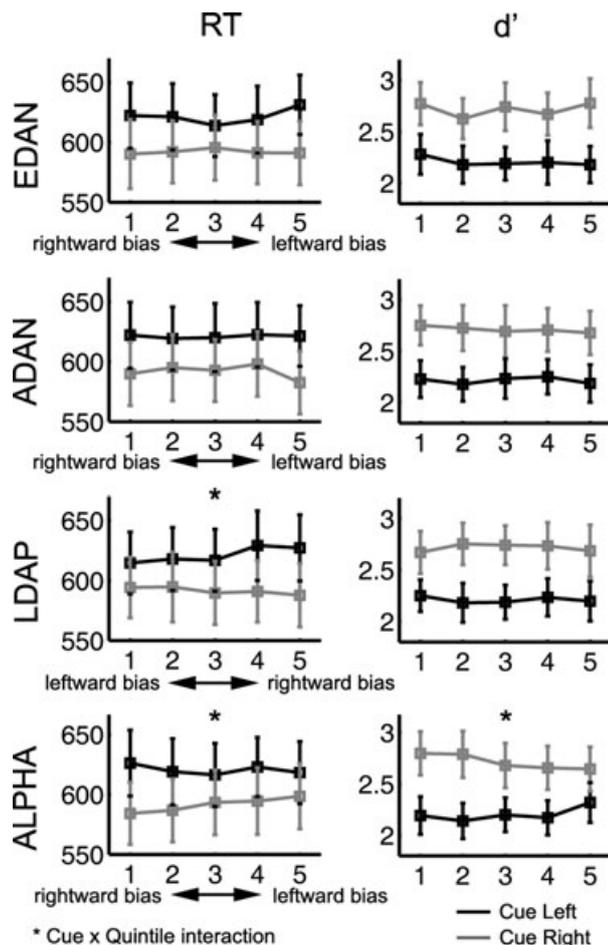


FIG. 3. Behavioral measures RT (left column) and  $d'$  (right column) plotted against the 'attention-directing' indices EDAN, ADAN and LDAP and pre-target alpha lateralization. Each index was derived on a single trial by subtracting the RH from the LH amplitude. Trials were sorted into quintiles such that the first contained the most negative index values and the fifth contained the most positive. Thus, for the EDAN, ADAN and alpha lateralization, which are defined by relatively more positive amplitude over the ipsilateral than contralateral hemisphere with respect to the direction of attention, the first quintile should contain the strongest attention deployments toward the right hemifield. Because the LDAP is defined by a relative positivity contralateral to attention direction, the first quintile contains the strongest deployments to the left in this case. Error bars indicate SEM. \*Significant Cue  $\times$  Quintile interactions ( $P < 0.05$ ).

the more alpha was biased toward the LH (marking attention directed to the left), the more positive the combined amplitude across hemispheres over the frontal cortex in this timeframe. Conversely, this bilateral activity was more positive with stronger rightward bias on cue-R trials. The three electrode pairs where the linear relationship achieved significance for the most consecutive timepoints (15–16, i.e. ~30 ms) are highlighted in green on the scalp montage reconstruction. The locations and timeframe match those of the component labeled 'P3f' in Fig. 2, a bilateral positivity distinctly visible in the 390 ms L + R topographic map. This topography is reproduced in the middle panel of Fig. 4, again averaged across cue-L and cue-R conditions (note that a main effect of cue was not found in preliminary tests in this timeframe, indicating that combined amplitude across hemispheres is not dependent on cue direction).

Given that the P3f and ADAN occur during the same time interval over the frontal scalp it is possible that both processes arise from the same pair of cortical regions that are both active relative to baseline but

relatively less in the hemisphere contralateral to cue direction (see Praamstra *et al.*, 2005). To gain some insight into this issue we compared topographic distributions and source localization solutions for the grand average sum (cue-L + cue-R) and difference (cue-L - cue-R) waveforms. In the scalp topographies we measured a distance between foci of 2.9 cm on the LH and 4.6 cm on the RH with P3f foci lying anterior to those of the ADAN (Fig. 4, center panels). We estimated the intracranial sources of scalp activity using a distributed linear inverse solution based on a local auto-regressive average (LAURA) model of the unknown current density in the brain (Grave de Peralta *et al.*, 2001; Michel *et al.*, 2004), implemented in the Cartool analysis package. LAURA uses a realistic head model with a solution space of 4024 nodes, where voxels are restricted to the gray matter of the average brain of the Montreal Neurological Institute divided into a regular grid with 6 mm spacing. Disparate source locations are apparent in the output (Fig. 4, right panels). The most activated voxel was determined within each hemisphere for each type of frontal activity. The P3f was localized to the left and right inferior frontal gyrus (BA9; [-47, 10, 30] in the LH and [53, 10, 24] in the RH), whereas ADAN was localized to the posterior part of the left and right middle frontal gyrus (BA6; [-30, -3, 57] in the LH and [30, 3, 57] in the RH), close to the precentral sulcus. We would emphasize that, although estimated coordinates are quantified, this constitutes a qualitative analysis intended to provide visualization, rather than a statistical test.

## Discussion

This study was aimed at establishing the functional relevance of electrophysiological effects occurring during the cued shifting of attention in space. Specifically, both broad-band and alpha-band (8–14 Hz) processes evoked by directional cue stimuli were assayed for relationships with behavior. Spatially-selective ERP processes differing as a function of cue direction were elucidated by comparing rightward and leftward cue conditions, revealing a posterior contralateral negativity at 240–280 ms (resembling the typical 'EDAN'), a fronto-central contralateral negativity at 370–410 ms ('ADAN') and a late sustained contralateral positivity beginning at ~420 ms ('LDAP'). In the alpha band, we found a relative decrease in amplitude contralateral to the cued location, replicating the routinely observed spatial biasing effect (e.g. Worden *et al.*, 2000).

In a trial-by-trial prediction analysis we replicated the finding that RT is significantly predicted by alpha lateralization (Thut *et al.*, 2006), with faster responses resulting from a greater relative decrease in alpha over the contralateral visual cortex. We additionally found that perceptual sensitivity ( $d'$ ) is predicted by alpha lateralization in the same spatially-specific way. This supports the view that visual alpha biasing is not related to response preparation but rather reflects preparatory setting of excitability in visual processing areas. The LDAP predicted RT, with faster RTs observed on trials with a greater contralateral positivity, but this did not influence  $d'$ . The earlier spatially-selective processes, EDAN and ADAN, were not found to predict either RT or  $d'$ .

### Baseline shifts and anticipatory biasing

Recent fMRI work has successfully demonstrated predictive links between pre-stimulus preparatory 'baseline shifts' in visual cortex and behavior. For example, Ress *et al.* (2000) showed that visual detection performance could be predicted by anticipatory activity in the primary visual cortex on a trial-by-trial basis. In more recent studies, Sylvester *et al.* (2007, 2008) have demonstrated that differential levels of anticipatory modulation among visual areas representing attended vs.

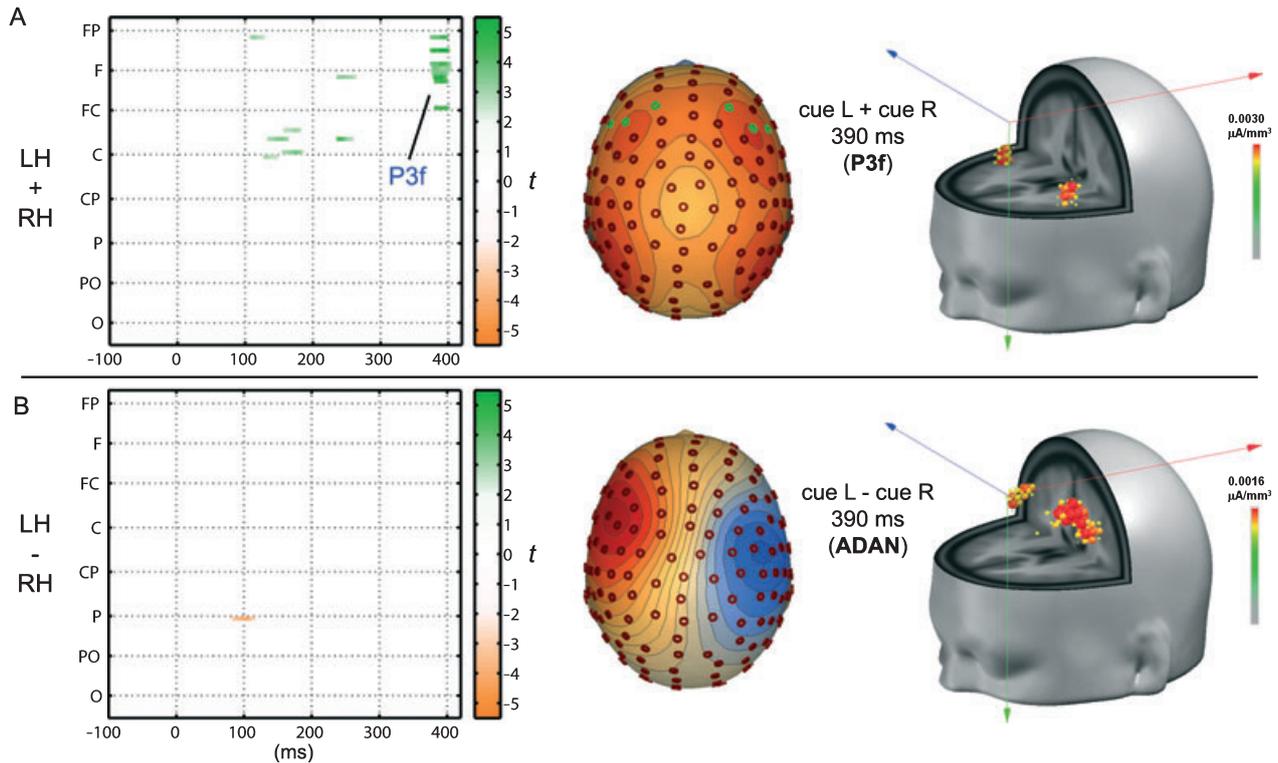


FIG. 4. Statistical cluster plots testing for a relationship between alpha lateralization and cue-evoked broad-band ERP amplitude when the latter is (A) collapsed (LH + RH) and (B) subtracted (LH – RH) across hemispheres. Also shown (middle and right panels) are the scalp topographies and distributed source solutions for (A) the P3f, measured at 390 ms by collapsing across cue directions, and (B) the ADAN, measured at 390 ms by subtracting the cue-right from the cue-left condition. The three electrode pairs where alpha lateralization and broad-band amplitude were significantly related for the most consecutive timepoints (15–16, i.e. ~30 ms) are marked as green discs. Relative activation across voxels marked in the source solutions is coded in both color and sphere radius. Note that different scales have been used for the P3f and ADAN solutions to facilitate a qualitative comparison.

unattended locations reliably predict performance during visuospatial cueing tasks.

The ERP correlates of such performance-critical baseline shifts have been elusive. The LDAP is thought to reflect sustained modulation of excitability in location-specific, and possibly feature-specific, areas of the early visual cortex in anticipation of the imperative stimulus (Praamstra *et al.*, 2005; Green & McDonald, 2006; Dale *et al.*, 2008). However, its specific contribution to pre-target biasing is muddled by the variability in its expression across studies. Although it persists until imperative stimulus presentation in many studies (e.g. Harter *et al.*, 1989; Jongen *et al.*, 2006), it has been found to fall short by several hundred milliseconds in others (Hopf & Mangun, 2000; Praamstra *et al.*, 2005; Talsma *et al.*, 2007). Further, late biasing activity has taken the form of a contralateral negativity in at least two studies (Grent-'t-Jong & Woldorff, 2007; Dale *et al.*, 2008). Jongen *et al.* (2006) found that, whereas non-lateralized anticipatory activity (i.e. the contingent negative variation and midline alpha) differed for trials with fast vs. slow RT on neutral trials, no such relationship could be seen for directionally-cued trials, and lateralized measures of spatial biasing were not found to be predictive of RT in either directional or neutral trials. Talsma *et al.* (2007) also separated trials on the basis of RT and looked retrospectively at the preceding preparatory processes but did not find direction-specific, sustained pre-target activity over the visual cortex. Only earlier non-lateralized activity (at least 250 ms prior to target) differed as a function of RT and only for the very slowest quartile. In our data a clear sustained contralateral positivity was observed, which had a significant influence on RT. Although this provides the new insight that anticipatory biasing activity can be measured in the broad-band ERP that bears directly on behavioral trial

outcomes, the determining factors in the abovementioned variation in the form of such activity across different tasks remain to be explained. Clearly, it will be crucial to take account of the ‘baseline shifts’ of fMRI studies in addressing this issue.

Differential biasing of alpha activity in the visual cortex with attention deployment appears to be an effect that is more consistently expressed. The present study adds to a long line of demonstrations of the spatial biasing effect (Worden *et al.*, 2000; Kelly *et al.*, 2005, 2006; Sauseng *et al.*, 2005; Thut *et al.*, 2006; Doesburg & Ward, 2007; Rihs *et al.*, 2007, 2009; Doesburg *et al.*, 2008; Gomez-Ramirez *et al.*, 2009). Moreover, attentional biasing of alpha is not only observed for spatial deployments but also for deployments between sensory modalities; when cued to attend to the visual modality, a sustained pre-target decrease in alpha power occurs, whereas alpha is relatively increased on attention deployment to the auditory modality, when suppression of visual distracters is required for task performance (Foxe *et al.*, 1998; Fu *et al.*, 2001; Gomez-Ramirez *et al.*, 2007).

Although the link between decreased alpha-band activity and increased visual cortical excitability has received compelling experimental support [most notably using transcranial magnetic stimulation (TMS); Romei *et al.*, 2008a,b; ], the evidence for links with behavior has been less strong. In particular, studies using non-spatial visual tasks have been inconsistent. Hanslmayr *et al.* (2007) failed to find a within-subjects relationship between alpha power and letter discrimination performance but instead found a relationship across subjects, with higher performance seen for subjects with lower alpha, and this held equally well when alpha was measured during a resting condition with eyes open. A similar across-subjects relationship was reported recently using only the contralateral hemisphere relative to spatially-

directed attention (Yamagishi *et al.*, 2008). In the context of sustained attention to a monotonous task, however, it has been shown that subjects with higher alpha are those who perform most optimally (Dockree *et al.*, 2007). A within-subjects relationship has been reported by van Dijk *et al.* (2008), who found lower pre-stimulus alpha power preceding hits compared with misses during a detection task performed at fixation. However, this was found for only eight of 21 subjects, who were retained on the basis of response patterns judged to reflect 'physical stamina and concentration'. A differential vigilance account is difficult to rule out in this case because alpha power measurements were not derived from specific task-related changes but rather captured background levels that are highly sensitive to both arousal changes and the opening and closing of eyes. We have avoided these concerns here by measuring differential alpha activity during cued attentional deployments. Following the approach of Thut *et al.* (2006), we sorted trials by the strength of this differential activity and computed discrimination sensitivity and RT. This analysis approach thus provides a strong basis for inferring a direct relationship between endogenously-deployed, spatially-specific, pre-target biasing mechanisms and behavioral outcome on a trial-by-trial basis.

Whereas alpha biasing was found to predict both RT and  $d'$ , LDAP predicted only RT. This may point to dissociation in the roles played by the two biasing indices. Evidence that they are not necessarily coexistent already comes from the fact that Dale *et al.* (2008) found broad-band biasing activity with fully reversed polarity (a late contralateral negativity) in the same dataset as used in the original alpha-mediated spatial biasing study of Worden *et al.* (2000). Conversely, in one other study that examined both broad-band and alpha-band biasing processes in the same subjects (Jongen *et al.*, 2006), a strong and long-lasting LDAP was observed but no direction-dependent lateralization of alpha was found in the 8–14 Hz range. Thus, a possibility that merits further investigation is that the LDAP and alpha biasing operate on different levels or aspects of visual processing and are thus invoked independently in accordance with the demands inherent in a given task. In the present paradigm, the two biasing processes were not only both present but also exhibited significant covariance across trials. Thus, a further possibility is that, when both are required for a given task, the efficacy of one is contingent on the other.

#### *Control signals giving rise to anticipatory bias*

The above finding shows that the variability in the magnitude of spatial biasing of alpha over the visual cortex can have direct consequences for behavioral outcome on a trial-by-trial basis. A pressing follow-up question is whether that variability in alpha biasing, in turn, is accounted for in some measure by variability in a preceding control process. To investigate this prospective 'source' of alpha biasing we conducted an exploratory analysis testing for relationships between the magnitude of the alpha bias and preceding broad-band ERP amplitude. It could be reasonably inferred that such biasing-related activity would be expected over regions of the well-known fronto-parietal network, whose involvement in the top-down control of attention has been shown repeatedly in functional imaging (e.g. Corbetta & Shulman, 2002; Woldorff *et al.*, 2004) and lesion (see Posner & Petersen, 1990). However, there is less basis for prediction of the precise timing of such a control process during the ~400 ms intervening between cue onset and beginning of anticipatory bias, as imaging work cannot provide accurate information in this regard. Therefore, we employed a statistical cluster plot analysis in which point-wise tests for linear variation with alpha lateralization quintile were conducted. We found no relationship with differential amplitude measured between symmetric sites across hemispheres but did find

that the combined bilateral amplitude of a frontal positivity 'P3f' occurring in the interval ~370–400 ms was significantly linked with alpha lateralization in the direction of the cue.

The quadruple-node topography comprising the bilateral frontal P3f and parietal P3p components is very similar to the distribution observed in a previous study of cue-directed attention and motor intention (Praagstra *et al.*, 2005) during the same time frame (350–400 ms). Those authors suggested that the ADAN might represent a lateralized modulation of the frontal part of this activation but did not examine this explicitly. The P3f foci observed in our 'sum' (cue-L + cue-R) topography can be seen to lie distinctly more anteriorly than the ADAN foci resolved in the 'difference' (cue-L – cue-R) topography. In addition, the estimated intracranial sources of the ADAN and P3f appeared to differ; whereas the ADAN was localized to the superior premotor cortex, the P3f was localized to more inferior and anterior coordinates, in or around the inferior frontal gyrus. Thus, the spatially-selective ADAN and non-selective P3f may not arise from the same bilaterally active regions with a superimposed directional asymmetry but rather come from distinct frontal areas. It is interesting to note that fMRI studies consistently find bilateral activation of the middle frontal gyrus (Hopfinger *et al.*, 2000; Corbetta *et al.*, 2002, 2005; Woldorff *et al.*, 2004), whereas the few studies directly testing for direction selectivity in frontal activation implicate regions approximating the frontal eye fields (Corbetta *et al.*, 2002, 2005). In a recent fMRI study by Sylvester *et al.* (2008), anticipatory blood oxygenation level-dependent (BOLD) activity was contrasted in two orientation discrimination tasks of the same structure and difficulty but with different perceptual demands. Greater suppression of visual areas (V1–V4 and V3A) processing unattended locations was observed when the major demand of the task was placed on low-contrast detection than when targets involved finer orientation judgments of suprathreshold stimuli. Interestingly, this was accompanied by greater activation bilaterally in both the inferior frontal sulcus and frontal eye field. Although these areas showed spatially-selective activation (greater for contralateral cue direction) this selectivity did not vary across conditions involving more or less suppression. Although the timing and duration of the BOLD activity cannot be precisely ascertained, a relationship between the inferior frontal activity and the P3f is plausible and may merit further study.

It should be noted that the lack of relationship between alpha lateralization and preceding direction-selective parietal and frontal activity (EDAN and ADAN) does not necessarily indicate that these processes do not play a role in establishing attentional bias. It indicates only that the variance in alpha biasing strength is not explained by variance in these processes. Indeed, areas of the parietal and frontal cortex known to encode spatial locations with predominant contralateral representation, such as the lateral intraparietal area and frontal eye field in monkeys, are strongly implicated in the directing of covert attention (Bisley & Goldberg, 2003; Moore & Armstrong, 2003; Thompson *et al.*, 2005; Gottlieb, 2007). Strong evidence for a role played by these areas in generating biased preparatory extrastriate activity has also been uncovered in humans, using granger causality measures (Bressler *et al.*, 2008) and combined TMS and fMRI (Ruff *et al.*, 2006). Thus, it is possible that direction-selective activity in such higher spatial processing areas is critical in encoding the location to be attended but the strength of the subsequent biasing signal, at least in the context of our task, is regulated by a dissociable process, such as that generating the P3f component.

#### *Approaches to examining the control of attentional shifts*

The trial-by-trial alpha lateralization-based sorting procedure applied here represents a novel approach to delineating the processes that are

critical to attention shifting in the cue-evoked ERP, which has long been a considerable challenge. A number of previous studies have employed a non-informative neutral cue (Talsma *et al.*, 2005, 2007; Green & McDonald, 2008) or a 'cue-interpretation' control stimulus (Grent-'t-Jong & Woldorff, 2007) as a baseline condition with which to compare both leftward and rightward cue processing. The power of this approach in 'isolating' attentional control (Green & McDonald, 2008), however, relies on the assumption that neutral cues involve no attentional control, i.e. that no attention shifts are initiated during neutral/passive cues and that states of preparation are confined to trials with non-chance directional probabilities. Behavioral and electrophysiological studies on the processing of neutral cues, in fact, provide evidence against these notions (De Gonzaga Gawryszewski *et al.*, 1987; Eimer, 1997; Jongen *et al.*, 2006). The use of 'interpret' cues (indicating no upcoming target) relies on the further assumption that these cues are equated with directional cues in terms of the interpretation processes carried out prior to shifting, even though they differ in both physical form and their actual meaning (Grent-'t-Jong & Woldorff, 2007).

Such a neutral cue-comparison approach was adopted in two recent ERP studies that applied source analysis techniques to examine the timing and sequence of fronto-parietal activity associated with the control of spatial attentional deployment (Grent-'t-Jong & Woldorff, 2007; Green & McDonald, 2008). In common between the two studies was a pattern whereby a broad sweep of activity in the frontal cortex at ~400 ms was succeeded by a much later parietal activation at ~700 ms. This characterization of fronto-parietal attentional control, involving slow successive transmissions of information between the areas, stands in contrast to other accounts of the temporal dynamics of attentional control. For instance, Doesburg and colleagues have put forward a far more interactive model where the frontal and parietal cortex are transiently coupled through long-range oscillatory synchrony in the gamma (Doesburg *et al.*, 2008) and alpha (Doesburg & Ward, 2007) bands. The present study identifies a short-lasting frontal component occurring roughly coincident with the onset of biasing in visual areas (400–450 ms), the P3f, as being involved in the generation and control of top-down attentional bias in the visual cortex. It is interesting to note that this transient process would go undetected in an analysis restricted to the theta band, where amplitude variations occurring over multiple cycles of a slow oscillatory period of 150–250 ms (4–7 Hz) are measured (Green & McDonald, 2008). Our analysis surmounts the problem of cue-comparison validity by instead comparing across levels of pre-target biasing magnitude. However, a limitation is that it can only detect control processes that are linearly related to biasing quintile and, although this bilateral frontal positivity explains a significant amount of variance in alpha biasing activity, it remains unknown what processes, in turn, form the source of this activity. Moreover, whether such processes can be classified as sources or targets of attentional control is not straightforward, as these roles may overlap and be realized in a distributed manner (Serences & Yantis, 2006). Fully understanding the control of top-down attentional biasing in humans will clearly entail the consideration of each of a variety of approaches and an awareness of their limitations.

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## Abbreviations

ADAN, anterior directing-attention negativity; cue-L, leftward cue; cue-R, rightward cue; d', target discriminability; EDAN, early directing-attention negativity; ERP, event-related potential; fMRI, functional magnetic resonance imaging; LDAP, late directing-attention positivity; LH, left hemisphere; RH, right hemisphere; RT, reaction time; TMS, transcranial magnetic stimulation; TSE, temporal spectral evolution.

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