

Human Frontal Eye Fields and Visual Search

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Muggleton, Neil G., Chi-Hung Juan, Alan Cowey, and Vincent Walsh. Human frontal eye fields and visual search. *J Neurophysiol* 89: 3340–3343, 2003; 10.1152/jn.01086.2002. Recent physiological recording studies in monkeys have suggested that the frontal eye fields (FEFs) are involved in visual scene analysis even when eye movement commands are not required. We examined this proposed function of the human frontal eye fields during performance of visual search tasks in which difficulty was matched and eye movements were neither necessary nor required. Magnetic stimulation over FEF modulated performance on a conjunction search task and a simple feature search task in which the target was unpredictable from trial to trial, primarily by increasing false alarm responses. Simple feature search with a predictable target was not affected. The results establish that human FEFs are critical to visual selection, regardless of the need to generate a saccade command.

INTRODUCTION

The processes involved in visual selection and search have been classically segmented into perceptual and motor components that correspond to posterior visual and anterior motor or visuomotor areas (Desimone and Duncan 1995; Posner and Peterson 1990; Treisman 1996). This segregation has recently been challenged by neurophysiological recordings in the frontal eye fields (FEFs) of the macaque monkey (Bichot and Schall 1999; Schall 1997; Schall and Hanes 1993; Schall et al. 1995), an area traditionally associated with oculomotor responses (Schiller and Chou 1998; Tehovnik et al. 2000). It is now known, for example, that FEF responses are consistent with a sensory contribution to visual selection in addition to and independent of its role in eye movements (Bichot and Schall 1999; Blanke et al. 1999; Schall 1997; Schall and Hanes 1993; Schall et al. 1995; Thompson et al. 1997). This electrophysiological work on nonhuman primates has not been matched by any lesion experiments or by any evidence that *human* FEFs are important for visual selection in the absence of eye movements (Paus 1996; Rivaud et al. 1994; Ro et al. 1999; Thickbroom et al. 1996; Tobler and Muri 2002). A recent exception is the demonstration that human FEFs are important for preparatory vision in a modified Posner paradigm (Grosbras and Paus 2002).

The challenge set by the recent neurophysiological work is that, in FEFs, “the visual selection process may be an explicit interpretation of the image and not an obligatory saccade command” (Murthy et al. 2001). To examine this claim, we

tested subjects on visual search tasks and interfered with the normal functioning of FEFs by applying repetitive transcranial magnetic stimulation (rTMS) to the FEFs during the tasks. The presentation of the search stimuli was brief enough to ensure that subjects could not saccade to elements in the array, and eye fixation was monitored. Thus saccades were neither required nor useful in the task (Fig. 1A). To allow comparison with the neurophysiological studies, three tasks were used: a feature task in which the targets and distracters were always the same; a feature task in which targets and distracters were interchangeable from trial to trial; and a conjunction search task (see Fig. 1B).

METHODS

Pilot study

Prior to the main experiment, a pilot study was carried out to establish that TMS (10 Hz, 500 ms at 65% of stimulator output—see *TMS*) delivered to the FEFs would result in an elevated reaction time on a visual conjunction search paradigm. Reaction times were chosen as the dependent variable because they have been a reliable guide in previous experiments (e.g., Ashbridge et al. 1997; Walsh et al. 1998a). This employed a design similar to that which has previously shown disruption of visual search reaction time due to posterior parietal TMS (e.g., Walsh et al. 1998a). Briefly, a large, 20° × 20°, array containing sixteen 2° × 2° array elements was presented, and subjects had to make a target present/absent response. Response time was measured with TMS delivered to the right FEFs, left FEFs, or no TMS. Analysis of the data (repeated measures ANOVA) showed a significant effect of stimulation condition (no TMS, left FEFs, or right FEFs) on target present trials [$F(2, 10) = 6.092, P = 0.019$]. This was due to an approximately 40-ms increase in response time with TMS over the right FEFs (no TMS, 609 ms; right FEFs, 646 ms; left FEFs, 606 ms; left FEFs vs. right FEFs, mean difference, 40.5; 95% CI, 8.90, 72.1; $P = 0.022$). No significant effect was seen on target absent trials.

Main study

On the basis of the pilot procedure, the main study, described here, was carried out using only right hemisphere TMS to clarify the role of FEFs in visual search performance. For the main study, controls sites for TMS of vertex and V5 were used. Right V5, rather than left FEFs, was chosen because this represents a more stringent control than left FEF stimulation, which we established was unlikely to affect search in the pilot experiment. Furthermore, V5 is part of the visual system at a similar hierarchical level to FEFs (Barone et al. 2000; Bullier 2001) and thus provides a control for nonspecific disruption of the visual

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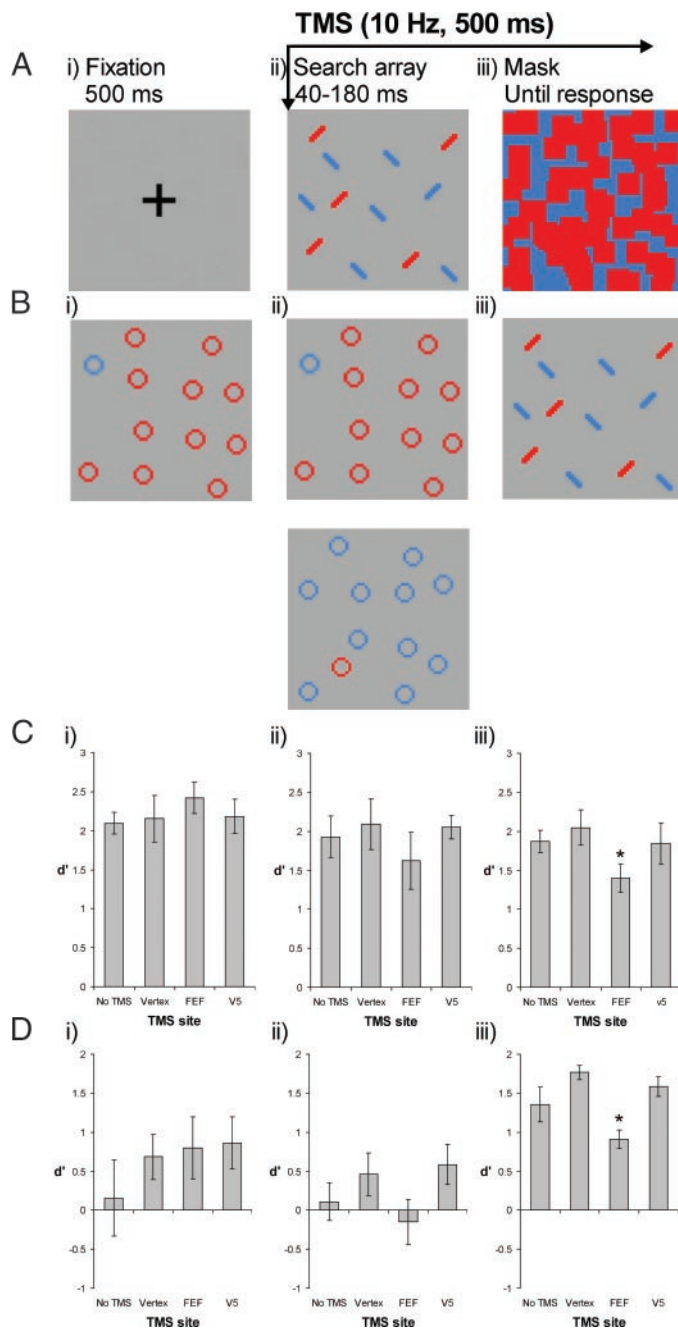


FIG. 1. Behavioral task and performance data. *A*: time course of a trial. *B*: 3 stimulus displays used. (i) In the constant feature search task, the target was always a blue circle (CIE: $x = 0.163$, $y = 0.140$, luminance $20 \text{ cd} \cdot \text{m}^{-2}$; $0.2^\circ \times 0.2^\circ$) among an array of 11 red circles (CIE: $x = 0.615$, $y = 0.346$, luminance $20 \text{ cd} \cdot \text{m}^{-2}$; $0.2^\circ \times 0.2^\circ$). (ii) In the interleaved search condition, the target was either a red circle among blue circle distracters or vice versa. The order of red or blue target trials was randomized with the constraint that each block of 60 trials contained 30 target absent trials and 15 of each target present trial type (red/blue target) in 30 target present trials. (iii) In the conjunction task, the target was a blue diagonal among an array of 6 red diagonals ($0.2^\circ \times 0.2^\circ$) in the same orientation and 5 blue diagonals in the orthogonal orientation. *C*: d' data (\pm SE) obtained in (i) constant feature search, (ii) interleaved feature search, and (iii) conjunction search task. *D*: $\log \beta$ (bias) values (\pm SE) obtained in (i) constant feature search, (ii) interleaved feature search, and (iii) conjunction search task. Positive values indicated a bias toward target absent responses, and negative values a bias toward target present responses.

system by TMS. This would not be the case for left FEF stimulation both because of the limited amount of TMS data relating to this area in tasks other than those investigating saccades and because it seems that the right hemisphere may contribute more to performance of conjunction search tasks than the left hemisphere (see *Pilot study*).

Subjects

Five subjects (4 male, 1 female), 24–32 yr old and all right-handed, were recruited from the Department of Experimental Psychology, University of Oxford. All gave informed consent before taking part in the study. The study was approved by the Oxford Research Ethics Committee (OXREC), and exclusion criteria conforming to current guidelines for rTMS research were applied (Wassermann et al. 1998). All subjects had previous experience participating in TMS experiments.

Equipment

Tasks were presented on a 17" VDU with a refresh rate of 100 Hz. Subjects were seated 57 cm from the screen and were restricted by a head and chin rest. Stimuli, responses, and TMS triggering were generated and measured by E-Prime software running on an IBM compatible Pentium IV computer. Stimulus arrays (see Fig. 1) subtended $2^\circ \times 2^\circ$ of visual angle. All subjects were tested on all tasks, and TMS conditions and the time-course of a trial are illustrated in Fig. 1. The probability of a target being present was 50%, and subjects made a target present/target absent decision via a keyboard response. The duration of the array presentation was individually determined for each subject by adopting a staircase procedure in which the duration of the stimulus was varied by one screen refresh (10 ms) until a performance level of 75% correct was reached. The mean threshold was 93 ± 12 (SE) ms (range, 50–180 ms). The experiment began with a block of 60 trials to verify the threshold level of performance. Accuracy, rather than speed, was emphasized to the subjects in the instructions.

TMS

TMS was delivered by a Magstim 200 Super Rapid Stimulator at 10 Hz for 500 ms at 65% of stimulator output beginning at the onset of the search array. This stimulus intensity was chosen because it was greater than the motor threshold in all subjects, but when applied to V5, did not produce phosphenes that obscured the stimuli. Intensity was not related to motor threshold because it has been shown that motor thresholds cannot be assumed to be a guide to visual cortex excitability (Stewart et al. 2001). Stimulation was delivered using a 50-mm figure-of-eight coil placed over the right FEFs, the vertex, or visual area V5 in the right hemisphere for one block of 60 trials at each site. For all sites, the coil was held anterior to the handle and was oriented parallel to the sagittal midline. For V5 stimulation, the coil was held ventral to the handle. The vertex was chosen as a control site for nonspecific effects of TMS such as acoustic and somatosensory artifacts, and area V5 in the right hemisphere was chosen as control for nonspecific effects of stimulating the visual system per se. The order of stimulation blocks was counterbalanced across subjects. For details of site localization, see Fig. 2.

Eye movement monitoring

To ensure that subjects' eye movements could not account for the results, we monitored fixation using a differential limbus reflection technique via infrared light transducers from a Skalar IRIS 6500 system headset mounted on a chin rest such that eye movements could be recorded while subjects viewed the stimulus monitor. Signals were sampled at a rate of 1,000 Hz by an analog-to-digital converter card

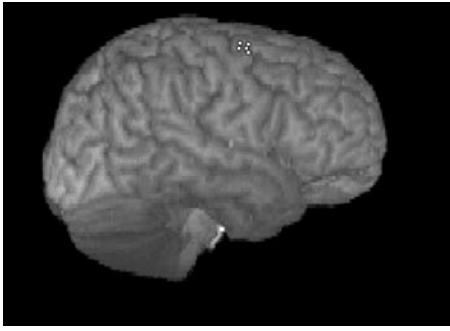


FIG. 2. Site localization. The vertex was defined as a point midway between theinion and the nasion and equidistant from the left and right intertrichial notches. V5 was initially localized by scalp coordinates that yielded motion deficits in previous studies (Campana et al. 2002; Walsh et al. 1998b) and verified by eliciting moving phosphenes from the site (Stewart et al. 1999). The frontal eye fields magnetic stimulation sites were localized using the Brainsight TMS-MRI co-registration system (Rogue Research, Montreal, Canada). FEFs localization began with stimulation 4 cm anterior to the optimal site for eliciting activity in the first dorsal interosseus (FDI) muscle of the left hand (Paus 1996) and proceeded by co-registering each subject's structural MRI scan with the location of the coil. The location of the center of the coil with respect to the cortex is illustrated. FEF transcranial magnetic stimulation (TMS) stimulation sites were all found to be in the area previously described as the FEFs (Paus 1996) and further confirmed by conversion of the coordinates of the stimulated sites to MNI Tailarach space. This showed an average stimulation location of 33 ± 3.0 , 0 ± 5.1 , and 65 ± 1.8 (SE) compared with coordinates of 30, 6, and 60 (the MNI coordinate equivalent of mean FEF Tailarach coordinates as reviewed by Paus (1996)).

(type PCM-DAS 16d/12, Computerboards) and recorded using DASYlab 5 software on an IBM compatible PC.

Data analysis and statistics

Performance was measured using signal detection analysis to calculate d' values. This approach, rather than using response times as a dependant variable, was chosen for two main reasons. First, use of d' allows for more direct comparison with data from the primate single unit recording literature that motivated this experiment. Second, measurement of response times in TMS experiments can sometimes be made more difficult by the acoustic artifacts associated with TMS delivery. These can sometimes cause reduced response times (putative enhancements) and lead to difficulties in data interpretation.

Changes in d' due to TMS were analyzed by MANOVA with TMS site (or no TMS) and task as factors. Post hoc planned comparisons were made with t -tests corrected for multiple comparisons.

RESULTS

There was a significant effect on task performance when TMS was delivered over FEFs [$F(2) = 5.011$, $P = 0.026$]. This effect was shown to be a d' decrease in the conjunction task relative to the constant feature task (mean difference 1.02; 95% CI, 0.17, 1.87; $P = 0.02$). Comparisons between TMS sites using the method of least significant difference showed a significant d' decrease with FEF stimulation compared with all other conditions in the conjunction task (TMS over FEFs vs. no TMS: mean difference 0.47; 95% CI, 0.02, 0.92; $P = 0.044$; FEFs vs. vertex: mean difference 0.649; 95% CI, 0.44, 0.86; $P = 0.001$; FEFs vs. V5: mean difference 0.44; 95% CI, 0.10, 0.79; $P = 0.024$). There were no differences between no TMS, vertex, and V5 TMS. In the interleaved feature task, the d' decrement seen when TMS was delivered over FEFs approached significance compared with the constant feature task

(mean difference 0.80; 95% CI, -0.05 , 1.65; $P = 0.056$). No difference in blinks or eye movements was associated with TMS at any site, and they rarely occurred during trials.

Log β (a measure of bias calculated from the target detection rate and false alarm rate) showed that, in the conjunction task, subjects were biased toward making target absent responses in no TMS trials (value: 1.35) as well as in TMS conditions (vertex, 1.77; FEFs, 0.91; V5, 1.59). However, comparison of the three TMS conditions indicated a significant reduction in bias with FEF stimulation (2-tailed paired Student's t -test: FEFs vs. V5; $t(4) = 8.43$, $P = 0.001$; FEFs vs. vertex; $t(4) = 3.26$, $P = 0.031$). Bias values were lower for both the simple feature task (values: no TMS, 0.16; vertex, 0.69; FEFs, 0.80; V5, 0.86) and the interleaved task (values: no TMS, 0.11; vertex, 0.46; FEFs, -0.15 ; V5, 0.59), but no significant differences between the effects of the stimulation sites were seen.

DISCUSSION

When rTMS was applied to the FEFs, performance was unaffected on the simple feature task but significantly impaired on the conjunction task (Fig. 1C). Detectability in the interleaved feature task was intermediate. Control stimulations over area V5/MT and over the vertex had no effect on any of the tasks and therefore confirmed that the results of FEF stimulation were specific to that site and not caused by acoustic or somatosensory artifacts. The effects were not a simple feature of task difficulty since the presentation durations of the stimuli were titrated to equate performance across tasks.

These results show that the human FEFs are essential for normal visual search performance in the absence of the requirement for eye movements. The absence of a FEF effect on the simple feature search is not surprising since the high saliency and predictability of feature targets is detectable with redundancy in several visual areas (Greenlee et al. 2002), many of which are connected with FEFs (Bullier 2001; Bullier et al. 1996). The modulation of performance in the conjunction task is consistent with neuronal recording evidence that has implicated FEFs in forming a saliency map during tasks that present complex visual scenes (Thompson et al. 1997, 2001).

A breakdown of the response changes contributing to a decrease in d' values with TMS shows that magnetic stimulation caused subjects to make significantly more false positive responses at the expense of correct rejections, without a change in target hit rate (mean false alarm rate: vertex, 2.67%; FEFs, 10.67%; mean hit rate: vertex, 56%; FEF, 52%). This is reminiscent of the errors made on such tasks by patients with damage to the posterior parietal cortex (PPC) who report conjunctions that are illusory (Friedman-Hill et al. 1995). The pattern of errors also suggests that the change is a result of reduced ability to process array items rather than an inability to covertly "search" the array, which would likely result in targets being missed, rather than causing more false alarms.

These data prompt a consideration of the interesting similarities between FEFs and PPC: both areas lie at the crossroads of visual and motor processing; both are commonly associated with loosely-defined roles in fronto-parietal networks that are important for visual search (e.g., Corbetta et al. 1995; Wojculik and Kanwisher 1999); and both areas have been associated with eye movements, spatial attention, motor responses, and visual saliency. There are, however, some important differ-

ences. The trend toward an effect in the alternating feature search (Fig. 1, *Bii* and *Cii*), and the physiological evidence, may be suggestive of a role for FEFs in visual feature priming (Bichot and Schall 1999), a function for which the PPC is not required (Campana et al. 2002). A second difference lies in the motor responses to visual stimuli; whereas FEFs have been shown to encode visual information independently of saccade commands (Thompson et al. 1997), there is no good evidence that PPC neurons encodes such information independently of affordances or action (Anderson and Buneo 2002; Milner and Goodale 1993; Platt and Glimcher 1999); rather, the contrary seems to be the case.

In concert with neurophysiological findings in nonhuman primates, these results establish that human FEF is important for visual selection in the absence of eye movements. The data also show that that FEF is more important when the visual target is less salient (cf. Fig. 1, *Ciii* vs. *Ci*) and suggest this is the case when the target is less predictable (cf. Fig. 1, *Cii* vs. *Ci*). The nature of the FEF effect—an increase in false positive responses reminiscent of parietal cortex damage—highlights the need for a greater understanding of the similarities and differences between the two visuomotor crossroads (PPC and FEF) in visual cognition and the importance of reciprocal constraints between psychologically and physiologically motivated theories (Schall 2002). To pursue these issues, we are currently engaged in studies of the timing of FEF involvement (Schall et al. 1995) and of the effects of learning on the role of FEFs in visual search (Walsh et al. 1998a).

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REFERENCES

- Andersen RA and Buneo CA. Intentional maps in the posterior parietal cortex. *Annu Rev Neurosci* 25: 189–220, 2002.
- Ashbridge E, Walsh V, and Cowey A. Temporal aspects of visual search studied by transcranial magnetic stimulation. *Neuropsychologia* 35: 1121–1131, 1997.
- Barone P, Bardiere A, Knoblauch K, and Kennedy H. Laminar distribution of neurons in extrastriate areas projecting to visual areas V1 and V4 correlates with the hierarchical rank and indicates the operation of a distance rule. *J Neurosci* 20: 3263–3281, 2000.
- Bichot NP and Schall JD. Effects of similarity and history on neural mechanisms of visual selection. *Nat Neurosci* 2: 549–554, 1999.
- Blanke O, Morand S, Thut G, and Michel CM. Visual activity in the human frontal eye field. *Neuroreport* 10: 1–6, 1999.
- Bullier J. Integrated model of visual processing. *Brain Res Rev* 36: 96–107, 2001.
- Bullier J, Schall JD, and Morel A. Functional streams in occipito-frontal connections in the monkey. *Behav Brain Res* 76: 89–97, 1996.
- Campana G, Cowey A, and Walsh V. Priming of motion direction and area V5/MT: a test of perceptual memory. *Cereb Cortex* 12: 663–669, 2002.
- Corbetta M, Shulman GL, Miezin FM, and Petersen SE. Superior parietal cortex activation during spatial attention shifts and visual feature conjunction. *Science* 270: 802–805, 1995.
- Desimone R and Duncan J. Neural mechanisms of selective visual attention. *Annu Rev Neurosci* 18: 193–222, 1995.
- Friedman-Hill SR, Robertson LC, and Treisman A. Parietal contributions to visual feature binding: evidence from a patient with bilateral lesions. *Science* 269: 853–855, 1995.
- Greenlee MW, Berg H, Stuhr V, and Mergner T. Visual search and visual working memory in patients with chronic focal cortical lesions. *Vision Res* 40: 3759–3773, 2002.
- Grosbras M and Paus T. Transcranial magnetic stimulation of the human frontal eye field: effects on visual perception and attention. *J Cog Neurosci* 14: 1109–1120, 2002.
- Milner AD and Goodale M. *The Visual Brain in Action*. Oxford: Oxford, 1993.
- Murthy A, Thompson KG, and Schall JD. Dynamic dissociation of visual selection from saccade programming in frontal eye field. *J Neurophysiol* 86: 2634–2637, 2001.
- Paus T. Location and function of the human frontal eye-field: a selective review. *Neuropsychologia* 34: 475–483, 1996.
- Platt ML and Glimcher PW. Neural correlates of decision variables in parietal cortex. *Nature* 400: 233–238, 1999.
- Posner MI and Peterson SE. The attention system of the human brain. *Annu Rev Neurosci* 13: 25–42, 1990.
- Rivaud S, Muri RM, Gaymard B, Vermersch AI, and Pierrot-Deseilligny C. Eye movement disorders after frontal eye field lesions in humans. *Exp Brain Res* 102: 110–120, 1994.
- Ro T, Cheifetz S, Ingle H, Shoup R, and Rafal R. Localization of the human frontal eye fields and motor hand area with transcranial magnetic stimulation and magnetic resonance imaging. *Neuropsychologia* 37: 225–231, 1999.
- Schall JD. Visuomotor areas of the frontal lobe. In: *Extrastriate Cortex of Primates, Cerebral Cortex*, edited by Rockland KS, Peters A, and Kaas JH. New York: Plenum, 1997, vol. 12, p. 527–638.
- Schall JD. The neural selection and control of saccades by the frontal eye field. *Phil Trans R Soc Lond B* 357: 1073–1082, 2002.
- Schall JD and Hanes DP. Neural basis of saccade target selection in frontal eye field during visual search. *Nature*: 366 467–499, 1993.
- Schall JD, Hanes DP, Thompson KG, and King DJ. Saccade target selection in frontal eye field of macaque. I. Visual and premovement activation. *J Neurosci* 15: 6905–6918, 1995.
- Schiller PH and Chou IH. The effects of frontal eye field and dorsomedial frontal cortex lesions on visually guided eye movements. *Nat Neurosci* 1: 248–253, 1998.
- Stewart L, Battelli L, Walsh V, and Cowey A. Motion perception and perceptual learning studied by magnetic stimulation. *Electroencephalogr Clin Neurophysiol Suppl* 51: 334–350, 1999.
- Stewart LM, Walsh V, and Rothwell JC. Motor and phosphene thresholds: a transcranial magnetic stimulation correlation study. *Neuropsychologia* 39: 415–419, 2001.
- Tehovnik EJ, Sommer MA, Chou IH, Slocum WM, and Schiller PH. Eye fields in the frontal lobes of primates. *Brain Res Brain Res Rev* 32: 413–448, 2000.
- Thickbroom GW, Stell R, and Mastaglia FL. Transcranial magnetic stimulation of the human frontal eye field. *J Neurol Sci* 144: 114–118, 1996.
- Thompson KG, Bichot NP, and Schall JD. Dissociation of visual discrimination from saccade programming in macaque frontal eye field. *J Neurophysiol* 77: 1046–1050, 1997.
- Thompson KG, Bichot NP, and Schall JD. From attention to action in frontal cortex. In: *Visual Attention and Cortical Circuits*, edited by Braun J, Koch C, and Davies JL. Cambridge, MA: MIT Press, 2001.
- Tobler PN and Muri RM. Role of human frontal and supplementary eye fields in double step saccades. *Neuroreport* 13: 253–255, 2002.
- Treisman A. The binding problem. *Curr Opin Neurobiol* 6: 171–178, 1996.
- Walsh V, Ashbridge E, and Cowey A. Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation. *Neuropsychologia* 36: 45–49, 1998a.
- Walsh V, Ellison A, Battelli L, and Cowey A. Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5. *Proc R Soc Lond B Biol Sci* 265: 537–543, 1998b.
- Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. *Electroencephalogr Clin Neurophysiol* 108: 1–16, 1998.
- Wojciulik E and Kanwisher N. The generality of parietal involvement in visual attention. *Neuron* 23: 747–764, 1999.