Lateralized Frontal Eye Field Activity Precedes Occipital Activity Shortly before Saccades: Evidence for Cortico-cortical Feedback as a Mechanism Underlying Covert Attention Shifts

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Abstract

■ When an eye movement is prepared, attention is shifted toward the saccade end-goal. This coupling of eye movements and spatial attention is thought to be mediated by cortical connections between the FEFs and the visual cortex. Here, we present evidence for the existence of these connections. A visual discrimination task was performed while recording the EEG. Discrimination performance was significantly improved when the discrimination target and the saccade target matched. EEG results show that frontal activity precedes occipital activity contralateral to saccade direction when the saccade is prepared but not yet executed; these effects were absent in fixation conditions. This is consistent with the idea that the FEF exerts a direct modulatory influence on the visual cortex and enhances perception at the saccade end-goal. ■

INTRODUCTION

When faced with an abundance of stimuli, the visual system must select certain stimuli over others for elaborated processing. This mechanism, *selective attention*, can be directed and biased in many ways, providing emphasis on certain perceptual components. Attention can be drawn toward an object or location by virtue of its characteristics and salience, which is referred to as stimulus-driven or bottom–up attention. When driven internally or top–down, attentional selection originates from an internal state. This type of attention is often driven by a specific goal or task, such as walking down the street or opening a door.

It has been found that action and attention are closely coupled in the brain. In fact, selective visual attention in the absence of eye movements (*covert attention*) is often attributed to unexecuted eye-motor commands, a theory known as the *premotor theory* (Rizzolatti, Riggio, Dascola, & Umilta, 1987). Numerous studies support this theory, or at least a large functional and anatomical overlap (Awh, Armstrong, & Moore, 2006; Thompson, Biscoe, & Sato, 2005; Grosbras & Paus, 2003; Corbetta et al., 1998; Kustov & Robinson, 1996; Hoffman & Subramaniam, 1995; for a review, see Moore, 2006). This theory has been contested (Juan et al., 2008; Castet, Jeanjean, Montagnini, Laugier, & Masson, 2006; Juan, Shorter-Jacobi, & Schall, 2004; Hunt & Kingstone, 2003), in that attentional shifts do occur without eye movements and vice versa. Despite this, it is generally acknowledged that preparing an eye movement is a strong bias in the locus of visuospatial attention, albeit not the only one.

Deubel and Schneider (1996) demonstrated a tight coupling between eye movements and spatial attention shifts. Performance on a discrimination task was enhanced only if the saccade end-goal and the target to be discriminated were at the same spatial location. Discrimination performance suffered severely when the saccade end-goal was different (although the target was spatially adjacent) from the discrimination target (DT). Importantly, no eye movements were yet made at the moment of DT presentation. This automatic coupling has also been shown in other studies (Neggers et al., 2007; Dore-Mazars, Pouget, & Beauvillain, 2004; Kowler, Anderson, Dosher, & Blaser, 1995).

Recent evidence suggests the existence of cortical (feedback) connections between motor and visual areas that could mediate attentional shifts. The FEFs are key cortical areas for saccade preparation and execution. Stimulation of the primate FEF resulted in increased activity in the monkey visual area V4 when receptive fields matched (Moore & Armstrong, 2003) and increased discrimination performance (Moore & Fallah, 2001, 2004). Super, van der Togt, Spekreijse, and Lamme (2004) found enhanced activity in the monkey primary visual cortex 100–200 msec before the initiation of a saccade when the recorded cells receptive field was in the saccade end-goal location.

In humans, evidence is emerging for these cortical connections. A study by Grosbras and Paus (2003) showed increased visual detection performance when TMS on

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the FEF was applied 100–40 msec before target presentation. Lowered phosphene thresholds were found after TMS on the FEF in a study by Silvanto, Lavie, and Walsh (2006). A concurrent TMS–fMRI study by Ruff et al. (2006) stimulated the right FEF while measuring BOLD response in posterior brain regions. It was found that FEF–TMS modulates activity in visual areas, including the primary visual cortex, which was confirmed by a recent EEG study (Taylor, Nobre, & Rushworth, 2007). Although the studies by Ruff et al. and Moore and Armstrong (2003) found effects in the periphery, indicating that these effects subserve saccade planning (as saccades are made into the periphery), this retinotopy has not been consistently found (Silvanto et al., 2006; Muggleton, Juan, Cowey, & Walsh, 2003).

Recently, in a study by Neggers et al. (2007), a brief train of three TMS pulses was applied to the FEF just before subjects made a saccade to a DT (using the exact same paradigm as Deubel & Schneider, 1996). This diminished the known discrimination performance gains at future saccade targets (STs), although it did not disrupt saccade execution. This showed that by modulating activity in the FEF, discrimination performance gains (and therefore presumably attentional shifts) before saccades could be affected and that there is a tight coupling of saccade preparation and visual attention.

The present study elaborates on the results of the preceding TMS study. From that TMS–FEF study, it seems apparent that the FEF can induce visual processing changes in another region upstream in the visual processing pathways. Most likely this region entails the visual cortex, although that was not explicitly demonstrated (for other options, see Neggers et al., 2007). Therefore, the same experimental design (the Deubel and Schneider task) was used while recording the EEG. This will give insight in the exact temporal order of activation for cortical regions contributing to attentional deployment during both directional cueing and saccade preparation. Specifically, after saccade-go but before the execution of the actual saccade, we expect to find activity that reflects the automatic coupling of eye movements and spatial attention. This would most likely involve the FEF, followed by activity in the visual cortex. The intraparietal sulcus (IPS) is also an important part of the attentional network (Van der Lubbe, Neggers, Verleger, & Kenemans, 2006; Giesbrecht, Woldorff, Song, & Mangun, 2003; Hopfinger, Woldorff, Fletcher, & Mangun, 2001; Hopfinger, Buonocore, & Mangun, 2000). However, on the basis of findings from a preceding TMS study from our group (van Ettinger-Veenstra et al., unpublished observations) and Ruff et al. (2008), we expect no IPS involvement here because no influence of the IPS has been found in these studies.

In addition, EEG during the cue-go interval can reveal mechanisms involved the control of attention as well. It has been shown that cueing the location of an upcoming DT elicits several distinct neural events, most notably the early directing attention negativity (EDAN), the anterior direction attention negativity (ADAN), and the late direct-ing attention positivity (LDAP) (Van der Lubbe et al., 2006; Van der Stigchel, Heslenfeld, & Theeuwes, 2006; Hopf & Mangun, 2000; Nobre, Sebestyen, & Miniussi, 2000; Harter, Miller, Price, LaLonde, & Keyes, 1989). The EDAN is a lateralized occipital negativity that was originally thought to reflect attentional deployment; however, more recently it has been linked to the relevant part of the cue, that is, the part that signals the direction of attention (Van Velzen & Eimer, 2003). The ADAN and the LDAP are thought to reflect (covert) attentional deployment and to originate from the FEF and the IPS, respectively (Van der Lubbe et al., 2006). In the current study, besides saccade-induced attentional shifts, we expect to find these established effects of attentional deployment during the cueing period in the FEF and IPS to assess the validity of the current paradigm.

METHODS

Subjects were asked to make an eye movement toward a peripheral target while a DT appeared either at or near the ST. This experiment is a replication of Experiment 2 from Deubel and Schneider (1996) with additional fixation conditions.

Participants

Thirteen right-handed subjects (8 women and 5 men) participated (including two of the authors). All participants had normal or corrected-to-normal vision. Subjects signed informed consent prior to participation.

Apparatus

EEG was recorded using a 70-channel Biosemi ActiveTwo system, which has 64 active Ag–AgCl electrodes (10–10 system). Recordings were sampled at 2048 and 0.16–100 Hz band-pass filtered.

Eye tracking was performed using the Eyelink II system (SR Research, Ottawa, Canada), positioned on the left eye, at a sampling rate of 500 Hz. The infrared camera was mounted on a rigid headrest and controlled by a dedicated PC. Subjects sat in a dimly lit room, secured in a chin- and headrest. Stimuli were presented on a 19-in. (40 × 30 cm) Iiyama monitor at 100 Hz and a resolution of 1024 × 768. The monitor was mounted 37 cm above a mirror at a 45° angle, which in turn was 35 cm away from the participant, yielding an effective viewing distance of 72 cm. Stimuli were generated and displayed using the Matlab psychophysics toolbox (version 7.0.4; Brainard, 1997; Pelli, 1997) on a Pentium PC. Both EEG and eye-tracker data were synchronized with stimulus presentation by TTL pulses from the stimulus presentation computer.

Behavioral Paradigm and Procedure

In this experiment, we used a modified version of Experiment 2 from Deubel and Schneider (1996), which is a

well-known demonstration of the coupling between saccade planning and discrimination performance. To be able to discern between saccade planning and other (task-related) activity, two fixation conditions were randomly intermixed.

Each trial started with a drift correction routine for the eye tracker. Trials did not start until the subjects gaze was centered and stable. At the start of every trial, a fixation cross ($0.52° \times 0.52°$) was presented for 700 msec with three colored ellipses on each side ($0.82° \times 1.64°$ per ellipse, spaced 5° from the fixation point and spaced 0.52° apart; see Figure 1). These ellipses were blue (closest to fixation), green (center), and red (outer). Five premasks were overlaid (the center three coinciding with the ellipses) on each side in the shape of a digital 8. After fixation, the fixation cross was replaced by an informative arrow cue. The duration of this cue was randomly chosen between 500 and 1000 msec (step size = 1 msec) to avoid anticipation effects. There were three types of cues: saccade, directional fixation, and nondirectional fixation cues (see Figure 1). Saccade cues were red, green, or blue and instructed the subject to saccade to the corresponding ellipse on the side the cue was pointing (the ST). Directional fixation cues were always yellow and indicated the side where a DT was going to be. Nondirectional fixation cues were also red, green, or blue but were double-sided arrows that did not indicate the direction of the upcoming DT. The color-coded cue made this condition comparable to the stimuli in the saccade condition, apart from the fact that the cue did not indicate a direction. In both direc-

tional conditions (saccade and fixation), the colored arrow was accompanied by a gray arrow pointing in the opposite direction to control for visual stimulation differences between conditions. In saccade trials, the disappearance of the cue marked the saccade-go signal. Sixty milliseconds after cue disappearance, the premasks disappeared and the DT appeared (either a normal or a mirrored "E") surrounded by randomly assigned distracters (digital 2s or 5s). The DT always appeared at the green ellipse (which was known to the subjects). The DT and the distracters were shown for 120 msec, leaving an empty display with only the ellipses visible. As the average saccade latency is well above 250 msec, hardly any saccades were made before the DT disappeared (which disappeared 180 msec after saccade-go). After the saccade had been made, subjects had ample time to indicate whether they had seen an E or the mirrored version (a "3"). Trials containing premature saccades (<200 msec) were removed from the data. In fixation trials, the same applied, but no saccade was made.

The experiment was divided in four blocks of 72 trials (lasting ~7–10 min) containing 24 (randomized) trials of each condition (saccade, directional fixation, and nondirectional fixation).

Analysis

Eye position data from the eye tracker were analyzed. Saccade onsets were detected using a velocity threshold of 30 deg/sec and an acceleration threshold of 8000 deg/sec^2. Rigorous analysis of the trials was essential to ensure that

Figure 1. Schematic overview of the stimulus presentation. Different cues instructed the subject to either make an eye movement or covertly attend the cued direction. The sequence of events is shown from bottom left to top right. Each trial started with six masked colored ellipses. A cue indicated the type of trial and, in all cases except nondirectional fixation, the direction of the upcoming discrimination target (DT). Disappearance of the cue marked the go signal in the saccade condition ($t = 0$). However, before a saccade could be made, the targets unmasked, briefly showing distractors and the discrimination target (60 msec), after which only the ellipses remained on screen. Afterward, subjects had ample time to respond. The bottom schematic depicts the time course of events. The variability of the timing is represented by an "x," which ranged between 0 and 500 msec.
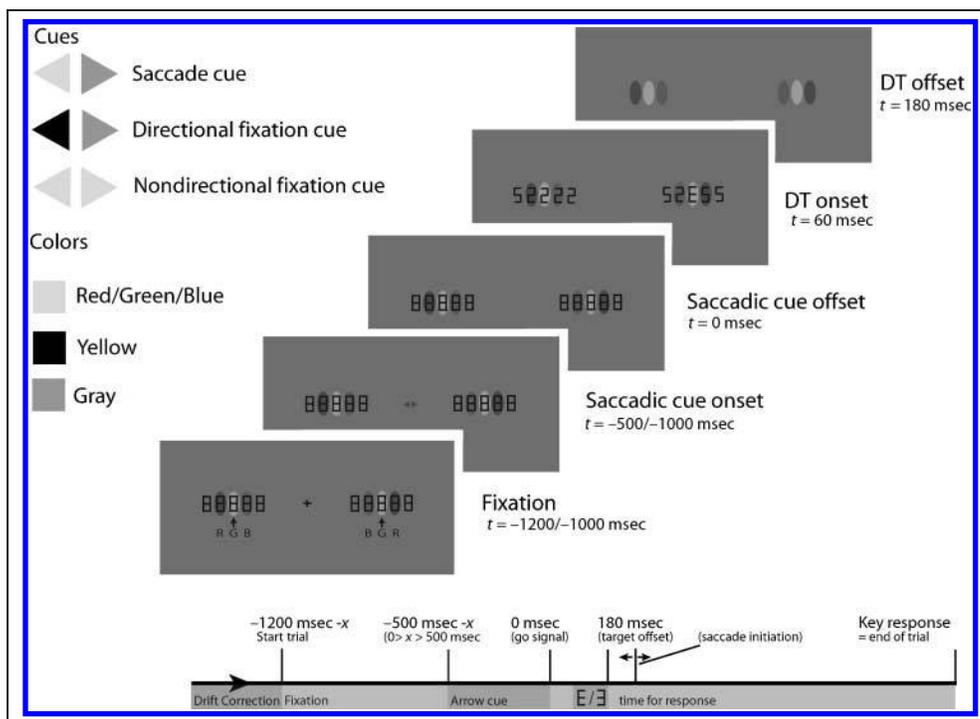
only correct saccades were allowed. Any trials with saccades before 200 msec after saccade-go (20 msec after DT disappearance) were discarded, as were trials in which saccades landed more than 50 pixels (2.07°) away from the ST. In fixation conditions, trials were rejected where the gaze position deviated more than 50 pixels from central fixation at any time during the entire trial.

EEG data were analyzed using EEGLAB (version 6.02b, http://sccn.ucsd.edu/eeglab; Delorme & Makeig, 2004), a Matlab toolbox. All signals were (off-line) average referenced. Both cue-onset- and offset (saccade-go)-locked analyses were made to asses both cue-related effects and saccade preparation activity. Cue-onset-locked epoch interval was −100 until 500 msec postcue, as this is the shortest interval of the variable cue-onset–offset duration. In the cue-offset/saccade-go-locked analyses, the epoch interval was −100 to 200 msec. For comparability, the same intervals were chosen for the fixation conditions.

Trials with premature saccades or small deviations from fixation were removed using data from the eye tracker. To ensure that no ocular artifacts (such as blinks) were left in the data built-in EEGLAB artifact, rejection routines were used (Delorme & Makeig, 2004) as well as visual inspection of the data. Rigorous rejection ensured artifact and saccade-free epochs. This led to relatively low acceptance rates (54 ± 15.9%) in the cue-offset analysis. Acceptance rates did not differ significantly between conditions, ANOVA, $F(2, 24) = 1.535\ p = .236$. Epoch acceptance rates for the cue-onset conditions were higher (81 ± 8.8%) but differed between conditions, ANOVA, $F(2, 24) = 5.142\ p = .014$. However, because the acceptance rates were high and the difference in acceptance rates is small (2–5%), it is unlikely that this will bias the data.

Separate analyses were done for cue-left and cue-right conditions. Data from the cue-left conditions were then mirrored with respect to the anterior–posterior midline and averaged with the cue-right conditions. This resulted in a scalp map, in which activity in the right hemisphere reflects activity ipsilateral relative to cue direction; the left hemisphere reflects activity contralateral to cue direction. For optimal comparability with the previous TMS study, time windows in the cue-offset condition were chosen on the basis of the TMS times of Neggers et al. (2007), which had stimulation times at 60, 90, and 120 msec after saccade-go. Average activity was extracted for time windows 60–90, 90–120, 120–150, and 150–180 msec for all cue-offset conditions at electrodes F7/8, FC3/4, P1/2, PO7/8, and O1/2.

To enable correlational analysis, average amplitudes were extracted for every subject over contralateral frontal electrodes FC3/4 for the early time windows (60–90 and 90–120 msec) and the last time window (150–180 msec) for occipital electrodes O1/2 from a saccade–directional fixation subtraction. As a control condition, the average peak of the N200 (O1/2 = 160–210 msec after cue onset) in the directional fixation condition was also extracted for all subjects.

Source localization was performed using the SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) soft-ware package using an empirical Bayes approach. Here, electrode activity is projected onto a three-dimensional brain model, with a large number of fixed (location and orientation) dipoles, where the amplitude of the dipoles is the parameter to be optimized. The location and the orientation of the dipoles are fixed by assuming a standardized folded cortical surface, with dipoles orthogonal to the cortical sheet (Dale & Sereno, 1993). Saccade and directional fixation EEG data (after saccade-go) for each subject were converted from EEGLAB to the SPM data format. A contrast of interest was defined, which is the saccade–directional fixation subtraction. The data were coregistered to the Montreal Neurological Institute (MNI) space using default Biosemi electrode locations. Inverse reconstruction was performed using the classical linear approach (Dale & Sereno, 1993) using multiple sparse priors with automatic relevance determination optimization (Friston et al., 2008) for the time window of interest (60–180 msec after saccade-go). This approach can test multiple restricted models and select the most relevant model using Bayesian model selection (Mattout, Phillips, Penny, Rugg, & Friston, 2006). Therefore, a number of plausible models were defined, including bilateral and unilateral FEF, occipital area, and IPS (see Figure 7). Coordinates were based on localizer findings of Neggers et al. (2007) for the FEF and IPS and MNI electrode location of O1 and O2 for the occipital ROIs. The radius for these areas was a default of 32 mm.

RESULTS

Discrimination Performance

Averaged discrimination performance for all 13 participants is plotted in Figure 2. A clear increase in performance can be observed when the ST coincides with the DT, ANOVA, $F(2, 22) = 15.11, p < .0001$; center/inner target, $t(12) = 3.62\ p = .004$; center/outer target, $t(12) = 6.05, p < .0001$. No significant difference was found between both targets adjacent to the DT (paired samples t test outer/inner target), $t(12) = 2.14, p = .056$. This is a replication of the results of Experiment 2 of Deubel and Schneider (1996) and thus indicates that the subjects performed the task as instructed. Discrimination performance on the directionally cued fixation condition was (nearly) the same as the coinciding ST/DT saccade condition (paired samples t test; $t = 1.98, p = .71$). Nondirectional cues impaired performance significantly compared with coinciding DT–ST trials in the saccade condition (paired samples t test), $t(12) = 4.63, p = .001$, and trials in the directional fixation (paired samples t test), $t(12) = 3.54, p = .004$.

Saccade Performance

Saccade latencies did not differ between the STs, $F(2, 22) = 1.289, p = .295$. On average, in 60.1 ± 18.2% of the trials,
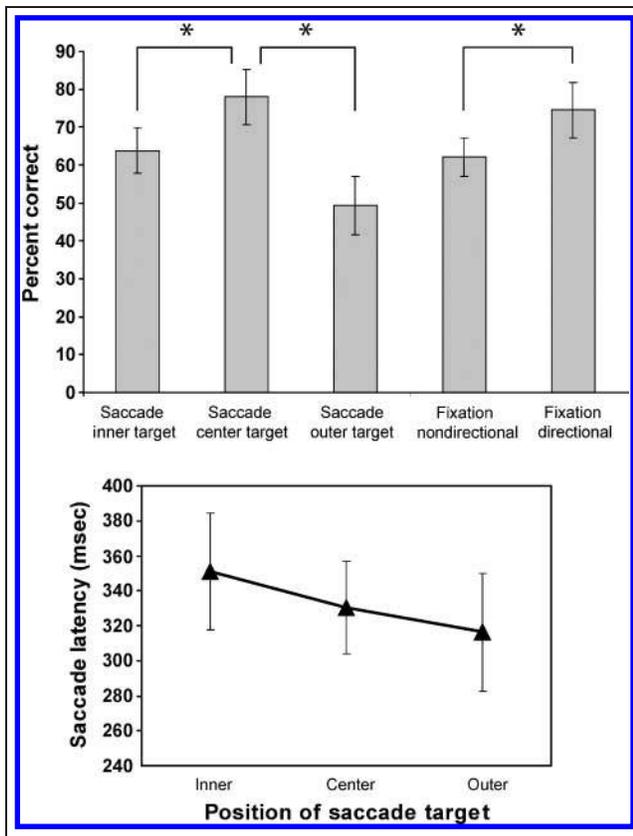
Figure 2. Behavioral performance. The top graph shows discrimination performance for all conditions. The left three bars display performance for the saccade conditions. As the discrimination target is always located at the center target, eye movements toward either inner or outer targets yielded lower performance. The two right bars display performance without eye movements, either with (right) or without (left) directional cueing. The bottom graph shows saccade latency for every saccade target. No significant differences were found between targets.

a saccade was made that was within the strict acceptance criteria (see Methods). Subjects did not break fixation in 67.6 ± 17.7%) of the fixation trials. The reason for this low performance is likely the intermixed saccade and fixation trials.

EEG—Cue-offset/Saccade-go-related Effects

The cue-offset/saccade-go-locked analyses revealed saccade preparatory activity. Time windows (60–90, 90–120, 120–150, and 150–180 msec) were chosen to correspond to the preceding TMS article (Neggers et al., 2007). Because the only difference between the saccade and the directional fixation condition concerned the saccade preparation (with similar directional cues), the latter was used as a baseline condition. Grand averages from the directional fixation condition were thus subtracted from the saccade condition.

In turn, activity from the nondirectional fixation condition was subtracted from the directional fixation condition to remove irrelevant task-related activity, that is,

correcting for all trial events except for the directionality of the cue possibly evoking covert spatial attention shifts. The latter contrast might therefore reveal lateralized EEG effects evoked by the directional cue itself.

Figure 3 shows saccade-go-locked ERPs for all selected electrode pairs. In the saccade condition (with directional fixation as baseline), a clear, lateralized, positive increase can be seen, contralateral to saccade direction at the frontal electrodes, peaking around 120–150 msec (see also Figure 4). Time window analysis shows that this increase is significant at all time windows between 60 and 180 msec after cue offset for the electrode pair F7/8 (paired samples t test), 60–90 msec, $t(12) = 2.16$, $p = .05$; 90–120 msec, $t(12) = 4.55$, $p < .001$; 120–150 msec, $t(12) = 4.63$, $p < .001$; and 150–180 msec, $t(12) = 4.30$, $p = .001$, and for the time window 90–120 msec for FC3/4 (paired samples t test), 90–120 msec, $t(12) = 2.52$, $p = .03$). A later, negative occipital effect can be observed at electrode pair O1/2, reaching significance level at 120–150 msec after cue offset. Time window analysis shows that this effect is significant at time windows 120–150 and 150–180 msec (paired samples t test), 120–150 msec, $t(12) = -2.47$, $p = .03$; and 150–180 msec, $t(12) = -3.01$, $p = .01$.

To check for possible baseline effects, the analysis was also performed using the nondirectional fixation condition as a baseline (see Figure 3). Results were very similar for both baseline choices. Lateralized activity in fronto-central electrodes FC3/4 was slightly higher, resulting in more time windows reaching significance level (paired samples t test), 60–90 msec, $t(12) = 4.06$, $p < .01$; 90–120 msec, $t(12) = 5.34$, $p < .001$; 120–150 msec, $t(12) = 3.63$, $p < .01$; and 150–180 msec, $t(12) = 3.65$, $p < .01$. The occipital effect at time window 120–150 msec was not significant (paired samples t test), 120–150 msec, $t(12) = -0.75$, $p = .47$, whereas it was significant when using the directional fixation condition as baseline, which indicates a possible baseline effect. This difference is reflected in the time window 120–150 msec in the directional–nondirection fixation subtraction (paired samples t test), 120–150 msec, $t(12) = 3.16$, $p = .01$.

A lateralization difference was found for the occipital effect between saccade directions (see Figure 5). When subjects were instructed to make an eye movement to a target on the right, a clear increase in negativity was observed in the contralateral (left) hemisphere. When instructed to make a saccade to the left, occipital negativity was observed in both hemispheres.

No significant effects were found at parietal electrodes P1/2 or parieto-occipital electrode PO7/8 in any time window.

EEG—Correlations

A significant negative correlation was found between the average amplitude of contralateral fronto-central electrode pair FC3/5 in early time window 60–90 msec and the late time window 150–180 msec of occipital electrode O1/2 (Pearson correlation FC3/5 contralateral O1/2 = −0.72,
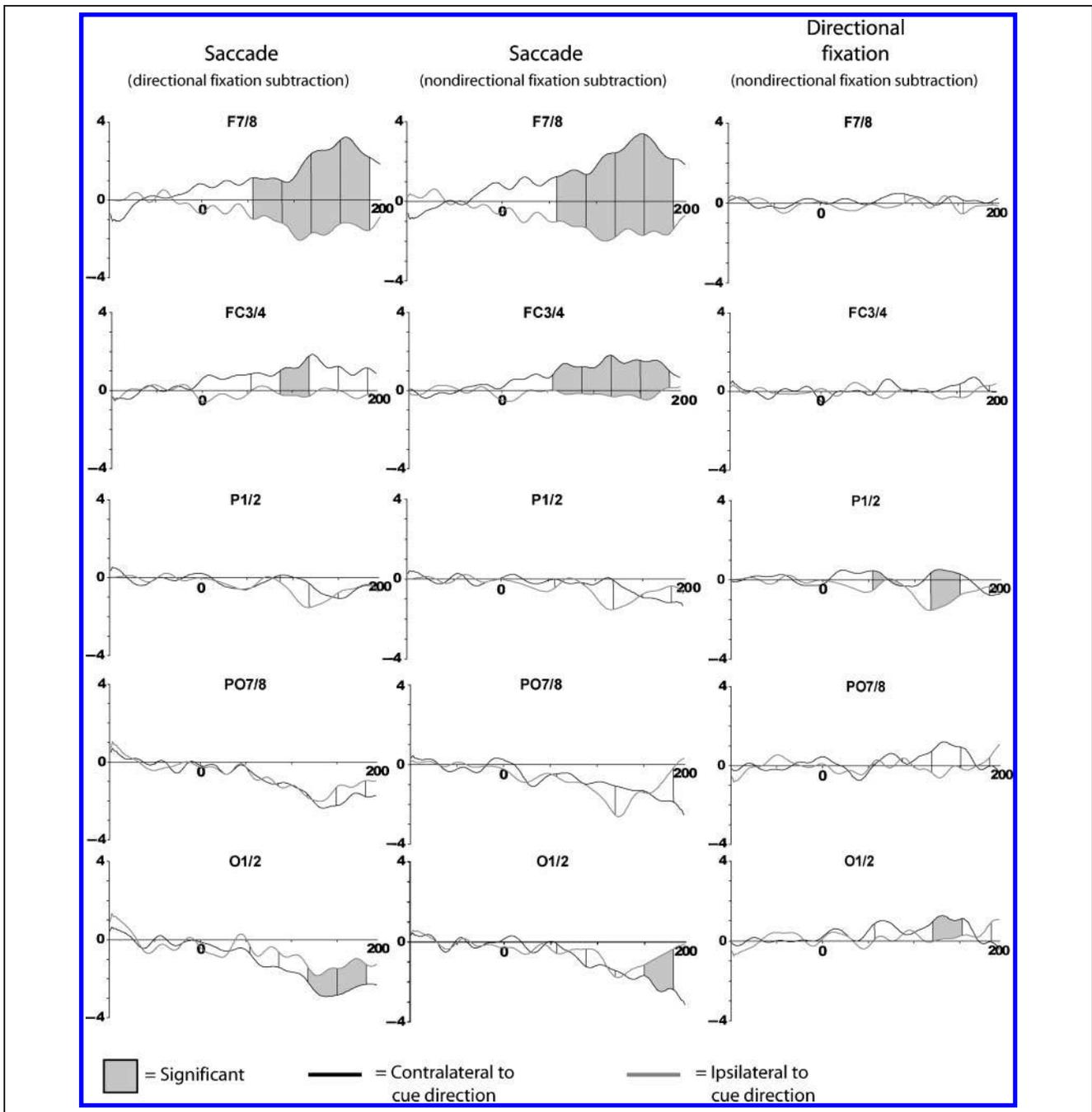
Figure 3. ERP plots after saccade-go (0 msec) for selected electrodes. Shown are plots for the saccade condition, with directional fixation subtracted (left); the saccade condition with nondirectional fixation subtracted (center) and the directional fixation condition with nondirectional fixation as baseline. Contralateral activity is shown in black, ipsilateral activity in gray. Significant differences between contra- and ipsilateral activity for time windows 60–90, 90–120, 120–150, and 150–180 msec are shown as gray-filled areas.

$p < .01$; see Figure 6). No significant correlation was found between the second time window (90–120 msec) frontal time window and the occipital electrode pair O1/2 (Pearson correlation FC3/5 contralateral O1/2 = −0.45, $p = .12$). We recognize that the correlations could be confounded by differences in conductance per subject. A higher average amplitude due to, for instance, skull thickness could result in higher (or lower) frontal and occipital activity for a particular subject without a neces-

sary neural link, which could artificially bias correlation coefficients. To control for this, the average N200 (160–210 msec) of electrodes O1/2 was extracted from the directional fixation condition during the cueing period as an individual measure of subject responsiveness. No significant correlation between occipital N200 and either occipital or frontal electrodes were found (Pearson correlation FC3/5 60–90 msec, N200 = −0.48, $p = .10$; FC3/5 90–120 msec, N200 = −0.16, $p = .60$; O1/2 150–180 msec,

N200 = 0.46 p = .12). This suggests that the obtained correlations are not due to individual differences in conductance but due to actual neural activity.

EEG—Source Localization

We performed source localization on the saccade–directional fixation subtraction to ensure that the observed activity originates from the proposed sources. Results can be found in Table 1 and Figure 7. Different models were tested, including an unconstrained model. The overall model evidence reflects the likelihood of this model, which incorporates the variance explained and model complexity (for details, see Stephan, Penny, Daunizeau, Moran, and Friston, 2009). As expected, the unconstrained model can explain the most variance, as it has most degrees of freedom, which is also reflected in the model evidence. Despite this, we believe that this unconstrained model yields implausible results to maximize the explained variance (for details, see the Discussion section). The proposed models (including the FEF, the IPS, and the

occipital sources) explain only a few percent less of the variance (95.97% unconstrained vs. 93.58% constrained) but are based on plausible sources. The model with the highest model evidence is the bilateral FEF–occipital model (154.2), followed by the bilateral FEF model (152.0). Adding the IPS to the model reduces model evidence (bilateral FEF–occipital–IPS = 145.8).

EEG—Cue Offset in the Fixation Conditions

Time window analysis of the directional fixation condition revealed a significant, lateralized positivity at parietal electrode pair P1/2 (paired samples t test) for time windows 60–90 msec, $t(12)$ = 2.34 p = .04, and 120–150 msec, $t(12)$ = −2.54, p = .03. Also, a lateralized occipital effect (O1/2) in the time window 120–150 msec was found (paired samples t test), $t(12)$ = 2.97, p = .012. However, this occipital effect is in the opposite direction compared with the occipital effect observed in the saccade condition: There is an increase in positivity contralateral to the cued

Figure 4. Double subtraction EEG topoplots for the saccade and directional fixation conditions for different time windows. To obtain the double subtraction plots, activity from the left and right hemispheres was subtracted for both conditions, and the resulting activity maps were subtracted again (saccade/cue-left minus saccade/cue-right). Activity in the left hemisphere reflects contralateral activity. Because of this subtraction, only lateralized activity is visible. Shown are plots for the saccade condition, with directional fixation subtracted (left); the saccade condition with nondirectional fixation subtracted (center) and the directional fixation condition with nondirectional fixation as baseline. Plots are averaged over the entire time window.
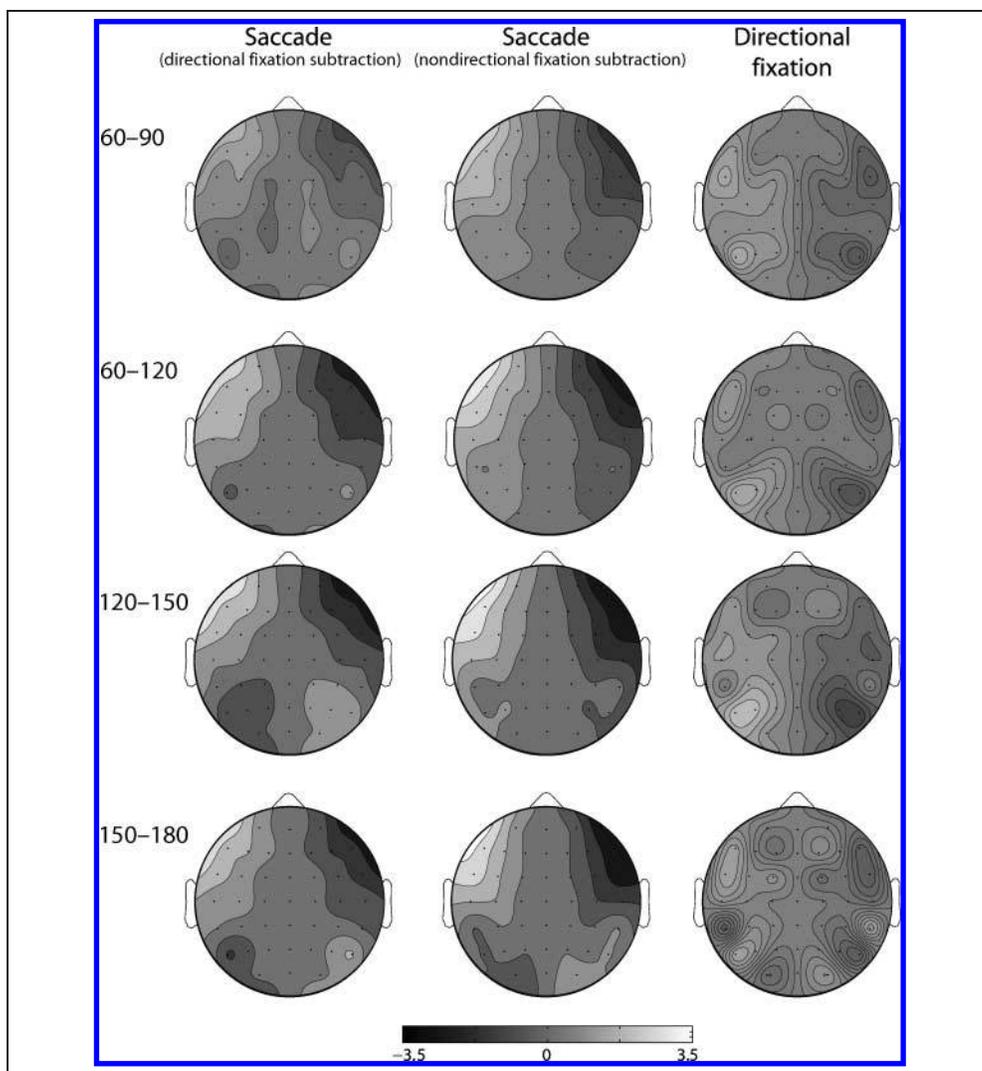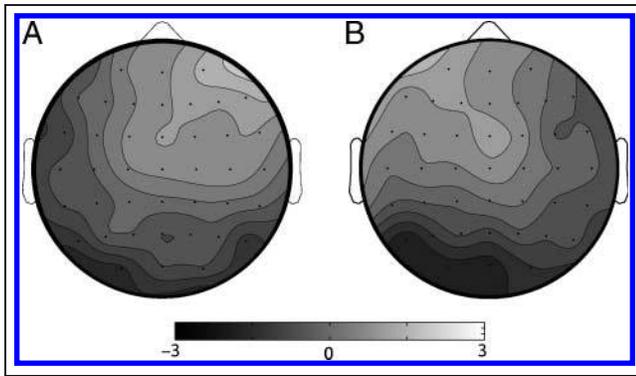
Figure 5. EEG topoplots for the saccade conditions (directional fixation subtraction), averaged over the entire 60- to 180-msec time windows. Shown are the plots for the saccade left (A) and saccade right (B) conditions. These plots were obtained without mirroring saccade directions. In the saccade left condition (A), activity can be seen in the right frontal and bilateral occipital areas; in the saccade right condition (B), activity can be seen in the left frontal and left occipital areas.

direction (see Figures 3 and 4). There were no lateralization differences between cue directions.

EEG—Cue-related Effects

Cue-onset-locked ERP analysis was done to assess attentional effects during the cue-target interval (Van der Lubbe et al., 2006; Van der Stigchel et al., 2006; Hopf & Mangun, 2000; Nobre et al., 2000; Harter et al., 1989; see Figure 8). A lateralized increase in negativity was found for parieto-occipital electrode pair PO7/8 and occipital electrode pair O1/2 for the directional fixation condition, contralateral to cue direction, starting at ~200 msec. This was found to be significant in the time window 200–320 msec (postcue): PO7/8 paired samples t test, $t(12) = -2.92$ $p = .01$; O1/2 paired samples t test, $t(12) = -2.42$ $p = .03$. This is con-

sistent with an EDAN, as found in previous studies. No significant effect was found at electrode pair P1/2 (paired samples t test), $t(12) = -0.70$ $p = .50$. Similar activity was observed in the saccade condition for electrode pair O1/2 (paired samples t test), $t(12) = -2.14$ $p = .05$. No significant differences were found in the nondirectional fixation condition.

In a 250- to 450-msec time window, increased negativity was found at frontal electrode pair FC3/4 in the contralateral hemisphere (relative to cue/saccade direction) in the directional fixation condition (paired samples t test), $t(12) = -2.56$ $p = .02$, and at electrode pair F7/8 for the saccade condition (paired samples t test), $t(12) = -2.13$ $p = .05$. This is consistent with an anterior directing attention negativity (ADAN). No effects were found at other electrodes (P1/2;PO7/8;O1/2). No significant differences were found in the nondirectional fixation conditions.

No indications of an LDAP were observed for any time window, at any of the selected electrodes F7/8, FC3/4, P1/2, PO7/8, or O1/2. There was, however, a lateralized positivity at electrode pair P5/6 in the directional fixation condition, as can be seen in Figure 8. However, this was just below significance at a 400- to 500-msec time window (paired samples t test), $t(12) = 2.13$ $p = .055$. As this effect is only observed in this particular electrode, not typical for an LDAP, and does not seem to be very robust, it is uncertain whether this represents a true LDAP.

No differences in the lateralization were found in the ERP effects described previously between hemispheres for left- and rightward cues.

DISCUSSION

Previous studies have established the coupling between eye movements and spatial attention (Dore-Mazars et al., 2004; Deubel & Schneider, 1996; Kowler et al., 1995) and

Figure 6. Scatterplots for the correlation analysis between electrodes O1/2 and FC3/4 for time windows 60–90 and 90–120 msec (shown left) and between the N200 peak and the O1/2 and FC3/4 (both time windows). A strong correlation can bee seen between the early time window of electrode pair FC3/4 and O1/2. No significant correlations were found for any other combination of electrode/time window tested.
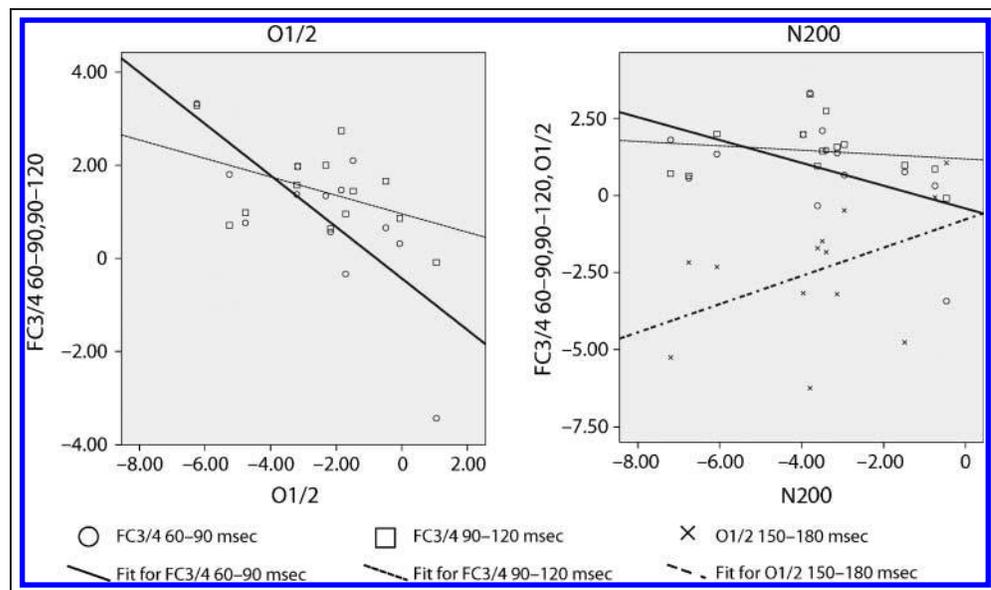
Table 1. Localization Results for Different Models Tested

Model	Explained Variance (%)	Model Evidence
Unconstrained	95.97	187.4
FEF bilateral	93.58	152
IPS bilateral	79	89.8
FEF–occ bilateral	92.24	154.2
FEF–occ–IPS bilateral	91.33	145.8
FEF contralateral	89.66	141.6
FEF–occ contralateral	90.46	146.2

The unconstrained model does not restrict solutions to specified neural sources, only gray matter. The model evidence reflects the amount of explained variance against the model complexity. IPS = intraparietal sulcus; occ = occipital cortex.

the coupling of the FEF and the visual cortex (Neggers et al., 2007; Taylor et al., 2007; Ruff et al., 2006; Silvanto et al., 2006; Grosbras & Paus, 2003). This study provides support for the cortical FEF–VC feedback connection as a neuronal mechanism coupling saccade planning in the FEF to attentional processing in the occipital lobe, as has been hypothesized for human observers.

Namely, in the saccade condition, after cue offset, a transient lateralized frontal positivity was found, peaking around 120–150 msec after saccade-go signal. This was followed by an occipital negativity contralateral to the upcoming target. This supports the view that saccade preparation, likely in the FEF, results in attentional shifts in the visual cortex (Neggers et al., 2007) through FEF–VC connections (Taylor et al., 2007; Ruff et al., 2006; Silvanto et al., 2006; Grosbras & Paus, 2003).

Consistent with our expectations based on the preceding TMS study (Neggers et al., 2007), significant frontal activity was observed contralateral to saccade direction during saccade preparation (after saccade-go). The frontal effect was slightly smaller when the directional fixation condition was used as a baseline. This may be due to the recruitment of the contralateral FEF (relative to cued direction) in the directional fixation condition, although this effect cannot be seen in the topography (see Figure 3, right column).

It has been shown that TMS on these frontal areas, the FEF specifically, causes modulation in discrimination performance (Neggers et al., 2007; Grosbras & Paus, 2003). Lateralized frontal activity was found in the current study at the same time points as the TMS stimulation times of the Neggers et al. (2007) study (see Figures 3 and 4). It therefore seems plausible to associate this activity with the deployment of spatial attention shortly before saccade execution (note that during any of the analyzed time intervals, no saccades were made yet, as ensured by the rigorous analysis, excluding trials with premature
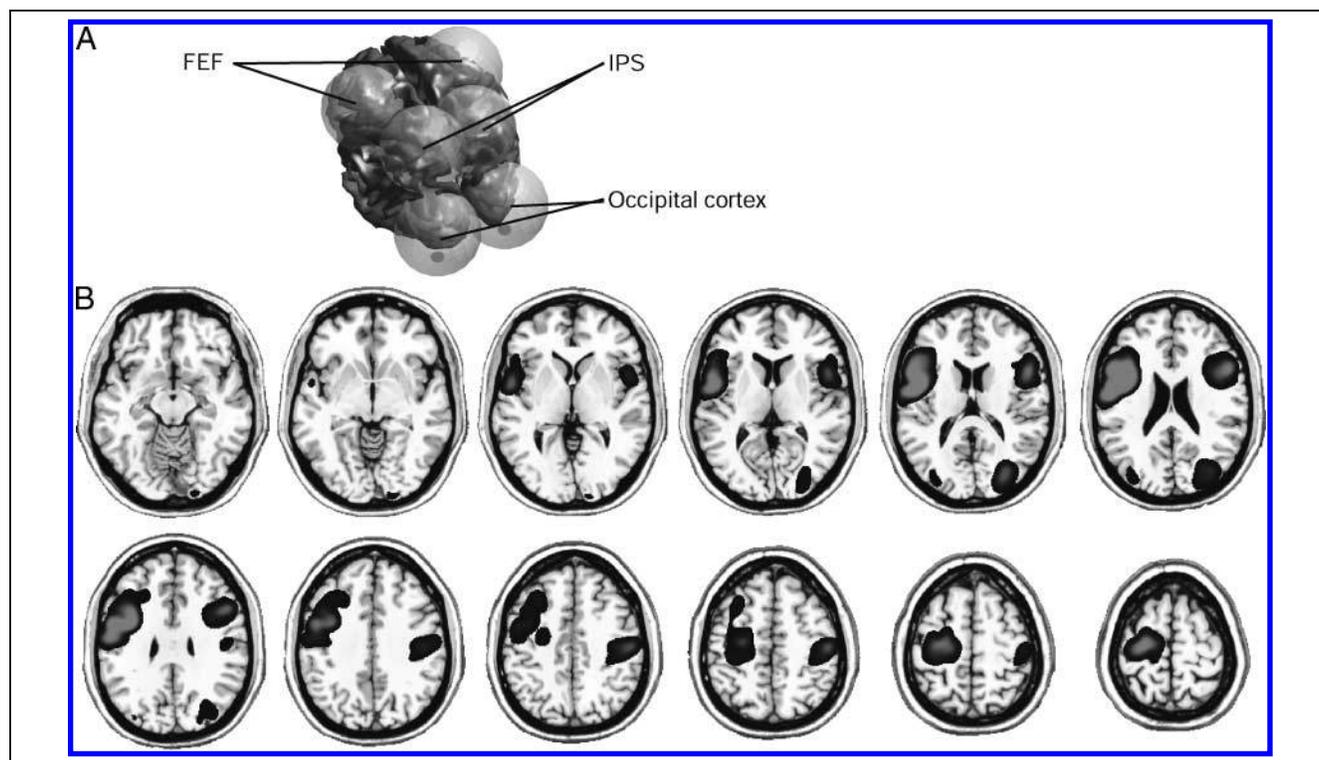

Figure 7. Localization of EEG activity during saccade preparation in the saccade condition (directional fixation subtraction). (A) Sources were restricted to spherical areas shown. Different combinations were used (see Table 1). (B) Localization results obtained using the bilateral FEF–occipital model. Slices run from MNI $Z = -12$ (top left) up to $z = 72$ (bottom right).
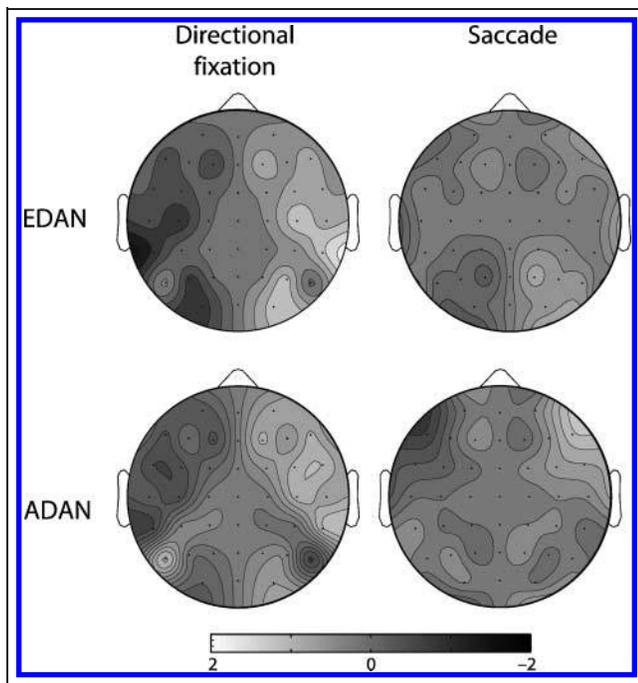
Figure 8. Double subtraction EEG topoplots for the directional fixation and saccade condition during the cueing period. To obtain the double subtraction plot, activity from the left and right hemispheres was subtracted for both conditions, and the resulting activity maps were subtracted again (cue left minus cue right). Activity in the left hemisphere reflects contralateral activity. Because of this subtraction, only lateralized activity is visible. The EDAN plots are averaged over a 200- to 320-msec time window; the ADAN plots are averaged over a 250- to 450-msec time window.

saccades). This frontal effect does not occur in the fixation conditions after cue offset. This might be due to some hemispheric preparations already having taken place for the cued hemifield. This is reflected by the presence of the ADAN in the cueing period. It is interesting to note the difference in polarity between the ADAN in the cueing period and the frontal positivity after cue offset. Both may reflect preparatory processes in the FEF, but the ADAN might reflect inhibition of the saccade, whereas the frontal positivity might reflect saccade activation. This fits well with findings by Van der Lubbe et al. (2006). As the FEF are heavily implicated in attentional shifts (Ruff & Driver, 2006; Van der Lubbe et al., 2006; Corbetta et al., 1998, for a review Moore, Armstrong, & Fallah, 2003), the combined TMS–EEG results suggest a strong (attention directing) influence of the contralateral FEFs on perceptual performance.

We observed a lateralized occipital negativity late in the saccade preparation period (120–180 msec after saccade-go). It is unlikely that this negativity is the result of target presentation. Activity from the directional fixation condition was used as a baseline, effectively subtracting any visual response to the presented stimuli. Also, target presentation was preceded by masking stimuli, resulting in low visual impact for the unmasking of the target stimu-

lus (and simultaneous unmasking of distracters). Therefore, it is likely that this negativity is the result of an attentional shift, mediated by the FEF and not by the target presentation. A number of observations support this view: The observed negativity occurs approximately 60–120 msec after the onset of frontal positivity, which is in line with an estimated 100-msec conduction time of the FEF to the visual cortex (for details on this estimation, see Methods section of Experiment 3 from Neggers et al., 2007).

Also, in the directional fixation condition, which is the same task in all respects except for the actual execution of the saccade, both the frontal positivity and the occipital negativity were absent after the go signal. This suggests that these processes are related and perhaps coupled. Furthermore, it can be noted that in the directional fixation condition (nondirectional fixation subtraction), a significant effect is present in the time window 120–150 msec (see Figure 3, right panel). Interestingly, this occipital effect is positive, whereas the occipital effect in the saccade condition is negative. This might be due to the different task instructions between these conditions. Whereas in the saccade condition an eye movement has to be executed after the go signal, any eye movements in the fixation conditions have to be suppressed (especially in the directional condition). This active suppression (as opposed to execution) may have differential effects on the occipital areas, perhaps also due to different modulations mediated by the FEF–VC connections.

Correlation analysis shows that the early frontal activity, contralateral to saccade direction, is significantly (negatively) correlated with the occipital activity seen late in the preparation period (150–180 msec after saccade-go). This means that more positive activity per subject is paired with more negative activity in occipital regions, as would be expected from FEF–occipital interactions. This, however, does not prove a causal relationship between frontal and occipital regions, as this cannot be inferred from the present data.

To justify our claims of source origins, a voxel-based source localization was performed on the saccade–directional fixation subtraction (see Table 1 and Figure 7). First, an unconstrained model was tested, which yielded the best results in terms of explained variance (and model evidence; see Table 1). However, we believe that these sources are unlikely to be the true neural sources of our data. The source model places large sources in deep brain regions, for example, near the cerebellum, brainstem, and posterior OFC. These are not only unlikely to generate large cortical surface potentials but are also not likely to be involved in the current task. We therefore compared a number of constrained models on the basis of plausible neural sources in this task, including bi- and contralateral (to saccade direction) FEF, IPS, and occipital areas. The bilateral FEF–occipital model yielded the highest model evidence and explained only slightly less variance than the unconstrained model. This is a good indication that these areas are the

actual sources of activity. It is interesting to note that the bilateral models outscore the contralateral models. Therefore, although the contralateral activity is stronger, there is some activity in the ipsilateral hemisphere. The addition of the IPS to the model results in lower model evidence, which confirms our previous results of (no) IPS involvement in this task (Veenstra et al., under revision) and the findings by Ruff et al. (2008). This is again confirmed when models on the basis of bilateral FEF and IPS are compared (model evidence FEF = 152.0, IPS = 89.8).

There is a difference in the 120- to 150-msec time window in the saccade condition, depending on the baseline used. One might argue that the occipital effect in the saccade condition at 120–150 msec could reflect a baseline effect (see Figure 3, bottom panel). For the final time window from 150 to 180 msec, however, this effect was not observed for the directional fixation condition (nondirectional fixation subtraction), and the saccade condition did show a significant difference for this time interval independent of baseline used. This means that the occipital effect at time window 150–180 msec is an effect of saccade preparation and is not a baseline effect.

Previous FEF–TMS studies (Grosbras & Paus, 2002, 2003) revealed a dominance of the right hemisphere in controlling visuospatial attention. Right FEF–TMS resulted in bilateral discrimination performance increases, where left FEF–TMS resulted only in unilateral (contralateral to cue direction) effects. Other more recent studies have found similar lateralization effects, such as Ruff et al. (2006), who found bilateral effects in the visual cortex after right FEF stimulation using fMRI, and Silvanto et al. (2006), who also found bilateral effects with right FEF–TMS and unilateral effects with left FEF–TMS. In the current study, a similar lateralization difference was found, where saccade preparation to the left invoked right frontal activity and a bilateral occipital effect (slightly lateralized to the right hemisphere). Preparation of saccades to the right invoked left frontal and left occipital activity. This striking similarity argues for an activation of the FEF–VC pathway in the current study.

Although in the current study we have emphasized the coupling between eye movements and attention, a number of studies report a dissociation (Juan et al., 2004, 2008; O'Shea, Muggleton, Cowey, & Walsh, 2004; Murthy, Thompson, & Schall, 2001; Thompson, Bichot, & Schall, 1997). For instance, Juan et al. (2004) shows that the locus of attention can be dissociated from an evoked saccade in the FEF of the macaque monkey. This shows that covert attentional shifts are not strictly coupled to saccade preparation. This is likely the result of different neural populations in the FEFs that serve different functions over time. The role of the FEF in visual search, in the absence of eye movements, has been well established (Muggleton et al., 2003). Although this is troublesome for the "hard" interpretation of the premotor theory of attention as posed by Corbetta et al. (1998) and Rizzolatti et al. (1987), this need not be a problem for the results obtained in the current study. The claim we make here is that just before the actual execution of the saccade, the attentional locus shifts toward the intended end point of the saccade and that this is mediated by the FEF. However, this does not imply that saccade preparation in the FEF is essential for attentional shifts; there could be other biasing sources, either within the FEF or elsewhere. It is very likely that the activity found in the current study in the frontal regions does not reflect activity from a homogenous neural population. Instead, it is likely that this is a cumulation of attention-related activity and saccade (motor) preparation. It is interesting to note that this is reflected in the correlation between frontal and occipital activity: Only the early frontal activity (60–90 msec after saccade-go) correlates significantly with the observed occipital effect (at 150–180 msec after saccade-go), not the later frontal time window (90–120 msec).

Cue-locked analyses revealed attentional preparation in the directional fixation and saccade conditions. In the directional fixation condition, activity patterns consistent with EDAN and ADAN (anterior attention direction negativity) were observed. The EDAN has been implicated as reflecting simple cue processing (Jongen, Smulders, & Van der Heiden, 2007; Eimer, van Velzen, Forster, & Driver, 2003), and the ADAN indicates that covert spatial attention was allocated to the cued location. The presence of an ADAN supports attentional preparation in the frontal brain regions, likely originating from the FEF during the cueing period. No activity was found resembling an LDAP. This may be due to the short cueing interval used in the current study. These effects were absent in the nondirectional condition. As expected, without directional cueing, no specific attentional preparation was made. Both EDAN and ADAN were found in the cueing period of the saccade condition. However, in the saccade condition, it was not as consistent as in the directional fixation condition. This may be due to a general reduction of attentional preparation, or it may be that subjects in some trials did not engage in attentional shifts until saccade execution. This does not rule out attentional shifts just before saccade execution, as can be seen in the poor behavioral results when ST and DT do not match.

As in a previous TMS study from our group using an identical procedure as in Neggers et al. (2007; van Ettinger-Veenstra et al., unpublished observations), no evidence was found for the involvement of the IPS in attentional modulation during saccade preparation, as can also be clearly seen in Figures 3 and 4.

The IPS has been implicated as an essential part of an attention controlling fronto-parietal network (Van der Lubbe et al., 2006; Giesbrecht et al., 2003; Hopfinger et al., 2000, 2001) and has been shown to have great functional overlap with the FEF (Capotosto, Babiloni, Romani, & Corbetta, 2009; Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Corbetta, Kincade, & Shulman, 2002). Time window analysis of the electrodes located at or near the IPS (P1/P2) showed no significant, lateralized activity in any time window for the saccade condition. This was observed both during

the cueing period and after saccade-go. Also, Bayesian model selection of source locations did not favor the IPS as a contributing source. However, a significant positive correlation was found between the early time window of the ipsilateral (to saccade direction) electrode pair P1/2 and ipsilateral occipital electrodes O1/2. As the effects are limited to the ipsilateral side and the activity is relatively small, we are unsure how to interpret these results. Also, significant lateralized activity was found after cue-offset for the directional fixation condition. It may be that parietal areas are recruited for covert attentional shifts. These seem to be independent of frontal attention directing activity. In addition, frontal activity was followed by a lateralized occipital negativity, whereas parietal activity was followed by an occipital positivity. Thus, it seems that the effects are qualitatively different, and it is therefore likely that the IPS does not function as a relay station for frontal signal inducing attentional shifts. This is consistent with findings in a study by Ruff et al. (2008) where TMS on the IPS evoked qualitatively different effect on the visual cortex than FEF–TMS in a preceding study (Ruff et al., 2006).

In conclusion, the present study, combined with the previous TMS study by Neggers et al. (2007), provides strong evidence for a crucial role of the FEF in spatial attention shifts before eye movements. Whether other areas such as the IPS and other frontal areas implicated in attentional shifts may be involved and what their contribution is in the current paradigm is still unclear. From the present results, it seems that they are not directly involved in the coupling of the locus of spatial attention to a saccade goal, as observed for the FEF.

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